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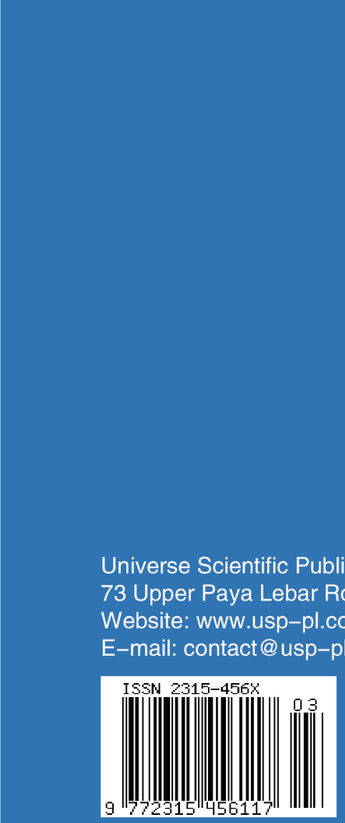

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Contents

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Clinical Significance of Nuclear Magnetic Resonance Therapy for the Treatment of Parasitic Diseases

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Abstract: **Objective:** To investigate the clinical significance of nuclear magnetic resonance (NMR) therapy for the treatment of parasitic diseases with slender lines and a length of about 0.25 cm. **Methods:** Three clinical experiences of NMR therapy for the treatment of parasitic diseases with a length of about 0.25 cm are presented to describe the failure and successful experiences of NMR therapy. **Results:** The different ways of infecting parasites cause different experiences of NMR therapy. Furthermore, matters requiring attention in the treatment of parasitic diseases by NMR are proposed. **Conclusion:** NMR therapy has obvious advantages for the treatment of parasitic diseases with slender lines and a length of about 0.25 cm.

Keywords: Nuclear Magnetic Resonance; Physical Therapy; Parasite; Itching Symptoms

Introduction

Parasites cause diseases in humans. Once a person is infected with a parasite, the parasite can invade various organs of the patient, leading to declining organ function, reduced work efficiency, and even loss of labor force[1].

At present, there are many antiparasitic drugs, such as albendazole, an insect repellent that is widely used worldwide. However, the drug used for the intestinal parasites such as ascarides is usually ineffective to the parasites diffuse in the body. And the drug treatment process is long. It can also lead to drug resistance. Therefore, parasites cannot be completely eliminated, resulting in recurrence.

I experienced two successful treatments for parasites to explore nuclear magnetic resonance (NMR) therapy as a novel treatment for parasitic diseases. This method can be used for elimination of all parasites in a short time, so the patient can avoid taking medicine for a long time.

1. NMR therapy

Magnetic resonance imaging (MRI) is a technique to obtain medical image information by exciting hydrogen protons *in vivo* with external electromagnetic energy to produce resonance relaxation effects. Magnetic resonance equipment mainly includes the main magnet, gradient system, and radio frequency (RF) system, forming three types of electromagnetic fields: static magnetic, gradient, and RF. The static magnetic field magnetizes h protons in biomolecules, the gradient field is used for imaging, and the RF field excites h protons to generate resonance.

Under the action of the electromagnetic field, h protons will precess and rotate which does not cause the parasite to wriggle and die inside the body. Therefore, the reason for the death of parasites is that the excitation frequency of parasites is close to the RF frequency in the magnetic resonance field. So the research field of this paper belongs to the category of vibration mechanics.

At present, the research on low-frequency resonance injury of organisms in China and many countries mostly focuses on organ damage[2, 3] such as under the condition of continuous low-frequency resonance to study the changes in physiological indexes such as blood pressure, heart rate, respiratory rate, and body temperature in rats[4] to study the resonance frequency and vibration characteristics of the rat liver at low frequency[5].

The NMR therapy in this paper applied a certain frequency range of NMR to the outside of my body. When the frequency of NMR is similar to the vibration frequency of parasites in my body, it causes parasites in my body to produce

resonance due to the external excitation force of NMR and sudden mass death after repeated NMR treatment, to completely cure parasitic diseases.

2. Infection experiences

When I was first infected with parasites, they were 0.25 cm in length. After the infection period reached 6 months, one morning I felt something moving on my eyes. I looked in the mirror and observed that there was a 0.25 cm long thin line bulge in the eyelid conjunctiva. After I pressed the eyelid with my hand, the thin line wriggled and disappeared instantly.

I experienced two similar parasitic infections in 2 years. One evening in April 2018, a dog's paw touched the scab wound on my calf and caused the first infection. At that time, the wound did not bleed, but I always felt that there was an invasion in the wound, and there was no disinfectant available. I felt slight itchiness in several body parts that night.

Then, one evening at the end of November 2020, a second infection occurred that was caused by directly eating weeds near the roots in the field. When eating that night, on my face and jaw there were inexplicably raised small bumps, which differed from the redness and swelling caused by mosquito bites. They were a little itchy and disappeared later. I felt uneasy for a long time. The parasite symptoms of both infections were the appearance of transitional mass on the skin surface, and the parasite was more active at night.

3. Treatment course of NMR therapy

3.1 Treatment course of the first infection

On January 28, 2019, the parasitic course was 9 months, and I went to the hospital for an NMR examination of the shoulder joint. During the NMR, I felt the parasites in the whole body wriggling quickly and instantly restored calm. I suddenly felt much more relaxed. Then I knew that by this time, the parasitic adults had died. It could be inferred that the vibration frequency of parasitic adults in my body was surprisingly close to the NMR frequency in the NMR magnetic field. Since there were still parasite eggs in my body, it would take a certain time for the eggs to develop into adults. Therefore, I insisted on undergoing NMR therapy every 5 or 6 days. The experimental records are shown in Table 1.

On February 11, 2019, the general NMR results were not good, and there was no feeling of improvement. On February 12, 2019, I emphasized to the operating doctor that the purpose of doing NMR was to cure the disease and it was necessary to increase the duration and gradient magnetic field strength when doing NMR. Thus, NMR therapy was performed a total of four times for about 17 consecutive days, and the parasites were completely eradicated without recurrence. Because of long-term continuous strong magnetic field NMR therapy, my eardrum was damaged. When flying, I heard the noise of the airplane engine and felt pain and pressure against my eardrum. Thus, I covered my ears with my hands. My eardrum gradually recovered over time.

Table 1. Experimental record of NMR therapy for the first infection

Time	Interval days	Trytosweeping position	Experimental status	Treatment effects
January28, 2019		Shoulder joint	Iunderwentgeneral NMR.	All parasites in my body were found wriggling then dying, and I felt much more relaxed. I was no longer afraid of the cold.
February 12, 2019	1 day	Shoulder joint	The strong magnetic field lasted for about 10 minutes.	I felt relaxed. At that time, I wore earmuffs with good airtightness, so the ear was not damaged.
February 18, 2019	6 days	Chest	Same as above	I felt relaxed. At that time, the tightness of the earmuff was not good, and my eardrum felt uncomfortable.
February 23, 2019	5 days	Lumbar vertebra	Same as above	Same as above.
March 1, 2019	6 days	Double iliac joint	Same as above	Same as above. I insisted on this being the last treatment.

3.2 Treatment course of the second infection

Similar to the first infection, I had two independent courses of NMR therapy for the second infection, namely general NMR and NMR with a strong magnetic field as follows.

(1) First course of treatment

On February 28, 2021, after 3 months of the second infection, the first course of NMR treatment was started. They performed general NMR twice, with an interval of 3 days. No emphasis was placed on the operating doctor to increase the duration or gradient magnetic field strength. It recurred later and there were still bumps and itchy pouches on my waist and body. The experimental records are shown in Table 2.

Table 2. Experimental record of the first course of NMR was made when the second infection occurred

Time	Interval days	Try to sweeping position	Experimental status	Treatment effects
February 28, 2021		Upper abdomen	Tried doing general NMR.	The itching disappeared that night, but it reoccurred 3 days later.
March 3, 2021	3 days	Upper abdomen	Same as above	Same as above

(2) Second course of treatment

On May 28, 2021, after 5 months of the second infection, the second course of NMR treatment was started. The first two treatments at the beginning of this period were also general NMR. Although, for instance, I felt slightly relaxed and felt a slight heat change in my body, there was no itching that night. Due to the lessons learned, the first course of treatment was unsuccessful. From June 5, 2021, I emphasized to the operating doctor that the purpose of doing NMR was to cure the disease, and was necessary to increase the duration and gradient magnetic field strength when doing NMR. Thus, NMR treatment was performed a total of four times, once every 5 or 6 days. After the first three times, the effect was the same as the last time except that I felt relaxed. On June 16, 2021, I felt a sense of relief in my whole body after completing the NMR treatment. On June 23, 2021, the last NMR was performed. At that time I did not feel anything and there was no slight heat change in my body. There was no later recurrence. The experimental records are shown in Table 3.

Table 3 Experimental record of the second course of NMR was made when the second infection occurred

Time	Interval days	Try to sweeping position	Experimental status	Treatment effects
May 28, 2021		Double iliac joint	For general NMR, two continuous strong magnetic field lasted for half a minute.	I felt a little relaxed. There was a slight heat change in my body and no itching that night.
May 31, 2021	3 days	Lumbar vertebra	Same as above	Same as above
June 5, 2021	5 days	Lumbar vertebra	The duration and gradient magnetic field strength had to be increased, and two continuous strong magnetic field lasted for 2 minutes.	The effect was the same as the last time except that I felt relaxed.
June 11, 2021	6 days	Lumbar vertebra	Same as above	Same as above
June 16, 2021	5 days	Lumbar vertebra	Same as above	Same as above
June 23, 2021	7 days	Lumbar vertebra	Same as above	This was the last treatment. I did not feel anything.

4. Results

4.1 Different infection pathways led to different NMR treatment effects

For the first time, parasites infected by scabby wounds migrated all over my body. During the NMR treatment, it was obvious that all parasites in my body were struggling with strong vibration in a short time, and there was a moment of silence after death. I felt much more relaxed (at that time, the course of infection was more than 9 months). However, for the second time, because parasites of the digestive tract infection were more parasitic in the digestive tract than parasites infected by scabby wounds. During the NMR treatment, there were no obvious struggling movements in my body, but I felt relaxed and also felt a slight heat change (at that time, the course of infection was more than 6 months).

4.2 About NMR treatment

Attention should be paid to the following during NMR treatment.

(1) To eliminate parasites in the whole body, choose the lumbar vertebra plain scan in the middle of the body for NMR.

(2) To eliminate parasites in the whole body, try to shrink and cross the legs when lying down, and retract the whole body into the NMR.

(3) Even if your doctor gives you earmuffs to wear to prevent the eardrum from being damaged under the noise of NMR, it is recommended to open your mouth wide during NMR treatment to balance the pressure inside and outside of the eardrum.

(4) Drink less water before NMR treatment to avoid the vibration of excess water in the body caused by NMR.

(5) During NMR therapy, eat light food to make the eggs grow according to the normal time, because if people eat food that promotes the growth of parasites, such as wine and meat, the growth cycle of parasite eggs will be shortened and the time intervals of repeat NMR treatment will be irregular.

(6) The general NMR does not have the effect of completely disinfecting and sterilizing the parasites. The effect of NMR treatment is better by increasing the duration and gradient magnetic field strength.

(7) To completely cure such parasitic diseases, it is necessary to undergo NMR at least four times, with an interval of 4–5 days, 5–6 times for serious cases.

5. Conclusion

NMR therapy is only needed outside the human body. In this way, parasites can be instantly eliminated from all corners of the human body, to address the issue of drug treatment not being able to completely disinfect and sterilize the parasites. Furthermore, NMR therapy saves resources and protects the environment. Thus, NMR is the best and most effective therapy that can completely cure parasitic diseases. Henceforth, it will open a new way for the treatment of parasites with a length of about 0.25 cm. In the future, we need to theoretically analyze the vibration of such parasites in vivo under the action of NMR. Moreover, the best scheme for NMR therapy should be introduced.

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Research Progress of Each Cell Signaling Pathway in Renal Interstitial Fibrosis and Anti-Fibrotic Intervention Countermeasures

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Abstract: Interstitial fibrosis is a common pathological feature of various progressive renal diseases, andthis result is mainly caused with the activation of renal interstitial innate cells (fibroblasts, pericytes, immune cells, mesenchymal stem cells, etc.) and the massive expression and deposition of extracellular matrix（ECM）. According to statistics,chronic kidney disease and interstitial renal fibrosis affect half of the world's adults over the age of 70 and 10% of the population.Although there are currently no drugs or other means to halt this process, as more and more key players affecting fibrosis are identified, this provides new research directions for anti-fibrotic therapy. In this review, we highlight the relationship between renal interstitial lamina propria and the progression of interstitial fibrosis and describe new advances in anti-fibrotic strategies.Finally,we hope to provide new ideas for the treatment of interstitial renal fibrosis.

Keywords: Interstitial Kidney; Fibrosis; Fibroblasts; Pericytes; Anti-Fibrosis; Mirna

1. Introduction

The renal interstitium is the space between the renal tubules,outside the glomerulus, and outside the renal vasculature[1]. It is surrounded on all sides by tubular and vascular basement membranes, which are filled with mesenchymal cells (dendritic cells (DC), lymphocytes and various types of fibroblasts), extracellular matrix (ECM) and interstitial fluid[2-4]. Fibrosis is a pathological extension of the normal wound healing process, and it can be dissolved and absorbed during minor injuries. However, in the process of chronic injury, fibrous degradation in the organ is weaker than expression generation, and activation of fibroblasts leads to massive expression and deposition of ECM. This leads to the destruction of organ structure and impaired organ function[5]. Fibrosis can occur not only in the kidneys but also in the heart, lungs, liver, digestive tract and other organs.It has been shown that non-mesenchymal cells (epithelial cells, macrophages/monocytes, endothelial cells) express only a small amount of ECM genes, andmost ECM is derived from mesenchymal cells[6].Mesenchymal cells play a decisive role in renal interstitial fibrosis.Here, we describe the connection between mesenchymal cells and renal interstitial fibrosis, and summarize the treatment of renal interstitial fibrosis. We hope to provide new ideas for all scholars to study anti-interstitial renal fibrosis.

2. Fibroblasts andrenal fibrosis

Kidney fibroblasts (KF) are the main site of ECM production in renal interstitial fibrosis[7].It receives TGF-β1 stimulation and eventually transforms into myofibroblasts through the classical TGF-β/Smad pathway, or non-classical

TGF-β/Smad pathways such as MAPK, ERK/JAK signaling pathways[8-11].A new study found that the endoplasmic reticulum protein TXNDC5 is required in the TGF-β1-induced activation of human kidney fibroblasts (HKF), and its overexpression is sufficient to promote HKF activation, proliferation, and collagen production, ultimately promoting fibrosis. And it was demonstrated that deletion of TXNDC5 slowed the progression of renal fibrosis, suggesting the potential of TXNDC5 for the treatment of interstitial fibrosis and chronic kidney disease(CKD)[12].In addition, Wang et al.[13]demonstrated that pharmacological inhibitors or siRNA targeting DRP1 could inhibit the expression of α-SMA and type I collagen.In a study of non-melanoma skin cancer, activator A was found to promote the binding of Smad2/3 to the "Smad-binding element" in the first intron of the mDia2 gene, which activates fibroblasts and eventually differentiates into different tumor-associated fibroblast subtypes[14]. Although the pathway of activation is different from that of normal fibroblasts, it can be a new direction for anti-fibrotic research.

In 2017, Mark et al.[15] proposed a third path of renal interstitial fibrosis:aberrant endothelial secretory proteins such as pro-fibrotic signals (Notch and ligands of the Wnt/β-catenin pathway). Studies have confirmed that tubule-derived WNTs are required for KF activation and interstitial fibrosis, and that Wnt plays a major role in driving MYO activation and renal fibrosis[16, 17].Experimental studies have confirmed that β-catenin in fibroblasts is increased by WNT protein stimulation and acts as a transcriptional co-activator together with TCF/LEF[18].β-catenin promotes the activation of fibroblasts and enables the migration and proliferation of MYO[19, 20], which ultimately leads to interstitial fibrosis.

3. Pericytes andrenalfibrosis

In the kidney, perinephric cells are divided into renin-producing perivascular cellsand perivascular cells, the former is capable of synthesizing, storing and secreting renin, and it activates the renin-angiotensin-aldosterone system (RAAS) and regulates renal medullary and cortical blood flow;the latter is a precursor cell of MYO and plays an important role in the remodeling of microvessels and the development of interstitial fibrosis [1, 6, 21-23].In CKD, chronic activation of the RAAS system leads to renal oxidative stress and inflammatory responses, ultimately promoting interstitial fibrosis[24-26].With the activation of the RAAS system, angiotensin-converting enzyme 2 (ACE2) exhibits a protective effect on the kidney by converting angiotensin 2 (Ang2) to Ang1-7, reducing inflammation and fibrosis[27].Furthermore, CHOU et al. [28]showed that hypermethylation of pericytes promoted the progression of acute kidney injury (AKI) to CKD, and 5-azacytidine demethylation reversed the pro-fibrotic properties of pericytes.

4. Immune cells and renal fibrosis

Inflammatory immune responses also contribute to fibrosis.In the development of interstitial renal fibrosis, various types of immune cells are recruited into the kidney, including macrophages, T cells, DCs, and mast cells[29].B cells are also important players in this, influencing fibrosis through the production of cytokines (IL-36, IL-17, IL-23, etc.) and interactions with other immune cells[3, 30].In astudy of IgA nephropathy, TLR7 was highly expressed in$CD19^+$B cells and was strongly expressed in the tubulointerstitial and periglomerular regions[31], which may correlate with the extent of renal interstitial fibrosis.FMS-like tyrosine kinase 3 ligand (FLT3L) stimulates the development of DCs, and FLT3L-dependent DCs promote the activation and accumulation of renal effector T cells aggregation, which leads to renal oxidative stress and ultimately promotes interstitial fibrosis[32].In renal transplantation[33], macrophages are converted to MYO via the TGF-β1/smad3 signaling pathway, and we can intervene in TGF-β1 downstream pro-fibrotic signaling molecules (JAK3, STAT6, etc.) for anti-fibrotic treatment[34].

5. Mesenchymal Stem Cells (MSCs) andrenalfibrosis

MSCs are present in the perivascular areas of many organs, including the kidney, lung, liver and heart. A study showed that Gli1 was able to label MSCs, and after kidney injury, $Gli1^+$ cellsproliferated, differentiated into MYO, and promoted renal interstitial fibrosis[35].However, several studies have shown the role of MSCs in reducing liver fibrosis, lung fibrosis, and corneal fibrosis have been demonstrated[36-39], and it has a preventive effect on renal fibrosis in mice with ischemia-reperfusion [40].This allows us to suggest that stem cell therapy may be a new therapeutic route for interstitial

fibrosis in the kidney.

6. Cellular aspects of therapeutic interventions for progression of interstitial renal fibrosis

6.1 Fibroblast aspects

Currently, the anti-interstitial renal fibrosis drugs mainly target known key players in the molecular mechanisms (mainly targeting fibroblast signaling pathways), such as transforming growth factor (TGF)-β, connective tissue growth factor (CTGF), bone morphogenetic protein (BMP)-7, endothelin-1, SMAD3 and 4, and NADPH oxidase (NOX) 1 and 4[41].Ruxolitinib[42], a potent and selective inhibitor of JAK1 and JAK2, was applied to unilateral ureteral obstruction (UUO) mice and TGF-β1-treated cells. It inhibits activation of mouse renal fibroblasts, ECM production and TGF-β1-treated fibroblasts, attenuates the activation of STAT3 and Akt/mTOR/YAP pathways.Discoidal structural domain receptor 1 (DDR1) is a receptor tyrosine kinase activated by collagen. The Borza experiment demonstrated that DDR1 is upregulated during renal injury, whichphosphorylating STAT3 and activating the TGF-β/Smad pathway, this leads us to speculate that DDR1 could be a new anti-fibrotic target[43].In the course of research on herbal medicines, Salidroside[44] and Rhein[45] have also been shown to slow the progression of interstitial fibrosis by partially blocking the phosphorylation of STAT3.

6.2 Pericellular aspects

PDGFR-β^+ pericytes are the main source of scar-forming myofibroblasts[46].Studies have confirmed that STAT3 is a key transcription factor involved in renal interstitial fibrosis, which not onlypromotes fibrosis by increasing inflammation, fibroblast and macrophage activation, but also by modulates pro-fibrotic signaling in pericytes.By studying STAT3 knockout or inhibited mouse, Ajay et al.[47] found that STAT3 deletion inhibited the transformation and migration of perinephric cells and saved mouse from interstitial kidney fibrosis injury, this provides evidence for STAT3 as a new target for therapy.Notably in RAAS, dual RAAS blockade is more effective than single RAAS blockade with minimal side effects[48].Jin et al. found that by injecting hepatic stellate cells (HSCs) and renal stellate cells (RSCs) with albumin and its derivative retinol-binding protein-albumin structural domain III fusion protein (R-III) could interfere with the process of interstitial fibrosis in the mouse kidney [49].Additional studies have demonstrated that low levels of vitamin D receptors and their activators could lead to secondary hyperparathyroidism and worsening of interstitial fibrosis. Paricalcitol (an antiparathyroid drug)[50] is effective in reducing interstitial fibrosis through inhibition of RAAS, inflammation and epithelial-mesenchymal transition.These studies illustrate that blocking the conversion of pericytes to MYO and inhibiting RAAS system activation would be promising therapeutic approaches to prevent interstitial renal fibrosis.

6.3 Other modes of intervention

6.3.1 Antioxidant therapy

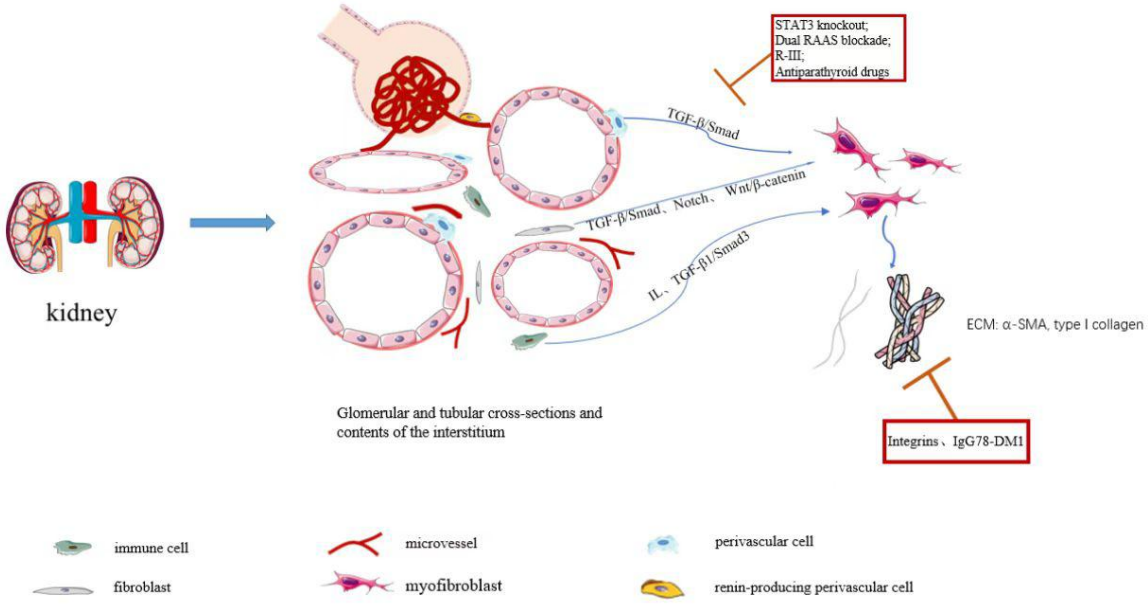
In interstitial renal fibrosis, oxidative stress is also an important causative factor.N-acetylcysteine (NAC)[51], Pterostilbene (Pts, a bioactive component in blueberries)[52] both have anti-inflammatory and antioxidant effects, the former attenuates renal interstitial fibrosis through Sirtuin1 (SIRT1) activation and p53 deacetylation, and the latter interferes with the progression of pulmonary fibrosis by affecting lipopolysaccharide (LPS).SIRT1 activation and p53 deacetylation can be potential targets to attenuate premature renal failure after AKI and delay CKD progression[51].5-methoxytryptophan (5-MTP) is an innate anti-inflammatory metabolite and an endogenous molecule metabolized by tryptophan via the tryptophan hydroxylase pathway.Recent studies have confirmed that 5-MTPis effective in attenuating injury-induced liver, kidney, heart and lung fibrosis, itcould inhibit macrophage activation and prevent fibroblast form differentiating into MYO[53].

6.3.2 Gene therapy (miRNA intervention)

In the experimental study of renal interstitial fibrosis, two miRNAs (miR-27b-3p and miR-1228-3p)[54] were found to be candidate biomarkers of renal interstitial fibrosis.We can target and regulate TGF-β, SMAD, WNT10a and other pathways or proteins by up- or down-regulating miRNAs to achieve anti-fibrotic results[55].In MSCs[37], miRNAs attenuate fibrosis and inflammation through extracellular vesicle-mediated delivery; in T cells[56], miRNA-214 induces the production of pro-fibrotic cytokines (IL-17, TNF-α, IL-9, and INF-γ) and chemokine receptors (CCR1, CCR2, CCR4, CCR5, CCR6, and CXCR3) to influence fibrosis progression.Besides the kidney, miRNA also plays an important role in the treatment of liver fibrosis[55] and cardiac fibrosis[57]. All of these show that RNA interventions have great advantages in the treatment of fibrosis.

6.3.3 Protein and peptide therapy

Integrins are cell surface protein receptors consisting of α and β subunits, they participate in a variety of cellular functions, such as adhesion and anchoring to the ECM, TGF[58].Among them, αv integrins have proven to affect fibrosis by regulating TGF-β1 activity.Several studies confirms that integrin antibodies are protective against CCl-4-induced hepatic fibrosis,unilateral ureteral obstruction (UUO)-induced renal fibrosis and bleomycin-induced pulmonary fibrosis [59].CD248 is a type I transmembrane glycoprotein and it ishighly expressed and specific expression in MYO of CKD patients[60, 61].Xu et al.[62] found that an antibody-drug conjugate called IgG78-DM1, which specifically killed CD248^{+}MYO and had a good anti-fibrotic effect in mice with renal interstitial fibrosis. From this, we can guess that antibody-drug combinations may have better efficacy than single antibodies, which provides a new idea for anti-fibrosis.In the trend of new coronary pneumonia pandemic, SARS-CoV-2 virus was found to directly infect kidney cells and cause interstitial fibrosis, the protein and peptide therapy provides feasibility for anti-COVID-19 interstitial fibrosis[63].



7. Summary

In summary, we can find that the renal interstitium is the interstitial space between the renal tubules, outside the glomeruli, and outside the renal blood vessels.With the increasing maturity of cellular studies, it is found that the main

influences on interstitial fibrosis are fibroblasts and pericytes.On the one hand, renal interstitial fibrosis is caused by renal interstitial innate cells through TGF-β/Smad signaling pathway and RAAS system activation, leading to MYO proliferation and a large amount of ECM being expressed; on the other hand, pro-fibrotic cytokines (IL-17, TNF-α, IL-9 and INF-γ) and chemokine receptors (CCR1, 2, 3, 4, 5, 6 and CXCR3) affect the inflammatory response and oxidative stress in the kidney, promoting the process of interstitial fibrosis.Although there are no clinically effective drugs for the treatment of interstitial renal fibrosis, new advances in targeted cellular, anti-inflammatory antioxidant, and genetic anti-fibrotic therapies continue to be made.

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Application of 640-Volume CT in Idiopathic Pulmonary Hemosiderosis in Adults

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Abstract: **Objective**: To have a deep understanding about idiopathic pulmonary hemosiderosis (IPH). **Methods**: Clinical and imaging data of 6 patients of IPH in adults were collected and analyzed. **Results**: Imaging findings must be combined with clinical laboratory examination to make a diagnosis of IPH. Transbronchial lung biopsy (TBLB) is the gold standard for evaluation of suspected patients. **Conclusion:** IPH is extremely rare amid adults, and imaging results on single chest CT are nonspecific. The longitudinal follow-up is critical for diagnosis and posttreatment evaluation.

Keywords: Idiopathic Pulmonary Hemosiderosis; Computed Tomography; Imaging Findings

Introduction

IPH is a rare disorder characterized by recurrent episodes of unexplained intra-alveolar hemorrhage, followed by accumulation of hemosiderin in macrophages. In selected populations, the prevalence of IPH alone is estimated to be 0.24 to 1.23 per [1]. IPH is most prevalent in children under the age of 10, although it is uncommon in adults, with a mean survival rate of approximately 2.5 years after diagnosis [2]. The most common clinical manifestations are chronic pulmonary symptoms (cough, dyspnea, or hemoptysis), iron deficiency anemia, and pulmonary infiltration [3]. However, one of the typical triads may be the leading symptoms.

1. Objective and methods

1.1 Objective

Data of 6 patients of IPH with biopsy-proven from February 2014-April 2022 were collected， chest CT plain scan was performed for each patient, including four males and two females, aged 23 – 65 years , the median age was 46 years. 4 patients had associated symptoms of cough, sputum, and hemoptysis symptoms, etc.

1.2 640-slice volume CT scan

Use of the 640-slice volume CT, all Patients were taken in the supine position, Arms on the head, Scanning ranges from the thoracic entrance to the bottom of the lung, Flat scanning at the end of deep inhalation; scanning collimator width is 64mm 0.6mm; Tube voltage: 120kV, Current: 35mAs; Spitch 0.55, Matrix 512*512, The reconstruction layer is 1mm thick, margin 1mm, The original imaging are transmitted to the post-processing workstation for post-processing technologies.

1.3 Imaging Diagnosis

Images were reviewed by 3 experienced radiologists (all with more than 15 years of diagnostic experience and associate chief physician), respectively, including lesion localization, morphology, size, density, margin,presence of adjacent pleural, hilum, mediastinum. The three people discuss to the consensus.

2. Results

2.1 CT findings

In the hilar, perihilar, and lower lobe regions, non-enhanced axial and coronal chest CT images revealed significant central ground-glass opacities and consolidation. The lung apices and the costophrenic sulci were spared (Fig 1a, b). After three days of antibiotic treatment, the lesions had progressed significantly (Fig 2). Based on the patient's symptoms, signs, and laboratory tests, idiopathic pulmonary hemosiderosis (IPH) was diagnosed, and the patient was given hormone and immunosuppressive therapy. The lesions were visibly absorbed after one week of treatment and vanished after two weeks (Fig 3 and Fig 4a, b).

3. Discussion

IPH is a rare disorder characterized by recurrent episodes of unexplained intra-alveolar hemorrhage, followed by accumulation of hemosiderin in macrophages. In selected populations, the prevalence of IPH alone is estimated to be 0.24 to 1.23 per [1]. IPH is most prevalent in children under the age of 10, although it is uncommon in adults, with a mean survival rate of approximately 2.5 years after diagnosis [2]. The most common clinical manifestations are chronic pulmonary symptoms (cough, dyspnea, or hemoptysis), iron deficiency anemia, and pulmonary infiltration [3]. However, one of the typical triads may be the leading symptoms.

The definite cause of IPH is still unknown, although, several hypotheses have been proposed for its explanation, including autoimmune, environmental, allergic, and genetic factors [3]. According to one study, patients with IPH are often linked with particular autoimmune illnesses, such as celiac disease, dermatitis herpetiformis, glomerulonephritis, and rheumatoid arthritis [4]. Based on its pathology, IPH is classified into three phases: acute phase, chronic phase, and sequela phase. In the acute phase, a large number of red blood cells are manifested and exudates in alveoli, alveolar edema, and alveolar septum thickening. In the chronic phase, the major symptoms include a large amount of hemosiderin being deposited in the alveolar interstitium, alveolar interstitial fibrous tissue proliferation, interlobular septum, and alveolar wall thickening. The development of extensive interstitial fibrosis within the lung is the most common symptom of the sequela phase. The pathogenic alterations influence the imaging findings. In the acute phase, the chest CT scan image shows extensive ground-glass opacities, which are mostly symmetrically distributed in the pulmonary hilum, middle, and lower lung regions; with the lung apices and costophrenic sulci being less affected. Ground-glass opacities indicate diffuse intra-alveolar hemorrhage when coexistence with consolidation indicates that the alveoli are full of blood. The interlobular septum can thicken due to the deposition of hemosiderin-containing macrophages in the interstitium [5]. The "crazy-paving" sign appears due to interlobular septum thickening coexistence with ground-glass opacities [6]. Recurrent pulmonary hemorrhage patients may develop pulmonary fibrosis, which includes thickening of the interlobular septum, reticulation, and small cystic foci. HRCT is an important tool for detecting diffuse tiny reticulation, fine nodules, and interlobular septum thickening. The patient studied in this report was in the acute phase.

Because of the non-specific imaging results of IPH, it must be combined with a clinical laboratory examination to distinguish it from other diffuse pulmonary diseases. For instance, pulmonary alveolar proteinosis, anti-neutrophil cytoplasmic autoantibodies (ANCA) are associated with systemic vasculitis and phylactic pneumonia. Ground-glass opacity, crazy-paving sign, and map-like alteration are all symptoms of IPH, although they're more common in pulmonary alveolar proteinosis [7]. Furthermore, the lesions of pulmonary alveolar proteinosis often involve the subpleural areas. In ANCA-associated systemic vasculitis, the serum ANCA is mostly positive and multiple organs can be involved, with the kidneys being the most frequently affected organs. The typical CT scan of phylactic pneumonia shows diffuse central lobular nodules, patchy attenuation or ground-glass opacities, and mosaic signs dominated in the upper and middle lobes [8]. It can be distinguished from IPH if the patient with a history of allergen exposure and the lymphocyte percentage in bronchoalveolar lavage fluid (BALF) solution is increased.

IPH is an exclusive diagnosis. The presence of hemosiderin-containing phagocytic cells in sputum, BALF, or gastric

aspiration liquid should be verified in patients suspected of IPH [9]. Other diseases such as infectious, cardiovascular, or immune-related diseases should be excluded in patients with pulmonary hemorrhage [10]. Lung biopsy is still the gold standard for the diagnosis of IPH.

IPH is typically treated with medications (glucocorticoid and immunosuppressant). Studies have shown that early administration of glucocorticoid can effectively delay pulmonary fibrosis [10]. In this study, hemoptysis recurred following glucocorticoid decrease, indicating that glucocorticoids should be lowered with caution during IPH therapy. In conclusion, IPH is rare among adults, and imaging results on single chest CT are not specific. The longitudinal follow-up would be very extremely beneficial in the diagnosis and assessment of efficacy. Early standardized therapy is essential; which would lead to a better outcome, fewer complications, and reduced sequela.

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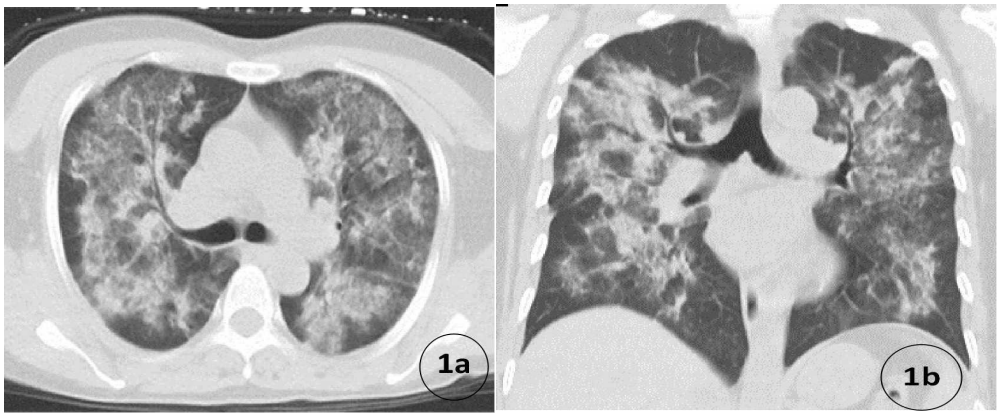


a. b.

Figure 1: (a) Axial and**(b)** coronal non-contrast composite computed tomography(CT) images of the chest shows diffuse ground-glass opacities and consolidation, within the hilar,perihilar,and lower lobe regions,the lung apices and the costophrenic sulciare spared.

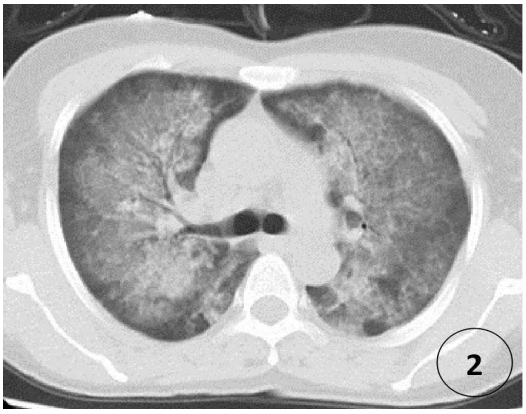


Figure2: Axial NECT chest images after three days treatment with antibiotic demonstrate the lesions are progressive,especially in bilateral subpleural regionsof lung apices.

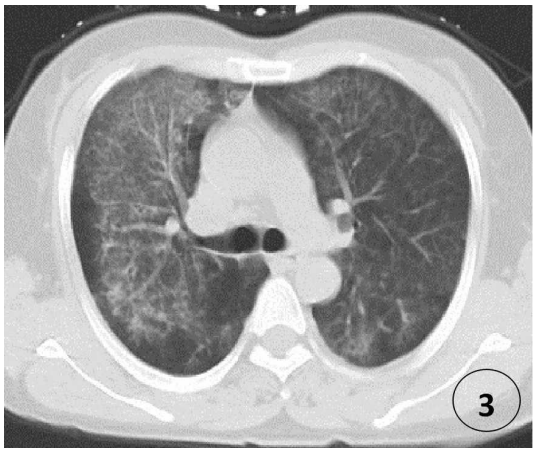
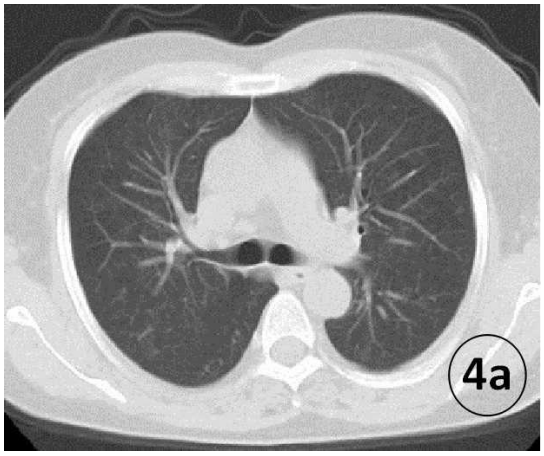


Figure 3: Axial unenhanced chest CT after one and two weeks' treatment with hormone and immunosuppressive show the lesions are obviously absorbed, and vanish.



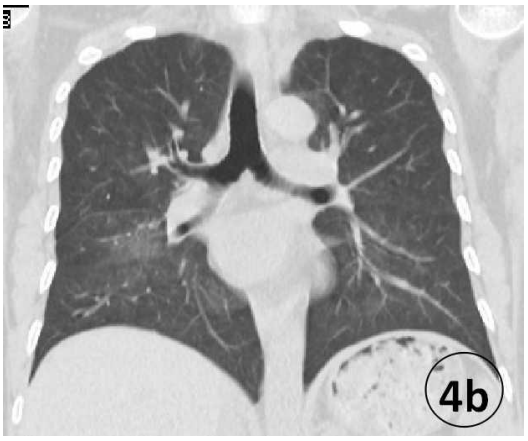


Figure 4: Axial and coronal unenhanced chest CT images after two weeks' treatment show the lesions totally absorb amid lung parenchyma.

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Development and Influencing Factors of Patients with Depression

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Abstract: Depression is the most common psychological disease, which is characterized by long-term depression. It is the main type of emotional disorder. This paper mainly summarizes the influencing factors in the occurrence and development of the disease, draws the disease types of patients with depression and their own personality characteristics, analyzes the existing problems, and affects the influencing factors in the occurrence and development of the disease, which is conducive to a more comprehensive and correct understanding of the disease, It has clinical significance for the prevention and treatment of depression.

Keywords: Occurrence of Depression and Development; Psychological Support

Introduction

In today's society, a world full of temptations and various pressures, most people have some anxious hearts, men and women, the risk of depression in young and old age, and troubles of different ages. If you don't realize the seriousness of the problem, it will aggravate the occurrence of symptoms. Depression is the most common mental disorder. Depressed people are extremely pessimistic. They look at everything. They can always think of the bad side. In their eyes, everything that happens in the future is negative and dark.

The main symptoms are persistent mood swings and loss of interest. This paper mainly summarizes and analyzes some factors that lead to the occurrence of depression and the influencing factors in the process of disease occurrence and development.

I hope that through this article, we can better understand the factors of depression from occurrence to development to the final result, and put forward effective methods to prevent depression, which is of great significance to ensure people's healthy, normal and high-quality life. I hope that patients with depression can get rid of the haze as soon as possible and live a better life!

1. Factors affecting the development of the disease

1.1 Family support

Family is a warm port. If a family loses its original warmth, which leads to family dysfunction, the bad family atmosphere has a significant impact on depression. The relationship between depression and the original family. Now the trend of young people suffering from depression is obviously high, and the relationship with the family. In 2021, a data survey showed that the proportion of Chinese patients with depression is the highest among teenagers. This data is not fixed, and is increasing every year, Every year, many young people die of depression. For family relations, if parents do not take care of their children for a long time and have a cold attitude towards their children, husbands and wives will often hurt their children's hearts in front of their children, and the poor family environment will lead to children and adolescents with unbalanced biological stress response system, which may become an important factor in the depression of adolescents and adolescents.

The first one is that young people with depression have a bad family atmosphere without treatment. The overall family

culture is not high. They have pessimistic thinking problems in the face of diseases. Parents' excessive interference, preference and doting on their children will lead to the occurrence of diseases. Therefore, any role in the family should fulfill its due obligations and give the family a warm and relaxed family atmosphere.[1] Especially for the elderly patients with depression, when the disease begins, the patients will have a huge psychological burden. No matter physical or mental trauma, they are vulnerable to trauma. At this time, through the development of family nursing intervention and hospital nursing through connection, the development of the disease can be effectively controlled, which is conducive to the outcome of the disease and restore the expectations and hopes of the elderly for life. [2]

1.2 Psychological support

Depression patients may have negative and pessimistic thoughts and suicidal thoughts in their inner world during their illness. Whether they are family members, friends or medical personnel, they must always communicate with the patients, encourage them to actively express their inner thoughts, correctly guide them when they find dangerous thoughts, always pay attention to their words and deeds, and strengthen psychological care. Especially in the process of psychological treatment for depression patients, psychological support is particularly important, This effect has a great impact on the final overall treatment effect, especially the cognitive psychological reconstruction, which is a very important psychological intervention method and the main factor affecting the mental health of patients with depression, and the judgment, cognition and evaluation of patients. We should not only rely on medication to control it. We must pay attention to psychotherapy to enable patients to carry out psychological reconstruction and change their way of thinking about problems. We can always pay attention to the development of the disease, correctly analyze the psychological changes of patients, analyze the patients' cognitive errors, and correctly guide patients to establish a good and healthy cognitive level. The implementation of psychological support for patients with depression can reduce their anxiety and depression, It can guide patients to establish a good life attitude and help improve their quality of life.[3]

1.3 Treatment

A study found that baseline meditation and meditation had a certain degree of predictive effect on the efficacy of antidepressant therapy in patients with first-time depression. The meditation mentioned in his research includes two sub types: Meditation and reflection. Meditation as a whole means that an individual is immersed in his own emotions, thinking over and over again, but does not know how to solve the problem. It is found that baseline meditation and meditation can predict the efficacy of antidepressant treatment in patients with initial depression.[4]

The use of depression drugs is particularly important, which is valued by clinicians. When the disease is in the acute stage, some studies recommend fluoxetine as the first-line drug for the treatment of depression in children and adolescents, followed by sertraline and sitaglandin as the second-line drug. However, the use of many types of depression drugs in children is more limited, such as escitalopram, which can be used in adolescent patients, It can be added as a second-line drug to treat adolescent depression, but not for child depression. The use of drugs can directly affect the development trend of diseases. In addition to the efficacy of drugs, there are many psychological suggestion methods, such as mindfulness cognitive therapy (MBCT), including meditation and meditation. More and more studies have confirmed that MBCT is a practical and effective treatment for patients with depression. Esmethiol phthalate combined with repeated transcranial stimulation of the brain of dizzy patients has a significant effect, can improve the patient's condition, and has a positive effect on the treatment of patients.[5] Music is a beautiful existence, which can make impatient emotions slow down, relax and create a good atmosphere. Especially for children with depression, music can open their inner world. Interactive music intervention is a powerful way to treat children with depression, which can help them relax their emotions, establish a healthy and happy atmosphere, and help children experience a better life as soon as possible. [6] There are many factors that do not have high adherence to medication for patients with depression, such as nursing management plan, regular telephone return visit, good and comprehensive health education, explaining the importance of medication before discharge, and instructing the family members of patients to actively supervise the correct time and quantity of medication.[7] Horticultural therapy can effectively improve the condition of patients with depression, improve their symptoms and quality of life, which

is worthy of clinical health care reference. [8]

The incidence rate and recurrence rate of depression are high. It is necessary to give drugs regularly and quantitatively during hospitalization. Motivational interviews can be conducted by healthcare professionals and continue after discharge, which can have a positive impact on patients.[9] Home visit can effectively improve the correct medication compliance of discharged patients and promote the early rehabilitation of discharged patients. [10] Transcranial direct current stimulation is an important treatment method for patients with depression. When the patient's disease development is controlled, it can strongly stimulate the patient's brain, thus affecting the development of the disease, and has been widely used in clinic. [11] Brain derived neurotrophic factor plays an important role in clinical management by actively guiding the treatment of patients with depression. [12] Studies have shown that before the onset of unipolar depression, there is an obvious precursor symptom, which is usually characterized by physical discomfort, such as anxiety and tension. [13] In the adjuvant therapy, except for moderate aerobic exercise, all exercise interventions significantly improved sleep outcomes. [14] Adult depression has a high risk of relapse and relapse. Lack of social support and social health problems may relapse. [15]

Conclusion

This paper summarizes the research results from the occurrence and development of the disease and some factors affecting the cure of the disease, draws important contents from them, and analyzes the various factors of depression from many aspects. It is hoped that through this article, we can better understand the influencing factors of depression patients from occurrence and development to the final outcome, so as to put forward effective methods to prevent depression. Depression this research topic is of great significance to understand the depression population, the development of the disease and the influencing factors.

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Computed Web Learning Software Design with a Medical Psychological Perspective: Depression as an Example and Economic Analysis

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Abstract: We have tried to use computer technology in teaching and designing the necessary knowledge points for the diagnosis, treatment, and prevention of depression. We have also used computer platforms to elucidate this model as an economics product and carry out the necessary investigation and study of the market prospects, and we have proposed innovative points in solving the problem based on basic knowledge in medical psychology, and we have reported the results in conjunction with the results of the study.

Keywords: Clinical Psychology; Computer Science; Depression; Economics

1. Introduction

Medical psychology deals with psychological problems in diagnosis, treatment, care, prevention of diseases, serving people's health care. Psychology is the science of studying human psychological phenomena and the psychomotor functions and behavioral activities that affect them, taking into account outstanding theoretical and applied (practice) pathies. Complicating both basic and applied psychology, psychology deals with many areas of perception, cognition, emotion, thinking, personality, behavioral habits, personal relationships, social relationships, etc. and much of daily life – family, education, health, social. Medical psychology includes branches such as pathological psychology, clinical psychology, pharmacological psychology, care psychology, psychosocial counseling, and psychotherapeutics. Depression is a common psychiatric disorder characterized by low mood, diminished appetite, pessimism, thought delay, lack of initiative, self-blown guilt, poor diet, poor sleep, fear of suffering from various illnesses, widespread discomfort, and, in severe cases, suicidal thoughts and behavior.

2. Background

The primary outcome was significant and persistent affective depression and depression pessimism. The milder is dull, unhappy, and less interested; the heavy is not in life, the pessimistic is in despair, the days are as old as the old, and the life is not as good as the death. Typically, depressed mood is tempered by morning-to-night rhythms. On the basis of depressed mood, there is a decrease in self-assessment, producing a sense of futility, hopelessness, helplessness, and valuelessness, often accompanied by self-consumption, serious delusions and delusions, and hallucinations in some patients. 2. Patients with mental retardation are slow in their thinking, slow in their response, occlusive in their thinking, and consciously "the brain seems to be a rusty machine"", "the brain is as if it had been coated with a layer of glum. "Clinically, there was a reduction in speech propensity, a significant slowing of speech speed, low voice, difficulty in responding, and severe communication. 3. Patients with reduced voluntary activity have a significant and durable inhibition of voluntary activity. The clinical picture is slow, life is passive and lazy, does not want to do anything, engage with people around them, often sit alone, or stay in bed all the time, stay alone, alienate family and friends, and avoid social relationships. The physical needs of

eating, drinking, and other personal hygiene are often disregarded when severe, and the patient continues to show pain and depression by careful psychiatric examination, even when the patient is dull, immobile, or even “depressive stupor”. Patients with anxiety may have restlessness, finger grips, handshakes, or clumsiness. Severe patients often have negative suicidal thoughts or behaviors. Passive pessimism and self-punitive self-congratulation and a lack of self-confidence give rise to despair, holding that "ending your life is a relief, " "being redundant in the world" and will lead suicide attempts to develop into suicide. This is the most dangerous symptom of depression, and vigilance should be heightened. 4-Cognitive impairment has been suggested in depressed patients. The main presentations were reduced recent memory, attention problems, prolonged response time, increased alertness, poor abstract-mindedness, poor learning, poor verbal fluency, visuoscence, eye-hand coordination, and reduced flexibility. Cognitive impairment contributes to social dysfunction and affects long-term outcome. 5. Symptoms of the body include, principally, sleep disturbances, fatigue, loss of appetite, loss of weight, constipation, pain in any part of the body, loss of sexual appetite, impotence, and amenorrhoea. Physical complaints of physical discomfort may involve organs such as nausea, vomiting, panic, chest cramps, sweating, etc. Symptoms of autonomic dysfunction are also common. The complaint of pre-existing somatic disease is usually aggravated. Sleep disturbance manifests itself as an early awakening, usually 2 to 3 hours earlier than usual, and the inability to fall asleep after awakening is characteristic of a depressive episode. Some patients present with difficulty falling asleep and poor sleep; a few patients present with excessive sleep. Weight loss is not necessarily proportional to appetite loss, and a few patients may have increased appetite and weight gain. Computer teaching platforms are a new modern way of teaching classrooms that integrate traditional classroom instruction. Teachers in this platform guide students at every step of the process, while organizing steps to monitor students’ every practice to guide students to the right standards, while students actively participate and actively explore during the learning process. The interactive message delivery pattern of the computer system under medical mimicry is a new, student-based educational concept that is conducive to stimulating students' interest in learning and developing students' innovative awareness and ability to practice. It also resolves the contradiction of reinterpreting, less practice, more content, and less time spent in traditional teaching, while taking into account the important role of emotional communication and emotional factors in the learning process. Quality teaching is provided for the training of innovative nursing talent. Computer medicine teaching models offer broad promise, such as online training in medicine, a selection of specialized live-to-live platforms, which can diversify the forms of online training in medicine, eliminate monotonous programming, and enrich the style of live broadcasting with tools such as documents plus lecturer images, screen sharing, and penboards. There will also be more user-to-peer interactions in training. Training can also include permissions, video encryption, and authorization for some trainees to watch, thereby protecting users’ privacy. Surgical live, with a dedicated online live broadcast fee platform, the content of live broadcast in the health-care industry could be more professional and allow for live surgery. Specialized live broadcast platforms, which support access to medical devices, allow live multi-planar imaging of the procedure, more stereotactic presentation of the procedure, multi-plane audio-visual transmission, and tele-discussion of medical problems. The live video of the operation supports retroplay clips, which can be stored permanently. By teleconferencing, health-care providers could open a dedicated live broadcast space for patients to see, which would not only increase the efficiency of the call, but would also be effective in relieving current health-care resource constraints. In academic conferences, in the face of large or local academic conferences, at a time when the pandemic is relapsing, it is best not to gather on a large scale, but isn’t it good to solve the troubles? Through live conference calls, experts or doctors can communicate online, and through live interactions with wheat, saving more costs.

3. Computer medicine teaching platform analysis

With advances in science and technology and the spread of the internet, computer network technology is increasingly being applied to educational fields, and computer teaching platforms are becoming popular because of their advantages of convenience, efficiency, and abundance. Computer companies should invest heavily in developing experimental systems for skills training such as medical emergencies, diagnostics, care, women and children, pediatrics, anatomy, traditional medicine, and oral medicine. Meanwhile, simulators of cardiopulmonary resuscitation of products produced by computer companies have become

popular among education systems such as health care, medical education, the Red Cross, electricity, transportation, fire control, safe production, and the public community, and will be favored and praised by their clients. Computer companies as manufacturers, suppliers, and service providers of modern medical educational equipment have achieved the primary goal of “specific, technologically advanced, and service delivery. ”Computer companies should have focused on quality, innovation, brands, decency, service, integrity, talent, and institutional enterprise goals. The active, modernized, managed enterprise will strive to serve the motherland's medical education, make outstanding contributions to the health and well-being of all mankind, and join hands in creating a new era of modern medical education.

4. Strategy and Conclusion

Computer medicine education for PD is an empiric-based form of education. It aims to inform and guide families in distress so that they can develop the skills to understand and deal with problematic candidates or to deal with difficult family relationships. In some cases, this approach provides information and education to prevent conflicts or teach specific skills for daily nonclinical situations. Cognitive behavioral therapists are well suited for the computer medicine educational program integrated system theory. The study of pedagogy is concerned with educational phenomena and problems, summing up scientific theories and practices of human educational activities, and exploring practical educational problems in the course of education and development, thus revealing a social science of general educational law. Computer education is a widespread social phenomenon in life, and it is a purposeful activity to train people. To be effective, educational campaigns must be studied. In particular, the development of modern society, the development of modern educational practice, requires new and higher requirements for the study of pedagogy. There are many issues in education that require further study, such as education’s essential problems, education, society, human relations, educational purposes, content, ways, methods, forms, and their relationships, educational processes, main issues, institutional problems, management issues, and various educational theories and practices that reflect Chinese characteristics. Therefore, the study of pedagogy is of far-reaching significance, combined with the above knowledge, and we believe that computational teaching models should be designed under the guidance of the humanities and social sciences, and conducted educational experiments, investigations, and, in due course, global dissemination.

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Effect of Pain on Quality of Life in Patients with Parkinson's Disease

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Abstract: Objective: To analyze the impact of pain on the quality of life of patients with Parkinson's disease. Methods: 200 patients with primary Parkinson's disease admitted in the Shaanxi Provincial People's Hospital from August 2019 to November 2020 were selected for the experiment, and these patients were divided into pain group and non-pain group in turn. Among them, there were 98 patients in the pain group and 102 patients in the non-pain group. King's Parkinson's disease pain scale was used to evaluate the severity and type of pain, and then ess and HAMD-17 were used to evaluate patients' depression and daytime sleepiness. Results: the incidence of pain in patients with Parkinson's disease was about 49%, including 38% of wave related pain and 74% of musculoskeletal pain. The score of quality-of-life Scale-39 in the pain group was higher than that in the non-pain group, and the difference was statistically significant ($P < 0.01$). Conclusion: musculoskeletal pain is a common type of pain in patients with Parkinson's disease, followed by nocturnal pain and fluctuation related pain. Its pain will have a direct impact on the quality of life of patients with Parkinson's disease.

Keywords: Pain; Parkinson's Disease Patients; Quality of Life; Influence

Introduction

Parkinson's disease is a particularly common progressive neurodegenerative disease, which is accompanied by a series of symptoms such as autonomic dysfunction and dysphagia. The main reason for its symptoms is the selective loss of dopaminergic neurons in the dense part of the substantia nigra, which is related to dopamine depletion in the striatum. Among patients with Parkinson's disease, the incidence rate of pain is about 30% to 83%. Musculoskeletal pain and wave related pain are the most common two types of pain. There is no exact relationship between different types of pain and abnormal movement of Parkinson's disease. Pain is a kind of more complex emotional response, which will be associated with negative experience, and it will also be affected by many factors. Therefore, this study takes 200 patients treated in the Shaanxi Provincial People's Hospital in China as experimental objects and applies the king's Parkinson's pain scale to evaluate the distribution characteristics of pain types and whether there is pain in patients with Parkinson's disease and analyzes its impact on the quality of life of patients with Parkinson's disease.[1]

1. Object and method

1.1 Research object

The experiment was conducted on 200 patients with primary Parkinson's disease treated in the Shaanxi Provincial People's Hospital from August 2019 to November 2020, including 130 male patients and 70 female patients; The youngest is 42 years old and the oldest is 75 years old; The minimum length of education is 7 years, and the maximum length of education is 9 years; The lowest age of onset was 43 years old, and the highest age of onset was 62 years old; The shortest course of disease is 3 years and the longest is 10 years. Excluding Parkinson's syndrome, mental disease caused by encephalitis, trauma and other factors, or the patient's history of alcohol or drug abuse, combined with whether there are pain symptoms, they are divided into pain group and non-pain group, of which the minimum age of the pain group is 54 years old and the maximum age is 72 years old; The minimum age of onset was 42 years old, and the maximum age of onset was 67

years old; The shortest course of disease is 3 years and the longest is 7 years; The minimum length of education is 8 years, and the maximum length of education is 9 years. The minimum age of the group without pain was 52 years old, and the maximum age was 70 years old; The minimum age of onset was 43 years old, and the maximum age of onset was 66 years old; The shortest course of disease is 4 years and the longest is 6 years; The minimum length of education is 7 years, and the maximum length of education is 9 years. There was no significant difference in the age of onset and the time of education between the two experimental groups, and $P > 0.05$. All patients and their families who participated in the experiment signed the informed consent form.[2]

1.2 Research methods

Under quiet conditions, assign professional specialists to evaluate the patient's medical history and physical examination of nervous system, score all scales at one time, collect the patient's demographic and medical history information, and record the patient's status of taking anti Parkinson's drugs. The kpps scale is used to evaluate the pain experienced by patients with Parkinson's disease in different types and stages. The scale will have multiple items, including musculoskeletal pain, fluctuation related pain, nocturnal pain, etc. the severity of each item is (0 to 3) multiplied by the frequency (0 to 4), and then the total sub score is (0 to 168), which is the sum of the pain burden of patients with Parkinson's disease, Medical staff need to communicate with patients and ask them about the specific location and nature of pain.

2. Results

2.1 Pain assessment results of patients with Parkinson's disease

In this experiment, there will be 82 Parkinson's patients with kpps scores ranging from 1 to 36. 55 Parkinson's patients have only one type of pain, and Parkinson's patients have more than two types of pain symptoms, of which 2 patients will be accompanied by five different types of pain at the same time. Musculoskeletal pain is a particularly common type of pain, and its incidence is about 74%, the incidence of fluctuation related pain is about 38%, the incidence of nocturnal pain is about 28%, the incidence of orofacial pain is about 3.5%, and the incidence of limb burning is about 5.5%. 34 patients with Parkinson's disease with pain complained that pain had the characteristics of "switching period" and needed to take dopaminergic drugs to link the patient's pain.[3]

2.2 Comparison of PDQ-39 scores of 2 groups

Compared with the two experimental groups, the total scores of hama-14, PDQ-39 and other dimensions of Parkinson's disease patients in the pain group were increased, and the difference was statistically significant ($P < 0.05$). However, there was no significant difference between the two groups in the total dose of ledd, mds-updrs Ⅲ, MMSE, AHRS, ESS and PDQ-39 in daily activities, humiliation, social support, cognition and communication ($P > 0.05$).

2.3 Multiple linear regression analysis of influencing factors of quality of life in PD patients

Predictors of quality of life in PD patients: considering the age of onset, course of disease, and exercise and non-exercise variables may affect quality of life, stepwise multiple linear regression model was used to study the factors affecting quality of life. In the multiple linear regression model, demographic factors (onset age, levodopa equivalent daily dose, course of disease), motor symptoms (mds-updrs Part III, Hoehn Yahr stage) and non-motor symptoms variables that may affect the quality of life were included. Multiple linear regression analysis was used. Finally, the variables included in the equation were HAMD-17, Hoehn Yahr stage, ESS Kpps, age of onset ($P < 0.05$). The adjustment R2 of the whole model is 0.626, which shows that five factors such as HAMD-17 and pain can explain the variation of PDQ-39 score of about 62.6%, and it can be considered that the regression effect of the equation is better.[4]

3. Discussion

At this stage, there is no cure for Parkinson's disease. It will be treated in the form of improving exercise and non-exercise symptoms, to reduce the pain of patients and improve their quality of life. Although at this stage, the research content of the medical community on the quality of life of Parkinson's disease has begun to increase, there is only less literature to explore the impact of pain on Parkinson's patients. Pain is a common non motor symptom of Parkinson's disease, its nature is different, and the triggering factors are more complex. Therefore, this study will use kpps scale to classify and evaluate the pain symptoms of patients. Through experimental analysis, we can understand that musculoskeletal pain will have a greater impact on patients with Parkinson's disease, and it is the most common type of pain, but musculoskeletal pain is more common in Parkinson's disease, which does not mean arthritis. Wave related pain and nocturnal pain are also the main types of pain, and the rarest pain is limb burning pain. The incidence of Parkinson's disease combined with pain will be relatively high in women. The main reason for the formation of this gender difference may be that psychological and social factors work together, and sex hormones and different endogenous opioid systems will also have a certain impact. In addition, patients with Parkinson's disease with pain are likely to have more serious depressive symptoms, so emotional problems such as anxiety and depression may also affect the pain of patients.[5]

Conclusion

Pain is one of the important factors affecting the quality of life of PD patients. It is very common in Parkinson's disease and an important cause of disability. However, both doctors and patients have insufficient understanding of PD associated pain, resulting in insufficient clinical treatment. The evaluation of pain symptoms according to King's Parkinson's disease pain scale provides the possibility for accurate diagnosis and management.

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Health economics perspective: Genetic mutation test reports utilize mathematics and computer science to study and analyze cryptographic encryption strategies

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Abstract: Health economics is the focus of current research, and genetic testing has become an emerging and universal means of disease surveillance based on the ever-changing perspective of the global basic medicine in the field of cellular genetics. But genes represent the genetic information of the human physiology, and therefore must be handled in a confidential manner. With the use of current computational and codon knowledge structures, the authors propose and report strategies for problem solving in computer medicine based on genetic properties.

Keywords: Genomic Mutations: Codonology;Health Economics; Mathematics; Cross- Domains

1. Background

Genetic variation refers to sudden, heritable variation in the occurrence of genomic DNA molecules. At the molecular level, genetic variation refers to the alteration in the structure of the base pairs or sequences of genes. Genes are quite stable and can precisely reproduce themselves in cell division, but this stability is relative. Under certain conditions, a gene can also be abruptly altered from its original form into another new form of existence, i. e. , at one locus, a new gene emerges suddenly, replacing the original gene, a gene called the mutant gene. As a result, the offspring's appearance suddenly appears as something new that their ancestors never had. The Queen Victorian family in England, for example, did not find a patient with hemophilia before her, but one of her sons had hemophilia and became the first member of her family to have hemophilia. Later, several hemophiliac patients appeared in her grandchildren. Obviously, a mutation in the hemophilia gene was created in her father or mother. The mutant gene was passed on to her, and she was heterozygous, so the phenotype was still normal, but it was passed on to her son through her. The consequences of genetic variation, in addition to the genetic pathogenesis described above, can produce stillbirths, spontaneous abortions, and postnatal deaths, which are termed fatal mutations; they may, of course, have no effect on the human body and result only in normal genetic differences between the human body; and they may even have some beneficial effect on the individual's survival. (1) Pathogenic genetics can be identified by the use of microarray analysis of the human genome. Cancer, diabetes mellitus, etc. are all diseases caused by genetic defects. Researchers in medicine and biology will be able to identify, within seconds, mutations that will eventually lead to cancer, among other things. With a drop of test fluid, doctors can predict the efficacy of the drug to the patient, diagnose the side effects of the drug in the course of treatment, and identify the bacterial, viral, or other microorganisms infecting the patient on the spot. Microarray analysis of genetic genes will result in a 10-year diagnosis of diabetes of more than 50%. In the future, blood is taken from the examiner by a microarray-based diagnostic robot, and instantaneous findings can be visualized on a computer screen. Using genetics, health care will move from a one-size-fits-all era of "general medicine" to one of "customized medicine," based on an individual's genetic genes. (2) Genetic testing is a technique for the detection of DNA by blood, other body fluids, or cells. Genetic testing can diagnose disease or be used to predict disease risk. Diagnosis is the use of genetic testing to detect mutant genes that cause inherited diseases. The most widely used genetic tests are tests for hereditary diseases in the newborn, diagnoses of genetic disorders, and adjuvant diagnoses of certain common diseases. More than 1,000 inherited diseases are currently diagnosed by genetic testing. Tumor gene testing in men

and women predicts whether one is a high-risk population and improves his or her health immunity through good preventive measures. Screening for diseases such as colorectal adenomas, nasopharyngeal cancer, esophageal cancer, leukemia, hepatocellular carcinoma, gastric cancer, colon cancer, prostate cancer, bladder cancer, lung cancer, breast cancer, cervical cancer, dermatitis, etc. (3) The encryption technique consists of two elements: algorithms and key. Algorithms are processes that combine ordinary text (or understandable information) with a string of numbers (keys) to produce incomprehensible cryptons, an algorithm used to encode and decode data. In security secrecy, network communication can be secured through appropriate key encryption techniques and management mechanisms. The cryptosystem of key encryption is divided into symmetry and asymmetry. Accordingly, there are two types of technologies for data encryption: symmetry (private key encryption) and asymmetric encryption (open key encryption). Asymmetric encryption is typically represented by the data encryption standard (DES, Dada Encryption Standard), and asymmetric encryption is typically represented by the RSA (Rivest Shamir Ad1eman) algorithm. The cryptokey and decryption key are the same for symmetry, but not symmetry, which is different from the cryptokey and decryption key, which is public and confidential. Cryptotech is generally divided into two main categories: “symmetry” and “asymmetry”. Symmetry encryption is the use of the same key for encryption and decryption, commonly referred to as “Session Key,” which is now widely used, such as the DES encryption standard used by the United States government, which is typically a “symmetrical” encryption, with its Ssession Key length of 56 Bits. Asymmetric encryption is that encryption and deciphering use a key that is not the same key, usually has two keys, called “keys” and “keys”, which must be paired to use, otherwise the encrypted file cannot be opened. The “key” here refers to the “key” that can be published to the outside world, but the “key of the private” cannot be known only by the holder. This is where its superiority lies, because symmetrical encryption can hardly be used to transfer encrypted files to the other side, any method that can be missed. Non-symmetrical encryption has two keys, and the “key” in which it is public, rather than anyone who knows it, can be decrypted with your own key, thereby safely avoiding the key’s transmission safety concerns. (4) Mathematical algorithms are the core of password encryption, but in ordinary software encryption it seems to be less of a concern, because most of the time the encryption itself is a programming technique. In recent years, however, the role of mathematical algorithms in software encryption appears to have grown as a result of the popularity of sequence number encryption programs.

2. Research Methods

Therefore, we present the following macroscopic requirements (under the cross-sectional conditions of medicine):

It maybe related with it which promote the development of computer network technology, because computer technology cannot be used or involved in many aspects, not because it is not developed as a result of the lack of safety, but because it is explored continuously by technical personnel to make up for safety problems.

Promoting the development of society as a whole, because once computer technology’s vulnerabilities can be bridged by technological means, computer technology has the status and rationale to be applied in areas where it has not been hunted or denied before. The application of new technologies to the development of the times offers a convenient condition for wider and deeper communication among all sectors, not only for the proliferation of computer networks, but also for the rise of social significance, which can be said to have contributed significantly to the development of society as a whole. The display of human wisdom, the ability and responsibility of humans to create the Internet, computer technology, and the ability to make up for the problems that have been fed back, and the creation of another technology that can also have scientific and technological properties and arithmetic, must be acknowledged as the externalization of human wisdom and the great wealth of society as a whole, as individuals assume that data encryption is a manifestation of human intelligence in cyber-security issues.

At the working microscopic level, we propose the following strategy: symmetry encryption, symmetry encryption to decrypt and encode processes using the same key. Safety and effectiveness are particularly critical in the transmission of key signals. During symmetric encryption, decryptation with the same key is performed more quickly and is widely used because the signature is indeterminate and undeniable. DES, 3DES, AES, and DES are all data encryption standards that are

commonly used to encrypt large data and run faster. DES is one of the algorithms for group encryption. Data are available for 64 pairs. Of these, the odd-coup correction was eight, with a password length of 56. The sequence of the original data set was first distended, divided, and finally inserted into the key, and the code was obtained by an iterative process. Whereas 3DES is based on DES, the higher strength is to encrypt a piece of data three times with three keyages. The faster second-generation cryptography algorithm AES is also safer. In gene report monitoring, the current algorithmic engineers should perform a large number of experimental and social procedures. This is more socially desirable.

Asymmetric encryption, in the process of deciphering and encryption, whether the key used is different is the most obvious difference between asymmetric encryption and symmetric encryption. The key and the key are two keys to asymmetric encryption. For encryption, two sets of keyes can be used together. It is known publicly as the “key,” and absolutely confidentially as the “private key”. The advantage of two keyes in the process of deciphering information is that they simply need the receiver to open a “private key” to perform information-efficient secrecy. The “key” has no “key” flexibility, but encryption speed and decryption speed is much faster than the “key”. Thus, in gene reports, different genes are encoded, and more efficient encryption is possible in different coding systems, so model design and algorithmic experiments are needed.

3. Health economics discussion

Individual gains from genomic data may be even more beneficial. These commercial compensations encourage individuals to participate in research and share their information, which in turn leads to greater scientific progress. Some scholars have described the “cyber effect” of respecting health-care data sharing: with more health-care data, the potential value of such data is greater. However, we are currently unable to extract the full value of medical data. As a result of network effects, increased data sharing has actually increased the sharing of information’s value, ultimately generating greater social and economic benefits. But the development of codons is also important, as encryption of genes can trigger the commercialization of shared genetic data and yield truly valuable economic benefits.

4. Conclusion

The growing market for genomic data has led an increasing number of companies to consider the business model of data sharing compensation. This strategy is not only a good model, but also a recipe for profit for consumers. Nevertheless, economic compensation for personal genetic information can also backfire and undermine altruism. Moreover, companies and individuals must also decide how to respect the commercialization of genetic data. Defining the best way to motivate individuals to share genomic data is essential to Big Data and precise health care. Given the growing value of the human genome, it seems logical for individuals to capture their benefits by sharing data. It is therefore important to make up for the cross-over between current genetic testing reports and codonology, and we should begin modeling as a way to anticipate our involvement in specific algorithmic studies, as well as the publication of scientific research papers in subsequent studies.

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Effect of YKL-40 RNA Interference on VEGF Gene Polymorphism Expression in Atherosclerotic Mice

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Abstract: **Aims:** To investigate the effect of YKL-40 RNA interference on VEGF gene polymorphism expression in atherosclerotic mice. **Methods:** After the atherosclerosis models in mice were built, the mice were divided into three groups including control group, negative control group and observation group, which were separately given to normal saline, negative virus (5×10^7 TU) and YKL-40 RNA interference lentivirus. Then the whole blood DNA was extracted and genotyped in each group of mice and the expression of VEGF in each group of mice was detected by PCR, while the expression level of inflammatory factors in each group of mice was detected by ELISA. Meanwhile, the aortas of mice in each group were pathologically analyzed and the atherosclerosis of mice was detected. **Results:** Compared with the control group, the VEGF content in both the virus negative control group and the observation group was significantly increased（$P<0.05$）. The detection rates of CC genotype and C allele at rs699947 of VEGF gene in the observation group were significantly higher than those in the control group and the virus negative control group, and the difference was statistically significant. There were no significant changes for the expression of HDL-C, LDL-C, TC and TG in mice of each group（$P>0.05$）. Moreover, the levels of Lp-PLA_2 and MCP-1 in the negative control group were significantly increased ($P < 0.05$), while those in the observation group were significantly decreased ($P < 0.05$) compared to that in control group. What's more, the histomorphology of the observation group was significantly different from that of the control group and the virus negative control group. The thickness of the fibrous cap of the as plaque was significantly higher than that of the control group and the virus negative control group, but the plaque area and fat content were significantly lower than that of the control group and the virus negative control group and the NC group. Besides, there was no significant difference in lipid content, fiber cap thickness and plaque area between the control group and the virus negative control group. **Conclusion:** YKL-40 RNAi could improve the VEGF polymorphism, reduce the expression of LP- PLA_2 and MCP- 1, and significantly inhibit the occurrence and development of atherosclerosis, which was expected to provide a new target for the prevention and treatment of atherosclerosis.

Keywords: YKL-40; VEGF; Single Nucleotide Polymorphism

Introduction

Atherosclerosis (AS) is a chronic progressive vascular disease, which is an important cause of global cardiovascular disease and the main cause of death [1] and is often found in large and medium arteries and is characterized by lipid accumulation and inflammation [2]. A variety of inflammatory cells participate in the occurrence and development of AS [3]. In recent years, the discovery of a large number of as inflammatory factor markers has provided new ideas for the early diagnosis of as, and also provided new targets and new directions for the treatment of diseases [4]. However, the interaction between various inflammatory factors needs further study in the process of atherosclerosis.

Vascular endothelial growth factor (VEGF) is a heparin binding protein family that participates in angiogenesis, lymphopoiesis and lymphangiogenesis, resists oxidative stress, regulates lipid metabolism and inflammation [5, 6]. Studies have found that there are more than 30 single nucleotide polymorphisms (SNPs) in VEGF. These gene polymorphisms affect

the expression and transcription of VEGF, and then affect its role. The polymorphism analysis of VEGFR gene showed that two single nucleotides in the promoter region and coding region of VEGFR-2 gene: rs2071559 (- 604T / C) and rs1870377 (+ 1719a / T) were associated with the risk of peripheral arterial disease. VEGF is a powerful mitogen, which can promote the proliferation and migration of endothelial cells and the formation of new blood vessels[7], and plays an important role in the development of as and the stability of plaque. The gene polymorphism of VEGF and its receptor leads to the difference of expression and affects the physiological efficacy of VEGF. Other studies have shown that YKL- 40 is highly expressed in AS [8]. The aim of this study was to study the changes of VEGF gene polymorphisms in the process of atherosclerosis in apoE -/-mice interfered by YKL-40, and to elucidate the interaction between YKL-40 and VEGF in AS.

1. Matrials and methods

1.1 Experimental animals and reagents

A total of 72 male apoe-/- mice of 12-week-old were purchased from the medical department of Peking University, which were housed in IVC-II isolation cages and fed with high fat at the atmosphere of 20-25 °C, 55 ± 5% of relative humidity, 20-50 PA pressure and 12 hours light / dark cycle. The experiment was approved by the Ethics committee of Jinan People's Hospital Affiliated to Shandong First Medical University, and conform to the guidelines for the care and use of experimental animals of the National Institutes of health and the ARRIVE guidelines.

The construction of YKL-40 shRNA lentiviral vector (target gene sequence: 5 ′ - gctccagtgctgcata-3 ′) was completed by Shandong Weizhen Biotechnology Co., Ltd. Trizol reagent was purchased from GIBCO (USA), while ELISA kits such as oil red O, monocyte chemotactic protein-1 (MCP-1) and lipoprotein associated phospholipase A 2 (Lp-PLA 2) were purchased from Zhengzhou sensike Biological Products Co., Ltd. Besides, ELISA kits such as mouse vascular endothelial growth factor (VEGF), mouse high density lipoprotein cholesterol (HDL-C), mouse low density lipoprotein cholesterol (LDL-C), mouse triglyceride (TG) and mouse total cholesterol (TC) were purchased from Shanghai Kexing Trading Co., Ltd.

1.2 Establishment of mouse AS model and animal grouping

The AS model of apoe-/- mice was established by inducing the formation of as with the left common carotid artery constriction cannula method and kept high-fat feeding. 8 weeks later, the apoE-/-mice were randomly divided into control group（n=24）, negative control group（NC, n=24）and observation group（n=24）. In the control group, the left common carotid artery was isolated and the silicone cannula was removed, and then saline was infused locally; The negative control group was injected with negative virus (5×10^7 TU）； The observation group was given YKL-40 RNA interference lentivirus (5×10^7 TU). Plaques were collected after 6 weeks to make 6 μ M U.M frozen sections, which were then stained with HE and oil red O and analyzed by histopathology.

1.3 Whole blood DNA extraction and genotyping

200 ml of blood cells were collected and the genomic DNA was extracted according to the instructions of UNIQ-10 column clinical sample genome extraction kit, and the colorimetric quantification and purity identification were conducted with ultraviolet spectrophotometer. The extracted DNA was stored in a refrigerator at 4 ° C or -20 ° C. Genotyping was performed by polymerase chain reaction, restriction fragment length polymorphism (PCR-RFLP) and sequence-based typing (SBT). The DNA fragment containing VEGF rs699947-471f was PCR amplified. The primer sequence was synthesized by Shanghai Sangong Bioengineering Co., Ltd., and the amplified PCR product was recovered and subjected to first-generation sequencing (Sanger sequencing).

1.4 Fluorescence quantitative PCR

10 mg of sample, 200 μ L buffer SA and 10 μ L proteinase K was put into the centrifuge tube and mixed well, which was then incubated at 56 ° C for 10 minutes, treated at 95 ° C for 5 minutes, and centrifuged for 5 minutes at 13000 RPM (~

17900 × g). The supernatant was taken into a new centrifuge tube for PCR amplification with the reaction procedure in Table 1. Finally, quantitative PCR analysis was performed.

Table 1. The reaction conditions of PCR

Procedure	Temperature	Time	
Pre-denaturation	94℃	2min	
Denaturation	94℃	30s	30-40 cycles
Annealing	55-65℃	30s	
Extension	72℃	60s	
Final extension	72℃	5min	

1.5 ELISA analysis

The blood was taken from the anesthetized mice, and the upper plasma was taken after centrifugation for detection. The levels of VEGF, Lp-PLA $_2$, MCP-1, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and total cholesterol (TC) were determined using the corresponding ELISA kits.

1.6 Histomorphological examination

Image Pro Plus 5.0 image analysis software was used for quantitative analysis of HE stained and oil red O-stained sections, and the plaque area, fiber cap thickness and lipid content were detected.

1.7 Statistical analysis

The data were analyzed using SPSS 21.0 software. All measurement data were expressed as mean ± SD. After the normality test, one-way analysis of variance (ANOVA) was performed. Student Newman Keuls (SNK) test was used for comparison between two groups. If $P < 0.05$, the difference was considered statistically significant.

2. Results

2.1 Comparison of VEGF content and site polymorphism in mice of each group

Compared with the control group, the VEGF expression was significantly increased in both the NC group and the observation group ($P<0.05$, Fig. 1). According to the sequencing results, we found that the detection rates of CC genotype and C allele at rs699947 of VEGF gene in the observation group were significantly higher than those in the control group and the NC group ($P < 0.05$, table 1).

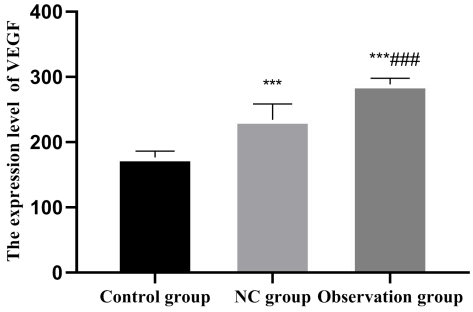

Figure 1. The expression of VEGF in each group，*P<0.05，**P<0.01，***P<0.001, vs control group；#P<0.05，##P<0.01，

###P<0.001, vs NC group.

Table 2. Comparison of polymorphisms of VEGF gene rs699947

	Genotype frequency			Allele frequency	
	CC	CT	TT	C	T
Control group（n=24）	13（54.2%）	7（29.2%）	3（12.5%）	17（70.8%）	6（25.0%）
NC group（n=24）	14（58.3%）	6（25.0%）	4（16.7%）	18（79.2%）	5（20.8%）
Observation group（n=24）	16（66.7%）	8（33.3%）	1（4.17%）	20（83.3%）	4（16.7%）

2.2 The expression of HDL-C, LDL-C, Lp-PLA2, MCP-1, TC and TG levels in each group

As shown in Figure 2, there was no significant change in HDL-C, LDL-C, TC and TG in mice of each group (P>0.05). Compared with the control group, the levels of Lp-PLA$_2$ and MCP-1 in the virus negative control group were significantly increased (P<0.05), while the levels of Lp-PLA$_2$ and MCP-1 in the observation group were significantly decreased (P<0.05).

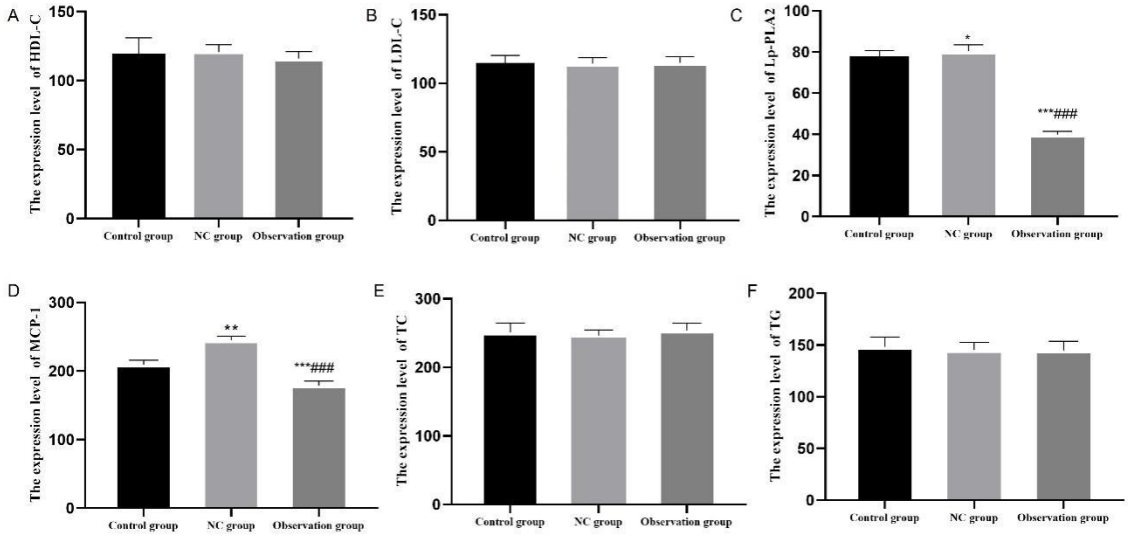

Figure 2. The expression of HDL-C, LDL-C, Lp-PLA2, MCP-1, TC and TG levels in each group. * P<0.05，**P<0.01，***P<0.001, vs Control group；#P<0.05，##P<0.01，###P<0.001, vs NC group.

2.3 Morphological changes of mice in each group

The histomorphology of the nice in observation group was significantly different from that of the control group and the NC group. The thickness of the fibrous cap of as plaque was significantly higher than that of the control group and the virus negative control group (P<0.05, Fig. 2), but the plaque area and fat content were significantly lower than that of the control group and the virus negative control group (NC group) (P<0.05, Fig.3). There was no significant difference in lipid content, fiber cap thickness and plaque area between the control group and the NC group, which indicated that the beneficial effect of the observation group was not caused by the non-specific immune response caused by virus infection, which further confirmed that the interference of RNAi was effective.

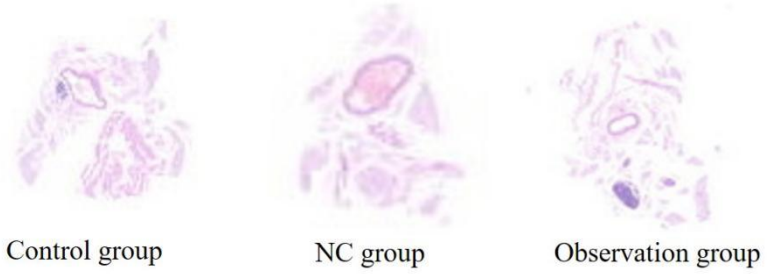

Figure 3. Morphological changes of mice in each group

3. Discussion

AS is a lipid driven chronic inflammatory disease that usually forms plaques in large and medium-sized arteries [9], and is the main cause of ischemic heart disease and stroke[10]. AS has a serious impact on people's quality of life and health, and has become a hot topic in the cardiovascular field.

As a growth factor, VEGF is widely expressed in normal and pathological tissues and plays an important role in angiogenesis [11]. Studies have shown that VEGF-A is related to the proliferation of vascular endothelial cells and the prevention of atherosclerotic plaque formation [12], and VEGF can induce the neovascularization of atherosclerotic plaques and the expansion of aortic calcification lesions [13]. In addition, VEGF protein may play an important regulatory role in the pathogenesis of endothelial dysfunction and atherosclerosis by mediating intimal hyperplasia, thereby improving the progression of atherosclerotic plaques in coronary arteries in human and animal models. VEGF expression is regulated by some single nucleotide polymorphisms (SNPs), some of which, including VEGF – 2578a/c (rs699947), - 1154g/a (rs1570360), + 405c/g (rs2010963) and + 936c/t (rs3025039), are associated with coronary artery disease susceptibility. However, these findings are controversial. This study found that VEGF – 2578a / C (rs699947) was related to the occurrence and development of atherosclerosis, and the expression of VEGF was decreased in AS. This was consistent with previous research results, which might be a manifestation of rs699947's protective effect on coronary artery disease [14].

YKL-40, also known as human cartilage glycoprotein-39 (HC-GP39), belongs to the mammalian 18 glycosylhydrolase family. As the immune inflammatory response theory of atherosclerosis is more and more accepted, the extensive role of YKL-40 in the inflammatory response suggests that it also plays an important role in the development of AS. It has been found that smooth muscle cells in carotid atherosclerotic plaques of some patients express YKL-40, and the high expression of YKL-40 mRNA can also be detected in giant cells in atherosclerotic plaques. However, the mechanism of YKL-40 in atherosclerosis is still unclear. In the early stage of AS, monocytes adhering to the vascular wall, under the action of monocyte chemoattractant protein-1 (MCP-1) produced by vascular endothelial cells and smooth muscle cells, migrate to the vascular wall along the concentration gradient, invade or activate into macrophages, and then combine with the modified LDL-C deposited in the vascular intima to form foam cells, thus forming atherosclerotic plaques. Studies have shown that YKL-40 can upregulate MCP-l expression, chemotactic more monocyte infiltration, and promote plaque formation and development. In vitro proteomic studies on biochemical indicators of AS indicated that the expression of YKL-40 in the supernatant of macrophages treated with oxidized low-density lipoprotein (ox LDL) was increased, which was similar to the formation of "foam cells", indicating that YKL-40 can promote the differentiation of monocytes into lipid loaded macrophages during the formation of atherosclerotic plaques. This was consistent with the findings that the atherosclerotic vascular smooth muscle cells also express YKL-40 protein in vivo. In this study, YKL-40 was interfered and its expression level of inflammatory factors was detected. The results showed that YKL-40 RNAi had no significant effect on the expression levels of HDL-C, LDL-C, TC and TG in mice, but could significantly reduce the expression of Lp-PLA_2 and MCP-1, indicating that YKL- 40 RNA interference reduces plaque lipid content and reduces plaque vulnerability by reducing the levels of inflammatory factors such as LP- PLA_2 and MCP- 1. In addition, the pathological experiments also showed that YKL-40 RNAi had obvious inhibitory effects on plaque formation, plaque fiber cap thickness, plaque area and

plaque fat content, which indicated that ykl-40rnai was effective in interfering with atherosclerosis.

In conclusion, YKL-40 RNAi could improve VEGF polymorphism, reduce the expression of LP- PLA_2 and MCP- 1, and significantly inhibit the occurrence and development of atherosclerosis. It is expected to provide a new target for the prevention and treatment of AS. However, this study also had some limitations, the number of animals used was relatively small, and further validation and mechanism research are needed in the later stage.

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Universe Scientific Publishing

Influencing Factors and Etiological Analysis of Incision Infection after Abdominal Surgery in Patients with Multiple Traumas

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Abstract: **Objective:** To analyze the influencing factors and etiological characteristics of postoperative incision infection in patients with multiple traumas. **Methods:** A retrospective analysis was carried out on the clinical case data of 195 patients with multiple trauma who underwent abdominal surgery in our hospital. All patients were admitted to the hospital from January 2016 to December 2021. According to the information obtained, the postoperative incision infection and pathogen distribution of the patients were counted, and the risk factors affecting postoperative incision infection were analyzed. **Results:** According to the analysis, after abdominal surgery, 38 patients had incision infection, and the infection rate was 19.49%. Through the cultivation of pathogenic bacteria, there were 54 strains of pathogenic bacteria, and the highest proportion was gram-negative bacteria, which was 59.26%, and the lowest was fungus at 9.26%; through univariate analysis, it was found that age, hospital stay, white blood cells, albumin, diabetes, C-reactive protein, blood loss and ISS score between the infected and uninfected groups. There was a significant difference ($P<0.05$); multivariate logistic regression analysis found that incision infection in patients with multiple traumas after abdominal surgery was associated with increased age, increased albumin level, combined diabetes, increased blood loss and ISS score factors ($P <0.05$). **Conclusion:** For patients with multiple traumas who underwent abdominal surgery, the probability of postoperative incision infection was higher, and gram-negative bacteria were the main pathogenic bacteria, and postoperative infection was not only related to one factor, but it is related to a variety of factors, and appropriate amount of antibiotics should be given according to the actual situation of the patient.

Keywords: Multiple Traumas; Abdominal Surgery; Incision Infection; Etiology

Introduction

Multiple traumas have a high incidence in clinical practice. The tissues and organs of such patients have been damaged to varying degrees. The patient's condition is very critical, and a large amount of blood loss is prone to occur, which seriously threatens the life safety of the patient [1]. Therefore, patients need to receive surgical treatment as soon as possible to control the amount of bleeding and improve the survival rate of patients. However, the surgery is invasive and prone to incision infection after surgery, which not only aggravates the patient's condition, but also increases the risk of death. In view of this, this study selected multiple trauma patients who underwent abdominal surgery in our hospital, and analyzed the influencing factors and pathogenic bacteria characteristics of postoperative incision infection according to the patient's case data, hoping to provide reference for clinical disease treatment.

1. Materials and methods

1.1 Normal information

A total of 195 patients with multiple traumas admitted to our hospital from January 2016 to December 2021 were selected for analysis. All patients received abdominal surgery. After surgery, patients were divided into two groups according to the presence or absence of incision infection, namely, patients without incision infection were classified as non-infection group, with 157 cases in total. There were 38 cases of incision infection in the infection group.

1.2 Methods

All patient data were collected, including basic data, past history, surgical conditions and laboratory tests. The collected information and data were sorted out, and retrospectively analyzed, and statistical analysis was performed on all single factors. Determine the influencing factors of postoperative incision infection. After the surgical treatment is completed, the patient needs to be given routine care according to the nursing requirements of the department, and the incision of the patient should be closely observed. The cotton swab is dipped in the foreign body at the incision, the collection volume is 2ml, the collected specimen is placed in a sterile test tube, and the specimen is sent to the laboratory for testing in the shortest time, and the analysis of pathogenic bacteria is analyzed and identified.

1.3 Statistical methods

Input the data into SPSS21.0 system software for calculation, use ($\bar{x}$ ±s) for measurement statistics, use (%) for count statistics, t test and x^2 test, P<0.05 means statistical significance.

2. Results

2.1 The ratio of patients with incision infection and pathogenic bacteria

Among the 195 patients in this study, after postoperative statistics, it was found that 38 patients developed incision infection after surgery, accounting for 19.49% of the total number of patients. The infected patients were cultured with pathogenic bacteria, and the number of strains cultivated was 54, of which 54 strains were cultivated. Gram-negative bacteria were the most common, followed by gram-positive bacteria and fungi. The number and proportion of strains were 32 (59.26%), 17 (31.48%), and 5 (9.26%), respectively. See Table 1.

Table 1 The composition ratio of pathogenic bacteria in patients with incision infection

Pathogens	Number of plants（n=54）	Composition ratio（%）
Gram-negative bacteria	32	59.26
Gram-positive bacteria	17	31.48
Fungus	5	9.26

2.2 Univariate analysis of patients with postoperative incision infection

Univariate analysis of the patients showed that there was no significant difference in gender and hemoglobin between the infected group and the uninfected group (P>0.05), while the age, hospital stay, white blood cells, albumin, diabetes mellitus, C-reactive protein, bleeding volume and trauma severity score (ISS) were compared and analyzed, and there was a significant difference between the two groups (P<0.05).

Table 2 Univariate analysis of patients with postoperative incision infection

Clinical features		Infected group (n=38)	Uninfected group (n=157)	t/x^2	P
Gender	Male	28	95	2.280	＞0.05
	Female	10	62		
Age(years)		47.48±11.38	41.62±10.97	2.933	＜0.05
Combined diabetes	Yes	17	18	4.457	＜0.05
	No	48	112		
Hospital stay（d）		14.35±5.29	8.73±3.80	7.531	＜0.05
Hemoglobin（g/L）		125.06±13.04	118.92±14.63	2.369	＜0.05
Leukocyte（10^9/L）		12.38±3.59	8.40±2.43	8.180	＜0.05
Albumin（g/L）		28.57±9.73	33.62±6.18	3.990	＜0.05
C-reactive protein（mg/L）		23.49±7.26	17.34±6.49	5.120	＜0.05
ISS score（score）		16.81±5.42	10.59±4.91	6.865	＜0.05
Bleeding（ml）		584.37±183.05	354.28±117.26	9.610	＜0.05

3. Discussion

The results of this study showed that after abdominal surgery in 195 patients with multiple traumas, some patients developed incision infection, a total of 38 cases, and the infection rate was 19.49%. Pathogenic bacteria were cultured in 38 infected patients, and 54 strains were cultivated. Among them, the most distributed strains were gram-negative bacteria, with 32 strains, accounting for 59.26 of the totals, followed by gram-positive bacteria and gram-positive bacteria. For fungi, the number of strains was 17 and 5, accounting for 31.48% and 9.26%, respectively. From this, it can be known that in abdominal surgery of patients with multiple traumas, it is necessary to select appropriate antibiotics according to the actual situation of the patients, and take antibiotics treatment as soon as possible, which has a positive effect on preventing infection.

This study also found that with the increase of age, ISS score, diabetes mellitus, decreased albumin level, and increased blood loss. These factors were all important risk factors for postoperative incision. With the increase of age, various functions of the body gradually decline, and the resistance and immunity are significantly reduced. After the body is traumatized, it is easy to cause infection. The ISS score is closely related to the severity of the patient's trauma. The higher the score, the more serious the patient's condition, and the higher the risk of postoperative incision infection [2]. In diabetic patients, the ability to metabolize blood sugar decreases, and the blood sugar level in the body increases. In this state, the patient's immune function will decline, resulting in an increased risk of pathogen invasion, and the high blood sugar environment provides favorable conditions for the growth and reproduction of pathogenic bacteria. conditions that increase the risk of infection [3]. Albumin is closely related to the body's resistance, and a decrease in its level will lead to a decline in resistance, thereby increasing the risk of infection. When the amount of bleeding in patients increases during surgery, the effective circulating blood volume of the body will be reduced, resulting in protein loss, the decline of body's ability to resist pathogenic bacteria infection, and the increase of incision infection rate . Therefore, for the above-mentioned high-risk groups, it is necessary to strengthen the observation of the condition after surgery, and to give the patients antibiotics in a

timely manner. When using antibiotics, it is necessary to pay attention to the addition of gram-negative bacteria sensitive drugs, so as to better prevent infection.

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Universe Scientific Publishing

Pharmacological Study of Phenolic Components in Parkinson's Disease

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Abstract: In this study, cell experiments were conducted to investigate the effects of extracts on cell viability and apoptosis of Parkinson model in vitro, as well as the expression of cysteine protease-3 (Caspase-3) and B lymphocytoma-2-associated X protein (BAX). The results showed that extract of phenols could improve the loss of cell viability and apoptosis induced by MPP+, and inhibit the enhanced expression of Bax and Caspase-3 by MPP+. The potential targets and signaling pathways of phenols in the treatment of Parkinson's disease were predicted by network pharmacology.

Keywords: Gastrodia elata Bl; Phenols; Caspase-3; BAX; Parkinson's disease; Network pharmacology

Introduction

The pathogenesis of PD in modern medicine is not clear, and it is generally believed to be caused by various factors such as genes, environment and lifestyle.As a traditional Chinese medicine, gastrodia elata has the effect of calm and calm. Therefore, doctors combine gastrodia elata with other Chinese medicine to treat PD, such as [1], gastrodia elata drink [2], qi, blood and [3], have achieved good results in clinical treatment.We found that the phenolic components of Gastrodia elata in Gastrodia elata have good effects on CNS diseases such as PD, [4].Pharmacological experiments proved that gastrodin could improve that in model animals Movement disorders, reduces loss of dopamine neurons [5-7]; vanicol improves cell survival in PD model cells [8]; vanillin inhibits neuroinflammation caused by microglial activation, weakens dopamine neuronal degeneration, and plays a potential role in treating PD [9,10].

In this experiment, we proved that the extract can improve the cell survival rate and inhibit apoptosis of PD cell model, predict the potential target and pathway of PD, and explore the mechanism of action in treating PD.

1. Instruments and materials

1.1 Clone

PC 12 cells.

1.2 Laboratory apparatus

Table 1: Experimental Instrument Information

Instrument name	Manufacturer	Model
Micropipet	ThermoFisher	
Superclean bench	Suzhou Group Antai Air Technology Co., LTD	SW-CJ-1FD
CO_2constant-temperature incubator	SANYO	MCO-15AC
Inverted microscope	OLYMPUS	IX51
Conventional centrifuge	Eppendorf	5702R
ELIASA	Thermo	MULTISKAN MK3
Electrophotometer power supply	Beijing 61 Instrument Factory	DYY-7C
Vertical electrophoretic tank	Beijing 61 Instrument Factory	DYCZ-24DN
Transfer electrophoresis instrument	Beijing 61 Instrument Factory	DYCZ-40
Horizontal shaking bed	Jiangsu Haimen Qlinbel Instrument Manufacturing Co., LTD	TS-1
pH count	Metter-Toledo GmbH, Germany	LP115
Magnetic stirring apparatus	Jiangsu Jintan City Zhongda Instrument Factory	T8-1
Centrifuge	Hunan Xiangyi Laboratory Instrument Development Co., Ltd	HI650
Biological microscope	Olympus	BX53

1.3 Experimental reagents and consumables

Table 2. Experimental reagents and consumables

Name of reagents and consumables		Vender	Art.No
0.25% Trypsin		Gibco	15050065
Cell culture dishes, cell culture flasks		Corning	
FBS		Gibco	10091-148
1640		Gibco	11875-093
PS		Gibco	15070-063
Phosphatase inhibitors		Shanghai Biyuntian Biotechnology Co., Ltd	S1873
PMSF		Aladdin Reagent (Shanghai) Co., Ltd	P105539
RIPA lysate		Shanghai Biyuntian Biotechnology Co., Ltd	P0013B
BCA protein concentration determination Kit		Shanghai Biyuntian Biotechnology Co., Ltd	P0010
TEMED		Sinopharm Group Chemical Reagent Co., LTD	80125336
SDS loading buffer	Trise-Base	Biofroxx	1115GR500
	HCl	Xinyang city chemical reagent factory	GB622-89
	Dithiothreitol	Biofroxx	1111gr005
	SDS	Sinopharm Group Chemical Reagent Co., LTD	30166428

	Bromophenol blue	Sinopharm Group Chemical Reagent Co., LTD	71008060
	Glycerol	Sinopharm Group Chemical Reagent Co., LTD	10010618
30% Acrylamide		Biosharp	BL513b
TG	Trise-Base	Biofroxx	1115GR500
	Glycocoll	Biofroxx	1275GR500
	SDS	Sinopharm Group Chemical Reagent Co., LTD	30166428
Electrophoretic transfer buffer	Tris-base	Biofroxx	1115GR500
	Glycocoll	Biofroxx	1275GR500
	Carbinol	Sinopharm Group Chemical Reagent Co., LTD	10014118
PBS	NaCl	Sinopharm Group Chemical Reagent Co., LTD	10019318
	KCl	Sinopharm Group Chemical Reagent Co., LTD	10016318
	$Na_2HPO_4.12H_2O$	Sinopharm Group Chemical Reagent Co., LTD	10020318
	KH_2PO_4	Sinopharm Group Chemical Reagent Co., LTD	10017618
TBST	Tris-base	Biofroxx	1115GR500
	NaCl	Sinopharm Group Chemical Reagent Co., LTD	10019318
	Glacial acetic acid	Sinopharm Group Chemical Reagent Co., LTD	10000218
	Twain 20	Sinopharm Group Chemical Reagent Co., LTD	30189328
Protein marker (14-120KD)		Beijing Total Gold Biotechnology Co., Ltd	DM111
PVDF membrane(0.45μm)		Millipore	IPVH00010
PVDF membrane(0.22μm)		Millipore	ISEQ15150
Rabbit polyresistance GAPDH	37KD	Hangzhou Xianzhi Biological Co., Ltd	AB-P-R 001
		Detection of antibodies	
RabMab cleaved caspase3 （17/19KD)		Cell signaling	9664
Rabbit polyresistance，Bax （21KD)		Wuhan Sanying Biotechnology Co., LTD	50599-2-AP
HRP-labeled sheep anti-mouse secondary antibody		Wuhan Doctor De Biological Engineering Co., Ltd	BA1051
HRP labeled sheep anti-rabbit secondary antibody		Wuhan Doctor De Biological Engineering Co., Ltd	BA1054
ECL, the substrate solution		Beijing Priilai Gene Technology Co., Ltd	P1050

X-ray film	Ruike (Xiamen) Medical Equipment Co., LTD	6535876
Development-fixing kit	Tianjin Hanzhong Photography Materials Factory	
Slides and cover slips	Jiangsu Shitai Experimental Equipment Co., Ltd	
Paraformaldehyde	Sinopharm Group Chemical Reagent Co., LTD	80096618
Concentrated normal goat serum (closed)	Wuhan Doctor De Biological Engineering Co., Ltd	AR1009
Fluorescence (Cy3) labeled sheep anti-rabbit IgG	Wuhan Doctor De Biological Engineering Co., Ltd	BA1032
Fluorescence (Cy3) labeled sheep anti-mouse IgG	Wuhan Doctor De Biological Engineering Co., Ltd	BA1031
Triton X-100	Shanghai Biyuntian Biotechnology Co., Ltd	ST795
DAPI	Shanghai Biyuntian Biotechnology Co., Ltd	C1002
Anti-fluorescence ququenching agent	southernbiotech	0100-01
Triton X-100	Shanghai Biyuntian Biotechnology Co., Ltd	ST795
TUNEL Apoptosis detection kit	Roche Applied Science	12156792910

2. Method

2.1 Effect of Gastrodia elata phenolic extracts on PD cell models

2.1.1 Cell culture

PC 12 cells were removed from liquid nitrogen, quickly placed into a 37℃ water bath, gently shaking the frozen tube, transferred to a centrifuge tube containing 5 mL medium, collected, centrifuged at 1000 r/min for 5 min, the supernatant was discarded, suspended with complete medium containing 10% FBS (1640 + 10%FBS + 1% penicillin-streptomycin), and mixed with 37℃ 5%CO_2 saturated humidity.The cells reach a density of, 80%, on fine Cell passage: discard medium and wash it with PBS; add 1~2m L 0.25% trypsin digested cells, observe under microscope for 30~60s, see cells separated and rounded, or digestion; add complete medium, blow cells to make single cell suspension, passaged in 1:3 ratio, expand culture under saturated humidity of 37℃ and 5% CO_2.

2.1.2 Cell viability detection

Cell viability was determined by the 3- (4,5-dimethyl-2-thiazole) -2,5-diphenylbromide thiazole blue (MTT) reduction method.

Cells with good growth were connected to 5103,96-well plate with blank group and 37℃ overnight (100 L sterile PBS in the wells around the wells); media with different drugs to each well in 37℃, 5%CO_2 incubator for some time.Subsequently, 10 μL MTT was added to each well and 37℃ for 4h and 150 μL DMSO was added for 10min; the absorption value of each well was measured with a microplate reader and the wavelength was set at 568 nm; Each experiment was repeated three times.

2.1.3 TUNEL Apoptosis detection

Slides of scrambled cells were immersed in 4% paraformaldehyde (pH 7.4) and fixed in the solution for 25 min at room temperature, and subsequently washed three times with PBS for 5 min each.Cell tiles were immersed in 0.1% TritonX-100 solution prepared with PBS for 10 min (operated on ice) and then washed twice with PBS for 5 min each.The TUNEL reaction mixture was prepared, and the treatment group was mixed with 50 μL TdT + 450 L fluorescein-labeled dUTP solution; but was negative Control group add only 50 L of fluorescein-labeled dUTP solution, positive control group first add 100 μL DNaseI at 15 to 25℃ for 10 min; drying of glass slides add 50 μL TUNEL reaction mixture (50 L of fluorescein-labeled dUTP solution) to the specimen, incubated at 37℃ for 60 min, washed three times with PBS, 5 min each.Samples were incubated with DAPI for 5 min and stained by PBST Wash the excess DAPI 4 times in 5 min; drain the liquid with suction paper and seal with sheet liquid containing anti-fluorescent quencher.Images were acquired under a fluorescence microscope.

2.1.4 Immunofluorescence detection

Slides of scrambled cells were washed three times with PBS for 3 min; the slides were fixed with 4% paraformaldehyde for 15 min and PBS for 3 min; 0.5%Triton X-100 (PBS) for 20 min; PBS for three times and PBS for 3 min and closed at room temperature for 30 min Primary antibody (1:100) and placed in a wet box, 4℃ incubation overnight; PBST immersion slide for 3 times, 3 min, suction paper on excess liquid after fluorescence (Cy3) labeled sheep anti-rabbit IgG secondary antibody (1:100), fluorescence (Cy3) labeled sheep anti-mouse IgG (1:100), wet box 37℃ incubation for 1h, PBST immersion section for 3 times, 3 min; Samples were incubated with DAPI for 5 min, and the excess DA was washed away 4 times in PBST 5 min PI; drain the liquid on the climbing sheet with suction paper and seal the sheet with sealing sheet liquid containing anti-fluorescent quencher.The images were collected under a fluorescence microscope.

2.1.5 Western blot detection

Cellular proteins were extracted, separated by SDS-PAGE, electrically transferred to PVDF membrane, blocked with blocking solution containing 5% skim milk powder for 2 h, phosphorylated protein blocked with 1% BSA; primary antibody was added, 4℃ incubated overnight; secondary antibody (1:50000), incubated at room temperature for 2 h; development, scanned, and film gray was analyzed by BandScan.

2.1.6 Data statistics

All data were averaged as ±S.E.M. Representation, cell viability differences between groups were determined by one-way analysis of variance (One-Way ANOVA).All analyses were performed using the SPSS (23.0) software.

2.2 Network pharmacology predicts the mechanism of action of phenolic components in PD

2.2.1 Database

PubChem(https://pubchem.ncbi.nlm.nih.gov/)

PharmMapper(http://lilab-ecust.cn/pharmmapper/index.html)

TTD(Therapeutic Target Database,http://db.idrblab.net/ttd/)

Drugbank(http:/www.drugbank.ca)

Genecards(http://www.genecards.org)

DisGeNET(https://www.disgenet.org/home/)

OMIM(Online Mendelian Inheritance in Man, http://www.omim.org)

STRING(Search Tool for the Retieval of Interacting Genes/Proteins,http://string-db.org/cgi/input.pl)

Matescape（http://metascape.de）

2.2.2 Screening of the active ingredients

By searching and consulting the literature related to the chemical composition of gastrodia elata in "CNKI", "Wanfang" and "Pubmed", the phenolic compounds verified by clinical studies or pharmacological experiments were selected.

2.2.3 Screening of target sites

2.2.3.1 Target prediction of the active components of Gastrodia elata

Drug active components act by acting on relevant targets, so this study queries the targets potentially regulated by active components by PharmMapper to select targets with scores> 0.7.

2.2.3.2 Collection of the PD targets

Using TTD [11], Drugbank[12], Genecards[13], DisGeNET[14], and OMIM [15] databases to search targets related to PD with "Parkinson's disease", select genes with high likelihood by scores, and construct the disease gene database.

2.2.3.3 PD-related drug-active component targets

The action target gene number of "2.2.3.1" and the PD target of "2.2.3.2" were crossed to obtain the potential action target of the treatment of PD.

2.2.4 PPI Network and Network Topology Analysis

A network of PPI (Protein-Protein Interaction Networks) was constructed through the STRING[16] database.

2.2.5 GO and KEGG analysis

In order to reveal the potential action mechanism of phenolic components on PD, the main action pathway analysis and GO functional enrichment analysis of the potential targets of PD were conducted using Matescape[17] database.

2.2.6 The "Component-target-pathway" network construction

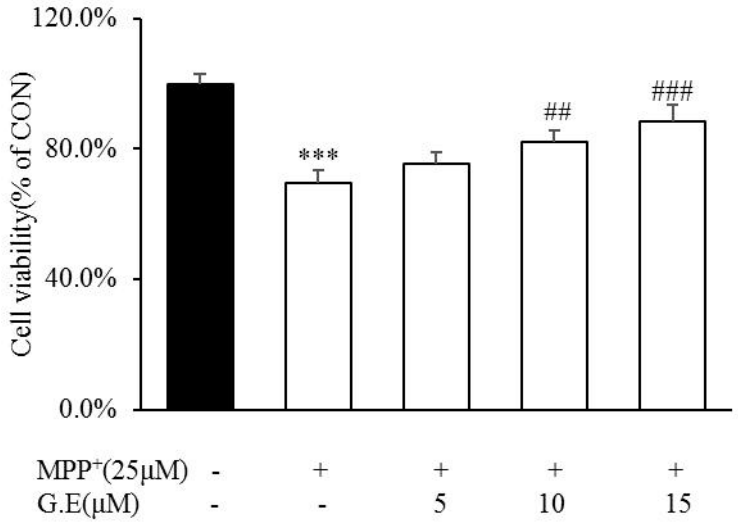
The "component-target-pathway" network was constructed according to "" Cytoscape3.6.1 " software.

3 Results and analysis

3.1 Effect of Gastrodia elata phenolic extracts on PD cell models

3.1.1 Phenolic extracts ameliorated MPP + -induced loss of nerve cell viability

The effect of Gastrodia elata phenolic extracts on MPP + -induced PC12 cells was determined by MTT reduction.When cell survival in control conditions was defined as 100% survival, the activity of PC 12 cells was significantly reduced to 69.4 ± 3.9% after 48 h of 25 μM MPP + treatment.Before addition of MPP +, 4 h pretreatment with Gastrodia phenolic extracts (5,10,15 g / mL) increased MPP + -induced cell survival to 75 .3 ± 3.7%, 82.0 ± 3.8%, and 88.3 ± 5.3%, and were presented in a dose-dependent manner.This result suggests that Gastrodia elata phenolic extract was protective against MPP + -induced nerve cells.



G.E represents Gastrodia elata phenolic extract;**** indicates the p <0.001 of MPP + group compared to control, n=3;# # indicates p <0.01 for MPP + + GE10μM compared to MPP + group, n=3; # # # indicates p <0.001 for MPP + + GE15μM compared to MPP + group, n=3

Figure 1.Cell survival rate of PC12 cells under different conditions

3.1.2 Apoptosis detection

TUNEL detection results are shown in Figure 2.The apoptosis rate was increased in the model group compared to the control group, and decreased in cells treated with Gastrodia elata phenolic extracts.

3.1.3 Effect of Gastrodia elata phenolic extracts on the expression of apoptosis-related proteins

Whether Gastrodia elata phenolic extracts affected the expression of Bax and Caspase-3 in MPP + -treated cells was investigated by Western blot and immunofluorescence assays.As shown in Figure 3, Bax expression was increased in the MPP + -treated group when compared to the control group, which is consistent with previous studies on [18,19]. Bax expression was inhibited by phenolic extract treatment and 25 μM MPP + treatment improved Caspase-3 activity, while addition of different concentrations of phenolic extracts enabled MPP + -induced PC 12 Lower expression of Caspase-3 in the cells.

The results of immunofluorescence are shown in Figure 4, and the intracellular staining intensity was significantly enhanced after MPP + treatment.In the treated group of phenolic extracts, the fluorescence intensity decreased with the increasing concentration of phenolic components.

In conclusion, the results indicate that the inhibition of MPP + by phenolic extracts on the enhanced expression of Bax and Caspase-3.

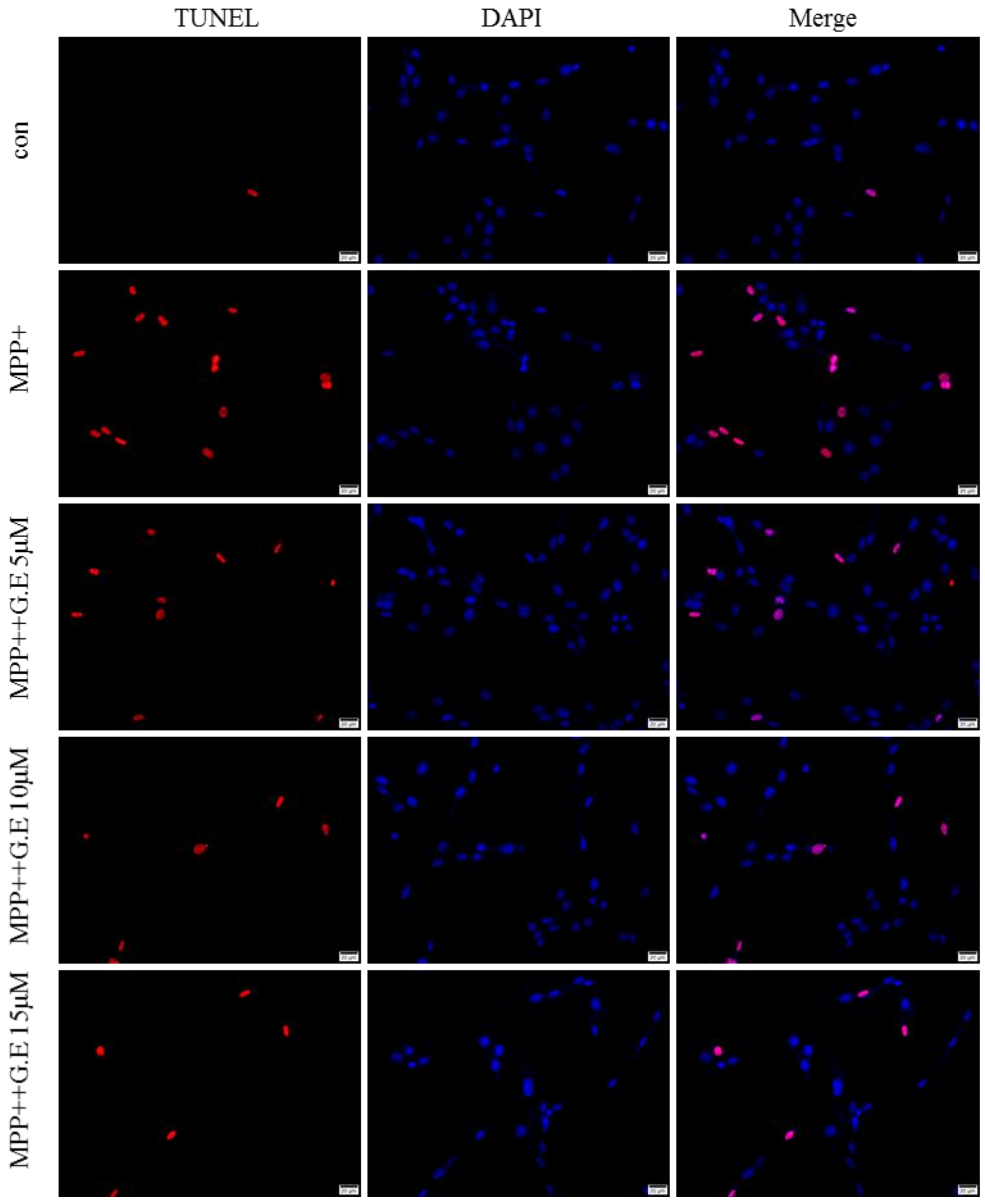


Fig 2 TUNEL Detection (400)

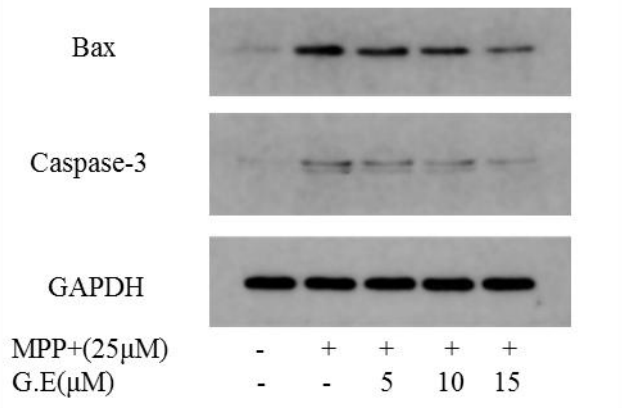


Figure 3 Effect of Gastrodia elata phenolic extracts on the expression activity of Bax and Caspase-3

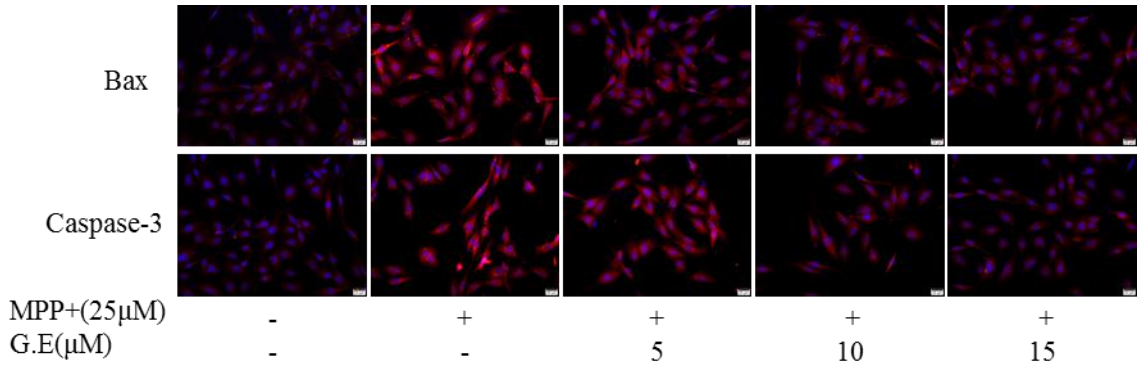


Figure 4 Micrographs of cells in each group visualized by immunofluorescence (400)

3.2 Network pharmacology prediction results

3.2.1 Potential targets of phenolic components of Gastrodia elata for the PD treatment

Previous experiments have proved that the phenolic extracts of Gastrodia elata contain 9 active ingredients in Table 3.A total of 125 targets were obtained by PharmMapper.The intersection of the active components and the PD targets yielded 43 potential targets of the treatment of PD, as shown in Figure 5.

3.2.2 PPI Network and Network Topology Analysis

The PPI network data constructed from the STRING database were imported into Cytoscape3.6.1 to obtain the PPI network maps, as shown in Figure 6.A.It consists of 41 nodes and 163 edges where nodes represent proteins and degree values represent the number of lines connected to 1 node were used to assess the importance of each node in the network.Larger nodes and redder colors indicate larger degree values. Each edge represents the interaction relationship between protein and protein. The thicker the line, the more red the color, the stronger the correlation, the thinner the line The weaker the correlation degree is.

All nodes in the PPI network are analyzed with three topological parameters: Degree, CC, Closeness Centrality, and BC, Betweenness Centrality.Take the median of 3 parameters as the card value, and the nodes with greater than 3 card values are selected as the core target (Figure 6.B).The result filter threshold is set to meet Degree Value 6, Node tightness 0.476, and Node Mediation 0.0144 The core targets are 16, as shown in Table 4 below.

Table 3 List of the active phenol ingredients of Gastrodia elata

ID	name	CAS
MOL1	Gastrodin	62499-27-8
MOL2	4-Hydroxybenzyl alcohol	623-05-2
MOL3	4-Hydroxybenzaldehyde	123-08-0
MOL4	Vanillyl alcohol	498-00-0
MOL5	Vanillin	121-33-5
MOL6	Parishin	62499-28-9
MOL7	Parishin B	174972-79-3
MOL8	Parishin C	174972-80-6
MOL9	Parishin E	952068-57-4

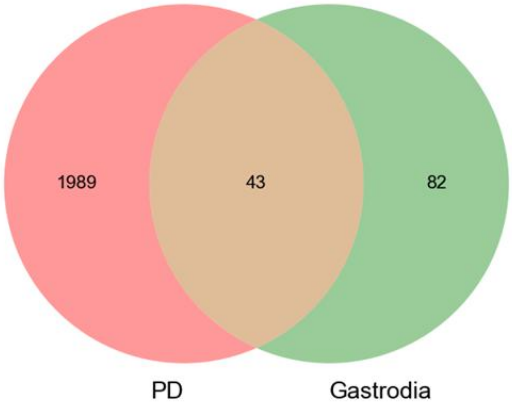


Figure 5 Wayne diagram of the target of Gastrodia elata phenolic components in the treatment of PD

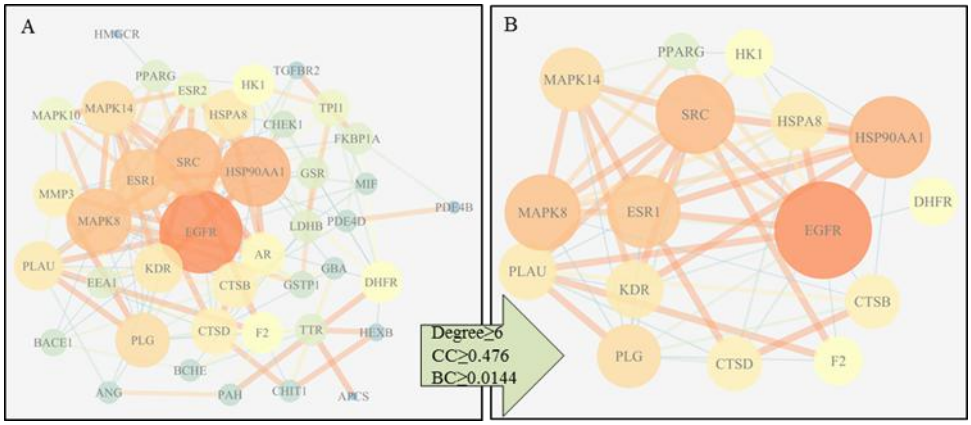


Figure 6 Topological screening process of the PPI network diagram

Table 4 Core target information of phenolic components for PD

Uniport ID	Gene name	Protein name	Betweenness Centrality	Closeness Centrality	Degree
P00533	EGFR	Epidermal growth factor receptor	0.191721	0.689655	24
P07900	HSP90AA1	Heat shock protein HSP 90-alpha	0.114298	0.606061	19
P12931	SRC	Proto-oncogene tyrosine-protein kinase Src	0.113682	0.625	18
P45983	MAPK8	Mitogen-activated protein kinase 8	0.056607	0.588235	17
P03372	ESR1	Estrogen receptor	0.031152	0.571429	16
P00747	PLG	Plasminogen	0.075991	0.571429	13
Q16539	MAPK14	Mitogen-activated protein kinase 14	0.017241	0.540541	13
P35968	KDR	Vascular endothelial growth factor receptor 2	0.019249	0.526316	11
P00749	PLAU	Urokinase-type plasminogen activator	0.018531	0.540541	11
P11142	HSPA8	Heat shock cognate 71 kDa protein	0.026039	0.512821	11
P07858	CTSB	Cathepsin B	0.034104	0.540541	10
P07339	CTSD	Cathepsin D	0.0438	0.526316	10
P00734	F2	Prothrombin	0.06427	0.526316	8
P00374	DHFR	Dihydrofolate reductase	0.068667	0.526316	8
P19367	HK1	Hexokinase-1	0.019337	0.5	8
P37231	PPARG	Peroxisome proliferator-activated receptor gamma	0.05061	0.47619	6

3.2.3 Biological function annotation

In order to reveal the potential mechanism of phenolic components on PD, 43 potential targets of Gastrodia elata for PD were analyzed by Matescape database. A total of 12 pathways for the treatment of PD were selected according to P <0.01, minimum count of 3 and enrichment factor> 1.5, as shown in Figure 7. The first three are "cancer signaling pathway", "estrogen signaling pathway" and "endocrine resistance".

GO functional enrichment analysis of 43 potential targets of Gastrodia elata for PD, including 15 GO Molecular Functions, 20 GO Biological Processes and 8 GO Cellular Components at P <0.01,3 and enrichment factor> 1.5, showing biological functions as shown in Figure 8.

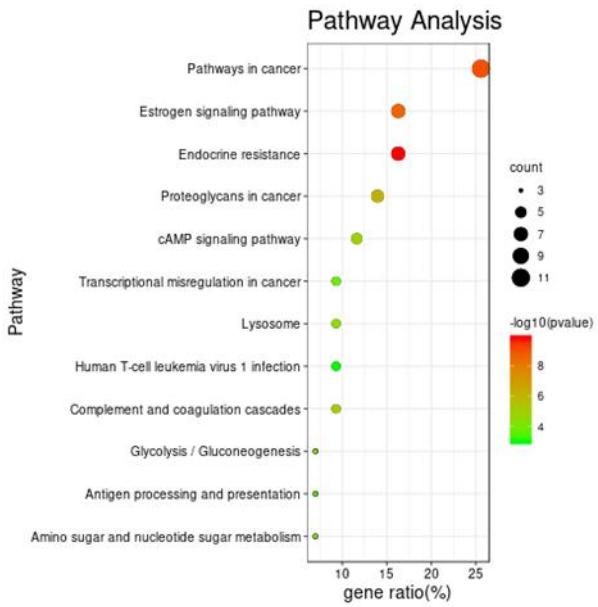


Figure 7 KEGG pathway enrichment analysis of Gastrodia elata phenolic components and PD intersection targets

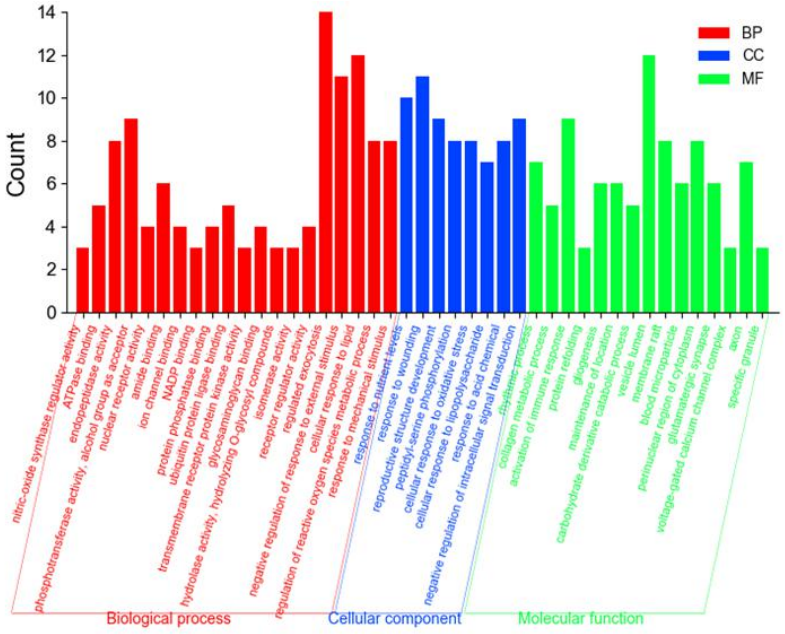


Figure 8 GO enrichment analysis of intersection targets of phenolic components and PD

3.2.4 The "Component-target-pathway" network construction

Cytoscape3.6.1 software was used to correlated 9 active components, 43 targets and 12 KEGG pathways to build a "component-target-pathway" network.The network results showed that 43 targets connected a total of 8 active components, of which 16 core targets connected 5 active components, mainly 4-hydroxybenzaldehyde, balisenside A, balisenside B, balisenside C and balisenside E.The network consists of 65 nodes with 219 edges.

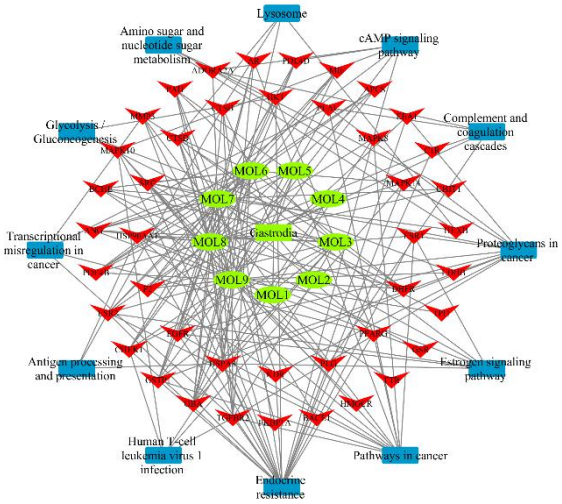


Figure 9 Component-target-pathway Network

Oval nodes represent Gastrodia elata and phenolic components, V-shaped nodes represent the intersection targets of active components and PD, and square nodes represent KEGG enriched pathways.

4. Discussion

The presence of a proapoptotic environment in the nigrostriatal region of PD patients is an important cause of PD, [20].Apoptosis is an important way for the body to maintain cell homeostasis by timely removal of aging and abnormal cells.Caspase-3 and Bax play a key role in the apoptosis process in dopaminergic neurons.Bax has proapoptotic activity, and one of the main mechanisms for inducing the mitochondrial apoptotic pathway is the elevated [21,22] at Bax levels.Caspase-3 is an important biomarker of neuronal apoptosis and [23], the executor of apoptosis.Caspase-3 It can inhibit the activity of poly (ADP-ribose) polymerase and increase the activity of endonuclease, leading to DNA fragmentation and cause apoptotic [24]. Previous studies have found that gastrodin increased Bcl-2 mRNA expression, reduced Bax mRNA expression, inhibited Caspase-3 activation and inhibited PARP shear [25] in MPP + -induced SH-SY5Y cell model; vanillin increased Bcl-2 expression, decreased Bax expression in Wistar rat model Cyt-C expression, downregulation of Caspase-3, Caspase-8 and Caspase-9 expressed [26]; vanicol reduced [27] of Bax / Bcl-2 in MPP + -induced MN9D cell model.In this experiment, the phenolic extracts of Gastrodia elata downregulated the expression of Bax, inhibited the MPP + -induced Caspase-3 activation, and improved cell survival.This suggest that phenolic components of Gastrodia elata have neuroprotective effects in in vitro PD models, possibly by inhibiting apoptosis-induced neuronal death.

When predicting active ingredients through network pharmacology, Integrative Pharmacology-based Research Platform of Traditional Chinese Medicine (TCMIP) or Swiss ADME[29,30] database are often used to screen the known chemical components in TCM using drug-forming rules.However, by using this method, most of the phenolic components of Gastrodia elata have been confirmed to have pharmacological activity The components were screened, such as gastrodin, balisenside, etc.; selected substances lacking known reports, non-major components, such as 4- [(4- (ethoxy methyl) benxy) methyl) phenol, palmitic acid, double (hydrophenyl) methane, affecting the reliability of the prediction results.Therefore, in

this study, the phenolic compounds verified by clinical studies or pharmacological experiments as the active components of Gastrodia elata were used for subsequent network pharmacological prediction.

5. Conclusion

(1) The results of cell experiments showed that the phenolic components of Gastrodia could improve the MPP + -induced loss of nerve cell viability and downregulate the expression of Bax and Caspase-3. It is speculated that the phenolic components of Gastrodia elata may have a neuroprotective effect by inhibiting apoptosis.It provides a basis for further study of the phenolic components of Gastrodia elata in the treatment of PD.

(2) Through literature search, the phenolic compounds verified by clinical studies or pharmacological experiments mainly include gastrodin, 4-hydroxybenzol, 4-hydroxybenzaldehyde, vanillol, vanillin, balisenside A, balisenside B, balisenside C and balisenside E.Gastrodia phenolic extracts contain these phenolic components.Using the prediction of network pharmacology, the potential core targets of these components for PD are mainly EGFR, HSP90AA1, SRC, MAPK8, and ESR1.

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Observation of the Effect of Low Molecular Weight Heparin Calcium Combined with Acetylcysteine in the Treatment of Idiopathic Interstitial Pneumonia

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Abstract: **Objective:** To analyze the effect of low molecular weight heparin calcium combined with acetylcysteine in the treatment of patients with idiopathic interstitial pneumonia. **Methods:** The subjects selected for this study were patients with idiopathic interstitial pneumonia admitted to our hospital from June 2020 to June 2021, with a total of 56 cases. They were divided into control group and experimental group by random number table method. The control group was treated with acetylcysteine (28 cases), and the experimental group was treated with low molecular weight heparin calcium on the basis of the control group (28 cases). The treatment effects of the two groups were compared. **Results:** There were significant differences in the effective rates of treatment between the two groups, and the experimental group was higher ($P<0.05$). There were significant differences in pulmonary function indexes between the two groups, among which the experimental group was higher ($P<0.05$). **Conclusion:** Low molecular weight heparin calcium + acetylcysteine is effective in the treatment of patients with idiopathic interstitial pneumonia, and this combined treatment method can be promoted.

Keywords: Low Molecular Weight Heparin Calcium; Acetylcysteine; Idiopathic Interstitial Pneumonia; Treatment Response Rate; Pulmonary Function Index

Introduction

Idiopathic interstitial pneumonia is a diffuse lung parenchymal disease of unknown cause. The symptoms of the disease include progressive shortness of breath and dry cough. The symptoms of the disease include progressive wheezing and dry cough. The disease is characterized by restrictive ventilation dysfunction and chronic progressive diffuse pulmonary fibrosis[1]. If the patient does not take timely and effective treatment, it can lead to progressive dyspnea, which in turn leads to respiratory failure, resulting in death of the patient. The disease is mainly treated with drugs in clinical, and anti-inflammatory drugs are often used. For this reason, the subjects selected for this study were patients with idiopathic interstitial pneumonia admitted to our hospital from June 2020 to June 2021, with a total of 56 cases. To analyze the effect of low molecular weight heparin calcium combined with acetylcysteine in the treatment of patients with idiopathic interstitial pneumonia. The results of the study are detailed below.

1. Materials and methods

1.1 Basic information

The subjects selected for this study were patients with idiopathic interstitial pneumonia admitted to our hospital from June 2020 to June 2021, with a total of 56 cases. They were divided into control group and experimental group by random number table method. The control group was treated with acetylcysteine (28 cases), and the experimental group was treated with low molecular weight heparin calcium on the basis of the control group (28 cases). The age of the experimental group was 26-67 years old, with an average of (47.54±3.54) years old. The age of the control group was 27-66 years old, with an average age of (47.43±2.54) years. The analysis of the basic data of the two groups of patients showed that there was no significant difference in the age of the patients ($P>0.05$).

1.2 Methods

1.2.1 Control group

This group was treated with acetylcysteine. The patients were treated with oxygen therapy, antiasthmatic, antispasmodic and phlegm-relieving treatment. The patients were additionally treated with acetylcysteine effervescent tablets (manufacturer: Atlantic Laboratories; approval number: H20070281; Specification: 600 mg × 4s), 1 tablet each time, 2 times a day, dissolved in warm water to take. The patient was treated for 3 months.

1.2.1 Experimental group

On the basis of the control group, this group was treated with low molecular weight heparin calcium, and the patients were given low molecular weight heparin calcium injection (production unit: Shenzhen Saibaoer Bio-Pharmaceutical Co., Ltd.; approval number: Guoyaozhunzi H20060191; specification: 0.5ml: 5000AXa units) subcutaneous injection treatment, 1ml once a day, 2 times a day, the patient was treated for 3 months.

1.3 Effect standard

(1) Evaluate the therapeutic effect according to the improvement of the patient's symptoms, markedly effective means that the symptoms disappear, effective means that the symptoms are improved ideally, and invalid means that the symptoms have not improved. Calculation method: (markedly effective + effective)/total number of cases × 100%.

(2) Observe the pulmonary function indexes of the patients after treatment, including FEV1, FVC, and FEV1/FVC.

1.4 Statistical methods

The data obtained in the study were processed by SPSS 23.0 software. ($\bar{x}$ ±s) is used to represent measurement data, using t test; (%) is used to represent count data, using (x^2) test. When the calculated P<0.05, it was suggested that there was a significant difference between the compared subjects.

2. Results

2.1 Comparison and analysis of the effective rate of treatment between the two groups

There were significant differences in the effective rates of treatment between the two groups, and the experimental group was higher (P<0.05). See Table 1 for details.

Table 1 Comparative analysis of the effective rate of treatment between the two groups [n, (%)]

Groups	Number of cases	Markedly effective	Effective	Invalid	Treatment effective rate (%)
Experimental group	28	19（67.86%）	6（21.43%）	3（10.71%）	89.29%（25/28）
Control group	28	12（42.86%）	5（17.86%）	11（39.29%）	60.71%（17/28）
χ^2	-	3.541	0.113	6.095	6.095
P	-	0.060	0.737	0.014	0.014

2.2 Comparative analysis of pulmonary function indexes between two groups

There were significant differences in pulmonary function indexes between the two groups, among which the experimental group was higher (P<0.05). See Table 2 for details.

Table 2 Comparative analysis of pulmonary function indicators between the two groups ($\bar{x} \pm s$)

Groups	Number of cases	FEV_1（L）	FVC（L）	FEV_1/FVC（%）
Experimental group	28	1.95±0.34	2.54±0.32	67.65±5.43
Control group	28	2.54±0.56	3.45±0.42	61.24±7.64
t	-	4.765	9.119	3.619
P	-	0.001	0.001	0.001

3. Discussion

Idiopathic interstitial pneumonia is a common clinical disease, which is caused by chronic inflammation caused by diffuse hyperplasia and fibrosis of pulmonary interstitial connective tissue. Relevant studies have pointed out that the increase of reactive oxygen species in patients can cause damage to the body's biofilm system and cause intracellular oxidative phosphorylation disorders, thereby promoting the progression of pulmonary interstitial fibrosis. Acetylcysteine is the precursor of glutathione, which can scavenge oxygen free radicals through reduced glutathione, increase the content of glutathione in the alveoli of patients, and obtain antioxidant effects. The significance of adhesion is improved, and the hypersecretion of airway mucus cells is reduced [2].

Low molecular weight heparin calcium is an anticoagulant and antithrombotic drug, which can play an anti-inflammatory and block effect on cell proliferation. Some studies have pointed out that low molecular weight heparin calcium can inhibit leukocyte adhesion and neutrophil chemotaxis to block the release of various inflammatory mediators, thereby playing an anti-inflammatory effect. The drug releases exogenous glucopolyamine and increases the anionic charge of the vascular wall to inhibit the proliferation of mesangial cells, thereby playing an anti-pulmonary fibrosis effect [3]. In the results of this study, there was a significant difference in the effective rate of treatment between the two groups, and the experimental group was higher (P<0.05). It is suggested that low molecular weight heparin calcium + acetylcysteine treatment can promote the therapeutic effect of patients. There were significant differences in pulmonary function indexes between the two groups, among which the experimental group was higher (P<0.05). It shows that low molecular weight heparin calcium + acetylcysteine treatment can improve the pulmonary function indexes of patients. It can be seen that the treatment of low molecular weight heparin calcium + acetylcysteine can play a synergistic effect, which can further improve the therapeutic effect of patients, thereby improving their related symptoms and promoting their recovery.

In conclusion, low molecular weight heparin calcium + acetylcysteine is effective in the treatment of patients with idiopathic interstitial pneumonia, and this combined treatment method can be promoted.

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Prediction of Overall Survival in Gastric Cancer by a Six-Gene Cox Proportional Hazards Model

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Abstract: This study aims to investigate prognostic genes that are correlated with overall survival in gastric cancer. A list of 43 critical genes is first selected from literature review and is narrowed down using marginal analysis, false discovery rate (FDR). This study used the 16 differential genes selected by FDR to create a cox proportional hazards regression model. Using a stepwise approach, the cox model is refined. From the 16 genes, 6 genes significantly correlated with overall survival are chosen and kept in the cox model. A principal component regression model was also constructed based on the principal component analysis results. The concordance of the principal component regression model is then compared to the concordance of the cox proportional hazards regression model. The final 6 identified genes are NRP1, STK11, MCM2, MARCKS, CTS6, C5. Of the 6 genes, MARCKS, NRP1, STK11, MCM2 are in line with previous research. CTS6 and C5, although studied in other cancers, are comparatively novel in the field of gastric cancer.

Keywords: Prognostic Genes; Gastric Cancer; Six-Gene Cox Proportional Hazards Model

1. Introduction

Gastric cancer (GC) is the fifth most common cancers worldwide, accounting for 35% of all cancer-related deaths (bray et al, Arnold et al). The American cancer society estimates that there are about 26,380 new cases of GC in United States during 2022. More than 90% of GC have been reported to be adenocarcinomas which develop from mucosa, the inner most layer of the stomach (Ilic and Ilic).

As a multifactorial disease, there are well-established non-omics risks factors that contribute to the progression of GC. One of the best-known risk factors is H. pylori infection, bacteria in the digestive tract that attacks the stomach lining. Tobacco, obesity, radiation and dietary factors, such as consuming a high in-take of salt-preserved food and low in-take of vegetables and fruits, are also potential risk factors (Ilic and Ilic). Overall, people are likely to be diagnosed with the cancer around 60-80 years of age (Julita et al). It uncommon for patients to be diagnosed with GC under the age of 45 (Ferlay et al, Howlader et al). In addition, the frequency of being diagnosed with GC in men is double the frequency of being diagnosed in women (Ilic and Ilic).

Over the past decade, research have been carried out to study critical genes and biomarkers to understand the disease's progression and survival rates. Historically, genes such as CLDN1, THBS2 and SPOCK 1 are shown to be upregulated in GC and to be associated with decreased survival (Marimuthu et al, Jung et al, Pan et al, Eftang et al). More recently, genes such as MARCKS, NRP1, COL10A1 and CD109 have been previously identified to be correlated with overall survival, and many prognostic gene models have been made accordingly (Sun et al, Quan et al, Wang et al, Huang et al, Dai et al). However, the identification and confirmation of prognostic genes are still incomplete due to the complexity of the genetic interactions. Some new biomarkers such as CST6 have been identified to be correlated with the survival in GC but was previously known to be a critical gene in breast cancers (Li et al). Recently, genes such as P3H2 and C5 genes, previously not reported, have been identified in Zhou et al study. This emphasizes the importance to continue investigating into genetic factors that could influence the overall survival.

To investigate the genetic factors behind cancer, researchers use public data bases to conduct bio-informational analysis. A large and new data set with high quality is essential to reduce errors in research and come to more applicable, accurate and reliable conclusions. The TCGA database is widely used in the study of cancer as it includes a bigger sample size, data with

higher quality and newer data overall. Using gene and clinical data from TCGA, this study identified four genes that are significantly correlated with overall survival in GC and established a cox proportional-hazards regression model.

2. Methods

2.1 Data acquisition

This study is based on the public database provided by The Cancer Genome Atlas (TCGA). Over a 12-year period, TCGA analyzed and collected cancer samples from over 11,000 patients, generating data points including clinical information, molecular analyte metadata and molecular characterization data such as gene expression values.

Gene expression data and the corresponding clinical data were downloaded from the TCGA STAD database. All cases containing unreported, unspecified and unknown data points are excluded from this study. This study considered data from both genders and vital statuses. In addition, this study took into consideration of all reported races in GC including white, Asian, black/African American and native Hawaiian/pacific islander. Because the sample size of Asian, Black/African American and Native/Hawaiian islander cancer patients small compared to the sample size of white patients, this study separated race in two main categories: white and non-white. In total, 348 cases are analyzed. Details regarding the sample size can be seen in table 1.1 below and the appendix A.

Table 1 TCGA STAD

TCGA STAD (n=348)	
Gender	
Male	216
Female	132
Race	
White	255
Asian	80
Black/African American	12
Native Hawaiian/Pacific Islander	1
Cancer Stages	
Stage I/IA/IB	41
Stage II/IIA/IIB	110
Stage III/IIIA/IIIB/IIIC	154
Stage IV	17
Unknown	26
Age	65.13 (SD=10.74)

A list of 43 critical genes regarding GC is selected from conducting a literature review of published paper on gene expression and overall survival of GC. 39 articles are selected from journals including the National Library of Medicine, Nature, American Association for Cancer Research, Science Direct, Karger, Wiley Online Library, Springer Link, Frontiers, Hindawi, PeerJ and MDPI. Across the articles, there are some overlaps, though not strong, between the genes identified. The list of 43 genes then was narrowed down to identify the genes that most significantly correlate with survival in GC.

Table 2 List of 43 Genes

Gene Name	Ensemble ID	Biotype			
1). CDH1	ENSG00000039068	Protein coding	22). CD109	ENSG00000156535	Protein coding
2). NRAS	ENSG00000213281	Protein coding	23). PDGFB	ENSG00000100311	Protein coding
3). PARP1	ENSG00000143799	Protein coding	24). SPOCK1	ENSG00000152377	Protein coding
4). STK11	ENSG00000118046	Protein coding	25). CEP55	ENSG00000138180	Protein coding
5). CDC20	ENSG00000117399	Protein coding	26). CCNB1	ENSG00000134057	Protein coding
6). MDM2	ENSG00000135679	Protein coding	27). FGFR4	ENSG00000160867	Protein coding
7). UHRF1	ENSG00000276043	Protein coding	28). SFRP4	ENSG00000141510	Protein coding
8). BRCA1	ENSG00000012048	Protein coding	29). CLDN1	ENSG00000163347	Protein coding
9). CD38	ENSG00000004468	Protein coding	30). ANLN	ENSG00000011426	Protein coding
10). ITGB1	ENSG00000150093	Protein coding	31). COL10A1	ENSG00000123500	Protein coding
11). RARB	ENSG00000077092	Protein coding	32). SMAD4	ENSG00000141646	Protein coding
12). TP53	ENSG00000141510	Protein coding	33). P3H2	ENSG00000090530	Protein coding
13). SULF1	ENSG00000137573	Protein coding	34). CNTN1	ENSG00000018236	Protein coding
14). FEN1	ENSG00000168496	Protein coding	35). THBS1	ENSG00000137801	Protein coding
15). SPP1	ENSG00000118785	Protein coding	36). ACTA2	ENSG00000107796	Protein coding
16). THBS2	ENSG00000186340	Protein coding	37). P4HA3	ENSG00000149380	Protein coding
17). CXCL1	ENSG00000163739	Protein coding	38). GIPR	ENSG00000010310	Protein coding
18). TWIST1	ENSG00000122691	Protein coding	39). MSH6	ENSG00000116062	Protein coding
19). CST6	ENSG00000175315	Protein coding	40). C5	ENSG00000106804	Protein coding
20). MARCKS	ENSG00000277443	Protein coding	41). SIRT1	ENSG00000096717	Protein coding
21). PLAUR	ENSG00000011422	Protein coding	42). MCM2	ENSG00000073111	Protein coding
			43). NRP1	ENSG00000099250	Protein coding

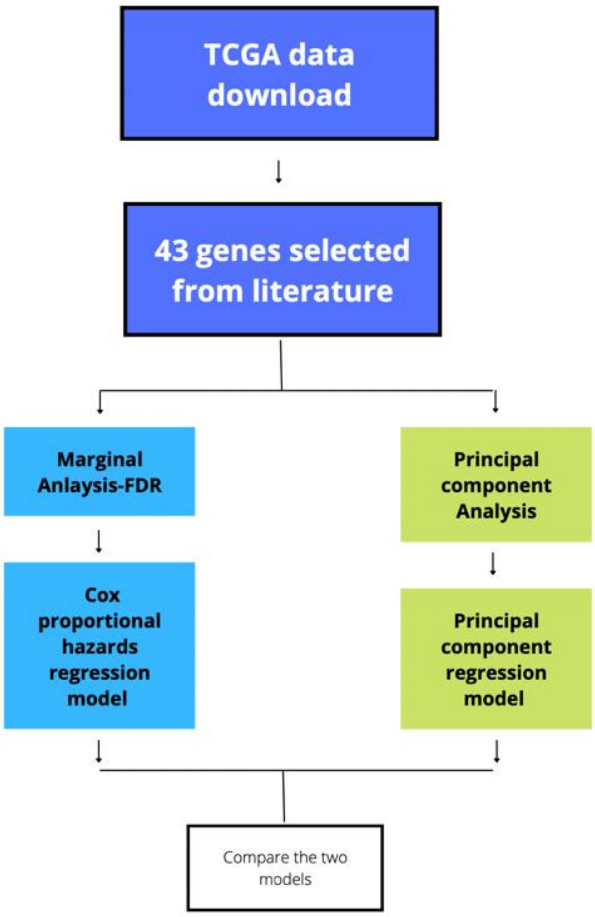
2.2 Statistical Testing

All statistical testing was conducted using the R software. The overall survival distribution was shown through plotting the relationship between the percent surviving and the survival time in days. To create the cox proportional hazards regression model, I implemented marginal analysis of false discovery rate (FDR) to narrow down the list of 43 genes by identifying the genes that are truly significant. The FDR uses adjusted p-value to eliminate false positive results and is defined as FDR=E(Q), where Q=V/R if R> 0. If R= 0, Q=0. This study set FDR adjusted values at the threshold of 0.05 and looked at the genes whose adjusted p-value is lower or equal to 0.05.

To then investigate into the correlation between non-omics risk factors as well as the significant genes identified, this study constructed multivariate cox proportional hazard regression model to determine the hazard ratios and the 95% confidence intervals for the association between overall survival and genetic and non-omics risk factors. For all variables, $P<0.05$ is established as the cut off value. The model has the overall function of $h(t)=h0(t)\times\exp(b1x1+b2x2+...+bpx)$. To improve the accuracy of the model, this study implemented the stepwise approach to choose which variables to keep using the step function in R.

To compare the accuracy of the cox proportional hazards regression model based on the genes identified by FDR to the principal component regression model, this study then conducted principal component analysis on the original list of 43 genes using the princomp function in R. The number of principal components selected for regression was based on the percent of the original data they contain. Majority of the original data must be present in the number of principal components selected for the regression to be accurate. A principal component regression model was then created with principal components selected as the independent variables; the dependent variable of survival time and status remained the same as the original cox proportional hazards regression model. Lastly, the concordance of the two models is compared to determine which model more accurately predicts the influence of genetic and non-omics risk factors on overall survival. The overall procedure is summarized in the flow chart below.

Figure. 1 Flowchart of Overall Procedure

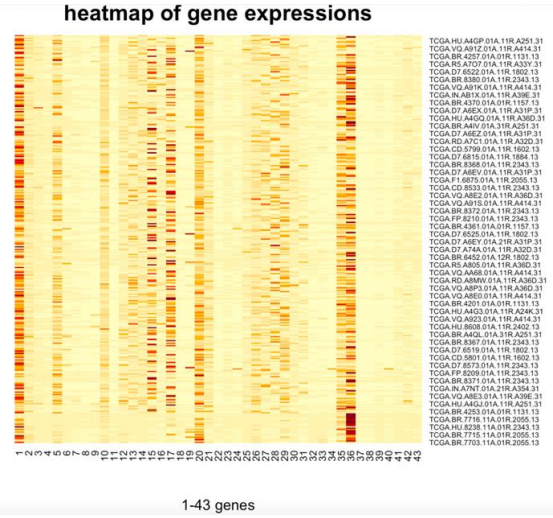


3. Results

3.1 EDA

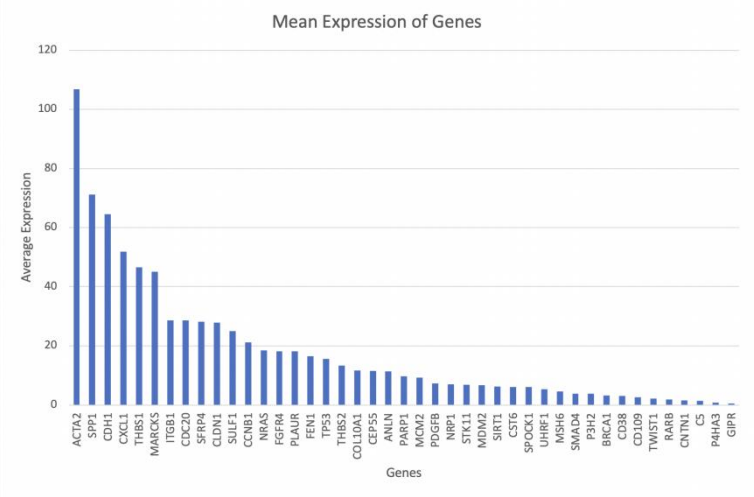
The heatmap shown below shows the overall gene expression for the list of 43 genes across 348 cases. The numbers on the x axis correspond to the 43 genes in the order of table 2.1.2. The Y-axis shows 348 cases in which each gene's expression data is collected.

Figure. 2 Heatmap of Gene Expressions



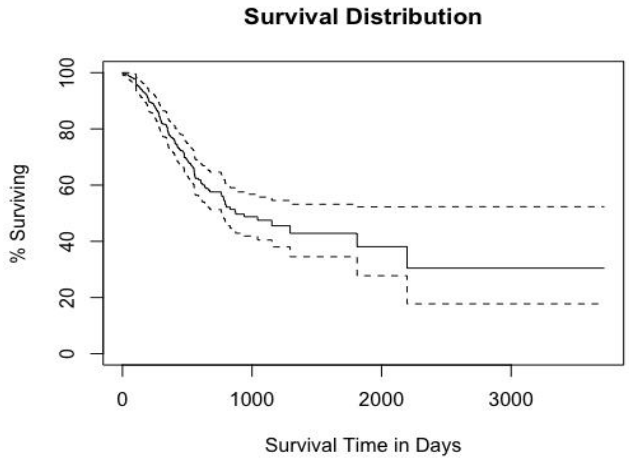
In the bar graph summarizing the average expression of each gene, there are no gene that is not expressed at all. The gene expression varies greatly, ranging from 106.8 to 0.5.

Figure. 3 Mean Expression of Genes



The survival distribution across the sample clearly shows that as time progresses the percent of people surviving decreases quite significantly. By the 3000's day, the percent of surviving people is less than 40. Overall, the survival distribution suggests that the mortality rate of GC is relatively high. Based on this assumption, this study then built models to determine the factors that influence survival.

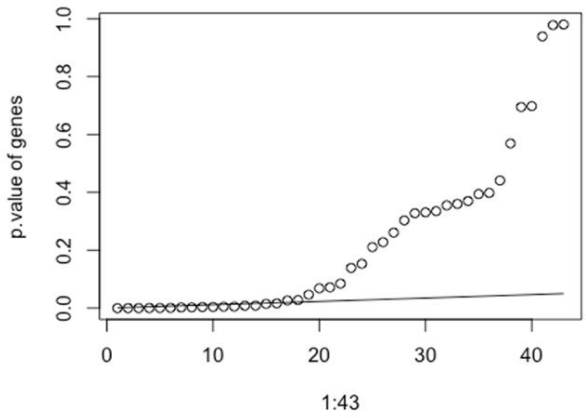
Figure. 4 Survival Distribution



3.2 Differential Genes

FDR results conducted on the 43 genes indicate that only 16 genes are truly significant according to their adjusted p-value at the cut off $p<0.05$. Three non-omics factors, age, gender and race, are also included the FDR analysis to be considered as covariates alongside with critical genes. In the plot of adjusted p-value versus the 1-43 gene shown below, the datapoints under the linear line, which indicates the cut off value, are interpreted to be truly significant. The 16 significant genes identified in the order of their p-value rank are CD109, NRP1, SPOCK1, P4HA3, STK11, MARCKS, UHRF1, CTS6, CNTN1, MCM2, THBS2, FEN1, P3H2, C5, ACTA2 and SDRP4 (see appendix B).

Figure. 4 P.Value of Genes



3.3 Cox Proportional Hazards Regression Models

In the original cox model that includes all 16 genes identified by FDR as well as non-omics risk factors including gender, race and age, the result of the model indicates that not all variables are significant. Only gene NRP1, STK11, and P3H2 are significant as they have p values less than 0.05. NRP1 and P3H2 are shown to be risky candidate genes as there is a positive correlation between their increasing expression and increasing risk of death. NRP1 has the hazard ratio of 1.059 which indicates that as its gene expression increases, the risk of death or estimated hazard increases 1.059 times or 5.9%. P3H2 has the hazard ratio of 1.048 which indicates that as its gene expression increases, the estimated hazard increases by 4.8%. On the other hand, STK11 is shown to be a protective candidate gene as there is a correlation between its increasing expression and decreasing risk of death. STK11 has the hazard ratio of 0.90 which suggests that as its gene expression increases, the risk of death decreases by 0.10 times or 10%.

The only non-omics risk factor that is shown to be significant age. In fact, age has a p value that is 0.001 which makes it the most significant variable in this model. In line with previous research and understanding of cancer, the hazard ratio of age is 1.043 which means that as age increases by one, the risk of estimated hazard increases by 4.3%.

Table 3 Cox Model for 16 Genes

	coef	exp(coef)	se(coef)	z	p
CD109	0.005	1.005	0.024	0.227	0.820
NRP1	0.053	1.054	0.025	2.095	0.036*
SPOCK1	0.015	1.015	0.018	0.837	0.402
P4HA3	0.110	1.117	0.071	1.557	0.120
STK11	-0.095	0.909	0.047	-2.029	0.043
MARCKS	0.009	1.009	0.006	1.443	0.149*
CST6	0.004	1.004	0.003	1.341	0.180
UHRF1	-0.060	0.942	0.050	-1.209	0.227
MCM2	-0.038	0.963	0.023	-1.635	0.102
THBS1	-0.002	0.998	0.003	-0.620	0.535
FEN1	0.017	1.017	0.019	0.882	0.378
CNTN1	0.063	1.065	0.045	1.406	0.160
P3H2	0.035	1.036	0.023	1.519	0.129
C5	0.153	1.166	0.056	2.759	0.006
ACTA2	-0.001	0.999	0.001	-0.885	0.376
SFRP4	0.001	1.001	0.003	0.492	0.623
Age	0.043	1.044	0.011	3.919	0.000 ***
Gender MALE	0.384	1.468	0.217	1.772	0.076
Race WHITE	-0.097	0.908	0.240	-0.404	0.686

*Note: significance indicated by * P <0.05, ** P <0.01, *** P <0.001*

After implementing the stepwise approach using the step function in R to create a more accurate model by selecting more significant variables, the 16 genes in the original model were narrowed down to 6 including NRP1, STK11, MCM2, MARCKS, CST6 and C5. In this updated model, non-omics risk factors are narrowed down to only age. In terms of significance, age remains to be the most significant with a p value less than 0.001. Genes such as NRP1, STK11, MCM2 and C5 are the second most significant with p values less than 0.01. MARCKS and CST6 have p values less than 0.05. All 6 genes in this model are significant in predicting the overall survival in GC. Consistent with the original version of the model, NRP1 is a risky candidate gene. MARCKS, CST6 and C5 are all risky candidate genes. As the level of their gene expressions increase, the risk of death increases.

The hazard ratio for NRP1 is 1.064 which means that as the gene expression increases, the estimated hazard increases by 6.4%. MARCKS has a hazard ratio of 1.012; as its expression increases, the risk of death increases by 1.2%. The hazard ratio of CST6 is 1.004, suggesting that as its gene expression increases, the risk of death increases by 0.4%. Finally, C5 is shown to have a hazard ratio of 1.148, which means that as its gene expression increases, the risk of death increases by 14.8%. From the hazard ratios of the risky candidate genes, we can see that the increasing gene expression of C5 increases the risk of death by the highest percentage, 14.8%, when compared to the other genes.

On the other hand, STK11 and MCM2 are protective candidate genes as its increasing gene expression is correlated with a decrease in estimated hazard. The hazard ratio for STK11 is 0.890 which demonstrates that as its gene expressing increases, the estimated hazard decreases by 11% or 0.890 times. Finally, the hazard ratio for MCM2 is 0.952 which suggests that as its gene expression increases, the estimated hazard decreases by 4.8%. From the hazard ratios of the protective candidate genes, we can see that the increasing gene expression of STK11 decreases the risk of death by the highest percentage, 11%, when compared to MCM2. The detailed results of this 6-gene prognostic model are shown in the table below.

Table 4 Cox Model For 6 Genes

	coef	exp(coef)	se(coef)	z	p
NRP1	0.062	1.064	0.020	3.028	0.002 **
STK11	-0.116	0.890	0.045	-2.580	0.010 **
MCM2	-0.049	0.952	0.017	-2.898	0.004 **
MARCKS	0.012	1.012	0.006	2.080	0.038 *
CST6	0.004	1.004	0.002	2.120	0.034 *
C5	0.138	1.148	0.053	2.620	0.009 **
Age	0.038	1.038	0.010	3.609	0.000 ***

*Note: significance indicated by * P <0.05, ** P <0.01,*** P <0.001*

3.4 Principal Component Regression

In the principal component analysis conducted on the original list of 43 genes, the screeplot of the principal components versus variance shows that only the first three principal components need to be taken into consideration (see appendix C). However, when viewing the summary of the importance of components using the princomp function, the first three principal components only account for 36.8% of all the gene data which does not cover enough of my data to produce accurate results in the principal component regression model. Therefore, this study chose to take the first 15 principal components into consideration when creating the regression model as the first 15 principal components covers the majority, 75%, of my data.

The results of the regression model demonstrating the correlation between first 15 principal components, age, and survival show that not all components are significant. Principal component one is the most significant with a P values less than 0.001. Principal component four is the second most significant with a p values less than 0.01. Principal component two and five are significant with a p values less than 0.05. After implementing the stepwise approach to select the most significant variables to include, 15 principal components are narrowed down principal component one, two, four, five, nine and fourteen. Age as a variable also remains significant. In this model, principal component one and age remain to be the most significant with p values less than 0.001. The rest of the principal components are significant with p values less than 0.05. The details results are shown in the table below.

Table 5 Principal Regression Cox Model

	coef	exp(coef)	se(coef)	z	p
z1	-0.125	0.882	0.034	-3.686	0.000 ***
z2	-0.080	0.923	0.037	-2.176	0.030 *
z4	0.120	1.127	0.050	2.413	0.016 *
z5	-0.187	0.829	0.082	-2.280	0.023 *
z9	-0.206	0.814	0.088	-2.328	0.020 *
z14	0.264	1.302	0.112	2.352	0.019 *
Age	0.038	1.039	0.011	3.632	0.000 ***

*Note: significance indicated by * P <0.05, ** P <0.01, *** P <0.001*

Overall, the cox proportional hazards regression model has a concordance of 0.0692 and a standard error of 0.024. On the other hand, the principal component regression model has a concordance of 0.663 and a standard error of 0.027. The cox proportional hazards regression has a concordance closer to 0.07 and a smaller standard error compared to the principal component regression model. Therefore, this study will focus on the 6-gene cox proportional hazards regression model to predict overall survival instead of the principal component regression's model.

5. Discussion

Overall, the significant correlations between MCM2, MARKS and NRP1 and overall survival in GC identified in this study is in line with previous research. The overexpression of MARCKS and NRP1 is shown to be correlated with poor prognosis in GC (sun et al, Zhang et al, Quan et al, Dai et al, Huang et al). MCM2 have been consistently identified as an important gene across all cancer types (Yuan et al). C5 and CTS6 identified in this study, however, have not been identified repeatedly and researched on extensively in the field of GC before (Zhou et al, Wang et al).

MARCKS was identified to be a potential prognostic biomarker and a therapeutic target for GC patients. As a protein that is membrane-associated, MARCKS plays an important part in different cellular functions including cell motility, cytoskeletal control, motility and inflammatory pathways and can further increase metastasis, leading to high risk of death (Quan et al). Furthermore, MARCKS exacerbates GC and progression depended on the EMT pathway whose activation triggers metastasis (Quan et al). NRP1 is involved in tumorigenesis, development, invasion and metastasis of GC cells (Sun et al). In addition, research demonstrates that the overexpression of NRP1 is significantly correlated malignant phenotype of GC (Wang et al). According to Zhang et al study, the novel tumor-homing peptide iRGD can improve 5-FU (standard chemotherapy drug from metastatic GC) effect on GC through NRP1. Thus, NRP1 can be also potential therapeutic target. The findings of this study are consistent with these studies and research.

STK11 is a tumor suppressor gene. Thus, its high expression decreases the risk of death and is protective against metastasis, which is supported by the results of this study (Liang et al). However, it is important to note that STK11 is complicated by its potential indirect correlation with the risk of GC. The susceptibility to GC is influenced by germline genetic syndromes including juvenile polyposis syndrome, li-Fraumeni syndrome, Lynch syndrome, familial adenomatous polyposis and Peutz-Jeghers syndrome (Slavin et al). It is shown that a disrupted STK11 gene causes Peutz-Jeghers syndrome (Slavin et al). According to the NCCN clinical practice guidelines in oncology, Peutz-Jeghers syndrome increases the risk of GC up to 29%. Furthermore, STK11 disruption is also shown to be related to other types of cancers such as breast and pancreatitis cancer (NCCN). Thus, disrupted STK11 gene becomes risk as it is indirectly correlated with increasing risk of GC..

MCM2, minichromosomal maintenance 2, is a part of the monochromical group of proteins which focuses regulating DNA replication and cell cycle (Tsaniras et al, Fraggos et al, Li and Xu). Extensive amount of previous research show that MCM2 is important in cancer cell replication and the development of cancer across different types of cancers (Yuan et al). Furthermore, MCM2's gene expression is deeply associated with immune-related molecule expression and immune cell infiltration in various cancers, suggesting that MCM2 is a potential biomarker for immune therapy (Yuan et al). According to the findings of this study, MCM2 is identified to be significantly correlated with the overall survival in GC. This is consistent with previous research that demonstrates MCM2 as important gene across all types of cancer.

Although having been identified as associated with GC before, CTS6 and C5 identified in this study has not been extensive researched on in the field of GC (Zhou et al, Wang et al). CST6 was previously identified to be a critical gene for breast cancer. According to emerging research, high gene expression of CST6 is associated with poor prognosis in Triple-Negative breast cancer and is also correlated with lymph-node metastasis (Li et al). As a subtype of cystatin, CTS6 is shown to be significantly more up regulated in the TNBC tissues compared to healthy breast tissues (Li et al). This also appears to be the case for GC. According to the results of this study, as the gene expression of CST6 increases, the risk of death also increases which suggests that CST6 is a risky candidate gene promoting GC. Future research needs to be conducted to confirm the correlation between CTS6 and overall survival. In addition, the biological processes behind CTS6 that are associated with GC need to be further investigated.

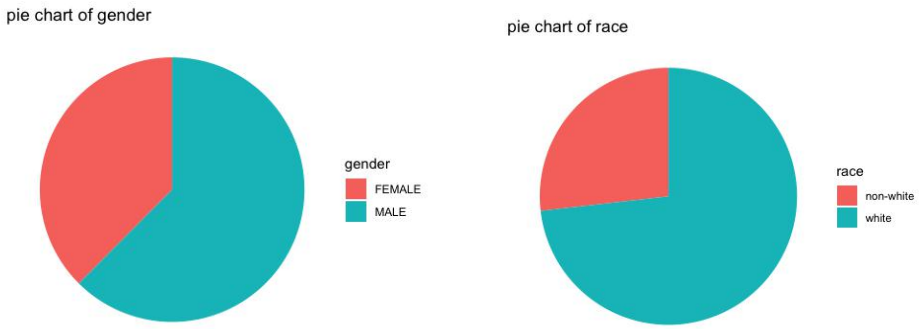
C5 gene have not been extensively identified in GC before, but however is shown to be associated with the tumor genesis and cancer progression in other types of malignant tumors (Zhou et al). C5 is shown to play a critical part in the coding complement system's components (DeMartino et al). The gene is also shown to be related to pathways such as immune response, GPCR signaling pathway and lectin-induced complement pathway (Zhou et al). It was suggested that the cell C5a release from C5 contributes to cancer progression due to its new mechanism of self-activation of C5aR-expressing cancer cells enhancing invasion and microenvironment favorable for the progression of cancer (Nitta et al). Because there are not enough reports on the role of C5 in GC, future research is needed to investigate and confirm its relationship with the overall survival and development of GC.

To evaluate the findings of this study, it is important to acknowledge that although TCGA is a relatively large database with new and accurate data, it is not representative of all GC cases across the world. For example, TCGA data tends to have a significant amount of data on white patients but less information on patients of other races. In addition, this study did not consider many of the non-omics risk factors that previous studies have shown to be associated with over survival such as dietary factors, radiation, and H. pylori infection because TCGA's information on other risk factors are limited. Therefore, the 6-gene prognostic model could have been more accurate if all potential risk factors are included. However, it is very difficult to have a complete set of data on every single factor that potentially influences a type of cancer. Therefore, despite the dataset does not include all non-omics risk factors, the results of the model are still important due to the new and big sample of genetic information provided in the TCGA database. The findings build onto our understanding of critical genes in GC.

Conclusion

In summary, the 6-gene cox proportional hazards regression model was created using the data from TCGA, compared to the principal component regression model and was shown to be more accurate. Four genes (MARCKS, NRP1, STK11, MCM2) in the 6 gene model supports previous research on their correlation with survival overall survival in GC. Two comparatively novel gene (C5, CTS6) in the field of GC have also been identified. Further experimental studies should continue to investigate the relationship between novel genes and their association with GC and investigate the implication significant gene on potential treatments such as chemotherapy and immune therapy.

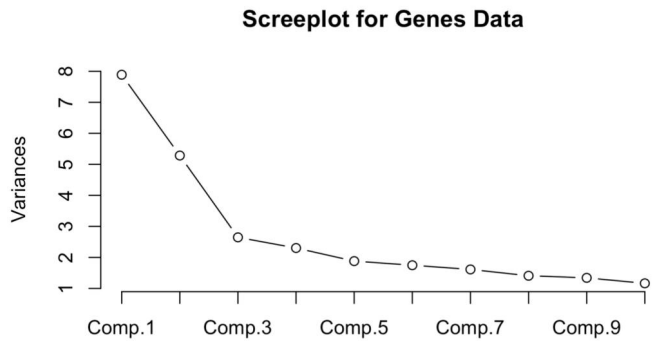
Appendix A



Appendix B

	Gender	Age	Race	p.value of gene	p_adjust	rank_pvalue	fdr	differential
CD109	0.112	0.713	0.00445	6.36E-06	0	1	0.0011627906976744 2	TRUE
NRP1	0.168	0.854	0.00322	6.46E-06	0	2	0.0023255813953488 4	TRUE
SPOCK1	0.0643	0.622	0.00137	0.000218	0.003	3	0.0034883720930232 6	TRUE
P4HA3	0.0762	0.89	0.0047	0.000447	0.005	4	0.0046511627906976 7	TRUE
STK11	0.0979	0.57	0.00275	6E-04	0.005	5	0.0058139534883720 9	TRUE
MARCKS	0.133	0.746	0.00584	0.000882	0.006	6	0.0069767441860465 1	TRUE
UHRF1	0.175	0.762	0.00266	0.00241	0.013	7	0.0081395348837209 3	TRUE
CST6	0.162	0.698	0.00617	0.0025	0.013	8	0.0093023255813953 5	TRUE
CNTN1	0.0837	0.597	0.00392	0.00383	0.018	9	0.010465116279069 8	TRUE
MCM2	0.0941	0.763	0.004	0.00417	0.018	10	0.011627906976744 2	TRUE
THBS1	0.126	0.642	0.00439	0.00495	0.019	11	0.012790697674418 6	TRUE
FEN1	0.185	0.962	0.00289	0.00532	0.019	12	0.013953488372093	TRUE
P3H2	0.0663	0.813	0.00537	0.00836	0.026	13	0.015116279069767 4	TRUE
C5	0.158	0.677	0.00485	0.00862	0.026	14	0.016279069767441 9	TRUE
ACTA2	0.0672	0.602	0.00243	0.0145	0.042	15	0.017441860465116 3	TRUE
SFRP4	0.121	0.924	0.00313	0.0163	0.044	16	0.018604651162790 7	TRUE

Appendix C



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The Impact of Parental Young Onset Dementia on Children and Young People's Educational Careers

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Abstract: The aim of Sikes and Hall's(2018) study was to discover the impact of having a parent with young onset dementia (YOD) on children or young people's educational careers by interview 24 subjects among the ages from 6 to 31 years old (Sikes & Hall, 2018). In this paper, the theoretical perspectives will be identified from the perspective of ontology and epistemology. Methodology and methods will also be discussed. Furthermore, evaluating consistency of the relationship between theoretical perspective and the chosen methodology with the methods conducted is also focused on. Finally, the discussion of ethical issues in the study is also an important part of this paper, not only the ones claimed by the author but also the implicit ones should be considerate.

Keywords: Young People; Influence; Dementia; Research Methods

1. Theoretical perspective

Sikes and Hall (2018) put their effort on study a phenomenon related to social construction from different individuals' unique perspective of world, thus, the paradigm in this research is interpretivism (Collins, 2010). To illustrate the theoretical perspective of a research, it is necessary to identify the ontological and epistemological assumptions applied in it. Ontological stance identifies the nature of reality (Della et al., 2008), to this extent, the research of studying the impact of YOD to children or young people's educational careers is conducted based on different human interpretation of the reality. Sikes and Hall (2018) discovered how the disease influenced children and young people's educational careers through the participants' unique experiences, and drew conclusion on the basis of these experiences. Epistemology focuses on how the knowledge was obtained. The purpose of the study is to privilege the voices which ware historically neglected from children and young people who lived with parental dementia. To cohere with the aim and ontological assumption of this study, the authors applied interviews on children and young people who had a parent that suffered from the disease and under this context, the epistemological assumption was also consistent with the purpose of the study.[1]

From the discussion above, this research consists a set of interpretive material practices such as interviews to make the world visible. Thus, this research satisfied the definition of qualitative research. In qualitative research, the researchers usually study things in their natural context which means they are likely to go into the context and to interact with different participants to examine better understanding of a subject and to collect different angles of a phenomenon (Denzin & Lincoln, 2008). As a distinct form of qualitative research, narrative focused on lives of individuals and write narratives of individual experiences (Connelly & Clandinin, 1990). As a narrative research, the data collection and analysis can be very difficult for researchers since the actual things they are collecting are the self-organised information from the participants (Miller, & Salkind, 2002). [2]In this study, as the interviewees had similar background they may share some common points in their stories which may make the process of collection and analysis easier. Moreover, the researched was designed to use purposeful sampling, 24 British in certain ages related to educational career and conducted to unstructured interviews to "situates personal experiences of dementia within the broader social context (Shakespeare et al., 2017)." The small and purposeful sample is required in this study because the in-depth and unstructured interview are beneficial to explore the personal construction of the individual world. What's more, qualitative research is associated to inductive reasoning, inductive reasoning works "bottom-up", begin with specific observation of the world developed to abstract generalizations

and ideas (Neuman, 2003).[3] In this research, the authors studied the impact form a specific group of subjects and by collecting and analyzing data, moved to suggestions that could improve the current situation for the whole group of children and young people who had a parent with YOD. However, there is no evidence of systematic solutions are provided by the authors, and after the unstructured interviews, no exact patterns or theories of how parental YOD impact on children and young people's educational career emerged. [4]

2. The effectiveness of the methodology and methods

According to Coe, researchers need to choose the methodology and methods that answer the research questions most appropriately to make the research be practical and the methodology and methods are required to consistent with the theoretical perspectives of the research. The study of Sikes and Hall (2018) was based on an Alzheimer's society-funded investigation that concerned about similar questions with them and decided to focus on educational careers. The authors put efforts on examine the sample, how they chose the participants and what they required from them. For qualitative research, sampling is not just a sole decision, but a serious of reduplicative decisions through the whole research (Emmel, 2013). It is vital to determine sample sizes and sampling practices to conduct a good research and to budget resources (Guetterman, 2015).[5] In this study, the sample size was small which made the data collection and analysis more accurate and in-depth. The authors advertised the project on specific website to YOD and recruit voluntarily participants to take part in it. Bernard (2002) indicated that availability and willingness to participate, the skills to communicate experience are very important factors in purposeful sampling. Thus, the method the authors took to recruit subjects is an appropriate one and the snowballing to select the participants reduced the potential bias by the researchers.[6] Although the method applied to choose sample was rational, it still had limitations: narrative inquires required good communication skills but the participants under 10 were likely to fail on that.

Interviewing is a method that frequently used to conduct qualitative research to collect participants' ideas and experiences, and based on the degree of structuring, this research used unstructured interview. Unstructured interviews do not require predetermined questions or answers, they are more informal, in-depth like conversations.[7] Punch (1998) noted that unstructured interviews provide a way to understand the complex human experience without limiting the field of inquiry. This research aimed to figure out the impact of parental YOD, but based on the ontological assumption, the realities are various from individuals. The researcher need to acknowledge the whole background and the progress of every participant when they were affected by their parent who suffered from YOD. The unstructured interview may help the author to develop a better understanding of the social reality from the interviewee's perspectives (Zhang & Wildemuth, 2009). From the interviews, the experiences of the participants and the impact of parental YOD to them individually are primary and direct which is useful when analyzing data.[8] Thus, the use of unstructured interview is effective. However, the authors not focused the general impact of parental YOD but they got a more specific purpose which was to study the educational career impact of spending time with the parent with the disease.[9] The unstructured interviews seemed too flexible to the aim. As the authors had a target aspect, the questions of the interviews should be more related to educational career. Semi-structured interviews are also open whilst concerned on one or several themes. Thus, changing the unstructured interviews to semi-structured interviews may make the research more effective less overwhelmed.[10]

To study the impact of the parental YOD to educational career was to collect and analyze the experience and interpretation of individuals who shared similar situation (Overcash, 2003), and in this case, narrative research is an appropriate choice for this research. YOD is a progressive disease and the impact of parental YOD is various from time to time, that's why the research sustained for 18 months. Since narrative inquires are the stories and experiences people tell over time (Casey, 1995), it is suitable for this research to continue. [11]

Maxwell (2013) noted that different types of consideration such as description, interpretation, theory, generalization, researcher bias and reactivity could cause different threats to the validity of a research. To consider the validity, the first thing is to discuss the authenticity of the data. The interviews in this research were recorded and transcribed in full, thus, the threats are reduced. However, the authors did not mention the exact questions they asked when interviewing, which may lead to a decrease of credibility of the research. Because the topic of this research is vague and subjective, researchers potential

bias or priori thoughts may appeared in the interviews.[12] Overall, the choice of methodology and the research design are appropriate for the study. For qualitative research, reliability is closely connected with consistency (Carcary, 2015). The ontological and epistemological consistency is discussed above and to verify the accuracy of data, the researchers need constant comparison among the data. This research continued for 18 months and all the participants are interviewed more than once in different period, thus the comparison can be granted so as the consistency.[13] So this research possessed the ability of reliability. Most qualitative research studies a specific phenomenon in a certain population but that does not mean the criteria of generalizability is not important. Generalizability is often assessed by the extent to which the finding of this research can be generalized to another under similar circumstance (Kvale & Brinkmann,2009).[14]Since that the relationship between theoretical perspective and methodology and methods chosen of this research is effective and the findings are valid, the results could be generalized but limited in the study that related to the similar disease like dementia. [15]

3. Ethical issues related to the research

Gray (2014) noted that with increasing personal involvement, the relationship and interaction between researchers and participants could be ethically and morally challenged. [16-18]In Sikes and Hall's (2018) research, they clearly demonstrated that the "Ethical approval was granted by our university" which means most of ethical aspects were covered and approved, and it is clear that the authors got all the consent of participants include the children under ten. And more specifically, they make the interview about sensitive topics anonymous to further protect the participants. However, the authors considered the children under 10 years old were deemed to have the capacity to consent after spoken to them. This behaviour may make the consent being involuntary. [19-21]Moreover, the confidentiality was not presented in the research. It is important to protect the data of participants, and the protection of data of children and young people was even more important in a research process (Greig et al., 2007).[22] But there is no clear explanation in this research of how they deal with the data or the "stories" of the participants after the study. What's more, participants are also part of the whole research, hence, they should have rights to know different stages and changes of the research including the publication and dissemination (Munhall, 1988).[23] This research is published on *British Educational Research Journal* but the authors did not mention about getting participants' permission to publish the interviews and the research based on. In additional, the ethical consideration of gender may potentially exist since that the authors did not clearly note that how many girls and boys were selected to conduct the interview, this may cause a potential gender bias to the results of the research.

4. Conclusion

This research focused on the question related to social constructions and the ontological and epistemological assumptions consistent with the paradigm interpretivism. And the methodology and methods adopted revealed it is a qualitative research. Sike and Hall (2018) aims to discover the impact of parental YOD on children and young people educational careers by conducting unstructured interview of individuals who experienced it. The methodology and methods contributed to the process and results of the whole research. The purposeful sample provided an in-depth interpretation of the experience and the unstructured interview gave a whole picture of the impact from different individuals' perspective. By narrative inquiry, the authors collected valid data and better understandings to the participants' situation. There are small limitations in the research design such as lack of exact interviewing questions and ethica issues about confidentiality. The research of Sike and Hall's (2018) is valid and reliable one.

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Universe Scientific Publishing

Current Status and Prospects Towards the Road of Universal Health Coverage (UHC) in China: a Systematic Review

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Abstract: **Background:** Over the past decade, China has successfully extended its basic healthcare safety net to more than 95% of the population. The Chinese government aims to provide universal health coverage for all citizens by 2030. However, China still suffers from an inadequate tiered medical care system, lack of information sharing on hospital visits, and medical staff with low salaries and excessive overtime. This paper will further discuss China's current status and prospects in six building blocks of the WHO health system framework. **Methods:** We used various popular search engines, such as PubMed, Google, Google Scholar, etc., to identify studies on achieving universal health in China. The purpose of the search was to understand the state of the existing health system in China, especially in mobile health (mhealth), mental health, and medical personnel protection. **Findings:** We found nine articles related to health service delivery, three articles related to the medical workforce, four articles related to health information systems, three articles related to medical products, vaccines, and technologies, five articles related to health financing, and five articles related to health system management. **Discussion:** The findings based on the six health system building blocks are summarized in conjunction with other literature.

Keywords: Universal Health Coverage; Current Status and Prospects; Health System; China

1. Background

Health was declared a fundamental human right by the World Health Organization (WHO) in 1948, and the 1978 Alma-Ata Declaration identified "health for all". Health for All cuts across all health-related Sustainable Development Goals (SDG) and is considered the foundation for achieving most of the others. Universal Health Coverage (UHC) is a broad concept that aims to: firstly, everyone has equitable access to health services. Secondly, the quality of health services should be good enough. Thirdly people are protected from financial risks. UHC included 17 indicators in four categories (reproductive, maternal, newborn, and child health; infectious diseases; non-communicable diseases; and service capacity and access) [1]. Thus, UHC implies providing adequate quality health promotion, prevention, assistance, rehabilitation, and palliative care services [2].

Health for all involves three dimensions of coverage: population, financing, and health services, and it is a dynamic and continuous process that changes with demographic, epidemiological, technological trends, and people's expectations [3]. Quality health care, financial management, and ensuring equity and accessibility of health care are equally important [4]. In practice, universal health coverage is defined as coverage greater than 90% and prepaid health insurance with legal guarantees [5]. According to this criterion, more than 58 countries (30.41%) have achieved UHC, and most of them are Organization for Economic Cooperation and Development (OECD) countries, including some developed and developing countries as well [6].

The 2017 monitoring report of the World Bank and the WHO summarized the status of UHC, including service coverage and financial protection in each country [7]. In economic respect, out-of-pocket expenditures and catastrophic medical expenditure assessments were indicators [8]. To counter the entire population's financial burden during illness and access quality health services without discrimination, the UN emphasized the need to achieve UHC in the Sustainable Development Goals (SDGs) in health [9].

Health for All programs contribute to the population, health service, and financial protection coverage and significantly increase life expectancy [10] and reduce adult mortality [11, 12]. All 193 Member States of the United Nations (UN) aim to

achieve a safer, more equitable, and healthier world by 2030. However, the current global burden of non-communicable diseases increases while facing pandemics and severe climate change. Overall, achieving SDG-3.8 requires health systems that are resilient and able to take a cross-sectoral "integrated health" approach to prepare for and respond to emergencies.

The People's Republic of China (PRC) covers an area of approximately 9.6 million km [14] and has 1.42 billion people. Today, China is the most populous country [15]. The urban population accounts for 58.0% of the total population [16]. On October 1, 1949, the founding of New China was one of the world's poorest health care delivery systems due to the recent end of the war [17]. Today, China has become the second-largest economy, with a GDP that has grown at an average annual rate of 9.5% over the past 40 years. In addition, China has lifted more than 850 million people out of poverty [18].

Along with its rapid economic growth, China has made great efforts to achieve universal health. Socioeconomic and health indicators in China have improved significantly from 1990 to 2017. Compared to other Emerging 7 countries (India, Brazil, Mexico, Russia, Indonesia, and Turkey), China has performed well in economic and population health [19].

China has undergone three phases of health care reform since its inception. In the first phase in the health sector, the government managed a centrally directed health service system and identified four principles to guide health and medical work: (1) service to workers, peasants, and soldiers; (2) prevention-oriented, primarily through patriotic health campaigns; (3) integration of Chinese and Western medicine; and (4) integration of health work with mass movements [20,21]. The second phase began in 1978 when China began its "reform and opening up" policy. As privatization and marketization progressed, the health care system changed: financing mode from total public financing to partial private funding to reduce the government's financial burden; public hospitals and clinics earned part of their revenues by selling drugs and taking test orders to replace the reduction in government finances; medical management began to be devolved from state to local governments; and incomplete pricing strategies were implemented to allow medical institutions to earn a certain amount of profit [22, 23]. In the third phase, the Chinese government launched a new round of healthcare reform in 2009 [24]. This comprehensive reform plan can be summarized as "one goal, four beams, and eight columns" [25, 26]. To achieve the goal of universal health, China has focused on establishing four systems (i.e., public health service system, medical service system, health insurance system, and drug supply guarantee system). The four systems are based on eight functional mechanisms that can provide the necessary support [23,27].

Over the past decade, China has successfully extended its basic healthcare safety net to more than 95% of the population [23]. In October 2016, the Chinese government announced the "Healthy China 2030" blueprint, aiming to provide universal health coverage for all citizens by 2030 [27]. Although China has made many significant achievements in universal health insurance, it still suffers from an inadequate tiered medical care system, lack of information sharing on hospital visits, and medical staff with low salaries and excessive overtime. To achieve universal health coverage, this paper will further discuss China's current status and prospects in six building blocks of the WHO health system framework, including 1. service delivery, 2. health workforce, 3. information, 4. medical products, vaccines and technology, 5. financing, 6. leadership/governance.

2. Methods

2.1 Search strategy to acquire the sources

The search strategy to identify UHC studies in China included searching Google, Google Scholar, Baidu, PubMed, the WHO research portal, and the web pages of the China Health Economics Association, the National Health Commission of the People's Republic of China, the Chinese Center for Disease Control and Prevention, and the Chinese Preventive Medicine Association. We used all the following keywords: 'UHC', 'SDG-3.8', 'health system', 'health services coverage', 'financing', ' insurance', 'China's healthcare system and reform', 'China' in PubMed with Boolean operators (AND, OR) linking ((health system [Title/Abstract]) OR (UHC [Title/Abstract])) AND (China [Title/Abstract])).

As public policy documents are neither included in PubMed/Medline nor published electronically elsewhere, we further expanded the search to the web pages of the Ministry of Health and related departments. For Google Scholar, we used the above terms and fixed searches based on date (selection of post-2016) and relevance (proximity to the term). On the web

page of UHC 2030, we found UHC 2030 Strategic focus (Global compact for progress towards universal health coverage). We also used the WHO website and fixed the search by WHO regional website (Western Pacific), content type (publications and guidelines), and all available formats. The reference lists of the selected articles were potential sources for this study as a bibliographic search. The remaining sources were obtained from Google and Baidu searches as gray materials. This search targeted the latest health-related policies of the Chinese government, such as the 14th Five-Year Plan and the new health care reform, etc.

In the first phase, we identified 2193 records that met the inclusion criteria from Google Scholar, PubMed/Medline, the web pages of the World Health Organization, the Ministry of Health and Population and its affiliates, and Baidu and Google search. In the first screening stage, we removed 2135 sources due to duplication of records and title distortion. In the second phase, we evaluated 58 full-text articles. we excluded 29 sources (due to incomplete matches to the six system building blocks in the Health Systems Integrated Framework - 16, duplicate content deletions - 6, unavailable - 2, outdated - 3, and controversial results - 2). Finally, we identified 29 exact matches of sources for this study.

2.2 Inclusion and exclusion criteria

The data search inclusion criteria were relevant to China, with universal health coverage (broad and operational definition), and usually published since 2016. Relevant domains were the six health system building blocks. At this stage, the final selection of articles was based on the following criteria: i) content related to the topic of the source (health service delivery systems, health workers, health information systems, health medicine vaccines and technologies, health financing, health government management), and ii) detailed scope of China. Items unrelated to China, meaningless political discourse, and sources with unpublished data were excluded from the study.

3. Findings:

3.1 Service Delivery (9 Articles)

First, China is currently facing an aging population. As the population ages, the need for hospital beds and medical staff will increase. The elderly has no source of income, which requires Medicare to increase reimbursement rates to improve healthcare utilization [28].

Not only is aging an issue, but mental health is also gaining attention in the country. Mental health services are also lacking in the country [29]. In addition, health services for maternal and child health and oral health are still inadequate [30,31].

Second, the efficiency and productivity of the Chinese health system regarding non-communicable diseases (e.g., disability, chronic diseases) declined from 2008 to 2015. For non-communicable diseases (NCDs), there is a need to strengthen relevant financial guarantees, optimize health resources (especially between human resources for health and hospital beds), and promote cost-effective technologies within the health sector to improve their efficiency and productivity [32]. In addition, the inefficiency of China's healthcare delivery system is primarily due to the weakness of the primary healthcare system [33].

Third, since the 2009 health system reform, China has made significant improvements in health care access and financial security: 1) The utilization of both inpatient and outpatient services has increased significantly. 2) People have begun to receive better financial security through health insurance, hospital reimbursement, support for catastrophic medical expenditures, and poverty subsidies. 3) Inequality in financial protection has been significantly reduced. However, people are more likely to seek care in hospitals than in primary care facilities. China's health system reform should establish a tiered health service system [34].

Fourth, most elderly patients skipped primary care centers in favor of higher-level hospital care. Urban patients produced such behavior twice as often as rural patients. Reducing the cost of primary health center visits was not known to be very helpful. Only improving the quality of services, providing integrated person-centered care, focusing on family health care needs, and providing critical preventive services could help improve the utilization of primary health care facilities and the effectiveness and efficiency of the health system [35].

Fifth, studies have shown that public health resources in China are mainly concentrated in the western region. This region also has more skilled personnel and bed allocations [36]. Similarly, highly sophisticated hospitals are focused on the area of the west. Thus, China needs to pay attention to the rational layout of quality medical resources and medical elites [37].

3.2 Health Workforce (3 Articles)

First, China's rural areas are relatively backward, and the health care system is also slow to develop. Medical students are generally reluctant to seek employment in rural areas. With policy guidance, China has trained about 1.5 million barefoot doctors since 1968, providing essential health services to 800 million rural people. The development of rural doctors in China has been divided into two phases: the barefoot doctor phase (1968-1985) and the rural doctor phase (1985-present.) After 1985, rural doctors relied mainly on drug sales for their income and thus required continuous and stable financial compensation from the government. In addition to this, there is still a significant gap between the medical level of urban and rural doctors [38].

Second, Chinese regions currently face an unequal distribution of public health personnel, with the workforce concentrated in western China. The Guangdong-Fujian region has a severe workforce shortage in the public health system [39].

Third, Chinese medical workers are frequently subjected to violent attacks. A survey in Zhejiang Province, China, noted that 17.4% of people were physically assaulted in the past year. Level II hospitals would be more likely to be attacked [40]. This phenomenon, known as "medical disturbance" in China, has even resulted in the death of doctors. It suggests that China needs to improve its laws to protect the safety of medical personnel.

3.3 Information (4 Articles)

First, among the problems contributing to the low quality of primary health care in China is poor clinical care integration with essential public health services, and poor coordination between primary health care and hospitals. China should consider modernizing its primary health care system by learning new technologies to create a unified database to address communication problems [41,42].

Furthermore, mobile health (mHealth) is currently in an exploratory phase in China. Since mHealth is an emerging field in China, many laws and regulations have not yet been implemented. In general, mHealth is now only used in a particular hospital, and there is no unified digital system [43].

Finally, the integrated delivery system is the way forward for China. In some areas, diabetes management has already been integrated and has achieved some results. The integration of services has enabled the implementation of a tertiary care system, saving medical costs, reducing the financial pressure on patients, and reducing the burden on health workers in elite hospitals [44].

3.4 Medical Products, Vaccines, and Technology (3 Articles)

First, China offers two types of vaccines: expanded Program on Immunization (EPI) vaccines, government-sponsored and non-EPI vaccines, voluntary and self-paying. The government plans to convert some non-EPI vaccines to EPI in the next few years. Recommended candidate EPI vaccines are varicella, mumps, and hand, foot, and mouth disease vaccines. However, HPV vaccines are in short supply in China and are age-restricted. Only Chinese women under 26 years of age can receive the nine-valent vaccine. Since China does not have its own nine-valent HVP vaccine, the nine-valent can only be imported from abroad. Most Chinese women are eager to solve this problem [45].

Second, by implementing the three policies of stopping the collection of immunization fees or immunization insurance, managing the immunization certificates well, and strengthening the immunization of special children, including mobile children, the latest and age-appropriate immunization rate of mobile children has increased significantly [46].

The Chinese pharmaceutical industry currently faces barriers to accessing new drugs. These barriers include drug regulation and financing, intellectual property protection, and innovation capacity development. However, China is implementing several policies to gradually remove multiple barriers to access, and medicines have shifted from primary

generic drugs to drugs with world-class breakthrough technologies [47].

3.5 Financing (5 Articles)

First, with an aging population, China has an increasing number of patients with multiple physical illnesses. Multimorbidity is significantly associated with healthcare service use and catastrophic medical expenditures. Health inequalities caused by multimorbidity have a negative economic impact on the Chinese economy. Therefore, social health insurance must reduce the out-of-pocket costs of multimorbid patients and provide them with more excellent financial risk protection [48]. In addition, multimorbid patients may have physical and mental illnesses. To manage multimorbid patients effectively, healthcare systems need to shift from a single disease model to a new service model [49].

Second, the health care reform since 2009 has increased the coverage of essential health insurance, but the average health care cost per patient has shown a continuous increase [50]. It indicates that people's healthcare needs have increased in recent years. In addition, the incidence of catastrophic medical expenditure (CHE) in China decreased from 19.37% to 15.11% after the 2009 health care reform. The poverty rate in rural areas has declined less than in urban areas, and the poverty gap is widening. Therefore, more attention needs to be given to low-income families with members with chronic diseases to optimize integrated urban and rural health insurance and enhance poverty alleviation [51]. Finally, a study has shown that China's potential health expenditure is 13.4% compared to the current 4.8%, so China is severely underspending on health care [52].

Third, current health expenditures in China are projected to increase by 8.4% per year. By 2035, spending on circulatory diseases will increase to 23.4% of health spending. A 25% reduction in the prevalence of hypertension could reduce health spending by 3.4% in 2035, and a halving of smoking could reduce it by 3.5%. Targeted risk interventions could help control future health expenditure growth in China [53].

3.6 Leadership/Governance (5 Articles)

First, public health crises have recently taken on a new systemic, cross-border character and uncertainty [54]. During the COVID-19 pandemic, non-medical measures (quarantine and masks) effectively contained and controlled the novel coronavirus epidemic, thanks to a unified leadership structure of the Chinese government [55]. However, the Chinese health system management system still suffered from unbalanced attention to health care and resources, untimely information disclosure, and inadequate grassroots public health efforts and control capacity [56].

Second, during both the Patriotic Health Movement (PHC) in China in the 1950s and the New Cooperative Medical Scheme (NCMS) in the 2000s, the Chinese government adopted a model in which each city explored and accumulated experience on its own, encouraging local governments to pilot innovative measures. Valuable lessons were learned from each other, and there was clear accountability and oversight at all levels. Higher-level government departments set policy goals and targets for lower-level governments, and the lower classes were responsible for implementation and enforcement [57]. However, these policies have drawbacks, as the decentralization of power to local governments has led to the prevalence of corruption, and some local governments are only superficial and do not do real work. Each locality has its own set of local laws, a complexity that makes government accountability implementation difficult [58].

4. Discussion

The results of this study were analyzed and summarized together with other articles. For service delivery, primary health care still needs to be improved to narrow the gap between urban and rural areas and strive to develop integrated services. For health workforce, even distribution of health personnel and improvement of relevant laws to protect the safety of medical personnel. For information, the Chinese health information system lacks uniformity and transparency and needs to promote cooperation among multiple parties and improve a unified information platform. For medical products, vaccines, and technologies, Chinese hospitals and providers rely on prescription drugs for revenue, leading to severe drug over-prescription and poor antibiotic management. In addition, China needs to accelerate the development of its vaccines and overcome the difficulties of developing new drugs. For financing, the Chinese health care payment system is based on

fee-for-service, which can incentivize excessive health care delivery. Furthermore, Chinese health spending remains grossly inadequate and needs to increase primary health insurance coverage further and reduce catastrophic healthcare spending. For leadership/governance, there is a lack of coordination among multiple relevant government agencies. Moreover, the Chinese government should gradually summarize the experience of each local exploration and slowly develop unified health laws and regulations [59-60].

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Universe Scientific Publishing

The Value of Sacubitril and Valsartan in Adjuvant Treatment of Coronary Heart Disease and Heart Failure

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Abstract: **Objective:** To analyze the intervention effect of adjuvant sacubitril-valsartan therapy in patients with coronary heart disease and heart failure. **Methods:** A total of 89 patients with coronary heart disease and heart failure who were treated in our hospital in the past 3 years (January 2019-February 2022) were selected, and the clinical data were reviewed. 45 patients treated with conventional treatment + sacubitril and valsartan were used as the observation group, and the application values of the two groups were compared. Results: The improvement of various cardiac function levels in the observation group was better, the 6min walking distance was longer, and the adverse reaction rate was lower, and the difference was statistically significant compared with the control group ($P<0.05$). **Conclusion:** Sacubitril-valsartan has good effect in adjuvant treatment of coronary heart disease and heart failure, can effectively improve its cardiac function, improve exercise endurance, and has few adverse reactions, high safety, and definite clinical application value.

Keywords: Coronary Heart Disease; Heart Failure; Sacubitril-Valsartan; Benazepril; Cardiac Function; 6min Walking Distance; Adverse Reactions; Efficacy

Introduction

Coronary heart disease is caused by coronary sclerosis, and clinically, patients are prone to angina pectoris, palpitation, shortness of breath, and chest tightness. If the disease is not controlled, the disease may continue to develop may lead to heart failure. Heart failure manifests as lower extremity edema, dyspnea, severe inability to lie supine, and some patients may cause cardiogenic asthma, resulting in water and electrolyte balance disorders, which can be life-threatening in severe cases. Therefore, patients with coronary heart disease should be treated as soon as possible to avoid the occurrence of heart failure or other more serious diseases. Treatment of heart failure is generally drug therapy. Sacubitril-valsartan is a class of angiotensin receptor/enkephalinase inhibitors. Experimental studies have shown that sacubitril and valsartan can reduce the re-hospitalization rate and mortality of patients with heart failure more than ACE inhibitors, and is currently the first-line drug recommended by domestic and foreign guidelines for patients with heart failure.[1] Therefore, this paper aims to explore the clinical value of sacubitril and valsartan in the adjuvant treatment of coronary heart disease and heart failure. The reports are as follows:

1. Research materials and methods

1.1 Research materials

The clinical data of patients with coronary heart disease and heart failure admitted to our hospital in the past 3 years were selected. Among them, there were 44 cases in the control group, 24 males and 20 females; the age was 45-84 years (mean 64.54±3.51 years); the course of disease was 1-5 years (mean 3.08±0.07 years). There were 45 cases in the observation group, including 29 males and 16 females, aged 47-86 years (mean 66.54±4.16 years), and disease duration of 1-5 years (mean 3.14±0.10d). The above case data were well balanced ($P>0.05$) and comparable.

1.2 Methods

All cases were treated with conventional treatment including diuretics, statins, aldosterone receptor antagonists, digitalis, beta-blockers, etc. On this basis, the control group was given benazepril treatment (Guangzhou Nanxin Pharmaceutical Co., Ltd., Chinese medicine Zhunzi H20090004), the recommended dose is 10/12.5mg, once a day.

The observation group was additionally treated with sacubitril and valsartan on the basis of conventional treatment (Beijing Novartis Pharmaceuticals Co., Ltd. (individual packaging), approved by Chinese medicine J20190002). For those with systolic blood pressure ≤100 mmHg, sacubitril and valsartan sodium 50 mg/time, 2 times/d; for those with systolic blood pressure >100 mmHg, 100 mg/time, 2 times/d. And according to the patient's tolerance, the dose is increased to 200 mg/time every 7-14 days, 2 times/day.

Both groups continued treatment for 1 month.

1.3 Observation index and judgment criteria

The cardiac function level[2] and 6min walking distance of the two groups of patients were measured, and the occurrence of adverse reactions in the two groups was also counted.

1.4 Statistical methods

The data were analyzed with statistical software (SPSS 23.0 version).

2. Result

2.1 Comparison of cardiac function levels between the two groups of patients

It can be seen from Table 1 that the improvement of cardiac function in the observation group was better than that in the control group (P<0.05).

Table 1 Comparison of cardiac function levels in two groups of patients [n, (%)]

Groups	Number of cases	Before treatment			After treatment		
		LVEF（%）	LVEDD（mm）	NT-proBNP（pg/ml）	LVEF（%）	LVEDD（mm）	NT-proBNP（pg/ml）
Observation group	45	35.17±6.42	68.75±4.05	2071.32±249.36	48.36±8.15	59.37±3.98	865.14±176.35
Control group	44	34.76±6.38	68.35±3.98	2067.14±251.45	43.16±7.68	61.96±3.65	993.45±167.15
t	-	0.302	0.470	0.079	3.096	3.198	3.521
P	-	0.763	0.640	0.937	0.003	0.002	0.001

2.2 Comparison of 6min walking distance between the two groups of patients

It can be seen from Table 2 that the 6min walking distance of the observation group was significantly better than that of the control group (P<0.05).

Table 2 Comparison of 6min walking distance between the two groups of patients ($\bar{x} \pm s$), m

Groups	Number of cases	Before treatment	After treatment
Observation group	45	289.37±89.38	416.35±91.11
Control group	44	293.46±87.38	369.16±86.38
t	-	0.218	2.506
P	-	0.828	0.014

2.3 Comparison of adverse reaction rates between the two groups of patients

It can be seen from Table 3 that the adverse reaction rate of patients in the observation group was significantly lower than that in the control group (P<0.05).

Table 3 Comparison of adverse reaction rates between the two groups of patients [n, (%)]

Groups	Number of cases	Low blood pressure	Mild impairment of renal function	Angioedema	Adverse reaction rate
Observation group	45	1	1	0	4.44
Control group	44	3	4	2	20.45
χ^2	-	-	-	-	5.740
P	-	-	-	-	0.017

3. Discussion

Coronary heart disease is a kind of myocardial ischemia and hypoxia caused by organic stenosis or lumen blockage of coronary artery, also known as ischemic heart disease[3]. Heart failure is one of the common complications of coronary heart disease, most of which occur in the late stage of coronary heart disease. Clinically, most of the patients will be accompanied by chest tightness, asthma, and even breathing difficulties in the supine position. In severe cases, the patient will die. Although the current clinical combined intervention and drug treatment have made progress, some patients still have different degrees of cardiac dysfunction as the disease progresses, eventually leading to chronic heart failure. Therefore, it is of great significance to find a more effective treatment method.

The routine clinical treatment of this disease is to improve cardiac function first. Generally, digitalis is selected to enhance myocardial contractility, diuretics and vasodilators are selected to reduce the burden on the heart, improve cardiac function, and relieve the symptoms of heart failure. The second is to remove the incentives, such as infection in the body, especially lung infection, endocarditis, and the need to actively control the infection. Then there is treatment for the cause. For patients with coronary heart disease and heart failure, the addition of benazepril on the basis of conventional treatment methods can not only play a role in lowering blood pressure, but also effectively protect myocardial cells, which has a good effect on coronary heart disease and heart failure. But the actual treatment of heart failure, can not rely solely on a certain drug. Sacubitril-valsartan is mainly used in clinical practice to prevent the progression of heart failure. It can replace angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) in combination with other heart failure treatment drugs[4]. This drug can further reduce cardiovascular mortality and the risk of heart failure hospitalization, reverse left ventricular remodeling and left ventricular hypertrophy, and play the role of sodium excretion, drainage, and

vasodilator[5]. At the same time, it can also delay the progression of heart failure, improve the quality of life of patients, improve their long-term prognosis, and improve the quality of life. The results of this study showed that the improvement of cardiac function in the observation group was good, the 6min walking distance was longer, and the adverse reactions were less ($P<0.05$), which fully confirmed the high clinical application value of sacubitril and valsartan improve cardiac function and high safety. In-depth analysis of sacubitril and valsartan can be rapidly absorbed after oral administration, decomposed into sacubitril and valsartan, and give full play to its efficacy; each component of sacubitril and valsartan is highly bound to plasma proteins. The tissue distribution rate is high; most of sacubitril is excreted in urine, which brings benefits to patients with heart failure and has good safety.

In conclusion, sacubitril-valsartan has significant curative effect in the treatment of patients with coronary heart disease and heart failure, which can well improve their cardiac function and reduce adverse reactions, which is an effective and safe treatment.

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Universe Scientific Publishing

The Relationship between Core Knowledge of Tuberculosis and Mental Health: A Cross-Sectional Study Among University Students in Tibet

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Abstract: The relationship between core knowledge of TB and mental health among students in a university was investigated. The results showed that the overall knowledge rate of core knowledge of tuberculosis was 71%. The main effects of coping style and standard level on mental health, anxiety, and self-denial were significant. In terms of mental health, the results had borderline significant, and the positive attitude of the "not up to standard" participants was conducive to a good mental state. This suggests that schools should not only strengthen the education of students on TB prevention and control but also cultivate positive attitudes among students.

Keywords: Awareness Rate; Mental Health

1. Introduction

Tuberculosis is mainly respiratory transmitted and is a tuberculous lesion that occurs in the lung tissue, trachea, bronchi, and pleura [1]. To effectively curb the prevalence of tuberculosis, China's 13th Five-Year Plan for the Prevention and Control of Tuberculosis aims to achieve a public awareness rate of more than 85% of the core knowledge of tuberculosis prevention and control. In June 2017, The Code of Practice for Tuberculosis Prevention and Control in Schools (2017 Edition)[2] (hereinafter referred to as the Code), which standardizes the core knowledge of TB health education in schools into eight articles. so this study first explored the knowledge of college students about the core knowledge of TB health education in the Norms.

Mental health is not only the absence of mental illness or psychopathy, but also the ability of an individual to recognize his or her potential [3][4]. Individuals who use positive coping have higher levels of psychological health[5].In the current study, the participants were selected from classes in which they had a history of TB or were found to have TB in previous screenings, and schools are characterized by high population density and mobility, so the level of knowledge about tuberculosis may affect their mental health status. In addition, considering that different coping styles may also affect mental health [5], different coping styles may lead to different levels of mental health in cases where subjects are unable to determine whether they have been diagnosed with TB and have little knowledge of this area.

2. Subjects and methods

2.1 Investigation subjects

A questionnaire based survey was conducted among university students in Tibet reported tuberculosis cases or had been diagnosed with tuberculosis in a tuberculosis screening.

2.2 Investigation content

The questionnaire includes the following four aspects: (1) general information; (2) Eight core knowledge items of TB; (3) Simple Coping Style Questionnaire (SCSQ): The scoring converts the scores of negative coping and positive coping into Z-scores, and a positive coping tendency is positive if the standard score of positive coping is subtracted from the standard score of negative coping, and negative coping if the opposite is true [6]. (4) The General Health Questionnaire (GHQ-20), including three subscales: the Self-Affirmation Scale, the Anxiety Scale, and the Depression Scale[7]. Self-affirmation scores were reverse scored to create self-denial scores. The anxiety score, depression score, and self-denial score were added to obtain the mental health score, and the higher the total score, the lower the level of mental health.

2.3 Statistical analysis

SPSS 25. 0 statistical software was used to analyze the data.

3. Results

3.1 Basic information

A total of 287 questionnaires were distributed, and the actual number of valid copies collected was 269 (93.7%)

3.2 Univariate analysis of the core knowledge of tuberculosis prevention and treatment that affects the “up to standard”knowledge

The significant differences were statistically significant ($P < 0.05$) when comparing students' professional field, area of origin, whether they have received TB-related health education, and whether they have read information about TB prevention. See Table 1.

Table 1 Awareness of the core knowledge of TB control of participants

Type Number of Participants	up to standard	Not up to standard	χ^2	P
Gender			0.006	0.937
Male（n=138）	30	108		
Female（n=131）	29	102		
Ethnicity				
Tibetan（n=154）	40	114	2.289	0.318
Han ethnic group（n=104）	32	72		
Other ethnic groups（n=11）	5	6		
area of origin			3.990	0.046*
Countryside（n=202）	33	169		
City（n=67）	16	41		
Grade			8.363	0.079
Freshman year（n=37）	13	24		
Sophomore（n=35）	6	29		
Junior（n=135）	25	110		
Senior Year（n=24）	3	21		
Grand 5th grade（n=38）	13	25		
professional field			11.298	0.001*
Medical category（n=92）	31	61		
Non-medical category（n=177）	28	149		
whether they have received TB-related health education			5.189	0.023*
Yes（n=215）	65	150		
No（n=54）	8	46		
whether they have read information about TB prevention			4.742	0.029*
Yes（n=224）	71	153		
No（n=45）	7	38		
whether they have a family history of TB			0.011	0.916
Yes（n=5）	1	4		
No（n=264）	58	206		

3.3 The Relationship between Core Knowledge of Tuberculosis and Mental Health

A two-factor ANOVA with 2 (standard level: up to standard, Not up to standard) × 2 (coping style: positive, negative) was conducted with the dependent variables of anxiety scale, depression scale, self-denial scale, and mental health score, respectively.

Firstly, on the anxiety scale, The results found that: the main effect of the standard level was significant $F(1, 266)=4.558$, $p=0.034$, $\eta_p^2=0.017$, and anxiety scores were significantly lower for people who up to standard ($M=0.356$, $SD=0.996$) than for those who did not ($M=0.938$, $SD=1.616$); the main effect of coping style was significant $F(1, 266)=9.639$, $p= 0.002$, $\eta_p^2=0.035$, and anxiety scores were significantly lower for positive coping ($M=0.306$, $SD=0.970$) than for negative coping ($M=1.164$, $SD=1.724$); the interaction between standard level and coping style was not significant $F(1, 266)=1.442$, $p=0.231$, $\eta_p^2=0.005$. Secondly, On the depression scale, the main effect of standard level was not significant $F(1, 266)=1.797$, $p=0.181$, $\eta_p^2=0.007$; the main effect of coping style was not significant $F(1, 266)=0.844$, $p=0.359$, $\eta_p^2=0.003$; the interaction between standard level and coping style was not significant $F(1, 266)=0.195$, $p= 0.660$, $\eta_p^2=0.001$.Thirdly, On the self-denial scale, the main effect of the standard level was significant $F(1, 266)=8.598$, $P=0.004$, $\eta_p^2=0.031$, and the self-denial scores were significantly lower for people who up to standard($M=4.610$, $SD=3.068$) than for those who did not ($M=6.090$, $SD=2.921$); the main effect of coping style was significant $F(1, 266)=9.459$, $P=0.002$, $\eta_p^2=0.034$, and self-denial scores were

significantly lower for positive coping (M=4.766, SD=3.081) than for negative coping (M=6.465, SD=2.762); the interaction between standard level and coping style was not significant F(1, 266)=1.354, P=0.246, η_p^2=0.005. Finally, On the mental health scores, the main effect of the standard level was significant F(1, 266)=19.996, P=0.001, η_p^2=0.070, and the mental health scores were significantly lower for people who up to standard(M=5.559, SD=0.385) than for those who did not (M=7.516, SD=0.209); the main effect of coping style was significant F(1, 266)=24.050, P=0.001, η_p^2=0.083, and mental health scores were significantly lower for positive coping(M=5.464, SD=0.312)than for negative coping (M=7.611, SD=0.307); The interaction between level of attainment and coping style reached borderline significant F(1, 266)=3.645, p=0.057, η_p^2=0.014, and further simple effects analysis revealed that for those who did not up to the standard, mental health scores were significantly lower with positive attitudes (M=6.025, SD=3.081) than with negative attitudes (M=9.008, SD=2.053), t(209)=7.099, p=0.001, CI95% [-3.813, -2.153]; for those who up to the standard, there was no difference in mental health scores in terms of coping style. As shown in Figure 1.

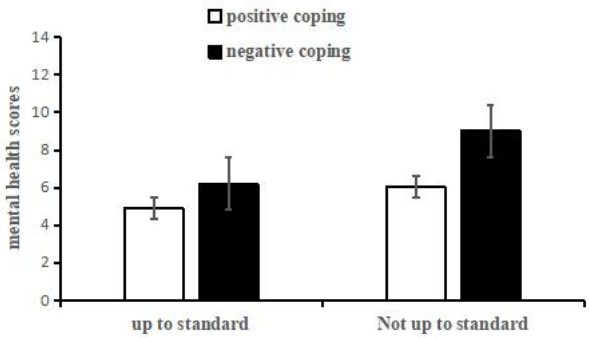

Figure 1. Mental health scores at the different standard levels under different coping styles

4. Discussion

From the analysis of this survey, the overall standard of core knowledge of TB prevention and treatment in this group was 72%, which did not reach the target of “public knowledge of TB prevention and treatment reaching over 85%” proposed in the 13th Five-Year Plan. This suggests that schools should further strengthen the dissemination of core knowledge about TB prevention and treatment to raise the awareness of students.

Our other concern is the effect of core knowledge of TB prevention and control on mental health. The main effects of standard level and coping style were found to be significant in the ANOVAs for the anxiety scale, the self-denial scale, and the total mental health scores. In terms of coping style, the results are consistent with previous studies [6], which also found lower anxiety scores and self-denial scores among active copers in the current study. possibly because individuals are more optimistic and more sure of themselves when adopting a positive attitude. Importantly, the standard levels of core knowledge of TB control were also found to influence self-denial and anxiety. This may be related to our choice of the group, as the participants had contact with the TB patients in the class and therefore became worried. At this point, when the participants had more knowledge about the core knowledge of TB control, they were able to reduce their worries, anxiety, etc. to some extent and were able to live their lives normally as usual. On the contrary, they worry about whether they are infected and thus become more upset.

However, on the depression scale, there were no differences in standard levels or coping styles. We speculate that this may be related to the content of the scale, such as "I would feel like a useless person", which may not be experienced in the current context.

It is interesting to note that in the overall mental health scores, there is a significant borderline between the coping style and the level of standard. For those who did not up to the standard, mental health scores with positive attitudes were lower than negative attitudes, suggesting that even though knowledge of core TB control knowledge did not up to the standard, adopting attitudes such as learning from others' approaches to similar difficult situations, seek advice from relatives, friends

or classmates, etc., may be able to motivate individuals to make up for their knowledge about TB and thus reduce their bad feelings.

5. Shortcomings

The current study questionnaire was collected before the PPD results were known, so it may have influenced the results, and in addition, considering the specificity of the participants group, it is necessary to continue to validate the results of this study in the next study by considering the above two reasons together.

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Universe Scientific Publishing

Using Chimeric Antigen Receptor Modified T-Cell to Treat B-Cell Leukemias

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Abstract: Leukemias are cancers that happened in the blood of organisms, which affect the immune system's T cells and B cells. Therefore, investigating studies to cure this disease are crucial. Several researchers demonstrated the use of modified receptors of T cells to fight leukemia. CTL019 (tisagenlecleucel) is a type of therapy that transplants the CD19 receptors into T cells to help them recognize the CD19+ B cells. They are used to detect and kill the cancerous B cell leukemia cells. The chimeric antigen receptor-modified T-cell (CAR-T) is a method that extracts the blood cells from the patients to cultivate the CD19 receptors. Finally, the blood would be injected back into the patients. Even though this method effectively kills CD19+ B-cells, it may have some side effects, such as the quick release of cytokines that can cause high systemic effects. With these side effects, scientists should investigate a better way to reduce the side effects in the future.

Keywords: Lymphocytic Leukemias; Cytotoxic T-Cells; CAR-T; CTL019

1. Background

Leukemias are cancers that happen in a person's bone marrow. "According to estimation, 61090 people of all ages in the United States will be diagnosed with leukemia in 2021"(Cancer.net, 2021). Leukemia can be separated into two main types: lymphocytic leukemia and myeloid leukemia. Lymphocytic leukemias are caused by cancerous lymphocytes; myeloid leukemias are caused by cancerous myeloid cells. (Mayoclinic, Jan 13, 2021). There are two types of lymphocytic leukemia: acute lymphocytic leukemia and chronic lymphocytic leukemia. Acute lymphocytic leukemia is when leukemia cells in the bone marrow abnormally replicate without being controlled. They produce immature cells that block other healthy cells. Patients who have this disease may have symptoms such as gum bleeding, bone pain, fever, weakness, and frequent infections. (Mayoclinic, Feb 10, 2021) Chronic lymphocytic leukemia (CLL) also occurs in the bone marrow. CLL leukemias happen slower than other leukemias. They mostly happen in older adults, who cannot use bone marrow transplantation. The symptoms contain enlarged lymph nodes, fever, night sweat, fatigue, weight loss, and frequent infections. (Mayoclinic, 2019) The research question I have is how immunotherapy, especially CAR-T, works. How does CTL019 affect lymphocytic leukemia patients?

2. Cytotoxic T-cells

Cytotoxic T cells belong to the third defense line of the human body. They use cell-mediated responses to protect our bodies. They would target infected cells and kill them. (Humphrey, 2020)

2.1 Receptor Structure of T-cells

T cell receptors (TCR) are composed of 2 polypeptide chains. They are named as α & β, and sometimes γ & β. Both chains have sections called constant domains and variable domains. Their functions are similar to enzymes. When they bind to molecules, the variable sections would change the shape to bind to the antigen. T cells only have 1 binding site. (Humphrey, 2020) The T cell hinge regions that are composed of flexible amino acids link the peptide chain and the cell. They have a disulfide bond between them. (Adlersberg JB., 1976). There are also CD3 molecules in the cell. CD3s are used

for intracellular signaling. They can be phosphorylated within the cell and send the signal. (Wah, M., 2014) CD8 molecules are used as coreceptors of the cytotoxic cells. They are able to recognize MHC I molecules and bind to them. (Sharpe, 2015)

With these cytotoxic T cells, scientists are able to create modified cell-mediated immunity by using chimeric antigen receptor T-cells. They are generally called immunotherapy.

3. Chimeric Antigen Receptor T-cells

Immunotherapy for cancer was to use our immune system to fight against malignancies, which was different from chemotherapy. Scientists first used lymphocytes to treat leukemia. In the 1990s, Zelig Eshhar created the first chimeric antigen receptor for the treatment. Later on, many institutions - "Memorial Sloan Kettering Cancer Center , University of Pennsylvania and the Children's Hospital of Philadelphia , Fred Hutchinson Cancer Research Center , and the National Cancer Institute (NCI)" (Vairy, 2018)- started to investigate anti-CD19 therapies.

3.1 CAR-T Cell Therapy

Chimeric antigen receptor T cells (CAR-T therapy) is a therapy that modifies the patients' cytotoxic T-cell and uses it to kill cancer cells in patients' bodies. People genetically modify the lymphocytes to target certain diseases and inject them back to the patients. The cytotoxic T cells injected back to the body would target the infected cell to defend the body. One of the benefits of this treatment is that there wouldn't be much graft-versus-host disease (GVHD) because it uses the patient's own immune cells. (NCI Dictionary of Cancer TERMS)(Sharpe, 2015)

3.2 Structure of CARs

Chimeric antigen receptors are composed of three regions: antigen binding domain, a transmembrane domain, and an intracellular signaling domain. The antigen-binding domain would bind to the antigen, and they usually originate from antibodies. The intracellular domain would signal to the cell to perform the anti-tumor effect. The first-generation CARs only have CD3 as a signaling domain. However, in the second generation, coreceptors, such as CD28, were added to the cell too. The coreceptors would aid the cell to perform a stronger response. (Sharpe, 2015)

3.3 The Procedure of CAR-T Therapy

The patient's blood is extracted out to pass the apheresis machine that removes the white blood cells, including the cytotoxic cells. The rest of the blood would be sent back to patients. The cells that are extracted are modified by adding a certain virus inside. The modified cytotoxic T cells would express the receptors on their surface. Scientists would grow the cells in vitro. After the modification and cultivation, the T-cells are injected back to the body of the patients by infusion to enhance their immune system. (NCI Dictionary of Cancer TERMS)

4. CTL019

CTL019 uses CAR-T technology to apply the receptors on the T cells. They would target CD19 cells to treat leukemia. (Vairy S., 2018)

CD19 are proteins on the surface of normal B cells and leukemia B cells, but they are not on other normal cells' surfaces, which reduce the destruction of the cytotoxic T cells. It is acceptable to fight the tumor by killing the normal B cells. (Vairy S., 2018)

4.1 Structure

The basic CAR-T structure has "an intracellular T-cell activation domain, an extracellular hinge region, a transmembrane domain, and an extracellular antigen-recognition moiety" (Vairy S., 2018) The second generation of CAR-T has a costimulatory domain. CD 28 and CD137 (4-IBB) raise the production of cytokine, proliferation of cytotoxic cells, and persistence of the CAR-T cells. CTL019 has CD8-α as the hinge part of the cell, sc-Fv (anti-CD19) as the recognition section, CD137 as the costimulatory domain, and CD3ζ as the signaling domain. (Vairy S., 2018)

4.2 Mechanism

The 4-IBB (CD137) binds to TNF(tumor necrosis factor)-receptor-associated factor 2 (TRAF2). It sends signals to NF-kB via proteins p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK). 4-IBB also raises the anti-apoptotic factors, stimulates the proliferation of T cells and cytokine secretions, provides more cytolytic potential (power to destroy cells), and elongates the cell's lifetime. Intracellular signals phosphorylate CD3ζ, interact with the TCR, and activate the MAPK molecule. With more cytotoxic T cells, the T cells can easily detect the CD19 cells. Then, they will bind to it and release the cytotoxin to kill the cell. (Vairy S., 2018)

4.3 Side Effects

CAR-T cells cause toxicity which damages normal cells that have that antigen. Cytokine-release syndrome and neurotoxicity can occur. Patients may also have other symptoms like fever, hypogammaglobulinemia, viral infection, loss of weight, diarrhea, and vomiting. Scientists are trying to investigate the best way that reduces the disadvantages of CTL019 and improve the antitumor effect. Doctors should track the adverse reactions, determine what grade the patient was at, and use a reliable treatment to reduce the adverse reaction. (Vairy S., 2018)

4.4 Cytokine Release Syndrome (CRS)

CRS is an inflammatory reaction that was caused by the raised level of cytokines. It was caused when T-cells proliferate massively in the body. It causes patients to experience symptoms like high fever, fatigue, malaise, and capillary leak. It mostly happens in patients who received infusions within 14 weeks. Interleukin-6 (IL6) was used to produce the C-reactive proteins, which mediates the CRS effect, but it causes other cytokines to increase, such as IL-10, IL-5, and interferon-gamma. (Vairy, 2018)

4.5 Treatments

Tocilizumab (Atlizumab [Chugai Pharmaceutical Co., Tokyo, Japan], Actemra [Hoffmann-La Roche, Basel, Switzerland]) is a humanized monoclonal antibody against the IL-6 receptor (IL-6R). It binds to IL-6 to prevent it from signaling. However, it may increase the level of IL-6 as it binds to it, causing neurotoxicity in the central nervous system. (Vairy S., 2018) "Siltuximab (CNTO 328, Sylvan; Janssen Pharmaceutica, Beerse, Belgium) is a human murine chimeric monoclonal antibody against IL-6." (Vairy S., 2018) It causes many patients to have rapid reversal symptoms. Corticosteroids are useful for CRS, CRES, HLH/MAS, but it inhibits the function of T-cells and causes T-cell apoptosis. (Vairy S., 2018)

5. Clinical Examples

5.1 Acute Lymphocytic Leukemia

According to the journal from Grupp, S. and his team, two children with relapsed and refractory pre-B-cell ALL had experienced CAR-T therapy. Both of them had experienced two relapses. Patient 1, a 7-year-old girl, used chemotherapy, but her cancer recurred, and further chemotherapy didn't work. Patient 2, a 10-year-old girl, received cord blood transplantation from a stranger, but she GVHD after transplantation. She didn't receive any immunosuppressive therapy, and the target antibody treatment didn't work for her. Finally, they used CTL019. The CTL019 quantity expanded 1000 times in their bodies. The cells were found in the bone marrow and had lasted in the cerebrospinal fluid for more than 6 months. However, both of them experienced fever after the infusion, which was probably caused by the cytokine-release syndrome. Patient 1 experienced a high fever on day 4, and she was transferred to the pediatric intensive care unit. 2 weeks later, both patients' lymphocytes had increased. Most of their T cells had expressed the CARs. About 1 month later, morphologic remission of ALL in both children was achieved. The remission in patient 1 was associated with molecular remission that lasted 9 months. Unfortunately, patient 2 had a relapse about 2 months later. (Grupp, S., 2013)

5.3 Chronic Lymphocytic Leukemia

According to the journal that was published by Kalos, M in 20,16, Science Translational Medicine, Porter, et al. presented the data of 14 CLL patients treated at the University of Pennsylvania on September 2, 2016, some patients' clinical activity experienced logarithmic expansion, contraction, and long-term persistence in T cells, with side effects like cytokine-release syndrome. The final result was that the immunotherapy was viable for treating CLL. 3 CLL patients were in late-stage, and they had a strong anti-tumor response after the CTL019 treatment. Their long-lasting T cells expanded a lot in vivo. The engineered T cells mediate the profound activity in CLL patients. However, ⅓ of the patients didn't respond to the therapy. CTL019 is able to mediate complete molecular remission of CLL patients. CLL response to CTL019 is lower than ALL's response, but the expansion of cells is still effective in treating CLL. (Kalos, M., 2016)

6. Conclusion

CAR-T, as a new technology, opens the door to using immunological cell-mediated therapies to treat diseases. It allows scientists to modify the cell's genes, proliferate the cells, and target special infections with great efficacy. It is safer since the patients wouldn't receive the GVHD. A special type of therapy that uses CAR-T, CTL019, has been created to treat lymphocytic leukemias. It functioned well in some patients to proliferate their cytotoxic T cells, but some patients, especially those who had CLL, didn't respond to it. This therapy still needs to be optimized in later research.

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Trimethylamine-N-Oxide: Its Role in Cardiovascular Disease, Mechanism and Potential Therapeutic Targets

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Abstract: Cardiovascular disease (CVD) is a common circulatory system disease and the collective name of all kinds of heart diseases, such as rheumatic heart disease, congenital heart disease, hypertensive heart disease and so on. According to WHO's publishment, CVD is the top three leading cause of death in the world. Therefore, it is necessary to study the risk factors of CVD. In recent years, there has been increasing research on the effect of diet on CVD, and red meat caught the attention of researchers. L-carnitine in red meat can eventually be oxidized to trimethylamine-n-oxide (TMAO) by the gut flora. In this review, I give evidence-based conclusions about the relationship between L-carnitine and CVD, metabolism of TMAO in the presence of intestinal microorganisms. I also discuss the mechanism by which TMAO increases the CVD risk and possible therapeutic targets offered by TMAO. Overall speaking, it is a promising research direction to find therapeutic targets by blocking L-carnitine's formation.

Keywords: Cardiovascular Disease; Trimethylamine-N-Oxide; L-Carnitine; Therapeutic Targets

Introduction

With economic development, the red meat diet has reached a high point in the developing world, and overconsumption of this diet has been linked to an increased risk of CVD [1]. L-carnitine, which is abundant in red meat, is digested by gut bacteria to produce two metabolites, trimethylamine (TMA) and TMAO. According to clinical research, L-carnitine has a positive inotropic effect on the heart and can improve the state of ischemia and hypoxia of myocardial cells [2]. However, TMAO is one of the crucial factor in the occurrence and development of CVD, such as AS and stroke . Although the mechanism between TMAO and CVD remains highly uncertain, some studies suggested that elevated plasma TMAO levels may lead to an increased risk for some adverse cardiovascular reactions, such as arrhythmia and myocardial ischemia. TMAO, as an important intestinal microbiota metabolite, Its formation can be effectively promoted by an intestinal bacteria called E.timonensis . What's more, Hazen and his colleagues identified a gene cluster—"gamma-butyrobetaine utilization" (gbu), which plays a critical role in the metabolic process of TMAO. So there are many potential therapeutic targets in the metabolic pathway of L-carnitine conversion to TMAO that are worth investigating.

1. Possible role of L-carnitine in CVD

L-carnitine is an amino acid, which can change fat into energy, which mainly comes from red meat, can balance cardiac energy metabolism by promoting mitochondrial oxidation. It is believed that L-carnitine has benefits for cardiomyopathy. The cardioprotective mechanism of L-carnitine has a connection wtih the reduction of the oxidative stress response, inflammation, and necrosis in cardiogenic cells. The meta-analysis shows that L-carnitine can reduce the area of myocardial infarction and relieve angina pectoris symptoms, helping diminish the mortality rate[3].

Ventricular remodeling is mediated by kappa B(a nuclear factor), and L-carnitine can restrain the abilities of some oxidases that control the procession. What's more, an animal experiment suggested that L-carnitine can reduce some main manifestations of arrhythmia, including eliminating abnormal cardiomyocyte discharge and atrioventricular nodal reentrant tachycardia and tachycardia. Some studies have shown that L-carnitine has a protective role in the heart and against heart failure, but its specific links with other physical organs stay unrevealed. Thus, more in-vitro trials with L-carnitine need to be conducted, leading to figuring out the mechanism underlying their correlation.

2. TMAO metabolism

TMAO is an metabolite of intestinal flora, compounded in the human's liver, and the generation of precursor TMA is inseparable from the intestinal microbiota. Some intestinal flora can produce TMA lyase, which converts choline, betaine, carnitine, and TMAO from direct dietary intake or indirect production into TMA[4]. With hydrophobic and hydrophilic double groups, TMAO can regulate protein activity and stability, increase foam cell formation and inhibit cholesterol reverse transport.

Precursors to TMA production include TMAO, carnitine, gamma-butylbetaine, croton betaine, and so on.

E.timonensis can effectively promote the conversion process in the bowels of the busymen, while that ability is weaker in the vegetarian gut due to the lower abundance of the E.timonensis. Additionally, researchers used samples and clinical data collected from patients followed for three years, then they founded that plasmaγBB levels are positively associated with CVD risk andγBB can modulate the expression level of gbu (six-gene cluster) which is crucial for TMAO metabolism[2].

3. TMAO and CVD risk

High levels of TMAO may be a new risk factor for CVD. However, some other research indicates that TMAO levels may not be associated with CVD. So in my view, the relationship between TMAO and CVD may be more complicated than that, and the uncertainty is strong, so using TMAO phenotype to identify CVD risk needs to be cautious.

Heart failure (HF) is an end-stage manifestation of CVD, and some recent evidence indicates that TMAO, may contribute to HF. In 2013, based on an untargeted metabolomics analysis of 4407 patients undergoing coronary angiography, researchers put forward that TMAO levels predicted an increased risk of CVD for the first time[5]. It seems that elevated TMAO levels can be a warning sign of CVDs, but is it the whole truth? I'm afraid not. A random trial showed TMAO circulated rapidly in the blood and was mostly excreted in the urine, in other words, TMAO didn't stay in plasma for so long, which was quite different from the elevated TMAO concentrations in AS patients and animal models of CVD[6].

4. Potential therapeutic target

Here are some possible treatments for CVD by lowing plasma TMAO levels.

4.1 Ginger

In 2019, Zouyan He et al[7] built a TMAO-exacerbated hypercholesterolemic mice model, they divided mice into five groups, each group had different levels of ginger extract (GE) and TMAO, after 12 weeks, they found GE could reduce the increase of plasma total cholesterol (TC) in mice fed with high cholesterol, and partially reversed the TMAO-induced reduction of total acid sterol in feces. That's to say, GE could reduce vascular inflammation caused by TMAO, thereby achieving cardiovascular protection.

A systematic review showed systolic blood pressure (BP) and diastolic BP were decreased by ginger dosage, this may be associated with an organic compound similar to salicylic acid in GE, which has a special effect on falling blood fat and arterial BP of body circulation, preventing myocardial infarction. However, CVD patients should not eat excessive ginger, because gingerol has a bad influence on the digestive organ.

4.2 Regulate intestinal flora

Dysbiosis occurs when the proportions of these bacteria change quantitatively or qualitatively, which may lead to increases in TMAO. Some bacteria are responsible for fermenting carnitine in food to produce TMAO, and these bacteria contain genes for enzymes involved in the synthesis of TMA. So changing the concentration of TMAO by regulating the abundance of intestinal flora may be a feasible approach. In 2019, a study applied spectroscopic low-absorption antibiotics in mice and then measured plasma TMAO levels, then they concluded: improving gut microbiome abundance can reverse the increased inflammation of blood vessels and arterial dysfunction associated with aging. But I don't recommend that people use antibiotics in large quantities for a long time because of possible adverse effects (dysbacteriosis, drug-resistant bacteria,

etc). Compared to antibiotics, probiotics can safely maintain the balance of intestinal flora, because it has been known that appropriate intake of probiotics can stimulate beneficial bacteria and inhibit harmful bacteria, thus regulating the balance of intestinal flora. By contrast, there was no reduction in TMAO levels during one month of probiotic supplements in males. The relationship between probiotics and TMAO cannot be generalized as different probiotics have different ways of acting on the gut.

4.3 Vitamin D

Vitamin D is a steroid derivative, which has been linked to immune system diseases, and gut microbiome also have influences on the immune system. Recently, more and more studies have shown that vitamin D may have a close relationship with the intestinal barrier. An in vitro test showed vitamin D inhibited the growth of some mycobacteria, so the bacteriostatic effect of vitamin D may be related to its immunomodulatory effect on intestinal microorganisms. However, bacteria may actually control the metabolism of vitamin D by synthesizing some related enzymes, such as CYP105. The mechanisms of how vitamin D affects intestinal flora stay unrevealed. In 2020, a secondary analysis suggested that the mechanism underlying the increased tendency for carnitine and TMAO with the vitamin supplements is changes in skeletal muscle. Studies have suggested that vitamin D may lead to high plasma TMAO levels, and then further lead to increased intestinal permeability. However, according to Obeid R et al research, vitamin D could bring down TMAO levels associated with homocysteine reduction.

5. Conclusion

In last few years, there is grown concert about the effects of diet and gut bacteria on CVD. L-carnitine, which is abundant in red meat, and TMAO, which is derived from its metabolic transformation through intestinal flora, have also sparked a lot of research. Based on articles published in recent years, I believe that TMAO may indeed increase the risk of CVD, and the metabolic pathway of choline conversion to TMAO may has many therapeutic targets for human intervention. The most promising approach is to suppress TMAO production by controlling the genes involved in the synthase. Of course, many researchers have tried dietary therapy, but the experimental results vary greatly in different ages, genders and regions, so we have not yet determined whether TMAO levels can be modulated by dietary control. Currently, we do not know the specific mechanism of how TMAO plays a role in CVD, I think the next research direction should be to fill this gap. In addition, influencing TMAO metabolism through the regulation of intestinal flora by probiotics is an idea worth exploring further.

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A Review of Pharmacological Preconditioning for Hepatic Ischemia-Reperfusion Injury

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Abstract: Hepatic ischemia/reperfusion injury (HIRI) is a pathophysiological condition that occurs when the liver's blood supply is interrupted, resulting in organ hypoxia. It commonly happens when blood supply to the liver is reduced during liver resection due to prolonged obstruction of blood flow, shock, trauma, or heart failure. Prolonged hepatic ischemia followed by reperfusion, which occurs following a liver transplant, causes serious harm and contributes to increased morbidity and death. Several HIRI treatments, including pharmacological preconditioning, ischemic preconditioning, and remote ischemic preconditioning, have been proposed based on the further study on hepatic ischemia-reperfusion injury. Pharmacological preconditioning has demonstrated promising benefits in the prevention of liver injury in experimental models and a few randomised controlled human studies. The current state of pharmacological preconditioning for hepatic ischemia and reperfusion injury is discussed in this study.

Keywords*:* Ischemic Preconditioning; Ischemia-Reperfusion Injury; Hepatectomy; Liver Transplant; Drug

Introduction

Ischemia-reperfusion injury (IRI) is a joint experimental and clinical finding that tissue ischemia with insufficient oxygen supply followed by successful reperfusion triggers a broad and complex array of inflammatory responses involving multifactorial metabolic mechanisms pathways, ultimately leading to severe ischemia-reperfusion injury, circulatory dysfunction, organ failure, and death. Ischemia-reperfusion injury to the liver is a type of injury that occurs when the liver is deprived of oxygen and nutrients (HIRI) is a multi-factorial pathologic process that leads to post-ischemic organ failure and cell death.

Following liver surgery, there is an increased risk of death, resulting in an increase in morbidity and mortality. For irreversible acute and chronic liver disorders, a liver transplant has been the most effective treatment option so far. The primary cause of primary non-function or insufficiency of the transplanted liver after liver transplantation is ischemia-reperfusion damage. It is also the most common reason for liver transplantation and mortality. As a result, liver transplantation research is a prominent topic.

Ischemic preconditioning (IPC) is described as a brief period of ischemia followed by tissue reperfusion in order to increase ischemic tolerance for a prolonged length of ischemia. The adaptive pathophysiological process in the targeted organ allows IPC to reduce the size of IRI. Ischemic preconditioning can lower the severity of the ischemia-reperfusion injury and increase the success rate of liver transplantation.

Ischemic preconditioning has been proven to be a promising technique for improving postoperative outcomes after liver

resections in a number of experimental investigations and a few clinical series. Furthermore, many pharmacological intervention and preconditioning methods, such as remote preconditioning, heat shock, and hyperbaric oxygen, have been developed to reduce the functional impairment associated with ischemia-reperfusion injury. The primary mechanisms of pharmacological preconditioning for liver ischemia/reperfusion injury are currently: (1) reducing cellular calcium excess; (2) reducing oxidative stress; (3) reducing inflammatory factor production; and (4) modulating apoptosis, pyroptosis, or autophagy. The majority of HIRI pretreatment medicines reduce tissue and cell damage by one or more of the mechanisms listed above, enhance liver tissue and cell resistance to ischemia-reperfusion (IR), maintain liver function, and prevent postoperative liver damage.

1. Substances that are anti-inflammatories

Although the inflammatory response is protective in the repair of tissue damage, an overabundance of it can harm tissue and organ function. Activated Kupffer cells produce a lot of reactive oxygen species, proinflammatory cytokines, chemokines, and adhesion molecules during HIRI. During liver resection, neutrophils aggregate in ischemic parts of the liver, promoting the inflammatory response of liver parenchyma cells, thanks to ROS-activated inflammatory pathways.

1.1Antagonizers of the adrenergic receptor

Mohammed et al. proposed that carvedilol can selectively antagonise α1ARs and non-selectively β_1ARs and β_2ARs as an adrenergic receptor antagonist[1], inhibit G protein-coupled receptor signalling pathway and reduce the expression of protein kinase C. level, thereby reducing the release of NF-κB and reducing the inflammatory response. CF102 is a highly selective α3 adrenergic receptor antagonist. Ohana et al. [2] believed that CF102 exerted a practical anti-inflammatory effect by down-regulating the expression of the PI3K/NF-κB signalling pathway.

1.2Dipeptidyl peptidase-4 inhibitor

Sherif et al. [3] discovered that vildagliptin, a dipeptidyl peptidase-4 inhibitor, lowers HIRI, primarily by inhibiting high mobility group protein 1 (HMGB-1). TNF- levels also reduce the expression of the TLR4/NF-B signalling pathway, which helps to reduce inflammation. By activating the Nrf-2/HO-1 pathway, Abdel-Gaber et al. [4] discovered that sitagliptin might enhance the expression of Nrf-2 mRNA and the content of HO-1 and so have an anti-inflammatory impact.

1.3Anesthetics

Yang et al. [5] found that remifentanil, as an opioid receptor agonist, could activate β-arrestin and reduce the inflammatory response of HIRI. Dexmedetomidine, an α2 receptor agonist, commonly used in clinical anaesthesia, can trigger the presynaptic α2A receptor on Kupffer cells' surface, inhibiting the expression of norepinephrine, inhibiting the inflammatory response, and reducing HIRI during hepatectomy.

1.4Endogenous active substances

Not only exogenous drugs can reduce HIRI damage, but many endogenous active substances can also play an important protective role. The Ang II/AT1R pathway, as a critical hypoxic/ischemic organ damage regulatory axis, activation of AT1R increases oxidative stress and the expression of inflammatory cytokines. Ye et al. [6] also found that pretreatment with galectin-1 (Gal-1), mainly expressed in macrophages, neutrophils, dendritic cells, and other cells, can increase anti-inflammatory cells. The expression of factor IL-10, while significantly attenuating the expression of pro-inflammatory cytokines and chemokines (CXCL-1, CXCL-10) such as TNF-α, IL-1β, IL-6 and IFN-γ, and reducing the inflammatory response.

In addition to the drugs included in the above categories, new drugs are continually being demonstrated to exert anti-inflammatory effects during HIRI. Kamel et al. [7] proposed that the angiotensin-converting enzyme inhibitor perindopril can alleviate the impact of Nrf-2-related signalling pathways, TLR4/NF-κB, JAK1/STAT-3, PI3k/Akt/mTOR and other signalling pathways. Yu et al. [8] found that L-tetrahydropalmatine can directly reduce the production of inflammatory

cytokines TNF-α and IL-6, further inhibiting the ERK/NF-κB signalling pathway and playing a protective role in the process of IR.

2. Medications to reduce cellular calcium overload

When IR occurs, the production of adenosine triphosphate (ATP) is reduced, the sodium-potassium pump activity is decreased, and the intracellular Ca2+ concentration is abnormally increased, that is, calcium overload. In addition, the damage to mitochondrial structure and function caused by cellular ischemia and hypoxia can also cause intracellular calcium overload. Calcium overload mainly induces cell death or apoptosis by activating calcium-dependent enzymes such as neutral protease and protein kinase C [1]. The current common drugs specifically reduce the cellular calcium overload during HIRI by protecting the structure and function of mitochondria. Neda et al. [2] proposed that silibinin can neutralise a large amount of ROS to maintain mitochondrial membrane integrity, reduce mitochondrial membrane fusion, reduce calcium overload, and reduce HIRI while regulating the expression of OPA1 and MFN1 genes. Gu et al. [11] [3] confirmed through experiments that ursodeoxycholic acid lysophosphatidylethanolamide could protect mitochondria, maintain ATP production, balance mitochondrial fission and fusion, reduce the reduction of mitochondrial fission and fusion calcium overload, and inhibit mitochondria-mediated apoptosis pathway and play a role in lowering HIRI.

3. Medications to reduce oxidative stress

Under physiological conditions, the reactive oxygen species (ROS) produced by hepatocytes maintain a dynamic balance with the superoxide dismutase (SOD) they contain. In the process of IR, Kupffer cells and neutrophils generate a large amount of ROS. The SOD produced by the body cannot be removed entirely, resulting in mitochondrial dysfunction, destruction of protein, cell membrane integrity and lipid peroxidation to produce propanediol. Aldehydes and other lipid peroxides. Therefore, scavenging excess ROS or increasing SOD expression can inhibit the occurrence of oxidative stress during IR, thereby alleviating HIRI.

De Almeida et al. [6] confirmed that methylene blue (MB) could exert its reducing properties at low concentrations, replacing oxygen molecules as the electron acceptor of xanthine oxidase in the electron transfer of IR, thereby reducing the amount of ROS.

4. Multi-mechanism medicines

Nobiletin, a natural flavonoid, is a beneficial antioxidant with anti-inflammatory and anti-cancer activities. In recent years nobiletin has received extensive attention due to its various medicinal properties and biological effects. Dusabimana et al. found that nobiletin can activate the SIRT1/FOXO3α signalling pathway to induce autophagy. Recent studies have shown that liver-selective MMP-9 inhibitors can reduce HIRI and accelerate liver tissue regeneration.

In the latest study, PPAR-γ agonists, the diabetes treatment drugs, were also found to play a protective role during liver ischemia/reperfusion. Oral administration of PPAR-γ agonists 1-3 days before liver surgery can effectively alleviate HIRI by activating the FAM3A-ATP-Akt signalling pathway, reducing oxidative stress and reducing the inflammatory mediator NF-κB . In addition, petrolatum can also reduce oxidative stress and inflammation by up-regulating the expression of PPAR-γ, regulating the downstream NF-κB-p65 and JAK2/STAT1 pathways .

Irisin, a newly discovered hormone, appears to be a novel and potential HIRI treatment. This kind of protein, which is released by skeletal and cardiac muscle after exercise, has many protective benefits in HIRI. After hepatic I/R, exogenous irisin treatment improved liver function, reduced liver necrosis and cell apoptosis, and lowered inflammatory response[14]. In hepatic I/R, exogenous irisin significantly reduced the expression of the mitochondrial fission related proteins dynamin-related protein 1 (drp-1) and fission 1 (Fis-1). Exogenous irisin therapy also boosted mitochondrial content as well as peroxisome proliferative activated receptor (PPAR) co-activator 1 (PGC-1) and mitochondrial transcription factor (TFAM) expression, all of which are associated to mitochondrial biogenesis. Irisin also reduced oxidative stress in the hepatic I/R by upregulating the production of uncoupling proteins (UCP) 2. Exogenous irisin therapy reduced hepatic I/R injury by inhibiting mitochondrial fission, boosting mitochondrial biogenesis, and alleviating oxidative stress, according to the

findings.

Conclusion

Ischemia-reperfusion damage is a serious side effect of liver surgery that is linked to a high rate of morbidity and mortality. Many studies have shown that pharmacological preconditioning can protect the liver by significantly reducing or preventing reperfusion injury throughout the last few years. However, most of these researches have been conducted on animals, and despite encouraging outcomes in experimental models, the majority of the findings cannot be applied to humans. Despite the fact that I/R injury appears to be reduced in terms of biochemical indices, most trials, particularly in the clinical situation, have failed to show any reduction in morbidity and mortality. As a result, the positive impacts on biochemical indicators must be translated into better clinical outcomes and validated in larger human investigations. More criteria, such as the patients' age, the pathology of the liver, the duration of ischemia, and the amount of the surviving liver, must also be investigated. On the following points, pharmacological preconditioning research and application still need to be improved: (1) The medication pretreatment study is currently in the early stages of development. (2) Based on the mechanism of action and pharmacokinetic characteristics of different drugs, what method and when to administer the medication during the perioperative period of liver surgery can exert the best protective effect of the drug is still being explored in the clinical application; (3) Whether pretreatment drugs with differing mechanisms of action and pharmacokinetic characteristics can exert the best protective effect of the drug is still being explored in the clinical application.

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Update and Application Analysis of Resident Health Records in Basic Public Health Services

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Abstract: Under the new era background, people's material living standards gradually improve, attention to self health also continue to improve, and through the establishment of residents' health records, can ensure the timely update of health information, can also provide effective reference for basic public health services, help people develop good health awareness, and improve the efficiency of basic public health services, maintain residents' health, promote social harmonious development. Based on this, this paper discusses the value of residents' health records in basic public health services, and proposes specific strategies for update and application for reference.

Keywords: Residents' Health Records; Basic Public Health Services; Value

Introduction

Residents 'health records are to integrate and record residents' health information, including medical treatment, health care, rehabilitation and other related information, and build it into a complete document after integration. After the establishment of residents' health records, medical staff only need to understand the health status of residents in detail through the examination of them, implement targeted disease diagnosis and treatment measures, and improve the efficiency of disease treatment. Therefore, the establishment of the residents 'health records has a very far-reaching significance, which not only facilitates the residents' personal medical treatment, but also promotes the development of the basic public health services toward the trend of comprehensive and information technology. To ensure that residents' health records play their due role, timely update and proper application are crucial.

1. The value of residents' health records in basic public health services

1.1 Detailed record and dynamic presentation of the health situation of the residents

Residents 'health records the residents' physical condition, medical records, medical information, etc., is the dynamic record of residents 'health, such as cases, medication information, family history, drug allergies, file has been tracking the health of residents, for residents to improve the efficiency of medical treatment, to ensure the targeted and scientific diagnosis and treatment, and residents' health records is with residents 'health changes and dynamic update, is a powerful basis for residents' health monitoring. At the same time, combined with the analysis of residents' health records, high-risk diseases in communities can be selected in the community, which is conducive to the development of community health services and improves the efficiency of disease prevention and control.

1.2 Lay a foundation for improving the quality of basic public health services

With the support of information technology, the residents' health records have been continuously improved, laying a solid foundation for the subsequent application. In public health services, community grassroots service centers can

understand the situation of residents in detail in the residents 'health records, and carry out hierarchical management of residents' physical status. Provide targeted health guidance for residents according to different ages, gender, disease and other characteristics, which can improve the quality of grassroots health services. For example, for the elderly, through the integration of community residents' safety files, targeted common disease lectures, can improve the efficiency of disease prevention for the elderly, for women and children, maternal and child health care knowledge lectures, can strengthen the self-protection ability of women and children. Through a full range of health training, the improvement of national health awareness, is conducive to the popularization of a healthy lifestyle. At the same time, the community grassroots health service centers have mastered the health situation of local residents and the community environment, and can carry out dynamic community health services, high-risk diseases have been quickly screened and handled, and chronic diseases and infectious diseases have been effectively controlled.

1.3 To ensure the physical health of the residents

Residents 'health records record the personal physical condition, the occurrence, development, treatment and improvement process are recorded, residents through archives can clear information, clear their body state changes, it is beneficial to prevent the occurrence of all kinds of diseases, from the perspective improve the health awareness, to adjust living habits, improve diet, etc., to health records to ensure the residents' healthy life. At the same time, the application of residents 'health records in the basic public health services, on the one hand, improves the efficiency of residents' diagnosis and treatment, on the other hand, it improves the residents' health awareness, which is conducive to the construction of a national healthy social atmosphere.

2. Update of residents' health records

After the residents complete the filing of their health records, the residents 'personal health information will also be dynamically improved in the relevant medical and health services, such as the residents' medical treatment, return visit, physical examination, etc., and the medical staff will integrate the relevant information into the archives, so as to realize the update of the residents' health records. At the same time, the community is also the main residents 'health records update, community through regular visits, physical examination, form timely communication with residents, understand health changes, realize the residents' health records update, in the process of visiting, should be the elderly, children, women and other people as a key visit object, to ensure that their health information update efficiency, and provide reference for medical services. In addition, it builds a grassroots health service system integrating medical treatment, health education and prevention to continuously promote the optimization of basic public health services.

3. Application strategy of residents' health records in basic public health services

The filing of residents 'health records makes China's medical and health services develop towards the trend of informatization, which has a strong role in promoting the quality of medical services, and is an important measure to maintain social stability and development. Therefore, we need to pay attention to the reasonable application of residents' health records and give full play to their good application value.

2.1 Improve the awareness of residents and implement dynamic updates

Only when residents' health records can be fully utilized can the value of filing be fully played. Therefore, after the establishment of residents 'health records, should be timely update of health status information, health check and records work should be fully paid attention to, gradually form a sound health information database, and continuous update database through dynamic monitoring, need to arouse the enthusiasm of residents' participation, strengthen the residents 'health training, let residents clearly understand the importance of sound health records and personal convenience of residents, ensure that the community can provide targeted health management services, with efficient archives sharing guarantee

residents' health, effectively improve the level of basic public health services.

2.2 Building a high-quality storage system for residents' health records

The data and information of residents' health records is dynamically updated, so the establishment of archives is characterized by sustainability and accumulation. How to ensure the effective preservation of data in this process has become a key problem. It is necessary to strengthen the construction of the storage system, and then meet the storage needs of massive data. Therefore, it is necessary to build a resident health records storage system to ensure that the data and information will not be lost or omitted in the long-term update process of data and information, so as to facilitate the extraction and application of health records. It is worth noting that in the construction of resident archives storage system, should improve the traditional data backup method, but with the help of advanced computer technology, applied data archiving technology, storage technology, etc., build up hierarchical storage structure, realize the goal of combining access storage, realize data automatic archiving function, maximize the quality of data storage. At the same time, the residents' personal health records storage system should also have a good function of restoring the online status, which can deal with the data loss caused by various emergencies and ensure the integrity of the data.

2.3 Strengthen the safety guarantee of residents' health records

Residents 'health records involve residents' personal privacy, so the protection of privacy and security must also be paid full attention to in the application of residents' health records. Security should start with the application of security technology, such as Cookie encryption, SQL code injection prevention technology, etc., through the scientific use of security technology, overall improve the security of residents' health records system, do not give illegal molecules an opportunity, but also can effectively avoid disputes caused by file problems in public health services.

2.4 Clarify the application objectives of residents' health records

In the process of the continuous development of China's medical and health undertakings, more and more attention is paid to the construction of regional platforms, aiming to realize the overall planning and coordination of health service institutions, so as to realize the sharing of medical and health information, and then provide the source of power for the development of medical and health undertakings. Therefore, residents' health records in the process of application, should also be under the support of information technology to improve the document efficiency of electronic archives file, build up the standard, scientific file system, clearly improve the quality of medical and health services, for rehabilitation, medical care, health care and other functions to provide data information support, and improve the medical and health services, to provide good health care for residents.

In addition, our country social economic development rapidly in recent years, the pace of medical and health services also accelerated, so should combine residents health management, performance appraisal, medical services and other functions to build up the integration of health system, to carry out the information construction, combining medical behavior and performance appraisal, and arouse the enthusiasm of medical personnel, to ensure that residents health records and other related resources maximum use, by improving utilization efficiency to promote social progress.

Conclusion: To sum up, in the process of developing basic public health services, improving and updating residents' health records is the top priority, and it is an important cornerstone to ensure the development of basic public health services. Therefore, the relevant managers must pay attention to the update and application of residents 'health records, on the one hand, arouse the enthusiasm of community workers, actively carry out visits and investigation activities, improve residents' health records, on the other hand is to strengthen the health education of residents, guide residents to actively participate in the health file management work, make the community and residents form a good force, jointly realize the sound health records system, and for the basic public health service quality to lay a solid foundation.

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Universe Scientific Publishing

Analysis of the Health Needs of Inpatients and Hospital Health Service Strategies

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Abstract: Hospitals exist to provide medical care to the community with a passion to exceed client requirements and expectations. The hospital's positive trend toward client outcomes, awards, and recognition is a combination of excellent service and rapid response to community needs, and we should support the hospital's vision, mission, and values. A superior service leadership system creates and balances the value of three customer groups, placing the customer at the heart of organizational decision-making. The key to guiding the results is the leadership development process and corresponding rewards, as well as the management experience of the hospital's "hire service", which becomes the basis for achieving the organizational leap.

Keywords: Health Needs of Inpatients; Hospital's Health Service Strategy

Introduction

Hospitals apply health promotion theories, concepts and strategies to medical institutions, build a comprehensive medical service system centered on patient needs and health, and provide a good interactive platform for hospitals, medical staff, patients and community residents. Clinical services not only contribute to health and disease policy, an enabling environment for the physical and mental health of physicians and patients, and community action, but also to enhance health education and provide optimal health services. It can further improve the knowledge and skills of patients and their families, community residents and medical staff on disease control and prevention of healthy lifestyles, and improve their health and fitness levels.[1] This paper analyzes the health needs of the inpatient population and the analysis of the hospital health service strategy. Details are as follows:

1. Health needs of inpatients

1.1 Needing a good health care environment

The medical environment, as well as the nursing hygiene environment, should have a positive impact on the patient, be therapeutically effective, and be able to meet the needs of the patient. One of the duties of nurses is to provide people with a safe and comfortable treatment environment and to promote national health. The arrangement and workflow of a medical environment should be patient-centred, consider patients' comfort and convenience, and minimize patient suffering. Therefore, it is very important to create and maintain an optimal physical and social environment for the recovery of the patient's health.

1.2 Needing happiness and company

When people get sick, it is often accompanied by changes in mood and behavior.From a healthy person to a patient suddenly, it is difficult to adapt, and it is difficult to enter the role of a patient, and various reactions may occur. For example, they do not admit that they are ill, refuse to be taken care of by others, do not trust their work, and do not let go of the role of the family. Patients often feel fear, loneliness, anxiety, and dependence. New patients generally hope to adapt to the new environment as soon as possible, be emotionally welcomed by the patient, and become a member of the group. For hospitalized patients, the care, love and support of families are essential. Inappropriate family visits can affect the patient's

rest and recovery.[2]

1.3 Physiological and Pathological Needs

Generally speaking, telling patients truthfully is beneficial to examination, treatment, and drug cooperation. Of course, some diseases can be properly treated conservatively without raising suspicion. Otherwise, the idea of being deceived will build up in the patient's worries and anxieties, and eventually aggravate the condition. A correct pathology report is necessary. First of all, the doctor should check the clinical diseased tissue, fix it with fixative in time, and make an appointment with patients. The pathologist's specification of pathological sections should be standardized. A pathologist must have a certain level of production and experience to gain a more detailed understanding of a patient's symptoms, as well as other test results, to rule out the possibility of other pathologies.

1.4 Wanting to be known and respected more than usual

Once the patient enters the role of the patient, the medical staff is expected to understand what kind of social role he originally was, his importance and contribution. In this way, the medical staff can take him seriously, care about his condition, and let him get better treatment. All patients expect healthcare workers to call them by their first names, not their bed numbers. In addition, the patient's family, colleagues, and friends should go to the hospital for treatment in time to eliminate loneliness. When this need is satisfied, patients will have a sense of security and trust, their condition will be stable, and they will be willing to cooperate with doctors.

1.5 Hoping to recover as soon as possible without any sequelae

Patients hope that there will be no accidents during the treatment, and the treatment measures given by the medical staff are safe, reliable and less painful. If these needs can be met, they believe that medical staff are serious and responsible. Patients feel more confident in their treatment, feel more stable, and feel happier. They can cooperate with medical care, and the effect is more obvious. They can also strive for a speedy recovery and discharge from the hospital, get rid of the role of a patient psychologically and physically as soon as possible, return to work and study, and assume the responsibilities of their original social roles.

2. Hospital's Health Service Strategies

2.1 Environmental protection

The layout of the ward should be simple, neat and beautiful. The indoor temperature is generally between 18°C and 22°C in winter and around 25°C in summer. Humidity 50 ~ 60% is appropriate. Paying attention to ventilation and keep the air in the ward fresh. Reducing noise and try to create a quiet environment. Staff should pay special attention to their words, actions and work. In addition, with proper sun exposure, it improves the nutritional status of skin and tissues, increases appetite, and makes you feel comfortable and happy. Therefore, in the ward we have to open the windows to let the sun shine directly in, but not let the sun shine directly on the face.[3]

2.2 Psychological care

Nurses should first be enthusiastic when receiving patients, and should take the initiative to introduce themselves, the environment and regulations. There is good emotional communication and help among patients. Mutual help and care among patients is conducive to eliminating the heterogeneity and anxiety of new patients, and promoting friendship and solidarity among patients. For the emergence of some negative emotions, we must be good at perception, patiently explain, and guide them correctly. The caregiver is the primary regulator of the patient environment, appropriately guiding the patient to positively influence various influences. Instead, nurses can take advantage of this positive atmosphere and do their nursing work better. Therefore, we should appropriately limit the number of visits and inform the relatives of patients of relevant precautions. Individual patients will change their appearance due to surgery. We must fully respect, try to control the scope

of visitation, and talk more about the condition to avoid affecting the patient's good mood. If the patient cooperates well, timely encourage the progress of rehabilitation, so that the patient can obtain psychological satisfaction and confidence. When contacting patients, medical staff should answer the questions clearly and without hesitation. Conversations between health care workers and family members need to be kept confidential and should be avoided with patients. If the patient can participate and listen, we should talk face-to-face to reduce the patient's psychological suspicion.

2.3 Respect patients

When performing their duties, nurses should eliminate the physical and mental pain of patients in specific medical and nursing activities, and should treat them equally regardless of nationality, belief, gender, occupation, position, distance. Nurses should be generous and decent in front of patients, patiently and meticulously answer questions raised by patients, reduce patients' fear and anxiety about symptoms, win patients' trust, and enable patients to actively cooperate with treatment and nursing. The relationship between good care and the patient is itself therapeutic. Everything starts from the interests of patients, meets the physical and mental needs of patients, and respects the rights and personality of patients. Nursing staff should listen to the opinions of patients often and in a timely manner, especially patients who are hospitalized for the first time and elderly patients. They should take active care, scientifically explain the patient's physical symptoms, so that the patient can be relieved and cooperate with the treatment. Unresolved issues show that patients feel safe and trusted to receive hospital care.[4]

2.4 Organizing Rehabilitation Exercises

We should introduce the patient's condition, diagnosis and treatment methods in a timely manner, and provide information such as rehabilitation measures and prognosis. Medical staff often seek the opinions and requirements of patients, offer hope to patients, and encourage patients to actively participate in treatment and rehabilitation activities. According to the specific situation of the patient and the objective conditions of the hospital, they organize appropriate activities and fresh stimulation to meet the spiritual needs of the patient. It can not only stabilize the patient's mood, but also help the patient quickly adapt to social life after recovery.

3. Conclusion

To sum up, everyone wants to have a healthy body. Of course, getting sick is not voluntary. Similarly, the occurrence of the disease cannot be controlled by oneself, and once hospitalized, the mental and physical pain is very painful. The hospital's service is not only patient-centered, but also "patient-centered needs", that is, professional services. Health services emphasize the attentiveness of people and the whole process. Medical staff participate in the whole service chain from outpatient to hospitalization, from hospitalization to discharge, and provide warm services throughout the process. The attitude of health service is an important part of the competitiveness of the hospital, and it is also an aspect that can be rapidly improved after we complete the environmental transformation. Only by understanding the difficulties of one patient and realizing the importance of treating all patients well, can the satisfaction of patients be improved in practical work. Once customers are loyal to the hospital, the hospital can maintain the long-term stability of the medical market share, reduce the operational risk in the future market, resist the attack of competitors, and reduce the pressure of competition.

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Universe Scientific Publishing

Application and Safety Evaluation of Integrated TCM-WM in the Treatment of COVID-19

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Running Title: The Intergrated TCM-WM treatment for COVID-19

Abstract: Introduction: With the emergence of more infectious mutant strains and the appearance of new crown sequelae, early precise treatment is particularly important. The traditional Chinese medicine and Western medicine (TCM-WM) treatment plan exhibits unique superiority in the COVID-19 treatment, but the efficacy and safety have not been fully elucidated. Methods: A analysis of the clinical characteristics of 7 COVID-19 patients diagnosed in our hospital, as well as the results of precise individual intervention treatment with TCM-WM, including laboratory examination, and CT changes of imaging. Results: On admission, laboratory results showed that 7 patients' overall Lymphocyte count (LYM#), Percent Lymphocytes (LYM %), and Alanine aminotransferase (ALT) were reduced, but Neutrophil percentage (NEU%) were increased. CT imaging showed that most patients had multiple patchy shadows and ground-glass shadows in both lungs. After TCM-WM treatment, the above pathological states were significantly improved. All patients were followed up and had a good prognosis. Conclusions: Accurate therapy with TCM-WM can quickly and effectively alleviate and treat patients with COVID-19, without severe Long Covid.

Keywords: COVID-19; TCM-WM; CT; Long Covid; Omicron

Introduction

COVID-19 is a respiratory system disease and followed by a series of sequelae. Therefore, early and precise intervention treatment is particularly important.[1] Through continuous improvement of TCM-WM treatment plans and a series of medical measures, more patients have benefited.[2]

The main Clinical manifestations of the COVID-19 infection are fever and dry cough, along with pneumonia.[3] Based on the basic treatment plan combined with the clinical efficacy of Lianhua Qingwen Granules, Qingfei Paidu Decoction and other TCM prescriptions, the observation shows that TCM can significantly improve the clinical symptoms and laboratory indicators of patients, which establishes the value of TCM treatment in this field.[4]

In this article, we retrospectively analyzed the clinical characteristics and outcomes of 7 cases of COVID-19 patients who passed the integrated TCM-WM precision diagnosis and treatment plan. The purpose is to help clinical teams to clarify the individualized TCM-WM precision diagnosis and treatment plan. Early development of individualized treatment regimens can speed up treatment and reduce disease progression and aftereffects.

1. Materials and Methods

1.1 Ethics

Our institutional review committee waived written informed consent for this retrospective case series, which evaluated unidentified data and presented no potential risk to patients. There was no link between the patient and the researcher.

1.2 Inclusion and Exclusion Criteria

We reviewed the laboratory data and CT images of the 7 patients with COVID-19, from January 20, 2020, to May 27, 2020. Other pneumonias caused by common bacterial and viral pathogens were excluded.

1.3 Study Design

Individualized precision treatment plans are formulated according to the patient's admission diagnosis and treatment progress. Followed the Mild and Common prescription (Qingfei Paidu Decoction). On the basis of this general prescription, the patient was given antiviral treatment with drugs (Abidor hydrochloride, Ribavirin granules, Lianhua Qingwen capsule).

1.4 Data Collection

2mL of cubital venous blood from COVID-19 patients was collected. Routine blood test and liver and kidney function test were performed by sysmexXN-9000 automatic blood cell analyzer and KHB ZY-1280 automatic biochemical analyzer within 4h at room temperature.

All patients underwent thin-section CT scans. CT imaging examination recorded the changes of CT imaging during the whole process from early onset to TCM-WM treatment, and prognosis tracking. Three fellowship-trained cardiothoracic radiologists used a viewing console to independently review all CT images and finally reached a consensus.

1.5 Statistical Analysis

Statistical data comparisons were performed using GraphPad Prism 5 software. Data are expressed as mean ± standard deviation (SD). Paired t-test was used for the changes of a single indicator before and after treatment. One-way analysis of variance and analysis of variance of repeated measurement data (One-way ANOVA) was used for comparison between groups and then Tukey test. $P< 0.05$ indicates a statistically significant difference.

2. Results

2.1 Clinical Features

The subjects included 3 men and 4 women, aged between 25 and 55. The most common symptoms were fever and cough, mostly low-grade fever. No other symptoms included fatigue, abdominal pain, chest tightness, et al, as detailed in Table 1.

Table 1: Clinical Characteristics of COVID-19 patients (n=7)

Characteristic		Number of patients (%)
sex	Men	3 (43%)
	Women	4 (57%)
Age(years)	Mean	40.14
	Standard Deviation	11.23
	Rang	25-55
Symptoms	Fever	4 (57%)
	Cough	3 (43%)
	Expectoration	1 (14%)
	Fatigue	0
	Chest distress	0

2.2 Laboratory test results before and after the intervention

The 7 COVID-19 patients were all positive for nucleic acid tests. Laboratory examination results at admission showed

that 7 patients had overall declines in LYM#, LYM% and ALT, and increased NEU%. Among them, hs-CRP was significantly increased in 4 patients; Cr was significantly increased in 1 case (case 8, previous gout 6 years); Some patients had elevated UA, LDH and AST (Table 2).

Combined with the actual situation of the patients, and carry out precision individualized intervention treatment for 7 COVID-19 patients. Results indicated that LYM# and LYM% are increased, while NEU% and ALT are decreased. Follow-up results indicated a good overall prognosis (Table 3).

Table 2: Comparison of blood routine, liver and kidney function test results between early COVID-19 patients and healthy subjects

Index	COVID-19 patients (n=7, ≥15 years)							Healthy subjects (n=7, ≥15 years)
	1	2	3	4	5	6	7	Median (reference range)
WBC (10^9/L)	6.30	4.62	4.89	4.18	7.10	4.70	7.65	6.50 (3.5-9.5)
LYM (%)	14.0	32.9	31.1	21.8	30.4	31.4	27.5	35.91 (20-40)
NEU (%)	84.6	58.6	63.2	73.7	63.5	65.8	61	56.25 (50-75)
LYM# (10^9/L)	0.88	1.52	1.52	0.91	1.9	1.76	2.1	2.06 (0.8-4)
NEU# (10^9/L)	5.34	2.71	3.09	3.08	4.50	3.15	4.67	3.28 (2-7.7)
hs-CRP (mg/L)	0.48	2.12	0.36	29.36	0.46	6.53	2.57	1.02 (0-2.1)
ALT (U/L)	23.4	50.8	12.5	21.5	20.5	25.4	56.5	24.5 (7-40)
Cr (umol/L)	66.6	66.5	47.7	45.2	73.7	86.4	83.4	62.3 (41-73)
UA (umol/L)	285.4	335.6	300.5	85.8	358.3	385.1	514.8	305.1 (90-357)
LDH (U/L)	213.7	158.7	125.9	285	165	135.7	135.4	152.4 (120-250)
AST (U/L)	26.1	28.9	15.1	27.8	18.5	16	21.9	19.4 (13-35)

Table 3: Changes in blood routine, liver and kidney function related indicators of COVID-19 patients before and after treatment

Index	COVID-19 patients (n=7, ≥15 years)			Reference range
	Pro treatment	Post treatment	Prognosis review	
WBC (10^9/L)	5.42±1.21	5.18±1.17	5.50±1.44	3.5-9.5
LYM (%)	27.88±7.19	33.94±6.35	37.62±6.19#	20-40
NEU (%)	66.51±8.66	59.56±6.02	55.51±7.33#	50-75
LYM# (10^9/L)	1.48±0.41	1.8±0.30	2.13±0.36##	0.8-4
NEU# (10^9/L)	3.42±1.0	3.10±0.94	3.16±1.07	2-7.7
ALT (U/L)	38.99±14.66	28.81±11.41	26.18±9.35#	7-40
AST (U/L)	22.06±1.73	19.52±3.66	21.03±2.60	13-35
Cr (umol/L)	64.32±15.13	64.34±10.91	65.96±9.19	41-73
UA (umol/L)	337.6±87.71	326.00±58.77	335.1±113.20	90-357
LDH (U/L)	170.1±50.39	158.4±18.47	186.2±15.30	120-250

Mean±SD. #P < 0.05; ##P < 0.01 vs. Pro treatment.

2.3 CT test results before and after treatment

Six patients were diagnosed as ordinary types and presented early imaging manifestations. All patients with COVID-19 were given individualized treatment with TCM-WM in accordance. The results showed that the pulmonary lesions were obviously absorbed, and after 2-3 courses of treatment, the pulmonary lesions disappeared. CT Follow-up showed good prognosis (Figure 1).

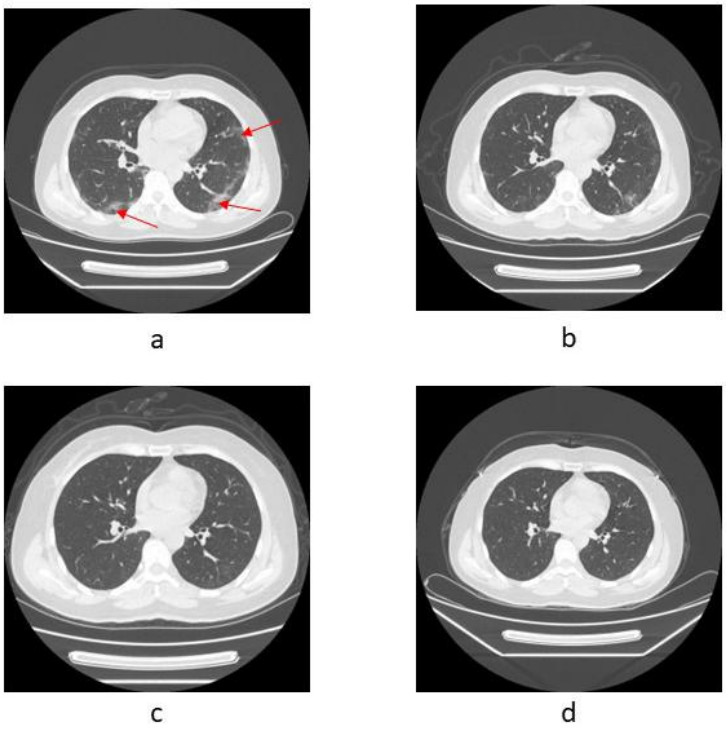

Figure 1 Imaging CT of Mild COVID-19 patients. a. Strip and ground glass shadows in both lungs, with unclear boundaries. b. Some lesions were resolved. c. The lesions had subsided significantly. d. Reexamination results showed that the lesions are fully absorbed in both lungs.

3. Discussion

COVID-19 is a new and highly contagious disease that spreads mainly through the respiratory tract and contact.[5] At present, omicron has become a major circulating variant in the world, with faster transmission, and atypical symptoms.[6] Early isolation and treatment is important to prevent the spread of the virus in the population.[7]

The rapid guidelines for the diagnosis and treatment of COVID-19 recommend that its CT findings be divided into early-stage, progressive stage, and severe stage.[8] The combined treatment of TCM-WM can reduces the chance of mild COVID-19 patients developing into severe.[9] Based on the retrospective analysis of 7 confirmed COVID-19 patients admitted to our hospital, To evaluate the role of TCM-WM precision therapy in the treatment of patients, to provide reference for the early diagnosis and treatment of diseases.

Related reports pointed out that COVID-19 patients had mild symptoms in the early stage, but suddenly worsened in the later stage. The analysis of clinical experts in the first-line treatment is related to the “inflammatory storm”.10 TCM advocates strengthening immunity, reducing pulmonary inflammation, and protecting vital organs.11 Our study showed that the curative effect of integrated TCM-WM is clear.

To sum up, with the evolution of virus mutations, the virus is relatively mild, coupled with the vaccination and rapid screening, the cases are mainly mild.12 With the introduction of the COVID-19 Diagnosis and Treatment Program (Trial Ninth Edition), the integration of TCM-WM is closer, and personalized precision medicine is developing rapidly.13 At present, these strategies and measures are very effective.

Of course, our study had several limitations. Due to the small sample size and single-center clinical research, the results may not fully reflect the efficacy of integrated TCM-WM. At present, a more thorough and comprehensive research on the precise and individualized treatment plan of integrated TCM-WM is being carried out in local cases.

4. Conclusion

This work affirmed the role of integrated TCM-WM precision therapy in the treatment of patients, providing a reference for the early prevention and treatment. Future research will be helpful to formulate more precise integrated TCM-WM diagnosis and treatment plans based on patients, and reduce the occurrence of sequelae of Long Covid.

Author Contributions

Designed and wrote the manuscript: Dr. Qu, Mr. Wang. Performed the experiments: Mr. Wang, Mr. Ma, Ms. Wang, Dr. Yue, Mr. Chen, Dr. Dong. All co-authors have reviewed the manuscript and agreed with the manuscript results and conclusions.

Author Disclosure Statement

The authors declare no conflict of interest.

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Universe Scientific Publishing

Effects of Ultra-early Intervention on Gross Motor Function in Neonates with Hypoglycemic Brain Injury

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Abstract: Objective: To investigate the effect of ultra-early intervention on gross motor function of neonates with hypoglycemic brain injury and evaluate the application value. Methods: we choose thirty four children with hypoglycemic brain injury who hospitalized in the neonatology department of Tai'an City central hospital from January 2017 to December 2019. They were randomly divided into conventional treatment group and ultra-early intervention group, each with 17 people. The conventional treatment group received conventional treatment. In addition to conventional treatment, the ultra-early intervention group was given ultra-early intervention . When two groups of children's corrected gestational age at 40 weeks, 42 weeks and 44 weeks, they need to be tested for NBNA neonatal neurobehavioral testing, and Alberta Infant Exercise Scale (AIMS) assessment. Results: When the child's corrected gestational age is 40 weeks, there is no significant difference in the scores of NBNA and AIMS between the ultra-early intervention group and the conventional treatment group; When the child's corrected gestational age is 42 weeks, the NBNA and AIMS scores of the ultra-early intervention group are higher than those of the conventional treatment group, but there is no statistical significance; When the child's corrected gestational age is 44 weeks, the ultra-early intervention group had higher NBNA and AIMS scores than the conventional treatment group, which was statistically significant (P<0. 05). Conclusion: After ultra-early intervention, the development level of gross motor in the ultra-early intervention group was significantly higher than that in the conventional treatment group. Ultra early intervention has obvious effect on the improvement of gross motor function in neonates with hypoglycemic brain injury.

Keywords: Ultra-Early Intervention; Hypoglycemic Brain Injury; Gross Motor Function

Hypoglycemia is a common disease of metabolic disorders in the neonatal period. Continuous or repeated hypoglycemia can affect the development of the central nervous system and even lead to irreversible and permanent brain damage[1]. It has placed a heavy burden on the family and society. Early intervention is an organized and purposeful educational activity in a rich environment. According to the law of intellectual development of infants and young children, it can promote the development of their potential and prevent or reduce their disability. [2]. In general, high-risk children with a high risk of developmental disorders should receive early intervention as soon as possible[3]. The treatment of infants and young children from birth to less than 3 months is called ultra-early treatment. At present, the routine treatment of neonatal hypoglycemia is the main clinical treatment, and the ultra-early intervention treatment is less involved. In order to further explore the effect of ultra-early intervention treatment on gross motor function in children with hypoglycemic brain injury, the authors conducted relevant research, and the report is as follows.

1. Data and Methods

1.1 General Information

Inclusion criteria: ① gestational age ≥ 37 weeks, blood glucose level below 2. 2 mmo/L to diagnose hypoglycemia. ②Have related clinical symptoms co-occurring with hypoglycemia, or a history of severe hypoglycemia (0-1. 7mmol/L); ③Have neurological symptoms at the occurrence of hypoglycemia and a period of time after blood sugar correction, such as convulsions, poor response,etc;

Exclusion criteria: ① Severe intracranial hemorrhage ② Intracranial infection ③ Abnormal brain development ④ Brain injury caused by congenital metabolic diseases and endocrine diseases.

A total of 34 children with hypoglycemic brain injury who were hospitalized in Tai'an Central Hospital from January 2017 to December 2019 were selected. Randomly divided into ultra-early intervention group and conventional treatment group. There were 17 cases in each group, and there was no significant difference in general data between the two groups.

1.2 Treatment methods

Routine treatment group: give routine oxygen inhalation, maintain the balance of blood pressure, blood sugar, intracranial pressure and water and electrolyte quality, correct acidosis, and do the routine treatment such as fluid rehydration, anti-infection, improve microcirculation and so on. The ultra-early intervention group gave the ultra-early intervention (15 points / time, 2 times / day) on the basis of routine treatment for 4 weeks. The specific treatment methods are as follows:

1.2.1 Sensory integration training

① Visual perception training: The child is placed in a supine or semi-sitting position in a quiet and aroused state, with a vertical distance of about 20cm from the child's eyes, and a black and white card or a red ball is moved left and right for visual tracking training. At the same time, focus on strengthening and looking at the face, 2 times a day, 1 ~ 2min/time. ②Auditory training: select low-frequency band (between 16-160HZ) soft and pleasant music, gentle speech and singing for auditory stimulation in the awakened state, 2 times a day, 3-5 min/time. ③Tactile training: wrap the child with wrapping pressure or wrap the limbs in a thin cotton hug, try to keep the fingers close to each other, try to get a large area of stable, deep deep sensory stimulation 2 times/day, 3-5 minutes each time Second-rate. ④Vestibular training: Supine position, prone position, lateral position and conversion between various positions. ⑤Proprioceptive training: gentle passive activities of limbs, variable movements of limbs, etc.

1.2.2 Posture management

①Correct limb positioning of the child to suppress abnormal postures and abnormal patterns: lie supine in the "nest" shaped warm box made of bedding, forming a symmetrical flexion posture with a slightly curved head and symmetrical limbs.

1.2.3 Traditional Chinese Medicine Massage

①Using pushing and pressing along the meridians, massage along the meridians of the limbs, 5-8 times/time, 1 time/day. ②Press the acupoints and select "Sishencong, Baihui, Yongquan, Qihai, Guanyuan, Yintang, Quchi, Hegu, Huantiao, Biguan, Yangling, etc. ” Do point pressure, 2-3min/each time. ③Routine health care techniques: open the gate of heaven, push the palace, rub the sun, rub the high bones behind the ears, knead the spine 5-8 times/time, 1 time/day.

2. Evaluation method

At 40, 42, and 44 weeks of corrected gestational age, the infants were evaluated by NBNA neonatal neurobehavioral measurement and Alberta Infant Motor Scale (AIMS).

2.1 NBNA determination method

NBNA scoring criteria are mainly divided into 5 items and 20 items. It mainly includes: behavior ability (6 items), passive muscle tone (4 items), active muscle tone (4 items), original reflection (3 items), and general valuation (3 items). Each item was divided into three grades of 0,1, and 2 points, with a total score of 40 points and 37 points as normal. The test was performed by 1 experienced physician in a quiet, semi-dark environment at a room temperature of 22 to 27℃.

2.2 Alberta determination method

In the prone, supine, sitting and standing positions, the score under each position was obtained, and the total AIMS score was calculated. According to the total AIMS score and month age, the percentile corresponding to the AIMS score is less than 10% as the criterion for abnormal motor development[5-6].

3. Statistical methods

Analysed using SPSS 22. 0 statistical software, measurement data were represented by $\bar{x}$ ± s and t-test for mean comparison between groups. A P <0. 05 was considered as a statistically significant difference.

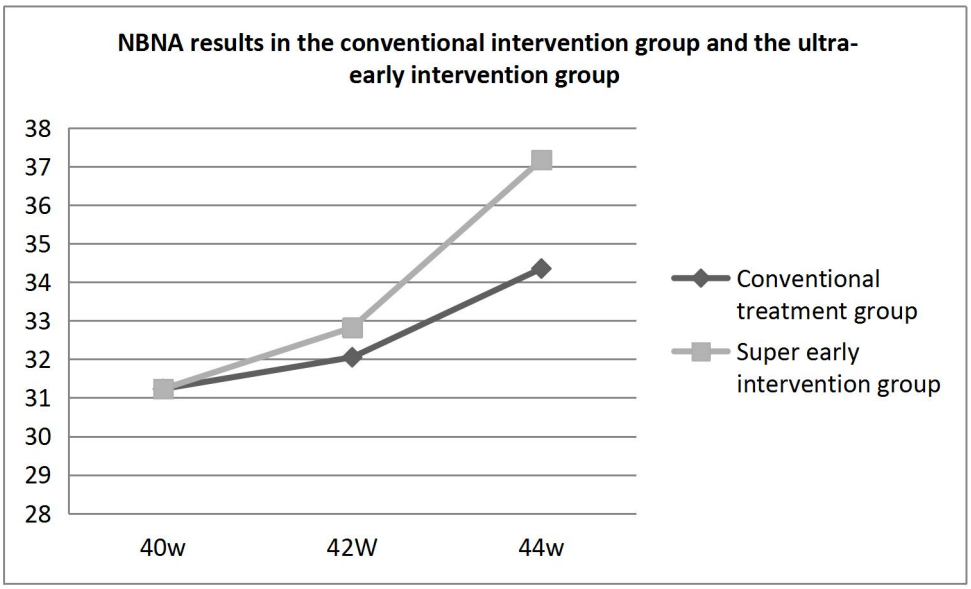
4. Results

(1) The NBNA scores were not significantly different at 40 and 42 weeks (P> 0. 05), and significantly higher in the ultra-early intervention group at 44 weeks compared with the conventional treatment group, and the difference was significant (P <0. 05). See Table 1,2.

Table 1 Comparison of w NBNA measurement results of 40w, 42w, 44 among the groups in conventional treatment group and super-early intervention group ($\bar{x}$ ± s, points)

group	n	gestational age	capacity for action	Passive muscle tone	Active muscle tone	primary reflection	General reaction	total points
Conventional treatment group	17	40w	8. 94±1. 19	6. 70±1. 04	5. 29±0. 68	4. 82±0. 72	5. 47±0. 71	31. 23±1. 85
ultra-early intervention group			9. 0±0. 86	6. 58 ±1. 27	4. 94±0. 55	5. 05±0 5. 6	5. 64±0. 49	31. 23±2. 07
Conventional treatment group	17	42w	9. 17±1. 13	6. 82±0. 95	5. 47±0. 62	5. 0±0. 86	5. 59±0. 51	32. 05±1. 98
ultra-early intervention group			9. 29±0. 68	6. 82±1. 07	5. 52 ±0. 51	5. 29±0. 46	5. 76±0. 43	32. 82±1. 66
Conventional treatment group	17	44w	9. 94±0. 74	7. 17±0. 88	6. 17±03. 6	5. 41±0. 71	5. 64±0. 49	34. 35±1. 61
ultra-early intervention group			10. 88±0. 69	7. 82±0. 39	6. 64±0. 49	5. 88±0. 33	5. 94±0. 24	37. 17±0. 80

Table 2 NBNA Results

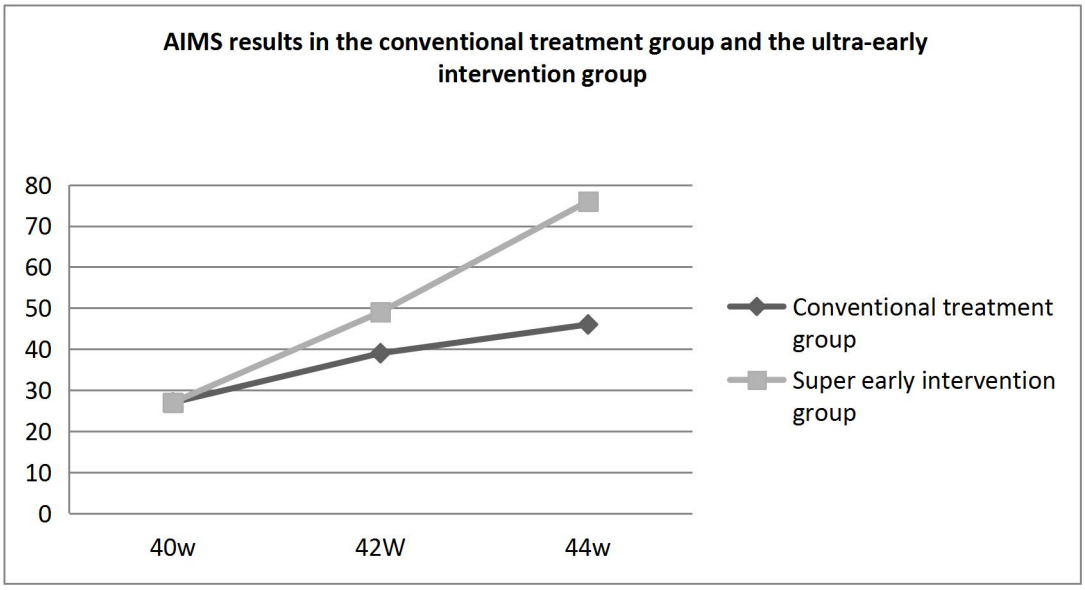


(2) The AIMS scores and total scores of the two groups were compared at 40 and 42 weeks of corrected gestational age (P> 0. 05), and the ultra-early intervention group at 44 weeks was significantly higher than the conventional treatment group, and the scores were significant (P <0. 05). See Table 3,4.

Table 3 Comparison of w AIMS measurement results of 40w, 42w, 44 conventional treatment groups among conventional treatment groups in conventional treatment group and super-early intervention group ($\bar{x} \pm s$, points)

group	n	gestational age	prone position	dorsal decubitus	a place to sit	erect position	total points
Conventional treatment group	17	40w	1. 0	0. 58±0. 5	0	0	1. 58±0. 5
ultra-early intervention group			1. 0	0. 58±0. 5	0	0	1. 58±0. 5
Conventional treatment group	17	42w	1. 05±0. 24	1. 41±0. 50	0	0±0. 11. 33	2. 29±0. 58
ultra-early intervention group			1. 23±0. 43	1. 11±0. 33	0	0±0. 23. 43	2. 88±0. 78
Conventional treatment group	17	44w	1. 58±0. 50	1. 52±0. 51	0	0. 17±0. 39	3. 29±0. 77
ultra-early intervention group			2. 11±0. 48	2. 05±0. 65	0. 23±0. 43	0. 52±0. 51	4. 94±1. 08

Table 4 AIMS Results



Discussion

Neonatal hypoglycemia is a common metabolic disorder. Continuous repetition can cause irreversible damage to the nervous system, resulting in different degrees of sequelae and dysfunction[1]. The early infancy brain has great plasticity and compensation, and early intervention and rehabilitation training can promote the proliferation of nerve cells and the regeneration of myelin after brain injury to increase the information transmission between neurons[7-8]. Early in life, the brain has enormous plasticity. During passive and active movement in early intervention, synapses are always connecting with each other, establishing connections between nerve cells and compensating for damaged brains[9]. Therefore, actively conducting ultra-early intervention is of profound significance.

ultra-early intervention treatment for visual, auditory, tactile, vestibular, proprioception and other sensory integration training. Sensory integration theory holds that basic senses such as sight, hearing, touch, taste, and smell have been acquired in the neonatal period, and the development of muscle tone, balance, body posture control, and emotional adjustment is closely related to the continuous input of multiple senses. Multiple sensory inputs are integral to promoting the perfection of the developing brain. When these important sensory stimuli are insufficient or impaired, there will be different degrees of paresthesia, which will affect higher-level development such as cognitive ability, action planning, emotion regulation, and hand-eye coordination. [10]Visual training increases visual stimulation through face (red ball) to improve social ability. Hearing training adopts different tones, sound quality and volume sound input, which can guide children to actively find the sound source and enhance the discrimination ability and sensitivity of sound. Body compression (limb pressing) can increase tactile input, reduce tactile sensitivity, and enhance the perception of the limbs. Vestibular perception training increases the sensory input to position perception and vestibular perception through the supine, prone, and lateral lying interposition transformation, which facilitates the regulation of muscle tone. Ontoception training increases proprioception and induces active movement of the limbs through passive limb activity and joint extrusion. Zhang Yanan et al. showed that the input of multiple sensory stimuli can improve the ability of sensory reception and processing in high-risk children[11]And the neurobehavioral ability[12]。

Children in the neonatal period, due to the lack of muscle tension, the limbs are often in a stretched state; and for a long time in this position can lead to muscle movement and development disorders, serious can cause deformity[4]. Through the "nest" shaped position, can promote the development of limb symmetry, make the limbs in the midline flexion position, in order to promote the development of their hand and mouth comprehensive ability, improve self-comfort, and improve self-regulation ability, is conducive to the neuromuscular maturation and autonomic stability[4]; Therefore, early postural

management can suppress abnormal posture and promote the development of correct movement patterns.

Traditional Chinese medicine massage is an important part of the essence of traditional Chinese medicine, and the theory of traditional Chinese medicine massage serves as an auxiliary means to promote the development of the rough motor function of high-risk children[13]。

After treatment in the ultra-early intervention group of this study, the gross exercise capacity was significantly higher than that in the conventional treatment group. After treatment, 2 groups compared behavioral ability in NBNA score, significantly and statistically different. This is related to the visual perception and auditory training in the sensory integration training, which improves the habituation of sound and light, and improves the active participation of the children through the adult interaction ability during the training process. Comparison of the AIMS scores in the supine and prone positions of the 2 groups showed a statistically significant ability improvement in the supine and prone positions. This is related to the improvement of the integration ability of visual and hearing, vestibular perception, and position perception, as well as the conversion of various positions, passive limb activity, and traditional Chinese medicine massage, which promotes the muscle activation of the head, neck and back. However, the AIMS scores compared between the sitting and standing positions showed no significant difference, which may be related to the monthly age and the growth and development rules of the children included in the study.

Therefore, the implementation of ultra-early intervention for newborns with hypoglycemic brain injury can significantly improve the gross motor function, promote exercise development, improve the doctor-patient relationship, improve parents' confidence in rehabilitation, and promote the potential of children.

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Universe Scientific Publishing

Application Comparison of Contrast-Enhanced Ultrasound-Guided Microwave Ablation and Traditional Surgery for Benign Breast Nodules

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Abstract: **Objective:** To analyze the therapeutic effect of contrast-enhanced ultrasound-guided microwave ablation and traditional surgery in the treatment of benign breast nodules. **Methods:** The research subjects included in this study were 68 patients with benign breast nodules admitted to our hospital from January 2020 to January 2021. They were divided into control group and experimental group by random number table method. The control group received traditional surgical treatment (34 cases), and the experimental group received contrast-enhanced ultrasound-guided microwave ablation (34 cases). The treatment effects of the two groups were compared. **Results:** There was no significant difference in operation time between the two groups, which did not meet statistical significance (P>0.05). Intraoperative blood loss, incision healing time and pain score were lower in the experimental group than in the experimental group (P<0.05). There were significant differences in postoperative hematoma, scar formation rate and lesion residual rate between the two groups, among which the experimental group was lower (P<0.05). **Conclusion:** Contrast-enhanced ultrasound-guided microwave ablation and traditional surgery are used in the treatment of benign breast nodules. The former is better than the latter. This treatment method can be promoted.

Keywords: Contrast-Enhanced Ultrasound-Guided Microwave Ablation; Traditional Surgery; Benign Breast Nodules; Surgery-Related Indicators; Postoperative Hematoma, Scar; Residual Lesions

Introduction

Benign breast nodules are a common clinical cystic proliferative disease, which is more common in young and middle-aged women. Most patients have multiple lesions, and only a small number of nodules are cancerous. Up to now, the preferred treatment for this disease is surgical resection. Traditional surgery is a common method for the treatment of this method, and an ideal therapeutic effect can be obtained. And the probability of postoperative infection is high, which makes it difficult for patients to accept. Microwave ablation is a new clinical treatment method, which uses thermal energy to coagulate and necrotic local tissue cells. In order to verify the effect of this surgical treatment. This study analyzed the therapeutic effects of contrast-enhanced ultrasound-guided microwave ablation and traditional surgery in the treatment of benign breast nodules. The results of the study are detailed below.

1. Materials and methods

1.1 Basic information

The subjects included in this study were patients with benign breast nodules admitted to our hospital from January 2020 to January 2021, with a total of 68 cases. They were divided into control group and experimental group by random number table method. The control group received traditional surgical treatment (34 cases), and the experimental group received contrast-enhanced ultrasound-guided microwave ablation (34 cases). The age of the experimental group was 31-49 years old,

and the mean was (37.65±2.34) years old. The age of the control group was 32-48 years old, with an average of (37.54±2.65) years old. The analysis of the basic data of the two groups of patients showed that there was no significant difference in the age of the patients (P>0.05).

1.2 Methods

1.2.1 Control group

This group was treated with traditional surgery. Before surgery, color Doppler ultrasound was performed to identify and mark the nodule. After anesthesia, a radioactive incision was made at the marked position.

1.2.2 Experimental group

This group was treated with contrast-enhanced ultrasound guided microwave ablation. The patients underwent preoperative color Doppler ultrasound to clarify the location, size, and number of nodules, and then underwent gray-scale angiography to perform real-time contrast imaging of breast nodules to learn more about the contrast agent in the breast nodules. Perfusion and blood flow distribution. The range of microwave ablation was determined by the maximum diameter of the longitudinal section through the contrast medium perfusion area, and the ablation power was controlled at 30-40 W. Contrast-enhanced ultrasonography was performed 15 minutes after surgery to evaluate the effect of ablation. If there is no contrast agent filling in the breast nodule, and there is no enhancement, it means that the lesion is completely ablated. If there is enhancement in and adjacent to the lesion tissue, it means that the ablation is not complete, and the residual lesion needs to be supplemented and ablated.

1.3 Performance criteria

(1) The relevant indicators (operation time, intraoperative blood loss, incision healing time, postoperative pain score) during the two groups were observed and recorded, and a comparative analysis was carried out. The postoperative pain score was evaluated by the VAS scale, and the lower the score, the lighter the pain.

(2) The postoperative hematoma, scar formation and residual rate of lesions were observed and recorded in the two groups, and were compared and analyzed.

1.4 Statistical methods

The data obtained in the study were processed by SPSS 23.0 software. ($\bar{x}$ ±s) is used to represent measurement data, using t test; (%) is used to represent count data, using (x^2) test. When the calculated P<0.05, it was suggested that there was a significant difference between the compared subjects.

2. Results

2.1 Comparative analysis of surgery-related indicators between the two groups

There was no significant difference in operation time between the two groups, which did not meet statistical significance (P>0.05). Intraoperative blood loss, incision healing time and pain score were lower in the experimental group than in the experimental group (P<0.05). See Table 1 for details.

Table 1 Comparative analysis of surgery-related indicators between the two groups（$\bar{x} \pm s$）

Groups	Number of cases	Operation time（min）	Intraoperative blood loss（ml）	Incision healing time（d）	Pain score（score）
Control group	34	36.65±12.33	15.43±3.24	12.23±3.54	5.64±1.23
Experimental group	34	37.21±12.35	5.43±1.24	6.54±1.43	2.34±1.65
t	-	0.187	16.807	8.690	9.349
P	-	0.852	0.001	0.001	0.001

2.2 Comparative analysis of postoperative hematoma, scar formation rate and lesion residual rate between two groups

There were significant differences in postoperative hematoma, scar formation rate and lesion residual rate between the two groups, among which the experimental group was lower (P<0.05). See Table 2 for details.

Table 2 Comparative analysis of postoperative hematoma, scar formation rate and residual lesion rate between the two groups [n, (%)]

Groups	Number of cases	Postoperative hematoma	Scarring rate	Lesion survival rate
Control group	34	11（32.35%）	31（91.18%）	10（29.41%）
Experimental group	34	3（8.82%）	6（17.65%）	2（5.88%）
χ^2	-	5.757	37.053	6.476
P	-	0.016	0.001	0.011

3. Discussion

Benign breast nodules can have a great impact on patients' daily life. The incidence of this disease is increasing year by year, and it is gradually developing towards a younger age. Surgical treatment is the first method for the treatment of this disease, but the operation is more traumatic, and the probability of postoperative infection and scarring is high, so it is difficult for young patients to accept.

Contrast-enhanced ultrasound-guided microwave ablation is easy to operate, less invasive, and less likely to cause postoperative scarring. It has been widely used in clinical practice in recent years [2]. This type of surgery is a physical therapy method. High-frequency microwaves promote high-speed rotation of tissue water molecules to generate heat energy. High temperature can necrotize tumor tissue, and at the same time, it can destroy the blood supply of nodules and block the source of nutrition for nodules. This procedure does not require the removal of breast tissue, and the necrotic target tissue can be absorbed by the body. The results of this study showed that there was no significant difference in operation time between the two groups, which did not meet statistical significance (P>0.05). Intraoperative blood loss, incision healing time and pain score were lower in the experimental group than in the experimental group (P<0.05). It is suggested that contrast-enhanced ultrasound-guided microwave ablation can reduce intraoperative blood loss, promote postoperative incision healing, and reduce pain. Traditional surgery requires multiple incisions, and the incisions are large, resulting in multiple scars on the breast after surgery. The results of this study showed that there were significant differences in the postoperative hematoma, scar formation rate and lesion residual rate between the two groups, and the experimental group was lower (P<0.05). It is suggested that contrast-enhanced ultrasound-guided microwave ablation can reduce the generation of postoperative hematoma and scar, and has a good lesion clearance rate, which can meet the aesthetic needs of patients and

has high safety.

To sum up, contrast-enhanced ultrasound-guided microwave ablation and traditional surgery are used in the treatment of benign breast nodules, and the former is better than the latter. This treatment method can be promoted.

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Effect of NE Infusion on Postoperative Delirium in Elderly Patients Undergoing PFNA Internal Fixation

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Abstract: **Objective**: To observe the effect of blood pressure management by norepinephrine infusion on postoperative delirium (POD) in elderly patients undergoing PFNA internal fixation. **Methods**: 80 elderly patients undergoing elective PFNA internal fixation under spinal anesthesia, aged >65 years, ASA II or III, with body mass index(BMI) of 16.9 kg/m^2 to 27.8 kg/m^2, were included and divided into a test group(group T) and a control group (group C) using the random number table method, with 40 cases in each group. In group T, patients received an infusion of 8μg/mL norepinephrine (NE) that was begun at 15 mL/h immediately after spinal anesthesia, and then adjusted within the range 0-30mL/h according to systolic blood pressure(SBP) values measured noninvasively at 2-minute interval until the patients left the operating room, with the goal of maintaining values from baseline to 20% above the baseline; in group C, SBP values was allowed to fluctuate ±20% baseline by giving a bolus of 8μg NE(8 μg/mL). The incidence of POD within 7 days after surgery was recorded. SBP values, SpO2, and HR were recorded at the following endpoints: before the induction of anesthesia (T_1),4 minutes after anesthesia (T_2), before incision (T_3), 4 minutes, 10 minutes, 20 minutes after incision (T_{4-6}), at the end of surgery (T_7), 5 minutes before leaving the room (T_8).NE amount and occurrence of adverse events were recorded. **Results**: Compared with group C, the incidence of POD was reduced, SBP values at T2 to T8 and NE amount was increased (P<0.05). **Conclusion:** Infusion of 8μg/mL of NE maintaining SBP values from baseline to 20% above the baseline reduces the incidence of POD in elderly patients undergoing PFNA internal fixation.

Keywords: PFNA; Elderly; Delirium; Norepinephrine

1. Introduction

Elderly patients are prone to femoral trochanteric fractures or intertrochanteric fractures, and the preferred treatment option is surgery, which is PFNA (Proximal Femoral Nail Antirotation) internal fixation. This procedure is less invasive and has a shorter operating time, so the spinal anesthesia method is fitting. Elderly patients are more likely to have perioperative complications due to their physiopathological characteristics, such as co-morbidities and frailty. POD is one of the common complications in such patients, and its incidence can reach 5%-61%[1], while Xu Ming et al[2] reported a 31% incidence of POD in elderly patients undergoing PFNA internal fixation. POD occurs from 0 to 7 days postoperatively, with a high incidence within 3 days postoperatively[3], and it affects prognosis and increases morbidity and mortality.

POD belongs to the postoperative cognitive dysfunction, and its pathogenesis has not been fully clarified so far, and its occurrence may be related to many factors, such as age, anesthesia, drugs, surgery, and infection, hypotension is also one[4, 5]. However, some studies have concluded that intraoperative hypotension is not statistically significant for POD and that the risk factor is intraoperative blood pressure variability[6], namely, blood pressure fluctuations. In this study, we managed SBP by infusion of NE during operation to stabilize it from baseline to 20% above the baseline value to observe the effect on POD in elderly patients with PFNA internal fixation.

2. Material and methods

The study was approved by the ethics committee of our hospital and informed consent was signed by the patients. Eighty patients undergoing elective PFNA internal fixation were selected for the study. Inclusion criteria: accurate and

complete clinical data; age >65 years, ASA II-III; cardiac function II or above; no serious dysfunction of organs such as lung, liver, kidney, and brain; no shock or contraindications to spinal anesthesia; informed and voluntary participation in this study. Exclusion criteria: ASA IV or above; those with neuropsychiatric disorders; those taking benzodiazepines or opioids within 3 months; patients with severe anemia or blood transfusion. The 80 patients were divided into group C and group T at a 1:1 ratio according to the random number table method.

All subjects routinely abstained from drinking and fasting for 8 hours. After entering the operating room, the upper limb venous access was opened, electrocardiogram (ECG), heart rate (HR), blood oxygen saturation (SpO2), non-invasive blood pressure (NIBP) (upper limb contralateral to the venous access), nasal catheter oxygenation with an oxygen flow rate of 2-4 L/min.Then the anesthesiologist received the envelope that contained the drug preparation instruction and the grouping. Spinal anesthesia was performed after liquid capacity expansion by infusion of compound sodium chloride (8 ml/kg). Patients were placed in the lateral position with the affected lower limb on top. The spinal needle was inserted at L_{3-4} vertebral interspace, and 0.75% ropivacaine (Batch No. 7B210201, Jiabao Pharmaceutical, Guangdong, China.) was administered 1.3 to 1.5 mL after seeing the cerebrospinal fluid. The maintenance fluids were compound sodium chloride and hydroxyethyl starch (HES) 130/0.4(Batch No.1C22011902, Qidu Pharmaceutical, Shandong, China.) in a 2:1 ratio in the operating room.

The baseline noninvasively SBP was measured in the ward. The SBP was measured at 10:00 a.m. on the day before surgery when the patient was quiet and stable without other discomforts, and it was taken as the baseline SBP (T_0) regarding the SBP in the same state on the previous day and the difference was less than 10%. In group T, patients received an infusion of 8μg/mL NE(Batch No. 2202121, Lijun Pharmaceutical, Xian, China.) that was begun at 15 mL/h immediately after spinal anesthesia, and then adjusted within the range of 0-30mL/h via an infusion pump (Model CP-1100, Slgo Technology, Beijing, China.)according to SBP values measured noninvasively at 2-minute interval until the patients left the operating room, to maintain values from baseline to 20% above the baseline; in group C, SBP values was allowed to fluctuate ±20% baseline by giving a bolus of 8μg NE(8 μg/mL). When the intraoperative SBP increased more than 120% of the baseline blood, nitroglycerin 50 μg/time was administered until the SBP was controlled in the target range. When the heart HR was <50 beats/min, IV atropine 0.5mg was done and repeated if necessary. At the end of the surgery, the patients were withdrawn from vasoactive drugs and sent back to the ward after observation of stable blood pressure.

The Confusion Assessment Method (CAM) was used to assess delirium[3] 7 days after operation in two groups, and among the evaluation tools for delirium, the CAM scale with its concise and clear items performed well in an emergency, postoperative, and mixed hospitalization settings and best in the psychiatric geriatric group[7]. Assessment criteria: <19 points means no delirium, 20-22 points with suspected delirium, and>22 points stands for delirium. The primary endpoint was the incidence of POD. In addition, SBP values, SpO2, and HR were recorded at the following endpoints: before the induction of anesthesia (T_1),4 minutes after anesthesia (T_2), before incision (T_3), 4 minutes, 10 minutes 20 minutes after incision (T_{4-6}), at the end of surgery (T_7), 5 minutes before leaving the room (T_8). Nausea and vomiting were recorded; the duration of anesthesia and operation, fluid balance, hemoglobin(HGB), and the amount of vasoactive agent used were recorded.

SPSS25(IBM SPSS, Inc, Chicago, IL) was used for statistical analysis. The mean±standard deviation ($\bar{x}\pm s$) was used to describe normally distributed continuous variables which were analyzed using Student's t-test; the count and categorical data were expressed as relative numbers and were compared using the χ^2 test. Statistical significance was determined at $p < 0.05$(two-sided).

3. Results

Baseline blood pressure was measured in 80 patients whose follow-up and assessment of POD were completed. There were no statistically significant differences between the two groups in terms of age, gender, BMI, ASA, hemoglobin (HGB), and comorbid diseases (P>0.05), as shown in Table 1.

Table 1. Baseline characteristics of the patients($\bar{x}$±s) or n

	group C n=40	group T n=40	P value
Age (year)	80.17±7.42	81.20±7.78	0.548
Gender(M/F)	12/28	17/23	0.352
BMI(kg/m^2)	22.65±2.96	21.84±2.87	0.217
ASA(Ⅱ/Ⅲ)	31/9	24/6	0.567
HGB(g/L Pre）	102.42±12.71	101.60±19.28	0.822
HGB(g/L Post)	84.13±12.46	83.45±16.77	0.839
hypertension(n)	23	26	0.646
DM(n)	18	10	0.101

Note: DM =diabetes mellitus, Pre= preoperative, Post= postoperative

There was no statistical significance in fluid intake, urine volume, blood loss, duration of anesthesia and operation, ropivacaine dosage, and anesthesia plane(P>0.05); the anesthesia plane was divided into two categories above (>T_{10}) and below the thoracic vertebra 10 plane (<T_{10}). No nausea or vomiting was observed during and after the operation. Nitroglycerin and atropine were not used, and the oxygen saturation was 99-100%. Compared with group C, the dosage of NE was increased(P<0.05). The incidence of POD was 37.5% in group C and 17.5% in group T, which was statistically significant (P<0.05). See Table 2.

Table 2.Intraoperative and postoperative characteristics($\bar{x}$±s) or n

	group C n=40	group T n=40	P value
Fluid intake (ml)	752.50±304.23	687.50±238.52	0.291
Urine loss (ml)	198.75±144.40	167.75±79.50	0.238
Blood loss(ml)	43.75±46.50	38.75±19.51	0.532
Duration of anesthesia (min)	68.20±16.82	62.73±13.82	0.116
Duration of operation (min)	51.12±14.13	46.35±14.54	0.14
Block height (<T10/>T10)	28/12	27/13	1
Ropivacaine(ml)	1.44±0.14	1.40±0.13	0.218
NE(μg)	42.23±41.61	87.83±61.14	0.001
POD(n)	15	7	0.045

Baseline blood pressure and heart rate measured at all time points were not statistically different between group C and group T (P>0.05). SBP from T_1 to T_8 was higher in group T than in group C but was statistically significant from T_2 to T_8. There was no statistical difference in heart rate at each point. See Table 3.

Table 3.HR(times/minute) and SBP(mmHg) characteristics($\bar{x}$±s)

	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8
group C	/	85±12	79±11	79±10	78±9	76±9	75±10	76±9	75±10
group T	/	86±12	82±12	80±10	79±11	79±11	77±10	77±10	77±10
group C	128±7	141±18	122±21	118±18	116±10	118±10	126±14	122±12	118±11
group T	126±7	148±17	139±13^a	137±11^a	135±11^a	136±11^a	138±12^a	135±11^a	130±8^a

Note: T0 represents baseline SBP, P^a<0.05

4. Discussion

Elderly patients are prone to hypotension after spinal anesthesia because of their frailty and their physiological characteristics. Clinically, blood pressure often drops 20% or even 30% of the baseline before vasoactive drugs are administered, which in turn leads to excessive blood pressure elevation, and this leads to drastic blood pressure fluctuations. Studies have shown that frequent blood pressure fluctuations affect cerebral perfusion, which in turn has a detrimental effect on cognitive function[8]. In contrast, intraoperative hypotension with excessive fluctuations may lead to cerebral infarction with cerebral ischemia-reperfusion injury[9], thus increasing the incidence of POD. Clinically, elderly patients' perioperative blood pressure fluctuations are permitted within ±20% of the baseline, but it is unclear whether there is an ideal blood pressure target for the prevention of POD in PFNA patients. Therefore, this trial was designed to maintain SBP from baseline to 20% above the baseline to observe the effect on POD.

Hypotension occurs in elderly patients after spinal anesthesia because of increased basal sympathetic tone and reduced baroreceptor sensitivity[10]. Decreased blood pressure can be manifested as irritability, nausea, and vomiting, which interferes with surgery and is not only associated with POD but is also a risk factor for postoperative mortality[11]. Therefore, the prevention of intraoperative hypotension in elderly patients is particularly necessary. NE is a strong α and weak β agonist that increases arterial pressure, improves mean systemic filling pressure, enhances cardiac contractility and cardiac output through vasoconstriction and positive inotropic effects, making it an ideal drug for the prevention of hypotension； and it can be administered through peripheral veins, as Mostafa et al[12] did in elderly patients by infusion of 8 μg/mL NE, and the NE dose of 8 μg was equal to a PE dose of 100 μg; Hasanin et al[13] used NE 0.05 μg/kg/min infusion during cesarean section; Ngan et al[14] managed the SBP at the rate of 0-60 mL/h during cesarean section. In practice, the infusion rate of vasoactive drugs is often adjusted by the target blood pressure, and considering the feasibility and convenience, furthermore referring to the study of Brassard et al[15] in which the rate of NE infusion greater than 0.1 μg/kg/min was detrimental to brain tissue oxygenation, NE at 8 μg/mL was selected in this study to be administered immediately after spinal anesthesia at 15 mL/ h via peripheral intravenous administration infusion, and then adjust within the range 0-30mL/h(0-4μg/min, less than 0.1μg/kg/min) according to SBP, with a bolus of 8 μg if necessary.

The incidence of POD in group C in this study was 37.5%, which was similar to the results obtained by Xu Ming et al[2]; and the incidence of POD was reduced to 17.5% by increasing SBP by 20% above baseline with NE, which was similar to the results of XingMei et al[3], who compared the effects of different blood pressure management strategies under general anesthesia on the incidence of delirium after hip replacement, MAP maintained at 10% above baseline helped to reduce the incidence of POD. The reasons for the result could be increased regional oxygen saturation in brain tissue with increasing blood pressure[16]; moreover, one study indicated that NE improved the oxygen supply to brain tissue, and that continuous infusion of NE avoided sharp fluctuations of hemodynamic and regional oxygen saturation[17], avoiding cerebral ischemia-reperfusion injury and the damage to various organs due to ischemia and hypoxia. Conversely, when administered intermittently, it is not conducive to the prevention of POD.

In this study, SBP at all points after anesthesia was higher in the group T, indicating that continuous infusion of NE was more effective in managing blood pressure and could better maintain blood pressure stability; the high blood pressure of T_1 was due to pain stimulation caused by moving of the patient during room admission, while Blood pressure often dropped to some extent after anesthesia, so it was not treated. However, the statistically significant difference in blood pressure from T_2 to T_8 indicates the difference between intermittent and continuous dosing, with continuous infusion of NE being more advantageous than single dosing for maintaining blood pressure. Although the amount of NE used and the heart rate at each moment was higher in group T, there was no statistical difference, probably because NE is a weak β agonist and this dose difference was not enough to produce significant changes in heart rate; in addition, the anesthetic level required for this operation was not high, and when the anesthetic level was below T_{10}, the sympathetic nerve was not inhibited, so the heart rate did not produce large fluctuations. In this trial, the maximum level of anesthesia was T_6, and although the decrease in blood pressure was dramatic compared with the level above T_{10}, the blood pressure could be better managed by the strategy. There were no statistical differences in other aspects such as duration of anesthesia and operation, ropivacaine dosage,

anesthesia plane, blood loss, and urine volume. No nitroglycerin and atropine were used, and there were no adverse effects such as severe hypertension or nausea, or vomiting, indicating that the dose of NE used in the study was relatively safe.

The study also had limitations in that local cerebral tissue oxygen monitoring and blood markers such as IGF-I, IL-6, and S100β could not be measured due to the limited conditions; and invasive arterial blood pressure monitoring was not performed in this study considering the short duration of surgery and the small amount of blood loss; and finally, only NE was used to manage blood pressure without the use of other vasoactive drugs, which needs to be further investigated.

In conclusion, maintaining the SBP from baseline to 20% above the baseline by infusion of NE can reduce the incidence of POD in elderly patients after PFNA internal fixation, and the mechanism may be related to improving the cerebral blood and oxygen supply and avoiding cerebral ischemia-reperfusion injury due to less blood pressure fluctuation.

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Meta-Analysis of Chinese Patent Medicine Combined with Zoledronic Acid in the Treatment of Primary Osteoporosis

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Abstract: Objective: To systematically evaluate the safety and efficacy of Chinese patent medicine combined with zoledronic acid in the treatment of primary osteoporosis. Methods: CnKI, VIP, Wanfang Database, Chinese Biomedical literature database, PubMed, Web of Science, The Cochrane Library, Embase and CnKI were searched by computer RCTs of clinical randomized controlled trials of Chinese patent medicine combined with zoledronic acid in the treatment of primary osteoporosis in Embase database were retrieved from the database construction to April 1, 2022, and meta-analysis was performed using RevMan 5. 3 software. Results: A total of 14 RCTs were included, and the results of meta-analysis showed that:Compared with the control group, Chinese patent medicine combined with zoledronic acid had significant effects on the improvement of total clinical response rate, VAS score, MDL score, lumbar vertebra bone mineral density, femoral neck bone mineral density, Ward's triangle bone mineral density, osteocalcin and ALP, and significantly reduced alkaline phosphatase, with statistically significant differences. It had no significant effect on serum phosphorus, calcium and adverse reactions (P >0. 05). Conclusion: The safety and efficacy of Chinese patent medicine combined with zoledronic acid in the treatment of POP are clear, but the quality of the included studies is limited, and more high-quality studies are needed to enhance the evaluation evidence.

Keywords: Chinese Patent Medicine; Zoledronic Acid; System Evaluation; Primary Osteoporosis; Randomized Controlled Trial

Introduction

Osteoporosis(OP) is a systemic progressive bone metabolic disease with reduced bone mass, damaged bone microstructure and increased bone fragility[1]. OP can be divided into three types according to etiology: primary, secondary and idiopathic. Primaryosteoporosis (POP) is a physiological degenerative disease that inevitably occurs with age [2]. Zoledronic acid, as a third-generation bisphosphonate drug, is the first-line drug in the clinical treatment of POP and is widely used in clinic [3].

1. Data and methods

1.1 Retrieval strategy

Computer retrieval of CNKI, VIP, Wanfang Database, Chinese Biomedical literature database,PubMed、 Web of science、 The Cochrane Library、 EmbaseThe retrieval period is from database construction to April 10, 2022. Retrieval method is given priority to with "subject + keywords", Chinese retrieval subject includes: "osteoporosis", "primary osteoporosis in postmenopausal osteoporosis"", "Chinese medicine", "proprietary Chinese medicine", "Chinese herbal medicine", "azole phosphonic acid", "capsule", "pill", "mixture", "fluid", "loose" and "a randomized controlled trial". English keywords included: "osteoporosis", "OP", "Chinese patent drug", "traditional Chinese medicine", "Azole Phosphonic acid", "RCT".

1.2 Inclusion and exclusion criteria

(1)Study type: Randomized controlled clinical trials (RCTS) published in Chinese and English about Chinese patent medicine combined with zoledronic acid in the treatment of primary osteoporosis; (2) Subjects: Patients with primary osteoporosis, gender and source of cases were not limited; (3) Intervention measures: the experimental group was treated with oral marketed Chinese patent medicine combined with zoledronic acid, and the control group was treated with zoledronic acid. Calcium, vitamin D and other basic treatments could be used in both groups.

1.3 Data extraction and quality evaluation

1.3.1 Data extraction

Two researchers independently screened the literature by title and abstract, and made judgment by reading the full text if they could not make judgment. Disagreement is resolved through discussion or by a third researcher. Two researchers independently extracted data, including basic information, intervention measures, sample size and outcome indicators of the included study.

1.3.2 Use of all data for quality

All data are managed by Revman5. 3 management software. The "Riskofbias" evaluation tool in the Cochrane manual was used to evaluate the methodological quality of the included literature[5], and judgments of lowrisk, highrisk, and unclearrisk were made for the final included literature.

1.4 Statistical methods

Meta-analysis was performed using RevMan5. 3 software provided by the Cochrane collaboration. The relative risk (RR) and 95%CI were used for categorical variables, and the mean difference (MD) and 95%CI were used for continuous variables. I2 test was used for heterogeneity of literature, and when I2 < 50%, fixed effect model was used for Meta analysis. If I2 > 50%, the source of heterogeneity was analyzed and sensitivity analysis or random effect model was used. Funnel plots were used to analyze publication bias when ≥10 articles were included in an outcome index.

2. Results

2.1 Literature screening process and results

A total of 68 related literatures were obtained by systematic retrieval of relevant databases, and the remaining 28 literatures were removed after the removal of duplicate literatures. After reading the title and abstract information, 20 literatures were initially selected for full-text reading and screening, and 14 literatures were finally included for data.

2.2 Basic Features of included Studies

A total of 14 RCTS were included in this study, including 1559 patients with primary osteoporosis. It involved 6 kinds of oral Proprietary Chinese medicine, including 5 studies on Jintiange capsule, 5 studies on Xianling Gubao capsule, 1 study on Hugu capsule, Gusongbao granule, Gambohuang Jiangu capsule and Guyuling capsule respectively.

2.2.1 Literature quality evaluation

Among the 14 original literatures, 5 [10, 12-15] used the random number table method for grouping, the rest only mentioned "randomness", and 14 literatures did not describe the allocation hiding. Considering the intervention measures of the study, blind method could not be implemented for the subjects and interveners, which was evaluated as high risk of bias.

2.3 Meta-analysis results

2.3.1 Effective clinical efficacy

A total of 7 studies were used to compare the effectiveness of clinical efficacy, and the effectiveness of each study was transformed by dichotomy. A total of 735 patients were enrolled.

2.3.2 BONE mineral density

Thirteen studies compared lumbar bone mineral density in 1399 patients. The heterogeneity test of mate analysis showed that P < 0. 00001, I2=77%, indicating large heterogeneity, so the random effect model was adopted and the effect size was combined [MD=0. 07,95%CI(0. 05,0. 09)]. The test of combined effect size Z=7. 11,P<0. 00001. Conclusion Compared with zoledronic acid alone, Chinese patent medicine combined with zoledronic acid can effectively improve the bone density of lumbar vertebra in the treatment of primary osteoporosis.

2.3.3 Serum alkaline phosphatase (ALP)

ALP was compared in six studies totaling 685 patients. The heterogeneity test of mate analysis showed that P=0. 52, I2=24%, and mate analysis adopted the fixed effect model. The results suggested that:Chinese patent medicine combined with zoledronic acid significantly reduced ALP level compared with zoledronic acid group, the difference was statistically significant [MD=-4. 55, 95%CI(-5. 18, -3. 92), P=0. 03), P < 0. 00001].

2.3.4 Osteocalcin

Osteocalcin was compared in seven studies involving a total of 698 patients. The heterogeneity test of mate analysis showed that P=0. 90, I2=0%, and mate analysis adopted the fixed effect model. The results suggested that:Chinese patent medicine combined with zoledronic acid significantly improved osteocalcin level compared with zoledronic acid group, the difference was statistically significant [MD=1. 85, 95%CI(1. 66, 2. 05), P < 0. 00001)].

2.3.5 Serum calcium

Serum calcium was compared in seven studies involving a total of 1032 patients. The heterogeneity test of mate analysis showed that P=0. 49, I2=0%, and mate analysis adopted the fixed effect model. The results suggested that:Analysis results showed that there was no statistically significant difference between the two groups [MD=0. 01, 95%CI(-0. 03-0. 05), P=0. 78], indicating that there was no statistically significant difference in serum calcium level between zoledronic acid combined with Proprietary Chinese medicine and zoledronic acid alone in this study, that is, proprietary Chinese medicine combined with zoledronic acid had no significant effect on serum calcium.

2.3.6 Serum phosphorus

Serum phosphorus was compared in seven studies involving a total of 748 patients. The heterogeneity test of mate analysis showed that P=0. 47, I2=0%, and mate analysis adopted the fixed effect model. The results suggested that:Analysis results showed that there was no statistically significant difference between the two groups [MD=0. 02, 95%CI(-0. 01-0. 06), P=0. 21], indicating that there was no statistically significant difference in serum phosphorus level between zoledronic acid combined with Chinese patent medicine and zoledronic acid alone in this study, that is, Chinese patent medicine combined with zoledronic acid had no significant effect on serum phosphorus.

2.3.7 Visual analogue scale of pain(VAS)

VAS scores were compared in 11 studies, with a total of 1178 patients. The heterogeneity test of mate analysis showed that P < 0. 00001, I2=85%, indicating great heterogeneity, so the random effect model was adopted, and the results suggested that:VAS score of Chinese patent medicine combined with zoledronic acid was significantly better than that of zoledronic acid alone, the difference was statistically significant [MD=-0. 72, 95%CI(-0. 82, -0. 62), P < 0. 00001)].

2.3.8 Daily living ability score(ADL)

ADL scores were compared in five studies [6, 19, 7, 12, 18] with a total of 398 patients. The heterogeneity test of mate analysis showed that P < 0. 00001, I2=40%, the heterogeneity was small, so the fixed effect model was adopted, and the results suggested that:VAS score of Chinese patent medicine combined with zoledronic acid was significantly better than that of zoledronic acid alone, the difference was statistically significant [MD=12. 30, 95%CI(10. 52, 14. 08), P < 0. 00001)].

2.3.9 Adverse reactions

A total of 7 studies reported adverse reactions, and a total of 792 patients were included to translate the effective rate of each study using dichotomies. The heterogeneity test of Mate analysis showed that P=0. 98, I2=0%, and the fixed effect model was adopted for Mate analysis. The analysis results show that:A total of 39 cases (9. 89%) of adverse reactions occurred in the integrated Chinese and Western medicine group, and 41 cases (10. 40%) in the alendronate group. Meta-analysis showed that there was no statistically significant difference in the incidence of adverse reactions between the two groups [OR=0. 96, 95%CI(0. 60-1. 53),P = 0. 86).

2.4 Publication bias

Bias analysis was conducted for lumbar bone mineral density and VAS score with more than 10 study samples among the outcome indicators. As can be seen from the funnel plot, there is asymmetry on both sides of the graph, suggesting a certain publication bias.

3. Discussion

This study found that the overall experimental design quality of the included literatures was not high, and the reliability of the conclusions needed further verification with potential publication bias. The randomization method of the included studies was not clear. Although random number table method was mentioned in some studies, the sequence generation process was not described. None of the 14 included studies mentioned or described the allocation hiding mechanism and whether blind method was used, which may lead to multiple risks of bias.

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Topic:

Shaanxi Academic School of Traditional Chinese Medicine Inheritance Studio (Construction) Project (Shaanxi TCM Medicine Fa [2018] No. 40); Construction of Key Laboratory of Shaanxi Administration of Traditional Chinese Medicine Project (Shaanxi Chinese Medicine Fa [2018] No. 32)

Analysis of the Willingness and Factors Influencing the Residents to Choose Between Chinese Medicine and Western Medicine under the New Coronavirus Pandemic: A Study in Zhejiang Province Community Health Service Center

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Abstract: **Objective:** To understand the willingness of Chinese residents to choose between Chinese and Western medicine in the face of sudden outbreak, this study aims to investigate and analyze the willingness and factors influencing Chinese residents (taking Zhejiang Province as an example) to choose between Chinese and Western medicine under the new coronavirus pandemic. **Methods:** The present study performed a large-scale cross-sectional online survey among 666 random residents in Zhejiang Province. We used questionnaires to investigate the feedback form from residents seeking medical care. In addition, a multivariate logistic regression model was used to analyze the influence of gender, education, medical reimbursement, and age on the choice of Chinese and Western medicine. **Results:** Among the patients with mild disease, 55.9% patients chose traditional Chinese medicine, while 44.1% chose Western medicine. Moreover, the proportion of patients with severe diseases who chose traditional Chinese medicine was 7.0%, while the rate of Western medicine was 93.0%. Among the patients suffering from mild diseases, the proportion of men who chose traditional Chinese medicine (46.2%) was lower than that of women (53.8%). The usage of Chinese medicine was preferred among residents of all ages, income levels, and educational backgrounds. A total of 93.0% of patients who chose Western medicine for treatment were severely ill, and the residents with severe diseases preferred Western medicine to Chinese medicine. People with high education and young were more inclined toward Western medicine for treatment compared with Chinese medicine. It was noted that people paid most attention to the medical insurance reimbursement ratio, followed by the distance between the medical institution and the place of residence. **Conclusion:** The acceptance of Chinese medicine among patients has generally increased; however, gender, educational background, and income still exert a great influence on the choice between Chinese and Western medicine.

Keywords: Chinese and Western Medicine; Willingness to Seek Medical Treatment; Influential Factors

1. Introduction

In the reform of the medical system, frictions have always existed between Chinese and Western medicine and attacks on the scientific nature of Chinese medicine.[1]-[3] Toward the end of 2019, the invasion of the new coronavirus (SARS-CoV-2) enabled the medical method of integrated traditional Chinese and Western medicine to advance public's vision.[4][5] A better clinical effect was obtained with the rate of cure and discharge being 76.5%.[6] To understand the willingness of Chinese residents to choose between Chinese and Western medicine in the face of sudden outbreak, this study aims to investigate and analyze the willingness and factors influencing Chinese residents (taking Zhejiang Province as an example) to choose between Chinese and Western medicine under the new coronavirus pandemic.

In a study of common diseases and symptoms in urban patients,[7] 292 people were randomly sampled, and data analysis was carried out. We deduced that hypertensive cardiovascular and cerebrovascular diseases and neuropsychiatric diseases

were the leading diseases among patients. The lack of proper and correct guidance of Chinese and Western medicine is one of the crucial reasons for this phenomenon. During the new coronavirus pandemic, studies illustrated that Chinese medicine could significantly shorten the disease course.[8] The successful fight with the new coronavirus pandemic also demonstrated that Chinese and Western medicine treatments have different benefits.[9]As the first to implement the community general practice system in the United Kingdom or Australia, single Western medicine treatment is the mainstay, and the public has no more choices.[10][11]

Thus, further detailed studies have been conducted on the application of Chinese and Western medicine in China, which prove that choosing between Chinese and Western medicine based on different diseases will lead to better results. Foreign countries lack a designated Chinese medicine department; hence, there are gaps in the related research. A part of the domestic population has a prejudice against traditional Chinese and Western medicine; however, the willingness of the domestic population to seek traditional Chinese and Western medicine and its influential factors have not been explored in detail, and there is a significant gap in research, and its practical value has not been explored.

The present study aims to examine the proportion of domestic Chinese and Western doctors seeking medical treatment under the new coronavirus pandemic. It is then compared with the current supply of Chinese and Western medicine and health resources to provide a reference for the rational allocation of health resources.

This study also analyzes and screens the factors that affect the willingness of residents to seek treatment with Chinese and Western medicine, integrate several major unfavorable factors that prevent residents from picking either Chinese medicine or Western medicine, and ultimately propose feasible improvement suggestions.

This study elucidates the primary factors that affect the residents' choice of medical treatment and residents' understanding of Chinese and Western medicine, and corrects their misunderstanding of Chinese and Western medicine.

2. Methods

2.1 Literature research

The literature was collected from CNKI, Weipu Chinese science and technology journal databases, online literature, and sorting, use of relevant papers and expositions at home and abroad. This provided the theoretical basis and support for the research.

2.2 Questionnaire survey

To investigate the medical condition of community residents, questionnaires were released through online and offline channels, and data were collected from multiple dimensions like hospitals and patients; the data were then summarized and analyzed to draw conclusions.

2.3 Interview method

Based on the interviewees' responses, we collected objective and unbiased factual materials, supplemented and improved the survey data, and expanded the research ideas of the subject.

2.4 Statistical analysis

Data analysis was performed using SPSS24.0 software. Then, descriptive statistics were applied to the survey results, and $\alpha = 0.05$ was chosen as the statistical test standard. The χ^2 test was performed on the correlation between different demographic characteristics in the questionnaire and the factors influencing each dimension.

3. Results

3.1 Basic characteristics of the research population

The study enrolled a total of 666 participants, including 117 males (22.0%) and 414 females (78.0%). Participants were mostly women (73.9%), 18–55 years (98.1%) and undergraduates (65.3%). Among female participants, the proportion of undergraduates and those aged 18–55 years was higher ($P < 0.05$) (Table 1).

3.2 Analysis of the tendency to seek a doctor and the main demographic factors when the research population suffered from mild diseases

In terms of mild diseases, a total of 55.9% of people chose traditional Chinese medicine for treatment, and the proportion of men who choose traditional Chinese medicine (46.2%) was lower than that of women (53.8%, $P < 0.01$). People aged 18–36 years had no tendency of picking between Chinese and Western medicine, while those aged 37–55 years were more inclined to choose Chinese medicine ($P < 0.01$). People with different education levels, different medical payment methods, and different monthly incomes were more inclined toward traditional Chinese medicine when they had mild illnesses ($P < 0.01$) (Table 2).

3.3 Analysis of the tendency to seek medical treatment and the main demographic factors in the study population with severe diseases

A total of 93.0% of severely ill patients selected Western medicine compared with mild illnesses. Among them, those who chose Chinese medicine for medical treatment were all women (100%, $P < 0.01$). People aged 18–36 and 37–55 years were inclined to choose Western medicine when they were severely ill ($P > 0.05$). High school, junior college, and undergraduate students were more inclined towards Western medicine when they suffered from severe diseases ($P <0.01$). With the increase in the medical reimbursement ratio, people are were willing to choose Western medicine for treatment ($P <0.05$). When the average monthly income was more than 2000, the people were more willing to choose Western medicine for treatment ($P < 0.01$) (Table 3).

3.4 Survey results of the impact of the condition of medical institution on the choice of Chinese and Western medicine

Per the survey results, people paid most attention to the medical insurance reimbursement ratio, followed by the distance between medical institution and the place of residence. Medical institutions/doctors that were advocated by acquaintances and the service attitude of medical staff had a crucial impact on people's choice of Chinese and Western medicine, while the doctor's professional title, the size of the medical institution, and the advanced level of equipment were generally not important (Table 4).

4. Discussion

4.1 Overall selection tendency of the study population

Utilizing an extensive cross-sectional survey data, we concluded that 55.9% of patients chose Chinese medicine for treatment when they had mild diseases while 44.1% preferred Western medicine to Chinese medicine. When suffering from severe diseases, the proportion of Chinese medicine consultation was 7.0%, while the consultation rate of Western medicine was 93.0%. Following the COVID-19 pandemic, the level of China's medical insurance governance has improved,[12] the proportion of medical insurance reimbursements for community medical populations, and the distance between medical institutions and their place of residence have been more attended to. Besides, the education level and the level of income of patients significantly correlated with the tendency to choose between Chinese and Western medicine. Simultaneously, gender also played a role in the patients' choice between Chinese and Western medicine.

In this study, 55.9% of patients chose Chinese medicine for treatment when experiencing mild diseases while 44.1% preferred Western medicine. When suffering from severe diseases, the proportion of Chinese medicine consultation was 7.0%, while the consultation rate of Western medicine was 93.0%. In 2016, a large-scale survey report illustrated that the investigation of the selection of Chinese and Western medicine services by community outpatients found that 556 community outpatients had a clear advantage in choosing Western medicine services in the treatment of mild and severe diseases, accounting for about 63% and 57%, respectively.[13] The key reason for this difference is that the medical law in the new concept period has been strongly advocated by the country and has attained crucial results, and the public acceptance has broadly increased.[14]

4.2 Highly educated, high-income people more inclined toward Western medicine

A study conducted in China[15] reported that people with high academic qualifications tended to prefer Western medicine. We speculate that people with high academic qualifications tended to use scientific and rational thinking and, hence, the preference for Western medicine, while the fundamental theories of Chinese medicine are more challenging to be understood by modern science. Through this study, we collected data after the new coronavirus pandemic. It is well accepted that traditional Chinese medicine has played a significant role during the COVID-19 pandemic. This study demonstrated that although people with higher education are willing to try Chinese medicine when they have mild illnesses, they prefer Western medicine when suffering from severe illnesses. Likewise, people in the 18–36 age group are willing to try Chinese medicine and Western medicine when they have mild illnesses, which accounts for 50% of people, but are more inclined toward Western medicine after suffering from severe illnesses. These findings suggest that although there is a specific effect of promoting traditional Chinese medicine during the new coronavirus pandemic, the high-income population and young adults are more willing to select familiar and relatively familiar Western medicine when they suffer from severe diseases.

4.3 Women are more willing to choose Chinese medicine than men

Men and women tend to choose Western medicine when they suffer from severe illnesses; however, there are differences in their tendency to seek medical attention when they have mild illnesses. One of the main reasons could be the difference in the curative effect between Chinese and Western medicine. Traditional Chinese medicine is simple and clean, and seeks to cure the root of the disease. It has excellent effects in chronic diseases, beauty and preventive health care,[16] and its “preventive treatment” idea is broadly accepted by the public.[17] However, women mostly suffer from various mild chronic diseases, such as irregular menstruation,[18] and traditional Chinese medicine has minimal side effects and apparent effects.

4.4 Medical reimbursement costs affect the choice of Chinese and Western medicine

The proportion of the reimbursement of medical expenses is a vital factor in people’s choice of medical institutions; this is in line with the conclusions from previous research.[19] Perhaps, to promote traditional Chinese medicine at the grassroots level and encourage patients to choose traditional Chinese medicine, the proportion of traditional Chinese medicine expenses that are included in the reimbursement need to be increased. Currently, the development of traditional Chinese medicine is at a higher historical starting point,[20] and the reform of traditional Chinese medicine drug costs should be used as a countermeasure to promote the rate of Chinese medicine treatment.

5. Limitations

This survey is limited by time, funding, workforce, and various other conditions. A total of 666 questionnaires were returned, and with a limited number of samples, these can only represent part of the characteristics of the choices of Zhejiang

residents of traditional Chinese and Western medicine. Among them, 73.9% were women, and the proportion of men was low, and the samples were under-represented. The research cannot be considered comprehensive and in-depth, and many limitations need further improvement.

6. Acknowledgements

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7. Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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Tables

Table 1 The basic characteristics of study population.

Variables	Total (n=666)	Male (n=174)	Female (n=492)	P value
Age, N（%）				0.018
<18	9(1.4)	3(1.7)	6(1.2)	
18-36	357(53.6)	102(58.6)	255(51.8)	
37-55	297(44.6)	69(39.7)	228(46.3)	
≥55	3(0.5)	0	3(0.6)	
Education level, N（%）				<0.01
Elementary school and below	12(1.8)	0	12(2.4)	
Junior high school	47(7.1)	5(2.8)	42(8.5)	
High school or technical secondary school	48(7.2)	18(10.3)	30(6.1)	
Junior college	108(16.2)	18(10.3)	90(18.3)	
Undergraduate	435(65.3)	117(67.2)	318(64.6)	
Postgraduate	6(0.9)	6(3.4)	0	
City, **N(%)**				<0.001
Hangzhou	33（5.0）	18(10.3)	15(3.04)	
Huzhou	3(0.5)	3(1.7)	0	
Jiaxing	3(0.5)	0	3(0.6)	
Ningbo	51(7.7)	18(10.3)	33(6.7)	
Wenzhou	354(53.2)	60(34.5)	294(59.8)	
Shaoxing	3(0.5)	0	3(0.6)	
Jinhua	12(1.8)	6(3.4)	6(1.2)	
Lishui	156(23.4)	51(29.3)	105(21.3)	
Taizhou	3(0.5)	0	3(0.6)	
Zhoushan	3(0.5)	0	3(0.6)	
Quzhou	45(6.8)	18(10.3)	27(5.5)	

Table 2 Multivariable Analysis: Patients with mild diseases and Major Demographic factors with Choice of Chinese and Western Medicine.

Variables	Total（n=531）	Choose Western Medicine（n=234）	Choose Chinese Medicine (n=297)	P value
Gender, N（%）				0.001
Male	117(22.0)	63(26.9)	54(18.2)	
Female	414(78.0)	171(73.1)	243(81.8)	
Age, N（%）				<0.001
<18	9(1.6)	0(0)	9(0.3)	
18-36	306(57.6)	153(65.4)	153(51.5)	
37-55	207(38.9)	81(34.6)	126(42.4)	
≥55	9(1.6)	0(0)	9(0.3)	
Education level, N（%）				<0.001
Elementary school and below	27(5.1)	9(3.8)	18(6.1)	
Junior high school	9(1.6)	9(3.8)	0(0)	
High school or technical secondary school	18(3.4)	0(0)	18(6.1)	
Junior college	135(25.4)	45(19.2)	90(30.3)	
Undergraduate	333(62.7)	162(69.2)	171(57.6)	
Postgraduate	9(1.6)	9(3.8)	0(0)	
Medical payment method, N（%）				0.004
Medical insurance	414(78.0)	198(84.6)	216(72.3)	
Public medical	63(11.9)	18(7.7)	45(15.2)	
Own expense	54(10.2)	18(7.7)	36(12.1)	
Average monthly income, N（%）				<0.001
<2000	180（33.9）	81（34.6）	99（33.3）	
2000-4000	63（11.9）	27（11.5）	36（12.1）	
4000-6000	162（30.5）	72（30.8）	90（30.3）	
≥6000	126（29.4）	54（23.1）	72（24.2）	

Table 3 Multivariable Analysis：Patients with serious diseases and Major Demographic factors with Choice of Chinese and Western Medicine.

Gender, N（%）	Total（n=516）	Choose Western Medicine（n=480）	Choose Chinese Medicine (n=36)	P value
Male				0.001
Female	120(23.3)	120(25.0)	0	
Age, N（%）	396(76.7)	360(75.0)	36(100)	
<18				0.519
18-36	318(61.6)	294(61.3)	24(33.3)	
37-55	198(38.4)	186(29.7)	12(66.7)	
Education level, N（%）				<0.001
Elementary school and below	6(1.2)	0	6(16.7)	
Junior high school	6(1.2)	6(1.25)	0	
High school or technical secondary school	30(5.8)	24(5.0)	6(16.7)	
Junior college	72(14.0)	60(12.5)	12(33.3)	
Undergraduate	396(76.7)	384(80.0)	12(33.3)	
Postgraduate	6(1.2)	6(1.25)	0	
Medical payment method, N(%)				0.008
Medical insurance	420(81.4)	390(81.25)	30(83.3)	
Public medical	60(11.6)	60(12.5)	0	
Own expense	36(7.0)	30(6.25)	6(16.7)	
Average monthly income, N(%)				<0.001
<2000	186(36.0)	174(36.25)	12(33.3)	
2000-4000	66(12.8)	54(11.25)	12(33.3)	
4000-6000	168(32.6)	156(32.5)	12(33.3)	
≥6000	96(18.6)	96(20.0)	0	

Table 4 Multivariable Analysis: Patients and Major Demographic factors with Choice of hospital.

Factors Affecting the Choice of Chinese and Western Medicine	Very important	Important	General	Unimportant	P value
Doctor's title	60(8.85)	105(15.49)	291(42.92)	222(32.74)	<0.01
The size of the medical institution and the advanced level of equipment	27(3.98)	51(46.2)	273(59.1)	327(49.7)	<0.001
Distance between medical institution and place of residence	66(9.73)	207(30.53)	267(39.39)	138(20.35)	<0.01
Medical insurance reimbursement ratio	66(9.73)	219(32.3)	225(33.19)	168(24.78)	<0.01
Service attitude of medical staff	30(4.42)	120(53.1)	288(42.48)	240(35.4)	<0.001
Does the medical institution/doctor have any acquaintances recommended	48(7.08)	177(26.11)	306(45.13)	147(21.68)	<0.001

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Clinical Research Progress on the Effect of Different Anesthesia Methods on the Prognosis of Elderly Hip Fractures

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Abstract: Hip fracture will have a great impact on the life of the patient. The treatment and recovery of hip fracture is an extremely long process. In the early treatment stage, the patient will feel a strong sense of pain. Hip fractures are the most common in the elderly, and the elderly are often accompanied by osteoporosis, and there is a risk of fracture when exposed to mild external forces in daily life [1]. Surgical treatment is most common in elderly patients with hip fractures. In order to reduce the pain of the patient, anesthesia is usually given to the patient. Anesthesia is divided into general anesthesia and local anesthesia, both of which can reduce the pain of the patient and improve the cooperation degree of the operation. Under general anesthesia, the patient is basically in a state of unconsciousness without any consciousness. General anesthesia is generally achieved by intravenous injection of anesthetic drugs or inhalation of gas, and local anesthesia is achieved by intrathecal or epidural injection of anesthetic drugs [2]. Studies have shown that these two anesthesia methods have been widely used in orthopedic surgery, and have achieved good results. However, the choice of anesthesia methods for elderly patients with hip fractures is still controversial. This article reviews the research progress on the effects of different anesthesia methods on the prognosis of elderly hip fractures by reviewing relevant literature.

Keywords: Different Types of Anesthesia; Elderly Hip Fracture; Prognostic Impact; Clinical Research Progress

Introduction

Hip fractures are a common phenomenon among the elderly. Some violent behaviors in daily life may lead to hip fractures. Hip fractures will not only bring pain to elderly patients, but even lead to limb deformities in severe cases, posing a huge threat to the life and health of elderly patients. At present, the most common way to treat hip fractures in the elderly is surgical reduction. The success of the surgery directly affects whether the patient can recover. In addition, the implementation of anesthesia during surgery has a great impact on the patient's surgical results. Studies have shown that the choice of anesthesia methods during surgery is closely related to the recovery status of patients after surgery. Choosing the correct anesthesia method can make the operation more effective, reduce the short-term mortality and the probability of postoperative complications. In this paper, the relevant literature is reviewed, and the research on the effect of different anesthesia methods on the prognosis of elderly hip fractures is reviewed and summarized from multiple perspectives.

1. Operation time

The operation time of hip fracture reduction operation in the elderly refers to the time from skin incision to skin suture. There is some controversy about whether the choice of different anesthesia methods during the operation affects the length of operation time. By reviewing the literature, it was found that some studies reported that there was no necessary relationship between the choice of anesthesia method and the length of operation, but there were also some studies that reported that the operation time of patients who chose local anesthesia was shorter than that of patients who chose general anesthesia. From the perspective of clinical effect, although the time used for local anesthesia and general anesthesia may be slightly different, the choice of anesthesia method is not enough to be an inevitable factor affecting the operation time. But this point of view also needs to be further research and consideration.

2. Complications

2.1 Arrhythmia

Arrhythmia is one of the common postoperative complications in elderly patients with hip fractures. Postoperative arrhythmias are generally classified into two types: tachyarrhythmias and bradyarrhythmias. There is no clear conclusion in the current research on the relationship between arrhythmia and the choice of anesthesia in elderly patients with hip fracture. The patient's arrhythmia after surgery is affected by a combination of many factors. In addition to the use of anesthetics, it is also affected by factors such as electrolyte imbalance, hypoxia, and acid-base balance. In conclusion, arrhythmia is relatively common in elderly patients with hip fractures. When such symptoms occur, patients should not panic and inform their physicians in time.

2.2 Postoperative pain

Elderly hip fracture patients experience some degree of pain after surgery, and the degree of pain varies from person to person. From a medical point of view, it is the subjective discomfort that the human body feels physiologically after being stimulated by external injuries or internal diseases. Anesthesia is one of the main causes of postoperative pain in elderly patients with hip fractures. General anesthesia and local anesthesia have different effects on postoperative pain. Studies have shown that 20%-70% of hip fracture patients suffer from moderate or higher pain levels after surgery. Among them, there are relevant literatures showing that patients with general anesthesia have more obvious pain one hour after the operation, and local anesthesia can still block the local nerves for a period of time after the operation [3]. Therefore, from this point of view, local anesthesia is better than general anesthesia in reducing postoperative pain in patients. However, some relevant experts believe that there is no obvious difference between the effects of general anesthesia and local anesthesia in terms of the long-term effect of alleviating pain. In a word, no matter what kind of anesthesia method the patient adopts, if they feel severe pain after surgery, they should seek the help of the doctor in time. Otherwise, other complications may occur, which will affect the recovery process.

2.3 Hypoxemia

Some elderly patients with hip fractures have bad habits such as smoking and alcoholism, and some patients have a history of other cardiopulmonary disorders. These factors greatly increase the probability of postoperative hypoxemia. If hypoxemia is not treated in time, it will seriously threaten the life and health of patients. Relevant studies have shown that the physical function of elderly patients is degraded, and the body resistance ratio is relatively weak. When the patient's hypoxemia is severe, there will be adverse symptoms such as dyspnea and myocardial ischemia, and the patient is at risk of death. Therefore, it is also very important to study the relationship between different anesthesia methods and the probability of hypoxemia in patients. Relevant literature reports that patients who choose local anesthesia for surgery are less likely to have hypoxemia, because local anesthesia does not require endotracheal intubation, and patients will not have generalized muscle relaxation. However, there are also some related studies that have reached the opposite point of view, that is, the probability of hypoxemia in patients with general anesthesia is relatively low, but from the long-term results after surgery, the difference between the two anesthesia methods on the probability of hypoxemia complicated by patients is minimal. [4]

3. Living ability and quality of life of postoperative patients

For elderly patients, whether they have the ability to live independently after surgery and the quality of life after surgery are important criteria to test the effect of surgery. Studies have shown that less than one-third of elderly patients with hip fractures can return to their previous living conditions within one year after surgery [5]. For the recovery of the patient's living ability within a short period of time after the operation, in this aspect, the patients with local anesthesia are obviously more advantageous. The patients with local anesthesia can recover their independent living ability after systematic functional recovery exercises within a period of time after the operation. faster. However, in the long term, patients under general

anesthesia also regain the ability to live independently after a prolonged period of functional recovery exercises. Therefore, in the long term, different anesthesia methods are not decisive for the recovery of patients' independent living ability after surgery. The recovery of the patient's ability to live independently is hampered by various objective and subjective factors, such as age, living habits, the presence or absence of other medical history, their own psychological state, and family companionship.

4. Conclusion

All in all, the adverse prognostic reactions of elderly patients with hip fracture include arrhythmia, postoperative pain, hypoxemia, etc. The recovery of patients' independent living ability and quality of life after surgery are also important manifestations of patients' prognosis and recovery. However, the relationship between general anesthesia and local anesthesia and these prognostic conditions has not been definitively concluded in the current research, and relevant scholars and experts have different research results and conclusions. Therefore, the topic of the effect of different anesthesia methods on the prognosis of elderly hip fractures still has a very high clinical research value, and the future research has broad prospects.

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Application of Modified POSSUM Scoring System in Patients Undergoing Thoracoscopic Surgery

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Abstract: Objective: To investigate the predictive value of a physiology and surgical severity-based score (POSSUM score) modified according to the characteristics of thoracic surgery for complications and mortality in patients undergoing thoracoscopic surgery. Method: To investigate the value of the modified POSSUM scoring system in predicting the complication and mortality rate of patients undergoing thoracoscopic surgery. The clinical data of 104 patients who underwent thoracic surgery in the Thoracic Surgery Department of Guangzhou Red Cross Hospital between May 2018 and May 2020 were retrospectively analyzed. The modified POSSUM score was used for preoperative patients to predict the number of postoperative complications and deaths, and compared with the actual number of complications and deaths. Result: The number of postoperative complications predicted by the improved POSSUM scoring system was 36, and the actual number of complications was 42. The difference was not statistically significant (P>0.05); The predicted number of postoperative deaths was 8, and the actual number of deaths was 1. The difference was statistically significant (P < 0.05). ***Conclusion:*** The modified POSSUM scoring system can be used to predict complications after thoracoscopic surgery but may overpredict postoperative mortality.

Introduction

In recent years, the Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) has been widely used. The system was first proposed by Copeland et al. [1] in 1991 and consists of probabilistic formulas for predicting complications and operative mortality. It contains 12 physiological indicators and 6 surgical severity indicators, and it is defined on four scales of 1, 2, 4, and 8. It calculates Physiologic Score and Operative Severity Score respectively to predict surgical mortality and morbidity of complications. 12 physiological indicators are age, cardiac signs, respiratory signs, systolic blood pressure, pulse rate, Glasgow coma score, hemoglobin, blood leukocytes, blood urea, serum sodium, potassium, electrocardiogram; The 6 surgical severity indexes were the type of surgery, the number of surgery, the contamination of the abdominal cavity, the total blood loss, the degree of malignancy, and the mode of surgery. They are mainly used for the assessment of the risk of specialized operations such as hepatobiliary, gastrointestinal, and pancreas in general surgery. Studies at home and abroad have shown that the POSSUM score is also suitable for predicting the risk of thoracic surgery [2-3], which indicates that the POSSUM scoring system can also accurately predict postoperative complications in pulmonary patients. With the popularization of thoracic surgery, thoracic surgery has become the mainstream, which puts forward higher requirements for targeted treatment and nursing after surgery, so it is particularly important to predict and reduce postoperative complications. The predictive formula for the incidence of surgical complications was Ln(R/1-R) =-5.91 + (0.16 × physiology score) + (0.19 × surgical severity score), and R was the predicted value. Prediction of complication rate = -5 .91 + (0 .16 × 12 physiology scores) + (0 .19 × 6 surgical severity scores). The mortality prediction formula was Ln(R/1-R) =-7.04+(0.13×physiological score) +(0.16×surgical severity score).

1. Materials and methods

1.1 General information

Patients who were hospitalized in thoracic surgery for thoracoscopic surgery from May 2018 to May 2020 were selected. Surgical methods: exploratory thoracoscopy, lung wedge resection, lobectomy, pneumonectomy; A total of 104 cases, 70 males and 34 females; Age: 16 to 80 years old.

1.2 Methods

1.2.1 Scoring method

The POSSUM scoring system was modified according to the characteristics of thoracic surgery, and the abdominal cavity contamination in the surgical invasiveness index was changed to thoracic cavity contamination. The specific scoring standard is: no pollution, 1 point; Clear pleural effusion, 2 points; Purulent pleural effusion, 4 points; 8 points for contamination of esophageal or stomach contents. The surgical method was changed to a classification score more suitable for lung surgery: simple thoracoscopic exploration, 1 point; Lung wedge resection 2 points; Lobectomy, 4 points; Pneumonectomy, 8 points; According to the modified POSSUM scoring system, the physiological indexes and surgical invasiveness indexes of each patient within 24 hours before surgery were collected and scored. The probability of postoperative complications (R1) was calculated according to the COPELAND equation. Postoperative complications were defined as all complications that occurred during hospitalization after surgery, that is, diseases or symptoms that did not occur before surgery but occurred after surgery were classified as postoperative complications. The definition of complications and standard reference [4].

1.2.2 Statistical analysis SPSS 17.0 statistical software was used for statistical processing

The POSSUM scores of the uncomplicated group and the complication group were expressed as mean ± standard deviation ($X \pm s$), and t-test was used for comparison between the two groups; The predicted and actual complication rates and mortality were expressed as percentages, and the comparison between the two groups was performed using the χ^2 test.

2. Results

2.1 Postoperative complications and death

Postoperative complications occurred in 42 patients (41.9%). Among them, 1 case of heart failure, 6 cases of fever, 3 cases of pneumothorax, 1 case of pulmonary edema, 3 cases of atelectasis, and 1 case of respiratory failure. There were 5 cases of pulmonary infection, 2 cases of phlebitis, 2 cases of infusion reaction, 5 cases of subcutaneous emphysema, 5 cases of wound infection, and 8 cases of arrhythmia. One patient died of pulmonary infection complicated with respiratory failure after operation.

2.2 POSSUM scoring system

The physiology score and surgical severity score of the patients with postoperative complications were 16.62±3.91 and 13.93±4.22, respectively, which were higher than those of the uncomplicated group, 15.15±2.66 and 11.58±4.05, with statistically significant differences.

2.3 Comparison of the modified scoring system prediction system with actual morbidity and mortality

The 104 cases in this group were evaluated by the modified POSSUM scoring system. The number of postoperative complications predicted by the Copeland equation was 36 cases, and the actual incidence was 42 cases. There was no statistically significant difference between the two ($\chi^2 = 0.738$, P = 0.390), as shown in Table 2. In this group of 104 patients, the number of deaths predicted by the Copeland equation after the modified POSSUM score was 8 cases. The actual number of deaths was 1, and there was a statistically significant difference between the two ($\chi^2 = 5.691$, P = 0.017), as shown in Table 3.

Table 1 Comparison of the two groups of POSSUM scoring systems

Groups	Number of cases	Physiological Score	Surgical severity score
Complication group	42	16.62±3.91	13.93±4.22
Uncomplicated group	62	15.15±2.66	11.58±4.05
t value		2.29	2.85
P value		0.24	0.005

Table 2 Comparison of predicted and actual complications

R1(%)	Number of cases	Average of R1	Predictive value	Actual value	Actual-forecast ratio
＜10	13	0.09	2	4	2
≥10＜20	30	0.14	5	7	1.4
≥20＜30	18	0.25	5	6	1.2
≥30＜40	15	0.35	6	7	1.16
≥40＜50	10	0.46	5	5	1
≥50＜60	6	0.54	4	4	1
≥60＜70	5	0.66	4	4	1
≥70＜80	3	0.75	3	3	1
≥80	2	0.83	2	2	1
Total	104	-	36	42	-

The results in Table 1 show that there was no statistical difference between the predicted value and the actual value of postoperative complications between the two groups, indicating that the POSSUM scoring system can also more accurately predict postoperative complications in patients with lung surgery.

Table 3 Comparison of predicted and actual deaths

R2(%)	Number of cases	Average of R2	Predictive value	Actual value	Actual-forecast ratio
＜10	84	0.04	4	0	0
≥10＜20	15	0.14	2	0	0.5
≥20＜30	5	0.25	2	1	0.5
≥30	0	0	0	0	0
Total	104		8	1	-

3. Discussion

Thoracoscopic surgery is a common operation in thoracic surgery. With the popularization of thoracoscopy and the advancement of equipment development, complications have been reduced compared with before, but postoperative

complications are still common, mostly cardiopulmonary complications [5]. This study showed that there was no statistically significant difference between the predicted value of postoperative complications and the actual value, which indicated that the POSSUM scoring system could also more accurately predict postoperative complications in patients with thoracoscopic surgery. Several studies have shown that the POSSUM scoring system over-predicts the postoperative mortality of patients [6-7]. This study agrees with seeing that even modified POSSUM overpredicts operative mortality.

This study found that the physiological POSSUM scoring system of thoracoscopic surgery is mainly concentrated between 10% and 30%, which may be related to the selection of thoracoscopic surgery population. Routine thoracotomy for critically ill patients. In addition, it may be caused by the small trauma of thoracoscopic surgery, the high degree of surgical precision, the less blood loss, and the relatively low surgical severity score.

The POSSUM scoring system provides medical staff with a scientific basis for objectively evaluating the perioperative physiological status and prognosis of patients. By early warning of complication rates and providing forward-looking information, it is helpful to formulate patient care plans, targeted and more comprehensive individualized care programs, and improve the quality of care. It can enable patients and their families to better understand the risks of surgery and reduce the occurrence of medical disputes. Strictly complete the treatment plan on time, check vital signs, cardiopulmonary function, etc. in time to minimize complications.

In conclusion, the modified POSSUM scoring system can be used to predict postoperative complications in patients undergoing thoracoscopic surgery. However, there is a possibility of over-prediction in predicting the number of postoperative deaths. The next step is to add pulmonary adhesions, pulmonary function tests, and refine the POSSUM score according to the preoperative TNM staging; The establishment of a postoperative prediction system with its own characteristics of thoracic surgery will have more application prospects.

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Self-Hemotherapy for the Treatment of one Case of Hyperglycemia

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Abstract: The clinical use of autohemotherapy for the treatment of hyperglycemia in type 2 diabetes mellitus has a remarkable effect.

Keywords: Autohemotherapy; Type 2 Diabetes; Acupuncture; Hyperglycemia; Case Analysis

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease commonly seen clinically[1], and hyperglycemia is an important indicator. With the change of people's diet structure, the severity of type 2 diabetes can not be underestimated, according to epidemiological statistics [2], there are about 260.4 million elderly people over 60 years old in China, of which diabetics account for more than 30%. Diabetes is not only manifested in the fact that blood sugar is different from ordinary people, but also its fatty acids and amino acids are different from healthy people in serum metabolomics [3], that is, diabetes is a disease of metabolic disorders of sugar, protein and fat. At present, modern medicine treats type 2 diabetes mainly by taking drugs or injecting insulin. First-line treatment for prediabetes is dominated by biguanide, α-glycosidase inhibitors [4]. Since the disease requires long-term or even lifelong use, the adverse reactions of the drug should also be taken seriously. There are many adverse reactions, including gastrointestinal reactions, hypoglycemia, lactic acidosis, vitamin B12 deficiency, and even liver damage [5]. TCM acupuncture for the treatment of type 2 diabetes has unique advantages, safety, and few side effects, not only improving blood sugar, but also alleviating peripheral neuropathy caused by diabetes [6].

1. Method - Autohematology

Acupuncture point injection, also known as water needle, is a new type of therapy that combines traditional acupuncture treatment in traditional Chinese medicine with the closure therapy of modern medicine by injecting certain Chinese and Western drug injections into the relevant acupuncture points of the human body to prevent and treat diseases [7]. Replacing a drug with its own blood is a self-hemorrhage therapy. Self-hemorrhage therapy is part of the acupuncture point injection method, and the self-hemorrhage therapy discussed in this article is significantly different from the "ozonated self-blood refusion therapy" of Western medicine, which is also referred to as "self-hemorrhage therapy".

In the "Difficult Scriptures", it is described: "Blood is the main substance", blood is a subtle substance, and can be replaced by other drugs. In the Twelfth Treatise on Thirst Quenching in Medical Management, it is described that in the treatment of this disease, it is necessary to pay attention to the yuanjing, which is the basis of creation and birth, and the yuanjing is the sperm blood, and both are the intersection of yin and yang. Quenching thirst for a long time, consuming liver and kidney yin blood, insufficient yin blood, eye loss, yin fire burning the eye network, causing diabetic eye disease, weak qi and blood movement, stasis of the vein, causing diabetic foot, it can be seen that blood and the later complications of thirst quenching disease are also closely related [8].

Autohemotherapy not only has the effect of acupuncture, but also takes into account the role of bloodletting and autologous blood. When one's own blood is inserted into the acupuncture point, the blood coagulation has a gentle and

long-term stimulation of the acupuncture point, which is conducive to prolonging the curative effect time. It can play a dual role of acupuncture and long-term acupuncture point stimulation. Blood stasis in type 2 diabetes mellitus is poor blood circulation, and the "bruise" in the blood veins is not the "bruise" of blood clotting on acupuncture point stimulation in autohematology. Bloodletting itself has the effect of heat dissipation, which plays a role in the treatment of the hot and fiery pathogenesis of early type 2 diabetes patients, and the self-blood therapy also plays a role in activating blood, which is beneficial to cold coagulation stasis or wet blood stasis.

2. Case investigation

The patient, a 54-year-old male, was first diagnosed on 18 November 2020. Main complaint: Found to have increased blood glucose for more than 1 year. Current medical history: The patient complained of an increase in blood glucose during the physical examination 1 year ago, diagnosed with "type 2 diabetes", after irregular oral metformin to control blood sugar, poor blood glucose control on weekdays, fasting blood glucose 7.0-8.5mmol/L, postprandial 2 h blood glucose 9.0-10.5mmol/L. This morning, I measured fasting blood glucose of 7.3mmol/L, and I complained that I was unwilling to take Western medicine for a long time, so I came to the clinic. Diagnosis: dry mouth and drinking, normal urination, loose stool, red tip of the tongue, tortuous veins under the tongue, purple and dark, thin yellow moss, weak pulse. Physical examination: the skin of both lower extremities of the patient is dry and untouchable. Diagnosis of Western medicine: type 2 diabetes mellitus; Diagnosis of traditional Chinese medicine: thirst quenching disease, dialectics: qi yin deficiency evidence; Treatment: healthy spleen and qi, invigorating blood and dispelling stasis. Prescription: diji acupuncture (bilateral), pancreatic Yu acupuncture (bilateral). Treatment: Autohematization. Specific operation: the patient's elbow skin disinfection, with a 2.5mL disposable syringe to draw the patient's venous blood 2.0mL; after iodine disinfection acupuncture points, quickly pierced into the subcutaneous, direct acupuncture of the machine, spleen Yu acupuncture to the spine direction obliquely stabbed, stabbed about 1cm, until there is a feeling of acid numbness and confirm that it has not pierced the blood vessel, slow injection, each acupuncture injection of 0.5mL. Communicate with patients in a timely manner, encourage care for patients, enhance patients' self-confidence in treatment, and instruct patients to avoid water within 1 day after each treatment, keep the skin clean and dry, and prevent infection. Course of treatment: 1 treatment every other day, 3 treatments per week, 5 sessions for 1 course.

2nd consultation: On November 26, 2020, the patient complained of monitoring blood glucose 30 minutes after the end of each treatment and observed that blood glucose decreased to the normal range. Monitoring of fasting blood glucose fluctuations of 6.0-7.0 mmol/L in the morning of the next day and 8.0-9.0 mmol/L in 2 hours after meals without taking the drug, although higher than the normal range, but better than when untreated, the symptoms of dry mouth were reduced, and the residual changes were not obvious.

3rd consultation: On December 18, 2020, the patient complained that he had not taken the drug to monitor his blood glucose on an empty stomach and 2h after a meal, and the symptoms of dry mouth were significantly alleviated, and the stool was formed.

After telephone follow-up in March 2021, the patient complained of monitoring blood glucose stability, no obvious dry mouth, and normal stool.

According to the language: The patient in this case is a middle-aged man, who is fat, and he loves to drink alcohol and never avoids his mouth, resulting in spleen loss; Qi yin dissolves fire, dissolves burning liquid, and lacks moistening, which is manifested as dry mouth and happy drinking; Temper is weak, and the transportation is weak. The tip of the tongue is red, the veins under the tongue are twisted, purple and dark, the moss is thin and yellow, and the pulse is weak, indicating that the patient has heat in the body, there is stasis, considering the deficiency of qi and yin, and the qi deficiency is that the blood runs astringently, coagulates into stasis, and the blood is obstructed internally, so it is necessary to strengthen the spleen and benefit the qi, and activate the blood to dispel stasis. The spleen is selected to treat hemorrhage, regulate the function of the spleen and stomach, strengthen the power of the spleen and stomach, strengthen the spleen to help transport, and strengthen the acquired nature; The selection of pancreatic Yu acupuncture points for the treatment of thirst quenching disease, the combination of two acupuncture points, a joint performance of hypoglycemic work, by simplifying the acupuncture points,

reduce the pain of patients. At the second diagnosis, the patient's blood glucose decreased, and the symptoms of dry mouth were alleviated, but the symptoms of non-forming stools were still not alleviated, and it was considered that the blood stasis gradually disappeared but it took time for the temper to recover, so the treatment was continued. At the time of 3 diagnoses, the patient's symptoms improved, and the blood glucose was able to be maintained smoothly in the normal range. Throughout the entire diagnosis and treatment process, the eye is set on the "stasis" treatment of type 2 diabetes, and the treatment method is unified with the evidence, and the effect is remarkable.

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Clinical analysis of tenofovir combined with sorafenib in patients with hepatitis B-related intermediate to advanced primary liver cancer

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Abstract: **Aim:** To investigate the clinical efficacy of tenofovir combined with sorafenib in the treatment of patients with hepatitis B-related intermediate to advanced primary liver cancer. **Methods:** Sixty patients with hepatitis B-related intermediate to advanced primary liver cancer admitted to our hospital between January 2021 and December 2021 were selected and divided into 30 cases each in the study group and the control group according to the random number table method, in which the control group was treated with sorafenib and the study group was treated with tenofovir on top of the control group. Finally, the liver function indexes and clinical efficacy of the two groups of patients were observed and compared. **Results:** The total effective rate of treatment in the study group was 83.33%, while the total effective rate of treatment in the control group was 46.67%, There was a significant difference ($P < 0.05$) between the two groups comparing, Liver function indexes such as TBIL, ALB, PT and AFP before treatment in the study group were not significantly different from those in the control group ($P > 0.05$)，there were significant differences in liver function indexes such as TBIL, ALB, PT and AFP after treatment compared with the control group ($P < 0.05$). **Conclusion:** The short-term clinical efficacy and safety of tenofovir in combination with sorafenib in the treatment of patients with hepatitis B-related intermediate to advanced primary liver cancer is remarkable and worthy of clinical application.

Keywords: Tenofovir; Sorafenib; Hepatitis B; Primary Liver Cancer

Introduction

Liver cancer is a kind of malignant tumor that seriously endangers human health. One of the important causes of primary liver cancer in China is hepatitis B virus infection (HBV), which is already in the middle or late stages when detected early and has lost the possibility of liver transplantation or surgical treatment, and radiotherapy and chemotherapy often fail to achieve the desired results.[1] How to improve the survival rate of patients with intermediate and advanced liver cancer is an urgent clinical research topic at present, therefore, looking for an effective treatment can greatly improve patient' quality of life. In this paper, we conducted a preliminary investigation of the therapeutic effects of tenofovir in combination with sorafenib in hepatitis B-related intermediate to advanced hepatocellular carcinoma, the report was as follows:

1. Materials and Methods

1.1 General Information

Sixty patients with hepatitis B-related intermediate and advanced primary liver cancer admitted to our hospital during January 2021-January 2022 were selected and divided into 30 cases in the study group and 30 cases in the control group, including 17 males and 13 females in the study group, aged 55-85 years, with a mean age of (70±15) years. There were 16 male and 14 female cases in the control group, aged 54-87 years, with a mean age of (70.5±16.5) years. The basic information of the patients in both groups was comparable ($P > 0.05$). All patients and their families were informed of the study and signed it. Permission for this study was obtained from the hospital ethics committee.

1.2 Methods

All patients were given liver protection and supportive symptomatic treatment with tenofovir fumarate (GlaxoSmithKline Tianjin Co., Ltd., State Drug Administration H20153090) 300 MG was given orally, 1 time/D； In the observation group, on the basis of tenofovir fumarate treatment, sorafenib mesylate (Bayer Pharma AG, approval number/registration certificate number H20160201, execution standard import drug registration standard JX20060053) 0.4G was given orally, 2 times/d, and observed for 12 months.

1.3 Observation indicators

Patients with an improvement of at least 20 points in Karnofsky score after treatment according to the Karnofsky Quality of Survival Scale were assessed as having a significant effect； After treatment, the patient's Karnofsky score improved by 10 to 20 points and was rated as effective； Patients with an improvement of <10 points or no change in Karnofsky score after treatment were rated as stable；Patients with reduced Karnofsky scores after treatment were assessed as ineffective. [2]

1.4 Statistical Methods

The study was analyzed by SPSS24.0 statistical package, and the measurement data were expressed by ($\bar{x}\pm s$), and the t-test was used for comparison between two groups, the count data were expressed by relative numbers, and the X2 test was used for comparison between two groups, and SPEARMAN correlation analysis was used for correlation analysis between non-variables, and $P < 0.05$ meant that the difference was statistically significant.

2. Results

2.1 Comparison of clinical efficacy between the two groups

The total effective rate of treatment in the study group was 83.33% compared with 46.67 in the control group, with a significant difference between the two groups ($P < 0.05$), as shown in Table 1.

Table 1 Comparison of clinical efficacy between two groups of patients [n(%)]

Groups	Number of cases	Significant effect	Effective	Stable	Ineffective	Total efficiency rate
Study Group	30	9	16	4	1	25（83.33）
Control group	30	4	10	9	7	14（46.67）
X^2						8.865
P						0.003

2.2 Comparison of liver function indexes between two groups of patients

Liver function indexes such as TBIL, ALB, PT and AFP in the study group before treatment were not significantly different from those in the control group ($P > 0.05$)，Significant differences in liver function indexes such as TBIL, ALB, PT and AFP compared with the control group after treatment ($P < 0.05$)，as shown in Table 2.

Table 2 Comparison of liver function indexes between the two groups ($\bar{x}\pm s$)

Groups	Number of cases	TBIL（μMOL/L）		ALB（μMOL/L）		PT（μMOL/L）		AFP（μMOL/L）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study Group	30	35.4±18.1	20.6±10.1	27.6±3.6	37.7±2.7	13.8±2.1	13.2±1.1	760.3±210.4	430.5±80.5
Control group	30	35.7±17.9	32.7±12.3	28.3±3.1	31.6±2.4	14.4±2.6	14.8±1.9	770.5±220.3	530.7±101.8
T		0.065	4.164	0.807	9.249	0.983	3.992	0.183	4.229
P		0.949	0.000	0.423	0.000	0.330	0.000	0.855	0.000

3. Discussion

The liver plays an important role in maintaining the balance of the coagulation system, mainly by synthesizing coagulation factors, physiological anticoagulation factors, and fibrinolytic factors in the liver. Patients with intermediate to advanced hepatocellular carcinoma will have more complete liver damage when their liver function is decompensated. The more severely the liver function is damaged, the synthesis of coagulation factors will be reduced and the coagulation ability will be decreased. Therefore, there is a certain correlation between liver function and coagulation function, and coagulation function is a good indicator. Prothrombin time (PT) is a method to detect the function of the human exogenous coagulation system by over-screening, which can be used to diagnose congenital coagulation and acquired bleeding disorders of the exogenous coagulation system, as well as to diagnose severe hepatitis and early cirrhosis.[3] The activated partial thromboplastin time (APTT) is a relatively sensitive assay that reflects the coagulation activity of the endogenous coagulation system, and it is an important test that reflects the combined viability of the endogenous coagulation pathways, especially the first phase of coagulation factors. TT is an indicator of anticoagulant substances in the body. Duration of TT indicates hyperfibrinolysis, and TT shortening is not clinically relevant in cases of hypofibrinogenesis, DIC and heparin-like substances. Plasma fibrinogen, a common blood clotting factor, is a protein found in plasma.

Alpha fetoprotein is a highly specific marker of HCC sensitivity that is made by juvenile cells similar to hepatocytes and can be detected at an early stage of hepatocyte development. Serum A-fetoprotein is elevated earlier than imaging, that is, earlier than ultrasound or CT, so it is best for early diagnosis. The detection rate of alpha fetoprotein in liver cancer is around 80%. If the content of alpha fetoprotein is high, it indicates that the prognosis is poor. Therefore, the detection of alpha fetoprotein is an important indicator of the efficacy of liver cancer [4]. Hepatitis B-associated liver cancer is a relatively common malignant tumor with a high incidence, usually in the middle and late stages, which cannot be treated surgically; radiotherapy and chemotherapy often fail to achieve the desired therapeutic effect. Hepatitis B virus binds to human chromosomes, which is the causative agent of liver cancer, making liver cells susceptible to mutation under a series of stimuli. Under the influence of different stimulating factors and growth factors, liver cells are altered, some proto-oncogenes are activated and oncogenes are mutated; therefore, to a certain extent, controlling the level of HBVDNA can be of great help in improving the quality of life of patients. [5]

Tenofovir fumarate is a new antiviral drug that can effectively and rapidly inhibit HBVDNA replication. It can reduce inflammation in the patients' liver and provide effective treatment for liver damage. Sorafenib is a novel multitargeted new anticancer drug that can inhibit tumor cell proliferation by blocking RAF/MEK/ERK-mediated cell signaling pathways and can indirectly inhibit tumor cell growth by inhibiting VEGFR, PDGF and other receptors for the treatment of liver cancer, so as to achieve the purpose of treating liver cancer.[6] The results of this study showed that the combination of tenofovir with sorafenib for the treatment of hepatitis B-related intermediate and advanced HCC significantly improved liver function and reduced AFP levels. This is due to the better synergistic effect of the two drugs, which can better improve the liver function of patients.

In conclusion, tenofovir combined with sorafenib in combination with hepatitis B-related intermediate and advanced hepatocellular carcinoma is a feasible method to effectively improve liver function and reduce the level of AFP; it has obvious effects in the short term and deserves further clinical testing.

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Current Status and Outlook of Research on Emergency Drills for Public Health Emergencies

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Abstract: Public health emergencies are major infectious disease outbreaks, mass unexplained diseases, major food and occupational poisoning and other events that seriously affect public health that occur suddenly and cause serious damage to the public health of society. In the absence of certain preplanned preparations and experience in emergency response, the outbreak of public health emergencies always catches us off guard and poses a huge challenge and burden to public health and social safety. At present, due to the late start of the emergency management of public health emergencies, the lack of a perfect theoretical system of emergency management, the weak public awareness of emergencies, the lack of scientific emergency measures, the lack of a perfect and flexible public health emergency management system, and the lack of an advanced emergency management level of society as a whole, all of these factors have led to inefficiency, communication and a lack of experience in dealing with public health emergencies such as the new coronary pneumonia outbreak in the early stage. In this context, it is important to take a deeper look at the problems of inefficiency and poor communication in handling public health emergencies. In this context, it is important to examine the current research status of emergency drills for public health emergencies in China, investigate the typical problems, and propose a series of innovative practical strategies for emergency drills for public health emergencies, such as exploring the closed-loop management mode of emergency drills for public health emergencies and giving full play to the role of information technology as a driver of innovation, according to the current development level of China as a whole.

Keywords: Public Health Emergencies; Emergency Drills; Research Status; Future Outlook

Introduction

Public Health Emergency is a major infectious disease outbreak, mass unexplained disease, major food and occupational poisoning and other events that seriously affect public health that occur suddenly and cause or may cause serious damage to public health[1]. The causes of public health emergencies are characterized by the diversity of causes, suddenness, group nature, differences, extensiveness and seriousness[2-3]. In particular, the occurrence of major public health emergencies is very likely to pose a great threat to people's health, life and property safety, stable social and economic development, and the implementation of national strategic planning[4-5]. Since the beginning of the 21st century, there have been outbreaks of public health emergencies in countries around the world, such as the SARS epidemic in 2003 and the new coronavirus pneumonia outbreak in 2019[6-7]. Therefore, an in-depth analysis of the current research status of public health emergency drills at home and abroad is carried out, and targeted considerations are made from the problems that still exist in the current society in the emergency response to public health emergencies. Innovative response implementation strategies are proposed from multiple perspectives, such as individuals, government administration, and the professionalism of conducting public health emergency drills.

1. Research Status

1.1 Current status of domestic research

Sudden public health events have obvious suddenness in time, complexity in cause, severity in consequence, and controllability in process[8]. Jiang Hui and Zhu Wentao comprehensively reviewed 5412 related studies in the field of public health emergencies from 2010 to 2019 in the Web of Seience database. IS pointed out that emergency medicine, infectious diseases, air pollution and emergency management, and major infectious viruses are hot issues in the research field of sudden public health events[9]. Lu Quan pointed out the multiple advantages and defects of China's social security system during the COVID-19 epidemic and put forward policy implementation suggestions on deepening social security reform and optimizing social insurance, public health and medical security, social assistance, social welfare services and charity systems with the support of relevant theories[10]. Dang Xiaohong and Zhang Jing pointed out that early Chinese research work on this aspect presents a research perspective on the whole, and the research focus is on the relevant system and mechanism construction. From 2020, Chinese research work on this aspect shows diversified characteristics on the whole. In addition, the research focuses on specific coping subjects, urban coping ability, and overall processing mode and makes scientific prospects for innovative practices in this field[11]. Chen Yang and Zhao Man provided certain theoretical innovation strategies for the construction of emergency mechanisms and the realization of agile governance in the case of epidemic prevention and control in Sichuan Province[12]. Li Lei and Zhi Mei conducted a specific analysis from the perspective of communication and pointed out that relevant government departments should adopt differentiated intervention policies for such problems to improve the specific work efficiency of regulatory departments[13]. Li Zhen developed a set of questionnaires to evaluate the response ability of primary medical institutions to public health emergencies in line with the actual situation in Guangxi border minority areas[14].

1.2 Current status of foreign research

Yi and Sweileh analyzed the current status and trends of Ebola research and the link between natural disasters and public health emergencies from 1977-2014 and identified the main research countries and research hotspot areas focusing on this topic[15-16]. In terms of emergency decision management for public health emergencies, Cosgrave argued that the emergency decision problem can be described in terms of quality requirements, acceptance requirements, and problem urgency [17], Ikeda et al. pointed out that the emergency decision organization should be composed of four subjects: decision executors, expert advisors, managers, and decision makers[18], Wybo proposed a four-pronged approach based on professional competence in terms of staffing, matching Wybo proposed four principles to construct emergency decision-making organization based on professional ability of staffing, matching degree, team type, and function assignment[19], Tamura et al. established a systematic decision analysis method based on decision tree analysis of expected utility theory[20], and Mendonca believed that the evaluation system should be composed of two elements: measurement system and evaluation system[21]. At present, foreign countries have many achievements in emergency exercise simulation system research; for example, the National ExerciseSimulation Center (NESC) in the United States has conducted simulation exercises for various types of disasters in a virtual environment and constructed scenario models, capability models, and decision models[22].

In summary, foreign scholars started their research activities on public health emergencies earlier and made important definitions of a series of basic concepts and classifications, which laid a solid theoretical foundation for the advancement of subsequent research activities. However, with the frequent occurrence of public health emergencies in recent years, an increasing number of scholars have started to pay attention to this issue and conduct in-depth research. In the face of socially dangerous public health emergencies, scholars in China have conducted research from various perspectives, such as psychology, economics and communication, and proposed corresponding response strategies, and their research results have important theoretical value. However, in general, the research activities from the perspective of guiding the public and related subjects to carry out advance planning and emergency drills are not very rich and comprehensive, and we need to carry out theoretical and practical research to address the lacking parts and propose constructive solutions.

2. Problems of emergency drills for public health emergencies and countermeasures

2.1 Problems

2.1.1 Personal perspective

From a personal point of view, the majority of our society has a serious lack of crisis awareness in their daily lives, and they always take a chance on possible public health emergencies, believing that the probability of being involved in a large public health emergency threat is extremely small. The general public lacks comprehensive knowledge of the events involved, their knowledge of public health emergencies is only superficial, and they do not know how serious the consequences of such events will be if they occur, which leads to a serious lack of emergency treatment capabilities in our society as a whole. In the absence of scientific knowledge of public health emergencies, the general public also lacks a certain amount of attention to long-standing public health emergency drill services and seldom takes the time and energy to participate in and learn from the relevant emergency drill activities, resulting in a state of panic and overwhelm when they are truly faced with danger. Due to panic about the danger of life, many people not only have difficulty making correct scientific handling measures in critical situations but also always aggravate their own critical situation in panic and disorientation, resulting in the low crisis response ability of society as a whole. From the perspective of the relevant emergency disposal staff, there is the problem of untimely and inadequate implementation of emergency disposal measures. Public health emergencies are often characterized by strong danger, suddenness, contagiousness and difficulty of control. If we do not carry out the corresponding emergency disposal at the first time after discovering its problems but waste time in a series of unnecessary procedural reviews, it is likely to delay the best emergency disposal time and cause serious consequences that are difficult to recover.

2.1.2 Government management perspective

From the perspective of government management, some systems and regulations related to public health emergencies are incomplete, and because the relevant managers lack a certain degree of attention to their work, the preparation of systems and regulations is more like a "decoration" used to deliver to the leadership, which looks cumbersome and complicated and professional, but in fact, it is difficult to truly use in the emergency response process of public health emergencies. The most typical problem is that the management department has to deal with the emergency situation. The most typical problem is that the management has a habit of distributing the authority to implement a measure among different management departments so that staff and people who want to mobilize local equipment and personnel in a crisis situation must first go to the management department with complicated documents for approval, and the staff responsible for signing and stamping will shirk their responsibility to confirm each other for fear of taking responsibility. At the same time, because public health emergencies are often secretive and delayed in their early stages, interventions and support from higher levels of government do not intervene in a timely and effective manner, requiring grassroots units in the governance hierarchy to take on the responsibility of early response[23]. In such a situation, a large amount of time and energy is already spent in the process of obtaining permission at each level, which in turn delays the optimal emergency response time for public health emergencies. In addition, the worldwide outbreak of novel coronavirus pneumonia, a public health emergency, not only made the public deeply aware of the importance of learning the relevant emergency response knowledge and skills in advance but also reflected the important problem of "fragmentation" and lack of social responsibility in the process of specific law enforcement and assignment of tasks by the relevant government management departments in China.

2.1.3 Professional perspective of conducting emergency drills for public health emergencies

While emergency drills for public health emergencies have achieved actual work effectiveness or purpose, there are also many common and prominent problems, such as the characteristics of drills, too many drills, too few drills, i.e., too many performance-type, display-type drills, too few test and examination drills, misconceptions, organizational irregularities, and task-complete perfunctory, coupled with the lack of standards for technical specifications in emergency drills in China, which

makes drills as ineffective as some irresponsible preplans[24-25].

2.2 Countermeasures

2.2.1 Personal perspective

From an individual perspective, it is important to focus on raising the importance of public health emergencies in the community and to raise the public's awareness of the importance of having the ability to deal with public health emergencies in their own lives. The community should be invited to participate in the activities to help them improve their knowledge and to be able to respond correctly to the signs of danger in their daily lives. In schools, students are encouraged to acquire the awareness and skills to deal with public health emergencies from an early age and are encouraged to pay attention to the importance of having the ability to deal with public health emergencies through continuous knowledge inculcation. At the same time, provinces and municipalities create special short video accounts by geographical departments and regularly update their accounts with theoretical knowledge and/or practical measures related to emergency response to public health emergencies. Other professional emergency response staff should mainly devote themselves to improving their work attitude, establishing a positive and responsible working attitude, maintaining responsibility in the specific public health emergency drill and disposal, and doing their best to help the social public deal with the relevant emergency problems. In addition to repeatedly disseminating information about emergency drill operations to the public in general, staff members related to public health emergencies also need to actively encourage people to participate in the specific drill process, and for each drill activity, select different social people to participate in the local public health emergency drill activities in the field to enhance the public's attention to this self-help activity and preparation. The permanent exhibition of similar scenarios and the provision of free places to experience public health emergencies in different areas through VR technology and model-making techniques encourage the public to realize the extreme importance of being prepared in the process of being close to the real experience.

2.1.2 Government management perspective

From the perspective of government management departments, it is necessary to fundamentally strengthen its departments in the simplification of the implementation procedures of emergency disposal of public health emergencies, enhance the publicity of relevant emergency disposal exercises, and improve the emergency handling capabilities of the general public in the region. While continuously raising the height of awareness of emergency drills for public health emergencies, government management departments should adjust and optimize the emergency disposal work system for public health emergencies as soon as possible, improve the emergency disposal protection work mechanism for public health emergencies, improve the decision-making, coordination, command and other work processes of relevant government management departments, and make the allocation of major decision-making powers precise and concise while actively promoting government. At the same time, we actively promote the digitalization of government information, promote the openness and transparency of data and important information, and ensure that the staff of various departments will not make mistakes in decision-making due to the existence of blind spots in relevant information in the process of task implementation and promotion. In addition, it is advocated to open an authoritative emergency drill display platform for public health emergencies, produce thematic short video works based on the application of applications such as WeChat Public, Jitterbug, Xiaohongshu and Weibo, and make full use of modern information technology to enhance the dissemination of relevant knowledge and information and improve the crisis response ability of the public.

2.1.3 Professional perspective of conducting emergency drills for public health emergencies

The concept of emergency management of public emergencies is "prevention oriented, combined with civilian warfare, promoted by exercises, and improved by exercises". The combination of civilians and combat is the key to rehearsal. The

modern disaster medicine rescue has the theory of "three out of seven": three out of war and seven out of rehearsal is a true reflection of it. To improve the emergency response capability of public emergencies, repeated rehearsals are needed[26].

Establishing a new view of emergency drills for public health emergencies, not for the sake of drills. First, it is necessary to establish a holistic view of emergency drills for public health emergencies. Second, it is necessary to establish a systematic view of emergency drills for public health emergencies. Third, it is necessary to establish a professional view of emergency drills for public health emergencies. Fourth, through emergency drills for public health emergencies, it is necessary to standardize the work system, support platform and concise and applicable operational procedures or guidelines for the disposal of public health emergencies[27-28].

Establishing and improving the analysis and evaluation system of emergency drills for public health emergencies. The evaluation of emergency drills for public health emergencies is mainly to assess and propose improvements based on the performance of the participants in completing key tasks against the requirements of emergency management capabilities and the objectives of emergency drills for public health emergencies[28]. By determining the assessment points, evaluation standards and methods for emergency drills for public health emergencies, we can provide a comprehensive and systematic understanding of emergency drills for public health emergencies, summarize and analyze the whole process of emergency drills for public health emergencies, and accurately evaluate the effectiveness of the drills, focusing on the interface of emergency plans at all levels, cooperation and coordination of emergency disposal subjects, resource integration and deployment, personnel, and other difficulties. It is an important way to further strengthen and improve the response to public health emergencies and enhance emergency response capabilities and levels[29-30].

3. Research outlook

Exploring the closed-loop management mode of public health emergency drills to inject new vitality into the emergency management of public health emergencies. By establishing a closed-loop management model for emergency drills for public health emergencies, under the guidance of the closed-loop management model for emergency drills for public health emergencies, and in accordance with the requirements of "long-term preparation and focused construction", we will first conduct a series of emergency drills for public health emergencies and, second, strengthen the basic work of preparation, implementation, evaluation, and optimization of emergency drills for different categories, different levels, different scenarios, and different stages of public health emergencies. The second is to strengthen the basic work of preparation, implementation, evaluation, and optimization of emergency drill management for different categories, levels, scenarios, and stages of public health emergencies, to continuously improve the comprehensive emergency response capabilities of medical institutions to deal with public health emergencies, and to optimize the construction of systems and processes on the basis of daily emergency drills for public health emergencies so that the management of emergency drills for public health emergencies is more scientific, standardized, refined, and process-oriented. Process.

The role of innovation-driven information technology is to provide new momentum for the high-quality development of emergency public health incidents. There are various limitations in organizing hierarchical and hierarchical public emergency drills, such as cost, personnel, and space, which in turn lead to lower drill frequency and lower quality of drills. With the development of modern science and technology, it is possible to develop a virtual emergency drill system, innovate the form of emergency drills for public health emergencies, and promote the normalization of emergency simulation drills for public health emergencies in medical institutions. Explore the construction of emergency rehearsal systems for public health emergencies based on virtual simulation technology and on the basis of 3D scenarios and data fusion, build a visualization platform for emergency management and simulation of emergency rehearsals for 3D wisdom emergency rehearsal scenarios and even larger regional spaces, use virtual reality technology to realistically restore the disaster site environment, and realize real-time monitoring of spatial data, historical playback, and simulation rehearsals through the presentation of all-time and spatial situations. Simulation rehearsal so that the law is clearly visible. The first is to make the decision of emergency management of public health emergencies countable and more efficient to improve the emergency handling capacity of medical institutions in response to public health emergencies; the second is that through the emergency management of public health emergencies and virtual simulation emergency drill platforms, it is conducive to the immersion of front-line

personnel in training and improving their emergency rescue capacity of public health emergencies and to the realization of multimedical institutions and multidepartmental joint cross-territory emergency response. It is also conducive to the realization of cross-regional joint emergency drills for public health emergencies between multiple medical institutions and departments. At the same time, the establishment of online emergency drills public welfare accounts, the use of VR technology to widely carry out virtual displays of relevant scenes, the establishment of emergency drills related to sudden public health event network self-learning websites, etc., through the full implementation of such work, China's emergency drills related to sudden public health events can get twice the effect of publicity and popularization with half the effort.

4. Conclusion

The occurrence of a sudden public health event is not an everyday occurrence, but whenever it breaks out, it means huge casualties and halting effects on social development. By actively carrying out emergency public health emergency response drills, we help the public master certain temporary emergency knowledge and skills in the demonstration of the professional staff's plan response drills to guarantee that the majority of the social groups remain calm in the face of sudden public health events and make the most efficient measures to save themselves and rescue others. In the future social development process, we should not only pay attention to the scientific promotion of social emergency public health incident drills but also carry out theoretical and high level of continuous investigation from the level of scientific research, think about how to strengthen the strengths and improve the deficiencies from emergency public health incident drills, take emergency public health incident drills as the grasp, and turn the results of drills into real power, which is the task of emergency public health incident emergency management in the future. The future tasks and goals of public health emergency management will provide more groundbreaking and effective guidance for specific practical activities.

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Correlation Between Blood System Impairment and Immune Index in Patients with Primary Sjögren's Syndrome

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Abstract: Objective: To analyze the relationship between blood system impairment and immune indexes, including autoantibody, immunoglobulin and lip gland biopsy in patients with primary Sjogren's syndrome (pSS). Methods: The serological data of patients with Sjogren's syndrome in hospital were collected and divided into hematological system impairment group and normal group. The incidence of hematological system damage in patients with pSS and its correlation with immune indexes were analyzed. Results: 123 patients with pSS were included in this study. There were 57 patients in the blood system involvement group (46%), in which the proportions of leucopenia, anemia and thrombocytopenia were in turn; 17. 89%; 33. 3%; 4. 88%. The antibodies in the blood system affected group were abundant, and the positive rates of anti SSA and Ro-52 antibodies were significantly higher than those in the normal group. The increase of serum IgG in pSS patients accounted for nearly 50%; The levels of serum IgG and complement C3 were significantly different from those in the control group. The positive rate of lip gland biopsy in pSS patients was more than 90%, and there was no significant difference between the two groups.

Conclusion: Hematological system involvement was common in PSS patients. The positive rates of anti SSA and Ro-52 antibodies increased significantly, the level of IgG increased and the level of complement C3 decreased; However, there was no significant difference in blood system involvement between high IgG and low IgG groups; The positive rate of lip gland biopsy in PSS patients was more than 90%.

Keywords: Sjogren's Syndrome; Hematological System; Immunoglobulin; Labial Gland Biopsy

Introduction

Primary Sjogren's syndrome (pSS) is a chronic autoimmune disease invading exocrine glands, mainly involving salivary glands and lacrimal glands, with focal lymphocyte infiltration as pathological characteristics, clinical manifestations of dry keratoconjunctivitis, oral dryness, can also involve many other organs, such as skin, skeletal muscle, kidney, lung, nervous system and blood system, etc. Epidemiology suggests an increasing prevalence of 0. 33% -0. 77%, and the prevalence of the disease is about 1:9-1:20[1], the age of onset is 40-50 years at most. Hematological manifestations in pSS patients include hemopenia, hypergammaglobulinemia, monoclonal gammaglobulinopathy, cryoglobulinemia and lymphoma, with hemocytopenia most common and can present as leukopenia, anemia, thrombocytopenia, primary or multilineage injury. At present, the pathogenesis of this disease is unknown, and hyperglobulinemia is very prominent in the disease of Sjogren's syndrome, especially the elevated IgG is mainly[2]. In this paper, the serological characteristics of pSS patients are further investigated for the correlation of hematological involvement and immune indicators.

1. Data and methods

1.1 Object

The selected cases were primary Sjogren's syndrome patients admitted to our hospital at 2018. 1-2021. 12, who all met

the 2002 International Classification of Sjogren's syndrome (diagnosis) standard[3], with a total of 123 cases. Patients with other connective tissue diseases, iron deficiency anemia, and tumors were excluded. Abnormal hematology criteria: ① leukocyte count <3. 5 * 10 ^ 9 / L; ② anaemia: male Hb <130g / L, female Hb <115g / L; ③ thrombocytopenia: Platelet count <125 * 10 ^ 9 / L.

1.2 Method

Clinical data of pSS patients, including sex, age, disease duration, laboratory indicators (including blood routine, humoral immunity, autoantibodies: anti-SSA, anti-SSB, anti-RO-52, anti-CENP-B antibody), and labial gland biopsy; selected cases were grouped according to hematological involvement.

2. Statistical treatment

Statistical analysis was performed using the SPSS 23. 0 software. Relevant data were tested for normality test, with mean ± standard deviation, t-test, mean comparison; non-normal measurement data (quartile P25-P75), Mann-Whitney U test, count data, 2 test, correlation with P <0. 05.

General: Among the pSS patients, 15 men, 108 women, 21-83 years, average age (49.85 ± 15.72). Blood system damage: 57 patients occurred in this study, accounting for 46. 34%; leukopenia, anemia, and thrombocytopenia; 17.89%; 33.3%; 4.88%. ① single blood system: 12 leukopenia, 9.76%; 33 anemia, 26.83%; 3 thrombocytopenia, 2.44%; ② 2 blood system: 7 leukopenia + anemia, 5.69%; 2 leukopenia + thrombocytopenia, 1.63%; 1 ③ blood triad, 0.81%.

Table 1 of Autoantibodies and Humoral Immunity between the two groups based on the hematological involvement

Observational indicators	Hematological normal group（n=66）	Hematological impairment group（n=57）	P value
anti-SSA	39（59.1%）	46（80.7%）	0.01＊
anti-Ro-52	38（57.6%）	44（77.2%）	0.021＊
anti-SSB	19（28.8%）	20（35.1%）	0.454
anti-CENP-B	5（7.6%）	6（10.5%）	0.567
IgG	16. 2（13.63; 19.65）	17. 7（15.4; 22.95）	0.02＊
IgA	3. 31（2.41; 3.9）	3. 4（2.42; 4.52）	0.436
IgM	1. 19（0.77; 1.72）	1. 1（0. 72; 1.67）	0.587
Complement C3	1. 04（0.93; 1.17）	0. 96（0.84; 1.11）	0.017＊
Complement C4	0. 2（0.18; 0.24）	0. 2（0.15; 0.27）	0.58

2. 1 Correlation analysis

Through statistical analysis, the correlation coefficient of blood system involvement and autoantibody SSA was 0.213, and the P-value was 0.018;

The correlation coefficient of anti-Ro-52 antibody was 0.208, P value 0.021, IgG correlation coefficient 0.224, and P value 0.013;

Complement C3 correlation coefficient was 0. 217; the P-value was 0.016.

In conclusion, the autoantibodies SSA, Ro-52 antibody, IgG and complement C3 were correlated.

2. 2 Lip gland biopsy results

A total of 45 lip biopsy in the group, including 41 or 91.1%, 59 in the normal group, 57 with 1 or more lymphocyte lesions, accounting for 96.6%; the positive rate was more than 90%, no significant difference between the two groups.

3. Discussion

Primary Sjogren's syndrome is a common autoimmune disease whose pathogenesis is currently believed to be the result

of multiple factors, including heredity, viral infection, and sex hormones. In addition to the damaging symptoms of exocrine glands such as dry mouth and dry eyes, pSS patients can also show extramandular damage of the blood system and nervous system. Blood system damage to blood triad decline is the most common, Nishishinya research found that repeated parotid gland enlargement, lymph node enlargement, lymphopenia, low complement C4 and hyperglobulinemia is an important predictor of lymphoma [4], the study mainly for analysis, identify system damage in patients with Sjogren's syndrome, early interventional therapy.

Blood system damage in Sjogren's syndrome can involve white blood cells, red blood cells, and platelets, and show a single or multilineage decline. The pathogenesis of blood system damage may be related to the destruction of blood cells by multiple autoantibodies or immune complexes produced by B cells in peripheral blood. Multiple autoantibodies can be detected in the serum of pSS patients, and studies have shown that SSA antibodies on the surface of blood cells can induce autoantibody formation against this cell, causing cytolytic[6] through an antibody-mediated complement-dependent pathway. This study also found that the positive rate of anti-SSA and Ro-52 antibodies was higher in the blood involvement group, which was consistent with previous studies;

The complement system can exert its biological effects through the classical pathway, bypass pathway and lectin pathway, and the damage of the target organs can occur when the complement inappropriately recognizes and attacks its own tissues. Complement plays an important role in autoimmune diseases. Previous studies have found that some gene variants encoding complement are related to the occurrence of systemic lupus erythematosus, leading to the deposition of circulating immune complexes, and clinically found decreased complement levels in SLE patients. In the study of Sjogren's syndrome, the complement C3 levels in the affected patients were lower than those in the normal group, considering the involvement of complement-mediated cytotoxic effects in the destruction of blood cells.

Through research, Zhang Youli et al found that pSS patients can be combined with various hematological abnormalities, including anemia 51%, leukopenia 25%, thrombocytopenia 23% and pancytopenia 7.7% [7]. This study suggests that anemia was the most common in the incidence of haematological abnormalities, consistent with previous studies. The mechanism of anemia in pSS patients is currently unknown, the most common are immune-mediated chronic anemia, and secondary anemia, including hemolytic anemia, iron deficiency anemia, mostly mild anemia.

In this study, leukocyte decline accounted for 17. 89%, and some patients took leukopenia as the first symptom, leading to misdiagnosis. Some scholars have shown that the bone marrow hematopoiesis of pSS patients is basically normal, and the reduction of leukocytes may be related to the destruction of autoantibodies and the reduced transfer to the peripheral pool in [8]. Anti-M3R autoantibodies were found to induce downregulation of plasma membrane-resident M3R and M H C class I molecules in leukocytes, and NK cells mediate leukocyte apoptosis of [9]. Combined with previous studies on the association of leukopenia and the occurrence of lymphoma, some attention should be paid.

Studies have found that the prevalence of thrombocytopenia in pSS patients is 5% -13%, which can occur at any period during the course of the disease, either alone, or combined with leukopenia, anemia and other conditions[10]. Severe thrombocytopenia is less common in pSS patients, where antiplatelet antibodies are important antibodies causing platelet destruction, which can directly bind to bone marrow megakaryocytes, and affect their growth and maturation, leading to megakaryocyte maturation and platelet production disorders [11]. This study found that the incidence of thrombocytopenia was low, and the sample size was considered small, with some experimental error.

Lipial gland biopsy is a means of examination for the diagnosis of Sjogren's syndrome, mainly for lymphocyte infiltration of labial gland tissue. In this study, most patients completed labial gland biopsy, and the positive rate accounted for more than 90%, which is more consistent with clinical cognition.

Through a retrospective study of SS patients with hyperglobulin, Sun Yu found that the hyperglobulin group was more prone to blood systemic involvement, accounting for 41. 7%, among which anemia was more common in [12] than leukocytopenia and thrombocytopenia. Among the people included in this study, 61 cases had high IgG, accounting for 49. 6%, indicating that hyperglobulinemia is very common in clinical work. The EULAR Sjogren's syndrome activity index, widely used in the clinic, has scoring criteria for only one laboratory class containing hyperimmunoglobulinemia, monoclonal components and hypocomplemenemia, and another 11 classes related to [13] with organ involvement.

In conclusion, it is not uncommon in patients with pSS, associated with anti-SSA, RO-52 antibodies in autoantibodies, and associated with IgG and complement C3.

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Universe Scientific Publishing

Clinical Study of Endocrine Hormone Combined with Trastuzumab in Maintenance Treatment of HR and HER-2 Positive Advanced Breast Cancer

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Abstract: **Objective:** To analyze the clinical effect of endocrine hormone combined with trastuzumab in maintenance therapy of HR (hormone receptor) and HER-2 (human epidermal growth factor receptor) positive advanced breast cancer. **Methods:** A total of 80 patients with HR and HER-2 positive advanced breast cancer admitted to our hospital from January 2020 to December 2022 were selected, and the 80 patients were divided into 2 groups by random number table method, the control group (N= 40) The patients in the observation group (N=40) were treated with trastuzumab, and the patients in the observation group (N=40) were treated with endocrine hormones and trastuzumab for maintenance. The therapeutic effects of the two groups were compared. **Results:** The two groups of patients had similar serum CD8+, CD4+, CD3+ before treatment and CD8+ after treatment (P>0.05). After treatment, the CD4+ and CD3+ in the observation group were higher than those in the control group (P<0.05). The total effective rate of the observation group was significantly higher than that of the control group. It was higher in the control group (P<0.05); the incidence of adverse reactions in the observation group was lower than that in the control group (P<0.05). **Conclusion:** Endocrine hormone combined with trastuzumab maintenance therapy for HR and HER-2 positive advanced breast cancer has significant clinical effect, can effectively improve the immune indexes of patients, and has less adverse reactions, which is worthy of clinical application.

Keywords: Endocrine Hormones; Trastuzumab; Hormone Receptors; Human Epidermal Growth Factor Receptor; Advanced Breast Cancer

Introduction

Breast cancer is caused by a variety of carcinogenic factors causing abnormal differentiation and proliferation of breast epithelial cells. At present, there is no clear conclusion on the cause of breast cancer. Some scholars believe that it is related to factors such as excess nutrition, endocrine hormones, excessive drinking, obesity, genetics and other factors. Later, the patient developed breast discharge, breast lump, and enlarged axillary lymph nodes. With the prolongation of the disease time, HR and HER-2 developed positive, the disease entered an advanced stage, cancer cells metastasized, and it may also cause multiple organ lesions, threatening the patient's life safety [1]. At present, there are many clinical treatment methods of acupuncture for advanced breast cancer, including targeted therapy, surgery, chemotherapy, endocrine therapy, drug therapy, and radiation therapy. In patients with HR and HER-2 positive advanced breast cancer, the effect of endocrine hormone combined with trastuzumab maintenance therapy was analyzed. The report is as follows:

1. Materials and methods

1.1 Normal information

A total of 80 patients with HR and HER-2 positive advanced breast cancer admitted to our hospital from January 2020 to December 2022 were selected. Inclusion criteria: ① The patients were diagnosed with advanced breast cancer by breast ultrasound, MRI, tumor markers and pathological examination breast cancer; ② Positive HR and HER-2 examinations,

breast lumps, and sunken skin; ③ Complete personal information; ④ Both patients and their family members are aware of the research content, voluntarily participate, and can cooperate with the research throughout the process; Exclusion criteria: ① Other serious organs disease; ② Drug allergy; ③ Mental illness, communication disorder, cognitive disorder; ④ Poor compliance, dropped out of the researcher; 80 patients were divided into 2 groups by random number table method, and the control group (N=40) was 21 males, 19 females, aged 32-75 years, mean age (53.5±4.2) years; observation group (N=40) 20 males and 20 females, aged 30-76 years, mean age (53.0±4.5) years; The two groups of patients were similar in gender and age (P>0.05) and were comparable.

1.2 Methods

The control group was only given trastuzumab (manufacturer: Shanghai Fuhong Henlius Bio-Pharmaceutical Co., Ltd.; Chinese medicine approved word: S20200019;) intravenous infusion, the initial dose was 8 mg/kg, and the infusion time was 90 min. The weekly maintenance dose was 6 mg/kg, the infusion time was 30 min, and the medication was administered once every 28 days for 6 months.

The observation group received the maintenance combination therapy of endocrine hormones and trastuzumab. The medication method of trastuzumab was the same as that of the control group. On the basis of trastuzumab, fulvestrant injection (manufacturer: AstraZeneca UK Limited; Approval number: H20100407), each dose is 10ml, once every 28 days, and the medication time is 6 months.

1.3 Observation indicator

(1) The CD8+, CD4+, CD3+ of the two groups of patients before and after treatment were recorded [2].

(2) Evaluate the clinical effect of the patient, markedly effective: the clinical symptoms of the patient disappeared completely, and the disease was well controlled; effective: the clinical symptoms of the patient were significantly improved, and the disease was well controlled; ineffective: the clinical symptoms and the condition of the patient did not improve; total effective rate = (number of markedly effective cases + number of effective cases)/total number of cases × 100%.

(3) The incidence of adverse reactions such as nausea and vomiting, fatigue, thrombocytopenia, and bone marrow suppression in the two groups were recorded.

1.4 Statistical methods

SPSS 24.0 statistical software was used for data analysis, measurement data were expressed as mean ± standard deviation (±s), and t-test was used for comparison between two groups; count data was expressed as rate, and $\chi 2$ test was used for comparison between groups, with P<0.05 as the difference was statistically significant.

2. Results

2.1 CD8+, CD4+, CD3+ in the two groups before and after treatment

Serum CD8+, CD4+, CD3+ before treatment and CD8+ after treatment were similar in the two groups (P > 0.05), and CD4+ and CD3+ after treatment in the observation group were higher than those in the control group (P < 0.05). The data are shown in Table 1 below.

Table 1 Comparison of CD8+, CD4+, CD3+ in the two groups before and after treatment (±s.%)

Group	Number of cases	$CD8^+$		$CD4^+$		$CD3^+$	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	40	29.32±6.96	29.91±6.85	30.72±5.33	27.81±5.04	61.14±5.46	50.63±5.32
Control group	40	29.54±6.50	29.86±6.72	29.89±6.14	24.02±5.10	61.05±5.69	38.71±5.67
t	-	0.1461	0.0329	0.6456	3.3430	0.0721	9.6962
p	-	0.8842	0.9738	0.5204	0.0013	0.9426	0.0000

2.2 Comparison of treatment effect between two groups of patients

The total effective rate of the observation group was 95.00%, and that of the control group was 65.00%. The total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$). The data are shown in Table 2 below.

Table 2 Comparison of treatment effect between the two groups [n. (%)]

Group	Number of cases	Excellent	Effective	Invalid	Total effective rate
Observation group	40	14（35.00）	24（60.00）	2（5.00）	38（95.00）
Control group	40	8（20.00）	18（45.00）	14（35.00）	26（65.00）
X^2	-				11.2500
P	-				0.0007

Comparison of the incidence of adverse reactions in the two groups of patients

The incidence of adverse reactions in the observation group was 10.00%, and that in the control group was 30.00%. The incidence of adverse reactions in the observation group was significantly lower than that in the control group ($P < 0.05$). The data are shown in Table 3 below.

Table 3 Comparison of incidence of adverse reactions between the two groups [n. (%)]

Group	Number of cases	Nausea and vomiting	Fatigue	Cytopenia	Bone marrow suppression	Incidence of adverse reactions
Observation group	40	2（5.00）	2（5.00）	0（0.00）	0（0.00）	4（10.00）
Control group	40	5（12.50）	4（10.00）	1（2.50）	2（5.00）	12（30.00）
X^2	-					8.6580
P	-					0.0032

3. Discussion

Breast cancer is a disease with high incidence in breast surgery, and ranks the forefront in the incidence of female malignant tumors. According to relevant statistics [3], the incidence of breast cancer in women worldwide accounts for 24.2%, and the incidence in developing countries accounts for 52.9%. In recent years, the incidence has been increasing, and the incidence group tends to be younger. The age of onset was mainly concentrated in the 45–50-year-old group. Early breast cancer has no obvious clinical symptoms, the breast bump, breast skin abnormalities, abnormal, nipple and areola of breast discharge, anemia, fever, the symptom such as anorexia, loss of appetite, emaciation, illness has developed to the late, after the surgery, if the patient testing positive for HR, its ehrs - 2, need to have targeted therapy and endocrine therapy after surgery, In order to avoid the metastasis of cancer cells and the aggravation of the disease leading to the death of patients [4].

Clinical on HR and its ehrs - 2 positive patients with advanced breast cancer mainly drug treatment, by bead sheet resistance is a recombinant DNA derived humanized monoclonal antibody, belong to solid tumor humanized against its ehrs - 2 receptor single drug resistance, drug antagonism in the antigrowth factor can control tumor cell growth, have ligand mediated the biological function of blocking effect, it is a common anti-HER-2 drug with high targeting and affinity in tumor cells. In the process of treatment, the HER-2 gene is taken as the target to block the signal transduction pathway mediated by HER-2, cause the degradation of HER-2 receptor protein, reduce the concentration of HER-2 in cell membrane, organize blood vessels and tumor growth, arrest cells in G1 phase, and kill tumor cells. Improve the survival rate of patients [5]. Fulvestrant is an endocrine therapy drug, which is a competitive estrogen receptor antagonist. In the process of treatment, the estrogen receptor on the surface of tumor cells competently binds, tissues cancer cells and estrogen, and tissues tumor growth to achieve anti-tumor effect [6]. In this study, it was found that the serum CD8+, CD4+, CD3+ indexes before treatment and CD8+ indexes after treatment were similar between the two groups ($P > 0.05$), and the CD4+ and CD3+ indexes after treatment in the observation group were higher than those in the control group ($P < 0.05$). The total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$). The incidence of adverse reactions in the observation group was lower than that in the control group ($P < 0.05$). The results suggest that endocrine hormone combined with trastuzumab maintenance therapy for HR and HER-2 positive advanced breast cancer is significantly more effective than single trastuzumab treatment, and can avoid nausea and vomiting, fatigue, thrombocytopenia, bone marrow suppression and other adverse reactions.

In conclusion, endocrine hormone combined with trastuzumab maintenance treatment for HR and HER-2 positive advanced breast cancer can effectively improve the immune indicators of patients with less adverse reactions, which is worthy of clinical application.

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Effect of Endocrine Therapy Combined with Trastuzumab Targeted Therapy on Response Rate and Quality of Life in HER2-Positive Metastatic Breast Cancer

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Abstract: **Objective:** To analyze the effect of endocrine therapy combined with trastuzumab targeted therapy on HER2 (human epidermal growth factor receptor-2) positive metastatic breast cancer on the treatment efficiency and quality of life. **Methods:** Selected 100 patients with HER2-positive metastatic breast cancer who were treated in our hospital from January 2019 to December 2021, and divided them into a control group and an observation group according to the random number table method, with 50 cases in each group, and were given the clinical effects of single trastuzumab targeted therapy and endocrine therapy combined with trastuzumab targeted therapy were compared. **Results:** There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$); the remission rate in the observation group was significantly higher than that in the control group ($P<0.05$); the overall health scale and function scale scores in the observation group were higher than those in the control group, and the individual items Measurement and symptom scale scores were lower than those in the control group ($P < 0.05$). **Conclusion:** Endocrine therapy combined with trastuzumab targeted therapy for HER2-positive metastatic breast cancer can effectively relieve the patient's condition and improve the patient's quality of life. The clinical effect is significant, and it is worthy of widespread application.

Keywords: Endocrine; Trastuzumab; Human Epidermal Growth Factor Receptor-2; Metastatic Breast Cancer

Introduction

As of 2020, there will be 420,000 new breast cancer patients in my country, of which HER2-positive breast cancer accounts for 20% to 25% of all breast cancer subtypes [1]. HER-2 is a proto-oncogene, which has an inhibitory effect on tumor cell apoptosis and accelerates the proliferation of tumor blood vessels, tumor cells, and lymph nodes. Therefore, HER2-positive breast cancer is not only more malignant, but may metastasize in the early stage of the disease. Chemotherapy sensitivity is relatively low, easy to relapse, treatment is relatively difficult, the survival period of patients is shorter [2]. Trastuzumab is the earliest drug used in the targeted therapy of HER2-positive breast cancer. It is a recombinant DNA-derived humanized monoclonal antibody that selectively acts on the extracellular site of HER2. It has anti-tumor effects in combination with endocrine therapy. protrude. In this study, 100 patients with HER2-positive metastatic breast cancer admitted to our hospital were specially collected to analyze the effect of endocrine therapy combined with trastuzumab targeted therapy. The report is as follows.

1. Materials and methods

1.1 General information

Selected 100 patients with HER2-positive metastatic breast cancer treated in our hospital from January 2019 to December 2021, and divided them into a control group and an observation group according to the random number table method, with 50 cases in each group, and the age of the control group was 32 ~69 years old, with an average age of (50.5±3.2) years old, including 13 cases of invasive ductal carcinoma, 10 cases of mucinous adenocarcinoma, 18 cases of invasive

lobular carcinoma, and 9 cases of medullary carcinoma; the observation group was 30 to 67 years old, with an average age of (48.5±3.2) years old, including 14 cases of invasive ductal carcinoma, 10 cases of mucinous adenocarcinoma, 16 cases of invasive lobular carcinoma, and 10 cases of medullary carcinoma; the general data of the two groups of patients were similar (P>0.05), and they were comparable.

Inclusion criteria: (1) The patient met the diagnostic criteria for metastatic breast cancer after histopathological examination, and the result of HER2 fluorescence in situ hybridization was positive (2) There was no missing personal data; (3) The patient and family members were aware of the research content, agree to participate in the research, and have signed the informed consent form; exclusion criteria: (1) heart, liver, and kidney organ function diseases; (2) autoimmune system diseases, primary malignant tumors, coagulation disorders; (3) drugs allergies; (4) mental disorders, mental illnesses, audio-visual impairments, and unable to communicate independently; (5) particularly poor compliance; this study was informed and approved by the ethics committee of our hospital.

1.2 Methods

The control group was given trastuzumab (manufacturer: Shanghai Fuhong Henlius Bio-Pharmaceutical Co., Ltd.; Chinese Medicine Approval: S20200019). At the beginning of administration, the loading dose was controlled at 4 mg/kg, and the infusion time was 90 minutes. We confirm the patient's tolerance to the first dose, control the maintenance dose at 2 mg/kg, complete the infusion within 30 minutes, and receive treatment once a week. On the basis of the control group, the observation group was given letrozole tablets (manufacturer: Zhejiang Hisun Pharmaceutical Co., Ltd.; Chinese medicine approved word: H20133109), each dose of 2.5 mg, orally once a day.

1.3 Observation indicator

(1) Complete remission: The patient's lesions disappeared completely, and there was no recurrence within 1 month; Partial response: The patient's lesion volume was reduced by more than 50% compared with that before treatment, and there was no recurrence within 1 month, and no new lesions appeared; Stable: The patient's lesion volume is less than 50% smaller than before treatment, or less than 25% increase in volume, no recurrence within 1 month, and no new lesions appeared; Progress: The patient's lesions increased by more than 25% compared with before treatment, and new lesions appeared; remission rate = (complete remission cases + partial remission cases)/total cases × 100%.

(2) The quality of life of patients was assessed by the core scale of quality of life. The higher the scores of the patient's overall health scale and functional scale, and the lower the scores of the symptom scale and single measurement, the better the patient's quality of life.

(3) The incidence of adverse reactions in the two groups, including gastrointestinal reactions, bone marrow suppression, skin damage, and fever, were recorded.

1.4 Statistical methods

SPSS24.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation (±s), and t-test was used for comparison between the two groups. $\chi 2$ test was used for comparison between groups, and P<0.05 was considered statistically significant.

2. Results

2.1 Comparison of remission rates between the two groups of patients

The remission rate of the observation group was 94.00%, and that of the control group was 72.00%. The remission rate of the observation group was significantly higher than that of the control group (P < 0.05), as shown in Table 1.

Table 1 Comparison of remission rates between the two groups [n. (%)]

Groups	Number of cases	Complete relief	Partial relief	Stabilize	Progress	Remission rate
Control group	50	15（30.00）	21（42.00）	13（26.00）	1（2.00）	36（72.00）
Observation group	50	34（68.00）	13（26.00）	3（6.00）	0（0.00）	47（94.00）
X^2	-					8.5755
P	-					0.0034

2.2 Comparison of quality-of-life scores between the two groups of patients

The scores of global health scale and functional scale in the observation group were higher than those in the control group, and the scores of single measurement and symptom scale were lower than those in the control group ($P < 0.05$), as shown in Table 2.

Table 2 Comparison of quality-of-life scores between the two groups (±s points)

Groups	Number of cases	Overall health scale	Functional scale	Single measurement	Symptom scale
Control group	50	57.33±8.92	60.23±10.12	43.28±5.21	47.85±6.57
Observation group	50	63.34±9.51	66.59±9.23	39.21±5.26	42.33±5.06
t	-	3.2593	3.2833	3.8872	4.7068
p	-	0.0015	0.0014	0.0002	0.0000

2.3 Comparison of adverse reactions between the two groups of patients

There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$), as shown in Table 3.

Table 3 Comparison of adverse reactions between two groups [n. (%)]

Groups	Number of cases	Gastrointestinal reactions	Myelosuppression	Skin damage	Fever	Occurrence of adverse reactions
Control group	50	5（10.00）	4（8.00）	2（4.00）	4（8.00）	15（30.00）
Observation group	50	6（12.00）	2（4.00）	1（2.00）	3（6.00）	12（24.00）
X^2	-					0.4566
P	-					0.4992

3. Discussion

Metastatic breast cancer incidence is higher in the group of women, place more focus on mammary gland flocculus, ductal epithelium. At present, about breast cancer pathogenesis, clinical, there is no clear conclusion, some scholars think with their immunity is low, genetic factors, such as patients exist genetic damage, HER2 gene amplification, The expression of HER-2 in the body is significantly increased [3]. As the breast belongs to the gonadal organ, it plays a functional role in regulating the endocrine system of the human body, especially the abundance of androgen receptors, estrogen receptors and progesterone receptors in the breast epithelial cells. Therefore, the incidence and progression of breast cancer are closely related to abnormal endocrine regulation [4]. In recent years, the incidence of breast cancer continues to rise, and the prevalence of breast cancer has exceeded that of lung cancer. In the early stage of the disease, nipple discharge, breast

swelling and axillary lymphadenopathy of patients will be caused. If not controlled in time, the HER-2 overexpressing cells of patients will generate a large number of HER-2 heterodimers, and the signal pathway will be activated to accelerate tumor progression, which may cause multi-organ lesions and shorten the survival time of patients [5].

At present, more than in the early treatment of breast cancer with surgery is given priority to, but for Ⅲ and Ⅳ period patients to control the effect not beautiful, with patients transfer cells within the body, the operation difficulty is higher, and have been unable to completely lesions in patients with amputated. Therefore, to explore safe and effective HER2 positive metastatic breast cancer drug treatments become clinical research important topic. Trastuzumab is a molecular targeted therapy drug, which can have a specific binding effect with HER2 receptor to prevent HER2 from forming heterodimer. At the same time, it can block the HER-2 pathway, promote the degradation and separation of HER-2 receptor, and its cytotoxic effect affects target cells, thus achieving the inhibitory effect of tumor cell proliferation [6]. To belongs to selective aromatase inhibitor letrozole, endocrine therapy is commonly used medicine, has high selectivity, can promote estrogen biosynthesis, decreased estrogen levels, and not in the process of drug for patients with thyroid function, mineralocorticoid, adrenal cortical hormone, glucocorticoid, aldosterone produced great influence, and cytochrome P450 enzyme subunit heme competitive binding, can inhibit tumor growth. The remission rate of the observation group was significantly higher than that of the control group ($P < 0.05$). The scores of global health scale and functional scale in the observation group were higher than those in the control group, and the scores of single measurement and symptom scale were lower than those in the control group ($P < 0.05$). The results suggest that endocrine therapy combined with trastuzumab targeted therapy is significantly better than single therapy in HER2-positive metastatic breast cancer.

In conclusion, endocrine therapy combined with trastuzumab targeted therapy for HER2-positive metastatic breast cancer can effectively alleviate the disease and improve the quality of life of patients, which is worthy of wide promotion and application.

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A Study on the Effect of IL-17A on Phenotypic Transformation of Fibroblasts in Bleomycin-Induced Pulmonary Fibrosis in Mice and Its Mechanism

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Abstract: Objective: In this study, lung fibroblasts were cultured and identified in mice lung fiber model with bleomycin. Under the induction of IL-17A, lung fibroblasts were gradually transformed into myofibroblasts in pulmonary fibrosis, and the specific induction effect of IL-17A in pulmonary fibrosis was analyzed, which could provide ideas for the prevention and treatment of clinical pulmonary fibrosis. Methods: To investigate the transcriptional expression of bleomycin-induced fractional pulmonary fibrosis in different pulmonary fibrosis processes. The 14-day mice model was taken as the research object, and the pulmonary fibrosis model was established by induction of myogenesis. After 14 days of modeling, lung tissue was removed, and after centrifugation and repeated adherent treatment, lung fibroblasts could be cultured at the origin. After three generations of culture, the morphological changes of lung fibroblasts could be observed under a microscope. Indirect immunofluorescence was used to establish the expression of vimentin, and IL-17 was used to stimulate primary cultured lung fibroblasts to detect the expression and specific localization of a-SMA in cells. Western blotting was used to stimulate the expression of lung fibroblast protein by IL-17A at different time points. Results: The typical characteristics of primary culture lung fibroblasts were obtained. After purification and culture, lung fibroblasts were obtained in morphology. The morphology of the 3rd and 4th generation cells was relatively uniform, showing long carboxyform. 1-2 nucleoli can be observed by microscope, which have distinct cell boundary and are lined up like fish schools. The results of indirect immunofluorescence showed that the vimentin staining in the third generation cells was positive, and the plasma was dark red. There were collagenous fibrous septa between the cells, which might make them develop into lung fibroblasts. A-SMA immunofluorescence results showed that in the absence of IL-17A induction, A-SMA signal was relatively weak in the lung fibroblasts of the control group and was in the cytoplasm, while after IL-17A induction, A-SMA signal was stronger in the lung fibroblasts of mice and the whole cells presented spindle structure. Western bletting showed that lung fibroblasts were stimulated by IL-17 in the 0h group. Compared with the 1h, 2h, and 4h groups, the expression of A-SMA in lung fibroblasts was significantly increased in the 1h, 2h, and 4h groups. The fibroblasts were very low in the 2h and 4h groups. There was no significant difference in the expression of AS MA signal. Compared with 0h, protein contents of p-IKB-a and p-p65 were higher in lung fibroblasts at 1h, 2h and 4h. Protein expressions of Acti, 1P6, IKB-a and P65 were different in lung fibroblasts, but there was no significant difference. However, there was no significant statistical difference in the expression of these proteins in lung fibroblasts at different times. Conclusion: By differential centrifugation and repeated adhesion, bleomycin-induced lung fibroblasts can be isolated and purified, and more cell production can be obtained. The staining vimentin was strongly positive after identification by indirect immunofluorescence. The stimulation of IL-17A could gradually transform non-fibroblasts into myofibroblasts and play an important role in pulmonary fibrosis. Therefore, through experimental studies, it was found that IL-17A stimulated F-kB signal and then increased the expression of P-IKB-a and P-P65 proteins, and transformed non-phosphorylated proteins into phosphorylated proteins, thus transforming lung fibroblasts into myofibroblasts and playing a role in pulmonary fibrosis.

Keywords*:* IL-17A; Pulmonary Fibrosis; Fibroblasts; Transformation

1. Introduction

Interstitial pulmonary disease is a group of pulmonary diseases with varying degrees of fibrosis and inflammation, and is also a disease of idiopathic pulmonary fibrosis. The clinical manifestations are dyspnea, dry cough and other symptoms, and the imaging manifestations are diffuse interstitial and parenchymal injury. The mortality and morbidity of this disease are high. However, there is no effective treatment for this disease and the cure rate is relatively low. Therefore, the focus of current clinical research is to explore the pathogenesis of pulmonary fibrosis and find effective therapeutic drugs[1].

2. Research materials and methods

2.1 Animal sample sources

In this study, a total of 20 SPF male mice with an average age of 7 weeks and a weight of 20 grams were selected and purchased from an animal experiment center of a university. During the feeding process, the temperature and humidity of the mice were required to be kept at 20℃ and 65% to ensure free water intake.

2.2 Reagents and instruments

The experimental materials used in this experimental study included IL-17A reagent, bleomycin powder, fetal bovine serum or anti-mouse antibodies, trypsin, 3% barbital solution, penicillin, streptomycin, recombinant mice, RIPA, BSA, PMSF, goat anti-rabbit IGg-HRP, and P-mouth DF membrane. The instruments used in the research include animal laboratory instruments, such as scalpel, gauze, transcendence table, alcohol lamp, scales, centrifuge, water bath, carbon dioxide incubator, etc.

2.3 Research Methods

How to select research objects? For the previous studies on the expression of IL-17RAMRNA in the lung tissues of PF mice induced by bleomycin in different stages of PF formation, the model mice on the 14th day could be selected as the research objects. The method and process of making mice PF model induced by bleomycin were consistent with previous experiments.

When drawing concrete materials, the culture bottle was wrapped with gelatin, and after one night culture, the gelatin was taken out. Meanwhile, 2 ml of the culture solution was poured into the culture bottle, and then place the culture bottle on super worktable and take out the lung tissue of the mice by dissecting the mice. In dealing with the specific operation, it can adopt routine cervical dislocation method to avoid death. Then it shall use ethanol for surface sterilization. The skin on the chest of mice could be disinfected with iodine first and then cleaned with alcohol. The left hand can pinch the neck and back of the mouse to expose the skin of the chest of the mouse, while the right hand can cut the skin of the mouse. After using alcohol disinfection, it can cut the ribs along the lower end of the sternum of the mice and cut the sternum transversally in the middle of the incision of the mice to take out the lung tissue, and then put the tissue in the double antibody culture flask. The primary lung tissue of mice was cultured, and the lung tissue was cut into multiple lung lobes through PPS buffer solution, and the excess blood vessels and bronchus at the hilum of the mice were subtracted, and the pleura was removed[2]. Then it shall transfer the lung tissue into the culture bottle containing penicillin. After repeated PPS cleaning, lung tissue fibers can be cut to a cubic millimeter size tissue block. And then double anti PBS suspension was used. After the tissue naturally sank, it shall abandon supernatant for three times repeatedly, until the supernatant keep clear. Then use 0.1% of the pancreatic enzyme to clean the tissue and add 1 ml of 0.1% trypsin for each mouse. After being digested at 37℃ for 20 minutes, most of the tissues can be digested into suspension. After adding the same amount of digestive solution, 10% DMEM containing FBS can be added to stop digestion after a period of time. After being beaten evenly, the cells are filtered to obtain cellular blood centrifugation. And then add 35ml of DMEM to the sediment. After 5 minutes' centrifugation, collect the supernatant and sediment respectively. Among them, LF is mainly distributed in the supernatant, and a few are epithelial cells. After centrifugation, the supernatant was discarded. Then use an incubator containing 5% carbon dioxide to culture the tissue at 37℃ for 40 minutes, and remove the unattached cells in time, among which the attached cells were mainly LF. 0.5ml of culture solution was replaced for overnight culture, and 2ml of culture solution was added on the second day for further

culture. The sediments are epithelial cells, and a few contains LF. The sediments can be removed by centrifugation for 5 minutes, and then add it into 10%FBS of DMEM culture solution. After resuspend the sediments, transfer it into a 25ml culture bottle. Then use the same method to continue culture, the most unattached cells are epithelial cells. After absorption and discarding, abandon the supernatant by centrifugation at low temperatures and resuspend the sediments in the culture bottle to remove unattached cells by repeatedly beating two or three times, among which LF are the attached cells. After adding culture solution into culture bottle for overnight culture, the structure and growth of the cells can be observed by telescope. At the same time, the survival of cells was determined by staining. After three days of isolation and purification, the cells were close to fusion state, and then they were connected into a network structure. When the cells reached 90% fusion, the subculture could be carried out according to a ratio of 1:2.

2.4 Observation Indicators

First, identify the lung fibroblasts of the mice. The cell slides of primary culture and third-generation culture can be selected and fixed with 4% paraformaldehyde for indirect fluorescence immunochemical staining of vimentin. Second, observe the structural changes of lung fibroblasts, and then observe LF form after cell culture with an inverted microscope. Third, after IL-17A stimulation, observe the expression of A-SMA signal and its specific localization. Fourth, observe phenotypic changes under the IL-17A simulation at different time points and then analyze transcriptional indexes and expression of transcriptional suppressor genes and activation of target genes[3].

3. Research Results

First, observe the morphology of lung fibroblasts(see Figure 1). When observing the structure of LF in vitro culture through inverted microscope, it can be found that in 30 minutes' meta-generation culture, the cells can grow adhere to the wall, but part of the hematopoietic cells may suspend in the culture solution. After 24 hours of culture to obtain new culture solution, remove suspending cells to improve the growth number of the attached cells, which are round or polygonal in shape. Such cells are mainly transparent and have relatively big cell nucleus and 2-3 nucleoli, which were in line with the structural morphological characteristics of Fb. After further culture for 36~48 hours, the cells entered the logarithmic phase, and the FB cells increased and were arranged radially or helically. After 72 hours of culture, most of the cells were found to be spindle-shaped, accompanied by some quasi-circular or circular structures. It can be observed through the microscope that local cells mainly grew in scattered forms. After one week of culture, attached cells showed long fusiform and abundant cytoplasm. 1~2 nucleoli and relatively clear cell boundaries could be observed through the microscope, which arranged like fish schools.

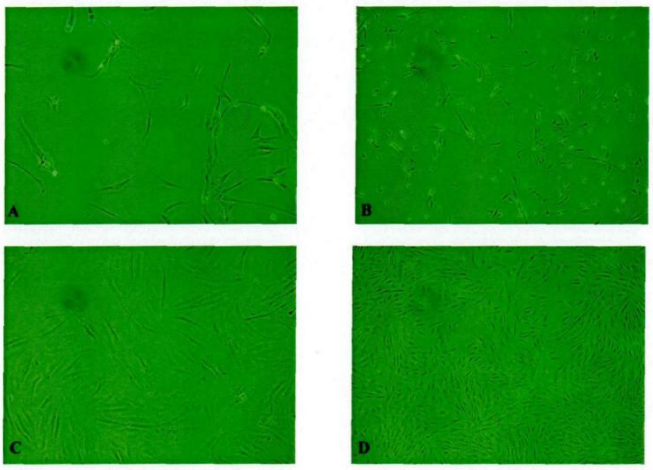

Figure 1. Morphology of lung fibroblasts

Identify lung fibroblasts (see **Figure 2**). After the observation of the vimentin cultured in the third generation by laser confocal microscope, since the protein staining of the vimentin cultured in the third generation showed strong positive with dark red cytoplasm and collagenous fibrous septa between the cells, it could be confirmed as LF.

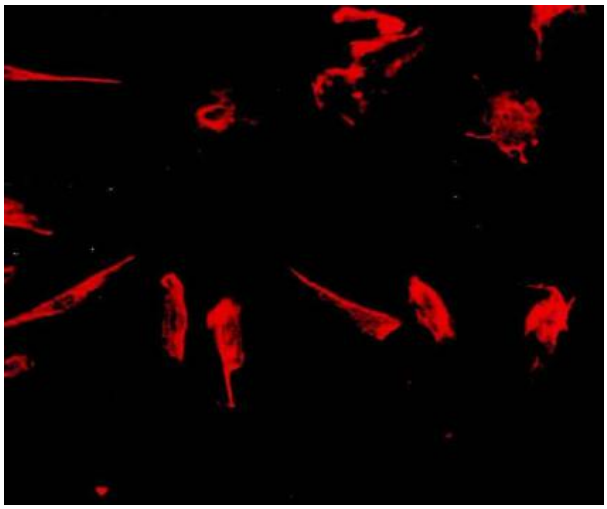

Figure 2. Identification of lung fibroblasts

According to the results of A-SMA immunofluorescence (**see Figure 3**), it was found that after the stimulation of IL-17A, the LF cells in childhood had a strong S-AM fluorescence signal, which was in the plasma envelope. After the stimulation of IL-17A, the mice had a strong A-SMA fluorescence signal, and the whole cells presented a spindle state. After the stimulation of IL-17A, the expression of different proteins in lung fibroblasts could be detected by using Western bloting at different time points, including p65, P-p65, IKB-a, p-IKB-a and ACTI.

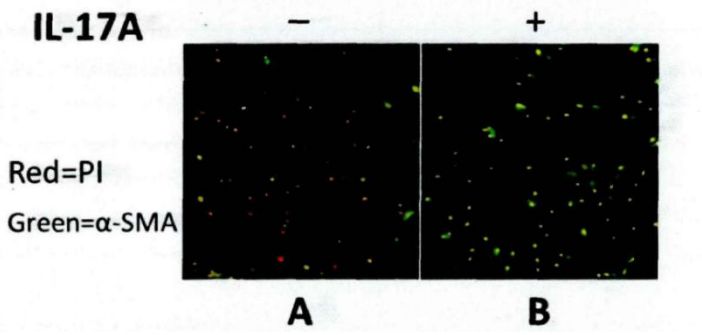

Figure 3. The results of A-SMA immunofluorescence

First, select LF with good growth condition, adjust its density to a certain range and inoculate it in the new solution, and the cells will grow adherently the next day. IL-17A was added to the serum-free culture solution after 24 hours, and then cells were collected after 0, 1, 2, and 4 hours respectively, and the cells were quantified by lysis. Western blotting assay was used to detect the expression of different proteins, including a-SMA, ACTL, p65, P-p65, IkB-a, and P-IkB-a (see **Table 1**). The results showed that the expression of a-SMA in LF of the 0 h group was weak. After 7 hours of IL-17A stimulation, the expression of a-SMA in LF in 1 hour, 2 hours and 4 hours was higher than that in 0h mice group. Compared with that in 1-hour group, the expression of a-SMA in 2h and 4h group was increasing. There was no significant difference in the expression of A-SMA in LF between the 2h and 4h group. In other words, after LF was induced by IL-17A, A-SMAs increased in 1h, and reached the peak in 2h, and then maintained high expression in 4h. The results of optical density and image table scanning showed that the protein expression levels of P-IkB-a and P-p65 in LF cells at 1h, 2h, and 4h after IL-17A stimulation were significantly higher than those at 0h. The protein expression of p-IKB-A and p-p65 was not significantly different between LF in 2h and 4h. After the stimulation of IL-17A, the protein expression of P65 and P-IkB-a in mouse LF was higher at different time points, and there was no significant difference in the expression of the two proteins at different time points. Once again, the expression of P65 and p-IKB-A proteins in mouse LF cells was not affected by IL-17A induction. However, after the stimulation of IL-17A, the phosphorylation of IkB-a and P65 protein reached the peak within 1 hour. The expression was lower in 2 hours group and higher in 4 hours group than that in 0 hour group. In addition, there was no significant change in the expression of Actl protein in LF cells after IL-17A stimulation at different time points, and the

expression of this protein was consistently low[4].

Table 1. Expression of a-SMA, ACtl, p65, P-p65, IkB-A and P-IkB-a proteins at different times

	N	0h	1h	2h	4h
α-SMA	20	0.290±0.007	0.445±0.010*	0.706±0.014*Δ	0.700±0.016*Δ
P-p65	20	0.248±0.009	0.570±0.011*	0.490±0.024*Δ	0.484±0.025*Δ
p65	20	0.944±0.015	0.950±0.016	0.943±0.017	0.942±0.015
P-IκB-α	20	0.368±0.012	0.718±0.013*	0.466±0.020*Δ	0.461±0.020*Δ
IκB-α	20	0.283±0.013	0.286±0.012	0.282±0.012	0.281±0.014
Actl	20	0.265±0.044	0.261±0.018	0.266±0.023	0.275±0.021

4. Discussion and conclusion

In vitro and in vivo studies have shown that GF-β1 plays an important role in the transition from Fb to MFb. According to studies, it can promote the transition of Fb from MFb through smads signal, but the smads signal pathway is not the only one involved in the transition from Fb to MFb. Hashimoto showed that GF-β1 could also promote MFb transformation through JNK. Studies have shown that both TGF-β1 and MAPK signal pathways can participate in the regulation and expression of a-SMA in lung fibroblasts. MAPK signal pathway is composed of ERk and P38MAPK, and other cytokines can utilize this signal pathway and participate in the phenotypic transformation process from Fb to MFb. In addition, the MAPK pathway can also be activated by mechanical tension to promote the regulation of non-tissue fibrosis. IL-17A plays an important role in the formation of PF, which is influenced by a variety of cytokines. Therefore, the following speculation can be proposed: IL-17A can participate in the formation of PF during the transformation from FB to MFB. In this study, the Western bloting experiment showed that IL-17A played an important role in promoting the formation of PF, and its A-SMA indirect immunofluorescence experiment was consistent with previous conclusions. It can be speculated that IL-17A can increase the protein expressions of P-p65 and P-IkB-a in cells through the activation of NF-KB signal pathway, and transform non-phosphorylated proteins into phosphorylated proteins, thus promoting the gradual transformation of fibroblasts into integrated fibroblasts, and finally forming pulmonary fibrosis.

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Universe Scientific Publishing

Regulating Intestinal Microbes to Decrease the Incidence of Heart Disease

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Abstract:This paper studies the correlation between intestinal microbes and heart disease. In the paper, the process of human body producing Trimethylamine-N-oxide (TMAO) under the role of intestinal microbes has been analyzed, and the ways to reduce the level of TMAO which can increase the incidence of heart disease has been designed. The expected result is that the level of TMAO in plasma is successfully reduced by regulating intestinal microbes. This paper can provide useful information for further studies in self-healing therapy by regulating intestinal microbes.

Keywords: Intestinal Microbes; Heart Disease; Ways to Reduce TMAO

1. Introduction

There are over 2,000 microorganisms in human body, and most of them are in gut. Among them, there are harmful bacteria that cause diseases and beneficial bacteria that are indispensable to the human body. As Neish (2009) said that human and normal microbes in the body have evolved together for thousands of years, optimizing the body's complex immune mechanisms to defend against and attacking pathogens that invade the human body. Although modern medical science has highly developed, some limitations are still existing, such as the side effects caused by medical treatments. In recent years, more and more research on intestinal microbiota. Patients who are unable to treat with modern medicine may reach the therapeutic goal by increasing the self-healing power through intestinal bacteria restoration. According to Trøseid et al. (2015), Trimethylamine-N-oxide (TMAO), which is a metabolite from dietary phosphatidylcholine and carnitine is related to the chronic heart failure (HF); TMAO depends on gut microbiota, and the high level of TMAO can increase the HF. In order to find out new therapies to prevent or cure heart disease, this paper examined how intestinal microbes affect the development of heart disease and focused on some of the ways to decrease the level of TMAO by manipulating gut microbiota.

2. Method

2.1 Association between heart disease and intestinal microbes

In recent years, many studies have found that high concentration of TMAO in plasma has connections with incidence of heart disease. According to Wang et al. (2011), by feeding choline-containing foods to mice, atherosclerotic plaque was observed in the aortic root and found that it's area was positively correlated with the concentration of TMAO. At the same time, the parallel experiment of this experiment confirmed that the formation of plaque has no correlation with cholesterol, triglyceride and blood glucose level. They also found that if mice were given antibiotics in their drinking water, the effect of TMAO on atherosclerosis was eliminated. This shows that the production of TMAO is dependent on intestinal microbes. In addition, Tang et al. (2013) found that under the same cardiovascular risk factors, patients with high plasma TMAO level had a higher prevalence of atherosclerosis than those with lower plasma level in 3 years. TMAO inhibits the transport of cholesterol, resulting in the accumulation of cholesterol in the cell, which becomes a risk factor for atherosclerosis. As Tang and Hazen (2014) mentioned, intestinal microflora can use substances that containing choline or trimethylamine structure to produce trimethylamine (TMA), and these TMAs are oxidized to TMAO in the liver. High concentration of TMAO can increase the occurrence of heart disease, so reducing the level of TMAO is very important.

2.2 Ways to decrease TMAO level

2.2.1 Eat less choline or trimethylamine oxide analogues

Phosphatidylcholine (PC), L-carnitine contain the structure of TMA. PC is the main source for the formation of TMAO. Eggs, milk, red meat, shellfish, and fish contain amounts of PC. The chemical structure of L-carnitine is similar to choline, which contains the structure of TMA, and it is rich in red meat. Therefore, we can eat less trimethylamine oxide analogues to protect from heart disease.

2.2.2 Inhibit the metabolism of choline to TMA

Intestinal microbes produce trimethylamine (TMA) by cutting the choline portion of Phosphatidylcholine (PC) at the carbon-nitrogen bond. TMA, a gas that diffuses in the body, is oxidized in the liver to trimethylamine-N-oxide (TMAO). It is possible that all trimethylamine-based nutrients produce TMA by cleavage and that TMA oxidizes TMAO to cause atherosclerosis. Therefore, preventing intestinal microbes cut trimethylamine-based nutrients can reduce TMAO level. Intestinal microorganisms may act by catalyzing an enzyme that cleaves the carbon-nitrogen bond. Wang et al. (2011) had already used the choline chemical structure analogue 3,3-dimethyl-1-butanol (DMB), and through experiment they found that DMB can inhibit the formation of TMA.

Additionally, TMA can also be reduced by directly regulating the microbes which can promote TMA formation. The experiment can be designed for four parts. First, finding out the microbes that work for forming TMA. A specific group of microorganisms is found by comparing microorganisms in stools of people who regularly eat red meat and eggs which contain choline or trimethylamine oxide analogues (group A) with people in a comparative group who have similar physical fitness but eat food which has no choline or trimethylamine oxide analogues (group B). Second, comparing the species and levels of microbes in the stools of participants in both experiment groups, and separating the high level of microorganisms in group A to study the microorganisms' living environment and characteristics. Third, finding beneficial bacteria that will compete with these microorganisms, and inject the beneficial bacteria into the human intestine. And also, by regulating the intestinal environment making the proportion of such microorganisms smaller than before. Fourth, measuring the microbes' quantity in the stools and the TMAO level in plasma.

2.2.3 Inhibit the oxidation of TMA to TMAO

The TMA formed by the gut microbes is oxidized to TMAO in the liver. This process needs further study.

3. Results

The microorganisms participating in the creation of TMAO will be successfully separated and their characteristics and growth environments will be analyzed. When a microorganism which can compete with the specific microorganisms is injected into the patient's intestine, the amount of plasma TMAO will be reduced and the incidence of heart disease will be lowered.

4. Discussion

Advantages:

1. Although modern medicine has highly devolved, side-effects from chemotherapy and surgery increase the chances of another disease. However, if the intestinal microbes in the human body can be controlled to prevent disease, human body can get rid of the adventures caused by side-effects of modern medicine.
2. Intestinal microorganisms are varied in their variety and number. Therefore, research on beneficial bacteria and harmful bacteria in the intestines has a good prospect. Previous studies have already shown that intestinal microbes are closely related to obesity and diabetes. In addition to the relationship between heart disease and intestinal microorganisms that studied in this paper, it can be a good stepping stone for treating another type of disease by

using intestinal microorganisms to increase the immune function and self - healing ability of the human body in the future.

Challenges:

1. Although an incensement in TMAO level is likely to increase the incidence of heart disease, there is no direct proof that the way to reduce TMAO can inhibit the incidence of heart disease. To prove this, many applicants are required to participate in the experiment, and the experiment need to be analyzed for a long period of time.
2. There are many kinds of microorganisms in the human intestine. Therefore, reducing the amount of TMAO by changing the intestinal environment before analyzing all characteristics of microbes is very dangerous. It is possible that changing intestinal environment may increase the amount of other harmful bacteria and give them an opportunity to produce more harmful substances.

Expectations:

Intestinal microbes produce TMAO to increase the incidence of heart disease is a very small part of their role. Intestinal bacteria can make up nutrients which are needed for the natural healing power of human body, and they also can produce more than half of enzymes that human body needed. Additionally, the intestinal microbes can make some nutrients that the human body cannot make itself, so human can increase the self-healing power to prevent and cure diseases. Also, the incidence of diseases is affected by chemicals that produced by intestinal bacteria. Therefore, by increasing the amount of beneficial bacteria and reducing the amount of harmful bacteria in intestine human can become healthier and farther away from cancer. In recent years, intestinal bacterial transplantation has also been achieved. Intestinal bacterial transplantation is a method of injecting a large number of health people's intestinal bacteria into a patient. Although the disease can be treated by transplanting intestinal bacteria, it is not widely used because there are many problems exist such as safety problems.

In the future, research can be focused on studying intestinal microorganisms, classifying them specifically, analyzing all types of intestinal microorganisms and their characteristics and growth environments. In this way, we can analyze the cause of chronic illness and find out new treatment methods. Although intestinal microorganisms have many indeterminate factors, they may contribute to the pathway of self-healing therapy in the future.

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Appendix

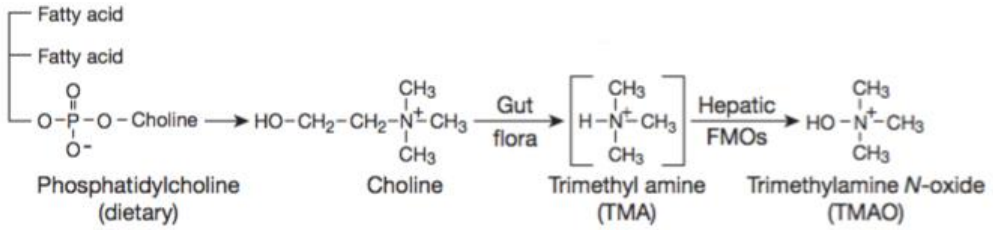

Figure 1: Gut-flora-dependent metabolism of dietary PC (Wang et al., 2011)

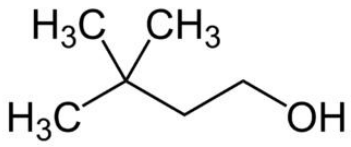

Figure 2: The molecular structure of DMB

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Study on the Bacteriostatic Effect of Baitouweng on Pseudomonas Aeruginosa Infection of Wounds in Rats

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Abstract: **Objective:** To analyze the bacteriostatic effect of Baitouweng on Pseudomonas aeruginosa infection of wounds in rats. **Methods:** Forty Wistar rats were enrolled in the study, among which excisions were made on 30 rats on their upper layer of dorsal skin with an area of 1 cm x 1 cm, the other 10 rats as the control group of sterile wound. Prepared Pseudomonas aeruginosa was applied on the wounds of rats to create infection models. Forty rats were divided into three groups (control group, mafenide group and Baitouweng group) according to different infection methods, and were treated with normal saline, 100g/L mafenide, and 1g/L Baitouweng respectively after 3 hours of injury. The changes in the number of white blood cells in both the wound surface and body of the three groups were observed within one to four days after injury. After that, the changes on the number of both white blood cells and body weight were continuously observed. The survival of the rats in each group was observed on the 14th day after injury. **Results:** From the observation after injury, compared with the other two groups, rats in control group had more exudation and moist wounds, and the activities of rats decreased while the death rate increased. On the 3rd day after injury, the number of white blood cells in each group decreased, and the number of Pseudomonas aeruginosa in the control group was significantly higher than that in the other two groups ($P < 0.01$). The rats in the sterile wound control group did not die and continued to gain weight. After 14 days, the survival number of rats in control group was significantly less than that in mafenide group and Baitouweng group ($P<0.05$). **Conclusion:** Baitouweng has obvious bacteriostatic and virus-killing effects on Pseudomonas aeruginosa infection of wounds in Wistar rats, reducing mortality rate effectively, and has practical value as well as development and application prospects.

Keywords: Baitouweng; Pseudomonas Aeruginosa; Wound Infection

1. Foreword

Pseudomonas aeruginosa, also known as pseudomonas, often occurs in nature, such as soil, and wet parts of the body, such as human intestinal tract. Pseudomonas aeruginosa has low nutritional requirements but with strong drug resistance and has great harm, especially to the middle-aged, the elderly and infants who has low immunity. This kind of bacterium is easy to cause disease, such as septicemia, and acute gastroenteritis. Therefore, early prevention, early detection and early treatment are the main treatment principle, and the inhibition of the bacteria has become a crucial issue to overcome. Baitouweng was first recorded in Shennong's Herbal Classic of Materia Medica and had been widely used in ancient Chinese medicine. With the development of modern medical science and technology, it has been found that Baitouweng has clear bacteriostatic effect on pathogens such as Escherichia coli and Paratyphoid Bacillus, and the extracted effective components are protoanemonin and anemonin. Safe drug usage has become a broad consensus in the medical field nowadays. In this case, exploring antibacterial drugs from traditional Chinese herbal medicines has become a hot research topic. This study deeply explores the antibacterial effect of Baitouweng on Pseudomonas aeruginosa. Details are reported as the following contents[1].

2. Materials and methods

2.1 Animal origin, strains tested and experimental drugs

Wistar rats were all male and introduced from animal experiment center of a medical university. Their body weight ranged from 200 g to 250 g. Pseudomonas aeruginosa was provided by microbiology laboratory. Baitouweng is purchased from the Chinese medicine pharmacy in our hospital.

2.2 Preparation and purification of protoanemonin

Baitouweng weighing 150g was put into a round bottom flask, and was mixed with distilled water at a ratio of 1: 10. After soaking for one hour and heating for one hour, the dregs were filtered with gauze. Then, eight times and six times of distilled water were poured into the dregs to repeat soaking and heating operation. The solution obtained from the above three treatments was concentrated and purified, so that the concentration of the liquid was stabilized at 1g/L and stored in the freezer.

2.3 Preparation of Pseudomonas aeruginosa suspension

Pseudomonas aeruginosa in culture medium was separated through centrifugal separation, with 2000r/min centrifugal rate and 15min duration. It was washed repeatedly with normal saline and then re-suspended to a concentration of 1×10^8CFU/ml. After incubation at 37℃ for 24 hours, the number of colonies was identified by blood cell counting plate.

2.4 Detection of antibacterial activity

Pseudomonas aeruginosa was cultivated on the culture medium, and solution and distilled water of Baitouweng were injected respectively as control group. After being cultivated at 37℃ for 24 hours, the results showed that Baitouweng had a strong inhibitory effect on Pseudomonas aeruginosa.

2.5 Establish infection models

One day before injury, 30 rats were selected, and the other 10 used as control group of sterile wound. After anesthesia, fixation and hair removal, the upper layer of the skin was cut with a wound area of 1cm×1cm by a scalpel. Prepared Pseudomonas aeruginosa bacterial solution was smeared on the wound of rats to establish infection models.

2.6 Groups

Randomized sampling and different nursing methods were used to divide rats into three groups, which are control group, mafenide group and Baitouweng group. A total of 40 rats in the three groups were kept in the same environment, where was clean and dry with 25℃ of constant temperature. The changes of the number of white blood cells in the wound and body of the three groups were observed within one to four days after injury. Then the changes of white blood cells and body weight were continuously observed, and the survival of the rats in each group was observed on the 14th day after injury[2].

2.7 Statistical analysis

All the collected prescription-related data in this paper are processed and analyzed through SPSS20.0 software, saving the cost of manual calculation and improving the accuracy and efficiency of calculation. The unit of measurement is expressed by ($\bar{x}\pm s$) with t test. If $P<0.05$, it is statistically significant.

3. Results

3.1 Changes of wound surface

From the observation after injury, compared with the other two groups, the wounds in the control group had more secretions and moist wounds. In addition, the activities of rats in the control group decreased and the death toll continued to

increase.

3.2 Quantification of Pseudomonas aeruginosa

After data collection and statistics, it was found that Pseudomonas aeruginosa in the control group was significantly higher than that in the other two groups. See **Table 1** for detailed data.

Table 1. Quantification of Pseudomonas aeruginosa in the scab of rats in each group on the third post-injury day

groups	Before injury	Different quantitative levels of bacteria		
		$<10^3$	10^3~10^5	$>10^5$
Control group	10	0	0	10
Mafenide group	10	5	5	0
Baitouweng group	10	10	0	0

3.3 Survival rate and weight test

After data collection and analyzing, it was found that on the 3rd post-injury day, the death number of rats reached five in control group, followed by mafenide group, two death rats, and Baitouweng group, one rat. By the 14th day, the survival rate of rats in control group was only 30%, and the other two groups remained unchanged. On the 6th post-injury day, the weight of rats decreased significantly in the control group compared with other two groups. Besides, there was little difference between the mafenide group and Baitouweng group. See **Table 2** for details.

Table 2. White blood cells on the third post-injury day and weight of rats on the sixth post-injury day

Rats number	White blood cell count ($\times 10^9$/l)			Weight (g)		
	control group	Mafenide group	Baitouweng group	control group	Mafenide group	Baitouweng group
1	—	3.95	3.9	—	19.1	20.9
2	—	5.65	4.25		18.3	19.5
3	2.95	4.10	3.1	16.9	20.3	18.4
4	—	4.3	4.25	—	20.8	19.0
5	3.65	—	4.2	16.7	—	18.8
6	3.35	3.75	4.9	16	19.7	19.8
7	—	3.95	3.9	—	19.4	19.1
8	3.5	4.05	—	—	19.8	—
9	3.45	4.25	3.6	—	20.6	20.4
10	—	—	5.95	—	—	19.6
$\bar{x}\pm s$	3.38±0.26	4.44±0.79	4.01±0.53	16.53±0.47	19.73±0.77	19.49±0.84

Notes: "-" suggests that the rat died.

4. Discussion

As one of the representatives of pathogenic bacteria in current clinical treatment, Pseudomonas aeruginosa, widely distributing in nature, its drug resistance is increasing year by year, while its morbidity and mortality are also high, being a

tricky issue in medical treatment. Even in hospitals, patients can be infected with Pseudomonas aeruginosa, because the pathogen mostly grows in humid environment. It is surveyed that the infection rate of Pseudomonas aeruginosa in hospitals is about 10% to 15% around the world. The isolation rate of Pseudomonas aeruginosa in the diagnosis of acquired pneumonia is as high as 20.9% in China, which is a very serious situation. Under such situation that there are many drug-resistant pathogenic bacteria strains at present, how to realize symptomatic prevention and treatment and maximize the effectiveness of antibacterial drugs in the treatment process has become an urgent issue for each clinician[3].

Baitouweng belongs to a kind of Chinese herbal medicine, which has been used to kill bacteria and insects since ancient times. In recent years, with the continuous advancement of the medical research and analysis on the chemical constituents and pharmacological effects, Baitouweng has drawn people's attention with a brand-new understanding. In modern research, Baitouweng has clear inhibitory effect on known strains such as Shigella dysenteriae and Bacillus subtilis. Compared with western medicine, Baitouweng will not produce too many toxic and side effects, especially in the case of antibiotic abuse.

Mafenide is recognized as an effective antibacterial drug against Pseudomonas aeruginosa in present clinical treatment. However, with the long-term use of the drug, it is inevitable that the therapeutic effect will be reduced due to the increase of bacterial drug resistance. Therefore, it is necessary to find new effective inhibitory components to alleviate this phenomenon. In this study, mafenide group and Baitouweng group were compared to on the one hand, verify the antibacterial effect, on the other hand, to verify whether the extract from Baitouweng can further replace mafenide as an antibacterial medicine for wound. From the wound infection, the wounds of the two groups of rats are basically the same, both of which are scabbed, dry and have little secretion. From the quantitative point of view of Pseudomonas aeruginosa, the antibacterial effect of Baitouweng group is better. It is because the protoanemonin and anemonin in Baitouweng can destroy the cell membrane and cell wall of Pseudomonas aeruginosa to achieve the bactericidal effect. At the same time, it will enhance the antibacterial effect with the extension of time. From the other indicators, there is little difference between the weight of the two groups and the number of white blood cells. The mortality rate of rats in the Baitouweng group will be lower, which indicates that it is feasible to use Baitouweng as an anti-Pseudomonas aeruginosa drug. However, whether it is functional in human body remains to be confirmed.

In summary, Baitouweng has obvious bacteriostatic and virus-killing effects on Pseudomonas aeruginosa infected wounds on Wistar rats. It effectively reduces rats' mortality rate, and has practical value and development and application prospects.

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Correlation Analysis of Patients with Adverse Reactions Caused by Postoperative Morphine Analgesia

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Abstract: In the current medical field of clinical surgery, we often have to contact a large number of patients with severe fractures caused by serious accidental injuries. Generally, these trauma patients often need to be treated by repair surgery. Postoperative patients usually have a certain degree of local pain. In order to alleviate the physiological pain of postoperative patients, And can prevent the braking caused by the aggravation of local pain of the injured patients. The use of analgesic pump for postoperative analgesia has become a common method after surgery and has been widely used in clinic. Good postoperative analgesia can inhibit the body's stress response and is conducive to restoring the coordination and stability of local breathing and circulation of the patients after operation, Reduce the local pain symptoms of some patients and effectively reduce their postoperative related complications, and indirectly promote the recovery of patients with pain. For the application of analgesic pump for pain relief, there are often a variety of auxiliary ways and preparation methods of analgesic drugs such as arteriovenous and epidural circulation, which should be selected and configured according to the physical conditions and medication conditions of patients with pain, such as ns100ml Morphine 5mg, bupivacaine 75mg, etc., of which morphine is often used as a common drug component for pain relief, but some special patients often have a series of dependent reactions after using morphine for pain relief. In view of this situation, combined with the physical conditions and adverse reactions of some special patients, this paper analyzes the possible adverse effects on patients with special constitution when using morphine for pain relief after clinical operation and relevant research.

Keywords: Special Patients; Surgery; Analgesic Pump; Morphine; Adverse Reactions

1. Clinical cases

A fracture patient, male, aged 47 years old, suffered from an accidental fall due to long-time work at height, resulting in a comminuted fracture of the patient's left foot. After 120 emergency treatment, he was transported to the hospital. The examination showed that the arch of the foot collapsed, the calcaneal bone was comminuted fracture, and the subtalar joint was damaged. He needed to undergo open reduction and plate internal fixation of the calcaneus. After surgery, the vital signs were stable and the mental state was good. Sbp130mmhg / dbp80mmhg, T37 1 ℃, R16 / min, SaO2 ↓, about 6h after operation, the effect of anesthetic gradually disappears and the pain begins to intensify. Connect the clinical postoperative analgesia pump to relieve the pain. 50ml of anesthetic is built in the pump, 1mg of fentanyl + 9ml of 075% bupivacaine + 36ml of 09% NaCl injection. The reference value of pump setting: loading dose: 4 ~ 6ml; Single dose (pcablous dose) 1ml.

2. Clinical response

After using the analgesic pump for analgesia for a period of time, the patient appears sweating, tense expression, unbearable pain and other manifestations, followed by a series of symptoms such as unconsciousness and shock. After emergency rescue, the patient has adverse reactions such as unbearable pain again about 5 ~ 10 minutes later. Consider whether the patient has allergic reaction to the drug components in the analgesic pump, According to the doctor's advice, stop the analgesic pump and inject morphine intravenously to relieve the pain. The patient's condition was relieved. The next day, after the efficacy was gradually eliminated, the patient felt pain again and asked the medical staff to continue to inject

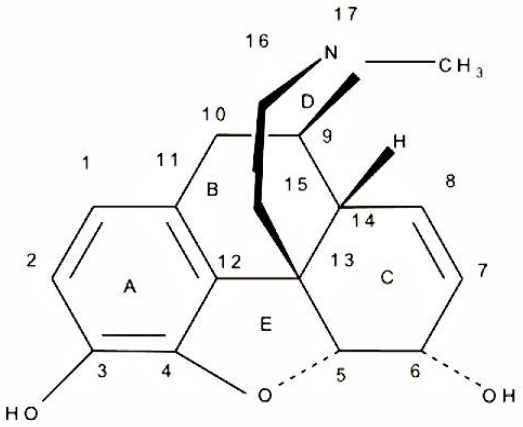
analgesic drugs. In order to achieve the maximum analgesic effect in the fastest time, the patient took the initiative to request morphine injection again for analgesia.

3. Clinical analysis

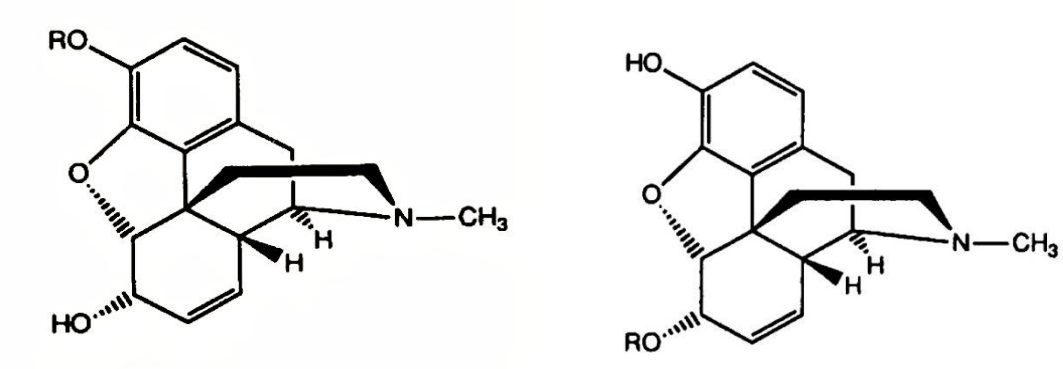
When the patient is in pain, morphine is used to relieve pain. When morphine is administered by subcutaneous injection, it can be absorbed by 60% after 30 minutes, and the absorption is rapid. When the drug effect disappears, the patient is in pain again and asks to use morphine for analgesia. As a medical staff, the injection of morphine drugs should be cautious, considering that morphine has certain addiction, Whether multiple injections will have side effects on patients to a certain extent. For example, patients may start to have a certain physiological dependence on morphine after a period of time. In addition, morphine can also produce respiratory depression, which is mainly manifested in end expiratory Paco ↑, Sao ↓, resting minute ventilation ↓, respiratory center co response threshold ↑. Therefore, in clinical practice, for patients with special circumstances, morphine should be used with caution for analgesia, which has certain adverse reactions. Its toxic mechanism is because morphine is used as opioid receptor in different brain regions, The activation of the second messenger system and the changes of gene transcription and translation will lead to the changes of Da, opioid peptide and GABA neural pathways in the brain, resulting in the compensatory adaptation caused by the long-term activation of opioid receptors; In addition, it should also be used with caution for special groups such as elderly children, patients with arrhythmias, patients with no recovery of intestinal peristalsis after gastrointestinal surgery, patients with convulsions or a history of convulsions, and patients with liver and kidney dysfunction.

4. Chemical structure analysis of morphine

Natural morphine has left-handed optical properties, and left-handed morphine ((-) - morphine) is composed of five components. A rigid structure made of fused rings. A. B and C rings form a partially hydrogenated acyclic ring, and C and D rings form a partially hydrogenated isoquinoline ring. There are five chiral centers in the molecule: 5R, 6S, 9R, 13s and 14R. B / C ring is cis, C / D ring is trans, C / E ring is cis, ring D is chair conformation, ring C is half ship conformation, and ring a is connected to position 4 of ring D (piperidine ring) by vertical bond. In the structure of morphine, there are phenolic hydroxyl groups at position 3. Phenolic hydroxyl groups are weakly acidic in nature and easy to be oxidized. Etherification of phenolic hydroxyl groups at position 3 often leads to the reduction of analgesic activity. They are mainly used for moderate pain relief or antitussive in medical clinic. In addition, morphine has 6-hydroxy alcohol, which is neutral and easy to dehydrate; Ether bridge bond, neutral, unstable to acid and easy to lose water; Morphine n-ch3, which is alkaline, loses its activity after removal and can be used for salt formation; 7,8-double bond, which can be used to reduce to saturated ring. (refer to relevant drawings：Refer to figure 1，Refer to figure 2)



【Refer to figure 1】



【Refer to figure 2】

5. Other adverse reactions of morphine:

The adverse reactions of morphine are relatively extensive and in various forms, not only in physiology, but also in spirit and psychology. In addition to certain addiction and dependence on the human body, they also include constriction of pupils, inhibition of breathing, drowsiness, emotional disorder, difficulty in urination, skin pruritus and other adverse reactions, Morphine can constrict the smooth muscle of digestive tract and dilate the surrounding blood vessels. It will lead to constipation and lower blood pressure (such as postural hypotension). A few patients will have laryngeal edema, bronchospasm and so on.

6. Summary

Morphine belongs to opioid narcotic drugs, and its acetate, also known as heroin, is an important part of drugs. It can make people feel happy to some extent, but long-term use will have serious adverse effects on the functions of human central nervous system, cerebral cortex and immune system, resulting in the decline of human thinking ability, attention, memory and other functions, At the same time, accompanied by pathological changes or organ dysfunction in other tissues of the body, the human body will suffer from slow response, dyskinesia, depression, disorientation and sexual dysfunction. If morphine is used for a long time and in a large dose, it will also lead to hallucinations, mental disorders, and even convulsions Shock or even death. Once addicted to morphine for a long time, it will produce varying degrees of dependence and harm to physiology, psychology and spirit, resulting in serious adverse consequences and great harm to themselves, families and even the whole society. Therefore, in clinical practice, we should be cautious about the use of morphine drugs and strictly clarify the specific scope of morphine use Specific requirements and relevant systems to ensure the standardization of morphine use, minimize the adverse harm and negative impact of morphine on patients and others, and create a good social atmosphere.

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The Important Role Played by Occupational Therapy in the Process of China's Community-Based Rehabilitation System

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Abstract: Community-Based Rehabilitation started in China in the 1990s, which is the inevitable result of the rapid development of social science、technology, and the continuous improvement of economic level and the gradual improvement of people's quality of life.Community-Based Rehabilitation (CBR) is an emerging social medical model that is people-oriented, community-linked, led by rehabilitation therapists and supported by various social forces.Different from the traditional biomedical model, the treatment scope of this model is not limited to individuals, but often extends to groups with common living habits.And this model is not disease-oriented, but with "Do Something" as the core of value.

Keywords: Community-Based Rehabilitation; Occupational Therapy; Social Medicine

1. Background of Community-Based Rehabilitation

For thousands of years, the small-scale peasant economy has implanted a deep-rooted regional concept for the Chinese people. The "community" formed by the transformation of villages and towns has a strong cohesion effect for residents and a high sense of belonging. Therefore, Community-Based Rehabilitation has a more significant effect and a higher acceptance than that in hospitals and institutions.

In the early 21st century, China's rapid economic development, along with the requirements of family planning, China's aging trend began to become prominent.The reform of administrative divisions has gradually formed the concept of "community".People's understanding of the community has been gradually deepened, and their dependence on it has been gradually enhanced.At present, when medical conditions are developed but medical resources are scarce, it is a great problem and we have to constantly explore to find a way that can greatly save medical resources and correctly improve the physical condition of patients locally.Community-Based Rehabilitation, it can well meet the above conditions.

The development of new things cannot be separated from the support of national policies.In the State Council of the People's Republic of China on speeding up the development of mental disorders Community-Based Rehabilitation service opinion, points out that Xi Jinping always concerned about the disabled production and rehabilitation services,and require the party committees and governments at all levels attaches great importance to the career development of the disabled people, special care, pay special attention to the disabled.In the report to the 19th National Congress of the CPC, the General Secretary also made a major decision to "develop the cause of the disabled and strengthen disability rehabilitation services", which pointed out the direction and provided fundamental guidance for the Community-Based Rehabilitation services for mental disorders in the new era.The Communist Party of China and The State Council attach great importance to the development of the cause of the disabled. During the 13th Five-Year Plan period, the goal of "building a moderately prosperous society in all respects without any disabled people" was achieved as scheduled.

2. The Development of CBR

At the end of the 20th century, the concept of rehabilitation was gradually adopted by the Chinese people.The development of rehabilitation treatment in the mainland is slower than some of Chinese city just like Hong Kong, Macao, Taiwan and other foreign regions. According to the research, the main reason for this situation is the lack of economic

support.Rehabilitation treatment in mainland China is mostly recovery function training and treatment after surgery, with a long cycle, long time, high cost, and the effect is not significant. The professional treatment process is still lacking, so it cannot be accepted by the majority of dysfunction with general economic conditions.In China, most people have misunderstandings about the cognition of rehabilitation treatment. Patients often think that the function can be restored to the normal level with rehabilitation . Therefore, therapists and doctors should declare the prognosis of patients, the necessity of rehabilitation treatment and patients in advance.More than half of the patients believe that the recovery of physical function is because of the time-based self-repair of the body itself works, often ignoring the value played by rehabilitation exercises and occupational activities.

In 2002, China's Third National Conference on Rehabilitation of Disabled Persons was held, which mentioned that "Community-Based Rehabilitation" is the cornerstone of "rehabilitation services" for people with functional disabilities in China. Community-Based Rehabilitation as the background color to carry out a distinctive rehabilitation model.In the following 20 years, the government's relevant community policies have surged, and the requirements for community transformation, community services and community governance are also increasing.With the development of economy, the community, as the basic unit of social governance, plays a "people" and is the backbone of stabilizing today's governance model.The newly revised Law of the People's Republic of China on the Protection of Persons with Disabilities further puts rehabilitation treatment in a prominent position in solving social contradictions among persons with disabilities.The Community-Based Rehabilitation 12th Five-Year Implementation Plan was introduced in 2015, which for the first time creatively incorporated "Community-Based Rehabilitation" into government planning and built rehabilitation on rich community resources.In 2021 written "difference" national career development and pension service system planning " mentioned, to promote the construction of the elderly friendly community, to respect the elderly love social atmosphere, make the elderly participate in the social degree, can make the old people to better adapt to and into the wisdom society.This also puts forward new requirements and new expectations for the modern Community-Based Rehabilitation.

We have reason to believe that in today's society where community governance capacity is constantly improving, government gradually pays attention, economic level is developing rapidly, and biomedical and social medicine is more professional, the road of CBR treatment will continue to accelerate, and homework treatment will play a more and more significant role.The large population base is one of the main social problems in China. However, because the population problems emerge in an endless stream, the Communist Party of China and the government have always been able to play a leading role to find ways to balance resources and demand. Among them, the development of rehabilitation treatment is an important way to save the relationship between supply and demand of medical treatment and patients.Rehabilitation is a long-term process, which requires the long-term efforts of patients and therapists to achieve good results. Therefore, the construction of a community-based rehabilitation system requires the efforts of generation after generation.

At present, digitalization and informatization are the development direction of the medical system, and the development of rehabilitation treatment cannot be separated from their support.However, at present, for most communities, digital development is still at a low level. Compared with the developed information level in the hospital, the development of rehabilitation treatment in the community is challenging and has certain limitations.Therefore, to develop CBR, we need to lay a good digital foundation, which still needs more than ten years of efforts for us.

3. The value of OT in the community

Compared with physical therapy, the concept of operation therapy is much less accessible to the broad masses of the people.National Society for the Promotion of Occupational Therapy, the predecessor of American Occupational Therapy Association, was established in 1917, and these pioneers of occupational therapists proposed the idea that active participation in meaningful daily activities can build healthy physical and mental states, laying the foundation for the future theoretical development of occupational therapists.What is occupational therapy?In popular words, occupation means a general term of things that can be done in life. Occupational therapy refers to the purpose of improving physical function and enriching the spiritual world by doing interesting and meaningful activities, work and behaviors.

Nowadays, occupational therapy, as a branch of the rehabilitation discipline, has been involved in emergency rehabilitation, ICR, severe rehabilitation, outpatient rehabilitation, sports rehabilitation, pediatric rehabilitation, mental illness rehabilitation and other fields in the United States.A large number of research on occupational treatment has also been published on ——— physical disorders, consciousness disorders, occupational treatment ideas and so on, and the scope of research involved is constantly expanding.[1]

Chinese community evolution is more and more rapid, community scale is more and more large, the problem is how to optimize the structure of community, improve the current community governance model, can provide multi-source, multidimensional help, especially pension is one of the pain points of community governance, in the mainland with the support of various policies, also constantly carry out the pilot work, is exploring more good Community-Based Rehabilitation model.Zhang Weifeng, Shi Meifang and others took 60 stroke cases who did not carried out occupational treatment and family environment transformation before community training as the control group, and 60 stroke patients who carried out occupational treatment and family environment transformation after community training as the observation group.Using modified Barthel index (BI) and Frenchay activity refers to the number table, respectively, two groups of patients after community treatment, finally concluded that the two groups of patients daily life activities are improved, 2 months after entering the community BI index and Frenchay activity index score is significantly higher than the control group ($P < 0.01$).This means that the appropriate working environment and appropriate working activities can improve the quality of life of patients, and also promote the physical and mental health of patients, in line with the current health administration departments to implement the hierarchical diagnosis and treatment system "minor diseases in the community, serious diseases into the hospital, rehabilitation back to the community, health into the family" requirements.[1]

4. Conclusion

For people, the most important thing is health.Only by vigorously developing Community-Based Rehabilitation can we save hospital resources to a greater extent, provide patients in more need, and be conducive to the management and benign development of the hospital.More meaningful is that Community-Based Rehabilitation allows people to pay close attention to health for a long time, continuously improve the curative effect of rehabilitation, and make the later effect of rehabilitation more stable.

To put occupational treatment in Community-Based Rehabilitation, attention should be paid to making community residents actively participate in the treatment in daily life activities, community residents think that training is useful and closely related to life, and can really improve self-care ability and social ability.At the same time, Chinese occupational therapists should also learn from the therapists in Europe and other western regions, master the thinking and professional ability of occupational therapy, can provide more comprehensive services to the residents in the community, and gain their trust and support.

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Endoscopic Injection of Recombinant Human Adenovirus Type 5 Combined with Chemotherapy in the Treatment of Gastric Cancer: A Case Report

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Abstracts: **Purpose:** To investigate the endoscopic injection of recombinant human adenovirus type 5 (H101) in the treatment of gastric cancer. **Method:** The diagnosis and treatment data of one patient with advanced gastric cancer were collected and discussed. **Result:** The patient ,a 51-year-old middle-aged male, was diagnosed with gastric malignant tumor (adenocarcinoma stage IV) with liver metastasis and lymph node metastasis combined with the results of gastroscopy, imaging and pathological examination. The patient underwent endoscopic injection of recombinant human adenovirus type 5 (H101) and chemotherapy.After 4 times of endoscopic treatment, the patient had no serious adverse reactions,pyloric obstruction was relieved, carcinoembryonic antigen was significantly reduced,intragastric ulcerated-like tumor was healed,the range of liver metastases was reduced.In outpatient follow-up, no tumor recurrence or metastasis was found, and the general condition was good. **Conclusion:** Endoscopic injection of recombinant human adenovirus type 5 showed good efficacy and safety and tolerability in patients with advanced gastric cancer.It is worthy of further promotion in clinical practice.

Keywords: Gastric Cancer; Adenovirus; Chemotherapy; Case-Reporting

1. Introduction

Gastric cancer is one of the most common digestive malignancies worldwide.There were 1.08 million new cases globally in 2020.It is the fifth most common cancer and the fourth leading cause of death worldwide.[1]At present, chemoradiotherapy is the main therapeutic measure to delay the progression of middle and advanced gastric cancer.However, the overall treatment effect was suboptimal.Oncolytic virus treatment is a new therapy of tumor biology and immunotherapy.It uses the virus's ability to replicate to selectively infect and destroy tumor cells while preserving normal cells and tissues.[2]Recombinant human Adenovirus type 5 injection (H101)is the application of genetic engineering technology to reconstruct human adenovirus type 5.It has achieved some curative effect in the treatment of some middle and advanced malignancies.A case of advanced gastric cancer treated with endoscopic recombinant human adenovirus type 5 (H101) injection combined with SOX regimen in our hospital is reported as follows.

2. Case data

The patient, a 51 years old male, was admitted to our hospital due to abdominal pain for half a month on May 26, 2017.More than 10 days before admission,Previous gastroscopy in another hospital suggested that he had gastric mucosal lesions and pyloric obstruction.Pathological examination was performed that he had adenocarcinoma of gastric antrum.Abdominal CT showed that he had gastric cancer in the antrum and gastric horn and multiple liver metastases with intraperitoneal lymph node metastases.He was diagnosed with gastric malignancy (adenocarcinoma stage IV) with liver metastasis and lymph node metastasis.The patient was healthy and had no history of hepatitis or tumor,and no history of drug allergy.The patient vomited at admission and lost 8kg of weight with 1 point according to the Stomach Outlet Obstruction Score System (GOOSS) and 5 points for nutritional risk screening score (NRS-2002).Physical examination on admission

showed clear consciousness and general spirit, no obvious abnormality was found in cardiopulmonary percussion and palpation, the abdomen was flat and soft, stomach type was visible, no mural varicose veins were observed, mild tenderness in the upper abdomen, no rebound pain, no tenderness or rebound pain in the rest of the abdomen, Murphy negative, and negative mobility dullness. The patient underwent a SOX regimen (oxaliplatin 200mg d1 + tiggio 50mg bid) combined with four endoscopic recombinant human type 5 adenovirus (H101)1.5ml multipoint injection). During the treatment, the patient only occasionally had mild abdominal pain and abdominal distension, without nausea, vomiting, fever, anemia and other serious adverse reactions.His GOOSS score was 4, and the NRS-2002 was 1. Abdominal CT showed that the range of multiple liver metastases was reduced and the carcinoembryonic antigen was significantly reduced.The patient was in good mental state, had a fair diet, felt better quality of life, and gained 5kg in weight.Patients were followed up after discharge and regularly reviewed at local hospitals. Due to personal economic reasons, the patients could not continue to receive endoscopic adenovirus injection combined with chemotherapy in our hospital. Specific examination and laboratory tests during hospitalization in our hospital are shown in Table 1. The image data are shown in Figure 1.

3. Conclusion

The incidence and case fatality rate of gastric cancer both ranked the third place among malignant tumors in China.According to global cancer statistics, there were 478,508 new cases of gastric cancer and 373,798 deaths in China in 2020, accounting for 44% and 49% of the world, respectively.[3]The treatment of gastric cancer includes surgery, chemoradiotherapy, targeted and immunotherapy.At present, it is believed that although the radical resection of early gastric cancer can completely remove the lesion, 30% of the patients will still have local or distal recurrence after surgery.[4,5]Patients with advanced palliative chemotherapy have many adverse effects, with a 5-year survival rate of 25 – 30%.[6]Targeted drugs have limited efficacy due to the complex tumor microenvironment, genetic instability, and heterogeneity of HER2 expression in both primary and metastatic sites.[7]Immunotherapy requires the selection of appropriate patients based on specific molecular markers, and some elderly cancer patients may be affected by immune system dysfunction.[8]So new treatments for gastric cancer are urgently needed. Oncolytic virus is a new type of tumor immunotherapy, which can change "cold" tumor into "hot" tumor by inducing chemokines and cytokines, promote anti-tumor immune response, and further enhance the efficacy of immunotherapy, with good safety and no serious adverse reactions.

Common complications of advanced gastric cancer include pyloric obstruction, gastrointestinal bleeding, perforation, etc.Pyloric obstruction is more common, which not only seriously affects the quality of life of patients, but also may promote the spread and metastasis of gastric cancer.Current common treatments are surgical procedures and self-expanded metal stenting (SEMS).Although both methods can relieved clinical symptoms, they did not inhibit tumor progression. Complications such as stent migration, tumor stent growth and anastomotic tumor recurrence will occur.[9]The patient's first gastroscopy revealed a large ulcer-like tumor in the gastric horn with pyloric obstruction, with a GOOSS score of 1. After 4 injections of recombinant human adenovirus type 5 (H101), the gastric horn ulcer-like tumor was healed and pyloric obstruction was relieved by gastroscopy. GOOSS score was 4.The patient was in good mental state and could eat normally without symptoms such as vomiting and food. The weight gain was about 5kg, and the NRS-2002 score was 1.Haemoglobin and albumin levels were also identified as indicators of dietary improvement.[10]After treatment, hemoglobin, total protein and albumin increased by 12g/L, 6.87g/L and 3.68g/L respectively.It can be concluded that endoscopic adenovirus injection can not only dynamically observe the pathological conditions of gastric lesions, but also directly inject adenovirus into the tumor to inhibit the tumor progression, thereby alleviating pyloric obstruction and improving the quality of life of patients. When necessary, endoscopic hemostasis and pathological biopsy can also be performed.Patients with advanced gastric cancer have a poor prognosis, usually palliative chemotherapy, and the SOX regimen is commonly used in China.However, more adverse reactions appeared, such as anemia, leukopenia, thrombocytopenia, fever, nausea and vomiting.Peripheral sensory neuropathy and oral mucositis also appeared in some studies.[11,12]In this case, the patient had no above adverse effects during the chemotherapy treatment of H101 injection combined with SOX regimen, with only mild abdominal pain and abdominal distension, and the pain score (NRS) was 1.A study by ZHANG et al found that adverse effects such as nausea, vomiting, constipation, granulocopenia, anemia, and alopecia were less common in single H101

treatment compared with monotherapy, chemotherapy plus H101.[13]Therefore, H101 injection is currently considered to have a good safety and tolerability.

Adenovirus (Ads) is a non-enveloped virus with a double stranded DNA genome of about 36KB, which is one of the most studied oncolytic viruses.[14]Ads monotherapy or combination chemotherapy has been widely used in the treatment of solid tumors such as head and neck tumors, oesophageal cancer, gastric cancer, lung cancer, and liver cancer.A study by CHEN et al showed that rAd-p53 inhibited the growth of gastric cancer cells and that cells with more differentiation were more sensitive to the treatment of rAd-p53.[15]Rad-p53 is a weakened adenovirus carrying the wild-type p53 gene. Previous studies have shown that rad-p53 inhibits tumor growth, promotes apoptosis and enhances the sensitivity of tumor cells to chemoradiotherapy by inducing the expression of Puma, Bax, Bak and Fas.[16]Recombinant human adenovirus type 5 (H101) is also a kind of oncolytic adenovirus, but it is relatively poorly studied in gastric cancer.H101 was obtained by genetic engineering techniques for the deletion of some human type 5 adenovirus E1B-55kD protein and the E3 region.[17]The deletion of E3 fragments can transmit tumor antigen information to the human immune system, activate T lymphocytes, and induce the body to produce an immune response against adenovirus, thus killing tumor cells infected with adenovirus and establishing lasting antitumor immunity.H101 can not replicate in the p53 normal cells, and p53 expression in gastric cancer, so the virus can replicate in the body and infect tumor cells, inhibit the production of vascular endothelial growth factor and the formation of tumor neovascularization, eventually lysis kill tumor cells, release the offspring virus to infection the surrounding tumor cells, thus play the anti-tumor role of targeted killing.H101 can also improve the efficacy of chemoradiotherapy.Therefore, consider that H101 may inhibit tumor progression and prolong the survival cycle of tumor patients through the above mechanisms.In conclusion, endoscopic adenovirus injection can flexibly observe gastric lesions, directly act on the tumor, relieve pyloric obstruction, improve patient quality of life, with no obvious adverse reactions, and good tolerance and safety.However, this paper only discusses a single case and is not extensive.Therefore, H101 needs to be further explored clinically in the treatment of gastric cancer.

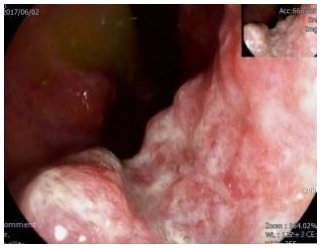
Table 1

result	2017.06.02 (First injection of adenovirus)	2017.06.28 （Second injection of adenovirus）	2017.08.16 （Third injection of adenovirus）	2017.11.15 （Fourth injection of adenovirus）
W.B.C. （10^9/L）	7.56	4.40	4.31	3.63
neutrophile granulocyte （10^9/L）	5.24	2.58	2.30	1.96
oxyphorase （g/L）	138	136	140	150
blood cells（10^9/L）	122	98	106	123
AFP (ng/ml)	1.68	2.59	3.11	2.55
carcinoembryonic antigen (ng/ml)	94.17	254.30	22.29	8.10
CA199(ng/ml)	<0.600	<0.600	<0.600	<0.600
CA125(ng/ml)	18.61	15.69	6.38	5.16
CA724(ng/ml)	NA	2.22	3.25	3.01
ALT(U/L)	38.16	39.10	55.43	19.41
AST(U/L)	58.10	43.65	38.39	22.71
total protein （g/L）	58.69	58.88	66.20	65.56
albumin（g/L）	41.69	40.09	46.77	45.37
total bilirubin （umol/L）	15.60	12.50	15.80	12.60
BRD（umol/L）	4.10	3.40	3.40	2.50
Indirect bilirubin	11.50	9.10	12.40	10.10

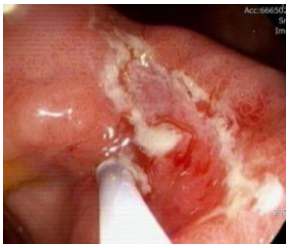
（umol/L）				
creatinine （umol/L）	95.70	75.90	79.34	63.63
usea nitrogen （mmol/L）	7.28	4.62	4.56	7.17

Figure 1

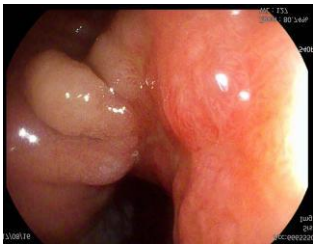
Gastroscope



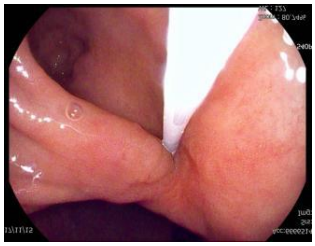
First injection of adenovirus



Second injection of adenovirus

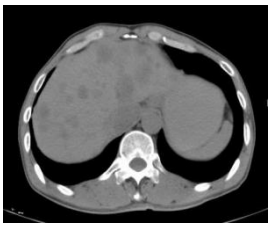


Third injection of adenovirus

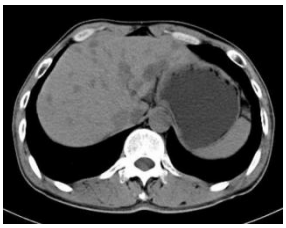


Fourth injection of adenovirus

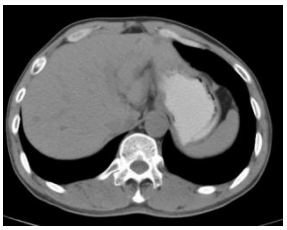
CT



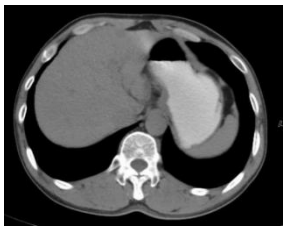
First injection of adenovirus



Second injection of adenovirus



Third injection of adenovirus



Fourth injection of adenovirus

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Universe Scientific Publishing

Research Progress of Neural Stem Cell Transplantation Combined with Biological Scaffold in the Treatment of Spinal Cord Injury

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Abstract: SCI is a kind of nerve injury disease caused by direct or indirect factors. The result is the damage of motor mechanism and the partial or total loss of sensory function below the injury site. The researchers found that planting neural stem cells in a biological scaffold and then colonizing the site of SCI greatly improved the survival rate of stem cells and promoted the repair of injury. However, different biomaterials have different differences. In order to better promote the recovery of function after SCI, it is important to select an appropriate scaffold combination.

Keywords: Neural Stem Cell; Biological Scaffold; Spinal Cord Injury

Introduction

Due to the low cure rate and high disability rate of SCI, exploring an effective treatment method to improve patients' function is the current research direction.[1,2] A large number of experimental studies have been carried out using neural stem cell transplantation. The mechanism of neural stem cell transplantation is mainly that neural tissue can differentiate into normal direction through stem cells. It has unique advantages in axon growth, synaptic remodeling and myelin formation. In view of the local inhibition of microenvironment and the lack of neurotrophic factors, it promotes the synthesis and secretion of local nutrients and improves the microenvironment.[3,4,5,6] However, the implantation of exogenous stem cells will lead to transplantation rejection, and the survival rate of stem cells is very low. The regeneration direction of axons cannot grow in the normal direction, so it is difficult to establish an effective synaptic connection with the host neurons, and the regenerated axons are difficult to grow outward from the transplantation area beyond the inhibition of glial scar. [7]

With the rise of tissue structure engineering, researchers found that stem cell transplantation combined with biomaterials has a certain prospect in the treatment of spinal cord injury. They found that biomaterials and stem cells have good biocompatibility and good degradation performance, which can improve the survival rate of stem cells, colonization and differentiation of transplanted cells to a certain extent, and separate the implanted stem cells from the host tissue, Thus, it provides an independent microenvironment for stem cell differentiation and proliferation, which is conducive to the release of exogenous cytokines without affecting the activity of endogenous factors. It can better bridge the gap of lesions and provide a bridge across glial scar for transplanted stem cell colonization.[8,9,10,11]

1. Neural stem cells

Neural stem cells are derived from neural tissue. They are one of the cells with the highest degree of differentiation and the strongest regeneration ability among seed cells. They can differentiate into neurons, astrocytes and oligodendrocytes, and play a vital role in the regeneration of the nervous system.[12, 13] studies have found that neural stem cells have the ability of unlimited proliferation and the potential of multi-directional differentiation. After transplantation, they can play a corresponding role by secreting corresponding nutritional factors instead of the cells at the injury, so as to promote the growth of neurons in the required direction and promote axon regeneration and neural tissue repair.[14]

2. Disadvantages of neural stem cell transplantation

The study found that the mechanisms related to axon regeneration are extremely complex, the microenvironment after

spinal cord injury is relatively complex, and it is difficult for stem cell transplantation to create a good microenvironment. In the study of stem cell transplantation, it was also found that some of them have the risk of tumorigenesis caused by immune rejection and ectopic diffusion. [15] Moreover, cell transplantation alone has the disadvantages of low cell survival rate and uncontrollable differentiation direction.[16]

At present, further research should be done to find more effective application methods for different SCI patients in different periods, so as to provide effective personalized treatment schemes for the rehabilitation of different SCI patients.

3. Types and characteristics of biological scaffolds

At present, the research of biological scaffold materials mainly focuses on the different structures of scaffolds. Natural scaffolds have suitable biodegradability, strong morphological remodeling and low toxicity to the body, but the mechanical properties of natural scaffolds are relatively poor, which can not provide sufficient mechanical support for cell climbing, and the degradation speed is fast; Synthetic scaffolds have good mechanical properties and can be synthesized easily, but their cell compatibility is poor. The acidic environment formed in the degradation process shows certain restrictions and damage to cell survival and growth. Composite scaffolds are composed of natural materials and synthetic materials, which have common advantages, but the cost is expensive. [17,18,19,20,21]

4. Treatment of SCI based on neural stem cell transplantation combined with biological scaffold

4.1 Neural stem cell transplantation combined with biological scaffold

Cao Zongrui et al. [22] observed that the collagen / heparin sulfate scaffold has good biological performance and stable structure. After planting the neural stem cells in the collagen / heparin sulfate scaffold and filling it in the spinal cord injury, they found that it showed a microenvironment suitable for regeneration, which can partially re-establish the neuronal pathway at the spinal cord injury of rats, promote the regeneration of nerve fibers at the stage, and partially improve the function of rats. Wang et al. [23] co cultured neural stem cells with chitosan gelatin scaffolds and found that neural stem cells can better adhere and grow on chitosan gelatin scaffolds and differentiate towards neurons and astrocytes, which slightly alleviates the recovery of limbs after spinal cord injury. Qi Guodong et al. [24] used stably subcultured neural stem cells and SCAs with removed cells and intact matrix to construct spinal cord tissue engineering. By observing the adhesion, growth and differentiation of neural stem cells on the scaffold, it was found that the adhesion state of neural stem cells in the scaffold combination group was better and could gradually differentiate into neurons and glial cells with plump cell bodies and clear axons on the scaffold, Stable connections can be established between differentiated neuronal axons, and the formed axons can also go deep into the pores of scaffold matrix.

4.2 Combined biological scaffolds based on neural stem cells from various sources and derivatives

It was found that after the transplantation of 3D printing scaffolds combined with UC derived iPSCs NSCs in rats, it was observed that the motor and sensory functions of rats recovered, and the spinal nerve fibers of the damaged segments grew well under electron microscope. [25] Zhou et al. [26] filled the injury area of rats with polycaprolactone scaffolds prepared by the combination of xuewang's cells and neural stem cells derived from induced pluripotent stem cells. The observation results showed that neural stem cells grew better on the scaffolds than those in the simple stem cell transplantation group, and this combination significantly reduced the spatial range of the lesion cavity and promoted the improvement of the motor system function of rats' lower limbs.

In a word, the effect of scaffold combined with stem cell transplantation group is better than that of simple transplantation group in all aspects of SCI in most cases. At present, the research direction of combined transplantation is

relatively diversified and there are great differences. More suitable combination methods need to be further explored in the future.

5. Summary and Prospect

The low cure rate and high disability rate of spinal cord injury have brought a heavy economic burden. The survival rate of simple stem cell transplantation is very low. Moreover, due to the continuous flow of cerebrospinal fluid in the spinal cord, it is difficult for cells to colonize the injury site, which not only reduces the therapeutic effect of stem cells, but also is likely to cause the risk of ectopic proliferation, It is also a difficult problem to solve at present that it is unable to differentiate directionally and difficult to cross glial scar.Some progress has been made in the treatment of spinal cord with biological scaffolds combined with stem cell transplantation. It has significantly improved the survival rate of stem cells, adjusted the microenvironment, supported and filled the lesion cavity to reduce the cavity in the injury area, induced its directional growth, slowly released the secreted neurotrophic factors, and is more conducive to crossing the glial scar, Promote the recovery of motor function after injury. Selecting reasonable scaffolds and the combination method that is easier to repair the injury can better inhibit cell apoptosis, provide connection for the axons at the damaged site, enable the seed cells to fully release and proliferate, and provide a suitable environment for promoting the recovery of spinal cord nerve function. However, different biomaterials have different strength and structure, and the ability of immune rejection, mechanical strength to support tissue growth and biodegradability after implantation need to be fully considered. In the future research on the combination mode, it is necessary to formulate the corresponding combination treatment scheme according to the characteristics of each stage of spinal cord injury, and choose the implantation mode with the least injury and better treatment effect is also the focus of the combination treatment scheme in the future.

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Universe Scientific Publishing

Research Review on Effects of Exercise on Neuroglial Cells after Central Nervous System Diseases

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Abstract: Astrocyte and microglia are two types of neuroglia that are relatively widely distributed and functionally important in the mammalian central nervous system. These two cells play an important role in CNS diseases. The mechanism of the effect of exercise on various CNS diseases is still unclear. In this paper, the effect of exercise on neuroglial cells after CNS diseases is investigated in depth from the function and structure of glial cells.

Keywords: Astrocyte; Microglia; Exercise; Alzheimer's Disease; Parkinson's Disease

1. Introduction

Neuroglial cells are widely distributed in the mammalian central nervous system and include astrocytes, microglia and oligodendrocytes[1]. They have a wide range of roles, including supporting neurons that nourish the central nervous system, participating in the formation of the blood-brain barrier, and participating in the immune response. In central nervous system diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and traumatic brain injury, both astrocytes and microglia are closely related to the pathogenesis and development of these diseases[2]. Currently, exercise has been shown to intervene in CNS diseases as a non-pharmacological intervention to affect astrocytes and microglia as well as brain trophic factors, but there is still a lack of in-depth understanding of the neuroprotective effects of exercise on CNS diseases. This article provides a review of the effects of exercise on glial cells after CNS disorders.

2. Astrocytes and microglia

Astrocytes are the most complex and abundant subtype of neuroglial cells in the central nervous system of all mammals, which originate from neuroepithelial-derived radial glial cells with protrusions extending from the cytosol and resembling a star, therefore it is named astrocyte [3]. When CNS injury occurs, such as chronic hypoxia, astrocytes undergo reactive astrocyte proliferation, which involves multiple changes in cell proliferation, morphological changes, increased cell surface GFAP expression, gene sequence changes, and metabolic changes [4], which astrocytes use to respond to acute injury. The increased immunopositivity of GFAP can be used as a ruler to judge the severity of injury [5]. Activated astrocytes exist in multiple subtypes, and studies have shown that they are transformed more towards 2 subtypes, A1 RAS and A2 RAS, respectively, A1 is neurotoxic and is associated with various neurodegenerative diseases such as AD, while A2 is neuroprotective. A1 upregulates complement cascade genes, etc. and induces the production of pro-inflammatory factors with deleterious functions, and the A1 may have lost its pro-synaptic function, NF-kB can also awaken A1 and release complement C3 [6]. In contrast, A2 can upregulate many neurotrophic factors, thrombospondin and anti-inflammatory cytokines and protect neurons, but current studies have mostly focused on type A1 and further studies on the function of A2 are still needed.

Microglia are immunoreactive macrophages that reside in the CNS and are an important component of the NVU. It has the phagocytic ability to destroy invading pathogens, remove cellular debris and apoptotic cells left after cellular injury, and remove toxins and pathogenic foreign bodies from the nervous system to protect the CNS from infection, ischemia, injury, and disease, and always plays an important role in the immune response. Activated microglia are divided into two phenotypes according to their surface markers and functions, M1-type microglia and M2-type microglia, both of which highly express IBa-1 on the cell membrane. IBa-1 is a marker protein on the surface of microglia, and the expression level of IBa-1 on the

surface of microglia increases after activation [7]. After TBI, with the time of A small amount of pro-inflammatory substances can activate microglia M1, leading to the release of more pro-inflammatory cytokines, chemokines and ROS, which can damage normal cells and tissues and eventually lead to the formation of chronic inflammation.

3. Alzheimer’s disease and parkinson’s disease

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, characterized by memory and learning loss, behavioral impairment, and cognitive dysfunction, and its pathology is characterized by the accumulation of hyperphosphorylated tau protein and amyloid (Aβ) plaques, neuronal fiber tangle formation, neuronal loss, neuroinflammation, and oxidative stress etc . Conversely, astrocyte overexpression of NGF leads to neurotoxicity and degenerative loss of hippocampal neurons; after activation by Aβ or the appearance of injury, it is involved in the secretion of inflammatory cytokines IL-1, IL-6 and TNF-α, thus promoting the neurodegenerative process of AD[8]. Microglia likewise play an important role in AD, and microglia dysfunction leads to the accumulation of Aβ plaques and tau proteins, which in turn can activate microglia and astrocytes via TLRs, releasing neuroinflammatory mediators and promoting neurodegeneration. However, in the later stages of AD, microglia transform to M1 type, which increases tau protein accumulation. Physical exercise has been shown to prevent AD, and an experimental animal study by Belaya et al. showed that voluntary physical exercise modulates the status of the RAS, which regulates the number of GFAP-positive astrocytes and the morphology of Aβ plaque-associated astrocytes in the hippocampus of 5xFAD mice, and that the molecular pathways involved in this regulation may be a therapeutic strategy for the treatment of AD [9]. Zhang et al. showed that running exercise inhibited TREM2 shedding and maintained TREM2 protein levels while promoting brain glucose metabolism, microglia glucose metabolism and hippocampal morphological plasticity in AD mice. Regulation of microglia glucose metabolism and morphological plasticity by affecting TREM2 may be a new strategy for AD treatment [10]. Parkinson's disease (PD) is a well-studied and common alpha-synaptic movement disorder, which is a progressive neurological degeneration caused by increased oxygen free radicals, mitochondrial dysfunction, protein degradation and aggregation dysfunction, and neuroinflammation resulting in a severe decrease in nigrostriatal tyrosine hydroxylase The pathology is characterized by the presence of a-synuclein deposits and protein inclusion bodies in the cytoplasm of neuronal cells [11]. Astrocytes play an important role in the pathology of PD by promoting dopaminergic neurodegeneration. Upon uptake of α-synuclein, astrocytes are thought to release a variety of cytokines including TNF and IL-6, which induce an inflammatory response that promotes the progression of PD. Studies have shown that after running, GFAP expression decreases and the number of TUNEL-positive cells decreases, resulting in a decrease in the number of apoptotic cerebellar cells and protection of dopaminergic neurons, which leads to improved motor behavior [12].

4. Conclusion

Both astrocytes and microglia have important roles in the mechanisms of action of various common CNS disorders, but the signaling pathways and mechanisms of action of various common CNS disorders are still unclear. There is no doubt that physical exercise can modulate microglia and astrocytes, affect neuroinflammation or neuronal cell survival, and thus provide targeted treatment for CNS diseases, but the intensity, type and duration of exercise and the mechanism of action need to be further investigated. It is expected to find a new direction for the future treatment of patients with clinical CNS diseases.

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Universe Scientific Publishing

Clinical Retrospective Study of Pterygomaxillary Implant Combined with Anterior Implant in the Repair of Atrophic Edentulous Maxilla

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Abstract: Objective: To retrospectively analyze the therapeutic effect of pterygomaxillary implant combined with anterior implant in the repair of atrophic maxillary edentulous jaw. Methods: The clinical data of 26 patients with atrophic edentulous maxilla who received pterygomaxillary implants combined with anterior implants from January 2019 to December 2020 were analyzed retrospectively. All patients were followed up for ≥ 1 year. The retention of anterior implants (105) and pterygomaxillary implants (45) were compared Patients' satisfaction with deep and middle periodontal examination (MBPD) and plaque (PLI). Results: The anterior implant retention rate was 97.14%, which was close to 93.33% in pterygomaxillary area (P > 0.05);The levels of PD, PLI, mesial MBL and distal MBL of anterior implants were similar to those of pterygomaxillary implants (P > 0.05); Patients' satisfaction with treatment was 92.31%. Conclusion: In the treatment of patients with posterior atrophic edentulous maxilla, the pterygomaxillary implant and the anterior implant supported complete arch fixed denture can bear the weight immediately, the short-term clinical effect is acceptable, and the patient satisfaction is high. It is a predictable and feasible repair method.

***Keywords*:** Atrophic Maxillary Edentulous Jaw; Pterygomaxillary Implant; Anterior Implant

Introduction

Atrophic maxillary edentulous jaw is a common type of implant repair in oral cavity. The main treatment of the disease is the restoration of complete arch denture supported by multiple implants, and the implant retention rate is high. However, due to the insufficient maxillary volume and maxillary sinus gasification, the process of posterior tooth restoration in the traditional restoration process is easy to be significantly limited, affecting the process of implant restoration [1]. Implant repair in pterygomaxillary area refers to passing the implant through the pterygoid process of sphenoid bone to strengthen the bone support of implant and support the posterior part of maxilla [2]. Combined with the anterior implant, it can eliminate the long cantilever effect and inhibit the bone increment. It can be considered as the treatment scheme of posterior atrophic maxillary edentulous. However, whether this treatment scheme can reduce the loss of marginal bone and improve the periodontal state of the implant is still lack of research. Therefore, this study retrospectively analyzed the clinical data of 26 patients with atrophic maxillary edentulous jaw from January 2019 to December 2020, and analyzed the therapeutic value of pterygomaxillary implant combined with anterior implant repair.

1. Data and methods

1.1 General information

The clinical data of 26 patients with atrophic maxillary edentulous jaw in our hospital from January 2019 to December 2020, including 16 males and 10 females, aged 45-74 years, with an average of (58.33 ± 4.20) years.A total of 150 implants were implanted, including anterior implants (105) and pterygomaxillary implants (45).Inclusion criteria: ① potential edentulous jaw, or maxillary edentulous jaw, posterior maxillary atrophy, and reduction of vertical bone mass (< 8mm);② Implant 1 ~ 2 pterygomaxillary implants with terminal torque > 30n · cm;③ Follow up time ≥ 1 year;Exclusion criteria: ① combined with metabolic diseases such as diabetes and hyperthyroidism;② There are mechanical movement habits of teeth

such as clenching teeth and molars;③ Poor oral hygiene habits.

1.2 Method

(1) Implant system: the pterygomaxillary implant system is Nobel Biocare active system. The anterior implant system is based on the pterygomaxillary implant and also includes the company's replace system;(2) Preoperative preparation: take cone beam CT, print the patient's 3D maxillary model, and determine the implant site with drill needle;Routine anti infection treatment before operation;(3) Surgical treatment: local anesthesia on the buccal and palatal sides of the distal maxillary tubercle and mucoperiosteal membrane, remove the remaining teeth without retention value, and clean the extraction socket;Incise along the palatal side of alveolar ridge until the contralateral maxillary tubercle is far in the middle;Two pterygomaxillary implants + four anterior implants were designed. When planting in pterygomaxillary region, a periosteal stripper was placed 10mm in front of the maxillary suture of pterygoid process. After the implantation site was determined in combination with the preoperative design implant scheme, holes were prepared step by step; The drill needle gradually passes through the pyramidal process of palatine bone through the proximal middle, posterior and posterior upper directions until it reaches the pterygoid process of sphenoid bone; In the process of pterygomaxillary implantation, the implant bed was prepared according to the patient's anatomy, the appropriate type of implant was implanted, the composite abutment was connected, and the soft tissue was sutured; (4) Repair: cone beam CT confirms the implant position, takes the mold beside the chair, takes the mold in the mouth and screws it into the abutment level, connects the mold taking columns with stainless steel wire, takes the mold with conventional silicone rubber and makes the wax dike with gypsum perfusion model, and carries out the immediate repair of the prosthesis after confirming the occlusal relationship of the patient, and tries to wear and adjust it in the mouth; Under the influence of the maxillary arch end of the implant in the pterygomaxillary area, the whole arch temporary denture can avoid the long cantilever arm.

1.3 Observation index

(1) The patients were followed up for 1 year to compare the retention of implants in pterygomaxillary area and anterior part; (2) The periodontal index and marginal bone resorption of pterygomaxillary region and anterior implant were compared, including probing depth (PD), plaque index (PLI), proximal middle and distal marginal bone resorption (MBL); (2) The treatment satisfaction of patients (including tooth function and aesthetics) is divided into very satisfied, general satisfied and dissatisfied. Satisfaction = (very satisfied + general satisfied) / cases×100%。

1.4 Statistical method

The（$\bar{X}$± s) and (%) represent measurement and counting data, and T and C2 tests;$P < 0.05$ means the difference is statistically significant;The data statistical calculation process is completed by SPSS 24.0 software.

2. Result

2.1 Implant retention

The anterior implant retention rate was 97.14% (102 / 105), which was close to 93.33% (42 / 45) in pterygomaxillary area ($C2 = 1.190$, $P = 0.275 > 0.05$).

2.2 Periodontal index and marginal bone resorption of pterygomaxillary area and anterior implant

The levels of PD, PLI, mesial MBL and distal MBL of anterior implants were similar to those of implants in pterygomaxillary area ($P > 0.05$), as shown in Table 1.

Table 1 periodontal index and marginal bone resorption of pterygomaxillary area and anterior implant（$\bar{X}$±s）

Implant location	*n* *N*	PD（mm） PD（mm）	PLI Pli	MBL Near middle MBL	MBL Far middle MBL
front	105	2.14±0.62 ±0.62	0.99±0.21 ±0.21	0.62±0.19 ±0.19	0.61±0.30 ±0.30
Pterygomaxillary region	45	2.28±0.50 ±0.50	1.02±0.23 ±0.23	0.63±0.18 ±0.18	0.65±0.15 ±0.15
t *T*		1.339	0.779	0.300	0.849
P *P*		0.183	0.437	0.765	0.397

2.3 Treatment satisfaction

After treatment, the patients were very satisfied in 10 cases (38.46%), generally satisfied in 14 cases (53.85%) and dissatisfied in 2 cases (7.69%), and the satisfaction was 92.31% (24 / 46).

3.discuss

In this study, these patients were treated with anterior fixed implant combined with pterygomaxillary implant, and all patients were followed up for ≥ 1 year. The analysis of the research results showed that the implant retention rates in the anterior and pterygomaxillary regions were similar. The analysis reason was that the implant retention rate was related to the fixed length, bone mass support, surrounding soft tissue support and other reasons, although there was still a lack of special implant in the pterygomaxillary region, However, the implant selected in this study is relatively long (15 or 18mm), which can pass through the pterygoid process of sphenoid bone during fixation to provide ideal bone support for implant fixation, so its implant retention rate is relatively ideal [3-4].

The results show that the level of periodontal tissue in the anterior and pterygomaxillary areas is similar, and there is no significant increase. The reason is that although the implant site in the pterygomaxillary area is relatively deep and daily cleaning is difficult, strengthening the guidance of patients' daily oral hygiene and cleaning can reduce the inflammatory reaction process of dental plaque on the periodontal tissue of the implant, so as to reduce the impact of inflammatory reaction of periodontal tissue on the stability of the implant, To provide soft tissue support for improving implant retention. The results showed that the marginal bone resorption of implants in the two regions was similar, suggesting that the implantation in pterygomaxillary region did not significantly increase the marginal bone resorption. The research results show that patients' treatment satisfaction is relatively high, which is related to the fact that the two implant schemes can better meet the needs of patients [5].

To sum up, in the treatment of patients with posterior atrophic maxillary edentulous jaw, the pterygomaxillary implant and the anterior implant supported complete arch fixed denture are loaded immediately, the short-term clinical effect is acceptable, and the patient satisfaction is high. It is a predictable and feasible repair method.

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Universe Scientific Publishing

Blood Oxygen Saturation Analysis Model Based on Multiple Normalized Regression

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Abstract:Several factors that may have an impact on the saturation of the oxygen saturation, respectively, are age, BMI, gender, and current smoking conditions. For the blood oxygen saturation of 36 patients collected, the data preprocessing, the abnormal data were removed, and the blood oxygen saturation was the dependent variable, with the BMI, age, gender, the current smoking condition is the independent variable, and the stata is normalized. In the case of significant sexual testing of variables, the discovery of the current smoking condition was significant for the oxygen saturation of the blood oxygen, while the bmi and gender in the t test were not different from zero, indicating that the blood oxygen saturation was affected by the BMI, and the influence of gender could be ignored, and the effect of age and current smoking condition on the oxygen saturation was mainly considered.

Keywords: Oxygen Saturation; Normalized Regression

1. Introduction

Normally, arterial blood has an oxygen saturation of 98 percent and venous blood 75 percent. Hypoxia Imbalance between oxygen supply and oxygen consumption in the body, that is, tissue cell metabolism in anoxic state. Whether the body is hypoxic depends on whether the oxygen transport and oxygen reserve of each tissue can meet the needs of aerobic metabolism. The harm of hypoxia is related to the degree, occurrence speed and duration of hypoxia. Severe hypoxemia is a common cause of death from anesthesia, accounting for about one-third to two-thirds of deaths from cardiac arrest or severe brain cell damage. Thus, it can be seen that blood oxygen saturation is important for a variety of diseases.

Oxygen saturation is an important indicator to describe cardiovascular diseases. We conducted multiple regression analysis on oxygen saturation of 36 patients with various physical characteristics.

2. Evaluation model of factors affecting oxygen saturation based on multiple linear regression

2.1 Data preprocessing

For Annex I, we take data on (+3, -3), according to reference, due to the love of measurement errors and the limitations of measurement instrument accuracy. Where means the sample mean and means the standard deviation. Because the data volume is large enough, based on the central limit law and the law of large numbers, we take the sample mean as the population mean and the sample variance as the population variance. The sample mean and sample variance of some patients are shown in Table 1:

Table 1 part of sample mean and sample variance

Patients with the serial number	Sample mean	Sample variance S^2
010217A	98.24	0.53
010217B	98.16	0.54
010217C	94.41	1.65

Due to the large number of patient data, only some relevant data of patients are displayed. Please refer to the attachment for the remaining data.

2.2 Introduction of factors affecting blood oxygen saturation

Blood oxygen saturation is the percentage of oxygen-bound hemoglobin capacity in the blood as a percentage of all binding hemoglobin capacity, that is, the oxygen concentration in the blood, which is an important physiological parameter in the respiratory cycle .Arterial blood has an oxygen saturation of about 98% and venous blood of about 75%.The process of human metabolism is the process of biological oxidation, and the oxygen needed in the process of metabolism, is to enter the blood through the respiratory system, and the hemoglobin in the blood red blood cells, combined into oxygenated hemoglobin, and then transported to the human body to all parts of the tissue cells. The ability of the blood to carry oxygen is measured by oxygen saturation.

Through consulting literature ， we know that hypoxia has a huge impact on the body. For example, there are effects on CNS, liver and kidney function. In a hypoxic state, compensatory heart rate increases, cardiac beat and cardiac output increases, and the circulatory system compensates for oxygen deficiency in a highly dynamic state. Redistribution of blood flow and selective dilation of brain and coronary vessels are also produced to ensure adequate blood supply. However, in severe hypoxic conditions, ATP synthesis is reduced due to subendocardial lactic acid accumulation, resulting in myocardial inhibition, leading to bradycardia, pre-phase contraction, decreased blood pressure and cardiac output, as well as ventricular fibrillation and other arrhythmias and even cardiac arrest. Therefore, we can see that the study of oxygen saturation is of high physiological and medical significance.

In order to establish a typical model to describe blood oxygen saturation, the following fields that may influence blood oxygen saturation are selected for study.

(1) BMI:

Body mass index is a standard commonly used in the international community to measure the degree of body fat and thin and whether a healthy standard. Abnormal BMI may be due to obesity or weight loss. The normal medical BMI ranges from 18.5 to 24.5, with a BMI below 18.5 considered too light and a BMI above 24.5 considered overweight, suggesting that this level of obesity may have an impact on oxygen saturation.

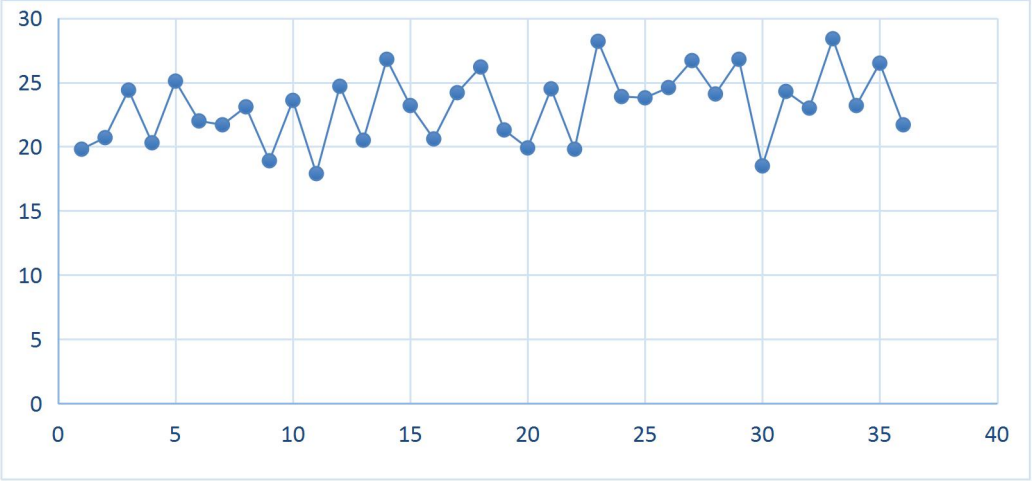

Figure 1 BMI of the patients given in the sample

By analyzing the BMI of the patients given in the sample, it was found that one patient was too thin, 15 patients were overweight, and the remaining patients were all normal.

(2) Gender

Does gender have any effect on human health? According to the lancet journals again , because men and women there is biggish difference in (1) physical structure, men have only one x chromosome from the mother, and on the y chromosome specific genes may make some disease increases, the probability for women, on the x chromosome genetic diversity more abundant, it may increase disease incidence, at the same time can also bring benefits. There are also large differences in lifestyle habits (men tend to smoke and drink, while women pay more attention to health and hygiene).

Thus, gender may indeed have an effect on oxygen saturation in both sexes.

(3) Age

With the increase of age, the water content of human body decreases significantly. At the same time, the activity of

various enzymes of human body decreases, energy demand decreases, and cell metabolism rate slows down, which is likely to lead to the reduction of oxygen demand of some cells, thus affecting blood oxygen saturation

Patients were roughly divided into three sections according to age, respectively enantiodromia the young (19,36), the middle-aged (36,53), and the elderly (53,70). The right side of the table represents the percentage of the total number of patients at a certain age, while the left side represents the total number of patients at a certain age.It was found that young patients accounted for the largest proportion, about 60% of the total number of patients, while the elderly patients accounted for the least, about 17%.

(4) Current smoking status

According to literature review, smoking is a major risk factor for many cardiovascular and cerebrovascular diseases. As high-density lipoprotein cholesterol (HDL-C) can stimulate the production of prostaglandin (PGI2) in vascular endothelial cells, PGI2 is the most effective substance for vascular dilation and inhibition of platelet aggregation. Smoking will damage vascular endothelial cells, resulting in decreased serum HDL-C, elevated cholesterol, and decreased PGI2 level, leading to contraction of peripheral blood vessels and coronary arteries, thickening of the wall, narrowing of the lumen and slowing of blood flow, resulting in myocardial hypoxia. In addition, carbon monoxide in smoke combines with hemoglobin to form carbon oxygen hemoglobin, which affects the oxygen-carrying capacity of red blood cells. Therefore, whether a patient smokes or not has a significant impact on blood oxygen saturation.

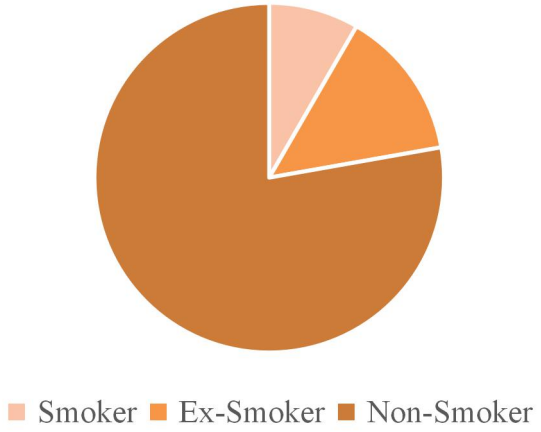

Figure 2 Statistical chart of current smoking status of patients

As can be seen from the figure, among the 36 patients, only 3 were smokers, 5 were smokers, and the vast majority were never smokers (28).

2.3 Evaluation model of factors influencing blood oxygen saturation based on multiple linear regression

Since gender and dummy variables are qualitative variables, they are not suitable for mathematical modeling, so it is necessary to introduce dummy variables to convert them into quantitative variables. A dummy variable is an artificial variable used to reflect the attributes of a quality. It is a quantized independent variable, often with the value of 0 or 1. The introduction of dummy variables will make the linear regression model more complex, but the description of the problem is clearer and the quantization of qualitative variables is completed.

After the introduction of dummy variables, the regression equation of blood oxygen saturation can be expressed as:

$$Oximetry = c_0 + c_1 BMI + c_2 Age + c_3 Gender + c_4 Smoking1 + c_5 Smoking2 + \mu_i$$

Oximetry is the virtual variables introduced by blood oxygen saturation, Gender and Smoking, c_0 is the constant term of the regression equation, c_i is the regression coefficient of the regression equation, μ_i is the perturbation term of the regression equation, and the equation should follow the normal distribution when there is no endogen.

Take Gender as an example to explain it:

Suppose that the I sample is male, and Gender=0 means that the I sample is female, then the expectations of Oximetry in these two states are discussed separately.

$$E(Oximetry|Gender = 1 Control\ other\ independent\ variables\ constant) = c_3 \times 1 + c$$

$$E(Oximetry|Gender = 0 Control\ other\ independent\ variables\ constant) = c_3 \times 0 + c$$

Under constant control of other variables, all independent variables except the target variable can be represented by constant C, then the difference of expected values:

$$E(Oximetry|Gender = 1 Control\ other\ independent\ variables\ constant) -$$

$$(Oximetry|Gender = 0 Control\ other\ independent\ variables\ constant) = c_3$$

Therefore, c_3 can be interpreted as the difference value of male and female oxygen saturation under the control of other independent variables remaining unchanged, which makes a reasonable explanation for the qualitative variable.

After pretreatment of the data and the addition of dummy variables, multiple linear regression with Oximetry as the dependent variable and BMI, Age, Gender and Smoking as the independent variables was carried out, and the results were as follows:

Table 2 Multiple linear regression analysis of blood oxygen saturation table of variance

source	ss	df	MS
model	17.98	5	3.40
residual	36.42	30	1.21
total	54.40	35	1.55

Number of obs = 36
F(5,30) = 2.96
Prob > F = 0.0273
R-squared = 0.3305
Adj R-squared = 0.2190
Root MSE = 1.102

First of all, we can see that *P=0.0273<0.05* indicated that the regression model passed the joint significance test.

At the same time, the goodness of fit of the regression model $R^2 = 0.219$, and the sum of squared errors SSE=54.40, if the model is used as a prediction model, the prediction results will have a large error. However , the regression models we are familiar with can usually be divided into two types, namely, explanatory regression and predictive regression.

(1) Predictive regression requires the regression equation to express the dependent variable to the maximum extent, which requires a high degree of goodness of fit R^2, otherwise it will lead to a huge deviation in the prediction results.

(2) Explanatory regression pays more attention to the statistical significance of each independent variable and the overall significance of the model, focusing on the causal relationship between the established research independent variable and dependent variable.

Table 3 blood oxygen saturation multiple linear variance coefficient of expansion

Variable	VIF
smoking2	1.95
smoking3	1.88
Age	1.50
BMI	1.47
gender1	1.21
Mean VIF	1.60

Variance coefficient of expansion (VIF) is an important index to measure the multicollinearity severity of multiple linear regression models.It represents the ratio of the variance of the estimator of the regression coefficient to the variance of the assumed independent variable with no linear correlation.

$$VIF = \frac{1}{1 - R_i^2}$$

It is generally believed that VIF<5 means that there is no multicollinearity among all independent variables. For example, each independent variable VIF in the table is less than 5, indicating that there is no multicollinearity in this regression model.

Table 4 Analysis table of multivariate linear regression coefficient of blood oxygen saturation

Variable	Coef	Std.Err	t	P>|t|
BMI	0.054	0.820	0.66	0.513
Age	-0.041	0.014	-2.87	0.007
smoking1			(omitted)	
smoking2	-0.457	0.617	-0.74	0.465
smoknig3	-2.068	0.911	-2.27	0.031
gender1	0.347	0.404	0.86	0.398
gender2			(omitted)	
cons	98.170	1.877	52.3	0

To eliminate multicollinearity for regression results, we will introduce the classification of the virtual variable number minus one, each independent variable corresponding t inspection P value, BMI and Gender were greater than 0.05, shows that the independent variable on the dependent variable and there is no difference between zero, that won't affect, and smoking and Age are all passed the test of significance, Oxygen saturation was only associated with age and current smoking status, but not with gender or obesity. At the same time, we also noticed that for the parameter smoking2 (who has quit smoking), there was no difference between the blood oxygen saturation and zero, indicating that only the current smoking status had an impact on the blood oxygen saturation by smoking, while there was no difference between the influence of never smoking and quitting smoking on the blood oxygen saturation relative to smoking.

3. Conclusion

For multiple factors that may affect the oxygen saturation: age, BMI, gender, standardized regression:

(1)Blood oxygen saturation is affected by a small amount of sex and bmi

(2)Blood oxygen saturation is significantly affected by age and current smoking conditions

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Research Progress of Breast Tissue Marker Clips and Their Application in Neoadjuvant Therapy for Breast Cancer

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Abstract: Currently, breast cancer being of rapidly increasing incidence rates and as the most commonly diagnosed malignant tumor in breast surgery, has attracted much attention. Neoadjuvant therapy (NAT) has been proved to be beneficial for reducing tumor size and breast-conserving surgery. As a new type of metal localization marker, breast tissue marker clips can be used to precisely locate tumor tissue and improve cure rates. This review focuses on the marker clips and their significance in the diagnosis and treatment of neoadjuvant therapy for breast cancer, hoping to provide more clinical bases for research and promote this technology.

Keywords: Breast Tissue Marker Clips; Neoadjuvant Therapy; Breast Cancer; Review

Introduction

Being the highest incidence of malignancy among women, breast cancer is seriously threatening their health[1]. China's incidence and mortality of this disease rank first in the world, and the burden brought with it continues to increase. Therefore, higher requirements are put forward on the corresponding prevention and treatment measures[2~3]. Neoadjuvant therapy (NAT) can reduce the size of breast adenoma, which can not only improve the resectability of inoperable tumors but increase the chances for breast-conserving surgery[4].

A breast tissue marker is a small metal marker, which has different shapes. It can be observed in the imaging system and can be directly placed in breast lesions through percutaneous for long-term lesions marking[5]. It has been already proved that placing the tissue masker for patients receiving NAT is helpful, safe, and reliable to locate the tumor[6]. Therefore, the application of this technology can increase the accuracy of localization, providing the possible decrease of tumor tissue and even achieving pathological complete response (PCR), which is beneficial for breast-conserving surgery and the therapeutic goal. This article mainly reviews the trend, research progress, clinical application, technical deficiency, and future research direction of breast tissue marker clips in NAT for breast cancer.

1. Overview and development of breast tissue maker clips

Breast tissue maker clips are a new accurate localization technology that serves for breast surgery. These clips have small sizes, different shapes and are of good features of tissue fixation. They are usually made of metal materials such as titanium alloy, nickel-chromium alloy, and nickel-free stainless steel, with less body toxicity and anti-anisotropy. It allows these clips to stay in the body for a long term and make full of their unique advantages especially in localizing small lesions.

As research continues, there are different materials in breast tissue markers used by many foreign institutions in various diseases which mainly focus on the application of NAT for breast cancer patients[7]. Volleamere et al., [8] indicated in their research that this technique can even be used as an international standard for breast specimen marking.

Furthermore, some scholars believe that compared with metal chips, biodegradable ones are more applicable and have few postoperative complications[9].

They have accurate localization function and considerable clinical significance, but there are still many unsolved issues. At present, the application of this technology is still under exploration in China and has not yet been in a stage of large-scale

clinical use.

2. Research progress and clinical significance of breast tissue marker clips in China

Because marker clips are very small, they were mainly used to locate small breast lesions (diameter <1.0cm) and axillary lymph nodes to precisely locate and completely remove them during operations, in the early clinical stage of breast surgery in China. Most of these small lesions are in the early stage of tumor development, and even if they possibly transform into malignancy, the prognosis is quite good when patients receive surgery at this time. Therefore, it is particularly important to completely remove the lesion when having an accurate location.

1. Locate non-palpable breast lesions and lymph nodes: A study of locating small breast lesions (diameter <1.0 cm) and axillary lymph nodes in Inner Mongolia People's Hospital indicated that 39 lesions and 9 lymph nodes in 31 patients who participated in this study were completely removed, with an average lesions diameter of 1.2±0.56 cm[10]. This makes it clear that with the help of the breast localization needle, clinically non-palpable breast lesions and lymph nodes can be completely removed and the early resection rate of malignant lesions can be further improved. Therefore, high-risk breast cancer patients can truly achieve the second-level prevention of early detection, early diagnosis, and early treatment. It is further suggested that a breast localization needle is gradually used in the location of breast lesions and axillary lymph nodes.

In the follow-up practice, many operators found the following problems: the volume of the needle is small and meanwhile, there is no technical support of real-time localization and resection of lesions in the imaging-guided system in China. Statistically, breast markers failed to identify localization in about 5%–20% of cases during surgery[11]. Therefore, based on the breast localization needle, it is also necessary to have the assistance of body surface localization to ensure that the operator well-localizes the lesion. The concept of double localization by combination with body mark and puncture was put forward, in the application of puncture combining with body mark to localization of non-palpable breast lesions by the First Affiliated Hospital of Sun Yat-Sen University. It was the first time that the combination was applied in the clinical treatment, which further supplemented and improved the experience of the marker clips in practical application. It also put forward potential problems and standardized the clinical practice of needle localization[12].

2. Auxiliary pathological diagnosis of localization: A clinical study, designed by Xinsteel Center Hospital at Xinyu, Jiangxi Province of China, showed that the pathological diagnosis after resection through localization technology indicated that all cases were malignant, with an accuracy rate of 100%[13]. Subsequent research also indicates that the needle can provide precise localization in pathological detection of small lesions, helping effectively detect malignancy in the early stage, which is of great clinical significance in the early prevention and treatment of breast cancer[14].

Currently, in China, some publications guide technical development. They recommend that localization markers can also be used in benign breast diseases, but are not yet included in the NCCN Guidelines for the diagnosis and treatment of breast cancer.

3. Clinical application of breast tissue marker clips in NAT

Studies abroad have shown that breast cancer patients who have achieved PCR through NAT before the operation is better than that patient who has not achieved PCR[15]. Placement of the clips before NAT can not only accurately locate breast lesions and regional metastatic lymph nodes, but also improve local control rates of breast-conserving surgery patients for five years[6]. Therefore, it is suggested to place clips at breast lesions and axillary positive lymph nodes of breast cancer after patients receiving NAT in quite a lot of guidelines and experts' consensus both at home and abroad[16-17].

1. Node-positive patients before receiving NAT: A systematic retrospective study confirmed the necessity and feasibility of sentinel lymph node biopsy before NAT for breast cancer with positive lymph nodes[18]. If the sentinel lymph node is negative, axillary lymph node dissection can be avoided during operation. However, the false-negative result is easy to appear after NAT for node-positive patients before NAT, which is not good for the accurate judgment of the operator[19]. Foreign scholars' studies have confirmed that the false-negative rates of sentinel lymph node biopsy after NAT can be effectively

reduced by inserting localization clips into biopsy nodules of patients with positive axillary lymph nodes[11]. And the research conclusion was also recommended by domestic experts consensus[17].

2. Breast cancer patients who receive NAT: On the one hand, for image-assistance, Hartmann and Rüland et al.,[20~21] reported that the ultrasonic detection rates of breast tumors and axillary lymph nodes after NAT were as high as 83.3% and 100% respectively. On the other hand, as for the surgical margin, the negative rate of patients who received NAT was slightly higher than that of those who did not[6]. Generally speaking, placing markers in NAT for breast cancer patients can not only increase the detection rate of B-ultrasound, MRI, and other imaging methods but also improve the accuracy of localization. Moreover, it is beneficial to fully remove lesions in breast-conserving surgery to ensure the negative surgical margin. In other words, ensuring the accurate location of the lesions is the premise to improve the negative rate of the margin during operation. And increasing the negative margin rate can improve the breast-conserving rate, thus reducing the local recurrence rate.

4. Common complications of breast tissue marker clips

Displacement is the most common complication. A marker clip should be placed within 10 mm within the preset position. Otherwise, it is called displacement which is mainly caused by the accordion effect[22-24]. In addition, around 5%–20% of cases may not be able to find the clips during operation, which means they disappear[25]. Moreover, bleeding could occur after implantation which may be caused by the coagulation disorders of patients, insufficient time for dressing and compression after the operation, or loosening- or shifting- wrapping. Very few patients have different degrees of complications, such as infection, pneumothorax, and pain after implantation.

5. Technical deficiency and future research direction

The technology of breast tissue marker clips is, on the one hand, a new one in the field of minimally invasive surgery, and has the function of long-term localization guidance. Meanwhile, it is also an invasive treatment technique and needs further evaluation on whether the safety and stability of the marker clips can meet the corresponding technical standards after it is placed precisely in the breast tissue of the body. On the other hand, benign breast diseases need long-term follow-up and return visits for clinical diagnosis and treatment of breast diseases. It will be the trend of accurate diagnosis and treatment to use the long-term localization advantage of the marker clips to guide the later re-examination and follow-up of patients.

Under the condition that the clinical efficacy has not been evaluated, the long-term therapeutic benefit of this technique has not yet been reflected, and the cost of placing a breast tissue marker clip is high for patients. It needs the support of government departments and medical insurance policies if widely use this technology in future diagnosis and treatment of breast surgical diseases. At the same time, it is also required that provincial and municipal hospitals, especially the grade A tertiary hospitals that offer breast specialties services independently, strengthen the guidance to junior general surgeons on the theoretical knowledge and practical skills related to markers. The research and application of this technology can be brought to basic-level hospitals.

6. Conclusions and prospects

Being an emerging technology, tissue marker clips were introduced into China after 2015. It can provide different degrees of localization function in dealing with non-palpable breast lesions, breast lump biopsy, mastitis, neoadjuvant treatment of breast cancer and its pre-treatment positive lymph nodes, etc. Its efficacy and importance have been confirmed by domestic and foreign institutions. Implantation has gradually been carried out in clinical practice in dozens of large-scale grade A tertiary hospitals in China.

Fewer developing units are in the stage of exploring and accumulating cases, compared with foreign countries. At present, there is still a lack of standardized guidance and standard operating procedures for the placement of ultrasound-guided marker clips based on NAT of breast cancer in China. In the future development of breast science, it is expected to carry out large-scale, multi-center, and random prospective clinical research, and explore the detailed implantation process to scheme standardization and popularize this minimally invasive technique.

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Conflict and Balance Between Intellectual Property Protection of Pharmaceuticals and Public Health

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Abstract: In December 2019, the emergence of unexplained pneumonia (later named COVID-19) caught people all over the world off guard. Until now, the epidemic situation is still not optimistic, and global health is seriously threatened. Prevention and control measures for COVID-19, accurately all infectious diseases, people are no longer strange. There are three ways, that is, to control the source of infection (isolation), cut off the transmission path (wearing masks), and protect the susceptible population (vaccines and specific drugs).[i] Among them, the last link - screening and developing new drugs and vaccines is the focus of the current efforts of medical institutions, pharmaceutical companies, and scientific research institutions. In January 2020, the news that Chinese researchers at the Wuhan Institute of Virology filed for a patent on the use of Remdesivir, an investigational drug from the US company Gilead, caused widespread controversy, because patent protection would limit people's access to vaccines and drugs.[ii] This also raises the question of how to balance the conflict between intellectual property protection for new pharmaceutical products and public health in the face of a global pandemic. This article mainly discusses three aspects, the fact of high cost, increasing complexities, and high rewarding of new pharmaceuticals, the status of strong protection in the pharmaceutical industry, and the negative public health impact of this strong protection. Although WTO members and some countries have responded accordingly to the consequences, the effect has been limited. This article will use this three-aspect analysis to in turn provide some information to increase the availability of vaccines and medicines for COVID-19 and other diseases.

Keywords: **Patent; Intellectual Property Protection; Pharmaceuticals; Availability of Vaccines And Medicines; Public Health; Covid-19**

1. The characteristics of pharmaceutical innovation: high cost, high difficulty, and high return

'The cost of this pill is one cent, but the first pill cost one hundred million dollars.' This is a popular phrase in the pharmaceutical industry. It also reflects the status of new drug research and development (R&D) - high costs. The cost here is broadly defined and includes the money, human and material resources, time, technical difficulty, and risk.[iii]

Overall, pharmaceutical R&D is a high-investment, high-difficulty, and high-reward process. Its investment and difficulty are reflected in the long R&D cycle and high technical requirements. At the same time, it involves the close cooperation and collaboration of multiple disciplines, professionals, and talents. Take the R&D cycle as an example, a conventional approved drug needs to go through five important procedures from R&D to marketing: 'new drug discovery, pre-clinical research, clinical phase, marketing application and approval for marketing and post-marketing testing', and there are several branches under each procedure, resulting in extremely high investment of time, economic and technical costs. For instance, the clinical phase is divided into 3 or 4 steps with a long time span, of which the phase III trial phase is the most task-focused and important part, and the trial cycle is often calculated in years. In general, it often takes over ten years for an approved drug to go from R&D to marketing.[iv] The cost and difficulty can be imagined, which are almost incomparable to those in other industries.

Moreover, the risk of new drug R&D is considerably high. As mentioned above, there are many steps in the process and any mistake at any step can lead to failure, not to mention patent applications that are rejected at the final stage of approval. These 'halved' applications mean that the efforts made by many organizations and personnel have been wasted. The number of failures far exceeds the number of best-selling drugs.[v] The ability to bear risks reflects an enterprise's economic strength, which is why ordinary enterprises dare not dabble in new drug R&D.

Given that new drug development is so costly, risky, and difficult, should it be protected and generate high returns? The affirmative answer is understandable. Without a large enough benefit, normal people would have no incentive to do something strenuous. After all, not everyone can live their lives on spiritual support and tangible monetary gains are essential. Thus, protection is necessary. However, too much is too little, and excessive protection can have some detrimental effects. The following sections discuss in more detail the various types of protection afforded to pharmaceutical products, and the conflict and balance between the protection and public health.

2. Strong protection in the pharmaceutical industry: patents, trademarks, and other methods

Admittedly, life and health are priceless, and as medicine is so closely linked to human health, it seems that no protection can be too strong to be given to medicines. This notion has been implemented in many aspects of national and regional laws. It is fair to say that the protection currently afforded to medicines is adequate and is showing an increasing trend.[vi] This article mainly analyses several means of protection: patents, trademarks, and other methods.

The first is patent protection. Compared with other industries, the pharmaceutical industry relies heavily on patent systems.[vii] Patent, which is a kind of intellectual property right, is stipulated in various laws, including the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement of the World Trade Organization (WTO), the European Patent Convention (EPC), and the domestic laws in different countries. Although these laws are not identical, the purpose of the legislation is basically the same - to promote innovation by granting the patentee a legal monopoly.[viii] Monopoly right during the limited period is the main way for pharmaceutical companies to make substantial profits. Therefore, it can be said that patent protection is related to the lifeblood of pharmaceutical industries.

At the level of being granted a patent, the threshold for granting a patent is lower for pharmaceuticals, which is considered to be 'privileged'.[ix] In general, the criterion of a patent is novelty, creativity, and utility.[x] As medicine has evolved, the study of human disease has gradually moved from the individual to the organ, to the cell, and even to the molecule. Individualised and precise treatments have become popular, so it has become common for treatments to be 'slightly different' (rather than significantly) from existing methods.[xi] For instance, as the saying goes, 'Talking about efficacy without talking about dose is nonsense', and a change in dose can affect efficacy. For example, a drug called Finasteride was found to treat an enlarged prostate and was patented, while another company used the same product, but with a change in dosage to treat male pattern baldness, which was also successfully patented.[xii] Similar examples are not uncommon where drugs are patented as 'new' drugs by changing the dosage, dosage form, route of administration, etc., while leaving the active ingredient unchanged. The patent system appears to be more receptive to minor inventions of low inventiveness and small novelty in the pharmaceutical field than in other fields. In other words, patent protection in the pharmaceutical field is easier.

Since a patent has been granted, the patentee enjoys a legal monopoly, but the monopoly needs to be bound, most intuitively in the form of a limited-term, which is generally 20 years.[xiii] Once a drug goes through patent expiration, pharmaceutical companies would experience a 'patent cliff' [xiv] - a precipitous drop in sales and profits from the patent due to the onslaught of generics. This may sound regrettable, however, according to some data, the 12 best-selling drugs in the US enjoy an average of 38 years of protection.[xv] Another study found that nearly 80% of the top 100 drugs had extended patent protection through a new patent.[xvi]

Then, why does the actual patent term far exceed the statutory period? As seen above, pharmaceutical companies can use minor differences to apply for new patents. In addition, there are a variety of ways to extend the protection period, such as data exclusivity (quasi-intellectual property)[xvii], patent linkage system, and the pharmaceutical patent term compensation

system (both provided for in the Trans-Pacific Partnership Agreement),[xviii] reverse payment settlements[xix], citizen petitions[xx], etc. Some have argued that this is understandable because, firstly, it is not illegal - there is no law against it - and, secondly, due to the existence of the patent cliff and the long delays in the approval process itself, it is reasonable for pharmaceutical companies to extend the profitability period. However, this practice has been much criticised. There is a term called 'evergreening' to describe this phenomenon, which is derogatory.[xxi] It is used as a metaphor for a phenomenon whereby pharmaceutical companies use various methods (not illegal but unethical) to extend the patent term. This phenomenon is detrimental to less affluent countries, as well as to generic companies, for whom access to patented medicines becomes more difficult.

In addition to patents, there is another type of intellectual property that can be used to protect drugs, which is trademarks.[xxii] Protection of pharmaceuticals is not normally associated with trademarks, because pharmaceuticals focus on intrinsic properties, such as efficacy, whereas trademarks protect relatively superficial objects, such as shape and colour. However, Pfizer's Viagra is a perfect example of how closely a trademark can be linked to the protection of a pharmaceutical product. Pfizer has taken Viagra, an erectile dysfunction treatment containing sildenafil, and engraved its image as a 'little blue pill' in the public mind through various strategies, including trademarks. In this case, therefore, the specificity of Viagra's appearance will prevent generic companies from selling a drug that looks like Pfizer's original product. Further, Viagra is not the only case. Many Chinese people know a 'pagoda candy' - a medicine that resembled a pagoda in shape and tasted like sugar but was essentially an insect repellent. The yellow, pagoda-shaped 'candy' has been imprinted on people's brains.[xxiii] It does not matter whether the medicine is patented or not, whether there are variations in the ingredients, or even which manufacturer produces it, as long as it is this colour and shape, almost everyone recognises its effects and efficacy. This is also a successful case of a trademark and a drug being tied together, effectively protecting the interests of the drug.

In summary, pharmaceuticals are more likely to be granted patents and when facing the patent cliff, the patent term can be extended directly or indirectly in various ways. In addition, even after the expiry of the patent term, pharmaceutical products can still be protected by trademarks and other ways. It can be argued that the protection afforded to medicines is quite adequate. However, there has been much criticism from a growing number of countries, particularly developing and least developed countries, that pharmaceutical protection is slightly excessive, and that this has undoubtedly been detrimental to the entry of cheaper generic medicines into the market, which has been detrimental to public health.[xxiv]

3. Conflict and balance between private rights (patent rights) and public interests (human rights)

'He just wants to live, what did he do wrong?' This is an impressive line from the movie Dying to Survive.[xxv] Adapted from a true event, the film tells the conflict between legal but expensive patented drugs, cheap but illegal generic drugs, and poor and life-saving cancer patients. In the film, the patented Gleevec for leukemia is very expensive, at over 20,000 RMB a box, it is unaffordable for an ordinary family, while generic Gleevec is cheap, at only 200 RMB a box, and there is no burden to use. For leukemia patients, as long as they can survive, there is no point in protecting intellectual property rights.

However, for pharmaceutical companies, the R&D of Gleevec has cost manufacturers more than ten years and a huge amount of money. To recover the cost as much as possible within the limited period, high-priced drugs are inevitable. If generic drugs, that is, drugs that are unauthorized to implement others' patents, are abused and cannot be effectively supervised, they will greatly infringe the interests of pharmaceutical companies, discourage their enthusiasm, and cause them to lose their motivation to R&D new drugs, and even endanger their survival.[xxvi] This is detrimental to public health and the public interest.

As can be seen, innovation, law, and public health are in a triangular relationship, with all three influencing each other.[xxvii] If innovation and public health are placed at opposite ends of a seesaw, then the law is the balance point of the seesaw, where the law encourages innovation while potentially infringing on public health. Countries are aware of this problem and have developed laws and policies, such as the Doha Declaration on the TRIPS Agreement and Public Health (Doha Declaration), which recognises the right of developing countries to maximise the flexibility of the TRIPS Agreement

to use compulsory licenses in situations where countries are experiencing emergencies, such as Aids, tuberculosis, malaria and other infectious diseases, like the COVID-19 now afflicting the world.[xxviii] The birth of the Doha Declaration, which politically and legally empowers developing countries to access medicines, is a major event in the international intellectual property landscape.[xxix]

However, has the Doha Declaration fulfilled its role of increasing access to medicines in poor countries? Unfortunately, the results have fallen far short of expectations.[xxx] The Doha Declaration is soft law, which may be less binding and less enforceable than hard law.[xxxi] It is a disappointing fact that the compulsory licensing system has been applied only once in the nearly 20 years since the Doha Conference. In October 2007, Canada notified the WTO that it had licensed a pharmaceutical company, Apotex, to produce a generic version of an exported patented drug for export to Rwanda. However, despite the efforts of both countries and Apotex, it still took five years before it could be exported. In the aftermath, Apotex stated that it would not use the compulsory licensing mechanism again unless reforms were made, as the process was too complex and cumbersome.[xxxii] In other words, neither the number of compulsory licenses nor the availability of medicines has changed substantially because of the Doha Declaration.

In addition, some countries have made measures to facilitate the entry of generic drugs into the market. For example, the Hatch-Waxman Act, a US law designed to streamline the generic drug approval process and retain incentives for innovation.[xxxiii] Then the Bolar exemption, which originated in the US and was later followed by several countries, deems the importation, manufacture, and use of a patented drug by others for testing without the consent of the patent owner, to obtain data and other information required by the drug regulatory authority, as not infringement.[xxxiv] These provisions provide a legal basis for generic drugs, and although they have some effect, their usefulness is limited in the face of unexpected events where there is a high demand for patented drugs.

Finally, in response to specific major public health events, WTO members can make proposals. For example, in the current case of COVID-19, two key proposals have emerged to address the shortage of COVID-19 vaccine production - the South African and Indian proposal for an intellectual property waiver, and the European Union (EU) proposal to clarify compulsory licensing. These two proposals are still being discussed by the WTO. It is argued that both compulsory licenses and intellectual property waivers, have their advantages and disadvantages and the conclusion after comparison is that the latter is a more effective solution to the current emergency.

In short, the protection of intellectual property rights of medicine has indeed conflicted with public health in practice, and the WTO has made a special response to this situation, namely the Doha Declaration, and individual countries have introduced corresponding assistance regimes. In addition, in the face of current major public health events, proposals have been put forward by South Africa, India, and the EU. However, in general, the accessibility and affordability of patented medicines in poor countries have not been effectively improved. The current situation of the epidemic is serious and the health of people around the world is at risk, so legal provisions such as the Doha Declaration need to be put in place and made more efficient.

Conclusion

Conflicts and disputes about the protection of intellectual property rights of medicines and public health have never stopped, and the outbreak of the COVID-19 has pushed this conflict to a climax. Due to the high difficulty and high cost of drug R&D, to encourage innovation and promote social progress, the protection of drugs is strong, mainly including patents, trademarks, and other methods. However, the increasing variety of ways to extend the term of patents has resulted in patentees gaining monopoly rights for too long, which, combined with other means of protection, has made medicines expensive, undermining their accessibility and affordability to the public, particularly in developing and least developed countries. Although laws and policies have been put in place to improve this poor situation, the results have been unsatisfactory.

Pharmaceutical intellectual property protection should be used as a means to promote social welfare rather than as the ultimate goal and should not be at the expense of public health. Especially in the context of the current serious epidemic, it is urgent to address public health issues. To resolve the conflict between pharmaceutical protection and the right to public health,

and to seek a balance between them, the existing legal effects are not sufficient. It is recommended that countries amend their national intellectual property laws, including by removing institutional, political, and procedural barriers and improving the enforcement and efficiency of relevant provisions such as the existing patent compulsory licensing system, which will be more conducive to the long-term development of the pharmaceutical industry and human health.

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Efficient Screening of nNOS-PSD95 Uncoupling Agents Based on Radiometric Fluorescent Molecularly Imprinted Sensors

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Abstract: Novel and efficient ratiometric fluorescent molecularly imprinted sensors (RFMIS) based on epitopes were developed, which can be used for the sensitive detection of neuronal nitric oxide synthase in the screening of neuronal nitric oxide synthase-postsynaptic density95 (nNOS-PSD95) coupling inhibitors. Under appropriate conditions, the fluorescence of the carbon dots quenched with the increasing concentration of $nNOS_{1-133}$, while the fluorescence of the quantum dots remained unchanged. The fluorescence ratio had a good linearity in the concentration range of 0-500 ng mL^{-1} for $nNOS_{1-133}$ and the determination limit was 0.14 ng mL^{-1}. Using the classical nNOS-PSD95 coupling inhibitor (ZL006) as a control, the RFMIS were used as the detector to detect the free nNOS released by Gnetol and 2,3,5,4′-tetrahydroxystilbene-2-O-β-Dglucoside from natural medicine after inhibition of nNOS-PSD95. The results have shown that the uncoupling efficiencies was consistent with co-immunoprecipitation experiments. The study provides a new idea and a new way for efficient screening of nature nNOS-PSD95 coupling inhibitors from natural medicine with the advantages of high efficiency, sensitivity and traceability.

Keywords*:* Molecularly Imprinted Polymers; Ratio Fluorescent Sensor; Rapid Screening; Ischemic Stroke

1. Introduction

Ischemic stroke is an important disease leading to disability and death in middle-aged and elderly people, which increases the risk of cognitive impairment and neurological dysfunction[1,2]. Neuronal damage from stroke has been linked to the excessive activation of N-methyl-D-aspartate receptors (NMDARs) and the resulting neuronal nitric oxide synthase (nNOS) activation[3]. To disrupt the postsynaptic density95-nNOS (PSD95-nNOS) interaction which is a downstream signaling pathway and has potential to be a better drug target, is a novel and great approach to selectively inhibiting the NMDA-PSD95-nNOS signaling pathway[4]. In our previous experiments, always using Co-Immunoprecipitation (Co-IP) to investigate the protein coupling inhibitory activity of the screening compounds from nature medicine. However, it was found that Co-IP was complicated to operate, and the antibodies used were expensive. What's more, the coupling inhibitory activity of the coupling inhibitor in the cells cannot be directly detected[5]. Therefore, a new uncoupling activity evaluation method should be established to simplify the operation, reduce the cost, and improve the efficiency.

Molecular imprinting is a simple and flexible strategy to generate specific identification sites which are chemically and spatially complementary to the pre-selected target molecule[6,7]. Recently, molecularly imprinted polymers (MIPs) have been used as promising recognition elements of nanosensors because of their satisfactory selectivity, good stability and low cost. While a few fluorescents molecularly imprinted polymers have been developed for optosensing a wide variety of small organic analytes such as bisphenol A, silver ions [8] and dibutyl phthalate [9], the imprinting of bio-macromolecules remains a challenge because of their conformational flexibility under harsh imprinting conditions and the difficulty in removing the template from the imprinted cavities. Therefore, we have proposed ratiometric fluorescent molecularly imprinted polymer (RFMIPs) based on epitopes for the rapid detection of nNOS proteins in the screening of nNOS-PSD95 coupling inhibitors.

In this paper, RFMIPs were prepared by sol-gel polymerization with nNOS as the template and carbon dots (CDs) as the detector. The evaluation of RFMIPs such as stability, response time, selectivity, sensitivity, and adsorption capacity were

investigated to show that RFMIPs can specifically identify nNOS protein. Finally, using the classical nNOS-PSD95 coupling inhibitor (ZL006) as a control, RFMIPs were used as the detector to detect the content of nNOS in cell supernatant after the action of Gnetol and 2,3,5,4′tetrahydroxystilbene-2-O-β-D-glucoside on cells. The results have shown that the uncoupling efficiencies was consistent with co-immunoprecipitation experiments.

2. Experimental

2.1 Materials and Apparatus

Lowry protein concentration assay kit was acquired from Sangon Biotech (Shanghai, China). BCA™ microprotein detection kit was obtained from Thermo Fisher Scientific (Shanghai, China). Ovalbumin (OVA), bovine serum protein (BSA) and lysozyme (Lyz) were purchased from solarbio science＆technology. $nNOS_{1-133}$ was kindly provided by the Department of pharmacology, Nanjing Medical University (Nanjing, China). All other chemicals used in this paper were of analytical reagent grade.

The fluorescence emission spectra were measured on an F-4600 spectrofluorometer (Hitachi, Japan). All Ultraviolet-Visible (UV-Vis) spectra were achieved using a Shimadzu UV-2100 spectrophotometer. About

2.2 Synthesis and evaluation of RFMIPs

A novel RFMIPs for the selective and sensitive assay of nNOS based on epitopes was synthesized by simple sol-gel process, using CDs as sensitive signal source and CdTe quantum dots as reference. Both the ratiometric fluorescent materials and imprinted sites were located on the surface of silica. The template protein $nNOS_{1-133}$ was not added during the preparation of ratiometric fluorescent molecularly non-imprinted polymers (RFNIPs). The rest of the preparation was the same as RFMIPs. The specific methods of the RFMIPs synthesis will be described in detail in another article.

In order to determine the adsorption isotherm, 5 mg RFMIPs and RFNIPs were suspended in 1mL PBS with different $nNOS_{1-133}$ concentrations (50-700 ng mL^{-1}), respectively. RFMIPs and RFNIPs emission intensity were determined by fluorescence scanning after shaking for 40 min at room temperature. The relation between $nNOS_{1-133}$ concentration and $\triangle(F_{450}/F_{610})$ was plotted. $\triangle(F_{450}/F_{610})$ was calculated as formula (1):

$$\Delta\,(F_{450}/\mathrm{F}_{610}) = (F_{450}/\mathrm{F}_{610})_0 - (F_{450}/\mathrm{F}_{610})_\mathrm{e} \quad (1)$$

Where F_{450} and F_{610} are the fluorescence intensity at 450 nm and 610 nm respectively. $(F_{450}/F_{610})_0$ represents the fluorescence intensity ratio without protein solution, and $(F_{450}/F_{610})_e$ represents the fluorescence intensity ratio after the protein was adsorbed.

Meanwhile, the dynamic adsorption was tested by monitoring the $nNOS_{1-133}$ concentration in the solutions at different times (5, 10, 15, 20, 30, 40 and 50 min). The molecular selectivity of RFMIPs and RFNIPs was performed with $nNOS_{1-133}$ and its structurally similar compounds OVA, BSA and Lyz. All the experiments above were conducted for three times in parallel.

2.3 Fluorescence measurement conditions

All fluorescence spectra had an excitation wavelength of 360 nm and a detection wavelength in the range of 400-700 nm. The parameters of the instrument were set as follows: the voltage of the photomultiplier tube was 700 V; the scanning speed was 1200 nm min^{-1}; and the slit width was 10 nm.

2.4 Application of RFMIPs in real samples

HEK-293T cells were cultured in DMEM medium containing 5 μg mL^{-1} penicillin, 5 μg mL^{-1} streptomycin and 10% (v/v) fetal bovine serum. When the cells reached a confluence of 70-90%, the same amounts of plasmids PRK5-nNOS and pcDNA3.1-PSD95 were transfected into the cells through liposomes 6000. After 24 h, the medium was discarded, then 60 μmol L^{-1} ZL006, Gnetol and 2,3,5,4′tetrahydroxystilbene-2-O-β-D-glucoside were added to the petri dish respectively. The

cells were collected after 12 h and lysed with RIPA lysate, then centrifuged at 12000 r min^{-1} for 30 min and the supernatant was collected for later use.

5 mg RFMIPs were dispersed in 1 mL the above-mentioned cell supernatant and then shook for 40 minutes at room temperature. The fluorescence intensity of RFMIPs was measured and $\triangle(F_{450}/F_{610})$ was calculated. The concentration of nNOS in the supernatant was calculated according to the linear equation and the experiment was performed for three times in parallel.

3. Results and discussion

3.1 Adsorption ability evaluation of RFMIPS

Static adsorption experiments were used to measure the fluorescence response of RFMIPs and RFNIPs in $nNOS_{1-133}$ (0-700 ng mL^{-1}) protein solutions. As shown in Fig. 1A, as the concentration increased, the value of $\triangle(F_{450}/F_{610})$ increased, indicating that the blotting material responded to the $nNOS_{1-133}$ protein solution. When the solution concentration was 400 ng mL^{-1}, the response of RFNIPs reached equilibrium, $\triangle(F_{450}/F_{610})$ was about 0.41; when the protein concentration was about 600 ng mL^{-1}, the response basically reached the maximum, $\triangle(F_{450}/F_{610})$ was about 0.86. The response of RFMIPs fluorescence signals was based on the special binding site of $nNOS_{1-133}$ on the imprinted polymer. Therefore, the response of RFMIPs fluorescence signals was more significant than that of RFNIPs in the same concentration of $nNOS_{1-133}$ protein solution.

The results of the dynamic adsorption experiments were shown in Fig. 1B. At 600 ng mL^{-1}, RFMIPs and RFNIPs had different response time to $nNOS_{1-133}$. The $\triangle(F_{450}/F_{610})$ of RFMIPs remained basically unchanged after 40 min, which was slightly slower than that of RFNIPs, probably because the response process of three-dimensional binding sites with complementary shapes on the surface of RFMIPs was more complicated than the random response on SMNIPs surface.

Selective fluorescence response to the template protein $nNOS_{1-133}$ and other protein was an important indicator to verify the successful synthesis of RFMIP. As shown in Fig. 1C, the fluorescence response of RFMIPs was about 1.5-2 times that of Lyz, OVA and BSA, while the fluorescence response of RFNIPs to each protein was not significantly different, indicating that RFMIPs could specifically recognize the template protein $nNOS_{1-133}$ with strong fluorescence response. This was because the surface of RFMIPs had a special binding site "tailored" for $nNOS_{1-133}$. $nNOS_{1-133}$ could bind to the site, which quenched the fluorescence intensity at 450nm and made the fluorescence ratio decrease.

3.2 Fluorescence detection mechanism

In this experiment, two kinds of fluorescent nanoparticles were introduced as detectors into molecularly imprinted polymers. For the principle of response, we proposed three possibilities based on the characteristics of the materials: (1) imprinted holes; (2) photoinduced electron transfer and (3) Foerster resonance energy transfer. The UV and fluorescence spectra were detected to further narrow the guesses. As shown in Fig.1D, the principle of Foerster resonance energy transfer was excluded first, because there was no overlap between the UV-Vis absorption spectrum of $nNOS_{1-133}$ and the emission spectra of CDs and CdTe. We speculate that the fluorescence change may be caused by the photoinduced electron transfer and imprinted holes. In RFMIPs, $nNOS_{1-133}$ and CDs were co-imprinted in the imprinting layer. When $nNOS_{1-133}$ was present, it could be adsorbed by three-dimensional binding sites on the imprinted polymer through hydrogen bonding and reversible covalent bonding. After fluorescence excitation, the electrons on the conduction band of CDs in RFMIPs transitioned to the lowest unoccupied molecular orbitals unoccupied by $nNOS_{1-133}$ through covalent bonds or hydrogen bonds, and then directly returned to the ground state and quench the fluorescence of CDs. Thereby, the fluorescence intensity of CDs changed with the increase of $nNOS_{1-133}$. CdTe in RFMIPs was wrapped in the silicon layer and did not directly contact $nNOS_{1-133}$. It remained unchanged without photoinduced electron transfer and imprinting holes. Hence, we speculate that the detection mechanism of RFMIPs was the combined action of imprinted holes and photoinduced electron transfer.

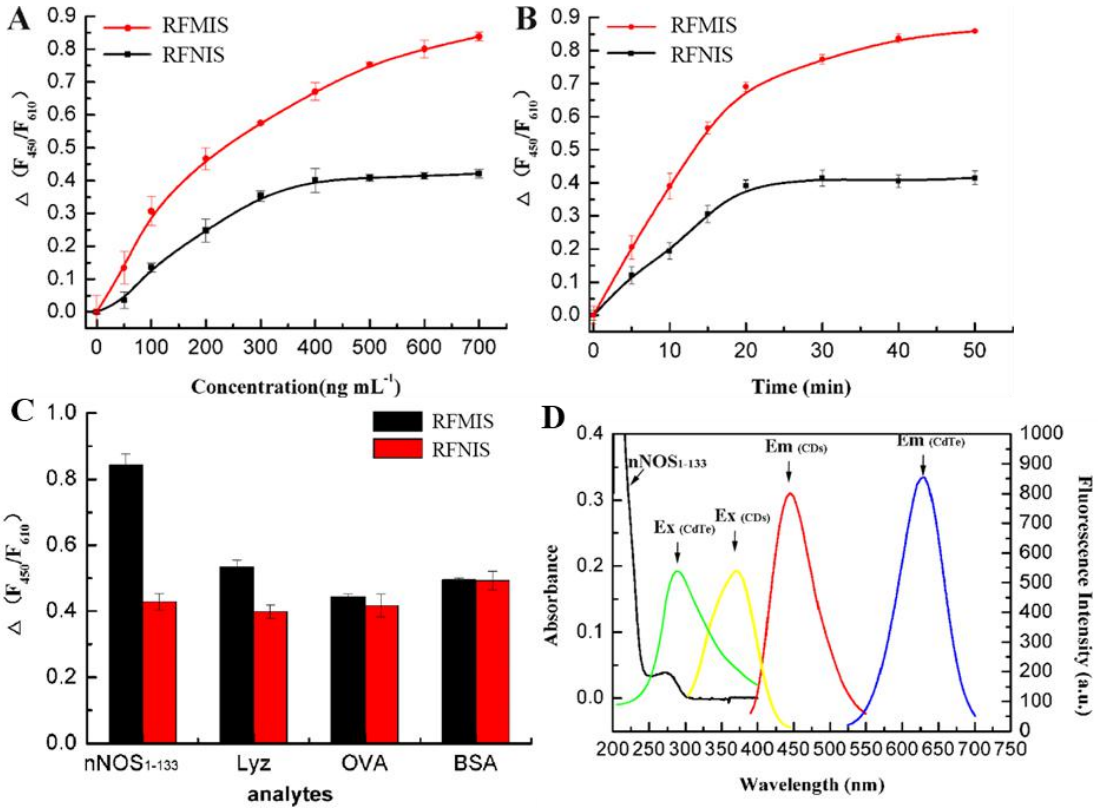

Fig. 1 (A) adsorption isotherms of RFMIPs and RFNIPs to $nNOS_{1\text{-}133}$, (B) adsorption kinetic curve of RFMIPs and RFNIPs to $nNOS_{1\text{-}133}$, (C) selective fluorescence response to $nNOS_{1\text{-}133}$, Lyz, OVA and BSA, (D) the UV-Vis absorption spectrum of $nNOS_{1\text{-}133}$ (dark line), the excitation (green line) and emission (blue line) fluorescence spectras of CdTe and the excitation (yellow line) and emission (red line) fluorescence spectras of CDs

3.3 Application of RFMIPs in real samples

3.3.1 Detection range and detection limit

5 mg RFMIPs were evenly dispersed in 1mL PBS, then 1mL $nNOS_{1\text{-}133}$ solution of different concentrations was added to make the protein concentrations of 0, 50, 100, 200, 300, 400 and 500 ng mL^{-1}, respectively. The solution was oscillated and shook at room temperature for 40 min. As shown in Fig. 2A, with the increase of the concentration of $nNOS_{1\text{-}133}$, the fluorescence intensity of CDs in RFMIPs quenched while CdTe QDs remained unchanged. As shown in Fig. 2B, the linear equation $y=0.0016x + 0.0604$ ($R^2=0.9843$) was obtained by linear fitting according to the relationship between $\triangle(F_{450}/F_{610})$ and the concentration. The LOD was 0.14 ng mL^{-1} based on $3\sigma/K$, which is found superior to the reported assays for nNOS. The experiments showed that the fluorescence ratio had a good linear relationship with the concentration of $nNOS_{1\text{-}133}$, and the method could be used to calculate the concentration of $nNOS_{1\text{-}133}$.

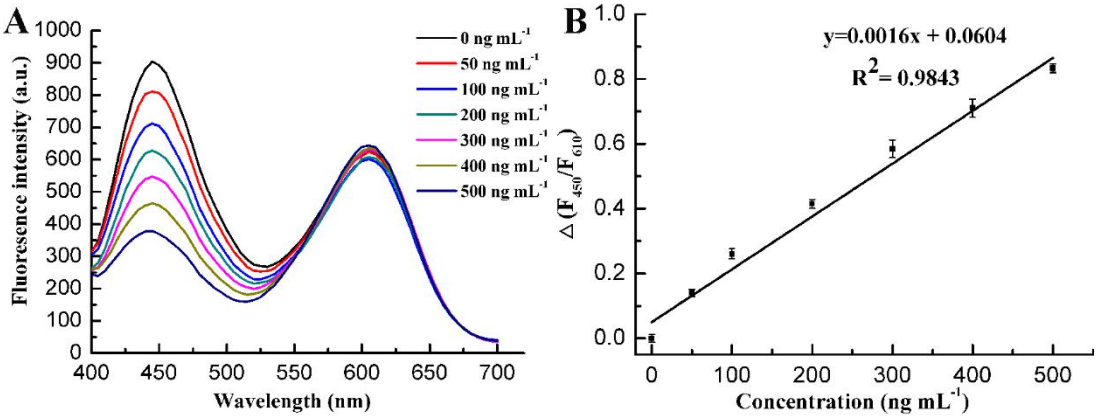

Fig. 2 (A) Fluorescence emission spectra of RFMIPs with increasing concentrations of $nNOS_{1-133}$; and (B) Stern-Volmer plots for the RFMIPs

3.3.2 Detection of nNOS in cells

As shown in Fig. 3A, ZL006, Gnetol and 2,3,5,4′tetrahydroxystilbene-2-O-β-D-glucoside were calculated based on the gray values of the PSD95 and nNOS bands, respectively. The coupling inhibition rate of glycosides was shown in Fig. 3B. Taking ZL006 as a reference, the coupling inhibition rate of Gnetol and 2,3,5,4′tetrahydroxystilbene-2-O-β-D-glucoside was 1.48 times and 2.17 times that of ZL006 respectively. Because $nNOS_{1-133}$ was the "epitope" of nNOS, RFMIPs had the ability to specifically recognize nNOS. The results of the detection of nNOS in the supernatant of cells treated with coupling inhibitors by RFMIPs were shown in Fig. 3C. The diluted supernatant reacted with ZL006, Gnetol and 2,3,5,4′tetrahydroxystilbene-2-O-β-D-glucoside containing 167.81, 233.00, and 318.35 ng mL^{-1} nNOS protein, respectively. The uncoupling efficiencies of Gnetol and 2,3,5,4′tetrahydroxystilbene-2-O-β-D-glucoside was 1.39 and 1.90 times that of ZL006 respectively. RFMIPs could be directly used for sensitive detection of nNOS protein in supernatant without expensive magnetic bead and antibody pretreatment, which had more advantages than Western-blot for protein determination.

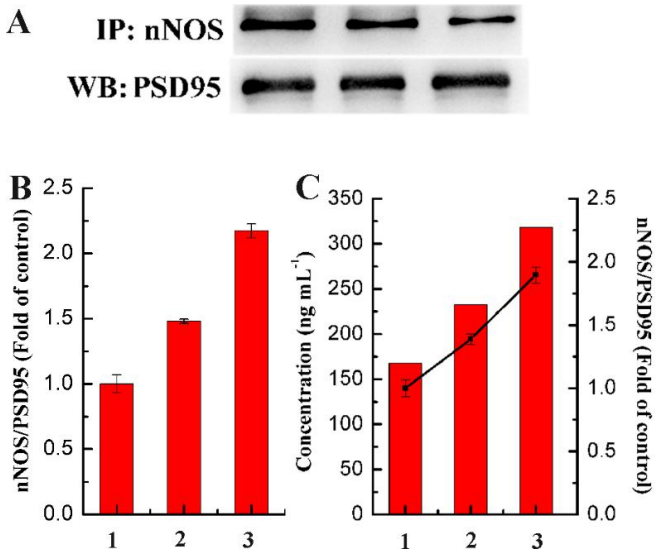

Fig. 3 Data is presented as mean±S.D. #P<0.05, compared with control. (A) the electrophoretic bands of nNOS and PSD95, (B) the coupling inhibition efficiency measured by Western-blot, (C) the concentration of nNOS and coupling inhibition efficiencymeasuredbyRFMIPs.Therecompoundsare(1)ZL006,(2)Gnetoland(3)
2,3,5,4'-Tetrahydroxystilbene-2-O-β-D-glucoside

4. Conclusion

In this experiment, we establishment a method that combines the selectivity and stability of an epitope-imprinted polymer with the sensitivity of ratio fluorescence, which was used for sensitive detection of nNOS. RFMIPs were used as the detectortodetectthecontentofnNOSincellsupernatantaftertheactionofGnetoland2,3,5,4′tetrahydroxystilbene-2-O-β-D-glucoside on cells. Compared with the content of free nNOS protein after the action of known active drug ZL006, the tests were consistent with the results of Western-blot analysis. Therefore, this experiment provides new ideas and new methods for rapid and sensitive detection of nNOS.

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Research Progress on Influencing Factors of Refractive Error in Preschool Children

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Abstract: Preschool is the key period of children's visual function development, which is called the "critical period of visual development plasticity". Any abnormal stimulus during this period can have an adverse impact on children's vision. Ametropia is the main cause of poor vision in preschool children. There are many reasons for ametropia. This paper reviews the influencing factors of ametropia in preschool children in recent years, which are classified into three aspects: demographic factors, physiological factors, and lifestyle factors.

Keywords: Influencing Factors; Ametropia; Preschool Children

1. Definition and research status of ametropia

Ametropia refers to that the parallel light cannot accurately focus on the retina of the fundus to result in a blurred image after the refraction of the refractive system of the eye. If the light is focused in front of the retina, it‘s myopia; When the light is focused behind the retina, it’s hyperopia; Light cannot converge into focus, which is astigmatism; All three will lead to blurred vision.

In recent years, with the wide use of electronic products and bad eye habits, more and more preschool children with ametropia have been detected. The National Health Commission released the survey results of myopia among children and adolescents in 2018. The results showed that the overall myopia rate among adolescents was 53.6% in 2018. Therefore, it is necessary to carry out myopia screening, correction and health guidance for children and adolescents in China from the pre-school stage.

2. Influencing factors of refractive errors in preschool children

2.1 Demographic factors

2.1.1 Age

The detection rate of refractive abnormalities in children is related to age distribution. According to the visual acuity screening of 3352 infants aged 6 months to 3 years, Chen L.S. [1] found that before the age of 3, the abnormal rate gradually decreased with the increase of age ($P<0.01$). Zhang G.Y. [2] 's survey of 4~7 years old children found that with the increase of age, the incidence rate of hyperopia decreased, and the incidence rate of myopia increased.

2.1.2 Gander

The differences in the investigation and statistics of refractive errors of children of different genders are not uniform. According to Gao H.Q. [3]’s research, the abnormal rate of total anisometropia in girls (2.3%) was higher than that in boys (1.9%). However, some studies [4] show that refractive errors of preschool children have nothing to do with gender, which may be related to regional differences and too few research samples.

2.1.3 Race

Research [5] shows that in the United States, there are differences in the myopia rate of children of different descent. The highest myopia rate is 18.5% for Asians, while only 4.4% and 6.6% for whites and black Americans. It points out that this is jointly affected by genetic and environmental factors. This may be due to related to the fact that Asian children are under more study pressure and the differences in educational methods between Asia and some western countries.

2.1.4 Regional distribution

The detection rate of ametropia in children is unevenly distributed in various regions, and the difference between urban and rural areas is obvious. The results of study [6] show that the detection rate of refractive errors in urban children is higher than that in rural children. There are significant differences in the prevalence of myopia between urban and rural children, and they all show an upward trend. This may be related to the gap between urban and rural economic income levels, heavy study tasks for urban children, more exposure to electronic products, more rural population, but less testing.

2.2 Physiological factors

2.2.1 Genetic factors

Parental myopia is a risk factor for ametropia in preschool children. At present, the genetic patterns of abnormal vision in clinic are mainly divided into autosomal inheritance and X-chromosome inheritance. Autosomal inheritance has nothing to do with gender, and the prevalence of children is 50%. In X-chromosome inheritance, the prevalence of women and the probability of carrying disease genes are higher than that of men. Zhang G.Y. [2] study showed that the incidence rate of abnormal vision in all age groups was significantly higher than that in family history without myopia and related ophthalmopathy (x^2= 48.08, P<0.001), which is consistent with the results of Long Qi [7].

2.2.2 Perinatal factors

Preterm birth, low-birth-weight infants, history of fetal protection treatment during pregnancy, history of asphyxia and oxygen inhalation in children, and history of smoking in mother's pregnancy are the influencing factors of children's ametropia. According to the screening of 7886 ametropic children in Haiyan County by Zhou Y.L. [8], children with a history of preterm birth and low birth weight have a high rate of refractive abnormalities. Some studies believe that it is due to the improvement of the current technical level, the survival rate of some low-birth-weight infants and preterm infants has also increased, the incidence of retinopathy in preterm infants is higher, and the blindness rate is significantly higher than that of full-term infants. The investigation results of Fan T, Shi H.Q. [9] and others showed that the infection of Toxoplasma gondii, rubella virus and other microorganisms during pregnancy and adverse drugs in patients with a history of pregnancy fetal protection treatment would lead to a higher rate of visual impairment during pregnancy than those without that, and the difference was significant. The research of Zhang G.Y. [2] shows that the rate of low visual acuity of those with intrapartum asphyxia is higher than those without asphyxia, and the difference is significant. Therefore, avoiding intrapartum asphyxia can reduce the ultraviolet radiation in neonatal warm box phototherapy and reduce the occurrence of fundus lesions. At the same time, At the same time, a study [8] found that the proportion of abnormal refraction of babies born to pregnant women with smoking and alcohol history was higher than that of normal children (P<0.05). Therefore, it is very important to prevent ametropia in children and carry out health care and physical examination during pregnancy.

2.3 Lifestyle factors

2.3.1 Activity factors

Outdoor activities, bad eye habits, use of electronic products and participation in after-school interest classes are the influencing factors of children's ametropia. Bad eye habits, including long-time eye use, not paying attention to active rest, too close eye use, etc., lead to excessive or harmful eye use, which will lead to abnormal vision of children. Tang M.H. [10]'s

research shows that outdoor exercise is a protective factor for ametropia because appropriate outdoor activities are conducive to reducing the synthesis of melatonin in the retina and increasing the content of dopamine. Long Qi [7] showed that many kinds or long time of bad eye use are independent factors affecting children's abnormal vision. Xie J.Y.'s research shows that children who participate in after-school interest classes are more likely to have abnormal vision. This result may be related to the fact that children who participate in after-school interest classes spend too much time with their eyes and do not pay attention to maintaining good eye habits.

2.3.2 Disease factors

Some disease factors may also lead to abnormal vision, which may be caused by the transmission of some pathogens to the eyes. For example, Jia Wei [4] found that allergic rhinitis is an independent risk factor for ametropia in children. Allergic rhinitis can lead to long-term eyes without rest and visual development disorders.

2.3.3 Dietary factors

Children's picky eating and chewing will affect children's nutritional status, resulting in abnormal vision. Xie J.Y. [11] found that children with picky eating habits will lead to abnormal vision (x^2= 6.398, $P<0.05$). Picky eating habits will lead to the lack of some trace elements (such as selenium, zinc, chromium, and other elements closely related to the incidence of myopia), and damage the structure of eye fundus tissue, thus affecting vision. Picky eating habits may also lead to children's light weight. Zhang G.Y. [2] found that the abnormal visual acuity rate of children in the group with weight lower than two standard deviations was higher than that in the group with normal weight (X^2= 7.70， $P<0.05$). Zhou M.Y. [12] showed that regular eating of green vegetables (OR=0.122) and hard food (OR=0.357) are the protective factors of children's refractive error.

2.3.4 Sleep factors

Children have enough sleep time is the protective factor of ametropia. Fan T [9] found that sleep time (≥8 hours) is a protective factor for children's vision. Less sleep time can affect people's overall mental state and physical constitution, which is associated with myopia.

2.3.5 Family environmental factors

Family environmental factors include physical environmental factors such as family lighting environment, social environmental factors such as parents' educational level and income level, parents' cognitive behavior of children's vision protection, etc. Some studies have pointed out that led lamps at home are more likely to cause myopia in children than incandescent lamps or fluorescent lamps. The reason is related to the continuous flashing light of LED lamps. Experiments have proved that the continuous flashing light can induce the binding of 5-HT and 5-HT2A receptor, resulting in progressive myopia in guinea pigs. Zhang G.Y.'s research shows that the children of fathers with higher education have a higher rate of normal vision. This may be related to the fact that parents with higher educational level pay more attention to their children's vision protection and can scientifically arrange their children's learning and activity time. Zhou Y.L.'s survey showed that the proportion of children with refractive abnormalities in low-income families was higher than that in other families ($P < 0.05$). This is contrary to the results of Xu LAN [13]. The reason may be that parents with higher education have high demands on children's study, which increases the length of children's eye use, and children in high-income families may use more electronic products.

Conclusion

Preschool children are the key period of visual development, in which demographic factors, physiological factors and lifestyle factors have important influence on children's visual development. Therefore, it is of great significance to strengthen the visual screening of preschool children, publicize the knowledge of perinatal prevention and health care and the basic

health knowledge of correct eye use, to improve the adverse environment and take active outdoor activities, these are of great significance in restoring the visual development of preschool children.

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Effect of Two Kinds of Bone Replacement Materials on Bone Formation in Repairing Bone Defects Around Mandibular Posterior Area: a Case Study of Bone Defects Around Mandibular Posterior Area Caused by Boxing

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Abstract: Objective: To investigate the effect of two kinds of bone replacement materials on bone formation in repairing bone defect around mandibular posterior area. Methods: A total of 60 patients with Bone defects around mandibular posterior area caused by boxing were selected from a hospital from January 2020 to June 2020. They were divided into Perio Glas (group P) and Bone Plant (group B) by random number table method, with 30 patients in each group. Perio Glas Bone graft was used in group P and Bone Plant graft was used in group B. The vertical height and buccal lingual bone plate width of the two groups were observed at baseline and after treatment, and the success rate of implants was compared between the two groups. Results: The success rate of implant in group P was significantly lower than that in group B ($P < 0.05$). The vertical height and buccal lingual bone plate width in group P were significantly lower than those in group B ($P < 0.05$). Conclusion: Compared with Perio Glas, Bone Plant can better maintain the vertical height and buccal lingual Bone plate width of patients with Bone defects around mandibular posterior area caused by boxing, and has better effect of inducing Bone regeneration and osteogenesis.

Keywords: Materials; The Mouth; Bone Regeneration; Implant

1. Introduction

Oral and maxillofacial injuries are the most common injuries in boxing. Oral and maxillofacial injuries caused by boxing are characterized by high incidence, high treatment cost and long treatment time, etc., and have long been the issue of highest concern []. Guided bone regeneration technology has been clinically established in the field of bone graft repair of bone defects []. At present, Perio Glas and Bone Plant are artificial inorganic Bone replacement materials commonly used in oral and maxillofacial bone grafting to repair bone defects. Perio Glas and bone plant have different physical and chemical properties and osteogenic properties. There are few reports on the effect of Bone regeneration and osteogenesis induced by Perio Glas and bone plant in repairing bone defects around mandibular posterior area. In order to provide reference for the clinical treatment of the bone defects around the mandibular posterior teeth caused by boxing, the effects of two kinds of bone replacement materials on the bone formation of the defects around the mandibular posterior teeth were studied.

2. Material and methods

2.1 General information

A total of 60 patients with Bone defects around posterior teeth caused by boxing were selected from A hospital from January 2020 to June 2020. They were divided into Perio Glas (group P) and Bone Plant (group B) by random number table method, with 30 patients in each group. P group, gender: 18 males, 22 females; The age ranged from 52 to 79 years, with an average of (68.81±5.25) years. Group B, gender: 17 males and 23 females; The age ranged from 53 to 80 years, with an average of (68.43±5.14) years. Inclusion criteria: Cone-beam CT examination indicated bone defects around the mandibular posterior tooth area, and immediate implant treatment was planned; The remaining buccal and lingual width of the implant

site and the height of the remaining bone were sufficient. Exclusion criteria: severe bone defect, periodontal disease and gingivitis; Malocclusion, night bruxism and lateral mastication.

2.2 Material

Perio Glas (manufacturers: American states biological products co., LTD., approval number: feed the drug safety machinery (into) the word no. 2003585, 2015 materials and ingredients: silicon dioxide, sodium oxide, calcium, phosphorus pentoxide, biocompatibility: good, indications: periodontal bone defects, maxillofacial surgery, bone defect filling, adverse reactions: Not). Bone Plant (Manufacturer: EZEKIEL Company, Korea, Approval No. : China Food and Drug Administration Wu (Jin), 2015 No. 3510312, material composition and composition: hydroxyapatite, tricalcium phosphate, biocompatibility: good, indication: periodontal Bone defect, maxillofacial surgery Bone defect filling, adverse reaction: none).

2.3 Surgical method

Minimally invasive flap implantation was used in both groups. 0.2% compound chlorhexidine gargled for 2.0-3.0 min, routine disinfection area of iodophor was covered with towel, local infiltration of lidocaine anesthetized mandibular rear tooth planting area, residual teeth were extracted, granulation tissue was removed, and physiological saline was rinsed. Alveolar ridge top horizontal incision to stick under the periosteum, buccal do zhang incision reduction, stripping periosteum separator sticky periosteal flap, exposed alveolar bone, pioneer drilling and reaming, parallel bar detection embedded direction, step by step to enlarge Kong Bei hole diameter, default saline flushing, observe the granulation tissue residue, implants implanted suitable types, manual torque, torque wrench Ensure that the implant torque > 35 N•cm to ensure the initial stability of the implant, implant covered with screws. Perio Glas or Bone Plant were implanted into the Bone defect area around the implant, and bio-Gide bio-collagen membrane was cut into appropriate size to cover the Bone replacement material, and the window was tightly sutured to ensure no Bone powder and periosteal exposure in the operative area. Postoperative oral antibiotics for 6 d, oral losolprofen sodium tablets or ibuprofen sustained-release capsules for local analgesia, 1 week later, stitches removed. Six months after the operation, the abutment was installed and repaired, the abutment horizontal impression model was made, the fixed denture was made, and the abutment was connected and fixed by 4 ~ 6 longitudinal screws.

2.4 Observation target

Implant success rate: evaluated 12 months after treatment, success was defined as no loosening of the implant, radiology suggested no low-density shadow around the implant, bone absorption less than 0.2mm after implant loading, and no discomfort, pain, numbness and other symptoms.

Bone tissue indicators: Cone-beam CT was taken at baseline and 12 months after treatment to measure the width and vertical height of buccal and lingual bone plates. The width and height of alveolar bone in the dental implant area were measured along the buccal and lingual bone plates, respectively, and the mean value of 3 measurements was taken.

2.5 Statistical method

All data were statistically processed by SPSS 20.00 statistical software. If the measurement data were normally distributed, the comparison between groups was performed by independent sample T test in the form of mean ± standard deviation (). The counting data were expressed in the form of N (%) by chi-square test. Test level α=0.05.

3. Results

3.1 Comparison of implant success rate between the two groups

The success rate of implant in group P was significantly lower than that in group B ($P < 0.05$). See table 1.

Table 1 Comparison of implant success rate between the two groups [N (%)]

Group	Number of implants	Failure	Successful
P	67	12（17.91）	55（82.08）
B	65	4（6.15）	61（93.84）
X^2			4.281
P			0.000

3.2 The vertical height and buccal lingual plate width of the two groups were compared at baseline and after treatment.

The vertical height and buccal lingual bone plate width in group P were significantly lower than those in group B (P < 0.05). Are shown in table 2.

Table 2 Comparison of vertical height and buccal and lingual plate width between baseline and after treatment [$\bar{x} \pm s$]

Group	Vertical height（mm）	Width of the buccal-tongue side bone plate（mm）
P（*n*=30）		
Baseline period	1.46±0.25	4.66±0.45
Post-treatment	4.15±0.33	5.09±0.46
B（*n*=30）		
Baseline period	1.44±0.27*	4.60±0.54*
Post-treatment	5.13±0.48△	6.27±0.51△

Note: Compared with P group, t=0.297, 0.467, *P > 0.05; T =9.215, 9.410, △P < 0.05.

4. Discussion

After the defect of bone around the mandibular posterior area, the alveolar bone is absorbed due to the increase of occlusal load and lack of corresponding physiological stimulation, and the residual alveolar bone width is often insufficient. Oral implant repair In order to achieve good oral aesthetics and long-term implant stability, patients treated with implant implantation need guided bone regeneration therapy to support the required bone mass during implant implantation []. Guided bone regeneration technology uses biofilm barrier to protect bone defects and bone replacement materials, block the external influence on the bone graft area, promote the generation of bone regeneration fibrocells, and support the space required for osteogenesis of osteoblasts, which can effectively solve the problem of bone defects encountered in implant surgery.

In Perio Glas, calcium and phosphorus can form carbonate hydroxyapatite layer under the influence of P-H value, causing calcium and phosphorus plasma migration, calcium phosphate and silicon release, stimulating osteoblast proliferation, further generating collagen fibers, forming bone-bioglass interaction interface, and mediating bone regeneration. However, Perio Glas has certain limitations. Perio Glas bioglass has high brittleness, and the planting effect is not ideal for planting areas with excessive pressure load []. Bone Plant is a new concept 3D-channel matrix porous massive Bone replacement material, which is designed and improved on the basis of traditional Bio-OSS theory. It is composed of 60% hydroxyapatite and 40% tricalcium phosphate, and is a hexahedral tubular honeycomb structure. Compared with the traditional Bio-OSS particles, the defects of bone meal loss and difficult to maintain the spatial structure of the defect site in the process of bone grafting can be solved to a certain extent. For large bone defects, the matrix porous block bone structure can retain the block shape. For small bone defects, the bone can also be crushed into granular shape, with flexibility and practicality. After Bone Plant is broken, it becomes a cavity structure instantly due to the special 3D-channel structure, which is stably fixed at the Bone defect site and can maintain a certain area of Bone graft. After gently pressing, the cavity structure is closed instantly, forming a dense and closed Bone graft effect, which significantly reduces material flow, dispersion and displacement. Secondly, the porous structure of Bone Plant can absorb part of blood to play a hemostatic role, and can increase the contact

between artificial Bone meal and blood hemoglobin factor, providing blood supply and nutrients for new Bone regeneration. The porous structure of Bone Plant can effectively absorb Bone marrow blood, thus leading to Bone conduction and inducing Bone tissue regeneration. Therefore, Bone Plant has more advantages in maintaining the spatial structure stability of regenerated Bone [].

5. Conclusion

In order to more objectively verify the effect of two bone replacement materials on bone formation in repairing the bone defect around mandibular posterior area, t test was used to compare the bone tissue indexes of vertical height and buccal and lingual bone plate width of the two groups at baseline and after treatment, and chi-square test was used to compare the success rate of implants between the two groups. The results showed that the success rate of implant in group P was lower than that in group B. The vertical height and buccal lingual bone plate width of group P were lower than that of group B. In conclusion, compared with Perio Glas, Bone Plant can better maintain the vertical height and buccal lingual Bone plate width of patients with Bone defects around the mandibular posterior area caused by boxing, and has a better effect of inducing Bone regeneration and osteogenesis.

In conclusion, this study investigated the effect of two bone replacement materials on bone formation in repairing the bone defect around the mandibular posterior area.

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Analysis of HER2 Gene Amplification and Certain Prognostic Factors in Breast Cancer

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Abstract: Objective: The HER2 gene amplification and certain prognostic factors in breast cancer were analyzed. Method: The gene amplification and protein expression of human epidermal growth factor receptor in 100 breast cancer tissues detected by FISH and IHC detection method in the hospital from January 2020 to December 2021 were analyzed. To analyze some breast cancer prognostic factors. Result: 0 is 8 cases of HER-2 protein breast cancer, (1+) is 11 cases, (2+) is 49 cases, (3+) is 32 cases. The HER2 gene was amplified in 49 cases, of which 23 cases showed red signals in clusters, and 26 cases showed red signals in dots. 51 cases of HER-2 gene were not amplified. There are differences in the detection results of FISH and IHC detection methods (P＞0.05). ER, PR and polysomy of chromosome 17 are prognostic factors associated with HER2 gene amplification in certain breast cancers. (P＜0.05) Conclusion: To analyze the HER2 gene amplification in breast cancer and targeted select FISH and IHC detection methods can improve the therapeutic effect and prognostic factor, which deserves clinical attention.

Keywords: Breast Cancer; HER2; Gene Amplification; Prognostic Factors

Introduction

Breast cancer is an uncontrolled proliferation of mammary epithelial cells under the action of various carcinogenic factors. Breast cancer has become the number one killer of women's health. The HER2 gene is an epidermal growth factor, and HER2 gene amplification indicates that the tumor has a higher degree of malignancy than non-amplified tumors. HER2 gene amplification is a gene infiltration of breast cancer and is a key gene marker for the diagnosis of breast cancer. Some scholars found that breast cancer patients with HER2 gene amplification are resistant to certain chemotherapy drugs. The prognosis of patients is poor, and recurrence and metastasis occur earlier, which directly affects the overall survival of patients.[1] At present, HER2 gene amplification has been used as an important reference for judging the prognosis of breast cancer. Therefore, by taking effective methods to detect the HER2 gene amplification in breast cancer, it can directly provide the best treatment and prognosis for patients. The details are as follows:

1. Data and Method

1.1 General Data

The gene amplification and protein expression of human epidermal growth factor receptor in 100 breast cancer tissues detected by FISH and IHC detection method in the hospital from January 2020 to December 2021 were analyzed. To analyze some breast cancer prognostic factors. The 100 patients were all female, with an age range of 28 to 72, and an average age of 44.32±3.33. Inclusion criteria: ① All patients were aware of the study and agreed. ② All patients had breast cancer. ③ The patients were all female. Exclusion criteria: ① The medical history data is incomplete.

1.2 Method

FISH Detection Method: All patients were detected by Fluorescence in Situ Hybridization. First, fix the sample, do

sample preparation, pre-treatment and pre-hybridization. We do a good job of denaturing probes and samples, and use different probes to hybridize to detect different target sequences. Unbound probes are removed by washing, the hybridization signal is detected, and the results are analyzed.

IHC Detection Method: They were fixed in 4% central formaldehyde, embedded in conventional paraffin, sectioned at 4um, and stained with HE. Immunohistochemical staining was performed by MaxVision method, and primary antibodies were ER, PR and HER-2.

1.3 Observation Target

Analysis of HER-2 protein and HER-2 gene.

The HER-2 gene was analyzed by FISH and IHC detection methods.

The relationship between some prognostic factors of breast cancer HER2 gene amplification was analyzed from the aspects of age, histological grade, lymph node metastasis, ER, PR and polysomy of chromosome 17.

1.4 Statistical Method

The data were included in SPSS 20.0 software for analysis, measurement data were compared using t test, and represented by ($\bar{x} \pm s$), and rate count data were examined by $\chi 2$ test, which was represented by rate (%), ($P<0.05$) was considered to be significantly different, with statistical significance.

2. Result

2.1 Analysis of HER-2 protein and HER-2 gene

HER-2 protein: In breast cancer, 0 is 8 cases, accounting for 8%; (1+) is 11 cases, accounting for 11%; (2+) is 49 cases, accounting for 49%; (3+) is 32 cases, accounting for 32%.

HER-2 gene：The HER-2 gene was amplified in 49 cases, of which 23 cases showed red signals in clusters, and 26 cases showed red signals in dots. 51 cases of HER-2 gene were not amplified.

2.2 Analysis of FISH and IHC test results

IHC detection: (0~1+) 18 cases, (2+) 34 cases, (3+) 6 cases. FISH detection: (0~1+) 4 cases, (2+) 20 cases, (3+) 18 cases. Two groups (0~1+) ($X^2=10.010$, P=0.002), (2+)（$X^2=4.972$，P=0.026), (3+) ($X^2=6.818$, P=0.009). The data show that there are differences in the detection results of the FISH detection method and the IHC detection method. (P>0.05)

2.3 Analysis of the relationship between some prognostic factors of HER2 gene amplification in breast cancer

The data showed that age, histological grade, and lymph node metastasis were not significant($P>0.05$), ER、 PR and polysomy of chromosome are prognostic factors associated with HER2 gene amplification in some breast cancers. ($P<0.05$) .Table 1 shows that.

Table 1 **Analysis of the relationship between some prognostic factors of HER2 gene amplification in breast cancer [n,(%)]**

Groups	cases	-	+	χ^2	P
Age（years）					
<50	49	26	23	0.243	0.622
≥50	51	27	24		
Histilogical grade					
I					
II	9	5	4	0.116	0.733
III	77	45	32		
ER	14	9	5		
-					
+	33	11	22	4.391	0.036
	45	30	15		
PR					
-	35	11	24	5.853	0.016
+	43	31	12		
polysomy of chromosome 17					
-					
+	76	45	31	4.160	0.041
	24	7	17		
lymph node metastasis					
exist	55	26	29	0.226	0.635
absent	45	22	23		

3. Discussion

Human epidermal growth factor receptor 2 over-expression is closely related to the degree of cancer progression in more epithelial cells. Tumors with high HER2 expression show strong metastatic ability and infiltration ability, are less sensitive to chemotherapy, and are extremely prone to recurrence. When the normal HER2 expression level is low, the expression level is high during embryonic development, which plays an important role in cytoplasmic proliferation, differentiation and migration during development. Abnormalities of the HER2 gene have been found in breast, ovarian, and gastrointestinal cancers. In HER2 breast cancer, over-expression is generally detected by immunohistochemistry.[2] Gene mutations are detected by gene sequencing.Gene amplification was detected by in situ fluorescence hybridization. Generally, the HER2 gene is amplified at the DNA level, which is almost manifested in protein over-expression, which can be confirmed in breast cancer. Breast cancer HER2 gene amplification rate will reach 15% to 20%, overexpression will reach 15% to 20%.[3]

FISH detection is an in situ fluorescence detection technology, that is, a specific labeled nucleic acid with a known sequence is a process in which the probe hybridizes with the nucleic acid in the cell or tissue section, so as to accurately quantitatively locate the specific nucleic acid sequence. In situ fluorescence detection technology does not require radioisotope labeling, and can simultaneously detect multiple sequences in the same sample through different labeled probes.[4]In situ fluorescence detection techniques take direct and indirect labeling methods. The direct labeling method means that fluorescein is directly covalently bound to the probe nucleotide or pentose phosphate backbone, or that fluorescein

nucleoside triphosphate is incorporated when the probe is labeled by the nick translation method. The indirect labeling method means that the DNA probes are labeled with biotin and detected with fluorescein or streptavidin after hybridization. At the same time, the avidin-biotin-fluorescein complex can also be used to amplify the fluorescent signal. FISH testing is used to examine chromosome 17 centromere and HER-2 gene amplification in breast cancer. FISH detection has high sensitivity and specificity, and is an effective clinical detection method.[5] IHC is an immunohistochemical assay. Since the 1970s, immunohistochemistry has been used in pathological diagnosis, which has a great impact on tumor diagnosis and prognosis. At the same time, it also expands people's understanding of various diseases and tumor formation processes, and improves the level of pathological diagnosis and research. The samples for immunohistochemistry are mainly frozen or paraffin-embedded tissues. The tissue was sliced into slices about 4μm thick and sealed before processing. Pathological diagnosis means performing histological examination under the microscope after the tumor specimens removed by surgery or autopsy are fixed and stained to facilitate the diagnosis of the disease. [6] IHC immunohistochemistry is a common clinical detection method for HER-2 receptor protein. IHC is simple to operate and has low cost. However, in the detection process, protein fixation specimens and processing are very easy to be damaged, resulting in lower detection accuracy. FISH detection has good stability and repeatability, and can be clearly displayed by microscope, which can make up for the shortcomings of IHC detection. This study analyzed the HER2 gene amplification in breast cancer and some prognostic factors of breast cancer. The result shows that, in the protein breast cancer, 0 is 8 cases of HER-2，(1+) is 11 cases of HER-2, (2+) is 49 cases of HER-2, (3+) is 32 cases of HER-2. The HER-2 gene was amplified in 49 cases, of which 23 cases showed red signals in clusters, and 26 cases showed red signals in dots. 51 cases of HER-2 gene were not amplified. There are differences in the detection results of the FISH detection method and the IHC detection method. ($P > 0.05$). ER 、 PR and polysomy of chromosome are prognostic factors associated with HER2 gene amplification in some breast cancers. ($P < 0.05$) . For the prognostic factors of HER-2 gene amplification in breast cancer, it is believed that there is no relationship with age, histological grade, and lymph node metastasis, but there is a certain relationship with EP, PR and polysomy of chromosome 17. Therefore, in order to ensure the outcome of patients, targeted measures should be taken according to the actual influencing factors.

All in all, analysis of the HER2 gene amplification in breast cancer and targeted select FISH and IHC detection methods can improve the detection accuracy and indirectly improve the treatment effect, which is worthy of clinical attention.

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Covid-19 Diagnosis Based on CT Images Through Deep Learning and Data Augmentation

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Abstract: Coronavirus disease 2019(Covid-19) has made people around the world suffer. And there are many researchers make efforts on deep learning methods based on CT imgaes, but the limitation of this work is the lackage of the dataset, which is not easy to obtain. In this study, we try to use data augmentation to compensate this weakness. In the first part, we use traditional DenseNet-169, and the result shows that data augmentation can help improve the calculating speed and the accuracy. In the second part, we combine Self-trans and DenseNet-169, and the result shows that when doing data augmentation, many model performance metrics have been improved. In the third part, we use UNet++, which reaches accuracy of 0.8645. Apart from this, we think GAN and CNN may also make difference.

Keywords*:* Covid-19; DenseNet-169; Data Augmentation; CT Images

1. Introduction

The outbreak of covid-19 is a big challenge for the whole world. It has infected more than 240 million individuals and cause almost 5 million deaths. Nowadays, the most popular way to detect covid-19 is nucleic acid testing，but it needs about 3-6 hours and costs tons of money. So people are seeking for ways to diagnose covid-19 efficiently for some clinical resource limited areas, etc. Deep learning has made a lot of extraordinary results these years and has been proved that is a good way to help detect potential patients when the result of nucleic acid testing has not come out. In the field of deep learning, Convolutional Neural Network makes a big difference in image classification. After the groundbreaking work of AlexNet[1], we have witnessed many milestones that CNN achieved. With GPU, it's possible to train a CNN model very fast and with great accuracy. When training a CNN model, the model can probably be overfitted if the dataset is too small[2]. To overcome this obstacle, data augmentation is an efficient way. In our study, we use CT images of lung as our dataset and DenseNet-168[3] as our model. We also use horizontal flipped, vertical flipped and diagonal flipped for data augmentation. And also we train UNet++ to do segmentation to detect focus of infection.

2. Literature review

Recently, artificial intelligence has been widely studied and used in medical field, like diagnosing diseases, surgical robot, virtual nursing. Inside, there are various DL framework like RNNs, AEs, GANs. One of the hottest research topics is about COVID-19. A mass of essays have been published during this epidemic, which fall into three categories: detection of COVID-19, severity assessment and infection segmentation. In this paper we will discuss the study of the COVID-19 binary classification issue using CT images.

When searching for information and technology of detecting COVID-19, we find that an army of paper with keywords of "detecting COVID-19 with CT scans" and "machine learning with covid-19 diagnosis". In their work, the majority of them used machine learning technology and deep learning or convolution neural network (CNN), which truly attained certain results. Typically, Ardakani [4] gave a detailed view of ten representative CNNs with comparing their performances in detection of COVID-19 : VGG-16, GoogleNet, ResNet-18, Xception, ResNet-101, AlexNet, MobileNet-V2 and so on. Among them, Xception and ResNet-101both reached effective results- an AUC of 0.994, which is better than the radiologist's

AUC of 0.873.

Nevertheless, a large quantity of data is needed in deep learning methodology which is impossible to gain right now. The limited and unbalance data influence the performance of deep learning hugely, so many first-class scientists and doctors are trying to figure out this drawn backs-limited above. Currently, for refining the diagnose accuracy, there are lots of ways to be explored.

Firstly, using data augmentation technique, like affine transformation (rotation, translation, scaling, reflection, shearing), image mirroring. Recently Li et al. [5] reduce data scarcity by decomposing the 3D CT scan into multi-view slices as input data and integrate prior domain learning into their model. In the end, they achieved an obviously improved accuracy from 0.867 to 0.966. Zhou [6] combined several 2D models and Taylor et al. [7] utilized photometric and geometric to deal with the data-scarcity issue to enhance the effect of the model. Sameena et al. [8] used AdaBoost of decision stump trees to diminish the degree of overfitting and generalization and achieved an accuracy of 0.96, whose classifier is dynamically chosen depend on test sample' s characteristics. Kamrul et al.[9] proposed a 3D-CNN structure, which is integrated with segmentation, class-rebalancing, progressive resizing, augmentation and can expand training data through being trained on the 3D-CT patches to study the inter- and intra-slice spatial voxel information. Ozturk et al.[10] two-stage data enhancement approaches-a shallow image augmentation and the Synthetic minority over-sampling technique algorithm to solve the deficient and unbalanced data problem, which contributes to next to 10% performance.

In addition to the data, the suitable hyperparameter is also vital to determine the classification performance. Sameena et al. [8] used WOA-BAT optimization to choose hyperparameters of CNN and proved that using WOA-BAT optimized CNN performed superior to the standard CNN architecture. Priya et al.[11] offered a SqueezeNet structure network based ResNet-50, which is used for lung infection segmentation of CT and can be automatically optimized.

Transfer learning also has a satisfying performance in detecting COVID-19, which can reduce the dependence on data while achieving better accuracy. A sort model to diagnose COVID-19 is proposed by Ilyas LAHSAINI et al. [12] based on deep transfer learning and the DenseNet-201 architecture with 0.988 of accuracy. Tuan D Pham [13] has conducted a comprehensive study on the use of pre-trained CNNs for COVID-19 diagnosed. He investigated 16 pre-trained CNNs and concluded that CNNs can performed well after using several epochs training and DenseNet-201 did the best work, which can reach the highest average specificity of 0.9667. Additionally, he proved the transfer learning with using image slices not data augmentation can do better classification. Contrastive self-supervised learning and transfer learning are combined and utilized by He et al.[14] to study unbiased and useful feature representations and this framework achieved an AUC of 0.94 under limited training CTs. Maghdid et al.[15] created an image dataset containing a mass of CT and X-ray images and utilizede a pre-trained AlexNet structure on the dataset based on transfer learning and deep learning, resulting accuracy up to 0.98.

There is one more point that design fresh neural network framework. A sequence of new-style neural networks is being proposed all the time. Hong et al.[16] put forward a lightweight convolutional neural network model derived from the attention mechanism and depth-wise separable convolutions named MGMADS-CNN, which achieved accuracy of 0.9825 on CT images. M.Polsinelli et al.[17] presented a light oriented capsule network derived from the SqueezeNet and achieved 0.830 of accuracy. The light of it is to achieve a satisfying result on medium power computers, alleviate the requirement for hardware. Hu et al.[18] put forward one kind of new weakly supervised deep learning structure instead of commonly used supervised learning framework to learning from image-level label, which can reduce the dependence of manual labelling of images

Another important way is to combine several models to make diagnose. Rohit et al.[19] raised a method of integrating four pre-trained models with Sugeno fuzzy integral and achieving 98.93% accuracy. Sameena et al.[18] built their architecture by utilizing features selected from five CNN architectures. Ardakani et al.[20] nurtured twenty radiological features extracted using CT scans into five classifiers to develop the best CAD system performing in COVID-19 diagnose, which has an AUC of 0.965.

In addition to the above methods, there are still many other ones, like the “deep domain adaptation “which is used to deal with the shortage of labeled data, removing images from the majority classed to down sample.

In conclusion, they explored and optimized each process of deep learning classification by proposing new ways of their own. One same limitation of the majority studies is that their models' performances don't be compared with radiologists. It will be a better framework by combination of methods.

3. Research methods

This study, we used the dataset collected by[14], which reported the biggest public dataset so far of CT images for detection of Covid-19. As for the model, we chose DenseNet-169 as it has the best accuracy in the same article above. We also used Self-trans[14] like what they do because in their article, it's proved that this is a practical way to improve the accuracy. And data augmentation is what our work wants to research if it is useful for improve the efficiency of our model.

3.1 DenseNet-169

We use pre-trained DenseNet-169 model as our model and Stochastic Gradient Descent (SGD) as our optimizer. DenseNet-169 is one of the DenseNet models families, which are designed to work image classification. There is a parameter **k** , called growth rate, which refers to the number of extra channels in each layer, or the convolution kernel of each layer. If the channel of the input feature graph is **K**, then the channel number of the **L** layer is **K+(L-1)k**, because each layer accepts the characteristic graphs of all the previous layers, so this **k** can be very small, usually 12 will have a good result. We should note that the actual meaning of this **k** is the newly extracted features. There are 1 x 1 bottleneck layers applied before each 3 x 3 convolution layer followed by transition layer. Diverse kind of Dense-Net has different **k**. So they have unequable sizes and accuracies .This is the main difference.

DenseNet exploit the potential of the network through feature re-use[1].This means that every layer can re-use the features produced by all previous layers. By doing so, it can deal with the degradation problem and vanishing gradient. DenseNet can be said to be an implicit strong supervision mode, because each layer establishes a connection with the previous layer, and the error signal can be effortlessly propagated to the former layer, so the earlier layer can obtain direct supervision from the last classification layer. At the same time, it has the characteristics of fewer parameters and higher computational efficiency. Besides, in DenseNet, it uses different levels of features, and it tends to give smoother decision boundaries. This also explains why DenseNet still performs well when training data is insufficient.

3.2 Self-trans + DenseNet-169

Transfer learning is a ideal way to mitigate data deficiency, which can use data rich source tasks to help learn target tasks with insufficient data through previously extracting useful features on big datasets and then finetuning the wights on the inefficient datasets. But there are some problems like the discrepancy in visual appearance and class labels between source data and target data, the over-parameterized pre-trained network.

For the sake of these problems, we integrate it with self-supervised learning(SSL), which is usually utilized to learn general representations without considering labels. But this time it is used to learn unbiased and powerful features without human annotations, which can get some intrinsic features and characteristics of the dataset. In other words, SSL is only based on data itself to learn meaningful results and satisfying performance. In this study, we construct some auxiliary tasks to provide self-supervision for the transfer learning process.

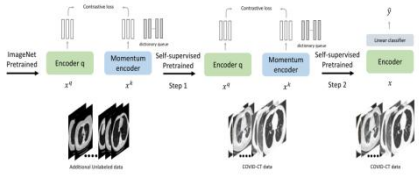

Figure 1 structure of Self-trans + DenseNet-169[31].

3.3 UNet++

3.3.1 Introduction to UNet++

UNet is a deep learning network using coder and encoder, which is widely used in medcal images segmentation problems.

To avoid the fusion of semantically dissimilar features of pure jump connections in UNet, UNet++ further strengthens th ese connections by introducing nested and dense jump connections, in order to reduce the semantics between encoder and dec

oder.

3.3.2 Our network Structure

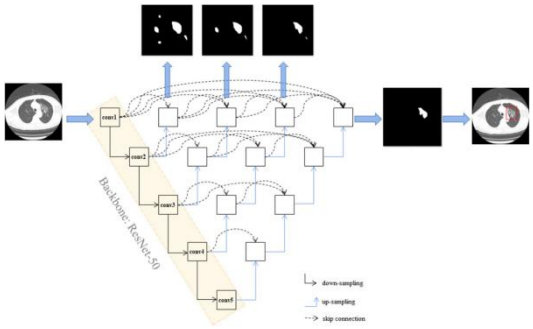

Figure 2 structure of our network

3.4 Data Augmentation

When the dataset is too small, it is likely that the model is overfitting. And data augmentation is a good way to solve this problem, because it helps the model extract more features from those images. We use horizontal flipped, vertical flipped and diagonal flipped as our methods to make the dataset larger. These ways do not change the nature of those CT images so the produced images share the same label with the original ones. We set 3 degrees as the flipped angle after lots of experiments that set different angles.

4. Result

4.1 DenseNet-169

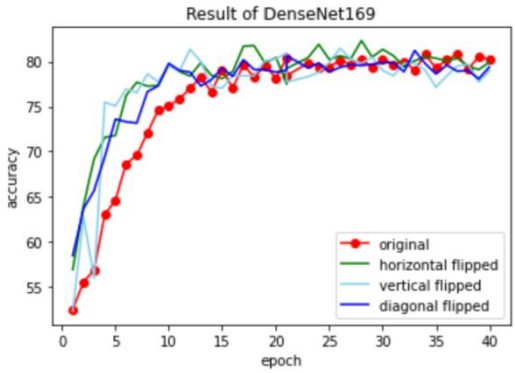

Figure 3 the result of DenseNet-169

The graph shows that data augmentation can improve before 15th epoch but its improvement is not evident after 15th epoch.

4.2 Self-trans+DenseNet-169

$$precision = \frac{TP}{TP + FP}$$

$$recall = \frac{TP}{TP + FN}$$

$$F1\ score = \frac{2 * precision * recall}{precision + recall}$$

We train the model with 200 epochs of train and 1 epoch of prediction. And the result is in TABLE 1. From the Table we can see that data augmentation did make a difference on improving the result, but not all data augmentation methods work. Self-trans+Horizontal flipped or Vertical flipped can improve the F1 score and accuracy apparently, but Self-trans + Diagonal flipped do not have an apparent effect, and the mix of 3 data augmentation methods make the result even worse than original results.

Table 1 The results after training the model with 200 epochs of train and 1 epoch of prediction.

	TP	TN	FN	FP	TP+FP
DenseNet-169 + self-trans	99	50	6	48	147
DenseNet-169 +self-trans + horizontal flipped	88	73	17	25	113
DenseNet-169 + self-trans+ vertical flipped	90	73	15	25	115
DenseNet-169 + self-trans+ diagonal flipped	72	85	33	13	85
DenseNet-169 + self-trans+ horizontal flipped + vertical fllipes + diagonal	82	61	23	37	119
	precision	recall	F1	acc	AUC
DenseNet-169 + self-trans	0.67	0.94	0.79	0.73	0.88
DenseNet-169 +self-trans + horizontal flipped	0.78	0.84	0.81	0.79	0.88
DenseNet-169 + self-trans+ vertical flipped	0.78	0.86	0.81	0.80	0.88
DenseNet-169 + self-trans+ diagonal flipped	0.84	0.69	0.76	0.77	0.87
DenseNet-169 + self-trans+ horizontal flipped + vertical fllipes + diagonal flipped	0.69	0.78	0.73	0.70	0.81

5. Discussion and conclusion

In our study, we chose DenseNet-169 as our model and used several data augmentation approaches to improve the accuracy of model. In the first experiment, the number of covid and noncovid images in training set are 234 and 191 respectively. Then we doubled the training set by using each of the 3 augmentation methods to produce one more image for each of the origin image in second, third and fourth experiment respectively. In the fifth experiment, we used all methods for origin images and enlarge the training set by 3 times. We also used self-trans to improve accuracy because this is a method that has been proved practical [19]. And we calculate the F1 score, test accuracy and AUC in each experiment.

As the results show, with F1 score and AUC almost the same, the test accuracy of second to fourth experiments are all 4% - 7% better compared with the benchmark accuracy, which means the accuracy became better when we only use one of the three methods of data augmentation. However, if we use all of these 3 methods in one (the fifth) experiment, all 3 measuring parameters became worse. This might because we use the same learning rate (0.001) in all 5 experiments, and it might be too large for the fifth experiment, the dataset in which is much bigger than the others. We noticed that during the training process in the fifth experiment, the train loss become oscillated after 7-8 epochs. According to previous articles [22], this is a sign of setting the learning rate too large.

The work published in [21] also used DenseNet-169 with self-trans and get an accuracy of 83% with the same dataset, which is 10% better than our first experiment (also used DenseNet-169 + self-trans), though their AUC and F1 score is almost the same as ours. We consider that one probable reason is that, according to the paper, they used unlabeled images from Lung Nodule Analysis (LUNA) for self-supervised learning, a learning form between supervised and unsupervised learning. However, we didn't do this due to the time limit.

One of the benefits of self-supervised learning is that it can solve the overfitting problem very well [23], which is also an advantage of data augmentation [24]. But our best accuracy, which was got in third experiment, is 3% worse than theirs,

though we our AUC is slightly better and we share the same F1 score. To improve our result, utilizing more data augmentation methods is a potential way. We only used horizontal flipped, vertical flipped and diagonal flipped, which are some basic ways for data augmentation. In Pham's paper[25], some other methods, such as reflection, horizontal translation, vertical translation, horizontal scaling and vertical scaling are also worth trying. And for those flipping method, it's a time-consuming work to test the best flip angle. If the angle is too small, than the produced images will be too similar to the origin images, which is not good for model to extract more features. If the angle is too big, than some part of lung shadow will fade out from the produced image. We tried several angles range from 1 to 5 with horizontal flipped as the data augmentation method and the result is almost the same. Furthermore, we have also thought of using GAN[26] for data augmentation, but GAN may change the nature of images, so we are not able to know the label of generated images, which was the problem that prevented us from using GAN to enlarge our dataset.

When it comes to the model we used, we chose DenseNet-169[27] because this net has the best accuracy according to[21]. Apart from this, we also used swin transformer[28] and unet++[29] with a new data augmentation method, mixup[30], and got very good results, with the accuracy of 84% and 86.5% respectively. However, it took too much time for us to write and tune these 2 nets and so far we have not known the F1 score and AUC of these 2 nets. In future work, we will continue working on complete the test results.

For the hyperparameters in DenseNet-169, we tried to modify some of those in[21] but didn't have good results. For instance, the images are resized to 224*224 originally, we tried some other scale, like 300*300 but the result is even worse. Therefore, we used hyperparameters the same as orinal ones. And for the function transforms.Normalize we used ((0.485, 0.456, 0.406), (0.229, 0.224, 0.225)), which is calculated by the mean and standard deviation of images in ImageNet. According to an answer in Stackoverflow, if images are special, like medical images such as CT or CXR images, than it's recommended to calculate the mean and standard deviation of images in our dataset to normalize our dataset better. This is also a time-consuming work and we don't have enough time to do this. We consider doing this will probably improve our test results. What's more, we tested both SGD and Adam as our optimizer, with learning rate=0.001, momentum = 0.9 for SGD and learning rate = 0.001 for Adam. The results are almost the same. But we consider using a lower learning rate, especially for the fifth experiment as mentioned above.

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