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Original Articles

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Case Report: Pneumocystis Pneumonia Following Liver Transplantation Identified by High-Throughput Second-Generation Gene Sequencing Technology

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Abstract: Pneumocystis, a fungus species, has emerged as one of the predominant infectious pathogens in immunocompromised patients, particularly in liver transplant recipients who require immunosuppressants. The pathogen colonizes the recipient's lower respiratory tract and induces a pulmonary infection. Respiratory failure is one of the leading causes of mortality in organ transplant recipients, as the disease progresses swiftly, its diagnosis is difficult, and it is simple for it to occur. This report details the case of a patient admitted to Calmette Hospital, affiliated with Kunming Medical University, diagnosed with pneumocystis pulmonary infection post liver transplantation. The diagnosis and successful treatment of the patient were facilitated by high-throughput second-generation gene sequencing technology based on metagenomics, enlightening future clinical diagnoses and treatments.

Keywords: Liver Transplantation; Pneumocystis; Metagenomics

1. Introduction

Pneumocystis pneumonia(PCP) is an opportunistic infection caused by pneumocystis pneumonia, which predominantly accumulates in the airways. Due to the disease's insidious onset and rapid progression, the lack of rapid and specific diagnostic methods in the past poses a grave threat to the lives of patients. This paper describes the successful treatment of pneumocystis pneumonia in a liver transplant recipient using Metagenomic next generation sequencing (mNGS) technology.

2. Case Presentation

A 28-year-old male was admitted to the hospital on February 17, 2021 with the chief complaint of "fever for six days, six months after liver transplantation." Six days prior to admittance, the patient experienced high fever (up to 41°C), cough, white and thin sputum due to a cold, along with chest discomfort, shortness of breath after activities, and fatigue. The physical examination of the patient revealed low vitality, minor coarse breath sounds in both lungs, and no evident rales. There were no positive abdominal indications. The patient underwent allograft orthotopic liver transplantation on September 20, 2020 at a different hospital due to acute liver failure and chronic viral hepatitis B. He recovered well and was discharged. The patient was given Tacrolimus sustained release capsule 4 mg/day, Sirolimus 1 mg/day, Prednisone acetate 5 mg/day, and Tenofovir alafenamide Fumarate tablets 25 mg/day after being discharged. Mycophenol sodium enteric-coated tablet 360 mg, twice daily; Ursodeoxycholic acid capsule 250 mg, twice daily. Regular follow-up in other facilities and discontinuation of hormone therapy.The patient was diagnosed with acute rejection following liver transplantation after undergoing a liver biopsy on January 6, 2021 due to irregular use of anti-rejection medications. In addition to Methylprednisolone pulse therapy, the patient received Tacrolimus sustained release capsule 7 mg/day, Sirolimus 1 mg/day, and Propofol tenofovir fumarate tablets 25 mg/day. Ursodeoxycholic acid capsule 250 mg/time, Mycophenolate sodium enteric-coated tablets 540 mg/time, and Kadsura japonica L. soft capsule 0.6 g/time, all three administered twice daily. The patient's condition improved following treatment, and he was discharged from the hospital.At the time of admittance, the patient was taking Tacrolimus sustained-release capsules 4 mg per day, Sirolimus 1 mg per day, Prednisone acetate 5 mg per day, and Tenofovir propofol fumarate tablets 25 mg per day. Ursodeoxycholic acid 250 mg twice daily and Mycophenolate sodium enteric-coated 360 mg twice daily.White blood cell count was $14.28*10^9$/L, neutrophil percentage was 75.7%, C-reactive protein was 118.77 mg/L, procalcitonin was 0.995 mcg/L, and fungal 1, 3-β-D-glucan (G test) was 235.73 pg/ml. The ratio between $CD4^+$ T cells and $CD8^+$ T cells was 1.11, and the concentra-

tion of FK506 in the blood was 6.2 ng/ml. alanine aminotransferase was 199 unit/L, aspartate aminotransferase was 161 unit/L, γ-glutamyl transpeptidase was 1160 unit/L, and alkaline phosphatase was 278 unit/L. The serum creatinine concentration was 60.3 umol/L. Negative IgM serum antibodies were detected against respiratory syncytial virus, adenovirus, influenza A virus, influenza B virus, parainfluenza virus, Chlamydia pneumoniae, Legionella pneumophila bacteria, and Mycoplasma pneumoniae. Negative results were obtained for the Aspergillus galactomannan test (GM test), sputum bacterial culture, fungal culture, and blood culture. Chest radiograph revealed radiographic evidence of pneumonia in both lungs, specifically pulmonary infection (Figure 1A). Chest computed tomography (CT) revealed extensive infectious exudative lesions in both lungs (Figure 1B). The patient was diagnosed with pulmonary infection and received antibacterial therapy with Cefoperazone sodium and sulbactam sodium 3 g every 8 h, as well as the initial dose of Caspofungin 70 mg, followed by 50 mg daily. Prednisone acetate was discontinued, Sirolimus was reduced to 0.5 mg once daily, Mycophenolate sodium enteric-coated tablets were reduced to 180 mg twice daily, and all other oral medications were continued at the original dose. However, the patient continued to exhibit elevated fever and worsening dyspnea. Analysis of arterial blood gases revealed that PaO^2 was less than 70 mmHg. The medication was altered on February 24 to include Imipenem and cilastatin sodium 0.5 g every 8 h, Micafungin 100 mg once daily, and Compound Sulfamethoxazole 0.96 g four times daily. The reexamination of the chest X-ray on February 25 revealed signs of bilateral pneumonia, including pulmonary infection and dense local lesions, and bilateral pneumonia that was more severe than before (Figure 1C). To prevent pulmonary fibrosis and rejection, intravenous Methylprednisolone 40 mg was administered daily. Imipenem was discontinued immediately, while Micafunzin and Compound Sulfamethoxazole were continued for two and three weeks, respectively. Simultaneously, Methylprednisolone was gradually discontinued. A reexamination of the patient's chest computed tomography(CT) on March 12 revealed extensive infectious exudative lesions in both lungs that were largely absorbed (Figure 1D). The blood concentration of FK506 was 4.9 ng/ml. Total bilirubin was 16.46 mol/L, direct bilirubin was 10.07 umol/L, and indirect bilirubin was 6.39 umol/L. Additionally, alanine aminotransferase was 77 unit/L, aspartate aminotransferase was 64 unit/L, -glutamyl transpeptidase was 527 unit/L, and alkaline phosphatase was 67 unit/L. The levels of serum creatinine, 1, 3--D-glucan (G test), and procalcitonin were 50umol/L, 46.48 pg/ml, and 0.119 mcg/L, respectively. Immunosuppressive therapy included oral Tacrolimus sustained release capsule 4 mg/day and Sirolimus 1 mg/day. Mycophenolate sodium enteric-coated tablets, 180 mg twice per day. Close post-discharge monitoring revealed that the patient did not experience chest tightness, shortness of breath, or abnormal physical activity.

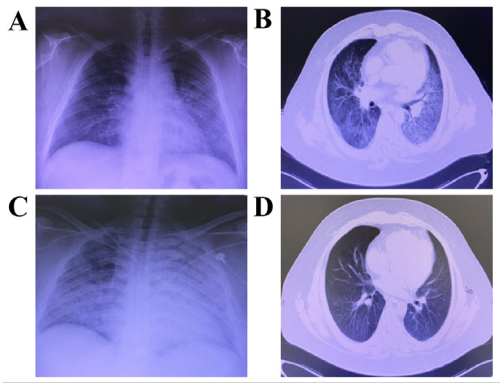

Figure 1 Chest X-ray on 17 February (A) , Chest computed tomography on 17 February (B), Chest X-ray on 25 February (C) ,Chest computed tomography on 12 March(D)

3. Discussion

Pneumocystis pneumonia (PCP), now referred to as Pneumocystis jirovecii pneumonia, is a fungal infection that typically affects immune function. This includes those with acquired immunodeficiency syndrome, organ transplant recipients, and individuals undergoing chemotherapy for malignant tumors or with autoimmune diseases. It also carries a high morbidity and mortality rate [1-2]. Due to the use of a large number of immunosuppressants in the early phase of anti-rejection after liver transplantation, the recipient's immunosuppression is severe, and the majority of cases develop within 6-9 months, more than 70% of cases develop within 12 months after liver transplantation, but

the development can occur as early as 1-3 weeks after liver transplantation [3-4]. The incidence rate among organ transplant recipients ranges from 5 to 15%, and the mortality rate can reach as high as 38% due to atypical clinical manifestations, rapid disease progression, critical illness, and difficulties in diagnosis and treatment, [5-6]. Therefore, rapid and accurate identification of pathogenic microorganisms and early clinical interventions are crucial for reducing mortality and enhancing the prognosis of PCP patients.

PCP is believed to be transmitted from person to person via the airborne route, asymptomatic colonization of the lungs may occur in individuals with healthy immune systems, and these individuals may unwittingly serve as reservoirs for Pneumocystis transmission to immunocompromised individuals [7].The clinical manifestations of PCP are fever, cough, chest tightness, dyspnea, etc., and the positive signs of specialist physical examination are usually less, dyspnea gradually appears within 1-2 weeks, and respiratory failure will occur in serious cases. The pulmonary signs are often not proportional to the severity of respiratory distress.In the typical imaging examination for PCP, chest X-rays demonstrate bilateral perihilar diffuse infiltrates, which become progressively more severe as the disease progresses. The computed tomography(CT) examination revealed shadows of ground glass density or cystic lesions. The primary diagnostic criterion for PCP still necessitates the detection of respiratory bronchoalveolar lavage fluid or sputum samples, but the vast majority of patients are critically ill and cannot tolerate it, thereby impeding clinical operations. If a pathogen infection is caused by a complex pathogen, deficiencies such as a lengthy cycle and limited precision can lead to diagnostic delay or neglect [7]. Due to the time-consuming and low positive detection rate of conventional detection methods, there is an imperative need for pathogen detection and identification techniques with greater diagnostic efficacy.

The rapid development of mNGS technology in recent years has made it a potent tool in medical microbiology, particularly for the detection of uncommon or emerging pathogens. mNGS has greater diagnostic advantages than conventional methods and provides a theoretical foundation for the diagnosis of human pathogens [8]. As a novel DNA/RNA sequencing technique, mNGS can directly extract the sample's nucleic acid sequence for detection, and then acquire pathogen data via bioinformatics analysis, which can theoretically identify all microorganisms [9]. Compared to the sequencing technology of the first generation, mNGS has thediagnostic advantages of high efficiency, high throughput, high sensitivity, and low cost [10]. It has been demonstrated that mNGS has a high clinical application value in the etiological detection and identification of respiratory tract infection [11].

This patient's primary clinical symptoms were fever, cough, expectoration, chest constriction, and shortness of breath. Specialized physical examination and supplementary examination revealed no evidence for the diagnosis of PCP.Due to the patient's severe hypoxemia and inability to cooperate with the operation, bronchoalveolar lavage was not performed at the time of admission. The symptoms were initially relieved by empirical broad-spectrum antibiotic therapy, but they progressively deteriorated until dyspnea developed. The results of a routine blood test revealed that the white blood cell and neutrophil counts were lower than in the past, indicating the absence of a bacterial infection. The result of G test was increased, and the possibility of fungal infection with rare pathogens was considered. The diagnosis was confirmed using mNGS technology, the treatment plan was actively modified, and the patient's condition improved progressively. In our experience, PCP should be considered and mNGS should be performed when pulmonary infection occurs in liver transplant recipients whose pulmonary signs are not proportional to the severity of respiratory distress, when traditional etiological tests are repeatedly negative, and when conventional anti-infective therapy is ineffective. After diagnosis, Compound Sulfamethoxazole tablets and Micafungin combination therapy is advised. The combination therapy was effective in treating this case, and it is deserving of applicability in PCP cases.

In conclusion, organ transplant recipients have a compromised immune system, mNGS technology should be utilized when mixed pathogens and rare pathogens are suspected in clinical diagnosis and treatment, particularly in the case of severely ill patients who who require prompt diagnosis to reduce the duration of bacterial and fungal infections and promote targeted antimicrobial treatment. The use of mNGS technology provides significant benefits in terms of improving the recipients' prognosis.

References

[1] Sokulska M, Kicia M, Wesołowska M, et al. Pneumocystis jirovecii-from a commensal to pathogen: clinical and diagnostic review[J]. Parasitol Res, 2015, 114 (10): 3577-3585.

[2] She WH, Chok KSH, Li I, et al. Pneumocystis jirovecii-related spontaneous pneumothorax, pneumomediastinum and subcuta-ne-

ous emphysema in a liver transplant recipient: a case report[J]. BMC Infect Dis, 2019, 19(1):66.

[3] Choi YI, Hwang S, Park GC, et al. Clinical outcomes of pneumocystis carinii pneumonia in adult liver transplant recipients[J]. Transplant Proc, 2013, 45(8):3057-3060.

[4] Sarwar S, Carey B, Hegarty JE, et al. Low incidence of pneumocystis jirovecii pneumonia in an unprophylaxed liver transplant cohort[J]. Transpl Infect Dis, 2013, 15(5):510-515.

[5] Yau AA, Farouk SS. Severe hypercalcemia preceding a diagnosis of Pneumocystis jirovecii pneumonia in a liver transplant recipient[J]. BMC Infect Dis, 2019, 19(1):739.

[6] Fishman JA, Gans H. Pneumocystis jiroveci in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice[J]. Clin Transplant,2019,33(9):e13587.

[7] Simner PJ, Miller S,Carroll KC. Understanding the Promises and Hurdles of Metagenomic Next-Generation Sequencing as a Diagnostic Tool for Infectious diseases[J]. Clin Infect Dis, 2018, 66(5) :778-788.

[8] Qian YY, Wang HY, Zhou Y, et al. Improving Pulmonary Infection Diagnosis with Metagenomic Next Generation Sequencing[J]. Front Cell Infect Microbiol, 2021, 10:567615.

[9] Forbes JD, Knox NC, Ronholm J, et al. Metagenomics:the next culture-independent game changer[J]. Front Microbiol, 2017, 8:1069.

[10] Huang YN, Ma YY, Miao Q, et al. Arthritis caused by Legionella micdadei and Staphylococcus aureus: metagenomic next-generation sequencing provides a rapid and accurate access to diagnosis and surveillance[J]. Ann Transl Med, 2019, 7(20):589.

[11] Leo Stefano, Gaïa Nadia, Ruppé Etienne, et al. Detection of Bacterial Pathogens from Broncho-Alveolar Lavage by Next-Generation Sequencing[J]. International Journal of Molecular Sciences, 2017, 18(9):2011.

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The Role of the Pro-Apoptotic Protein Bax in Colon Cancer

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Abstract: Bax is a pro-apoptotic member of the Bcl-2 family that plays a crucial role in the regulation of apoptosis. Bax can be activated by various stimuli and translocate to the mitochondria, where it induces cytochrome c release and caspase activation. Bax expression or activity can be altered in colon cancer cells, resulting in resistance to apoptosis and tumor progression. This article summarized the molecular mechanisms of Bax activation and function in apoptosis, the alterations of Bax expression or activity in colon cancer cells, and the potential therapeutic implications of targeting Bax or its regulators in colon cancer.

Keywords: Bax; Apoptosis; Colon Cancer

Introduction

Apoptosis is a programmed cell death process that eliminates unwanted or damaged cells in a controlled manner (Li et al., 2021). Apoptosis is essential for maintaining tissue homeostasis and preventing tumorigenesis. Dysregulation of apoptosis can lead to various diseases, such as cancer.

The Bcl-2 family is a group of proteins that regulate apoptosis by controlling the permeability of the mitochondrial outer membrane. The Bcl-2 family consists of anti-apoptotic proteins (such as BCL-2), pro-apoptotic BH3-only proteins (such as BID and BIM) and pro-apoptotic effector proteins (such as BAX and BAK) members that share homology in one or more of the four Bcl-2 homology (BH) domains. The interaction between BCL-2 family members determines the life and death of cells.

Bax is one of the most studied pro-apoptotic members of the Bcl-2 family. It plays an important role in the suppression of tumorigenesis by inducing apoptosis in response to various stresses (Spitz & Gavathiotis, 2022). However, cancer cells often develop mechanisms to evade apoptosis by altering Bax expression or activity.

Colon cancer is one of the most common types of cancer worldwide and has a high mortality rate. Colon cancer can be classified into two major subtypes based on the microsatellite status: microsatellite stable (MSS) and microsatellite unstable (MSI). Microsatellites are short tandem repeats of DNA sequences that are prone to replication errors. MSI tumors have a high frequency of mutations in microsatellite regions due to defects in DNA mismatch repair genes. MSI tumors account for about 15% of sporadic colon cancers and 90% of hereditary nonpolyposis colon cancers (HNPCC). MSI tumors have distinct molecular and clinical features compared to MSS tumors, such as better prognosis, resistance to 5-fluorouracil-based chemotherapy, and increased immune infiltration.

1. The Molecular Mechanisms of Bax Activation and Function in Apoptosis

Apoptosis is divided into the extrinsic (also called death receptor) pathway and the intrinsic (also called mitochondrial) pathway. The pro-apoptotic protein Bax is mainly involved in the mitochondrial apoptosis pathway (Figure 1). The mitochondrial apoptosis pathway is an endogenous apoptosis mechanism that mainly involves the following steps (Ichim & Tait, 2016):

- BCL-2 homology domain 3 (BH3)-only protein is activated after cells are exposed to internal or external apoptotic stimuli (such as DNA damage, oxidative stress, growth factor loss).
- BH3-only protein activates pro-apoptotic members of the Bcl-2 family of proteins, such as Bax and Bak, and interacts with anti-apoptotic members, such as Bcl-2, leading to mitochondrial outer membrane permeabilization (MOMP).
- The permeability of the outer mitochondrial membrane increases, resulting in a decrease in mitochondrial membrane potential and the release of a series of apoptotic factors, such as cytochrome c and SMAC.
- Cytochrome c binds to Apaf-1, forms apoptotic bodies in the presence of ATP, recruits and activates procaspase-9, and forms

caspase-9 holoenzyme.

- The caspase-9 holoenzyme further activates effector caspases, such as caspase-3 and caspase-7, initiating the caspase cascade reaction, cleaving a variety of substrates in the cell, leading to the destruction of the cell nucleus and cytoskeleton, forming typical apoptotic morphology feature.
- SMAC is released from mitochondria, binds to IAPs, and inhibits the inhibitory effect of IAPs on caspase, thus indirectly promoting apoptosis.

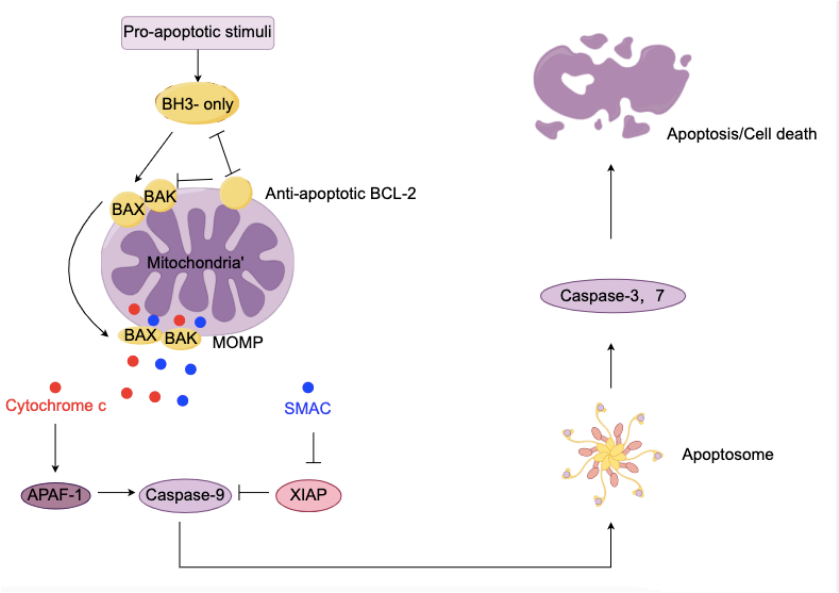

Figure 1. Mitochondria apoptotic signalling pathways

2. Alterations of Bax Expression or Activity in Colon Cancer Cells for Tumor Development and Progression

Bax expression or activity can be altered in colon cancer cells, resulting in resistance to apoptosis and tumor progression. The alterations of Bax expression or activity can be classified into two categories: genetic alterations and epigenetic alterations (Liu et al., 2016).

Genetic alterations refer to mutations or deletions that affect the structure or function of Bax. The most common genetic alteration of Bax in colon cancer is the deletion of one guanine in the microsatellite region of exon 3, which results in a frameshift and a premature stop codon. This mutation leads to the loss of Bax protein expression and function, which confers resistance to apoptosis and contributes to tumor progression. This mutation occurs predominantly in MSI colon cancers due to defects in DNA mismatch repair genes. The frequency of this mutation ranges from 30% to 70% in MSI colon cancers, depending on the study population and the detection method. However, alternative splicing can rescue the expression of a full-length Bax protein by skipping exon 2, which restores the reading frame. This Bax isoform is called BaxΔ2 and was first discovered in colon cancer patients with MSI. Unlike the parental Baxα, BaxΔ2 induces apoptosis through a non-mitochondrial pathway that involves caspase-8 activation. BaxΔ2 expression has been detected in various human tissues, especially in the colon, where it shows an inverse correlation with tissue malignancy. The mechanism of alternative splicing of Bax is not fully understood, but it may be influenced by factors such as splicing factors, RNA-binding proteins, or microRNAs.

Epigenetic alterations refer to modifications that affect the expression or activity of Bax without changing its sequence. The most common epigenetic alteration of Bax in colon cancer is the methylation of its promoter region, which results in the silencing of its transcription. Methylation of Bax promoter has been observed in both MSS and MSI colon cancers, but more frequently in MSS colon cancers. The frequency of methylation of Bax promoter ranges from 10% to 60% in colon cancers, depending on the study population and the detection method. Methylation of Bax promoter can be influenced by factors such as DNA methyltransferases, histone deacetylases, or microRNAs. Methylation of Bax promoter can be reversed by treatment with demethylating agents, such as 5-aza-2'-deoxycytidine (5-AZA) or zebular-

ine, which can restore Bax expression and induce apoptosis in colon cancer cells.

Other epigenetic alterations of Bax in colon cancer include post-translational modifications or interactions with other proteins that modulate its stability, localization, conformation, or interaction with other proteins.

3. Potential Therapeutic Implications of Targeting Bax or Its Regulators in Colon Cancer

Bax is a potential therapeutic target for colon cancer, as restoring or enhancing its expression or activity can induce apoptosis and inhibit tumor growth. Several strategies have been developed to target Bax or its regulators in colon cancer, such as gene therapy, small molecules, peptides, antibodies, or nanomaterials (Walensky, 2019).

Gene therapy involves the delivery of exogenous genes that encode Bax or its activators to colon cancer cells using viral or non-viral vectors. For example, adenovirus-mediated transfer of Bax gene can induce apoptosis and suppress tumor growth in colon cancer xenograft models. Adenovirus-mediated transfer of Bid gene can also induce apoptosis and suppress tumor growth in colon cancer xenograft models. However, gene therapy faces several challenges, such as low efficiency, immunogenicity, toxicity, or specificity.

Small molecules are organic compounds that can modulate the expression or activity of Bax or its regulators by binding to their targets with high affinity and specificity. For example, ABT-737 is a small molecule that mimics the BH3 domain of Bad and binds to anti-apoptotic proteins, such as Bcl-2, Bcl-xL, and Bcl-w, displacing Bax from them and activating it. ABT-737 can induce apoptosis and inhibit tumor growth in colon cancer cell lines and xenograft models. However, ABT-737 has limited efficacy against Mcl-1-expressing colon cancer cells, which can be overcome by combining it with other agents, such as obatoclax, sorafenib, or navitoclax. TW-37 is another small molecule that mimics the BH3 domain of Bad and binds to anti-apoptotic proteins, such as Bcl-2, Bcl-xL, and Mcl-1, displacing Bax from them and activating it. TW-37 can induce apoptosis and inhibit tumor growth in colon cancer cell lines and xenograft models. However, TW-37 has low solubility and bioavailability, which can be improved by using nanocarriers, such as liposomes, micelles, or nanoparticles.

Peptides are short sequences of amino acids that can modulate the expression or activity of Bax or its regulators by binding to their targets with high affinity and specificity. For example, BH3 peptides are synthetic peptides that mimic the BH3 domain of BH3-only proteins and bind to anti-apoptotic proteins, displacing Bax from them and activating it. BH3 peptides can induce apoptosis and inhibit tumor growth in colon cancer cell lines and xenograft models. However, BH3 peptides have low stability, permeability, and specificity, which can be enhanced by using modifications, such as D-amino acids, cyclization, stapling, or conjugation.

Antibodies are proteins that recognize and bind to specific antigens on the surface or inside of cells. Antibodies can be used to activate Bax or inhibit its inhibitors in colon cancer cells. For example, 6A7 is an antibody that recognizes and binds to the inactive form of Bax and induces its conformational change and activation. 6A7 has been shown to induce apoptosis and sensitize colon cancer cells to 5-fluorouracil or cisplatin. Alternatively, antibodies can be used to inhibit the expression or activity of epigenetic modifiers that repress Bax expression in colon cancer cells. For instance, EZH2 is an antibody that recognizes and binds to EZH2, which is a subunit of PRC2 that catalyzes H3K27 methylation of the Bax promoter, resulting in its silencing and apoptosis resistance. EZH2 has been shown to induce apoptosis and enhance the efficacy of 5-fluorouracil or irinotecan in colon cancer cells.

Nanoparticles are particles that have a size range of 1-100 nanometers and can carry various cargoes, such as genes, drugs, peptides, or antibodies. Nanoparticles can be used to deliver Bax or its activators or inhibitors into colon cancer cells with high specificity and efficiency. For example, liposomes are nanoparticles that consist of lipid bilayers that can encapsulate hydrophilic or hydrophobic substances. Liposomes can be used to deliver Bax gene, ABT-737, SAHB, or 6A7 into colon cancer cells and induce apoptosis and chemosensitization.

4. Conclusion & Discussion

Bax has shown amazing potential in targeting Bax or its regulators in colon cancer. However, there are still many unanswered questions and challenges that need to be addressed in future studies. For example, what are the molecular determinants and dynamics of Bax oligomerization and pore formation? How do different Bax isoforms interact with each other and with other proteins? How do different microenvironments and signaling pathways affect Bax expression or activity in colon cancer cells? How can we overcome the heterogeneity and

resistance of colon cancer cells to Bax-targeted therapies? How can we optimize the delivery and specificity of Bax-targeted therapies? How can we combine Bax-targeted therapies with other conventional or novel therapies for synergistic effects? These questions warrant further investigation and exploration to elucidate the role of Bax in colon cancer and to develop more effective and personalized treatments for colon cancer patients.

References

[1] Li, P., Dong, R., Zhang, B., Zhang, T., Liu, Z., Ma, S., & Ma, L. (2021). Molecular mechanism and therapeutic targeting of necrosis, apoptosis, pyroptosis, and autophagy in cardiovascular disease. Chinese Medical Journal, 134(22), 2647-2655.

[2] Spitz, A. Z., & Gavathiotis, E. (2022). Physiologic and Pharmacologic Modulation of BAX. Trends in Pharmacological Sciences, 43(3), 206.

[3] Ichim, G., & Tait, S. W. (2016). A fate worse than death: Apoptosis as an oncogenic process. Nature Reviews Cancer, 16(8), 539-548.

[4] Liu, Z., Ding, Y., Ye, N., Wild, C., Chen, H., & Zhou, J. (2016). Direct Activation of Bax Protein for Cancer Therapy. Medicinal Research Reviews, 36(2), 313.

[5] Walensky, L. D. (2019). Targeting BAX to drug death directly. Nature Chemical Biology, 15(7), 657-665.

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Research Progress of Mitochondrial DNA and Cancer

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Abstract: Mitochondrial DNA mutation will lead to a series of diseases, and Defective mitochondrial DNA will lead to organ dysfunction.The increase of mutation frequency caused by nuclear DNA repair defect, replication error, carcinogen exposure and aging is generally considered to drive the occurrence of cancer.In contrast, the status and role of mitochondrial genome mutation in cancer are not clear.We reviewed the variation in number and structure of mtDNA in colorectal cancer, liver cancer, breast cancer , aiming to illustrate the important role of mtDNA in the occurrence and development of cancer, and to provide some reference for early diagnosis, treatment and prognosis evaluation of cancer.

Keywords: Mitochondrial DNA Mutation; Mitochondrial DNA Copy Number; Cancer

Introduction

Mitochondria possess their own DNA, which encodes many key proteins used for the assembly and activity of mitochondrial respiratory complexes. The mtDNA does not bind to histones or form chromosomes, but instead forms a mtDNA-protein complex with many proteins, forming a nucleoid uniformly distributed in the mitochondrial matrix, which is essential for mitochondrial function. Since the structural characteristics of mtDNA are different from nuclear DNA with more than ten times more than nuclear DNA, defects or mutations in mtDNA cause a series of diseases and damaged mtDNA can be eliminated by mitophagy[1]. Mitochondria have been shown to play an important role in apoptosis, a fundamental biological process in which cells die in a controlled manner, playing a key role in cancer development and the cellular response to anticancer drugs. Therefore, it is important to understand the biological characteristics of mtDNA and its role in tumor development and development. Otto Warburg The observation that cancer has acquired the unusual property of absorbing and fermenting glucose into lactate in the presence of oxygen raises defects in mitochondrial respiration as the underlying basis for aerobic glycolysis and cancer. However, not all tumors have this aerobic glycolytic property, and it is now clear that defects in mitochondrial respiration are generally not often the cause of aerobic glycolysis[2]. In recent years, the research on mtDNA in cancer has attracted much attention, and many studies explain the role of mtDNA mutations and mtDNA copy number variants in cancer occurrence[3,4]. Therefore, this paper outlines the variant characteristics of mtDNA in multiple cancers and its role in cancer development, aiming to further elucidate the complex relationship between mtDNA and cancer,It provides some reference basis for the early diagnosis, treatment and prognosis evaluation of cancer.

1. Basic knowledge of mitochondria:

Mitochondria is a bilayer membrane organelle that generates about 90% of its cellular energy in mammalian cells, by oxidative phosphorylation (OXPHOS), in the form of adenosine triphosphate (ATP). Mitochondria also play important roles in a range of signaling pathways, including the tricarboxylic acid cycle (TCA), β -oxidation of fatty acids, and cell death in cell apoptosis[5,6]And the cell cycle[7,8]Play an important role in the process.

Unlike other organelles in mammalian cells, mitochondria have their own genetic material, which encodes a range of key proteins associated with mitochondrial respiration. Each mitochondrion contains one or more copies of mtDNA, located in the mitochondrial matrix[9]. significantly different from the structure of nuclear DNA, mtDNA is closed circular duplex DNA, the outer ring is rich in purine, called heavy chain (H chain), and the inner ring is rich in pyrimidine, called light chain (L chain). Therefore, the component of mtDNA is highly asymmetric. In human cells, mtDNA consists of 16,569 base pairs and encodes 37 genes, including 13 polypeptides, two ribosomal RNA, and 22 transport RNA[10]. Most of the non-coding DNA of the human mitochondrial genome is located within an ~ 1 kb region called the non-coding

region (NCR). The NCR is the most strongly polymorphic site in the mtDNA, with several known polymorphic sites within the two hypervariable regions (HVR) of the NCR[11]. Non-coding regions (NCR) exert a regulatory function in the mtDNA, exerting control on transcription and translation. The mtDNA control region contains the replication origin of one strand and the transcription origin of both strands, the control region is also the location of the mtDNA displacement loop (D-loop), and the mtDNA replication begins at the D loop, which also contains the promoter of the transcript adjacent to the D loop. Although the exact function of the D-loop is unknown, it is noteworthy that this region is highly sequence variability[12], And has been shown to be associated with the incidence of specific types of cancer[13]。

Mitochondrial dysfunction, often characterized by the loss of oxidative phosphorylation efficiency, is a hallmark of aging and various chronic diseases[14]. Mitochondrial dysfunction leads to inefficient cellular energy production and increased levels of reactive oxygen species (ROS), which may damage lipids, proteins, and nucleic acids[15]. Mitochondrial dysfunction also affects the expression of nuclear genes involved in metabolism, growth, differentiation, and apoptosis[16]. A major limitation of the routine assessment of mitochondrial dysfunction in clinical practice is the lack of reliable measures of mitochondrial dysfunction that can be used in the clinic. And mitochondrial DNA copy number (mtDNA-CN) is a promising biomarker of mitochondrial dysfunction and is likely to be widely used in clinical practice.

2. Mitochondrial DNA variants and cancer:

During cancer development, tumor cells not only undergo metabolic changes to support cell growth, but also other types of mtDNA damage. The mtDNA mutations have been identified in all types of human tumors, including the non-coding and coding regions of mtDNA. Larman et al studied different cancer types and found that the frequency of somatic mtDNA mutations ranged from 13% in glioblastoma to 63% in rectal adenocarcinoma[17]. There are data suggesting that at least one observed tumor mtDNA mutation can confer a selective advantage to cancer cells, further supporting the hypothesis that mtDNA somatic mutations play an important role in promoting tumor cell proliferation[18]. In addition to the structural abnormalities in mtDNA, mtDNA copy number changes have also been frequently described in cancer. For example, elevated mtDNA content was found in primary head and neck squamous cell carcinoma, papillary thyroid carcinoma, and endometrial carcinoma, while gastric cancers exhibited mtDNA depletion. The mtDNA copy number in a cancer may depend on the specific mutation site associated with this cancer. Thus, increased mtDNA copy number can serve as a compensatory response to mitochondrial dysfunction or mutations in nuclear genes indirectly involved in the control of mtDNA copy number. Conversely, mutations in the D loop region that controls mtDNA replication are expected to result in copy number reduction. In many cases, fewer mtDNA copies were accompanied by a reduction in mitochondrial gene expression, suggesting an inhibition of mitochondrial activity in these tumor types. The mtDNA damage causes not only mtDNA copy number changes, but also new point mutations and deletions in mtDNA, impaired mitochondrial function, and changes in cellular and tissue functions. Indeed, Reznik et al found that mtDNA copy number is associated with the incidence of key driver mutations leading to cell carcinogenesis[19]. It is noteworthy that although mtDNA copy number affects the transcript level of mtDNA genes, not all cancer types exhibit a correlation between mitochondrial gene expression and mtDNA copy number.

3. Molecular characterization of mtDNA in intestinal cancer:

Although colonoscopy is widely used for early detection and resection of colorectal adenomas, a precursor to most colorectal cancers, colorectal cancer remains a cause of cancer death and is the only major cancer that affects essentially equally in men and women[20]. Oxidative stress of reactive oxygen species (ROS) is believed to have an important role in colorectal cancer. In addition, several studies have identified oxidative stress as an important risk factor for colorectal adenoma, suggesting that abnormal oxidative stress may be important in early colorectal carcinogenesis. ROS are mainly derived from mitochondria, and they are by-products of aerobic respiration. Under physiological conditions, the amount of cellular mitochondrial DNA remains relatively stable, and it has been found that qualitative and quantitative mtDNA changes, such as somatic mitochondrial mutations and mtDNA copy number changes in colorectal tumor tissue, may play an important role in colorectal carcinogenesis[21,22]. Similarly, changes in mtDNA copy number in non-neoplastic tissues (e. g., peripheral blood) may reflect the end result of interactions between genetic and environmental factors that may increase oxidative stress and colorectal cancer risk. In support of this hypothesis, some studies have found an association between mtDNA copy number in peripheral blood and multiple

cancers[23,24]. In particular, a case-control study in the Singapore Chinese Health cohort[25]And a prospective nested case cohort study[26], Both found that mtDNA copy number in the peripheral blood was associated with an increased risk of colorectal cancer. Despite the association between mtDNA copy number and CRC, it is unclear whether the altered mtDNA copy number is a risk factor for CRC or a biomarker for a confirmed diagnosis of CRC.

Colorectal cancer is the result of the accumulation of multiple genetic alterations, for example point mutations, copy number variations and epigenetic modifications[27]. To date, two major pathways of colorectal carcinogenesis have been precisely described. The first pathway involves chromosomal instability (CIN) and is mainly characterized by the continuous accumulation of genetic alterations in APC, KRAS, and p53[28], The second pathway is the microsatellite instability (MSI)[29]. There is increasing evidence for the functional role of mtDNA abnormalities (including point mutations, deletions, inversions, and copy number alterations) in mitochondrial dysfunction and colorectal carcinogenesis. However, it is unclear whether these mutations initiate or promote tumorigenesis, or whether they are simply a result of genomic instability. Peripheral blood mitochondrial DNA content is associated with risk of colorectal cancer and is proposed as potential biomarkers, however, some studies have failed to confirm this association, suggesting that relative mtDNA copy number in peripheral blood is more likely to be considered as markers of early CRC occurrence than a biomarker that can be used to assess CRC risk[30]。

The molecular mechanisms leading to mtDNA copy number changes are still under investigation. In a study of 65 colorectal cancers, it has been proposed that hypomethylation of the D-loop region may be involved in the regulation of mtDNA copy number[31]. Recently, it has been reported that polymorphisms within the nuclear-encoded polymerase γ gene (POLG) may contribute to reducing a key component of the mitochondrial genome maintenance machinery, resulting in mitochondrial copy number changes[32]. The D loop region contains essential transcription and replication elements and is a well-known somatic mutation hotspot in colorectal tumors. This region is formed by two hypervariable regions, the HV-I (nt.16024-16383) and HV-II (nt.57-333)[33]. MtDNA variants in the D-Loop region are associated with risk and survival in colorectal cancer patients and, therefore, they are proposed as valuable markers for assessment of colorectal cancer outcome[34]. Mitochondrial microsatellite instability (mtMSI), the change in the length of the D loop repeat between normal and tumor tissues, has been described as a common molecular event in colorectal carcinogenesis (approximately 30% of colorectal tumors), but its prognostic value remains controversial[35]。

4. Molecular characterization of mtDNA in liver cancer:

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with the third highest mortality rate[36,37]. About 434000 new cases of HCC each year[38]. Several risk factors have been proposed to participate in the development of HCC, including aflatoxin exposure, alcohol consumption, viral hepatitis, etc.

Several types of somatic mtDNA alterations have been identified in human HCC, and these mtDNA alterations include point mutations, deletions, insertions, and copy number changes. Screening for somatic point mutations in the whole mitochondrial genome of HCC samples indicates that approximately 52% of HCC patients carry at least one homogenous or heterogeneous point mutation in their tumor tissue mtDNA. Of the identified point mutations, 76% are located in the D-loop regions, 2% in rRNA genes, 3% in tRNA genes, and 19% in mRNA genes[39]. The D-loop region is a hot spot for somatic mtDNA mutations in HCC and other cancers. That the D loop regions of mtDNA, especially mononucleotide repeats in the np 303-309 poly-C sequence, are the sites most susceptible to oxidative damage compared to other regions of mtDNA, implies that oxidative damage contributes to point mutations in the D loop and the instability of mononucleotide or dinucleotide repeats in mtDNA. And because the D-loop region controls mtDNA replication and transcription, mutations in the D-loop region may affect mtDNA copy number and expression of the mitochondrial genome. Thus, somatic mutations in the mtDNA D-loop region may affect mitochondrial function by reducing mtDNA copy number and transcription in HCC, thus leading to HCC progression. The reduction in mitochondrial DNA copy number is a common event in HCC, with more than 60% of HCC having lower mtDNA copy numbers than their corresponding normal liver tissue.

Several types of somatic mtDNA alterations have been identified in HCC, but the role of these mtDNA alterations in HCC progression

is still unclear, and some studies confirm the pathological role of mtDNA mutations and mitochondrial dysfunction in HCC. Most somatic point mutations in mtDNA copy number and reduction in the mitochondrial coding region may contribute to mitochondrial dysfunction in HCC, and these findings provide a molecular basis for the Warburg effect. Furthermore, it has been shown that low mtDNA copy number in HCC is significantly associated with large tumor size, liver cirrhosis, and poor 5-year survival[40]. Thus, mtDNA mutations and reduced mtDNA copy number and mitochondrial dysfunction may alter the progression of HCC. However, the presence of somatic mtDNA point mutations in HCC does not seem to be associated with patient age or sex, tumor size or grade, hepatitis virus infection, or survival of patients[41]. Furthermore, heterogeneous or homogeneous levels of the same mtDNA mutation may lead to different consequences of tumorigenesis. Therefore, the role of specific mtDNA mutations and their levels during HCC progression warrants further investigation.

5. Molecular features of mtDNA in breast cancer:

With regard to breast cancer, multiple studies have investigated the effect of mtDNA content on phenotype, prognosis, and drug response. Lower mtDNA content was observed in approximately 70% of breast cancer specimens when compared to the surrounding normal epithelium[42,43]. There are indications that low mtDNA content in breast cancer may produce a more aggressive phenotype and altered treatment response. Depletion of mtDNA in in vitro models affects the mRNA and protein expression levels of several genes involved in epithelial stromal transition (EMT)[44,45], The transition to a mesenchymal phenotype has been recognized as an important mechanism for promoting cancer metastasis[46]. Thus, the low mtDNA content used as a marker of the mesenchymal phenotype may identify tumor aggressiveness.

Somatic mtDNA variation is frequently observed in primary breast tumors[47]. Most of these variants are single-nucleotide variants rather than small insertions or deletions, which are distributed along the entire mitochondrial genome and show great heterogeneity between cases. To date, no somatic mtDNA mutations have been described that clearly affect breast cancer tumorigenesis or progression. With more somatic mtDNA variants in the primary tumors of patients diagnosed at a higher age. Furthermore, there is substantial heterogeneity in somatic mtDNA variants within primary breast tumors. Although mtDNA content in primary breast tumors is not associated with any traditional clinicopathological marker, low mtDNA levels in primary breast tumors indicate that cancers are more aggressive[48]。

6. Summary and Outlook:

Mutations in mtDNA affect tumor development and progression, which makes the presence of the mitochondrial genome add to both the unique and complex biological properties of this organelle. In recent years, with the vigorous development of next-generation sequencing technology and single-cell sequencing technologies, the biological characteristics of mtDNA in tumors have been gradually elucidated. The structure of mtDNA, mtDNA copy number and others have unique changes in the development of cancer. The mtDNA abnormalities (including point mutations, deletions, inversion, and copy number alterations) have a role in mitochondrial dysfunction and colorectal carcinogenesis, The mtDNA copy number in the peripheral blood is associated with an increased risk of colorectal cancer, The D loop region contains essential transcriptional and replication elements, Is a well-known hotspot of somatic mutations in colorectal tumors, Variation in this region is associated with risk and survival in colorectal cancer patients; Several types of somatic mtDNA alterations have been identified in human HCC, These mtDNA alterations include point mutations, deletions, insertions, and copy number changes, Somatic mutations in the mtDNA D-loop region may affect mitochondrial function by reducing mtDNA copy number and transcription in HCC, Thus leading to the HCC progression, besides, Low mtDNA copy number in HCC was associated with tumor size and cirrhosis of the liver; Single-nucleotide variants in somatic mtDNA are frequently observed in primary breast tumors, Low mtDNA content can be used as a mesenchymal phenotype marker, And then identify the aggresnature of the tumor. As mtDNA has certain clinical significance in many kinds of cancers, this paper reviews the features of mtDNA variation in cancer, and provides relevant basic information for clinical and scientific research staffIt provides some reference basis for the early diagnosis, treatment and prognosis evaluation of cancer.

References

[1] Yan C, Duanmu X, Zeng L, Liu B, Song Z.Mitochondrial DNA: Distribution, Mutations, and Elimination. Cells. 2019; 8(4):379.

[2] Zong WX, Rabinowitz JD, White E.Mitochondria and Cancer. Mol Cell. 2016; 61(5): 667-676.

[3] Yuan Y, Ju YS, Kim Y, et al.Comprehensive molecular characterization of mitochondrial genomes in human cancers [published correction appears in Nat Genet.2020 Feb 11;:] [published correction appears in Nat Genet.2020 Apr 27;:].Nat Genet. 2020; 52(3):342-352.

[4] Reznik E, Miller ML, Şenbabaoğlu Y, et al.Mitochondrial DNA copy number variation across human cancers.Elife.2016;5:e10769. Published 2016 Feb 22.

[5] Desagher S., Martinou J.C.Mitochondria as the central control point of apoptosis.Trends Cell Biol.2000;10:369–377.

[6] Suen D.F., Norris K.L., Youle R.J.Mitochondrial dynamics and apoptosis.Genes Dev. 2008; 22:1577–1590.

[7] Arakaki N., Nishihama T., Owaki H., Kuramoto Y., Suenaga M., Miyoshi E., Emoto Y., Shibata H., Shono M., Higuti T.Dynamics of mitochondria during the cell cycle.Biol.Pharm.Bull.2006;29:1962–1965.

[8] Finkel T., Hwang P.M.The Krebs cycle meets the cell cycle: Mitochondria and the G(1)-S transition.Proc.Natl.Acad.Sci. USA.2009;106:11825–11826.

[9] Mishra P., Chan D.C.Mitochondrial dynamics and inheritance during cell division, development and disease.Nat.Rev.Mol.Cell Biol.2014;15:634–646.

[10] Nicholls T.J., Gustafsson C.M. Separating and Segregating the Human Mitochondrial Genome. Trends Biochem.Sci.2018;43:869–881.

[11] Holt I.J., Reyes A.Human mitochondrial DNA replication.Cold Spring Harb. Perspect. Biol.2012;4:a012971.

[12] Ingman M., Kaessmann H., Paabo S., Gyllensten U.Mitochondrial genome variation and the origin of modern humans.Nature.2000;408:708–713.

[13] Yuan R.T., Sun Y., Bu L.X., Jia M.Y.Gene mutations in the D-loop region of mitochondrial DNA in oral squamous cell carcinoma. Mol. Med.Rep. 2015; 11: 4496 –4500.

[14] Nicolson GL. Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements.Integr Med (Encinitas).2014;13(4):35-43.

[15] Guyatt AL, Burrows K, Guthrie PAI, et al.Cardiometabolic phenotypes and mitochondrial DNA copy number in two cohorts of UK women. Mitochondrion. 2018; 39: 9-19.

[16] Pello R, Martín MA, Carelli V, et al. Mitochondrial DNA background modulates the assembly kinetics of OXPHOS complexes in a cellular model of mitochondrial disease.Hum Mol Genet.2008 Dec 15;17(24):4001-11.

[17] Larman TC, DePalma SR, Hadjipanayis AG, Protopopov A, Zhang J, Gabriel SB, Chin L, Seidman CE, Kucherlapati R and Seidman JG; Cancer Genome Atlas Research Network: Spectrum of somatic mitochondrial mutations in five cancers. Proc Natl Acad Sci USA.109:14087–14091.

[18] Jiménez-Morales S, Pérez-Amado CJ, Langley E, Hidalgo-Miranda A. Overview of mitochondrial germline variants and mutations in human disease: Focus on breast cancer (Review). Int J Oncol.2018 Sep;53(3):923-936.

[19] Reznik E, Miller ML, Şenbabaoğlu Y, et al: Mitochondrial DNA copy number variation across human cancers.eLife.5:e107692016.

[20] Thyagarajan B, Guan W, Fedirko V, et al. No association between mitochondrial DNA copy number and colorectal adenomas. Mol Carcinog. 2016;55(8):1290-1296.

[21] Lin PC, Lin JK, Yang SH, et al. Expression of beta-F1-ATPase and mitochondrial transcription factor A and the change in mitochondrial DNA content in colorectal cancer: clinical data analysis and evidence from an in vitro study.Int J Colorectal Dis.2008;23(12):1223–1232.

[22] Chang SC, Lin PC, Yang SH, et al. Mitochondrial D-loop mutation is a common event in colorectal cancers with p53 mutations. Int J Colorectal Dis. 2009; 24(6): 623– 628.

[23] Xie H, Lev D, Gong Y, et al.Reduced mitochondrial DNA copy number in peripheral blood leukocytes increases the risk of soft tissue sarcoma. Carcinogenesis. 2013; 34(5): 1039–1043.

[24] He Y, Gong Y, Gu J, Lee JJ, Lippman SM, Wu X.Increased leukocyte mitochondrial DNA copy number is associated with oral

premalignant lesions: an epidemiology study. Carcinogenesis. 2014; 35(8):1760-1764.

[25] Qu F, Liu X, Zhou F, et al.Association between mitochondrial DNA content in leukocytes and colorectal cancer risk: A case-control analysis. Cancer. 2011; 117(14): 3148–3155.

[26] Thyagarajan B, Wang R, Barcelo H, Koh WP, Yuan JM.Mitochondrial Copy Number is Associated with Colorectal Cancer Risk. Cancer Epidemiol Biomarkers Prev.2012;21(9):1574–1581.

[27] Wang C, Zhao S, Du Y, Guo Z.Single nucleotide polymorphisms in the D-loop region of mitochondrial DNA is associated with colorectal cancer outcome. Mitochondrial DNA A DNA Mapp Seq Anal.2016 Nov;27(6):4361-4363.

[28] Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010 Jun; 138(6):2059-72.

[29] Akbari M, Sykora P, Bohr VA.Slow mitochondrial repair of 5'-AMP renders mtDNA susceptible to damage in APTX deficient cells.Sci Rep.2015 Aug 10;5:12876.

[30] Thyagarajan B, Guan W, Fedirko V, Barcelo H, Tu H, Gross M, Goodman M, Bostick RM.No association between mitochondrial DNA copy number and colorectal adenomas.Mol Carcinog.2016 Aug;55(8):1290-6.

[31] Gao J, Wen S, Zhou H, Feng S (2015) De-methylation of displacement loop of mitochondrial DNA is associated with increased mitochondrial copy number and nicotinamide adenine dinucleotide subunit 2 expression in colorectal cancer.Mol Med Rep 12(5):7033–7038

[32] Linkowska K, Jawień A, Marszałek A, et al. Mitochondrial DNA Polymerase γ Mutations and Their Implications in mtDNA Alterations in Colorectal Cancer.Ann Hum Genet.2015 Sep;79(5):320-328.

[33] Tipirisetti NR, Govatati S, Pullari P, et al. Mitochondrial control region alterations and breast cancer risk: a study in South Indian population. PLoS One. 2014 Jan 30; 9(1):e85363.

[34] Wang C, Zhao S, Du Y, Guo Z (2016) Single nucleotide polymorphisms in the D-loop region of mitochondrial DNA is associated with colorectal cancer outcome.Mitochondrial DNA A DNA Mapp Seq Anal 27(6):4361–4363.

[35] Venderbosch S, Van Vliet S, Craenmehr MH, Simmer F, de Haan AF, Punt CJ, Koopman M, Nagtegaal ID (2015) Mitochondrial microsatellite instability in patients with metastatic colorectal cancer.Virchows Arch 466(5):495–502.

[36] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM.Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127: 2893–2917.

[37] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012; 379:1245 –1255.

[38] World Health Organisation (WHO) Databank. WHO statistical information system[Internet]. Geneva: WHO.

[39] Hsu CC, Lee HC, Wei YH.Mitochondrial DNA alterations and mitochondrial dysfunction in the progression of hepatocellular carcinoma.World J Gastroenterol. 2013; 19(47): 8880-8886.

[40] Yamada S, Nomoto S, Fujii T, Kaneko T, Takeda S, Inoue S, Kanazumi N, Nakao A. Correlation between copy number of mitochondrial DNA and clinico-pathologic parameters of hepatocellular carcinoma.Eur J Surg Oncol. 2006; 32:303–307.

[41] Yin PH, Wu CC, Lin JC, et al. Somatic mutations of mitochondrial genome in hepatocellular carcinoma.Mitochondrion.2010;10:174–182.

[42] McMahon S, LaFramboise T. Mutational patterns in the breast cancer mitochondrial genome, with clinical correlates. Carcinogenesis. 2014; 35: 1046–54.

[43] Hollestelle A, Peeters JK, Smid M, et al. Loss of E-cadherin is not a necessity for epithelial to mesenchymal transition in human breast cancer.Breast Cancer Res Treat. 2013;138:47–57.

[44] Naito A, Cook CC, Mizumachi T, et al. Progressive tumor features accompany epithelial-mesenchymal transition induced in mitochondrial DNA-depleted cells. Cancer Sci. 2008; 99: 1584–8.

[45] Guha M, Srinivasan S, Ruthel G, et al. Mitochondrial retrograde signaling induces epithelial-mesenchymal transition and generates breast cancer stem cells. Oncogene.2014;33:5238–50.

[46] Thiery JP. Epithelial-mesenchymal transitions in tumour progression.Nat Rev Cancer. 2002; 2:442–54.

[47] Ebrahimi E, Almasi-Hashiani A, Ghaffari K, Shirkoohi R. Mitochondrial DNA copy number instability in ERBB2-amplified

breast cancer tumors. EXCLI J. 2018; 17: 149-158.

[48] Weerts MJA, Sleijfer S, Martens JWM.The role of mitochondrial DNA in breast tumors.Drug Discov Today.2019 May;24(5):1202-1208.

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Based on the Theory of Chronic Liver Disease

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Abstract: Doctors discuss the treatment of chronic liver disease from the perspective of dampness, poison, and blood stasis, less from the perspective of spleen Yin loss. The author discusses the physiological function of spleen Yin and its relationship with chronic liver disease, and analyzes that spleen Yin deficiency is an important cause of chronic liver disease, and also an important manifestation of chronic liver disease, and puts forward three methods of solid spleen, liver and spleen treatment, sweet and flat tonic, sour and sweet Yin.

Keywords: Splenic Yin Deficiency; Chronic Liver Disease; Chinese Medicine Theory

Introduction

Chronic liver disease mainly includes chronic toxic hepatitis, autoimmune liver disease, fatty liver, chronic drug-induced liver injury and other unexplained liver damage, etc. If not controlled, it is easy to progress to cirrhosis, or even liver cancer. In recent years, a large number of clinical data show that TCM has certain advantages in inhibiting virus, protecting liver enzymes, fighting liver fibrosis, relieving symptoms, and few adverse reactions in the treatment process, which has become an important means for clinical treatment of chronic liver disease [1]. Most doctors for the treatment of this disease is detailed in the perspective of relieving liver and relieving depression, clearing heat and dampness, nourishing liver and kidney, less from the point of view of spleen Yin loss. The author discusses the relationship between the physiological function of spleen Yin and chronic liver disease, in order to provide useful reference for the traditional Chinese medicine diagnosis and treatment of chronic liver disease.

1. Theoretical origin

The meaning of spleen Yin was first seen in the Huangdi Neijing. "Su Wen" "its virtue is caring", "taste is too bitter, temper is not caring, stomach qi is thick" respectively discussed the performance of spleen Yin in the human body from the perspective of physiological pathology. In what Zhang Zhongjing, he proposed the spleen contract syndrome, which is the embodiment of the theory of spleen Yin, and further developed the theory of spleen Yin. The idea of "the Yin of the spleen soil was injured, and the official was negligent" was put forward by Zhu Danxi, a doctor in the Ming Dynasty, who believed that the spleen Yin was one of the basic conditions for the spleen to play its physiological function. Miao Zhongchun put forward the view that "the world only know that the fragrance and heat are the way to treat spleen deficiency, but do not know that the cold and nourishing Yin are beneficial to the spleen", and believed that the spleen and Yin deficiency should be governed by law with sweet and cold. Wu Pei in the treatment of the new, put forward "now in the palace, not dry its body fluid" like the prescription of Yin solid Yang, like spleen solid stomach, head and tail phase win-win method [2]. Mr.Zhang Xichun believes that "the spleen is too Yin, is the long of the three Yin, so the treatment of Yin deficiency, should mainly nourish the spleen Yin foot, can irrigate the viscera" [3]. Yang Jiutian [4] Based on the scattered records of spleen Yin deficiency in successive doctors, spleen Yin deficiency is divided into three common clinical evidence types: deficiency injury to spleen Yin, gastric heat injury and spleen Yin and dampness-heat injury to spleen Yin, which provides a better theoretical basis for clinical practice.

2. Splenic Yin theory and chronic liver disease

Chronic liver disease belongs to the category of "jaundice", "flank pain", "swelling" and so on. Traditional Chinese medicine believes that it is mostly based on "damp and heat" evil spirit. For example, as saying, "damp and heat alternate, and the people should be yellow"."Wet trapped spleen and stomach" and "hot knot Yang Ming", damp and heat evil gas is the most easy to invade the middle coke

spleen and stomach because of its pathological characteristics. Wet evil sticky, trapped Yang Qi, internal depression fire, damage spleen Yin; heat evil connotation, accumulation of spleen and stomach, also hurt Yin gas. This disease is easy to delay is easy to fire injury Yin, more see the image of spleen Yin loss, it can be seen that loose stool, grain, do not think about diet, etc."Su ask angry through heaven" said: "Yin is born in the five tastes."Eating bias can also lead to the imbalance of qi, blood and Yang, such as excessive drinking, excessive eating fat and spicy products are more likely to aggravate dampness and heat, damage spleen Yin. Moreover, liver wood by spleen soil, "Golden Chamber synopsis" cloud: "see liver disease know liver pass spleen", liver wood long disease, evil accumulation, straight into the spleen and stomach, Yin and Yang are damaged. Secondly, in terms of emotion, worry and think tired, injury and spleen Yin. Liver main drainage, like to tune up to, chronic liver disease patients liver qi is not smooth, many affection is not successful, depressed. Its disease is more likely to aggravate emotional failure, hard illness, internal consumption of Yin blood, damage to spleen Yin. For example, "disease because of the pulse" said: "the cause of dysentery: sad thinking will hurt the spleen."Long illness deficiency loss, too much use of warm dry, spleen dark consumption. The spleen is the length of the three Yin, the main irrigation four sides, for the source of qi, blood and body fluid. Liver, heart, lung and kidney four serious diseases, long illness, injury and Yin, can dark consumption spleen Yin. Medical see diarrhea for a long time, cloudy Yang has been empty, with a large dose of fragrance, warm dry products, resulting in hot and dry endogenous, can also further hurt the spleen Yin. Pan Ciming [5] put forward the idea of liver and spleen cooperation, body Yin with Yang, and further linked the two from the perspective of physiology and pathology. Splenic Yin deficiency syndrome characteristic is spleen Yin deficiency and spleen health symptoms in [6], such as food, abdominal distension, especially after eating, thin stools, or secret, loose knots, dry mouth, thin, face, fatigue, hands, heart heat, red tongue, moss less or no, pulse weak ", such symptoms and chronic liver disease late qi Yin two injury is very similar, and from the disease of the performance of the will link the two.

3. Treat prescription drugs

In the treatment of chronic liver disease, "softening the liver benefits the spleen, nourishing the Yin and nourishing the stomach". Xu Jingshi [7], a master of Chinese medicine, put forward four points of "nourishing the spleen, nourishing and nourishing the spleen, nourishing the spleen", and relieving the liver and regulating qi, and the prescription should be based on ganping. Therefore, the treatment should be based on the spleen, and to relieve the liver, the first place without evil.

3.1 Treatment of liver and spleen

"Soil wood and reach", liver wood smooth, can be transported for the spleen body fluid. The general adjustment of fluid fluid is Yin and Yang. Based on the perspective of the close relationship between the liver and the spleen, just as the "wood", the soil wet by evil, spleen disease born yan ". Some scholars put forward that in modern medicine, liver disease and spleen transmission is equivalent to bad emotions such as sadness, anger, sympathetic-adrenal system stress and parasympathetic nerve inhibition, weakened digestive function, anorexia, gas and acid swallowing, that is, soil, spleen transport loss [8]. At the same time, the spleen and stomach are weak, qi and blood are passive, liver loss, drainage disorder, and spleen disease into the liver. In different pathological stages of chronic liver disease, the methods of regulating liver are adopted flexibly. Shabuhu, tangerine peel, chuanxiong, sweet, slow, white peony root, angelica, white, soft, white peony root, angelica, xiong, and to strengthen the spleen, because the spleen soil "Yang", "spleen is Yin, not Yang medicine is not effective" characteristics [9], so in the selection of drugs can be mixed with a small dose of Poria cocos, gold, amomum, white and other spleen to smooth the gas machine, prevention and control of Yin damage and Yang, balance of Yin and Yang.

3.2 Gan weak flat fill

"The theory" cloud: "to make the spleen solid, gas without stagnation full, no sedentary, food without too acid, no food all creatures, should be sweet appropriate light", put forward the sweet and light products can nourish the spleen Yin, such as yam, lotus seed meat, dangshen, white surgery, etc., yam flat fill three Yin, can fill the spleen Yin. Wu Ju tong cloud: "the stomach Yin mo if gan cold, sour taste sour sweet Yin also", then with sour sweet products can nourish Yin Shengjin, and straight into the spleen and stomach, ping the Yin of the spleen

and stomach. At the same time, “the liver is bitter and urgent, urgent food to slow”, “the liver disease... with acid” so sour and sweet products in the treatment can also play a slow.

4. Conclusion

Chronic liver disease is difficult to treat clinically, especially when the disease develops to the stage of cirrhosis, which is a long process regardless of Chinese and Western medical treatment, and also brings pressure on the patient’s body, spirit, economy, etc. Therefore, we have to dig deeper into the classics of traditional Chinese medicine, which will bring more ideas for us to treat this disease. From the theory of spleen-yin, this article proposes three treatments, hoping to provide clinical ideas for the treatment of related diseases for the benefit of our colleagues.

References

[1] Qin XR, Chen YQ, Shi QL, et al. Research progress of Chinese medicine treatment of chronic viral hepatitis B [J]. Journal of Traditional Chinese Medicine, 2020, 48(07): 66-71.

[2] Cai M, Xiang M. Analysis of the thought of Wu Cheng’s method of “regulating the spleen and yin” [J]. Jiangsu Traditional Chinese Medicine,2022,54(10):13-15.

[3] Kou ZX, Chen KG. Chen precious spleen yin deficiency evidence treatment capture [J]. Jiangsu Traditional Chinese Medicine,2018,50(07):19-20.

[4] Yang JT, Liu XM. Spleen yin deficiency connotation and prescription evidence ruminations [J]. China Journal of Basic Chinese Medicine, 2021, 27(12): 1849-1850+ 1874.

[5] Pan ZM, Gao JM, Wang K, et al. Talking about spleen yin and liver yang based on the integration of liver and spleen [J]. Journal of Traditional Chinese Medicine, 2021, 27(10):158-161.

[6] Xu WC, Jia R, Li DG. On spleen yin deficiency and its clinical treatment rules [J]. Chinese Journal of Traditional Chinese Medicine,2017,32(01):57-59.

[7] Zhang GL, Li Y, Zhao JD, Li YP, Zhang L. An analysis of the spleen-yin method of Xu Jingshi [J]. Journal of Anhui University of Traditional Chinese Medicine, 2016, 35(03):48-50.

[8] Xue J, Wang XW, Lu S, Yan Q. Exploring the scientific connotation of “solid spleen method” in treating hepatocellular carcinoma based on the liver-intestinal axis [J]. Journal of Traditional Chinese Medicine, 2019, 60(07):551-555.

[9] Ye YA, Jin X, Li XK, Du HB. Traditional Chinese medicine treatment of chronic liver disease based on the “Liver-Spleen Synchronization” [J]. World Traditional Chinese Medicine.

[10] Sun YY, Huang X, Wang HY, Hao JM. Professor Yang Zhen’s experience of applying Zip Spleen Drink in treating blood evidence in the late stage of liver cirrhosis [J]. Shaanxi Traditional Chinese Medicine,2015,36(04):481+499.

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A Review of Treatment of Acute Ischemic Stroke

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Abstract: Treatment strategies for acute ischaemic stroke focus on two main areas: improving blood circulation to the brain and neuroprotection. However, these measures are only effective in the treatment of vascular stenoses. However, they are only effective within a narrow therapeutic window and are therefore limited. This article now provides a brief summary of the clinical treatment of acute ischaemic stroke and its future directions, with the aim of providing an updated direction and theoretical basis for relevant drug development.

Keywords: Acute Ischemic Stroke; Intravenous Thrombolysis; Intravenous Thrombolysis

1. Introduction

Stroke is the leading cause of death and disability worldwide, and the economic costs of treatment and post-stroke care are enormous[1]. Many factors are closely associated with the onset of stroke, including age, gender Acute ischaemic stroke is a condition in which the brain is damaged by the activation of neurons, astrocytes and oligodendrocytes.Treatment strategy of stroke focuses on improving cerebral circulation and neuroprotection[3].

2. Intravenous thrombolysis

The lysis technique has become the most commonly used treatment for vascular disease today. It uses the action of enzymes to dissolve the clot in the blood vessel, thus breaking up the clot in the vessel, and can effectively remove the tissue from the clot, thus improving the quality of life of the patient.Recent studies have found that thrombus composition may have a significant impact on the outcome of mechanical endothrombectomy, including a reduction in the number of recanalisation procedures, lower resistance to recovery and improved thrombolytic capacity. In a recent study, analysis of retrieved stroke thrombi revealed 2 main thrombotic zones with varying composition: (1) red cell-rich, fibrin-poor zones; or (2) platelet-rich, fibrin-rich zones.Embolism containing fibrinogen is associated with increased recanalisation operations, delayed treatment and poor clinical outcomes compared with embolism containing red blood cells. In general, intravenous thrombolytic therapy is the most effective means of managing severe ischaemic stroke, but his disadvantages are a tightly controlled time window, strict indications and the potential for serious adverse effects such as haemorrhage.

3. Endovascular therapy

In recent years, endovascular therapy has become an important tool for the diagnosis and treatment of acute ischaemic stroke, including mechanical thrombectomy and arterial thrombolysis techniques, which can significantly improve patient survival and prognosis [10-12]. Nevertheless, there are still many issues that need to be addressed. Firstly, how to select the right patients for the procedure, especially those who are not suitable for intravenous thrombolysis; and secondly, whether all patients can benefit from endovascular treatment Endovascular mechanical thrombectomy is performed by delivering an appropriate stent directly to the site of thrombotic occlusion, locally closing the stent, thereby creating a complete union between the cerebral embolus and the stent, and then slowly retracting the stent, where the stent and vessel will form The slow retraction creates friction between the stent and the vessel, using the adsorption function of the stent in the middle of the vessel to gradually bring up the cerebral embolus; arterial thrombolysis, on the other hand, is accomplished by introducing the catheter directly into the corresponding occluded vessel through an interventional device; and arterial thrombolysis technology can effectively inject thrombolytic drugs into the lesion of cerebral embolism quickly, thus achieving effective treatment. More revascularisation can be achieved and the risk of cerebral haemorrhage reduced, but this benefit is offset by delayed initiation [13]. Overall, endovascular treatment remains an important direction.

4. Antiplatelet therapy

Anti-platelet cell therapy is also one of the cornerstones of prevention in patients with ischaemic stroke. It reduces platelet clotting in damaged capillaries, thereby reducing cerebral embolism and clot production, keeping capillaries open [3], inhibiting the continued development of acute cerebral infarction and reducing its serious consequences. However, there are still many patients who have doubts and misconceptions about this approach. Therefore, there is a need to enhance knowledge dissemination in clinical practice to help patients understand and actively participate in antiplatelet therapy. Therefore, it is important to strengthen the prevention and treatment of stroke and to continuously explore and improve antiplatelet therapy protocols to reduce the incidence of stroke and disability.

5. Anticoagulation

In the acute phase of acute ischaemic stroke, anticoagulation may not be the only treatment, but rather because there is insufficient medical information to suggest that anticoagulation can prevent early recurrent stroke and thus prevent further deterioration of peripheral nervous system disease, thereby reducing mortality and disability and promoting recovery of peripheral nervous system function. In such cases, anticoagulation may be seen as a stopgap measure. However, in patients with other risk factors (e.g. hypertension, diabetes, etc.) or at risk of bleeding, anticoagulation should remain the first-line treatment option.Finally, anticoagulation therapy is not suitable for all people and needs to be considered in the context of individual differences. In conclusion, anticoagulation is an important secondary prevention measure that should not be overlooked, but should not be misused either.

6. Neuroprotective agents

Neurological monitoring has been one of the mainstays of ischaemic stroke prevention and treatment.Neuroprotective agents can reduce hypoxic damage and rescue brain cells in the hypoxic-ischaemic hemisphere by inhibiting aspects of the ischaemic cascade, thereby keeping brain cells undamaged prior to and during revascularisation, thereby extending the therapeutic window for intervention and thereby improving functional levels. As a result, there is growing interest in the development of effective neuroprotective agents.

Edaravone has emerged as an effective neuroprotective agent with multiple effects, one of the most important of which is the blocking of ion channels, the elimination of free radicals and its ability to effectively counteract oxidative induction, making it a safe and effective choice for randomised double-blind trials.

Conclusion

In recent years, progress has also been made in preventing acute ischaemic stroke and reducing the prognosis of mortality, but currently only rt-PA and MT intravenous thrombolysis are the most effective means of diagnosing acute ischaemic stroke. However, they are only effective within a narrow therapeutic window and are therefore limited. Neuroprotective therapies for neuron-focused AIS have failed. In conclusion, this paper concludes from a literature review that the pathogenesis of AIS is complex and requires a variety of approaches to prevention and treatment.

References

[1] GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 May;18(5):439-458.

[2] Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. Continuum (Minneap Minn). 2017 Feb;23(1, Cerebrovascular Disease):15-39.

[3] Zuo K, Yang XC, Zhong JC. Progress in the research of acute ischemic stroke injury mechanism and its therapeutic drugs[J]. Advances in Pharmacy,2019,43(08):576-583.

[4] Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative

stress, and inflammation. Lancet Neurol. 2016 Jul;15(8):869-881.

[5] Jolugbo P, Ariëns RAS. Thrombus Composition and Efficacy of Thrombolysis and Thrombectomy in Acute Ischemic Stroke. Stroke. 2021 Mar;52(3):1131-1142.

[6] Silva GS, Nogueira RG. Endovascular Treatment of Acute Ischemic Stroke. Continuum (Minneap Minn). 2020 Apr;26(2):310-331.

[7] Albers GW, Olivot JM. Intravenous alteplase for ischaemic stroke. Lancet. 2007 Jan 27;369(9558):249-50.

[8] Ahn SH, Hong R, Choo IS, Heo JH, Nam HS, Kang HG, Kim HW, Kim JH. Histologic features of acute thrombi retrieved from stroke patients during mechanical reperfusion therapy. Int J Stroke. 2016 Dec;11(9):1036-1044.

[9] Staessens S, Denorme F, Francois O, Desender L, Dewaele T, Vanacker P, Deckmyn H, Vanhoorelbeke K, Andersson T, De Meyer SF. Structural analysis of ischemic stroke thrombi: histological indications for therapy resistance. Haematologica. 2020 Jan 31;105(2):498-507.

[10]Goyal M, Menon BK, Van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016 Apr 23;387(10029):1723-31.

[11]Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018 Feb 22;378(8):708-718.

[12]Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999 Dec 1;282(21):2003-11.

[13]Warner JJ, Harrington RA, Sacco RL, Elkind MSV. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke. Stroke. 2019 Dec;50(12):3331-3332.

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Clinical Efficacy and Prognosis of Budesonide Nasal Spray in the Treatment of Allergic Rhinitis

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Abstract: To explore the clinical efficacy of budesonide nasal spray in the treatment of allergic rhinitis. Methods: 100 patients with allergic rhinitis who received treatment in our hospital from January 2022 to January 2023 were selected as the study subjects. Patients were randomly divided into two groups, a control group and an experimental group, with 50 patients in each group. Both groups of patients require treatment with loratadine. On this basis, patients in the experimental group were more likely to use budesonide nasal spray than patients in the control group. Observe the efficacy and adverse reactions of the two groups of patients. Results: The treatment effect and recurrence rate of rhinitis in the experimental group were better than those in the control group, and the treatment effect was good. The recurrence rate of patients was also decreasing. There was no significant difference in adverse reactions between the two groups (P>0.05). Conclusion The experimental group of budesonide nasal spray has good efficacy and prognosis in the treatment of allergic rhinitis, with safety assurance and ideal application effect, which is worthy of clinical promotion and application.

Keywords: Allergic Rhinitis; Budesonide Nasal Spray; Therapeutic Efficacy; Prognosis; Loratadine

1. Data and Methods

1.1 General information of the experimental group

During the period from experimental group 2022, experimental group year, experimental group 1, experimental group month, to January 2023, 100 patients with allergic rhinitis in the experimental group who came to our hospital for treatment were randomly divided into experimental group and control group, with 50 patients in each group. After comparing the basic data of patients in the two experimental groups, there was no significant difference, which can be compared (P experimental group>experimental group 0.05).

1.2 Inclusion and Exclusion Criteria

Inclusion criteria: The patient was identified as an allergic rhinitis patient after examination, and the patient was over 18 years old. The patient's disease cycle is more than 1 year, and before coming to our hospital for treatment, the patient has not received glucocorticoids, antihistamines, or other related treatment within the shortest three months. Personnel participating in the experiment should undergo blood routine tests and liver and kidney function tests to determine that the patient's organs do not have pathological changes. Before participating in the experiment, all patients and their families were informed and signed an informed consent form. Exclusion criteria: The patient was not tested for allergic rhinitis. Testing is required for the drugs used, and non drug resistant patients cannot participate in the experiment. Patients with nasal polyps, sinusitis, and bronchial asthma cannot participate in the experiment. Patients with mental and psychological abnormalities cannot participate, and patients during pregnancy and lactation are excluded from participating in the experiment. Patients with malignant tumors and a history of allergy to some drugs, who have been using other drugs for a long time, and patients with chronic diseases cannot participate in the experimental study.

1.3 Method

The included patients were first given symptomatic treatment such as spasmolysis, cough relief, and asthma relief; Antibiotic treatment is required for patients with infection. Both groups of patients were given oral treatment with loratadine (Hainan Xinshitong Pharmaceutical Co., Ltd., Guoyao Zhunzi Experimental Group H20041886). On the basis of this, patients in the experimental group were given budesonide

nasal spray (Swedish experimental group McNeil experimental group Sweden experimental group AB, Guoyao Zhunzi experimental group J20180024), Daily experimental group 2 experimental groups and each side of nasal spray experimental group 64 ug/experimental group times. Both groups of patients were continuously treated for 4 weeks in the experimental group. During the implementation of treatment, patients in both experimental groups were strictly prohibited from eating more greasy foods, and more attention should be paid to keeping warm and avoiding various allergens.

1.4 Observations of the experimental group

(1) Treatment effectiveness: It is divided into significant, effective, and ineffective. Significant indicates that the patient's clinical symptoms completely disappear after treatment, and there is no recurrence within three months. Effective indicates that the patient's clinical symptoms have significantly improved after treatment, and ineffective indicates that the patient's clinical symptoms have not significantly changed before and after treatment. The total effective rate of treatment is calculated based on significant and effective; (2) Adverse reactions: These include itching of the skin, dry nasal passages, and bloodstains in mucus; (3) Recurrence rate.

1.5 Experimental Group Statistical Methods

This research data was all analyzed using the experimental group SPSS22.0 experimental group software, and the count data was expressed as "[experimental group example (%)]"" χ 2 "Test data differences; The measurement data is expressed as "($x \pm s$)", and the data difference is tested with "t". If the experimental group P is less than the experimental group 0.05, it is significant.

2. Results

2.1 Comparison of clinical efficacy between the experimental group and the two groups

After treatment, the total effective rate of clinical treatment in the experimental group was significantly higher than that in the control group, with significant differences in data comparison between the groups (P<0.05 in the experimental group).

2.2 Comparison of adverse reactions in the experimental group

During the treatment period, the incidence of adverse reactions in the experimental group was 7 cases (14%), of which 2 patients in the experimental group developed itching of the skin, 1 patient in the experimental group developed dry nasal cavity, and 4 patients in the experimental group developed bloodstains in the nasal discharge; The incidence of adverse reactions in the control group was 5 patients (10.00%) in the experimental group, of which 1 patient in the experimental group developed skin itching and 4 patients in the experimental group developed nasal dryness. There was no significant difference in the incidence of adverse reactions between the two groups (χ 2=0.125, P=0.723, P experimental group>experimental group 0.05).

2.3 Comparison of recurrence

After months of treatment in experimental group 3, 4 patients in experimental group experienced recurrence, with a recurrence rate of 8% in experimental group 2; Patients in the control group experienced 10 relapses in the experimental group, with a recurrence rate of 10 cases (5%) in the experimental group. The recurrence rate of patients in the experimental group was significantly lower than that of patients in the control group, with significant differences in data comparison between the groups (χ 2=5.165, P=0.023, P experimental group<experimental group 0.05).

3. Discussion

Allergic rhinitis is mainly caused by the patient's own cell hypertrophy, while the IgE antibody in the experimental group binds to allergens on basophils, resulting in allergic lesions. The clinical manifestations of patients with allergic rhinitis include sneezing, nasal conges-

tion, and itching. Severe patients may experience shortness of breath and mutual shortness of breath. Therefore, in conducting the research experiment, the selected patients participating in the experiment cannot have diseases such as nasal polyps, sinusitis, and asthma. The most serious problem with allergic rhinitis is that the disease cannot be eradicated and is prone to relapse. After long-term medication, patients are prone to develop drug resistance. What is more serious is that patients are affected by the constant changes in the external environment, and eventually will have a more serious recurrence. The etiology of allergic rhinitis is relatively complex, and the pathogenesis cannot be determined at all. There are many causes of the disease, including air pollution, dietary structure, or sulfur monoxide issues.

At the present stage, conventional western medicine is often used in clinical treatment of allergic rhinitis, including the intervention of anti allergic drugs and hormone drugs. Although certain clinical effects can be achieved, there are many adverse reactions, and long-term use has drug resistance. The patient's disease recurrence rate is high, which is not conducive to improving the prognosis of the patient. As a long-term antihistamine, loratadine can competitively inhibit histamine by binding to receptors in the histamine experimental group H1 experimental group, thereby effectively relieving symptoms such as nasal itching, nasal congestion, and sneezing. However, this drug has a slow onset of action and its single use is not ideal. Therefore, on the basis of regular drug treatment, the use of glucocorticoid preparations for treatment has positive significance, As a glucocorticoid preparation, budesonide nasal spray has a good anti allergic effect. It can inhibit inflammatory mediators and reduce their secretion and synthesis, effectively control rapid local allergic reactions. It has a rapid and lasting effect, and has ideal curative effect. Budesonide nasal spray has good anti allergic and local anti-inflammatory effects. Nasal spray with aerosol can increase the concentration of local drugs, quickly improve airway inflammation, inhibit inflammatory damage mediated by immunoglobulin test group E, enhance the stability of smooth muscle cells and endothelial cells, reduce the sensitivity of stimulation receptors, and reduce the release of inflammatory mediators, thereby quickly relieving nasal congestion, runny nose Clinical symptoms such as nasal itching and sneezing can also regulate cytokines and eosinophils, thereby promoting the synthesis of anti-inflammatory proteins in cells. Budesonide nasal spray can play a therapeutic role in many ways, with strong anti-inflammatory effects, rapid onset, and lasting effects, which can promote patients' early recovery.

This time, patients in the control group were treated with loratadine orally. On this basis, patients in the experimental group were treated with budesonide nasal spray. The results showed that the clinical efficacy and recurrence rate of patients in the experimental group were significantly better than those in the control group ($P<0.05$ in the experimental group), and there was no significant difference in adverse reactions between the two groups ($P>0.05$); This shows that in patients with allergic rhinitis, the combination of loratadine and budesonide nasal spray has a more ideal effect, and can reduce the recurrence rate of patients without causing more adverse reactions. It can provide long-term and stable control of the condition, with higher clinical application safety.

References

[1] Liu M, Chen YY, Su L, Sun MQ. Clinical study on the treatment of acute sinusitis with nasal sinusitis oral liquid and budesonide in experimental group [J]. Modern Medicine and Clinical, 2021 (03).

[2] Zhang LY, Chen YF. Clinical efficacy of budesonide inhalation in the treatment of acute infectious laryngitis in children in the experimental group [J]. North Pharmaceutical, 2022 (07).

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Application of Single Hole Laparoscopic Technique in Gynecological Accessory Surgery

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Abstract: Objective: To explore the application of single hole laparoscopic technique in gynecological accessory surgery. Methods: From January 2021 to December 2022, 30 patients in the hospital department who applied single hole laparoscopic appendage surgery were selected for the experiment. Thirty patients were divided into the control group and the observation group, with 15 patients in each group. The patients in the control group were treated with conventional three hole laparoscopic surgery, and the patients in the observation group were treated with single hole Laparoscopy. The relevant indicators of patients in the two experimental groups during the operation and the scores of postoperative recovery were compared. Result: After the experiment, it was found that the sample removal time of the observation group patients was significantly faster than that of the control group. The pain score of the observation group patients at 24 hours after surgery was significantly lower than that of the control group, and the incision beauty score of the patients at 14 days after surgery was higher than that of the control group, with a statistically significant difference ($P<0.05$). Conclusion: The application of single hole laparoscopic surgery in gynecological accessory surgery has a good effect. This type of surgical treatment will make patients more satisfied. Compared with conventional Laparoscopy, it can better reduce the postoperative scar of patients.

Keywords: Single Port Laparoscopic Technique; Gynecology; Attachment Surgery; Application

Introduction

At present, three hole and four hole Laparoscopy are the most commonly used surgical methods in gynecological clinic in China. These operations have good effects. Single hole Laparoscopy is mainly performed with the help of natural scars on the human umbilical. According to relevant survey data, the effect of single hole Laparoscopy in the treatment of gynecological accessory diseases will be better. This type of surgery can achieve the goal of scar free abdominal wall, which is more beautiful and can effectively improve the quality of life of current young women. Exploring the application effect of single hole laparoscopic technology in gynecological accessory surgery, analyzing the safety and feasibility of its surgical treatment method, the following report is presented.

1. Experimental Data and Methods

1.1 Experimental data

Collect information on 30 patients who underwent single port laparoscopic appendage surgery in the hospital from January 2021 to December 2022, and use them as experimental subjects. Among them, the observation group had a minimum age of 22 years and a maximum age of 37 years, with an overall average age of 30 years; The minimum body mass is 20kg/m2, the maximum body mass is 23kg/m2, and the average body mass is 22kg/m2; 4 cases were unmarried and 11 cases were married; There were 8 cases of fallopian tube lesions and 7 cases of ovarian lesions. The minimum age of patients in the control group was 23 years old, and the maximum age was 36 years old, with an overall average age of 30 years; The minimum body mass is 20kg/m2, the maximum body mass is 22kg/m2, and the average body mass is 22kg/m2; 5 cases were unmarried and 10 cases were married; There were 9 cases of fallopian tube lesions and 6 cases of ovarian lesions. The general data comparison between the two experimental groups showed no statistically significant difference ($P>0.05$), indicating comparability.

1.2 Experimental Methods

The patients in the two experimental groups used the same preparation method before surgery. They prepared skin routinely and

cleaned the umbilicus position of the patients. They should abstain from eating and drinking. In the afternoon before surgery, they needed to take compound polyethylene glycol orally for intestinal preparation, and Tracheal intubation was used for general anesthesia.

The patients in the control group used conventional laparoscopic three hole surgery. The pneumoperitoneum needle was placed in the longitudinal incision at the lower edge of the patient, and carbon dioxide was injected. After the pressure reached 13 mmHg, the laparoscopic probe was used for exploration. In combination with the type of disease of the patient, appropriate operating instruments were selected for subsequent treatment such as removal of Ovarian cyst.

The patients in the observation group were treated with single hole Laparoscopy. Using the special equipment for single hole laparoscopic surgery, a 2 to 3 cm arc skin incision was made at the upper edge of the patient, and the pneumoperitoneum needle was punctured into it. The pneumoperitoneum was constructed. When the patient's pneumoperitoneum pressure was maintained at about 13 mmHg, a PORT was set in the middle of the arc incision to explore the patient's pelvic cavity and abdominal cavity, and evaluate the feasibility of single hole surgery through the umbilical cord. According to the type of patients, different operating equipment should be selected to perform partial salpingectomy or Ovarian cyst stripping on the affected side. If necessary, use a specimen bag to remove the specimen and send it to the pathological examination. After the surgery is completed, remove the puncture sleeve and stitch the position of the patient's umbilical incision layer by layer, with 2 intermittent stitches.

2. Results

2.1 Comparison of specimen retrieval times between two groups of patients

The sample removal time of patients in the observation group was significantly faster than that of the control group, and the difference was statistically significant ($P<0.05$), as shown in Table 1.

group	Number of cases	Sample removal time
Observers	15	15.30±5.64
control group	15	22.36±6.75
P		＞ 0.05

2.2 Comparison of surgical related indicators and incision beauty scores between the two groups

The pain score of patients 24 hours after surgery will be significantly lower than that of the control group, and the incision beauty score of patients on the 14th day will exceed that of the control group on the 14th day after surgery, with a statistically significant difference ($P<0.05$).

3. Conclusion

Laparoscopy is a particularly important treatment for gynecological accessory diseases, and its role is particularly significant. With the improvement of people's living standards at this stage, under the influence of various factors, the number of gynecological patients who choose Laparoscopy continues to increase, and with the improvement of people's requirements for the quality of surgery, Laparoscopy not only needs to ensure the treatment effect, but also should gradually achieve the goal of minimizing surgical trauma. The application of single hole Laparoscopy through the umbilical cord will cause less surgical trauma, and there is no statistical difference between the exhaust time, intraoperative bleeding, etc. and the relevant indicators of conventional Laparoscopy. However, the time for taking out the specimen of single hole surgery will be shorter, the overall patient's postoperative pain score will be lower, and the aesthetic satisfaction will be higher ($P<0.05$), which is roughly the same as the results of previous studies. Single hole Laparoscopy can significantly reduce the removal time, prevent the embarrassment of traditional treatment of cutting tissue and remove, and reduce the risk of specimen residue, because the removal hole is large during specimen removal. Single hole Laparoscopy has all the advantages of traditional laparoscopy, so it is more and more popular with patients, so it has good prospects for development. However, the traditional Laparoscopy instrument is difficult to overcome the bottleneck of single hole laparoscopy, and the bendable instrument has poor controllability and is not an ideal tool. At present, almost all research-

ers focus on the research and development of robot systems. LESS has many advantages that are worth promoting, and problems such as surgical instruments and techniques can also be effectively solved. However, it is not suitable for everyone and has its own indications. The evaluation of its safety and feasibility should be comprehensively considered based on the patient's situation. Individualization of Minimally invasive procedure is reflected in every link of diagnosis and treatment. Blind minimally invasive surgery will increase the potential risks of surgery and anesthesia. Therefore, when using LESS technology, it is necessary to understand the gynaecological diseases, the patient's age, basic status, whether there are complex complications and other complications, previous surgical history, beauty requirements, economic conditions and other factors, and also consider the local medical equipment and medical resources at the time. Using the existing Da Vinci robotic surgery system, KaouK and others have completed robotic single hole Laparoscopy. The new generation of flexible robot systems has successfully completed nephrectomy and pyeloureteroplasty on animals, and it is believed that they will also be applied in the field of gynecology in the near future, making greater contributions to the vast number of gynecological patients.

To sum up, the single hole laparoscopic technique is an important part of Laparoscopy. The application of its surgical method can effectively reduce the postoperative pain of patients, improve the body surface aesthetics, and its operation will be less difficult, with advantages such as convenient operation. Operators need to possess certain operational skills and grasp the indications of patients in order to provide more suitable surgical treatment services and reduce postoperative scars.

References

[1] Huang YP, Zhang SY, Huang XL, et al. The application of single hole laparoscopic technique in gynecological accessory surgery [J] Shenzhen Journal of Integrated Traditional Chinese and Western Medicine, 2021, 31 (20): 128-130.

[2] Jia ML, Yang J, Shi KG, etc The application of mini laparoscopy in gynecological surgery [J] Online magazine of Surgery, 2022,9 (4): 59-63.

[3] Jiang J, Mao SQ, Sun RF, etc The application of conventional instrument transumbilical microporous laparoscopic technique in gynecological surgery [J] Chinese Practical Medicine, 2018,13 (27): 66-67.

[4] Liu LY. Do you understand the advantages of gynecological Laparoscopy [J] Big Health, 2020 (35): 32,34.

[5] Yang X. Exploration of the application of single hole laparoscopic technology in gynecological diseases: a single center based clinical study [D] Jiangsu: Southeast University, 2021.

Universe Scientific Publishing

Research Progress on the Role of M6A Methylation Modification in the Genesis and Development of GC

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Abstract: Modification of M6A RNA methylation is the most prevalent form of RNA editing in eukaryotic organisms. The m6A-methylated regulatory protein is intimately associated with biological processes, including GC proliferation, invasion, and metastasis. This protein is anticipated to serve as a target for the clinical treatment of GC in the future. This comprehensive review delineates the most recent advancements and clinical implications of m6A aberrant modification in GC, aiming to furnish a novel research avenue for the exploration of GC's future direction.

Keywords: GC; m6A; ALKBH5; Epigenetics

Introduction

The term gastric cancer (GC) refers to a malignant tumor that develops within the digestive system. As per the Global Cancer Statistics Report in 2020, GC ranks as the fifth most prevalent cancer globally and stands fourth in terms of cancer-related mortality. Annually, more than one million new cases are reported[1]. The early signs of GC are subtle and often overlooked, resulting in a majority of diagnoses occurring in the middle to late stages. This delays the initiation of optimal treatment, placing patients at a higher risk of missing the best therapeutic window or experiencing intolerable systemic toxic reactions due to chemotherapy drugs. Consequently, the prognosis for these patients is generally unfavorable[2]. The development of GC can be influenced by numerous unmodifiable risk factors, such as advancing age[3], being male[4],and inheritable genetic factors[5],among others. Additionally, there are several modifiable pathogenic factors that can contribute to the onset of GC, including Helicobacter pylori infection[6],EB virus infection[7],and the presence of GC stem cells[8].

Precise epigenetic factors significantly contribute to the genesis and progression of tumors. The ever-expanding scope of epigenetic research has revealed a potential link between the invasive and metastatic capabilities of GC cells and epigenetics[9]. Among the various aspects, the investigation of the interaction mechanism between m6A RNA methylation and its regulatory molecules has emerged as a prominent research hotspot[10]. Modification of m6A RNA is intimately associated with the incidence, progression, prognosis, and drug responsiveness of GC. Consequently, targeting abnormal m6A modifications holds great. The present article reviews the current advancements in research and clinical application of m6A aberrant modification in GC, aiming to inspire the exploration of novel therapeutic targets for this malignancy.

1. Overview of M6A RNA Methylation

The term "m6A RNA methylation" refers to the modification of base A at its sixth nitrogen atom through methylation. This modification, known as m6A, is the most prevalent form of RNA modification and is widely observed in the mRNAs and lncRNAs of eukaryotes[11]. The regulation of m6A modification encompasses a wide range of RNA metabolic activities, including but not limited to RNA maturation, cleavage, transportation, degradation, and translation. The m6A modification, similar to DNA methylation or histone methylation, is a dynamic and reversible process primarily mediated by methyltransferase enzymes, demethylase enzymes, and RNA methylation-binding proteins[12].

The methylation of the sixth nitrogen atom in RNA adenine is catalyzed by methyltransferase, which primarily consists of methyltransferase-like protein 3 (METTL3), methyltransferase-like protein 14 (METTL14), and Wilms tumor 1 associated protein 1-associated protein (WTAP) et al. [13]. The demethylation of RNA is primarily catalyzed by two demethylases, namely fat mass and obesity-associated protein

(FTO) and alpha-ketoglutarate-dependent dioxygenase homolog 5 (ALKBH5) [14]. The methylated reading protein is capable of recognizing and binding the M6A-modified base, thereby recruiting the RNA into a specialized protein complex. This process influences the metabolic pathway of RNA and regulates the expression of target genes. The previously identified m6A recognition protein harbors the YT521-B homology (YTH) domain, encompassing YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2. These proteins play a pivotal role in facilitating mRNA degradation. The insulin-like growth factor 2 mRNA binding protein (IGF2BP), including IGF2BP-1, IGF2BP-2, and IGF2BP-3, is also a methylated RNA-binding protein. In contrast to the YTH domain family proteins, IGF2BP enhances mRNA stability and promotes protein translation[15].The present article provides a comprehensive review on the pivotal role of m6A-modified proteins in the initiation and progression of GC.

2. Research Progress of M6A Methylation and GC

With the continuous advancement of science and technology, our comprehension of m6A methylation modification has progressively deepened. Through intricate mechanisms, m6A modification exerts a certain impact on the occurrence and progression of GC.

2.1 M6A Methyltransferase and GC

The role of ADAMTS9 as a downstream regulator of METTL3 in GC has been demonstrated by multiple studies, highlighting its ability to activate the PI3K/AKT pathway and drive the progression of GC[16]. METTL3-mediated m6A modification of lncRNA SNHG3 accelerates GC progression by regulating the miR-186-5p/cyclinD2 axis[17]. The miR-181-5p/KLHL5 complex facilitates the proliferation, migration, and invasion of GC cells by modulating METTL3 to activate the m6A process[18]. The WTAP-mediated FAM83H-AS1 facilitates GC development through m6A modification, thereby offering a novel biomarker for the diagnosis and targeted therapy of GC[19]. The oncogenic role of KIAA1429 in GC is mediated by its ability to stabilize c-Jun mRNA, independent of m6A modification[20]. Studies have demonstrated that METTL16 can contribute to the promotion of GC by augmenting the stability of cyclin D1 mRNA[21]. These findings suggest that certain m6A methyltransferases play a role in promoting the initiation and progression of GC, thus necessitating further investigation into their mechanisms of action within this context.

The expression of METTL14 led to an increase in the m6A methylation level of circORC5 and a subsequent inhibition of its expression. This resulted in the up-regulation of miR-30c-2-3p and down-regulation of AKT1S1 and EIF4AB, ultimately leading to the suppression of GC progression[22]. The METTL14 protein serves as a prominent regulator of aberrant m6A modification in GC, exerting its tumor suppressor role by deactivating the PI3K/AKT/mTOR pathway and modulating the EMT pathway, thereby impeding GC cell progression and invasion[23]. The findings suggest that the m6A methyltransferase METTL14 exerts inhibitory effects on GC, indicating its potential as a promising biological target with significant implications in GC.

2.2 M6A Demethylase and GC

The M6A demethylase FTO has the ability to enhance PI3K/AKT signal transduction, thereby facilitating GC progression. Consequently, FTO serves as a valuable prognostic biomarker for GC[24]. The FTO enzyme also facilitates caveolin-1 mRNA degradation through demethylation, regulates mitochondrial fission/fusion and metabolism, and enhances GC proliferation and metastasis[25]. According to Hu et al., PKMYT1 is identified as the downstream target gene of ALKBH5, which undergoes m6A modification and can subsequently be recognized and bound by the “reader” protein IGF2BP3. This interaction leads to enhanced mRNA stability and increased expression levels of PKMYT1, ultimately resulting in a significant promotion of GC metastasis[26]. The diverse findings imply the necessity for further investigation into the mechanisms of various m6A demethylases in GC, aiming to offer novel insights and targets for clinical management of stomach malignancies.

2.3 M6A Reading Protein and GC

Chen et al. discovered that PLAGL2 enhances the expression of Snail and promotes GC progression through the UCA1/miR-145-

5p/YTHDF1 pathway, indicating that targeting PLAGL2 could be a potential therapeutic strategy for GC therapy[27]. The overexpression of YTHDF1 in GC is associated with a pro-tumor role. Loss of YTHDF1 leads to the upregulation of IFNGR1 and activation of JAK1/2-STAT1 pathways in tumor cells, potentially restoring sensitivity to anti-tumor immune responses. Targeting YTHDF1 can enhance adaptive anti-tumor immunity, thereby facilitating effective immunotherapy for GC[28]. The study conducted by Shen et al. demonstrated that YTHDF2 exerts inhibitory effects on the growth of GC cells through negative regulation of FOXC2, thus suggesting its potential as a prognostic marker for GC[29]. The m6A reader IGF2BP2 binds to and stabilizes CSF2 mRNA in GC MSCs, while CSF2 induces Notch1 ubiquitination for the reprogramming of MSCs[30].

3. Progress in the Clinical Treatment of M6A Methylation and GC

Chemotherapy plays a pivotal role as a non-surgical therapeutic modality for patients diagnosed with GC. Current research endeavors in the field of m6A modification in GC predominantly revolve around unraveling mechanisms underlying chemotherapy resistance. Wang et al.'s study demonstrated that knockdown of METTL3 induced apoptosis in oxaliplatin (OXA)-resistant GC cells and significantly inhibited the DNA repair pathway. Therefore, targeting METTL3 could potentially enhance the efficacy of oxaliplatin in treating GC[31]. The promotion of KIAA1429 enhances the resistance of GC cells to OXA by facilitating the stabilization of FOXM1 mRNA[32]. Zhu et al. discovered that KIAA1429 was upregulated in cisplatin-resistant GC cells, and its regulation of GC cell sensitivity to cisplatin was mediated through the stabilization of FOXM1 mRNA, providing supporting evidence for potential therapeutic strategies[33]. Liu et al. discovered that WTAP plays a crucial role in accelerating TGF-β signaling, thereby promoting the epithelial mesenchymal transition (EMT) of GC cells and conferring enhanced resistance to chemoradiotherapy. Consequently, WTAP exhibits promising potential as a predictive biomarker for GC[34].

4. Summary and Prospect

Currently, numerous studies have demonstrated the dual regulatory role of m6A modification in GC. The modulation of m6A modification levels can either facilitate or impede the progression of GC. The m6A modification system, comprising a diverse array of regulatory proteins, is intricately associated with GC. Although significant advancements have been made in current research, there remains a substantial gap in fully elucidating the complete picture, warranting further investigation.

In conclusion, the investigation of m6A modification and regulatory proteins presents a novel concept for the diagnosis, prognosis, and treatment of GC, thereby paving the way for exploring its underlying mechanisms. Anticipated advancements in clinical studies are expected to facilitate its application in medical practice, benefiting a substantial number of patients with GC.

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Conflict Of Interest

The researchers affirm that the study was carried out without any affiliations or financial associations that could be interpreted as a possible source of conflict of interest.

References

[1] Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021. 71(3): p. 209-249.

[2] Zong, L., et al., The challenge of screening for early GC in China. Lancet, 2016. 388(10060): p. 2606.

[3] Asaka, M., et al., GC deaths by age group in Japan: Outlook on preventive measures for elderly adults. Cancer Sci, 2020. 111(10): p.

3845-3853.

[4] Wang, S., et al., Global and national trends in the age-specific sex ratio of esophageal cancer and GC by subtype. Int J Cancer, 2022. 151(9): p. 1447-1461.

[5] Wang, F., et al., Family history of malignant tumor is a predictor of GC prognosis: Incorporation into a nomogram. Medicine (Baltimore), 2022. 101(35): p. e30141.

[6] Usui, Y., et al., Helicobacter pylori, Homologous-Recombination Genes, and GC. N Engl J Med, 2023. 388(13): p. 1181-1190.

[7] Comprehensive molecular characterization of gastric adenocarcinoma. Nature, 2014. 513(7517): p. 202-9.

[8] Nguyen, P.H., et al., Characterization of Biomarkers of Tumorigenic and Chemoresistant Cancer Stem Cells in Human Gastric Carcinoma. Clin Cancer Res, 2017. 23(6): p. 1586-1597.

[9] Lander, E.S., et al., Initial sequencing and analysis of the human genome. Nature, 2001. 409(6822): p. 860-921.

[10] Guan, K., et al., Expression Status And Prognostic Value Of M6A-associated Genes in GC. J Cancer, 2020. 11(10): p. 3027-3040.

[11] Liang, Z., et al., Epigenetic N6-methyladenosine modification of RNA and DNA regulates cancer. Cancer Biol Med, 2020. 17(1): p. 9-19.

[12] Melstrom, L. and J. Chen, RNA N(6)-methyladenosine modification in solid tumors: new therapeutic frontiers. Cancer Gene Ther, 2020. 27(9): p. 625-633.

[13] Weng, H., H. Huang, and J. Chen, RNA N (6)-Methyladenosine Modification in Normal and Malignant Hematopoiesis. Adv Exp Med Biol, 2019. 1143: p. 75-93.

[14] Mauer, J. and S.R. Jaffrey, FTO, m(6) A(m) , and the hypothesis of reversible epitranscriptomic mRNA modifications. FEBS Lett, 2018. 592(12): p. 2012-2022.

[15] Meyer, K.D. and S.R. Jaffrey, The dynamic epitranscriptome: N6-methyladenosine and gene expression control. Nat Rev Mol Cell Biol, 2014. 15(5): p. 313-26.

[16] Wang, N., et al., METTL3-Mediated ADAMTS9 Suppression Facilitates Angiogenesis and Carcinogenesis in GC. Front Oncol, 2022. 12: p. 861807.

[17] Ji, G., X. Wang, and H. Xi, METTL3-mediated m(6)A modification of lncRNA SNHG3 accelerates GC progression by modulating miR-186-5p/cyclinD2 axis. Int J Immunopathol Pharmacol, 2023. 37: p. 3946320231204694.

[18] Li, R., et al., miR-181-5p/KLHL5 Promoted Proliferation and Migration of GC Through Activating METTL3-Mediated m6A Process. Mol Biotechnol, 2023.

[19] Liu, N., C. Zhang, and L. Zhang, WTAP-Involved the m6A Modification of lncRNA FAM83H-AS1 Accelerates the Development of GC. Mol Biotechnol, 2023.

[20] Miao, R., et al., KIAA1429 regulates cell proliferation by targeting c-Jun messenger RNA directly in GC. J Cell Physiol, 2020. 235(10): p. 7420-7432.

[21] Wang, X.K., et al., METTL16 promotes cell proliferation by up-regulating cyclin D1 expression in GC. J Cell Mol Med, 2021. 25(14): p. 6602-6617.

[22] Fan, H.N., et al., METTL14-mediated m(6)A modification of circORC5 suppresses GC progression by regulating miR-30c-2-3p/AKT1S1 axis. Mol Cancer, 2022. 21(1): p. 51.

[23] Liu, X., et al., The m6A methyltransferase METTL14 inhibits the proliferation, migration, and invasion of GC by regulating the PI3K/AKT/mTOR signaling pathway. J Clin Lab Anal, 2021. 35(3): p. e23655.

[24] Zhu, Y., et al., Demethylase FTO enhances the PI3K/Akt signaling to promote GC malignancy. Med Oncol, 2023. 40(5): p. 130.

[25] Zhou, Y., et al., N6-methyladenosine demethylase FTO promotes growth and metastasis of GC via m(6)A modification of caveolin-1 and metabolic regulation of mitochondrial dynamics. Cell Death Dis, 2022. 13(1): p. 72.

[26] Hu, Y., et al., Demethylase ALKBH5 suppresses invasion of GC via PKMYT1 m6A modification. Mol Cancer, 2022. 21(1): p. 34.

[27] Chen, W., et al., PLAGL2 promotes Snail expression and GC progression via UCA1/miR-145-5p/YTHDF1 axis. Carcinogenesis,

2023. 44(4): p. 328-340.

[28] Bai, X., et al., Loss of YTHDF1 in gastric tumors restores sensitivity to antitumor immunity by recruiting mature dendritic cells. J Immunother Cancer, 2022. 10(2).

[29] Shen, X., et al., YTHDF2 Inhibits GC Cell Growth by Regulating FOXC2 Signaling Pathway. Front Genet, 2020. 11: p. 592042.

[30] Ji, R., et al., IGF2BP2-meidated m(6)A modification of CSF2 reprograms MSC to promote GC progression. Cell Death Dis, 2023. 14(10): p. 693.

[31] Wang, Y., et al., METTL3 promotes drug resistance to oxaliplatin in GC cells through DNA repair pathway. Front Pharmacol, 2023. 14: p. 1257410.

[32] Tang, B., et al., N(6)-methyladenosine (m(6)A) writer KIAA1429 accelerates GC oxaliplatin chemoresistance by targeting FOXM1. J Cancer Res Clin Oncol, 2023. 149(8): p. 5037-5045.

[33] Zhu, Z., et al., m(6)A Methyltransferase KIAA1429 Regulates the Cisplatin Sensitivity of GC Cells via Stabilizing FOXM1 mRNA. Cancers (Basel), 2022. 14(20).

[34] Liu, Y. and M. Da, Wilms tumor 1 associated protein promotes epithelial mesenchymal transition of GC cells by accelerating TGF-β and enhances chemoradiotherapy resistance. J Cancer Res Clin Oncol, 2023. 149(7): p. 3977-3988.

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The Development of Big Data & Artificial Intelligence in the Field of Healthcare——The Case of Ping An Health (Ping An Good Doctor)

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Abstract: This report explores the utilization of big data and artificial intelligence (AI) in the healthcare sector, focusing on the case of Ping An Health (formerly Ping An Good Doctor) in China. The rapid advancement of Internet technology has propelled the widespread adoption of these technologies across various industries. Ping An Health leverages its platform's advantages to continuously innovate and enhance user experience, positioning itself at the forefront of the industry. The report delves into Ping An Health's AI and big data technologies, offering critical analyses of the ethical, political, and social implications surrounding the company.

Keywords: Big Data; Artificial Intelligence; Ping An Health; Healthcare

Introduction

The rapid development of Internet technology has promoted the rapid popularization of big data and artificial intelligence. These two emerging technologies have been well applied in many fields (Mittelstadt & Floridi, 2016). In the field of healthcare, many medical technology companies have made breakthrough achievements by applying big data and artificial intelligence to online medical service systems. Ping An Healthcare and Technology Co., Ltd. makes full use of the advantages of the platform to continuously develop emerging technologies to create excellent medical experience for users, so that it has been at the forefront of the industry ("Ping An Good Doctor," 2021). This report will use the Chinese Ping An Health (Ping An Good Doctor) as an example to describe the company's artificial intelligence and big data technologies and critically analyse the ethical, political and social issues of the company.

1. Ping An Health (Ping An Good Doctor)

Ping An Good Doctor was renamed Ping An Health on January 27, 2021. However, as Ping An Good Doctor is more well-known to the audience, most people in China are still accustomed to calling it Ping An Good Doctor. Founded in November 2014, Ping An Good Doctor is a healthcare software company based in Shanghai, China ("Ping An Good Doctor," 2021). The company provides a platform for online consultations, hospital referrals and appointments services ("Ping An Healthcare and Technology Co Ltd," 2021). Social distance was important during the past three years, and the Internet medical platform alleviated the problem of difficult medical treatment at that time, even changed the medical habits of many potential users in a short time (Oak, 2020).

Currently, in China, most users with Internet medical needs will choose Ping An Health. Ping An Health is China's leading medical platform. Relying on the leading AI medical technology, Ping An Health integrates its own medical team, external contracted doctors and offline medical network resources to provide online consultations and drug purchases services ("Ping An Good Doctor Global Medical Consultation Platform," 2021). In addition, Ping An Health's real-time consultation and health content services are constantly changing people's health awareness. Ping An Health gradually establishes a personal health file for each user, so that they can have a clearer understanding of their health status ("Ping An Good Doctor," 2021).

2. Artificial Intelligence and Big Data

Big data is a method of processing and analysing data that is too large or complex to be processed by traditional data processing applications (Kitchin, 2014a). Big data is to collect, store, process, analyse, apply and display the generated data, and finally realize the value of the data (Kitchin, 2014a). Artificial intelligence is a new technological science that researches and develops theories, methods, and applica-

tion systems for simulating, extending and expanding human intelligence (Bartoletti, 2020).

Big data and artificial intelligence are inseparable and mutually promote each other. The rapid development of the new generation of information technology has enabled the value of big data to be demonstrated (Kitchin, 2014b). At the same time, with the rapid accumulation of massive data, artificial intelligence based on big data has gained the source for sustainable development (Bartoletti, 2020). Many big data applications are attributed to artificial intelligence. Big data and artificial intelligence technologies are closely integrated and can understand, analyse and make decisions on data, so that more accurate information can be obtained from data and the value behind data can be mined (Kitchin, 2014b).

Big data and artificial intelligence are new concepts emerging with the growth of network computing technology (Géczy, 2014). Big data is characterized by massive data, high speed, wide variety, detailed scope and flexibility. It can help enterprises in all walks of life dig out users' needs from massive data, so that data can truly generate value (Kitchin, 2014b). The application of big data and artificial intelligence has penetrated into agriculture, industry, commerce and medical field, etc., and become an important factor affecting industrial development (Mittelstadt & Floridi, 2016). Ping An Health's application of big data and artificial intelligence is a good example in the medical field.

3. The Emerging Technology Application of Ping An Health

On Ping An Health platform, users can first make a preliminary diagnosis of their physical condition through artificial intelligence, such as describing symptoms and past medical history to the artificial intelligence ("Ping An Good Doctor," 2021). In addition, the artificial intelligence of the platform can also make use of the online consultation function to prescribe different prescriptions for individuals according to their physical conditions, age, and geographical location, etc. In China, most people do not have enough health awareness and judgment about their health status. As the largest healthcare platform in China, Ping An Health is committed to providing each family with a family doctor, each person with an electronic health record and a health management plan through artificial intelligence ("Ping An Good Doctor," 2021). Artificial intelligence can regularly monitor the health of family members, and save the results as data to provide evidence support for users' future medical treatment ("Ping An Good Doctor," 2021).

Many patients need to go to offline hospitals for further diagnosis and treatment after going through the real-time consultation process through the Ping An Health platform (Kexuepindao, 2018). As a data open platform, Ping An Health has accumulated a large number of patients' medical and health information through big data. When users go offline for medical treatment, Ping An Health connects with cooperative hospitals through the intelligent auxiliary diagnosis and treatment system. With the consent of the patient, users' data is opened, allowing doctors to gain a deeper understanding of their health information through digitized medical records, thus reducing repeated consultations. This has improved the efficiency of the entire medical service ("Ping An Good Doctor," 2021). In addition, by combing and mining user medication data, Ping An Health can obtain rational drug use information of different patients, which helps pharmaceutical enterprises to develop new drugs and provide users with more reasonable health care and medication advice.

4. The Ethical, Political and Social Issues

Ping An Health is a platform with both praise and controversy. On the platform, users can use their mobile phones to ask doctors online and enjoy professional and convenient online consultation services. On the other hand, Ping An Health has also encountered many doubts. Firstly, some people think that a good doctor may not have enough time to treat online users every day, and they doubt the professionalism of doctors on the platform (Ji, 2018). Secondly, measurement bias will also cause some problems in the application of big data (Bishop, 2020). Therefore, some people are also skeptical about whether the platform's AI technology is accurate enough to diagnose human diseases (Ji, 2018). Thirdly, many people, especially the elderly, are not skilled enough in the use of new media technologies such as mobile phones, so they are unfamiliar with medical consultations and medicine purchases via the Internet. These are the risks faced by Ping An Health. If the above risks cannot be well solved and lead to the loss of users, the owners of the platform, as well as the doctors, hospitals, pharmacies, medical device companies, insurance companies, banks, and other stakeholders who make profits from the platform, will all be affected by these risks. Thus, the above issues need to be improved and resolved by Ping An Health as soon as possible.

Data is not neutral, and it is political in nature (Keyes, 2019). In China, the online medical industry is in line with the direction of policy encouragement. The government takes a positive attitude towards the inclusion of Internet medical services and online medical consultations into medical insurance reimbursements, and actively introduces relevant supporting policies (Jasanoff, 2017). National policies continue to benefit the development of the Ping An Health platform. When technologies are adopted and used, it is because they are considered to achieve a specific human purpose and improve a specific social environment or to promote the interests of individuals and social groups (Winner, 1993). There are many links in the medical industry, and these issues are both challenges and opportunities for Ping An Health. Ping An Health company can improve user experience and promote the overall development of the medical industry through big data and artificial intelligence technologies (Mittelstadt, Allo, Taddeo, Wachter, & Floridi, 2016).

5. Conclusion

The rapid development of Ping An Health is a successful example of artificial intelligence and big data application in the medical industry. The platform is controlled by Ping An Healthcare and Technology Co., Ltd. On this platform, doctors, hospitals, pharmacies, medical device companies, insurance companies, and banks will all profit from it. Besides, this report also conducts a detailed analysis of Ping An Health's artificial intelligence and big data applications, and believes that the company faces the risk of losing users due to the user's distrust of the platform's medical resources. So Ping An Health needs to further improve artificial intelligence, big data and other emerging technologies, and improve the accuracy of the platform in professional aspects so as to increase the trust of users and lay a good technical foundation for promoting the development of the entire medical industry.

References

[1] Bartoletti, I. (2020). An artificial revolution: On power, politics and AI: Indigo Press.

[2] Bishop, S. (2020). Algorithmic experts: Selling algorithmic lore on YouTube. Social Media+ Society, 6(1), 2056305119897323.

[3] Géczy, P. (2014). Big data characteristics. The Macrotheme Review, 3(6), 94-104.

[4] Jasanoff, S. (2017). Virtual, visible, and actionable: Data assemblages and the sightlines of justice. Big data & society, 4(2), 2053951717724477.

[5] Ji, H. (2018). Ping An Good Doctor's AI technology and the number of patients it serves have been questioned. Retrieved from https://www.cn-healthcare.com/articlewm/20180508/wap-content-1025005.html.

[6] Kexuepindao. (2018). Ping An Good Doctor Big Data Healthcare to Achieve Medical AI. Retrieved from http://science.china.com.cn/2018-03/14/content_40252241.htm.

[7] Keyes, O. (2019). Counting the Countless: Why data science is a profound threat for queer people. Real Life, 2.

[8] Kitchin, R. (2014a). Big Data, new epistemologies and paradigm shifts. Big data & society, 1(1), 205395171452848.

[9] Kitchin, R. (2014b). The data revolution: Big data, open data, data infrastructures and their consequences: Sage.

[10] Mittelstadt, B. D., Allo, P., Taddeo, M., Wachter, S., & Floridi, L. (2016). The ethics of algorithms: Mapping the debate. Big data & society, 3(2), 2053951716679679.

[11] Mittelstadt, B. D., & Floridi, L. (2016). The ethics of big data: current and foreseeable issues in biomedical contexts. The ethics of biomedical big data, 445-480.

[12] Oak, W. (2020). Ping An Good Doctor Launches Global Medical Consultation Platform in 24/7 Support of Anti-COVID-19 Efforts. Retrieved from https://www.wsj.com/articles/PR-CO-20200408-903943.

[13] Ping An Good Doctor. (2021). Retrieved from http://www.pagd.net/?lang=EN_US.

[14] An Good Doctor Global Medical Consultation Platform. (2021). Retrieved from https:// consult.jk.cn/#/63c2640afc540a-4fe221c879fbd90331.

[15] Ping An Healthcare and Technology Co Ltd. (2021). Retrieved from https://www. bloomberg.com/profile/company/1833:HK.

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Observation on the Clinical Treatment Effect of Gynecological Endocrine Disorders

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Abstract: Objective: To explore the clinical treatment methods and specific therapeutic effects of gynecological endocrine disorders. Method: An experiment was conducted on endocrine disorders patients admitted to the gynecology department of a certain hospital in China from November 2021 to November 2022. Forty patients were randomly selected as the experimental study subjects and divided into a control group and a study group. Among them, the control group adopts conventional treatment methods, while the research group adopts clomiphene capsules and hormone therapy based on conventional treatment methods. The clinical efficacy of the two experimental groups of patients is compared to determine the appropriate conventional treatment method. The levels of sexual hormones before and after the two experimental groups of patients and the clinical treatment effect are compared. Result: The treatment effect of the control group patients will be lower than that of the study group, and the treatment effectiveness rate of the control group patient group is about 70%. The effective rate of treatment in the patient group of the research group is about 95%. Conclusion: Through experimental argumentation, it can be understood that adding hormone and clomiphene capsules to the clinical treatment effect based on conventional treatment methods will be better, and it can be promoted and popularized.

Keywords: Gynecology; Endocrine Disorders; Clinical Treatment; Effect

Introduction

Under the influence of gender differences and other factors, once women have endocrine disorders, they will form many adverse reactions, such as irregular menstruation, Melasma on the face, etc., so they need to receive treatment in time, or their health will be affected. Exploring the current clinical treatment methods in China, the effectiveness of conventional treatment methods is relatively weak. To improve clinical treatment effectiveness, multiple methods such as adding clomiphene and pituitary stimulating hormone can be combined to effectively control patients' endocrine disorders and ensure their physical health.

1. Experimental Data and Methods

1.1 Experimental data

This experiment will select 40 patients with endocrine disorders admitted to the gynecology department in the hospital as the experimental research subjects. These 40 patients will be randomly sampled and divided into a study group and a control group, with 20 patients in the control group and 20 patients in the study group. Among them, the youngest patient in the control group is 25 years old, the oldest is 40 years old, and the overall average age is 31 years old. The youngest patient in the study group is 25 years old, the oldest is 41 years old, and the overall average age is 32 years old. Comparing the basic information of the two experimental groups, it was confirmed that there was no significant difference, and the basic information was not statistically significant ($P>0.05$).

1.2 Experimental Methods

The patients in the control group took the conventional treatment method, and the patients were treated with Estradiol valerate tablets+progesterone. Estradiol valerate tablets were mainly used, and the treatment was carried out every 15 days, with 15 days as a course of treatment. At the beginning of the second course of treatment, progesterone was added twice a day. The patients need to communicate with their families during the course of taking the drugs. And provide correct medication guidance, so that patients can strictly follow the pre-

scription to take medication correctly. The control group of patients received correct psychological health guidance, while also popularizing patients' understanding of endocrine disorders, which improved the effectiveness of drug treatment and increased patients' dependence. The study group needs to take the conventional group treatment scheme as the benchmark, and add pituitary Gonadotropin and clomiphene. The patients start treatment during the menstrual period. The patients use clomiphene capsules on the the fourth day of the menstrual period, with a daily dose of 80 mg. The patients receive pituitary Gonadotropin treatment on the 12th day of the menstrual period. During the drug treatment, the medical staff should always pay attention to the improvement of the patients' symptoms, In order to make timely adjustments to the medication, the daily dosage adjustment should be controlled within the range of five milligrams.

1.3 Observation indicators

The significant effect is that the patient's endocrine disorders have been effectively controlled, some obvious symptoms have been alleviated, and no adverse reactions have occurred during the treatment process; The effect is generally that the overall treatment effect of the patient can achieve the expected goals, with some symptoms noticeably disappearing, but there may be certain adverse reactions during the treatment process; Poor treatment effect means that the patient's treatment effect is average, and the symptom recovery effect is average. During the treatment process, there may be adverse reactions, which can be further refined into symptoms such as abdominal pain, physical fatigue, and dizziness.

1.4 Evaluation criteria

Clinical evaluation: After treatment, if there is no ovulation phenomenon, there is no improvement in clinical symptoms, and even more severe, it is considered ineffective; After treatment, ovulation occurs, with bipolar type being the basal body temperature type, and clinical symptoms are largely improved to be effective; After treatment, ovulation occurs, with bipolar type being the basal body temperature type and clinical symptoms completely disappearing as significant effect. The sum of significant and effective rates is the total effective rate of treatment.

2. Results

Firstly, the treatment effects of two experimental groups were compared. In the control group, there were 12 patients with significant effects, 2 patients with average effects, and 2 patients with poor effects. The overall group cure effective rate was 70%; The study group had a significant effect on 15 patients, a general effect on 4 patients, and a poor effect on 1 patient. The overall group cure rate was 95%. Through comparison, it can be seen that the treatment effect of the study group patient group is better than that of the control group group, and the effective rate and indicators of significantly effective patients are higher than those of the control group.

Table 1 Comparison of treatment effects between two experimental groups

grouping	Number of cases	significant effect	The effect is average	Poor effect	Cure effectiveness
control group	20	12	2	6	70%
study group	20	15	4	1	95%
P		$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

3. Discussion

Through experimental comparison, it can be concluded that the treatment effect of patients in the study group will be better, indicating that the use of clomiphene capsules and hormones as a benchmark for conventional treatment methods is worth popularizing and applying in clinical practice. If the patient has endocrine disorders and does not receive timely treatment, it can cause serious damage to the patient's body. Although traditional treatment methods can achieve certain therapeutic effects, in order to further improve treatment effectiveness, it is still necessary to optimize the treatment plan and add clomiphene capsules and hormones. In addition, in the process of formulating a treatment plan, it is necessary to pay attention to the following points. In terms of drug treatment, it is necessary to control the dosage of various

drugs. When giving a certain drug dosage, it is necessary to analyze the actual situation of the patient, determine the past medical history, and after determining the treatment plan, repeatedly confirm the main status of various drugs to ensure treatment effectiveness. Irritability is the main cause of endocrine disorders in patients. Qi and blood stasis or yin deficiency can lead to blood stasis in the patient's body, hindering the smooth operation of the patient's veins, and increasing the risk of external toxin invasion, resulting in endocrine disorders. And during the actual adjustment of medication administration, it is necessary to analyze the improvement status of endocrine disorders in patients, and optimize and adjust their plans based on their improvement status. If the patient's condition improves significantly, it is necessary to moderately reduce the dosage of medication. If the patient's condition does not recover, it is necessary to moderately increase the dosage of medication to control the patient's condition as soon as possible. In addition, patients also need to adjust their medication regimen based on the various adverse reactions they experience. During the treatment process, patients often need to take multiple types of drugs, which can lead to different adverse reactions that affect their physical functions and even have negative psychological effects. To ensure treatment effectiveness and reduce the probability of adverse reactions in patients, various forms such as reducing dosage or suspending administration are needed.

Conclusion

In summary, based on conventional treatment methods, increasing the application of clomiphene+hormone capsules will have a better effect and can quickly control the patient's condition. In this regard, relevant medical personnel need to further improve and optimize clinical treatment plans for endocrine disorders, adhere to targeted and personalized treatment principles, study the medicinal mechanisms of various drugs, and determine appropriate treatment plans based on the actual physical and mental conditions of patients to ensure treatment effectiveness. Regulating the imbalance of patients' endocrine system enables them to develop good lifestyle habits, while ensuring sufficient rest and sleep time, relaxing their mood, improving their endocrine disorders, enhancing their physical fitness, and enabling them to have strong resistance to diseases.

References

[1] Zhao XM. Clinical treatment and effect study of gynecological endocrine disorder patients [J]. Practical Gynecological Endocrine Online magazine, 2019 (08).

[2] Wang Q. Observation on the clinical treatment effect of gynecological endocrine disorders [J]. Journal of Practical Gynecological Endocrinology (Electronic Edition), 2019 (06).

[3] Diao JY. Clinical treatment and efficacy study on patients with gynecological endocrine disorders [J]. Journal of Practical Gynecological Endocrinology (Electronic Edition), 2017 (25).

[4] Xie MK. Clinical treatment research on gynecological endocrine disorders [J]. World's latest medical information abstract, 2018 (52).

[5] Chen YQ. Empirical research on the Clinical Treatment Effect of Gynecological Endocrine Disorder [J]. Journal of Practical Gynecological Endocrine (Electronic Edition), 2018 (23).

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Treatment of Acute Proximal Interphalangeal Joint Palmar Plate Injury by Bone Channel Suture

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Abstract: Objective: Objective: To explore the surgical effect of suture through bone canal in the treatment of reconstruction of acute proximal interphalangeal joint metacarpal anchorage. Methods From July 2018 to August 2021, we retrospectively analyzed 9 cases of avulsion of metacarpal plate near interphalangeal joint, including 7 males and 2 females, aged 17-40 years, with an average of 34 years. There were 4 cases of index finger, 3 cases of middle finger and 2 cases of ring finger. Early flexion and extension exercises were performed after operation. The last follow-up included the range of motion of the proximal interphalangeal joint and joint pain. Results All patients were followed up (4-12 months) after operation. According to the TAM method, 7 cases were excellent and 2 cases were good. Conclusion Transosseous suture for acute proximal interphalangeal joint metacarpal reconstruction has the advantages of simple operation, safety, firm fixation and rapid postoperative recovery.

Keywords: Palmar Plate Injury; Avulsion Reconstruction

Introduction

Injury of the proximal interphalangeal joint of the finger is a common injury of the finger, which is often accompanied by injury of the metacarpal plate when the finger is overstretched violently. If the injury of the metacarpal plate is not handled in time, joint stiffness will appear in different degrees. The palmar plate is located below the flexor tendon, and it is often torn off from the stopping point when there is great violence. At present, the methods of micro-anchoring are mostly used to reconstruct the palm plate, but the cost of micro-anchoring is high. From July, 2018 to August, 2021, 9 cases of avulsion of metacarpal joint near interphalangeal joint in our hospital were reconstructed by suture through bone canal, and satisfactory clinical results were obtained.

1. Materials and Methods

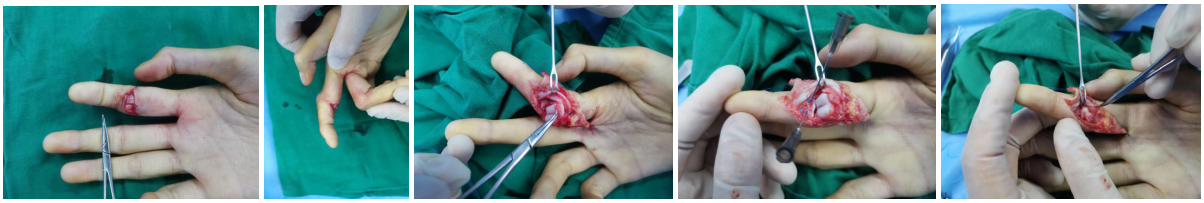
1.1 General information

There were 9 patients with 9 fingers, 7 males and 2 females, aged 17-40 years, with an average age of 34 years. There were 4 index fingers, 3 middle fingers and 2 ring fingers. There were 5 cases of sports violence injury, 3 cases of collision injury and 1 case of crush injury. All of them were open injuries. The time from injury to operation was 4-7 hours, and all patients underwent emergency surgery.

1.2 Surgical procedure

After successful brachial plexus block anesthesia, the patient takes the supine position, washes with normal saline and hydrogen peroxide, puts on a towel by routine disinfection, makes a "Z" incision on the palm side of the proximal interphalangeal joint of the affected finger, thoroughly debrides from shallow to deep, removes the contaminated tissue, explores the proper nerves and blood vessels of both fingers under a microscope, and repairs them together if there is any injury, cuts the sheath and A3 pulley, and pulls the flexor tendon to one side to expose the lower palmar plate, as shown in. Preserve the small piece of avulsion bone cortex connected with the metacarpal plate, rinse and soak it with normal saline, hydrogen peroxide and dilute iodophor again, and drill holes on both sides of the base of the middle phalanx (far from the articular surface) with a Kirschner wire with a diameter of 1.0mm from the palm to the back at an angle of 45 degrees to form a cross, and the cross point is located in the medullary cavity of the middle phalanx (try to complete it once to prevent fracture). 4-0 absorbable

suture was used to sew the joint capsule around the metacarpal plate, 5-0 sliding suture was used to sew the wound, and sterile dressing was used to bind and fix it. Plaster external fixation was performed at the position of slight flexion of the affected finger.



A B C D E

F G

Patient, female, volleyball player. A, B: External image of the patient's preoperative finger injury C: Intraoperative exploration of the palmar plate is completely broken at the point of insertion, and there is a small avulsion bone D: Kirschner needle parallel to the base at a and b, 45° angle cross punching, 3-0 Prolene's suture needle, from point A to point B, and then knotted at the suture proximal to the palmar plate. E: Firmly fix the palmar plate insertion point F: 1 year after surgery, left index finger front external image, left index finger fully extended, no obvious scarring G: 1 year after surgery, left index finger lateral external image, flexion function is normal.

1.3 Postoperative treatment and follow-up

Prophylactic antibiotics are used within 24 hours after surgery, patients are instructed to passively perform digital flexion and extension exercise after 1 week after surgery, routine stitch removal 2 weeks after surgery, external fixation of mild flexion cast of affected finger for 4 weeks after surgery, strenuous activities are strictly prohibited within 4 weeks, and the cast is removed for active flexion and extension activities after 4 weeks.

2. Results

After the postoperative follow-up was 4-12 months, all patients did not have infection of the postoperative wound and did not have skin necrosis. At the last follow-up, there were no joint contracture deformities, joint stiffness, limited flexion and extension movements, etc., and no pain in the affected fingers after surgery. According to the total active movement (TAM) [1]: 7 cases were excellent and 2 cases were good.

3. Discussion

The proximal interphalangeal joint is a synovial hinge joint with an active flexion-extension movement of 110°-0°, surrounded by a box-like complex, and the palmar side maintains the stability of the palmar side of the joint by the palmar plate. The palmar plate originates from the proximal phalangeal head, and its proximal part thickens laterally called the limiting ligament, and ends distally at the palmar side at the base of the middle phalange, and is composed of hard fibrocartilage. The palmar plate is an important structure for maintaining anteroposterior stability and preventing hyperextension of the proximal interphalangeal joint [2].

The palmar plate is typically avulsed at the distal insertion point, where fusion with the middle phalange is weak, while the proximal portion is confined to the proximal phalangeal bone where the confined ligament is firmly attached to the proximal phalange and rarely ruptures [3]. Clinically, palmar plate injuries are mostly classified by Eaton, type I is simple palmar avulsion injury, type II is an avulsion fracture

with a small mid-segment base, and type III is a larger fracture piece on the palmar side of the base of the middle phalange, often involving larger articular surfaces [4]. Clinically, type II is common.

For type II palmar plate injury, Adi M et al. [5] reported that the prognosis of proximal interphalangeal palmar plate injury does not depend on the presence of avulsion fracture. Thus, palmar injuries with closed stability can be managed conservatively [5]. The traditional brace external fixation, using flexion 30°, often causes the contracture of the palmar plate, further leads to joint contracture deformity, affecting the finger straightening function, therefore, Edward A. Stanley et al. [6] in the finger neutral dorsal splint treatment of palmar plate injury, can lead to less joint flexion deformity, less requirements for hand treatment, and faster recovery of daily activities. Paschos NK et al. [7] reported that stable palmar plate injury without fractures, orthodactyly fixation and aluminum orthosis are a safe and effective fixation method, and compared with aluminum orthosis fixation, orthodic fixation is associated with earlier recovery of activity, finger swelling and pain relief. Complications of conservative management of palmar plate injury are joint stiffness, proximal interphalangeal flexion deformity, and osteoarthritis. Failure of conservative management is associated with joint dislocation, fracture displacement, and possible rotation of bone fragments [8]. In order to minimize the occurrence of complications and achieve rapid recovery, it has become a clinical problem that needs to be solved. Therefore, the indications for surgery in this group: (1) open injury, there may be damage to blood vessels and nerves; (2) Type II palm plate injury

The traditional surgical treatment methods of palmar plate insertion reconstruction include steel wire suture dorsal withdrawal press fixation method, anchor fixation method, double-line compression fixation method, and improved suture anchor suture method. The tension strip wire fixation method [9] is simple and accurate to operate, but the steel wire is buried under the skin of the back of the finger, the steel wire irritates the skin, there is a risk of skin infection, and the steel wire needs to be withdrawn again. Anchoring is the most common method [10-11], but anchorage is expensive and difficult to place in the setting of multiple fractures at the base of the middle phalangeal bone. Double-line compression fixation has little damage to periarticular structures, but intraoperative procedures are more complicated. The transoskeletal suture fixation method used in this group has no compression on the skin of the back of the finger, little skin irritation, and no built-in remains, and there is no need for Kirschner needle to fix the joint after surgery, and no secondary surgery is required. After surgery, under the guidance of a physician, early finger flexion and extension exercise is performed. The effect was satisfactory during the follow-up, and the intraoperative operation was simple and easy to promote.

The key points of operation during the operation are to carefully clean up the small fracture block to prevent the small bone block from rotating, and to press and reset the small avulsion bone piece connected to the metacarpal plate. If it is difficult to handle, it can be removed. Fabrication of bone tunnel: drill holes on both sides of the metacarpal side at the base of middle phalanx, far away from the articular surface, with a Kirschner pin with a diameter of 1.0mm, showing an internal figure of eight, so as to avoid repeated drilling. Use 3-0 prolene thread to sew the stop point of metacarpal plate first, and then increase the arc of the sewing needle of 3-0 prolene thread appropriately, and pass through two bone holes. When tying the knot, the force should be moderate to prevent the suture from breaking.

Among the 10 patients, 9 patients have achieved satisfactory results, and 1 patient has a thicker proximal interphalangeal joint than the healthy finger, but the flexion and extension activities have recovered well. However, this operation method also has some limitations. When the avulsion fracture of the metacarpal plate is large, this method can not fix the fracture, and Kirschner wire internal fixation is needed at this time.

References

[1] Cheriyan T, Neuhaus V, Mudgal CS. Bony avulsion injury of flexor digitorum profundus- description of a new subtype [J]. J Hand Surg Eur Vol, 2013, 38(1): 91-92.

[2] Wolfe SW, Hotchkiss RN, Pederson WC. Green Hand Surgery [M]. Guanglei Tian, Xieyuan Jiang, Shanlin Chen, et al. Trans. Beijing: Peking University Medical Press, 2022: 287.

[3] Bowers WH, Wolf JW Jr, Nehil JL, et al.The proximal interphalangeal joint volar plate.I.An anatomical and biomechanical study[J]. J Hand Surg Am,1980, 5(1): 79-88.

[4] Eaton RG. Joint injuries of the hang[M]. Springfield: Thomas, 1971:9-39.

[5] Adi M, Hidalgo Diaz JJ, Salazar Botero S, et al. Results of conservative treatment of volar plate sprains of the proximal interphalangeal joint with and without avulsion fracture[J]. Hand Surg Rehabil,2017,36(1):44-47.

[6] Stanley EA, Seifman MA, Mills B, Fay P, Thomas DJ. Dorsal Block Splinting of Volar Plate Injuries at Neutral Position. Ann Plast Surg. 2019 May;82(5):520-522.

[7] Paschos NK, Abuhemoud K, Gantsos A, Mitsionis GI, Georgoulis AD. Management of proximal interphalangeal joint hyperextension injuries: a randomized controlled trial. J Hand Surg Am. 2014 Mar; 39(3): 449-54.

[8] Lee S, Jang SJ, Jeon SH. Factors Related to Failure of Conservative Treatment in Volar Plate Avulsion Fractures of the Proximal Interphalangeal Joint[J].Clin Orthop Surg, 2020,12(3):379-385.

[9] Niu AQ, Wang YJ, Wang J, et al. Analysis of 21 cases of avulsion fracture of proximal interphalangeal joint with tension band wire fixation [J]. Modern practical medicine, 2016, 28 (10): 1289-1290.

[10] Zheng HY, Liu J, Hong GX, et al. Treatment of chronic avulsion injury of palmar plate of proximal interphalangeal joint with micro bone anchor[J]. Orthopaedics, 2012, 3(1):4-6.

[11] Wang K, Ju JH, Jin GZ, et al. Reconstruction of avulsion injury of palmar plate of proximal interphalangeal joint by microanchoring [J]. Chinese Journal of Hand Surgery, 2019, 35(4): 267-269.

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A Case of Combining Coronary Angiography and CT Angiography to Diagnose an Acute ST Segment Elevation Myocardial Infarction and a Single Coronary Artery

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Abstract: Coronary artery anomalies encompass a wide spectrum of clinical presentations and pathophysiological mechanisms, exhibiting significant heterogeneity. The majority of coronary artery anomalies exhibit negligible clinical manifestations.. Among these anomalies, the occurrence of a single left coronary artery with congenital right coronary artery agenesis represents an exceedingly rare manifestation. This case report presents the clinical profile of a 37-year-old male patient who underwent intervention and coronary CT to confirm his acute myocardial infarction and a solitary left coronary artery. A thorough understanding of coronary variations and the identification of coronary lesions can enable cardiovascular physicians to adopt more personalized treatment strategies for their patients.

Keywords: Coronary Angiography; CT Angiography; Myocardial Infarction; Single Coronary Artery

1. A synopsis of the case

On November 10, 2022, a 37-year-old male patient was admitted to the hospital with a complaint of chest pain and tightness that had persisted for six hours. The patient presented with chest pain of unknown etiology that had begun six hours prior, characterized by persistent posterior sternal pressure pain that worsened in paroxysms without relief. The patient reported no accompanying symptoms such as fever, heartburn, acid reflux, nausea, vomiting, palpitations, or dyspnea. Following evaluation at a local hospital, an electrocardiogram indicated an acute inferior wall ST-segment elevation myocardial infarction, and urgent examination revealed ultrasensitive troponin T (hs-TnT)levels of 1556.0 pg/ml and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels of 773 pg/ml. The patient received treatment consisting of “BAY ASPIRIN 300 mg, POLIVET 300 mg”. Subsequently, emergency coronary angiography and percutaneous coronary intervention (PCI) were conducted through the emergency green channel. The catheter was directed to the left coronary artery using a 5F Tig, and multi-angle angiography was performed. The results indicated no apparent abnormalities in the left main trunk. However, the distal segment of the circumflex branch displayed a blood vessel occlusion stump, resulting in thrombolysis in myocardial infarction(TIMI) grade of 0 forward blood flow(Figure 1). Subsequently, the catheter was directed towards the right sinus utilizing 5F TIG, SAL 1.0, and AL0.75, consecutively. The absence of the right coronary artery was observed, leading to the conclusion that the patient possessed a solitary coronary artery (Figure 2). Following this, the femoral artery was punctured, and the 7F EBU3.75 was substituted into the left coronary artery orifice.An attempt to occlude the lesion via the circumflex using a Runthrough guidewire was unsuccessful. Subsequently, the PILOT50 guidewire was substituted to traverse the occlusion to the distal end, revealing that the lesion was obstructing the right coronary artery originating from the circumflex, as evidenced by the guidewire trajectory (Figure 3). After pre-expansion balloon Maverick 2.0×12mm was used to dilate the lesioned vessel, PROMUS PREMIER 2.75×38mm and RDESI I 3.0×24mm DES were delivered along the guidewire to the lesion site for accurate positioning and released at 10atm. Subsequently, post-expansion balloon Quantum 3.0×15mm was employed to dilate the stent. Upon conducting a subsequent coronary angiogram, it was observed that the stent had undergone satisfactory expansion, exhibiting robust walls and the reinstatement of antegrade flow with a TIMI grade of 3. (Figure 4-5).After undergoing surgery, a computed tomography angiography (CTA) of the coronary arteries indicated the presence of a single coronary artery (Type I). Following coronary artery stenting, the patency of the stent was confirmed(Figure 6-7). The patient continued to receive postoperative medication, resulting in a significant improvement in their chest pain and other symptoms compared to pre-surgery. Six months post-discharge, the patient remained asymptomatic and in good overall health without any notable discom fort.

2. Discussion

Coronary artery anomalies encompass a heterogeneous array of lesions that exhibit varying degrees of clinical significance. Literature reports a prevalence rate of 1.3% for coronary artery abnormalities, with the majority of such anomalies being asymptomatic and incidental findings[1]. Various forms of coronary variants comprise fistulous coronary arteries, single coronary arteries, aneurysmal dilatation of coronary arteries, and anomalous origins of coronary arteries. A solitary coronary artery, which emerges from the aortic arch, perfuses the entirety of the myocardium.. Smith[2] classified a solitary coronary artery into three distinct types based on the distribution of its arteries: type I, which exhibited a conformal alignment with the typical left and right coronary arteries; type II, which bifurcated into two branches following the left and right normal coronary arteries, respectively; and type III, which lacked a discernible travel pattern.

Myocardial ischemia can be induced in patients with coronary artery malformations and coronary atherosclerosis due to insufficient blood supply to the myocardium caused by coronary stenosis, as well as the potential for the malformed coronary arteries to exacerbate the flow-limiting effect[3]. The patient in this case presented with acute myocardial infarction and a solitary left coronary artery. Despite a decade-long smoking habit, which is a known risk factor for coronary heart disease, the patient was previously asymptomatic and in good health, without any atypical discomfort or symptoms such as chest tightness, chest pain, or syncope.The patient under consideration exhibited a singular left coronary artery and acute myocardial infarction. Prior to the onset of the ailment, the patient was asymptomatic with regards to chest tightness, chest pain, or syncope, despite having smoked for a decade, which is a significant risk factor for coronary heart disease. Multiple angiographies of the right coronary artery were conducted at varying angles, but failed to reveal its presence.Circumflex occlusive segments exhibit vascular morphology in their distal regions. Subsequently, the physician opted to employ a guide wire and balloon dilated vascular imaging technique to ascertain the presence of a solitary coronary artery in this region, which fell within the normal right coronary artery's blood supply range. Notably, there was a discernible amelioration in symptoms post-intervention.

Various techniques are available for identifying coronary artery malformations, such as coronary angiography, coronary computed tomography, coronary MRI, and stress echocardiography. Each imaging modality presents distinct advantages and disadvantages. It is widely acknowledged that coronary angiography is the benchmark for diagnosing coronary artery disease, while coronary computed tomography (CT) imaging is a valuable tool for detecting coronary artery abnormalities[4]. Owing to its ability to offer a detailed depiction of the coronary arteries, it furnishes a comprehensive account of the genesis and interrelation of anomalies in the coronary arteries, great vessels, and ventricles, thereby providing complete three-dimensional information. The principal therapeutic interventions for coronary anomalies that result in clinically significant events are cardiac surgery or percutaneous coronary intervention.In recent years, the advent of interventional catheterization devices has led to the emergence of distinctive advantages and features of percutaneous coronary intervention (PCI) in the management of patients with coexisting coronary malformations and coronary artery disease[5, 6]. In the context of acute myocardial infarction and an abnormal coronary origin, it is imperative for an interventional cardiologist to expeditiously assess and analyze the patient's coronary artery. This assessment is based on the findings of guidewire travel angiography. In order to effectively preserve the lives of patients, cardiologists must possess a comprehensive understanding of cardiac vascular anatomy and execute precise interventional procedures on the affected vessel in a timely manner.

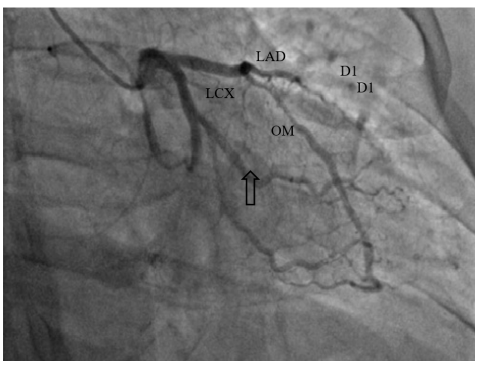

Figure 1

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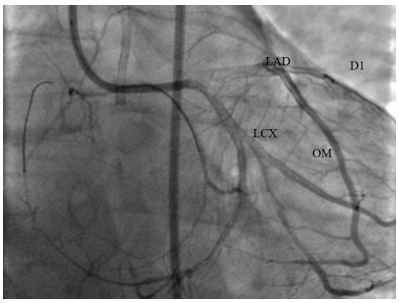

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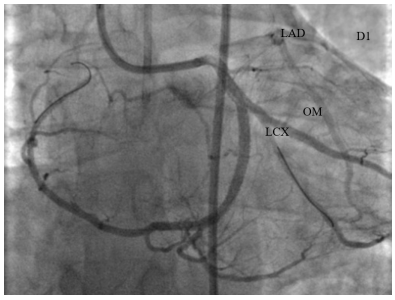

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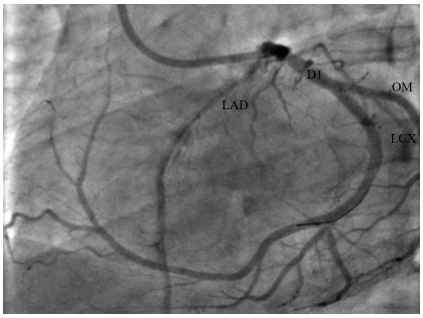

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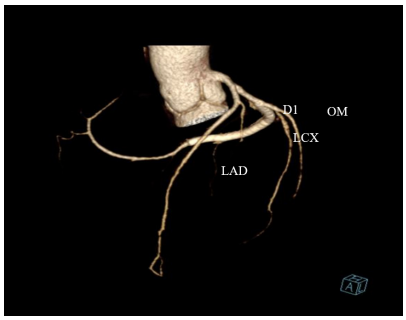

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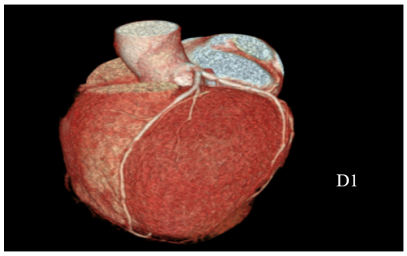

Figure 7

References

[1] Yamanaka, O. and R.E. Hobbs, Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Catheterization and Cardiovascular Diagnosis, 1990. 21(1): p. 28-40.

[2] Ogden, J.A. and A.V. Goodyer, Patterns of distribution of the single coronary artery. The Yale Journal of Biology and Medicine, 1970. 43(1): p. 11-21.

[3] Beecham, R., S. Prater, and J. Batlle, Coronary Artery Anomalies, in StatPearls. 2022, StatPearls PublishingCopyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).

[4] Chartrand-Lefebvre, C., et al., Coronary computed tomography angiography: overview of technical aspects, current concepts, and perspectives. Canadian Association of Radiologists Journal = Journal L'Association Canadienne Des Radiologistes, 2007. 58(2).

[5] Uthayakumaran, K., et al., Coronary intervention in anomalous origin of the right coronary artery (ARCA) from the left sinus of valsalva (LSOV): a single center experience. Indian Heart J, 2014. 66(4): p. 430-4.

[6] Cirillo, P., et al., Multi-slice computed tomography assessment of stent position in a patient with acute coronary syndrome and anomalous origin of the coronary arteries. Cardiovasc J Afr, 2013. 24(4): p. e1-3.

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COVID-19 Patients with Concurrent Acute Angle-Closure Glaucoma: A Retrospective Hospital Study."

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This study has been approved by the hospital's ethics committee (Ethics Review Number [2023]-(K-010)).

Abstract: This retrospective study investigates the interaction between COVID-19 and Acute Angle-Closure Glaucoma (AACG), analyzing clinical features, laboratory findings, and OCTA images in 20 patients diagnosed with both conditions. Elevated Intraocular Pressure (IOP) levels and a decrease in the deep capillary plexus (DCP) and choriocapillaris (CC) foveal vessel density were observed, with inflammation and coagulation markers also elevated. These findings suggest that the physiological changes induced by COVID-19 may exacerbate AACG symptoms. Despite the study's limitations, including a small sample size and retrospective design, these insights are pivotal for clinicians and underline the importance of careful ocular monitoring in COVID-19 patients. Further research is warranted to explore the long-term implications of these findings and the mechanistic pathways underlying the interaction between COVID-19 and AACG.

Keywords: COVID-19; Acute Angle-Closure Glaucoma; Intraocular Pressure; OCTA Imaging; Microvascular Alterations; Retrospective Study

Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has revealed a myriad of medical challenges, including its association with ocular conditions like Acute Angle-Closure Glaucoma (AACG). AACG, marked by a sudden rise in intraocular pressure, can lead to irreversible blindness without timely intervention. While COVID-19 is primarily a respiratory disease, it has shown extrapulmonary effects, including on the eyes. AACG is a pressing eye emergency, especially prevalent in Asian populations, while COVID-19 has a global footprint.(Barosco, Morbio et al. 2022).

Given the limited literature on the overlap between these diseases, this study delves into their comorbidity, aiming to detail the clinical attributes, examination results, and possible interrelations of COVID-19 and AACG in hospitalized patients. Recognizing how these diseases intersect is vital due to their significant health implications and the challenges they present when occurring simultaneously.

The need to explore this comorbidity stems from the severity of both conditions and their collective global health impact. Understanding their concurrent clinical manifestations aids healthcare professionals in effective diagnosis and treatment. Unraveling the shared mechanisms between these diseases enriches our knowledge, helping the medical community address patient care complexities during the pandemic.(Friedman, Masters-Israilov et al. 2022, Golabchi, Rezaee et al. 2022).

1. Methods

1.1 Study Design

This retrospective study examined the interaction between COVID-19 and AACG using medical records from Yancheng First People's Hospital from January 2020 to December 2022. Data extraction commenced after securing ethical approvals and maintaining privacy standards.

1.2 Participants

We included 20 patients aged 18 or older diagnosed with both COVID-19, confirmed by an RT-PCR test, and AACG, identified through comprehensive ocular examinations. Consent was secured from patients or their guardians. Exclusions were based on prior treatments, certain medical conditions, incomplete records, lack of ocular exams after COVID-19 diagnosis, or refusal to participate.

1.3 Retrospective Study Rationale

Using a retrospective design, we systematically analyzed pre-existing data, enabling an exploration of the COVID-19 and AACG relationship without new data collection. Medical records offered extensive details on patient histories, treatments, and outcomes. This method allowed for quick, efficient insights into the comorbidity while ensuring accuracy, bias mitigation, and ethical considerations.

1.4 Data Collection

Data was gathered to understand the link between COVID-19 and AACG, focusing on demographics, clinical features of both diseases, lab results, and imaging. Demographic details, such as age and sex, were noted. For COVID-19, information on infection severity, symptoms, and illness duration were collected. In the AACG context, we recorded clinical signs like intraocular pressure, visual acuity, anterior chamber status, and treatments administered.

1.5 Data Sources and Extraction

We used electronic medical records (EMRs) from a tertiary hospital. After identifying COVID-19 diagnosed patients within our study's timeframe, we narrowed down to those with a simultaneous AACG diagnosis. Two researchers independently extracted data, and discrepancies were resolved with a third researcher to ensure data accuracy.

1.6 Statistical Analysis

Analyses were done via SPSS, considering $p < 0.05$ as significant. This approach ensured a thorough data examination, shedding light on the studied comorbidity.

2. Patients' Examination Results

2.1 Patients' Demographics

Within the study's time frame from January 2020 to December 2022, a total of 20 patients fitting the inclusion criteria were identified. The participants comprised 11 males and 9 females, ranging in age from 48 to 81 years, with a mean age of 67.5 (±9.7) years. These patients hailed from various geographic regions, providing a diverse sample for the analysis.

Table 1: Demographic Characteristics of the Patients

Variable	Total (N=20)	Male (n=11)	Female (n=9)	P-value
Age (years)				
- Mean (±SD)	67.5 (±9.7)	69.3 (±8.5)	65.4 (±11.2)	0.342
- Range	48-81	51-81	48-78	
Geographic Location				
- Ting Hu	10 (50%)	6 (54.5%)	4 (44.4%)	0.758
- Yan Du	7 (35%)	4 (36.4%)	3 (33.3%)	
- Da Feng	3 (15%)	1 (9.1%)	2 (22.2%)	

2.2 Clinical Features of COVID-19

The severity of COVID-19 among the patients was variable, with 10 patients having mild symptoms, 7 experiencing moderate illness, and 3 with severe manifestations of the disease. The spectrum of symptoms recorded included fever (n=20), cough (n=18), dyspnea (n=14), fatigue (n=15), and loss of taste and smell (n=10).

The duration of COVID-19 illness in these patients was also diverse. The mild cases had a shorter duration, ranging from 5 to 10 days, while moderate and severe cases had prolonged illness, with durations spanning from 14 to 30 days and 20 to 45 days, respectively. It's imperative to note that the three patients with severe COVID-19 had underlying comorbidities, including diabetes and hypertension.

Table 2: Clinical Features of COVID-19 in Patients

Variable	Total (N=20)	Mild (n=10)	Moderate (n=7)	Severe (n=3)	P-value
Symptoms					
- Fever	20 (100%)	10 (100%)	7 (100%)	3 (100%)	1.000
- Cough	18 (90%)	8 (80%)	7 (100%)	3 (100%)	0.278
- Dyspnea	14 (70%)	5 (50%)	6 (85.7%)	3 (100%)	0.163
- Fatigue	15 (75%)	7 (70%)	6 (85.7%)	2 (66.7%)	0.762
- Loss of Taste and Smell	10 (50%)	6 (60%)	3 (42.9%)	1 (33.3%)	0.646
Duration of Illness (days)					
- Mean (±SD)	15.5 (±12.7)	7.5 (±1.6)	18.9 (±5.4)	32.3 (±7.5)	<0.001
- Range	5-45	5-10	14-30	20-45	

2.3 Clinical Features of AACG

The Intraocular Pressure (IOP) of patients varied significantly, ranging from 22 mmHg to 52 mmHg, with a mean pressure of 36 mmHg. Elevated IOP, higher than the normal range of 12-22 mmHg, was a consistent finding, indicating acute pressure build-ups in the eyes of the patients.

Visual acuity was assessed using the Snellen Eye Chart, with results ranging from 20/40 to hand motion (HM) at presentation. Patients with higher IOP levels were correlated with poorer visual acuity, though it's essential to consider that factors like the duration of elevated IOP and individual variations could impact these outcomes.

Table 3: Laboratory Findings in COVID-19 Patients with AACG

Variable	Mean (±SD)	Normal Range	P-value
D-dimer (mcg/mL)	1.2 (±0.3)	<0.5	<0.001
CRP (mg/L)	15 (±5)	<10	<0.001

2.4 Laboratory Findings

Patients with both COVID-19 and AACG exhibited certain laboratory abnormalities. COVID-19 patients with AACG had higher D-dimer levels, with a mean value of 1.2 mcg/mL (normal range < 0.5 mcg/mL), indicating a hypercoagulable state that is often seen in severe COVID-19 cases.

Additionally, C-reactive protein (CRP) levels, a marker of inflammation, were elevated, averaging at 15 mg/L (normal range < 10 mg/L). Elevated CRP levels were also associated with increased intraocular pressure in AACG, suggesting a possible link between systemic inflammation due to COVID-19 and the exacerbation of AACG symptoms.

Table 4: OCTA Findings in Post-COVID-19 Patients with AACG

Variable	Patient Group	Mean Vessel Density (±SD)	P-value
DCP Foveal Vessel Density	Healthy Control	52% (±4)	<0.001
Post-COVID-19 Patient	42% (±5)		
CC Foveal Vessel Density	Healthy Control	53% (±3)	<0.001
Post-COVID-19 Patient	40% (±4)		

2.5 Optical Coherence Tomography Angiography (OCTA) Images Study

OCTA images highlighted vascular changes in the eyes of patients with both post-COVID-19 diagnosis and AACG. A standard image from a healthy 52-year-old woman displayed normal vascular structures in the SCP, DCP, and CC. However, an image from a 39-year-old post-COVID-19 patient showed reduced vascular integrity, especially decreased vessel density in the DCP and CC layers, suggesting possible microvascular damage linked to COVID-19.

This decrease indicates potential impaired blood flow to the retina's deeper sections, possibly intensifying AACG severity. The findings emphasize the importance of closely monitoring retinal vascular changes in post-COVID-19 patients, particularly those with AACG symptoms. These imaging differences suggest a link between COVID-19's systemic vascular impact and AACG development or worsening. Recognizing these OCTA patterns can guide clinicians in AACG management for patients post-COVID-19, underscoring the value of a nuanced understanding in patient care for these concurrent conditions.

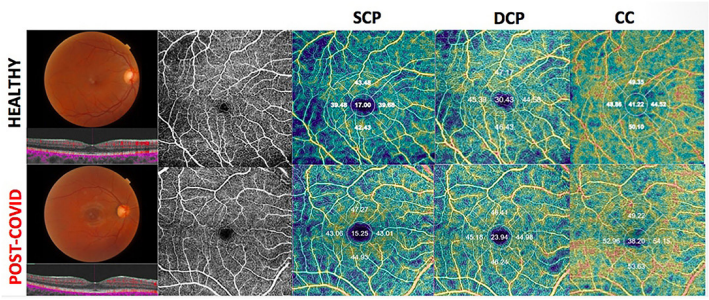

Figure 1: OCTA Images Comparing Healthy Eye with Post-COVID-19 Eye Affected by AACG

3. Discussion

This study delves into the potential relationship between COVID-19 and AACG by examining clinical features, lab results, and OCTA imaging. Elevated IOP levels and systemic inflammation markers suggest that COVID-19 might intensify AACG symptoms. While our findings align with previous research on COVID-19's systemic effects, the observed decrease in foveal vessel density in post-COVID-19 patients presents a fresh perspective on the virus's ocular impact(Özmen, Özkan Aksoy et al. 2023).

Limitations include a small sample size and the study's retrospective design, which might introduce biases. The lack of an AACG-only control group also hinders pinpointing observed effects as solely due to the comorbidity.

Clinically, these findings prompt increased monitoring for AACG symptoms in COVID-19 patients. The vessel density decrease further needs exploration for its long-term effects and treatment possibilities.

(Krishna, Odayappan et al. 2023)

Future studies should be larger, prospective, and include control groups. Delving into the mechanisms behind these observed interactions can pave the way for tailored treatments for patients with both conditions. This research acts as a stepping stone to better understanding and managing the intertwined effects of COVID-19 and AACG in the ongoing pandemic context(Zhu, Yan et al. 2023).

Conclusion

This study reveals a significant link between COVID-19 and worsened AACG symptoms, emphasizing increased IOP and unique vascular shifts in OCTA imaging. While limited by its sample size and retrospective nature, the findings stress the importance of ocular monitoring in COVID-19 patients, especially those predisposed to AACG. The noticeable retinal vascular changes in post-COVID-19 patients highlight the urgency for more research on the virus's long-term eye implications. Future studies should focus on larger cohorts, prospective approaches, and understanding the connection between these health issues to improve patient care in the post-COVID-19 clinical environment.

References

[1] Barosco, G., R. Morbio, F. Chemello, R. Tosi and G. J. E. J. o. O. Marchini (2022). "Bilateral angle-closure during hospitalization for coronavirus disease-19 (COVID-19): A case report." 32(3): NP75-NP82.

[2] Friedman, S. A., A. Masters-Israilov and M. S. Robbins (2022). Secondary headache disorders: approach, workup, and special considerations for select populations. Seminars in Neurology, Thieme Medical Publishers, Inc. 333 Seventh Avenue, 18th Floor, New York.

[3] Golabchi, K., A. Rezaee, D. Aghadoost and M. J. F. V. Hashemipour (2022). "Anterior ischemic optic neuropathy as a rare manifestation of COVID-19: a case report." 17(2): 71-76.

Universe Scientific Publishing

Research Progress on the Effect of 5-Methyltetrahydrofolic Acid on Hyperhomocysteinemia in Pregnancy

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Abstract: As the association of hyperhomocysteinemia in pregnancy with preterm birth, abortion, preeclampsia and other pregnancy complications has attracted increasing attention, 5-methyltetrahydrofolic acid has attracted much attention as a potential treatment. In this paper, the biological mechanism of 5-methyltetrahydrofolic acid, its relationship with hyperhomocysteinemia in pregnancy and clinical studies were reviewed to review the research progress of 5-methyltetrahydrofolic acid in regulating hyperhomocysteine levels in pregnancy. The purpose of this paper is to explore the role and influence of 5-methyltetrahydrofolic acid in the management of hyperhomocysteinemia during pregnancy.

Keywords: 5-Methyltetrahydrofolin; Hyperhomocysteine; Pregnancy Complications; Pregnancy Management

Introduction

Homocysteine (Hcy) is a sulfur-containing amino acid, mainly derived from methionine in the diet, and is the product of demethylation of methionine, which is the only source of Hcy [1, 2]. A variety of factors can lead to the accumulation of blood levels of total homocysteine (tHcy), resulting in hyperhomocysteinemia (HHcy), referred to as hyperhomocysteine [2]. Hcy, as a new type of toxin in the human body, has been named “the new generation of cholesterol” internationally. It can accelerate the oxidation of low density lipoprotein by promoting the generation of oxygen free radicals, and can activate the adhesion and aggregation of platelet, damage vascular endothelial cells, and is closely related to pregnancy-related diseases, affecting the pregnancy outcome to a certain extent [3].

In recent years, many studies have suggested that hyperhomocysteinemia may be closely related to adverse pregnancy outcomes and pregnancy complications in pregnant women, and we should actively manage and treat it. We can adopt healthy lifestyle intervention or supplement folic acid, vitamin B12 and other nutritional treatments to prevent or treat hyperhomocysteinemia [2]. Folic acid can effectively reduce the concentration of homocysteine in the blood, and is considered as one of the potential therapeutic drugs for vascular diseases caused by high homocysteine [4]. Folic acid itself is inactive in the human body, and it must be converted into 5-methyltetrahydrofolate by folate metabolizing enzymes in the body before it can participate in the remethylation of homocysteine, thereby reducing the serum homocysteine level and further reducing the occurrence of hyperhomocysteinemia in pregnancy.

1. Pathogenesis of hyperhomocysteinemia

Homocysteine is an intermediate product in the metabolism of methionine. Methionine generates homocysteine under the action of a series of synthases and hydrolases. The specific synthesis pathway is shown in

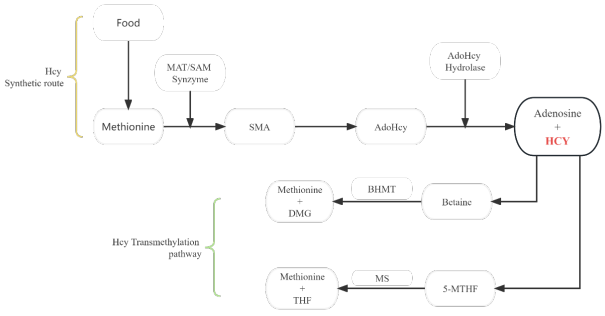

Fig. 1 Hcy synthesis and remethylation pathways

SMA: S-adenosyl methionine, 2.MAT: methionine adenosyltransferase, 3.SMA synthetase: S-Adenosyl methionase, 4.AdoHcy: S-adenosyl homocysteine, 5.Hcy: homocysteine, 6.5-MTHF: 5-methyltetrahydrofolate, 7.MS: methionine synthase, 8.THF: tetrahydrofolate, 9.DMG: dimethylglycine, 10.BHMT: betaine-homocysteine methyltransferase

The metabolic pathways of homocysteine mainly rely on the transmethylation pathway and the transsulfur pathway, and the transmethylation mainly includes two: 1 and 5-methyltetrahydrofolate (5-MTHF) provide methyl for homocysteine metabolism, and tetrahydrofolate (THF) and methionine are catalyzed by methionine synthase (MS). 2, betaine (trimethylglycine, from choline) as a methyl donor, zinc as a cofactor, and then methylated to produce dimethylglycine (DMG) and methionine, as shown in Figure 1 [4, 6-8].

The route of sulfur transfer: cystathione is catalyzed by cystathione bsnthase (CBS) to form cysteine, which is irreverably converted to cysteine by Cystathione c-lyase (CTL). Both enzymes require the assistance of pyridoxal phosphate (vitamin B6). In turn, cystathione, cysteine, and alpha-ketobutyric acid are used in protein synthesis, mediating a range of biological reactions [7, 8].

The causes of hyperhomocysteinemia can be roughly divided into five conditions: cofactor deficiency, enzyme deficiency, excessive methionine intake, certain diseases, and the effects of some drugs. 1, cofactor deficiency: Vitamin B2 is a cofactor of methylenetrahydrofolate reductase (MTHFR), involved in the production of 5-methyltetrahydrofolate reductase; Vitamin B6 is the co-factor of Hcy to thiotransferase; Vitamin B12 is the cofactor of MS, MS is involved in folic acid circulation; Folic acid, also known as vitamin B9, is indispensable in the metabolism of Hcy. B vitamins are water-soluble vitamins that are easily excreted in the urine, resulting in HHcy. Compared with other cofactors, supplementation with 0.5 to 5.0mg of folic acid daily has a good effect on reducing Hcy. 2, enzyme deficiency: enzyme deficiency or genetic errors of enzyme genes are directly related to homocysteine levels. Many studies have indicated that allele mutations of C677T TT and A1298C CC can increase homocysteine levels [9, 10]. CBS deficiency is the most common cause of Hcy increase, and the polymorphism of CBST833C gene can cause mild HHcy in different races. However, not all CBS gene polymorphisms can cause HHcy, and only C699T and T1080C gene polymorphisms can enhance folate and reduce Hcy function. MTHFR C677T and MS A2756G polymorphisms are caused by defects in the MTHFR and MS genes, and individuals with the MTHFR C677T genotype are at higher risk of HHcy in the presence of reduced folate and vitamin B12 levels and high blood lead concentrations. [11, 12]. Zaric et al. showed that decreased MTHFR activity was significantly associated with high homocysteine levels. Mutations in C677T and A1298C can lead to inhibition of MTHFR enzyme activity, resulting in reduced production of 5-MTHF, and thus reduced production of methionine and tetrahydrofolate from 5-MTHF and cysteine, resulting in impaired nucleic acid metabolism and inhibited fetal growth and development. 3, excessive intake of methionine: the only way to obtain methionine is to obtain it from food. Studies have found that the concentration of homocysteine-thiolactone (HTL) in urine of mice with normal diet or balanced diet is not as high as that of mice with high methionine diet, and the high methionine diet also causes changes in plasma HTL, but the changes are not significant. 4, some diseases and drugs caused: (1) Chronic renal failure: Hcy methylase and transferase exist in the kidney, chronic renal failure may inhibit or inactivate the activity of key enzymes of Hcy metabolism, resulting in HHcy; (2) hypothyroidism: Relevant data show that hypothyroidism and thyroid drugs may affect HHcy, but the relevant evidence is lacking; (3) Anemia: the deficiency of folic acid and vitamin B12 will lead to megalloblastic anemia, and the blood cells contain enzymes that transform Hcy, but the deficiency of folic acid and vitamin B12 will lead to abnormal blood cell function, and the enzymes cannot be activated, resulting in the normal transformation of Hcy and the formation of HHcy; (4) Malignant tumors: experiments have confirmed that tumor cells, compared with normal cells, highly release Hcy, and the density of specific areas in tumor cells increases, resulting in the rapid proliferation of tumor cells to deplete folate and inactivate the methylation reaction catalyzed by MS. (5) Drugs: Relevant studies have also shown that cholestyramine and metformin interfere with the absorption of gastrointestinal life-maintaining drugs, and methotrexate, niacin and fibrate derivatives directly interfere with folate and Hcy metabolism [7]. According to the relevant literature in recent years, there are many other disease factors causing the elevation of Hcy, which will not be listed in this paper.

2. The metabolic mechanism of 2, 5-methyltetrahydrofolate in the body

Folic acid can be obtained from foods such as beans and spinach, and can be divided into natural folic acid and synthetic folic acid according to its source, and inactive folic acid and active folic acid according to its activity [13].

Active folate refers to a group of substances, including dihydrofolate, tetrahydrofolate, 5, 10-methylene tetrahydrofolate, 10-formyl-folate and 5-methyltetrahydrofolate, among which 5-methyltetrahydrofolate is the most active form of folate, which is a necessary basic substance for human life activities and a key product of active metabolism of synthetic folate. It is also the main component of natural folic acid. The active folic acid mainly discussed in this paper is 5-methyltetrahydrofolic acid, and its metabolic form in the body is shown in Figure

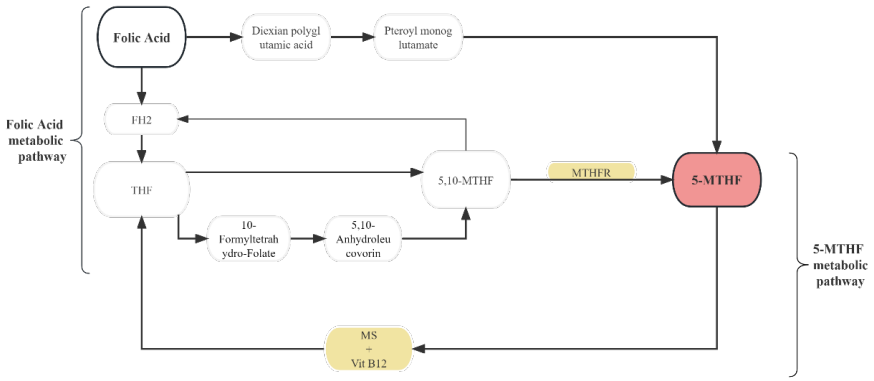

Figure 2 Folic acid metabolism pathway

1.THF: tetrahydrofolate, 2.5,10-MTHF: 5, 10-methyltetrahydrofolate, 3.MTHFR: methyltetrahydrofolate reductase

3. Comparison of 5-methyltetrahydrofolate with ordinary folate

Inactive folic acid generally refers to synthetic folic acid that is not active in itself, and active folic acid generally refers to 5-methyltetrahydrofolic acid that is active without metabolism. 5-MTHF as a component of folate is superior to inactive synthetic folate (pteroylglutamate) of active folate, the two are different biological characteristics of chemical substances, there is a relatively close relationship. The molecular structure is shown in Figure 3.

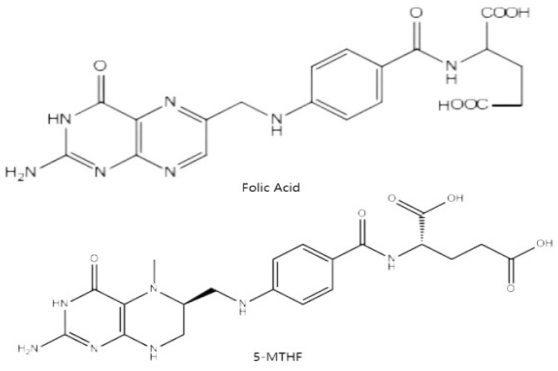

Figure 3 Molecular structure of synthetic folic acid and 5-methyltetrahydrofolic acid [14]

FA contained in supplements and fortified foods is metabolized to 5-MTHF in the body via the folic acid metabolic pathway [15]. In the cytoplasm, 5-MTHF provides methyl for homocysteine remethylation of methionine synthesis, which reduces blood homocysteine levels [16]. 5-MTHF has an advantage over synthetic folic acid in reducing Hcy levels in pregnancy: it is well absorbed even when gastrointestinal pH changes, and its bioavailability is not affected by metabolic defects. Use of 5-MTHF not only prevents the potential negative effects of the presence of unconverted folic acid in the peripheral circulation, but 5-MTHF in place of folic acid reduces the likelihood of hematological symptoms masking vitamin B12 deficiency, reduces interactions with drugs that inhibit dihydrofolate reductase, and overcomes metabolic defects caused by MTHFR polymorphisms [14].

4. 5-methyltetrahydrofolate in relation to hyperhomocysteinemia in pregnancy

Studies have shown that Hcy levels in pregnant women gradually decline to 50% to 60% of pre-conception levels and then remain relatively stable until delivery [17, 18]. Hcy levels increased in the third trimester, but remained low, which was associated with increased amino acid methylation and transmethylation in the third trimester and the needs of fetal growth and development [19]. Hyperhomocysteinemia during pregnancy leads to clinical manifestations of abortion, fetal dysplasia, gestational hypertension, diabetes and other pregnancy complications [20, 21]. Bo Liu et al. [22] designed a randomized controlled study to randomly supplement 164 pregnant women with folic acid (100 μg), L-MTHF (113 μg) or placebo daily supplements at 24 weeks of gestation. tHcy, plasma folic acid and erythrocyte folic acid (RCF) concentrations were analyzed at baseline and in blood collected at 8, 16 and 24 weeks. The study suggests that 5-MTHF is more effective than folic acid in reducing tHcy. 5-methyltetrahydrofolate, as a methyl donor, is involved in the remethylation of Hcy under the catalyst of methionine synthetase and vitamin B12 to reduce Hcy levels during pregnancy. The metabolic pathway is shown in the figure below.

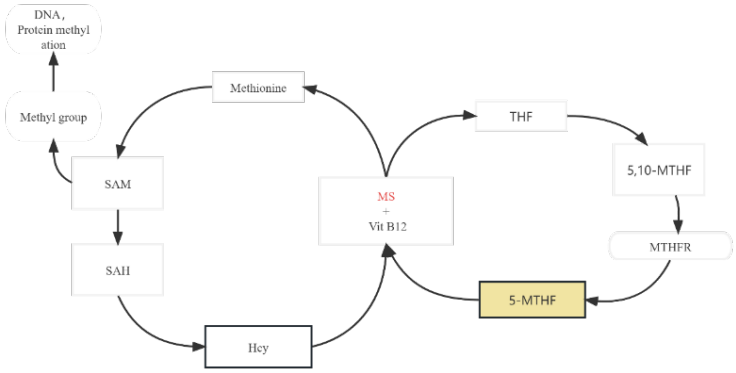

Figure 4. Interrelationship between folic acid and homocysteine metabolism

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism system and the main enzyme that causes folate metabolism disorders. This enzyme catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-MTHF, which provides methyl for Hcy, thereby reducing Hcy levels (Figure 5). According to domestic and foreign literature reports, MTHFR gene polymorphism can not only lead to neural tube malformation in newborns, but also has a close relationship with congenital heart disease, Down syndrome and other neonatal defects [23-26]. Folic acid metabolism enzyme gene polymorphism is the main cause of folic acid metabolism disorders, and there are three main genotypes: MTHFR 667TT, MTHFR 667CT and MTHFR 667CC genotypes, MTHFR 667TT gene carriers are known as severe folic acid metabolism disorders, their folic acid metabolism enzyme activity is only 1/3 of normal people, some even lower, so that the conversion of folic acid in their body is difficult to carry out successfully. Resulting in elevated homocysteine levels [27]. Depending on the metabolic pathway, 5-MTHF is unaffected by possible mutations in the MTHFR gene.

Folate is metabolized to 5-MTHF in the body, and 5-MTHF acts as a methyl donor to re-methylate homocysteine to methionine and reduce tHcy levels in pregnant women, a reaction catalyzed by methionine synthase (MS) and cofactor vitamin B12. A low vitamin B12 state, even when the folate state is sufficient, can trap folic acid as 5-MTHF, leading to impaired purine and pyrimidine synthesis. However, folic acid can be metabolized to tetrahydrofolate (THF) and is directly involved in nucleotide synthesis (Figure 2). Thus, folic acid can mask the hematological (megaloblastic anemia) signs of vitamin B12 deficiency, delay the diagnosis of vitamin B12 deficiency, and allow the neurological complications of vitamin B12 deficiency to progress unchecked [28]. Recent studies have also shown that 5-MTHF supplementation during pregnancy is more effective than folic acid in reducing Hcy levels, reducing the accumulation of unmetabolized folic acid in the body, and avoiding the masking of anemia caused by vitamin B12 deficiency (29).

5. Summary

In recent years, the necessity of folic acid supplementation for the prevention and treatment of hyperhomocysteinemia during pregnancy has been confirmed by many studies. As reported in relevant literatures at home and abroad, there are polymorphisms in the genes of

key enzymes in the process of folic acid metabolism, leading to individual folic acid metabolism disorders. Therefore, the development and research of 5-MTHF becomes the key [13, 21, 30]. However, the mechanism of 5-MTHF in the treatment of hyperhomocysteinemia in pregnancy is not fully understood, and more large randomized controlled studies are needed to verify the isotropic effect of 5-MTHF versus ordinary folic acid in pregnant women. The prophylactic dose and therapeutic dose of 5-MTHF for hyperhomocysteinemia in pregnancy still need to be confirmed and improved by more experiments in the future.

Hcy is an intermediate metabolite, and recurrent higher than normal Hcy levels during pregnancy may be associated with the risk of placenta-mediated complications, such as fetal growth restriction, preterm birth, hypertensive disorders of pregnancy, and recurrent miscarriage. However, the physical, mental and psychological trauma brought by adverse pregnancy outcome to a pregnant woman and a family is indescribable, and even causes irreparable consequences. Therefore, it is particularly important to reduce the Hcy level and reduce the occurrence of pregnancy complications by making pregnant women take 5-MTHF before and during pregnancy. In this paper, we summarized that 5-MTHF May replace folic acid to reduce Hcy level more effectively. Based on this review, we will further use prospective studies and randomized controlled experiments to track the Hcy level and pregnancy outcome of pregnant women who take oral 5-MTHF and ordinary folic acid. To provide favorable experimental evidence for subsequent obstetrical clinicians in pregnancy management of pregnant women.

References

[1] Gabbai D, Harlev A, Friger M, Steiner N, Sergienko R, Kreinin A, et al. Pregnancy outcomes among patients with recurrent pregnancy loss and uterine anatomic abnormalities. Journal of perinatal medicine. 2018; 46 (7): 728-34.

[2] Kong J. Expert Consensus on diagnosis and treatment of hyperhomocysteinemia. Electronic Journal of Tumor Metabolism and Nutrition. 2020; 7 (03): 283-8.

[3] Wei SQ. Changes of serum total homocysteine in hypertensive syndrome of pregnancy and its clinical significance. Journal of Harbin Medical University. 2001; 35 (1).

[4] Cheng S. Advances in the treatment of hyperhomocysteinemia. Advances in Physiological Sciences. 2011; 42 (5).

[5] Blom HJ, Smulders Y. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. J Inherit Metab Dis. 2011; 34 (1): 75-81.

[6] Annibal A, Tharyan RG, Schonewolff MF, Tam H, Latza C, Auler MMK, et al. Regulation of the one carbon folate cycle as a shared metabolic signature of longevity. Nat Commun. 2021; 12 (1): 3486.

[7] Wang SZ, Wang HS, Wang LZ, Li YJ. The pathogenesis of hyperhomocysteinemia and its pathophysiological significance. Chinese Journal of Brain Diseases and Rehabilitation (electronic edition). 2019; 9 (02): 117-20.

[8] Yan H, Xiang R, Yang JC, Chi YJ. Homocysteine metabolism and diseases. Advances in Physiological Sciences. 2023; 54 (4): 290-6.

[9] Zhao A. Correlation between MTHFR gene C677T and A1298C polymorphisms and plasma homocysteine levels in recurrent abortion. China Medical Review. 2021; 18 (15).

[10] Zarfeshan FY, Kooshkaki O, Kordi TD, Anani SG. Investigation of the association between C677T polymorphism of the MTHFR gene and plasma homocysteine level in recurrent fetal miscarriage. J Obstet Gynaecol Res. 2019; 45 (8): 1442-7.

[11] Yakub M, Moti N, Parveen S, Chaudhry B, Azam I, Iqbal MP. Polymorphisms in MTHFR, MS and CBS genes and homocysteine levels in a Pakistani population. PLoS One. 2012; 7(3):e33222.

[12] Qin X, Li J, Cui Y, Liu Z, Zhao Z, Ge J, et al. MTHFR C677T and MTR A2756G polymorphisms and the homocysteine lowering efficacy of different doses of folic acid in hypertensive Chinese adults. Nutr J. 2012; The men.

[13] Lian ZL, Liu K, Gu JH, Cheng YZ. Biological characteristics and application of folic acid and 5-methyltetrahydrofolate. Food Additives in China. 2022; 33 (02): 230-9.

[14] Scaglione F, Panzavolta G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica. 2014; 44 (5): 480-8.

[15] Patanwala I, King MJ, Barrett DA, Rose J, Jackson R, Hudson M, et al. Folic acid handling by the human gut: implications for food fortification and supplementation. Am J Clin Nutr. 2014; 100 (2): 593-9.

[16] Kubo Y, Fukuoka H, Kawabata T, Shoji K, Mori C, Sakurai K, et al. Distribution of 5-Methyltetrahydrofolate and Folic Acid Levels in Maternal and Cord Blood Serum: Longitudinal Evaluation of Japanese Pregnant Women. Nutrients. 2020; 12 (6).

[17] Luo CC. Investigation of serum homocysteine level in normal pregnant women. Laboratory Medicine. 2014; 29 (7).

[18] Seremak-Mrozikiewicz A, Bogacz A, Bartkowiak-Wieczorek J, Wolski H, Czerny B, Gorska-Paukszta M, et al. The importance of MTHFR, MTR, MTRR and CSE expression levels in Caucasian women with preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2015; 188: 113-7.

[19] Chen DL, Xu J. Advances in research on homocysteine and pregnancy-related diseases. Preventive Medicine. 2020; 32 (02): 147-51.

[20] Yuan YD, Gong XW, Yang YH. A meta-analysis of factors associated with re-embolization in the occurrence of pulmonary thromboembolism. Chinese Journal of Medicine. 2012(34):2419-25.

[21] Lee M, No HJ, Jang SY, Kim N, Choi SH, Kim H, et al. Hereditary Thrombophilia in Korean Patients with Idiopathic Pulmonary Embolism. Yonsei Medical Journal. 2012; 53 (3).

[22] Liu B, Liang Z, Li JP, Qin XH, Fan FF, Zhang Y, et al., editors. Comparative effect of supplementation with 5-methyltetrahydrofolate or folic acid on reducing plasma homocysteine: a systematic review and meta-analysis. The 7th Cross-Straits and Hong Kong and Macao Nutrition Science Conference; 2022; Qingdao, Shandong, China.

[23] Zhang CH. A meta-analysis of the relationship between maternal 5, 10-methylenetetrahydrofolate reductase gene C677T polymorphism and the susceptibility of offspring to neural tube malformation in a Chinese population. Health Research. 2018; 47 (2).

[24] Liao YP. The correlation between genetic polymorphisms of MTHFR, MTRR and MTR and the occurrence of Down syndrome. Chinese Journal of Laser Biology. 2010; 19 (3).

[25] Hou SN. Association between folic acid gene polymorphism and high risk of Down syndrome. International Journal of Laboratory Medicine. 2016; 37 (22).

[26] Chai O. Association between MTHFR polymorphism of methylenetetrahydrofolate reductase gene and risk of Down syndrome. Hebei Med. 2020; 42 (6).

[27] Zhang FQ. A meta-analysis of the relationship between maternal Methylenetetrahydrofolate reductase C677T polymorphism and offspring DS in a Chinese population. Chinese Journal of Reproductive Health. 2013; 24 (5).

[28] Henderson AM, Aleliunas RE, Loh SP, Khor GL, Harvey-Leeson S, Glier MB, et al. l-5-Methyltetrahydrofolate Supplementation Increases Blood Folate Concentrations to a Greater Extent than Folic Acid Supplementation in Malaysian Women. J Nutr. 2018; 148 (6): 885-90.

[29] Mei J. Study on therapeutic effect of active folic acid on adverse pregnancy. China Maternal and Child Health Research. 2017; 28 (12).

[30] Liang Z, Wang XF, Li SL. A clinical study on the change of homocysteine level between pregnant women and normal women. Chinese Journal of Health Inspection. 2018; 28 (8): 979-80 + 83.

Universe Scientific Publishing

A Literature Review Study: a Meta-Analysis and Investigation of the Frequency Pattern of Point Selection Based on Clinical Studies of Acupuncture for Postoperative Treatment of the Anterior Cruciate Ligament

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Abstract: Objective: Acupuncture is a common treatment for postoperative ACL reconstruction, however, there are still a large number of gaps in the literature related to acupuncture for postoperative ACL rehabilitation. This study was conducted by measuring the clinical observation indexes and meta-analyzing the efficacy of the literature related to acupuncture for postoperative ACL rehabilitation in the CNKI and PUBMED databases. Results: The top 5 acupoints were ST34 28 times (14.28%), ST36 27 times (13.77%), SP10 23 times (11.73%), SP 6 21 times (10.71%), and GB34 20 times (10.2%), and the combination of acupoints with the highest level of support was "ST34→ST36", followed by "ST34→SP10", both of which had a support degree of >50%.

Keywords: Meta-Analysis; ACLR; Acupuncture Treatment

Introduction

The anterior cruciate ligament (ACL) of the knee is an important structure for maintaining the stability of the knee joint [1]. And ACL injury is often accompanied by limitation of knee joint motor function [2]. Most of the patients with ACL injury are combined with medial collateral ligament and meniscus injury, and the patients suffer from knee pain and joint instability after injury, which greatly affects their daily life [3]. At present, the clinical treatment of ACL injury mainly adopts arthroscopic ACL reconstruction surgery (ACLR), which has achieved good therapeutic effect [4], and relevant studies have also shown that [5] traditional Chinese medicine (TCM) has excellent therapeutic efficacy in the treatment of postoperative rehabilitation of ACL injury.

Acupuncture is one of the commonly used therapies in traditional Chinese medicine, and several studies have proved [6, 7] that acupuncture has a positive significance in the recovery of proprioception after ACLR, and that acupuncture treatment has a significant analgesic inhibitory effect on pain that occurs in the process of postoperative rehabilitative functional exercise after ACLR [8]. Some researchers [9] found that analgesia and anti-inflammation were the two major therapeutic categories of acupuncture by analyzing the disease spectrum of acupuncture. Related studies also found that: 2 Hz low-frequency stimulation can cause the brain to generate and release enkephalins and endorphins, and 100 Hz high-frequency stimulation can cause the spinal cord to release dynorphins, which can play an analgesic role; the two can play a synergistic effect when used alternately to achieve analgesia [10].

However, reviewing the literature related to acupuncture for ACL postoperative rehabilitation, there is still a large gap in the literature related to acupuncture in regulating proprioception and pain after ACLR. Based on this premise, the present study aims to discover the current status of research and its future trend in the field of acupuncture in ACL reconstruction and rehabilitation, and to provide research ideas for related scholars through meta-analysis of the clinical observation indexes and the therapeutic efficacies of acupuncture in postoperative rehabilitation of the ACL in the CNKI and PUBMED databases. The purpose of this study is to investigate the current status and future development of acupuncture and moxibustion in the field of postoperative rehabilitation of ACL reconstruction, and to provide research ideas for related scholars.

1. Information and methods

1.1 Search strategy

The Chinese database CNKI and the English database PUBMED were searched for all relevant literature related to acupuncture for postoperative ACL treatment from the beginning of the database construction to April 01, 2023. The terms “Acupuncture”, “needling”, “Moxibustion”, “Electroacupuncture”, “Fire”, and “Fire” were used respectively. Electroacupuncture” “Fire needle” as a category of subject terms, and “AND” to connect “ACL “AND” to “ACL” or “Anterior Cruciate Ligament”.

1.2 Inclusion criteria

CNKI language was limited to Chinese, and PUBMED included English literature by default, with no restriction on the type of study and complete, authentic and reliable information. All studies with titles, abstracts, and keywords related to the search subject terms were included.

1.3 Exclusion criteria

(i)The type of disease studied excludes “rehabilitation treatment after ACLR”□(ii)Only “anterior cruciate ligament reconstruction” is involved, not “acupuncture and moxibustion” related content□(iii) The main subject of the article is “acupuncture therapy”, and the disease type is not related to “rehabilitation after ACL reconstruction”; (iv) reviews, animal experiments, and non-RCT related studies; (v) conference papers and news reports.

1.4 Literature Screening and Data Extraction

Two researchers reviewed the literature according to the inclusion and exclusion criteria, screened the titles and abstracts, and further evaluated the full text, and excluded the dissenting literature by third-party negotiation. The literature was downloaded in PDF or CAJ format, and then integrated and categorized into EXCEL for classification and statistical processing.

1.5 Results of the literature search

By searching the CNKI literature database with ACLR as the search term, the following search terms were logically connected by AND, respectively, and the following search results were obtained: Acupuncture 16, Needling 23, Electroacupuncture 20, Fire Acupuncture 0, Moxibustion 6; by searching the PUBMED database with ACL, Anterior Cruciate Ligament as the search terms, respectively, the following search terms were logically connected by AND The following search results were obtained: “Acupuncture” 25; “Needling” 110; “Moxibustion” 7; “Electroacupuncture” 8; “Needle warming moxibustion” 0. After de-emphasis and exclusion, a total of 41 papers were included.

2. Frequency of acupoints and attribution analysis

Among the 41 papers included, 37 acupuncture prescriptions were extracted, and these acupuncture prescriptions were imported into EXCEL for data statistics to obtain the following results:

2.1 Frequency of use of acupuncture points

From the 41 articles included in the literature, a total of 37 prescriptions for acupoints and 4 prescriptions for single acupoints (including 2 prescriptions for the Ah Yes point) were extracted, and the statistical results involved a total of 38 acupoints, with a total frequency of use of 248 times. The top 5 frequently used acupoints were ST34 28 times (14.28%), ST36 27 times (13.77%), SP10 23 times (11.73%), SP 6 21 times (10.71%), and GB34 20 times (10.2%). See Table 1 (only those with a frequency >5 are shown):

Name	Frequency	Percentage	Main and collateral channels
ST34	28	11.29%	ST
ST36	27	10.89%	ST
SP10	23	9.27%	SP
SP6	21	8.47%	SP
GB34	20	8.06%	GB
ST35	19	7.66%	ST
ST32	15	6.05%	ST
SP9	13	5.24%	SP
EX-LE5	11	4.44%	EX-LE
EX-LE2	8	3.23%	EX-LE
ST40	6	2.42%	ST
BL57	5	2.02%	BL

Table 1 Acupoints with a frequency of use >5 for ACLR in acupuncture treatment

2.2 Frequency of acupoint attribution to meridians

The included acupoints were categorized into meridians. The categorization results showed that the Foot Yangming Stomach Meridian was used 103 times (41.53%), followed by the Foot Taiyin Spleen Meridian 63 times (25.40%) and the Foot Shaoyang Gallbladder Meridian 33 times (13.31%). In terms of the number of acupoints, the Foot Yangming Stomach Meridian was dominated by 11 points (35.00%), the Foot Shaoyang Gallbladder Meridian by 6 points (15.79%), and the Foot Taiyin Spleen Meridian by 5 points (13.16%). See Table 2:

Main and collateral channels	Numbers of acupoints		Types of acupoints		Acupoint (Frequency)
	Frequency	Percentage	Frequency	Percentage	
ST	103	41.53%	11	28.95%	st32 (15) st36 (27) st34 (28) st31 (3) st40 (6) st35 (19) st37 (1) st38 (1) st21 (1) st44 (1) st39 (1)
SP	63	25.40%	5	13.16%	sp10 (23) sp9 (13) sp6 (21) sp8 (4) sp11 (2)
GB	33	13.31%	6	15.79%	GB39 (3) GB34 (20) GB33 (4) GB30 (1) GB31 (3) GB33 (2)
EX-LE	25	10.08%	4	10.53%	EX-LE5 (11) EX-LE2 (8) Siqiang acupoint (2) Ashi acupoint (4)
BL	13	5.24%	6	15.79%	BL23 (1) BL18 (1) BL40 (4) BL57 (5) BL37 (1) BL55 (1)
KI	6	2.42%	4	10.53%	ki10 (2) ki3 (2) ki6 (1) ki4 (1)
LI	3	1.21%	1	2.63%	LI4 (3)
DU	2	0.81%	1	2.63%	DU20 (2)

Table 2. Frequency of acupoint attribution to meridians

2.4 Association rule analysis

A total of 20 sets of eligible cave sets were analyzed according to the set conditions. According to the order of support, the top 5 combinations are: ① ST34→ST36; ② ST34→SP10; ③ SP10→SP6; ④ ST36→SP6; ⑤ ST34→SP6, see Table3, and the complex network diagram shows that the core acupuncture point group is “ST34-ST36”, see Table 3:

eventualities	antecedent (math.)	an actual example	Support/%	Confidence level/%
ST34	ST36	27	72.97	81.48
ST34	SP10	23	62.16	82.61
SP10	SP6	21	56.76	85.71

ST36	SP6	21	56.76	80.95
ST34	SP6	21	56.76	80.95
ST34	GB34	20	54.05	80
SP6	SP10, ST34	19	51.35	84.21
ST34	ST35	18	48.65	94.44
ST34	SP6, SP10	18	48.65	88.89
ST36	ST35	18	48.65	83.33

eventualities	antecedent (math.)	an actual example	Support/%	Confidence level/%
ST36	SP6, SP10	18	48.65	83.33
SP6	SP10, ST36	18	48.65	83.33
ST34	SP10, ST36	18	48.65	83.33
SP10	SP6, ST34	17	45.95	94.12
SP10	SP6, ST36	17	45.95	88.24
ST36	ST35, ST34	17	45.95	82.35
ST34	SP6, ST36	17	45.95	82.35
ST36	SP6, ST34	17	45.95	82.35
SP10	GB34, ST34	16	43.24	81.25
ST36	ST32	15	40.54	100

Table 3. Support and confidence level of association rule analysis

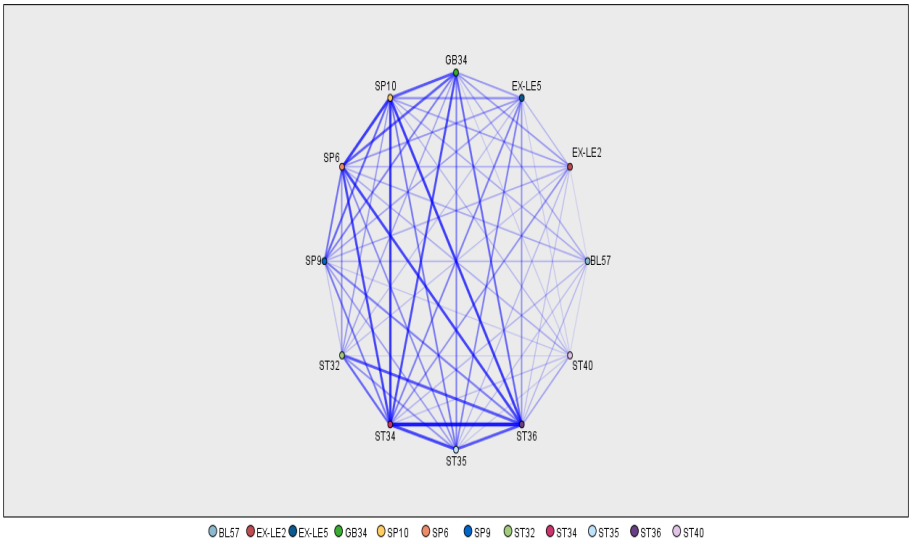


Figure 1. Network diagram of core acupuncture points

2.5 Cluster analysis

Using SPSS Statistic 25.0 to cluster the acupoints with frequency ≥5, as shown in Fig.2, the high-frequency selected acupoints for treating ACLR can be classified into five major categories when the scale is 15: ① SP10, SP9, SP6, GB34, BL57; ② ST35, EX-LE5, ST34; ③ EX-LE2; ④ ST36, ST32; ⑤ ST40.

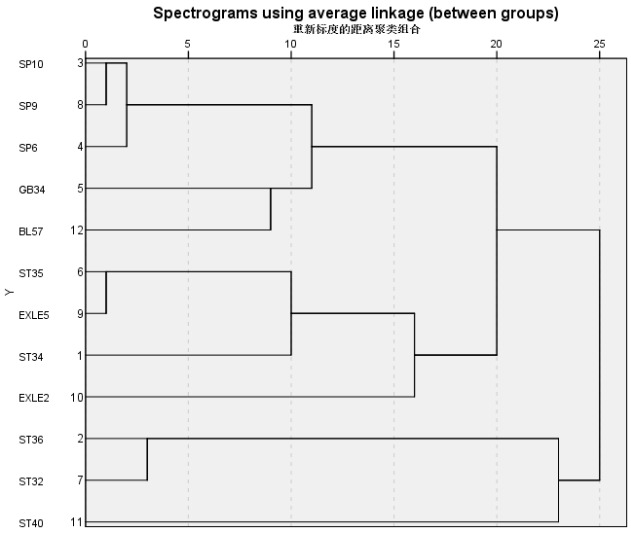


Figure 2. Dendrogram of cluster analysis of core acupoints

3. Meta-analysis

3.1 Search strategy and results

The search method and results were referred to the same as 1.1 above, and after excluding cohort studies and RCT trials in which non-acupuncture was used as a variable, a total of 28 papers with 1,747 subjects were included, and the quality of the literature was evaluated according to the Cochrane Handbook of Systematic Evaluation 5.3 of the Risk of Bias Assessment Tool for Treatment Evaluation. Data acquisition included the name of the first author, time of publication, intervention, and outcome indicators. Studies with incomplete data were supplemented by contacting the original authors.

3.2 Statistical analysis

Review Manager 5.3 software was used to analyze the data, and the heterogeneity of the included studies was first judged; if there was homogeneity among the included studies ($P > 0.1$, $I2 < 50\%$), a fixed-effects model was used, and if the heterogeneity among the included studies was obvious ($P < 0.1$, $I2 > 50\%$), a random-effects model was used, and at the same time, sensitivity analyses were performed to exclude the studies that could cause heterogeneity, and then Meta-analysis was performed; when the included literature > 10, a funnel plot was used to test for publication bias. studies, and then Meta-analysis was performed; when the included literature was >10 then the funnel plot was used to test for publication bias. The test level was set at $\alpha=0.05$.

3.3 General characteristics of included studies

The literature was published between 2012 and 2022; 17 of them used Lysholm score as diagnostic criterion, 19 used VAS diagnostic criterion, 17 used ROM diagnostic criterion, and 7 used IKDC diagnostic criterion.

3.4 Evaluation of the quality of literature

Twenty-two RCTs discussed the method of randomization and were judged to be “low risk”; six RCTs only mentioned randomization in the text but did not describe it specifically and were judged to be “unclear”; none of the literature reported allocation concealment; none of the text mentioned blinding; and the risk of bias was assessed as shown in Figures 3 and 4. Blinding was not mentioned throughout the text; the risk of bias assessment is shown in Figures 3 and 4.

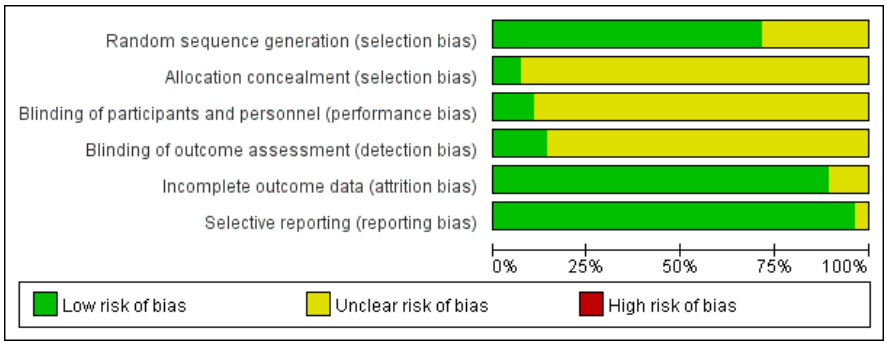


Figure 3. The risk of bias assessment(1)

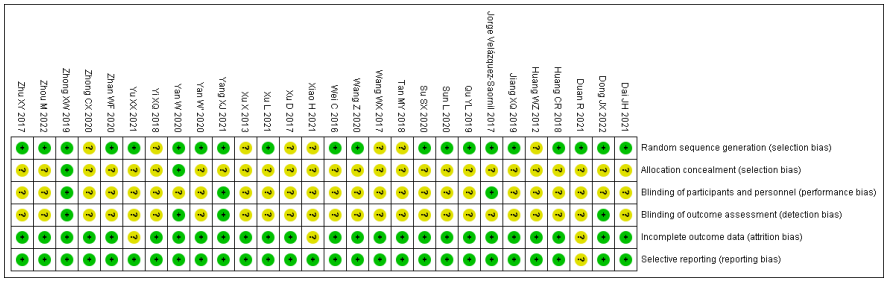
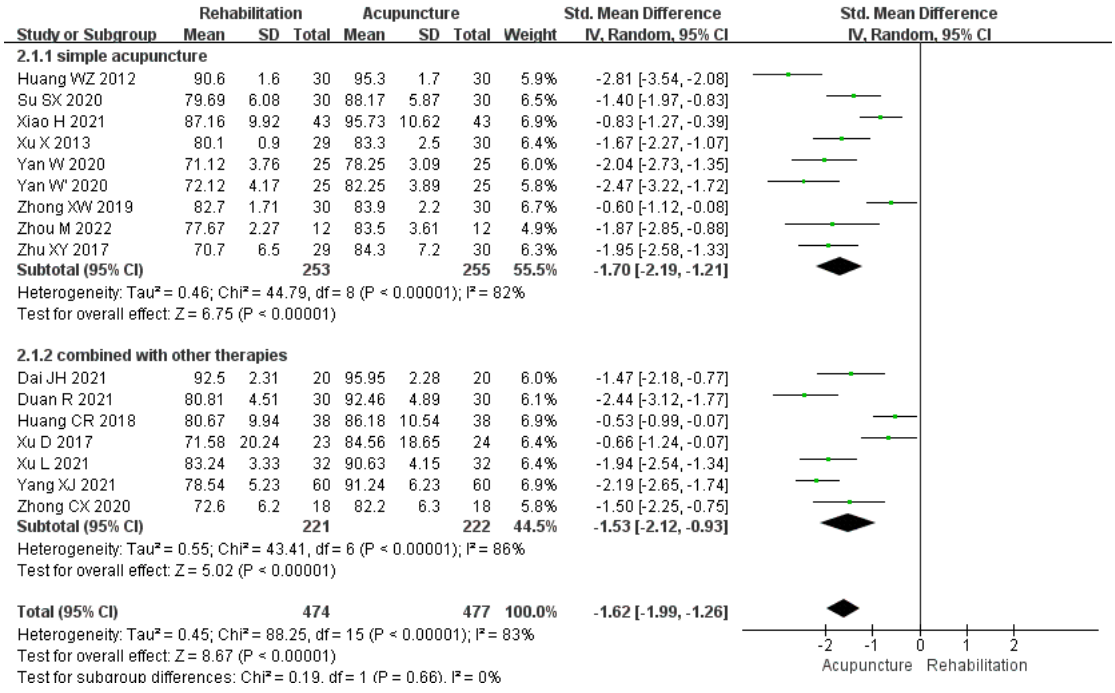


Figure 4. The risk of bias assessment(2)

3.5 Meta-analysis

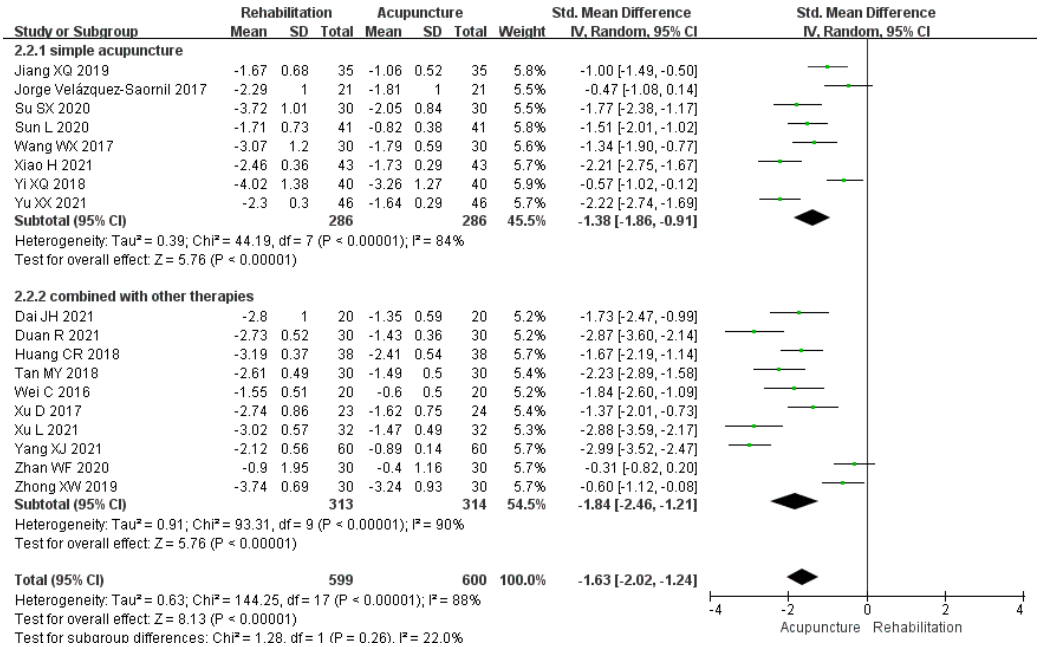
3.5.1 Lysholm score

A total of 16 papers reported the Lysholm score, of which 9 were acupuncture/ electroacupuncture therapy alone and 7 combined other therapies, after the test of heterogeneity, the results of subgroup 1, I2 = 82%, and the results of subgroup 2, I2 = 86%, with significant heterogeneity between groups, sensitivity analysis was performed, and the heterogeneity was >50% after excluding the papers one by one, and the results were more stable, and the random effect model was used. The results showed that the difference in Lysholm scores between the 2 groups was statistically significant [OR = -1.62, 95% CI (-1.99, -1.26), Z = 8.67, P < 0.00001].



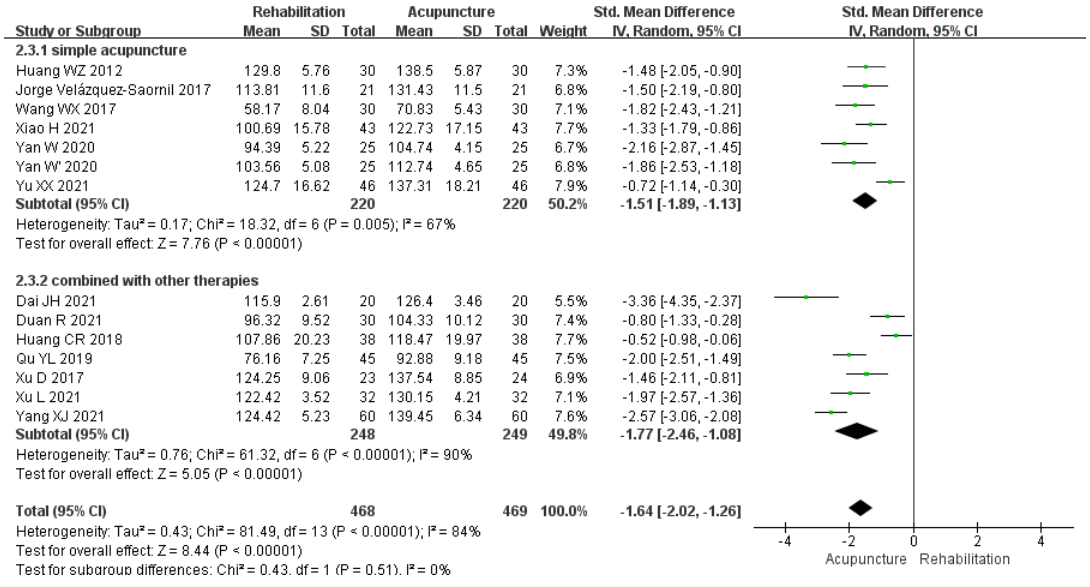
3.5.2 VAS score

A total of 18 papers reported the Lysholm score, of which 8 were pure acupuncture/electroacupuncture therapy and 10 combined other therapies, after the test of heterogeneity, the results of subgroup 1, I2 = 84%, and the results of subgroup 2, I2 = 90%, there was a significant heterogeneity between the groups, and sensitivity analysis was carried out, and the heterogeneity was all > 50% after excluding the papers one by one, and the result was more stable, using the random effects model. The results showed that the difference in VAS scores between the 2 groups was statistically significant [OR = -1.63, 95% CI (-2.02, -1.24), Z = 8.13, P < 0.00001].



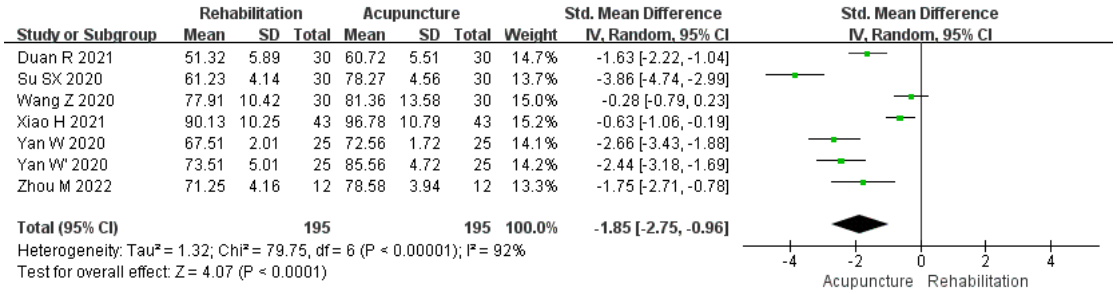
3.5.3 ROM score

A total of 14 papers reported the Lysholm score, of which 7 were acupuncture/electroacupuncture therapy alone, and 7 papers combined other therapies, after the test of heterogeneity, the results of subgroup 1, I2 = 67%, and the results of subgroup 2, I2 = 90%, there was a significant heterogeneity between the groups, and sensitivity analysis was carried out, and the heterogeneity was >50% after excluding the papers one by one, and the results were more stable, using the random effects model. The results showed that the difference in ROM scores between the 2 groups was statistically significant [OR = -1.64, 95% CI (-2.02, -1.26), Z = 8.44, P < 0.00001].



3.5.4 IKDC score

A total of 7 papers reported the Lysholm score, after the heterogeneity test, I2 = 92%, P < 0.00001, there is obvious heterogeneity between groups, sensitivity analysis, one by one after the exclusion of the literature, heterogeneity are > 50%, the results are more stable, the use of random effects model. The results showed that the difference in IKDC scores between the 2 groups was statistically significant [OR = -1.85, 95% CI (-2.75, -0.96) , Z = 4.07, P < 0.0001].



4. Discussion

4.1 Acupoint Frequency Mining

After data mining and analyzing the 41 articles included in this study, we found that the most frequently used acupoints for acupuncture-assisted postoperative rehabilitation of the anterior cruciate ligament were ST34, ST36, SP10, SP6, and GB34, and that ST34 Liangqiu is an acupoint of the foot-yangming gastric meridian, and is also a Xi point of the foot-yangming meridian, as mentioned in the book "Suwen-Impotence", which reads: "Treating myasthenia is only to take the Yangming "The ST36 Zusanli acupoint is a lower merging point of the stomach meridian, and both it and the ST34 Liangqiu point are rich in qi and blood of the foot yangming meridian, which has the effect of tonifying qi and blood of the yangming meridian and relieving qi and blood dysfunctions after ACLR surgery, and the depletion of blood and qi over a long period of time results in qi and blood deficiency and loss of nourishment of sinews, which leads to muscular atrophy and weakness, and limitation of flexion and extension [11]. The SP10 Sea of Blood acupoint is an acupoint of the foot Taiyin Spleen meridian acupoints, and ST34 and GB34 are ACL paraclinical acupuncture points, while SP10 specializes in the treatment of lower limb impotence, its location and ST34 relative to each other as a watchword [12] GB34 Yanglingquan acupuncture point is not only the joint point of the foot ShaoYang gallbladder meridian and gallbladder under the joint point, but also the eight will be points of the tendon will be ACL injuries in traditional Chinese medicine "tendon injuries" category, its take ACL injury is the category of Chinese medicine "tendon injury", and it takes the acupoint to take the meaning of relaxing tendons and activating collaterals. In addition, SP6 Sanyinjiao acupoint is the meeting place of the three meridians of the foot shaoyin, foot taiyin, and foot syncope, and the acupoint is taken to take the meaning of "the meridians and collaterals are passed, and the main treatment is reached", and at the same time, SP6 is also a commonly used empirical point for lower limb diseases.

The analysis of the association rules of acupoints showed that the combination of acupoints with the highest degree of support was "ST34→ST36", followed by "ST34→SP10", and its degree of support was >50%. The combinations with a confidence level of up to 90% include "ST34-ST35", "SP10-SP6-ST34" and "ST36-ST32". These acupoint combinations are also commonly used in the treatment of postoperative ACLR, and the complex network relationship diagram more intuitively demonstrated that "ST34-ST36" can be regarded as the core acupoints for the treatment of ACLR.

The results of cluster analysis of acupoints showed five valid clusters: cluster 1 SP10, SP9, SP6, GB34, BL57, whose selected acupoints involved the above commonly used SP6, SP10, and GB34, which are all commonly used acupoints for regulating qi and blood loss of glory in the knee joints of the affected knee joints after ACLR surgery; the second group of ST35, EX-LE5, and ST34, in which EX-LE5 is located around the knee joint and It is a commonly selected acupoint for knee joint diseases; in the third group, EX-LE2 is a commonly used proximal treatment point after ACLR [13]; in the fourth group, ST36 is a high-frequency acupoint for the treatment of postoperative ACLR; ⑤ ST40 is a meridian acupoint of the foot yangming meridian, which is uniquely effective for the treatment of impotence and paralysis of the

lower limbs [14]. In this study, we analyzed the data mining of the selection pattern of acupuncture points for the treatment of postoperative ACLR, and compiled the patterns of commonly used acupoints, meridians, sites, and the pairing of acupoints. It was concluded that the selection of acupuncture points for the treatment of postoperative ACLR follows the therapeutic principles of promoting qi and blood circulation, and relieving tendons and activating collaterals, which provides a reference for the direction of clinical practice and scientific research.

4.2 Meta-analysis

Meta-analysis of the selection of outcome indicators, this study mainly included four outcome indicators, including Lysholom score, VAS score, ROM score, and IKDC score, and the differences were statistically significant.

There are some limitations in this study.1. In the included literature, some of the studies were unclear about the randomization method, allocation concealment and blinding implementation, and some of them had high-risk factors, which had a certain risk of bias.2. Literature on late follow-up, long-term efficacy was unclear.3. Literature on safety evaluation was not clear.4. Literature on small sample size. In future clinical studies, it is still necessary to further conduct more rigorous, high-quality randomized controlled trials under the guidance of evidence-based medicine to provide more reliable evidence for the clinical effectiveness and safety of acupuncture for postoperative ACLR.

5. Conclusion

For the treatment of ACLR, ST34, ST36, SP10 and SP6 were selected for acupuncture, and the meridians of foot yangming gastric meridian and foot taiyin spleen meridian were selected for acupuncture. The core point group is “ST34-ST36”, which follows the therapeutic principles of promoting qi, activating blood circulation, relaxing tendons and activating collaterals, and focuses on the circulation of the meridians, which can provide a reference basis for the clinic.

References

[1] Yang XJ, Zhang PY, Li W, et al. Observation on the clinical rehabilitation effect of anterior cruciate ligament injury of the knee joint by combining acupuncture therapy with strong tendon and bone-strengthening blood-activating soup[J]. Chinese Journal of Traditional Chinese Medicine, 2021, 39(05):44-47.

[2] Wu SX, Yang H. The effect of peer education on rehabilitation after autogenous muscle reconstruction in patients with anterior cruciate ligament injury of the knee joint [J]. Journal of Nursing, 2019, 26(18):72-76.

[3] Wang W, Liu F, Wang XM, et al. Clinical effect observation of arthroscopic three-tunnel reconstruction for the treatment of anterior cruciate ligament injury of knee joint [J]. Journal of Clinical Military Medicine, 2019, 47(4):419-421.

[4] Xu SC, Lai HM, Zhang HC, et al. Clinical efficacy of exercise therapy combined with ozone in the treatment of anterior cruciate ligament injury of the knee joint [J]. Journal of Clinical Military Medicine, 2019, 47(11):1200-1203.

[5] Zhang PY, Xiong J, Yu HB. et al. Recent research on postoperative rehabilitation of anterior cruciate ligament injury treated with traditional Chinese medicine[J]. Hunan Journal of Traditional Chinese Medicine,2018,34(12):167-169.

[6] Yan W, Murong JY, Chong X, et al. Clinical study of acupuncture exercise therapy for the treatment of knee joint after anterior cruciate ligament reconstruction[J]. Journal of Guangzhou University of Traditional Chinese Medicine,2020,37(10):1918-1924.

[7] Yang KD. Research on the application of exercise therapy combined with acupuncture in postoperative rehabilitation of anterior cruciate ligament reconstruction [D]. Guangzhou University of Traditional Chinese Medicine, 2018.

[8] Jiang B. Preliminary observation on the effect of acupuncture on proprioception after anterior cruciate ligament reconstruction of the knee[D]. China Academy of Traditional Chinese Medicine, 2016.

[9] Chen HX, Xu Y, Guo Y, Xu ZF. Common research strategies and perspectives in the development of translational medicine in acupuncture and moxibustion[J]. Chinese Acupuncture,2022,42(12):1331-1334+1362.

[10] Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies[J]. Trends Neurosci, 2003, 26(1): 17-22.

[11] Li JX, Huang ZQ. The effect of internal and external application of traditional Chinese medicine on early recovery after arthroscopic knee anterior cruciate ligament reconstruction [J]. Journal of Changchun University of Traditional Chinese Medicine, 2017, 33(2): 292-295.

[12] Su SX, Ye YY, Chen JQ, Tong XY. Clinical study of "three-needle knee" in postoperative rehabilitation after anterior cruciate ligament reconstruction[J]. Journal of Traditional Chinese Medicine, 2020, 48(06):63-66.

[13] Wang J. Effects of acupoint acupuncture combined with rehabilitation training on functional recovery and prognosis after knee anterior cruciate ligament reconstruction[J]. New Chinese Medicine, 2020, 52(08):145-147.

[14] Yu XX, Lou HK, Li FJ. Effects of electroacupuncture combined with systematic rehabilitation training on isometric muscle strength, joint mobility and body function in postoperative patients with anterior cruciate ligament injury[J]. Shanghai Journal of Acupuncture and Moxibustion, 2021,40(08):974-981.

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Clinical Progress of Acupuncture in the Treatment of ACL after Reconstructive Surgery

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Abstract: Anterior cruciate ligament (ACL) injury of the knee is one of the common sports injuries, and ACL reconstruction is currently the mainstream treatment. However, ACL reconstruction often produces postoperative complications such as swelling, pain, muscle atrophy, joint adhesion and stiffness, and timely interventional rehabilitation is needed for patients to recover the expected level. Studies have shown that acupuncture treatment can regulate inflammatory factors and related signalling pathways, etc., and has obvious efficacy in joint rehabilitation after ACL reconstruction. The authors collated clinical reports on the use of acupuncture therapy such as general acupuncture, electroacupuncture, moxibustion with acupuncture, snap needling, and ethnic acupuncture in the rehabilitation process after ACL reconstruction in recent years, to explore the feasibility and effectiveness of the intervention of acupuncture therapy, with the aim of providing a more systematic reference for the treatment of ACL injury in the future clinic after surgery.

Keywords: Acupuncture Treatment; ACL Injury Reconstruction; Rehabilitation Treatment

1. Modern medical research on ACL injury

1.1 Epidemiology

ACL injury is a very common disease, with an annual incidence of 100,000 to 200,000 cases[3], the patients are mostly young people or athletes, and there are more males than females, of which males are mostly football, basketball sports injuries and accidental injuries, and females are mostly accidental injuries, badminton, skiing injuries[4]. If ACL injury is not treated in time, it is very easy to cause damage to the articular cartilage and meniscus, and promote joint aging[5].

1.2 Mechanism study

After ACL reconstruction, there are complications such as swelling and pain, and surgery is one of the main reasons. Even though minimally invasive techniques have minimised trauma, ACL tearing and intraoperative mechanical stimulation will still lead to different degrees of swelling and pain. Therefore, patients need to be under good pain management for a successful early rehabilitation programme. Currently, active contraction of the quadriceps muscle, ankle pumps, elevation of the affected limb, ice packs and other measures to promote tissue fluid return, anti-inflammatory and analgesic measures are generally recommended [6][7]. Furthermore, after performing ACL reconstruction, it is necessary to wear protective gear for a long period of time, and it is impossible to intervene in rehabilitation therapy early, which is prone to the adhesion of the joint. In addition, after ACL reconstruction, the joint-derived muscles will be in a state of inhibition, leading to changes in nerve pathways, quadriceps strength and activation is obviously insufficient, which will weaken the quadriceps strength, and postoperative knee swelling and pain will further aggravate the quadriceps atrophy through this state of inhibition [8, 9]. It has also been suggested that early after ACL reconstruction, due to changes in cortical signalling areas, the neural control of the knee joint on the affected side decreases, resulting in atrophy of the quadriceps [10]. In conclusion, the intervention of active and correct rehabilitation therapy in the early stage of ACL reconstruction is particularly important.

2. Knowledge of ACL injury in Chinese medicine

The motherland medicine, tendon is the bone joints attached to the tangible things. The Yellow Emperor's Classic of Internal Medicine says that "the tendons are rigid", "all tendons belong to the joints", and "the tendons bind the bones and facilitate the organs", which indi-

cates that the function of tendons is to restrain the bones and stabilise the joints. According to the theory of Chinese medicine, the etiology of ACL injury is mainly caused by trauma, which belongs to the category of "tendon injury" or "tendon breakage", and the basic mechanism of the disease is as follows: the local tendons of the knee joint are damaged after the trauma, and the qi and blood are not smooth, the qi is stagnant and blood stagnation, which results in swelling and pain; the tendons are unable to bind the bones and facilitate the organs, so the joint is unstable, and the flexion and extension are not favourable. Therefore, joint instability, flexion and extension are unfavourable [11]. The motherland medicine has rich means of rehabilitation treatment after ACL reconstruction, such as internal administration of traditional Chinese medicine, hot ironing, massage, etc., which have all achieved certain results [12].

Acupuncture and moxibustion have obvious advantages in the postoperative treatment of ACL reconstruction, which is the most characteristic diagnostic and therapeutic means of Chinese medicine, with the effects of dredging the meridians and collaterals, supporting the positive and dispelling the evil, and regulating the yin and yang. Acupuncture and Moxibustion A and B Jing said: "The pain outside the knee, can not flexion and extension, shin paralysis is not benevolent, Yang Guan main. Thigh paralysis leads to pain outside the knee and femur, not benevolent, tendon urgency, Yanglingquan is the mainstay." Acupuncture treatment is widely used at home and abroad to treat various diseases, such as neurological disorders, motor system disorders, etc., with remarkable efficacy [13]. Acupuncture treatment has the characteristics of easy operation, wide applicability, no side effects, and obvious efficacy in relieving pain, repair of injury, and psychological stress [14]. Studies have shown that in the treatment of orthopaedic and traumatic diseases, acupuncture therapy can reduce pain, improve joint mobility, bone metabolism and local blood circulation, as well as repair of injuries [15].

3. Clinical progress

3.1 General acupuncture treatment

The clinical efficacy of acupuncture combined with rehabilitation training for the treatment of quadriceps atrophy after ACL reconstruction in 92 patients by Fan Xiliang [16] and others. The total effective rate of the treatment group was 93.5%, by taking Fubu, Liangqiu, Shusanli, Blood Sea, Yanglingquan, Yinlingquan and Sanyinjiao points. It was found that the intervention of acupuncture therapy could regulate the immune function of the patients, shorten the course of the disease, improve the muscle atrophy and weakness, and promote the functional rehabilitation of the knee joint, which was more effective than the simple rehabilitation training. Zhou Bin et al [17] used personalised exercise prescription combined with knee three needles to promote the rapid recovery of pilots with multiple postoperative anterior cruciate ligament injuries in one case was reported. The affected side Liangqiu, Blood Sea and knee eye were taken as the main points, and the supporting points were the affected side foot Sanli, Sanyinjiao and Yinlingquan points. It was found that the combination of personalised exercise prescription and the three knee points was clinically feasible to promote the rapid recovery of ACL injuries after multiple operations. However, this report is only an isolated case and needs to be confirmed by a series of evidence-based medical studies and clinical application.

Modern medicine has shown that acupuncture can effectively relieve muscle spasm, improve local blood and lymphatic circulation, promote the recovery of atrophied muscles, and inhibit inflammatory factors. Acupuncture can also regulate the nervous system, such as stimulating the receptors and nerve endings of the human body, strengthening the activity of afferent coarse nerve fibres (α, β, γ class), and weakening the activity of efferent fine nerve fibres (C class), to achieve analgesia [18].

3.2 Acupuncture combined with moxibustion

Zhong Chongxin [19] and other use of warm acupuncture and moxibustion on the Sea of Blood, the inner knee eye, calf's nose, foot Sanli and other points in conjunction with isokinetic muscle training exercise rehabilitation treatment of anterior cruciate ligament injuries in 36 cases of patients for clinical observation. It was found that the clinical effect of warm acupuncture and moxibustion combined with isokinetic muscle training and rehabilitation was more obvious for ACL injury patients, and meanwhile, it was more important for the later recovery of ACL injury patients under long-term and effective exercise rehabilitation. Dai Juhong[20] and others observed 40 patients with ACL injuries with acupuncture and moxibustion in the 2nd, 4th, and 6th weeks, and found that the reduction of the difference between the circumference

of the healthy side and the affected side of the upper and lower legs was better than that of the control group in the 4th and 6th weeks after the treatment, indicating that patients with ACL injuries who were treated with acupuncture, warming and moxibustion combined with kinesiology had a better performance than the patients who were treated with exercise therapy alone in terms of the active maximum flexion of the knee, the VAS score and the Lysholm score, which was more effective in the later stage of rehabilitation. This indicates that patients treated with acupuncture and moxibustion in combination with exercise therapy for ACL injury rehabilitation have a significant advantage over patients treated with exercise therapy alone in terms of knee active maximum flexion, VAS score and Lysholm score, and the improvement of muscle atrophy of the affected limb is also significantly better than that of patients treated with exercise therapy alone.

Acupuncture and Moxibustion Volume 4" said: "Wang Jiezhai said: recent warm needle is the method of the Chu people. Its method, the needle points, to incense dahurica as a round cake, set on the needle, to moxibustion, more than to take the effect ....." In addition, warm acupuncture and moxibustion can be transmitted to the acupoints through the body of the needle, so that the warmth of the local limbs, enhance the stimulating effect of acupuncture points, and more effective in warming the menstruation and dispersing the cold, through the collaterals to relieve pain [21]. In addition, warm acupuncture and moxibustion can make the body maintain a high level of IGF-1, TGF-β expression, so as to achieve the role of promoting the repair of ACL injury, can effectively improve the ACL injury [22].

3.3 Electroacupuncture therapy

Zhou Xin [23] et al. treated 50 patients with partial ACL injuries with electroacupuncture on the 2nd day after surgery, and selected 4 points of the foot Shaoyang meridian on the affected side, namely, Hang Zhong, Yanglingquan, Knee Yangguan, and Huanjiao. It was found that for patients with partial ACL injury, electroacupuncture therapy with selected foot Shaoyang meridian points after ACL injury reconstruction surgery, knee joint proprioception was able to be improved more significantly to a certain extent, but long-term follow-up is needed. Yu Xiaoxia [24] et al. grouped 92 cases of ACL patients to observe the effects of electroacupuncture combined with systematic rehabilitation training on isometric muscle strength, joint mobility and body function of postoperative patients with anterior cruciate ligament injury (ACL). Fenglong, Xiangmen, Thigh Pass, Liangqiu, Ashigaru, Blood Sea, Diqi, Inner Knee Eye, Calvary and Sanyinjiao points on the affected side were selected. After treatment, it was observed that the knee joint mobility of the study group was greater than that of the control group ($P<0.05$), and the swelling of the affected knee was less than that of the control group ($P<0.05$). Wang Huajun[25] et al. randomly grouped 140 patients after reconstruction of ACL injury for observation, and took the affected side Fengshi, Fubu, Ashigaru, Shangjiuxu, Fenglong, Hangzhong, Diji, and Sanyinjiao points. Regular observation of the observation group showed that the knee ROM was greater than that of the control group ($P<0.05$), IKDC score and Lysholm score were higher than that of the control group ($P<0.05$). There were no complications related to laxity rupture in both groups within 1 year, and the axial shift test, the anterior drawer test, and the Lachman test were all negative. It is discussed that electroacupuncture combined with conventional rehabilitation training can significantly reduce the patients' knee pain, improve the degree of swelling, increase the mobility of the affected knee, promote functional recovery, and the efficacy is better than that of simple rehabilitation training.

Electroacupuncture is a therapeutic method that uses a certain frequency of electrical impulses to enhance the stimulation of acupoints after the millimetre needle is inserted into the acupoints. Electroacupuncture therapy can unblock the conduction of nerve pathways, inhibit inflammatory factors, and relieve stubborn pain through electrical stimulation.

3.4 Snap-needle therapy

Liu Xinyu [26] observed the effect of timely analgesia in 80 patients randomly grouped after ACL reconstruction, respectively, after 2 days of treatment. After sterilisation, snap needles were buried, and the following points were used: take Ah Yes point, calf's nose, inner knee eye, crane's top, Liang Qiu, Yang Ling Quan point. The timely analgesic effect of the observation group was found to be better than that of the control group, and the difference was statistically significant ($P<0.05$). Snap-needle therapy is safe, aseptic, convenient, effective in timely analgesia, easily accepted by patients, and meets the expectation of rapid recovery after ACL reconstruction, which is worth promoting in clinical rehabilitation treatment.

Snap-needle therapy belongs to intradermal needle therapy, which is the category of shallow stabbing and floating stabbing in acupuncture therapy, burying the needles under the skin or acupoints, and regulating the internal organs and meridians of the meridians and qi through the stimulation of persistent, weak and stable acupoints and subcutaneous nerves, which can promote the operation of qi and blood, and recover the imbalance of the organism.

3.5 Lotus Needle Cupping Therapy (Acupuncture and Moxibustion of Zhuang Medicine)

Lotus needle cupping and cupping and stasis expulsion method of Zhuang medicine is the core therapy of Professor Huang Jinming, a master of national medicine [27]. Liu Yongkun [28] et al. took 52 patients after reconstruction surgery as study subjects and randomly grouped 26 cases each. The control group was given conventional rehabilitation training such as quadriceps contraction; while the observation group was given postoperative rehabilitation by Lotus Needle Cupping and Blood Stasis Method of Zhuang Medicine with the following acupoints: taking the Sea of Blood, Sea of Qi, Baihui, Liangqiu, Calvary, Knee Yangguan, Inner Knee Eye and Outer Knee Eye, and so on. It was found that the Lotus Needle Cupping and Blood Stasis Removal Method of Zhuang Medicine, as a rehabilitation treatment plan, could better improve the stability and activity function of the knee joint and promote the effective recovery of the proprioception of the knee joint, which is safer and has certain clinical value.

According to Zhuang medicine, Lotus Needle Cupping and Blood Stasis Removal Therapy can dredge the three channels and two paths, balance the qi and blood, support the positive and eliminate the toxins, and synchronise the three qi. Modern medicine shows that Lotus Needle Cupping and Blood Stasis Relief Therapy can play a certain advantage in relieving knee pain and promoting the stability and functional recovery of the knee joint by improving the inflammatory factor [29].

4. Summary

ACL injury is a sports system disease with high morbidity and serious complications, and the main purpose of postoperative ACL injury is to restore the function and stability of the knee joint missing from the ACL and to promote the patients to return to the pre-injury activity level [30]. Therefore, rehabilitation research after ACL injury reconstruction has an important value. At present, many scholars have combined acupuncture treatment to rehabilitate patients after ACL reconstruction surgery, and all of them have achieved relatively significant therapeutic effects [31, 32-41]. The efficacy of combined acupuncture and moxibustion therapy is more obvious than that of single rehabilitation training, and it is very worthwhile to carry out extensive clinical research in the treatment of post-reconstructive rehabilitation after ACL injury, which can not only provide clinical scholars with multi-channel diagnostic and treatment means as well as different ideas of rehabilitation, but also enhance the patients' confidence in the treatment, and promote the patients' rapid recovery. However, at present, there is a lack of in-depth research on its mechanism, and more clinical scholars are expected to conduct in-depth investigations on how to choose better acupuncture treatment options, so as to provide better therapeutic ideas for post-reconstructive rehabilitation of ACL.

References

[1] Lai CCH, Ardern CL, Feller JA, et al. Eighty-three per cent of elite athletes return to preinjury sport afteranterior cruciate ligament reconstruction: a systematic reviewwith meta-analysis of return to sport rates, graft rupturerates and performance outcomes [J]. Br J Sports Med, 2018, 52(2) : 128-138

[2] Gao F, Sun SM, Ma D, He C. Research progress on postoperative rehabilitation of ACL reconstruction under arthroscopy [J]. Yunnan Medicine,2023,44(03):99-101.

[3] Wang J, Ao YF. Clinical epidemiology of anterior cruciate ligament injuries [J]. Chinese j Sports Med, 2001(04):380-382. (in Chinese)

[4] Chen LX, Fu LG. Clinical epidemiological analysis of anterior cruciate ligament rupture and reconstruction [J]. Chinese Tissue Engineering Research, 2016, 20(24): 3602-3608.

[5] Zhang L, Liang QZ, Zhao ZD. et al. Effect of robot-assisted arthroscopic reconstruction of anterior cruciate ligament [J]. Chin J

Trauma, 2012,38(02):142-148.

[6] Haber PS, Riordan BC, Winter DT, et al.New Australian guidelines for the treatment of alcohol problems:an overview of recommendations[J]. Med J Aust. 2021 Oct 4; 215 Suppl 7:S3-S32.

[7] Sun YY, Lin YP, Li Q, Li BH, Wang D, Huang XH. Effect of imrecoxib preemptive analgesia on postoperative analgesia in patients undergoing anterior cruciate ligament reconstruction: a randomized controlled study [J]. Chin J Reconstructive Surgery, 2023, 37(08): 982-988.

[8] Zhou X, Tian T. Effect of static progressive stretching combined with conventional physical therapy on joint adhesion after anterior cruciate ligament reconstruction [J]. Journal of Nantong University (Medical Edition),2018,38(06):488-489.

[9] Fukunaga T, Johnson CD, Nicholas SJ, McHugh MP. Muscle hypotrophy, not inhibition, is responsible for quadriceps weakness during rehabilitation after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2019 Feb; 27(2):573-579.

[10] Li Q, Chu XL, Li R. et al. Research progress on biomechanical changes of osteoarthritis after anterior cruciate ligament reconstruction [J]. Guangxi Med, 2018, 40(19): 2335-2337.

[11] Zhang XW, Liu KM, Cao Q. Effect of targeted medication of traditional Chinese medicine on patients with anterior cruciate ligament reconstruction [J]. Famous Physicians, 2022, (04):72-74.

[12] Zhang PY, Xiong J, Yu HB, Chen BB, Yang XJ. Research progress on postoperative rehabilitation of anterior cruciate ligament injury treated with traditional Chinese medicine [J]. Hunan Journal of Traditional Chinese Medicine, 2018, 34(12): 167-169.

[13] Liu PP, Li HY. Analysis of the current status and trend of overseas acupuncture therapy research based on bibliometrics from 2017 to 2022 [J]. Chinese Journal of TCM, 2023, 64(15):1593-1599.

[14] George, Wang SQ, Su B. Application of acupuncture and moxibustion therapy in the field of military medicine [J]. Medicine of Chinese Armed Police Force, 2023, 34(06):549-550.

[15] Yang Y, Cui YJ, Xu Y, Yang HX, Guo YM, Wang XY, Liu YY. Research progress on the application advantages and key mechanism of acupuncture and moxibustion rehabilitation technology in rehabilitation medicine [J]. Journal of Liaoning University of Traditional Chinese Medicine :1-11.

[16] Fan XL, Wang YX, Cao XQ, Yu YD. Effect of acupuncture combined with rehabilitation training on quadriceps femoris atrophy after anterior cruciate ligament reconstruction [J]. Shanghai Journal of Acupuncture and Moxibustion, 2023, 42(03): 294-299.

[17] Zhang B, Zhang JY, Sun YC, Zeng JH, Wang H, Shang HJ, Zhou B. Case report on personalized exercise prescription combined with knee three-needle to promote the rapid rehabilitation of pilots with multiple anterior cruciate ligament injuries [J]. Chin J Convalescent Med, 2023,32(09):1005-1008.

[18] Lu QG, Wang P, Huang DH, et al. Treatment of knee stiffness after knee ligament reconstruction by arthroscopic release combined with massage manipulation [J]. Chinese Medicine Bone Setting,2013,25(09):45-46+48.

[19] Zhong CX, Fan J. Clinical effect of warm acupuncture at Xuehai, Neixiyan, Dubi and Zusanli combined with isokinetic muscle strength training on ACL injury [J]. Journal of Clinical Medicine Literature Electronic,2020,7(25):53-54.

[20] Dai JH, Yang G, Huang JM, Sun YW, Wei YJ, Yang DD, Zhang QQ. Clinical study of acupuncture combined with exercise therapy on functional rehabilitation after anterior cruciate ligament reconstruction [J]. Chinese Journal of Acupuncture and Moxibustion Electronic, 2021,10(04):140-145.

[21] Jiang HY, Wu YM, Jin Y. Effect of warming acupuncture combined with Tongluo Xiaobi Decoction in the treatment of knee osteoarthritis caused by cold-damp obstruction [J]. Chinese Rural Medicine,2023,30(13):10-11.

[22] Li C, Zhang YL, Liu D, et al. Effect of warm acupuncture on anterior cruciate ligament repair and related factors in rabbits with knee osteoarthritis [J/OL]. China Tissue Engineering Research :1-6[2023-08-30].

[23] Zhang L, Xiong LJ, Li BK, Tang XG, Yu L, Zhou X. Application value of electroacupuncture at foot Shaoyang meridian in postoperative rehabilitation of knee anterior cruciate ligament injury [J]. Chinese Medicine Bone Setting, 222, 34(06): 9-16.

[24] Yu XX, Lou HK, Li FJ. Effect of electroacupuncture combined with systematic rehabilitation training on isokinetic joint range of

motion and body function in patients with anterior cruciate ligament injury after surgery [J]. Shanghai Journal of Acupuncture and Moxibustion,2021,40(08):974-981.

[25] Ding RB, Zhao J, Guan J, Li F, Nie XZ, Xie L, Wang HJ, Zheng XF, Xu X. Effect of electroacupuncture on knee joint motor function rehabilitation after anterior cruciate ligament reconstruction [J]. Chinese Acupuncture and Moxibustion, 2020, 40(02):142-146.

[26] Liu XY. Effect of intradermic press on immediate analgesia after ACL reconstruction of knee joint [J]. Abstract of World Latest Medical Information, 2019, 19(52):18+20.

[27] Huang JM, A master of traditional Chinese medicine: Introducing Zhuang medicine from the countryside to the school [J]. Journal of Guangxi University of Traditional Chinese Medicine, 222,25(04):2.

[28] Liu YK, Qin G, Fan Z, Han JY. Effect of Zhuang medical lotus needle cup-therapy for removing blood stasis on proprioception recovery after anterior cruciate ligament reconstruction [J]. Liaoning Journal of Traditional Chinese Medicine, 222, 49(08): 176-18

[29] Li JY, Zeng P, Chen JL, et al. Effect of Zhuang medical lotus needle cupping therapy for knee osteoarthritis [J]. Western Chinese Medicine,2020,33(07):73-76.

[30] Huang RL, Guo J, Zeng Y, Liu ZQ. Current status and influencing factors of functional rehabilitation in patients after anterior cruciate ligament reconstruction [J]. Medical Equipment, 2021,35(13):139-141.

[31] Yang et al., Wang HM, Geng JJ, Wang H, Zhou YY, Yang GN, Qie SY, Wang Y. Application of transcutaneous electrical acupoint stimulation combined with lower limb rehabilitation robot in the rehabilitation of knee joint after anterior cruciate ligament reconstruction [J]. Chinese Medical Equipment,2023,20(04):100-104.

[32] Li JY. Wrist ankle joint total internal needle technology the early clinical efficacy of anterior cruciate ligament reconstruction research [D]. University of Chinese medicine in guangxi, 2023.

[33] Zou WL. Clinical study of ultrasound-guided saphenous nerve block combined with electroacupuncture in the rehabilitation of patients after anterior cruciate ligament reconstruction [D]. Hunan university of Chinese medicine, 2023.

[34] Liu ZZ, Cui JM, Yang J, et al. Effect of joint mobilization combined with acupuncture on postoperative rehabilitation of anterior cruciate ligament injury [J]. Hubei Sports Science and Technology, 2021,41(03):220-226.

[35] Wang Z. Early clinical effect of electroacupuncture on proprioception recovery after anterior cruciate ligament reconstruction [D]. Beijing university of Chinese medicine, 2021.

[36] Yang Y, Yin JH, Ye GX. Electroacupuncture was used to treat knee swelling after anterior cruciate ligament reconstruction under knee arthroscopy Pain [J]. Chinese Medicine Bone Setting, 2016, 28(10):50-51.

[37] Pan XY, Wen H, Liu ZT, Yang XG, Zhang RF, Zhang Y. Acupuncture was applied in the treatment of the anterior cross of the knee Application of ligament rupture [J]. Bone Setting of Traditional Chinese Medicine,2012,24(11):11-13.

[38] Zhu XY, Yue LW. Clinical effect of acupoint catgut embedding on quadriceps femoris atrophy after anterior cruciate ligament reconstruction Research [J]. Henan Traditional Chinese Medicine,2017,37(06):1097-1099.

[39] Tang ZP, Li YJ, Li SH, Dai G, Zhao ZW, Wu JQ, Yuan LW, Yu H. Traditional Chinese and western medicine Effect of combined rehabilitation therapy on proprioception recovery after anterior cruciate ligament preservation reconstruction [J]. Traditional Chinese Medicine in western China Pharmacol, 2017,30(04):105-107.

[40] Jiang B. Preliminary observation on the effect of acupuncture on proprioception after anterior cruciate ligament reconstruction of knee joint [D]. China Academy of Chinese Medical Sciences,2016.

[41] Ortega-Cebrian S, Luchini N, Whiteley R. Dry needling: Effects on activation and passive mechanical properties of the quadriceps, pain and range during late stage rehabilitation of ACL reconstructed patients. Phys Ther Sport. 2016 Sep; 21:57-62.

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Universe
Scientific Publishing

Global Advances and Frontiers of Phytochemicals in Tumor Research: A Bibliometric Study (2010-2023)

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Abstract: Objectives: Analysis of advances, hotspots and frontiers of tumor-related phytochemicals by scientific bibliometric methods during 2012-2023. Background: Natural phytochemicals are abundantly found in nature and have a wide range of biological activities. Phytochemicals have been shown to provide both curative and preventive benefits on many chronic diseases such as cancers. Tumor research on phytochemicals is one of the fields with the greatest potential for expansion in the world. However, there is still much to explore about the action mechanism of phytochemicals, the efficacy and safety of application in vivo, and the value of clinical practice. Methods: A total of 6523 articles on tumor-related phytochemicals were identified from the Web of Science Core Collection (WOSCC) database for research on tumor-related phytochemicals. The bibliometric analysis was carried out using CiteSpace and the R package "Bibliometrix". Results: The analysis includes 6523 publications from 144 nations or regions, with China leading the way. The number of annual publications increased rapidly from 2012 to 2022 and reached a maximum in 2022. China published the most articles, followed by India and the United States. There is a wide range of collaborations between countries, with Saudi Arabia and Egypt being the closest partners. LI Y has produced the most research outputs, yet Prof. Liu RH has received the most local citations. Although MOLECULES has the most articles, FOOD CHEMISTRY is the journal with the highest H-index. The main topics include phytochemical mechanisms and clinical applications in carcinogenesis and development. "Secondary metabolite", "green synthesis", "functional food", and "degradation" all exhibit significant citation burstness between 2019-2023. Conclusions: This study is the first to apply bibliometrics to examine the development of phytochemicals in oncology research over the period 2010-2023, which gives researchers a brief overview of advances, hotspots, and potential future trends in the field.

Keywords: Bibliometrics; Phytochemicals; Cancer; CiteSpace; Future Trends

1. Introduction

With rising levels of industrialization, the global burden of cancer mortality and incidence has been rising quickly in the past few decades. According to WHO Figures, cancer has surpassed cardiovascular disease as the leading cause of death before the age of 70 in 112 nations worldwide[1]. In 2023, it is anticipated that there will be 609,820 cancer deaths and 1,958,310 new cancer cases in the U.S[2]. Over the last several years, a great deal of study has been done on the pathogenesis and treatment principles of malignancies, yet traditional surgery, radiation therapy, and chemotherapy are likely to have some major adverse effects, possibly even endangering patient life. Therefore, the need for more effective, safe, and inexpensive treatment options is urgent. The biologically active substances known as phytochemicals support plant interactions with their environment during biological evolution. Numerous well-known phytochemicals exist today, including carotenoid, phytosterol, saponin, glucosinolate, polyphenol, etc. According to research, phytochemicals have a variety of biological functions, including anticancer, antioxidant, and immunomodulation. In order to provide creative research guidelines and choose logical clinical therapy regimens, it is crucial to comprehend the hotspots in the field of phytochemical research and predict future developments.

By statistically assessing a significant amount of literary data, bibliometric analysis is able to objectively analyze the hotspots, dynamics, and development trends in a variety of sectors. The technique has developed and is frequently applied in sectors that relate to medicine. However, none of the papers used bibliometric analysis in regard to the Phytochemicals for anti-tumor research. none of the article used bibliometric analysis in regard to the Phytochemicals for anti-tumor research. Based on previous studies, the major areas of interest for phytochemicals include their inhibitory effects on cancer cells[3-5], chemopreventive effects[6-8], synergetic effects[9, 10] and reverse growing clinical multi-drug resistance(MDR)[11]. The earlier induction and summary methods based on the Review have significant drawbacks, including a

brief time period, subjective document selection, the ease with which crucial influencing elements can be missed, etc., which make it impossible to systematically examine the long-term dynamic development trends.

In any case, the aiticle aims to use bibliometric analysis to systematically investigate the advances in phytochemicals in tumor research.

2. Methods

2.1 Search Strategy and Data Source

Web of Science (http://www.webofknowledge.com), as a multidisciplinary worldwide academic information database, features the most comprehensive collection of international mainstream journals and rigorous retrieval patterns. All data for this study were obtained from the Web of Science Core Collection (WOSCC) database. On July 26, 2023, we used the advanced search to find publications about tumors and phytochemicals from 2010 to 2023, using the following search formula: TS= ((“Phytochemical*”) AND (“Tumo$r*” OR “Cancer *” OR “Oncology*” OR “Neoplasm*” OR “Carcinoma*”)). The Publication type was only restricted to article and the Language type is English. On July 26, we exported all eligible data in order to prevent bias brought on by database updates, obtaining a total of 6523 articles.

2.2 Statistics Analysis

To complete the bibliometric analysis, use the CiteSpce (version 6.1.R6) and the R package “Bibliometrix” (version 2.2.1), as well as Office 2019 for the correlation graphing. Scientific bibliometric software known as Bibliometrix is based on the RStudio. It can perform tasks like importing and converting texts, performing metrological analyses, creating matrices, normalizing data, creating networks, creating graphs, etc. Professor Chao-Mei Chen of the School of Computing and Intelligence at Drexel University created the visual literature analysis program called CiteSpace, which uses special algorithms to form co-occurrence networks and conduct clustering analyses. We used the Bibliometrix to show annual scientific production, average citations per year, countries scientific production and collaboration, most local cited authors, etc. CiteSpace was used to produce references co-cited and keyword co-occurrence networks, clustering, dual-map and citation bursts. The two pieces of software to jointly investigate the advances, hotspots and frontiers.

3. Results

3.1 General situation description

First, we selected 6523 articles from the WOS-core collection (WOSCC) that were particularly relevant to phytochemicals related to tumors. The selection process is shown in Figure 1. Figure 2A depicts the annual scientific production of Tumor-related phytochemicals from 2010 to 2022. 2023 is not shown in the statistics because it is only halfway through the year. The number of publication (NP) exhibits a general upward trend from 2010 to 2022, averaging around 300. Only 2018 (n=487, 7.41%) shows some the NP reduction, with rises in both 2011-2012 and 2018-2022 being particularly noticeable. The greatest NP was 2022 (n=1032, 15.82%). We created a polynomial regression equation, in Microsoft Office Excel 2019 to forecast the NP that will be published in 2023. The time prediction curve model was constructed by fitting the data with the equation (), which predicted that the NP in 2023 may reach approximately 980, and the fitted data were statistically well (). The average annual citations (AAC) of the papers in Figure 2B climbed quickly in 2010-2013, and despite some changes between 2013 and 2020, the total number of citations (TC) remained sTable. The maximum was attained in 2019 (n=3.31). Contrary to the yearly NP, the average annual citations from 2020 to 2023 showed a considerable decrease.

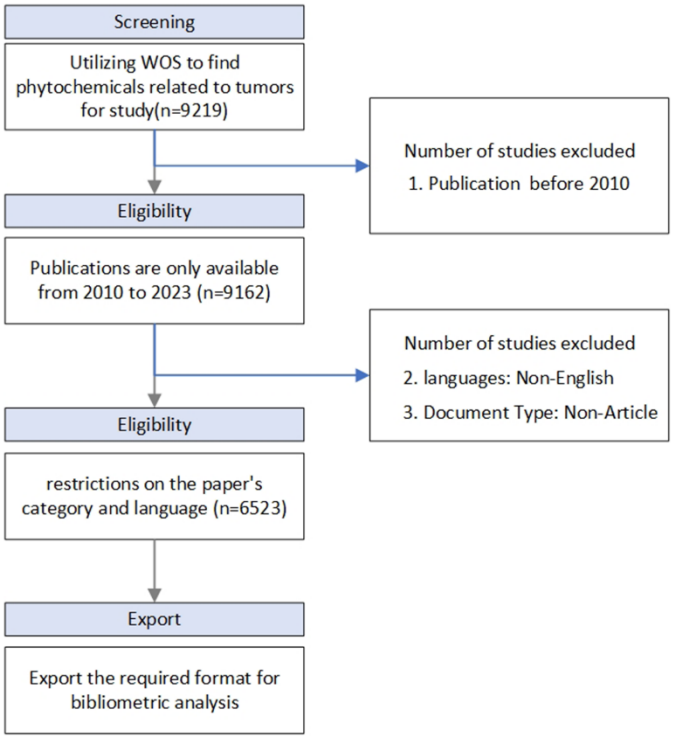


Figure 1 Document retrieval flow chart based on WOSCC

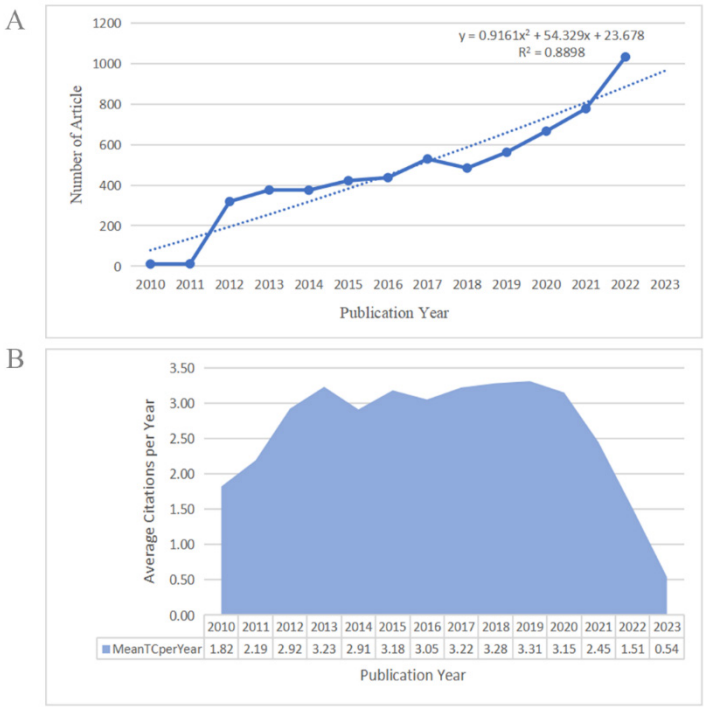


Figure 2 (A) Annual scientific production and polynomial regression modeling (B) Average citations per year during 2010 to 2023

3.2 Countries/regions analysis

In Figure 3, which compares the frequency of publications and national collaboration networks across 144 nations or regions, China (n=1197, 18.35%), India (n=930, 14.25%), the United States (n=520, 7.97%), and South Korea (n=384, 5.88%) are shown as the highest NP

countries. There has been a great deal of international cooperation, with Saudi Arabia and Egypt collaborating the most closely (Freq=185). India and Saudi Arabia (Freq=136) as well as China and the United States (Freq=172) followed after this. Table 1 lists the Top15 countries/regions according to the Total Citations (TC). China has the most NP (n=1197) and TC (n=20599) internationally, followed by the U.S and India. We were shocked to see that SYRIA (n=96.00), SWEDEN (n=31.80), and the U.S (n=31.60) had the most Average Article Citations (AAC) internationally. The Countries with the greatest NP and TC worldwide, China and India, are only ranked 26th (n=17.2) and 40th (n=14.9) in the AAC rankings, respectively.

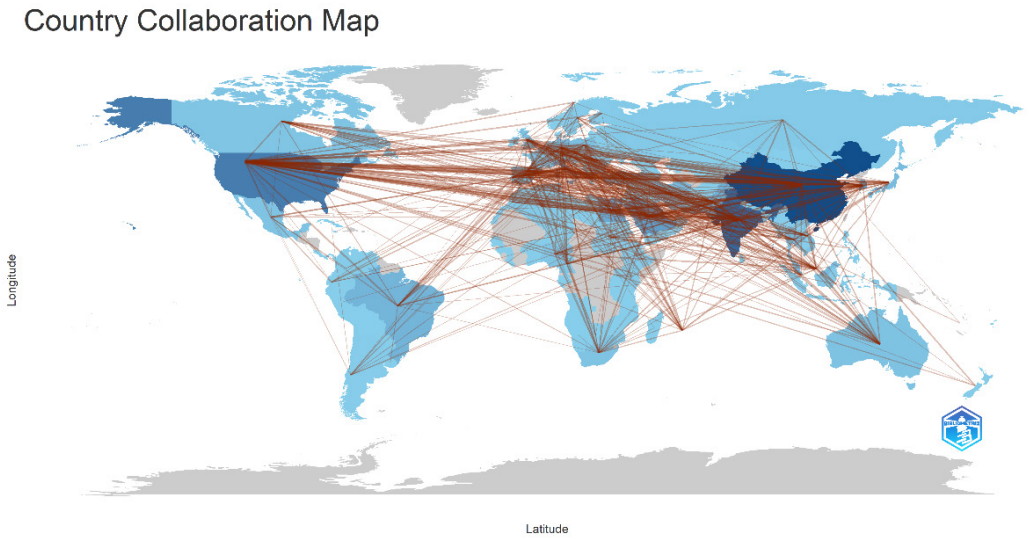


Figure 3 National/Regional Publications And International Cooperation Networks

Table 1 Top 15 Countries/Regions In Terms Of Total Citations

Rank	Country	NP	TC	Average Article Citations
1	CHINA	1197	20599	17.20
2	USA	520	16573	31.60
3	INDIA	930	13845	14.90
4	KOREA	384	5937	15.50
5	ITALY	283	5918	20.90
6	GERMANY	108	2778	25.70
7	PAKISTAN	228	2769	12.10
8	BRAZIL	230	2428	10.60
9	SAUDI ARABIA	239	2393	10.00
10	IRAN	177	2376	13.40
11	MALAYSIA	149	2313	15.50
12	EGYPT	197	2105	10.70
13	JAPAN	114	1821	16.00
14	SPAIN	75	1695	22.60
15	POLAND	116	1629	14.00

3.3 Author analysis

A total of 25103 authors were involved in the papers on tumor-related phytochemicals. Table 2 shows the Top15 authors with the most local citations, along with other relevant information including H-index, TC, and NP. Liu RH was ranked first (n=52). Additionally, individuals named EFFERTH T, KUMAR S, KONG ANT, SU ZY, and KUBATKA P had more than 35 local citations. Top10 authors' NP and the TC are depicted in Figure 4A (represented by the size of the circle and the darkness of the circle's color, respectively). In 2012, each author

had published a various number of papers, particularly is LI Y, the top-ranked author, first published in 2010 (n=2), who produced the most significant NP (n=12) and TC (n=57.14) in 2017. 2022 was the most prolific year for the 10 authors overall, with a total of 78 publications. In Figure 4B, co-authors' nationalities can be analyzed to reveal how well they collaborate internationally, it can be found that the countries with the greatest number of the multiple country publications (MCP) are India (n=228), China (n=199), Saudi Arabia (n=173), the United States (n=160), and Pakistan (n=117). However, Saudi Arabia had the highest percentage of the MCP in the total NP (n=173, 72.38%). China and India had MCP rates of 10.65% and 24.51%, respectively.

Table 2 The Top15 Authors' Local Citations

Rank	Author	Local Citations	H-index	NP	TC
1	LIU RH	52	20	28	2103
2	EFFERTH T	47	14	33	593
3	KUMAR S	46	15	35	662
4	KONG ANT	37	11	13	618
5	SU ZY	36	7	9	412
6	KUBATKA P	35	8	9	305
7	KELLO M	34	9	9	328
8	MOJZIS J	34	9	9	328
9	ADAMKOV M	32	7	7	271
10	BEALE P	32	7	10	161
11	FERREIRA ICFR	31	15	35	876
12	ZENGIN G	30	13	40	415
13	KAJO K	29	6	6	203
14	MAHOMOODALLY MF	29	10	25	307
15	PEC M	28	7	8	269

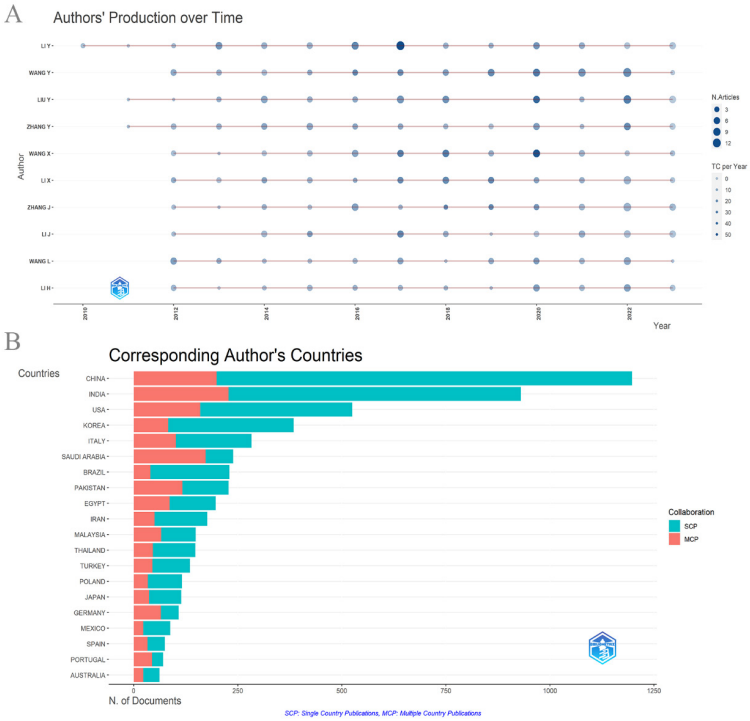


Figure 4 (A) Top10 authors' annual publications and total citation over time. (The size of the circle represents the NP, and the color of the circle represents the TC) (B) Percentage of co-authorship by authors of different nationalities

3.4 Journal analysis

The 6523 articles were published in a total of 969 distinct journals, and Figure 5 depicts the annual NPs variation in the top 10 journals. The most papers were published in MOLECULES (n=299, 4.58%), and the number of publications in this journal exhibited an upward trend each year, reaching peak in 2022 (n=90). Similarly, NATURAL PRODUCT RESEARCH, PLANTS-BASEL and SOUTH AFRICAN JOURNAL OF BOTANY follow the peaking, the maximum NP, trend as MOLECULES. Additionally, PHYTOCHEMISTRY LETTERS saw a dramatically increase between 2012 and 2016, and the NP decreases sharply after reaching the peak in 2017. The top 15 journals according to H-index are shown in Table 3, with FOOD CHEMISTRY journal having the highest H-index (n=40). Some journals are second only to it, including BMC COMPLEMENTARY AND ALTERNATIVE MEDICINE, PLOS ONE, and JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, etc.

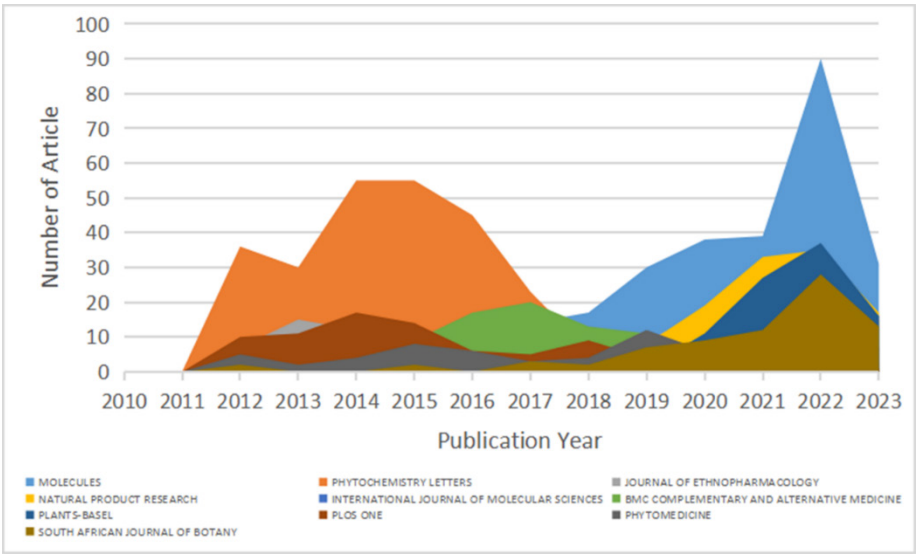


Figure 5 The cumulative number of publications of the top 10 journals

Table 3 Top15 journals impact by H-index

Rank	Element	H-index	G-index	TC	NP
1	FOOD CHEMISTRY	40	62	3934	73
2	BMC COMPLEMENTARY AND ALTERNATIVE MEDICINE	32	44	2642	94
3	PLOS ONE	31	50	2933	88
4	JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY	30	45	2209	62
5	MOLECULES	30	42	3431	299
6	SCIENTIFIC REPORTS	27	35	1512	68
7	JOURNAL OF ETHNOPHARMACOLOGY	26	34	2295	154
8	PHYTOMEDICINE	26	37	1694	79
9	FOOD AND CHEMICAL TOXICOLOGY	25	39	1682	53
10	PHYTOCHEMISTRY LETTERS	24	31	3430	276
11	JOURNAL OF NATURAL PRODUCTS	22	33	1239	51
12	BIOMEDICINE \& PHARMACOTHERAPY	21	34	1381	61
13	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	21	30	1211	102
14	JOURNAL OF FUNCTIONAL FOODS	20	31	1107	49
15	INDUSTRIAL CROPS AND PRODUCTS	19	30	981	44

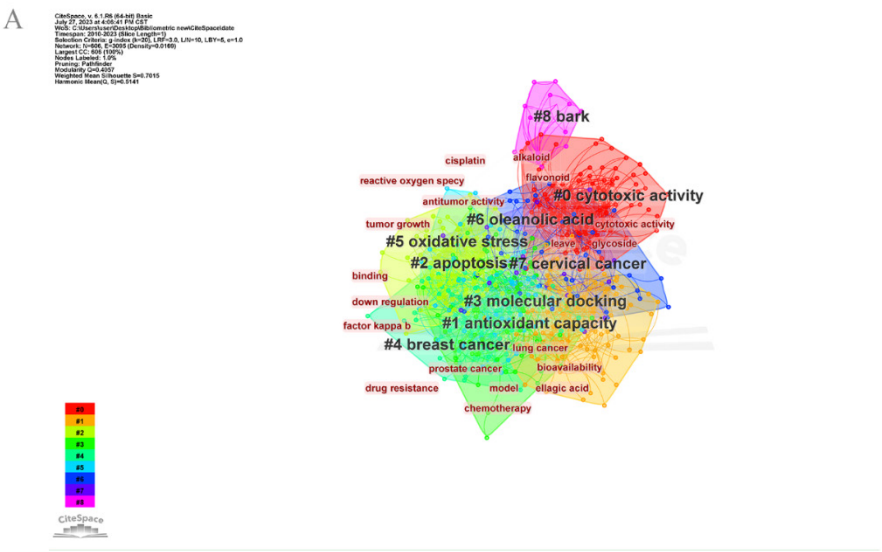
3.5 References analysis

With one year as the time slice, Figure 6A shows the co-cited network of references with high mediational centrality. There are 864 nodes and 1593 connecting lines in total. The reference was divided into 22 distinct clusters based on the co-cited network using the Log-Likelihood (LLR) clustering method in order to identify common themes among related references. The three clusters with the highest number of references found by this research were #0 withaferina, #1 drug combination, and #2 anti-inflammatry, with a Weighted Mean Silhouette value of 0.9368 suggesting that the results of the clustering were incredibly impressive.

Table 4 shows the three co-cited papers with the highest centrality (n=0.38) published in the CA-CANCER J CLIN (United States, IF=74.575), Siegel RL et al. provided 2021 global cancer burden statistics[12]. A 2018 reference by Chikara S et al. demonstrates how different phytochemicals affect oxidative stress and associated signaling pathways in cancer[13]. The sources and functions of phytochemicals that have been successfully applied as anticancer drugs in the clinic are summarized by Seca AML et al[14]. Shukla S et al. summarized the epigenetics regulation by phytochemicals in tumor chemoprevention[15].

Reference or Keywords with a high frequency of citations in a short amount of time are termed as citation bursts. Table 5 shows the Top20 citation bursts of references. The papers by LEE KW et al. and Hanahan D et al. both show the strongest bursts from 2012 to 2016, expressing the biology of phytochemicals in the progression of cancers[16] and the molecular targets of phytochemicals for cancer prevention[17], respectively. Several the bursts appearing after 2021 continue to be widely cited today, including the 2018 Global Cancer Statistics from GLOBALCAN[18], SwissADME, a web-based tool, for small molecule pharmacokinetics[19], and Choudhari AS et al. 2020 for an introduction to potential druggability and therapeutic uses[20].

Figure 6B is a dual-map overlay of bibliographic references in the tumor-related (2010-2023). With the distribution of journals where the citing articles is applied on the left and the corresponding cited articles on the right. We identified three sets of significant citation routes in total (three orange, two yellow, and one purple). Orange paths: VETERINARY, ANIMAL and SCIENCE; yellow paths: CHEMISTRY, MATERIALS and PHYSLCS; purple paths: CHEMISTRY, MATERIALS and PHYSLCS. The cited papers in the orange paths are typically published in Molecular, Biology and Immunology. It is interesting that all three sets of go-getters, major Journal Distribution of Cited references, with distinct colored paths have the most articles published in MOLECULAR, BIOLOGY, and GENATICS.



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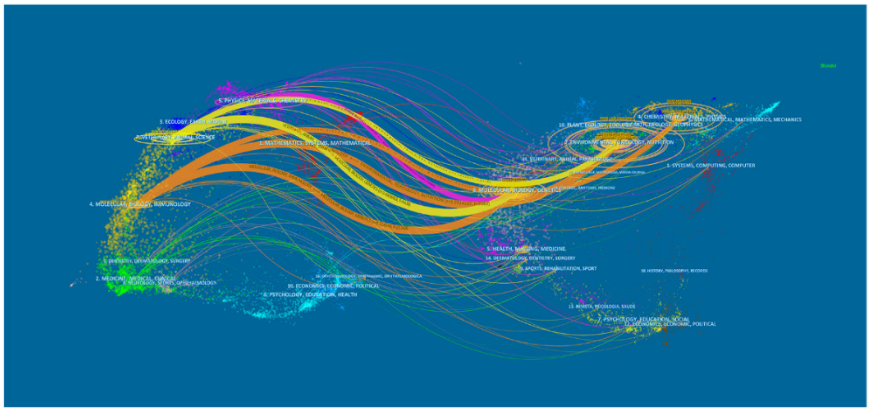


Figure 6 (A) The reference co-citation network and clustering analysis (B) Dual-map overlay plot concerning phytochemicals antitumor research

Table 4 Top15 co-citation reference based on the Betweenness Centrality

Rank	Count	Centrality	Year	Author	Source	DOI
1	198	0.38	2021	Siegel RL	CA-CANCER J CLIN	10.3322/caac.21654
2	42	0.24	2018	Chikara S	CANCER LETT	10.1016/j.canlet.2017.11.002
3	25	0.15	2018	Seca AML	INT J MOL SCI	10.3390/ijms19010263
4	62	0.12	2015	Ferlay J	INT J CANCER	10.1002/ijc.29210
5	18	0.12	2014	Shukla S	CANCER LETT	10.1016/j.canlet.2014.09.017
6	17	0.11	2010	Shu LM	CANCER METAST REV	10.1007/s10555-010-9239-y
7	30	0.09	2011	Hanahan D	CELL	10.1016/j.cell.2011.02.013
8	24	0.09	2018	Mohanraj K	SCI REP-UK	10.1038/s41598-018-22631-z
9	15	0.09	2016	Anantharaju PG	NUTR J	10.1186/s12937-016-0217-2
10	39	0.08	2011	Lee KW	NAT REV CANCER	10.1038/nrc3017
11	11	0.08	2016	Ahmed S	J ADV RES	10.1016/j.jare.2015.02.007
12	25	0.07	2012	Newman DJ	J NAT PROD	10.1021/np200906s
13	24	0.07	2020	Kopustinskiene DM	NUTRIENTS	10.3390/nu12020457
14	60	0.06	2016	Newman DJ	J NAT PROD	10.1021/acs.jnatprod.5b01055
15	22	0.06	2015	Greenwell M	INT J PHARM SCI RES	10.13040/IJPSR.0975-8232.6(10).4103-12

Table 5 Top 20 References with the Strongest Citation Bursts

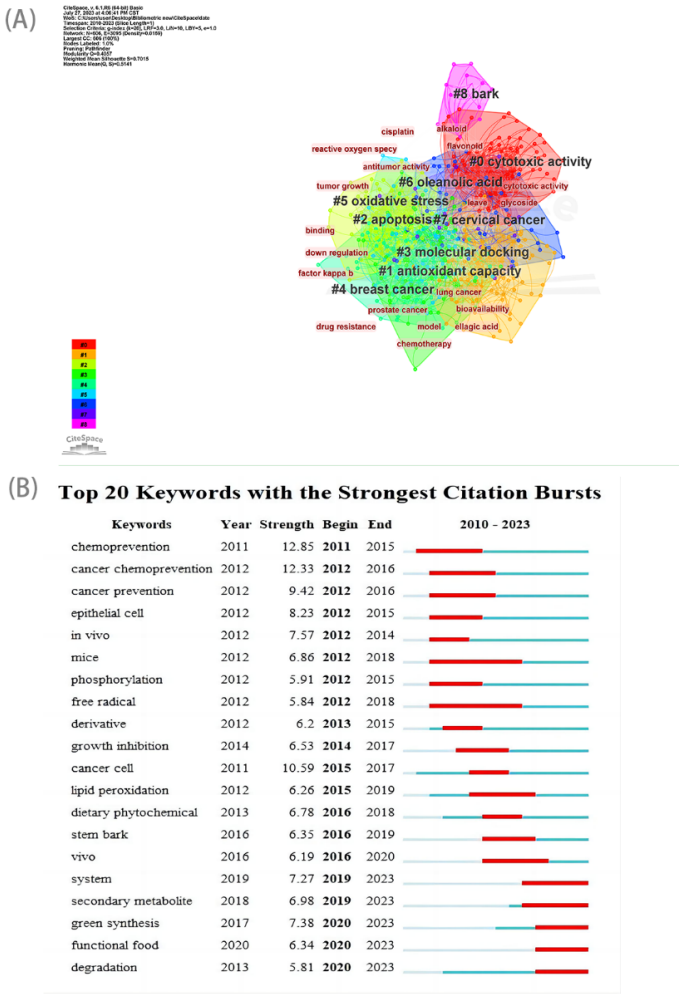
References	Year	Strength	Begin	End	2010 - 2023
Lee KW, 2011, NAT REV CANCER, V11, P211, DOI 10.1038/nrc3017, DOI	2011	17.15	2012	2016	
Hanahan D, 2011, CELL, V144, P646, DOI 10.1016/j.cell.2011.02.013, DOI	2011	13.16	2012	2016	
[Anonymous], 2014, CA-CANCER J CLIN, V0, P0	2014	11.61	2014	2019	
Shu LM, 2010, CANCER METAST REV, V29, P483, DOI 10.1007/s10555-010-9239-y, DOI	2010	8.37	2012	2015	
Newman DJ, 2012, J NAT PROD, V75, P311, DOI 10.1021/np200906s, DOI	2012	10.79	2013	2017	
Siegel R, 2012, CA-CANCER J CLIN, V62, P10, DOI 10.3322/caac.20138, DOI	2012	7.77	2013	2014	
Su ZY, 2013, TOP CURR CHEM, V329, P133, DOI 10.1007/128, 2012, 340, DOI	2013	8.04	2014	2018	

Siegel RL, 2015, CA-CANCER J CLIN, V65, P5, DOI 10.3322/caac.21254, DOI	2015	14.69	2015	2019	
Ferlay J, 2015, INT J CANCER, V136, PE359, DOI 10.1002/ijc.29210, DOI	2015	19.13	2016	2020	
Newman DJ, 2016, J NAT PROD, V79, P629, DOI 10.1021/acs.jnatprod.5b01055, DOI	2016	16.12	2017	2021	
Torre LA, 2015, CA-CANCER J CLIN, V65, P87, DOI 10.3322/caac.21262, DOI	2015	9.87	2017	2020	
Kotecha R, 2016, ONCOTARGET, V7, P52517, DOI 10.18632/oncotarget.9593, DOI	2016	8.53	2017	2021	
Zhang YJ, 2015, MOLECULES, V20, P21138, DOI 10.3390/molecules201219753, DOI	2015	7.89	2017	2020	
Greenwell M, 2015, INT J PHARM SCI RES, V6, P4103, DOI 10.13040/IJPSR.0975-8232.6(10).4103-12, DOI	2015	10.05	2018	2020	
Redza-Dutordoir M, 2016, BBA-MOL CELL RES, V1863, P2977, DOI 10.1016/j.bbamcr.2016.09.012, DOI	2016	9.36	2019	2021	
Panche AN, 2016, J NUTR SCI, V5, P0, DOI 10.1017/jns.2016.41, DOI	2016	8.97	2019	2021	
Atanasov AG, 2015, BIOTECHNOL ADV, V33, P1582, DOI 10.1016/j.biotechadv.2015.08.001, DOI	2015	8.28	2019	2020	
Bray F, 2018, CA-CANCER J CLIN, V68, P394, DOI 10.3322/caac.21492, DOI	2018	28.05	2021	2023	
Daina A, 2017, SCI REP-UK, V7, P0, DOI 10.1038/srep42717, DOI	2017	17.3	2021	2023	
Choudhari AS, 2020, FRONT PHARMACOL, V10, P0, DOI 10.3389/fphar.2019.01614, DOI	2020	10.78	2021	2023	

3.7 Keywords analysis

Figure 7A depicts the keywords co-occurrence network with a time slice of 1 year, which consists of 606 nodes and 3095 connecting lines. Eight clusters were produced by Log-Likelihood (LLR), including #0 cytotoxic activity, #1 antioxidant capacity, #2 apoptosis, #3 molecular docking, #4 breast cancer #5 oxidative stress, etc. The Top15 keywords with the highest betweenness centrality in the phytochemicals research from 2010 to 2023 are clearly listed in Table 6. The emergence of “alkaloid” in 2010 with the highest centricity, in addition to “chemotherapy”, “antitumor activity”, and “ellagic acid”, all of which play crucial roles in the research and development of tumor-related phytochemicals.

The Top20 keywords with citation bursts are listed in Figure 7B. The blue lines denote time intervals, and the red lines depict keyword burst time periods. During 2012-2018, the keywords “chemoprevention”, “epithelial cell”, “in vivo”, “mice”, “phosphorylation”, and “free radical” came into view. In which the chemoprevention has the strongest citation bursts (STRENGTH=12.86). Additionally, researchers have continued to pay close attention to some keywords, such as “system”, “secondary metabolite”, “green synthesis”, “functional food”, “degradation”, etc. since 2019 or 2020 till now.



(B) **Top 20 Keywords with the Strongest Citation Bursts**

Keywords	Year	Strength	Begin	End	2010 - 2023
chemoprevention	2011	12.85	**2011**	2015	
cancer chemoprevention	2012	12.33	**2012**	2016	
cancer prevention	2012	9.42	**2012**	2016	
epithelial cell	2012	8.23	**2012**	2015	
in vivo	2012	7.57	**2012**	2014	
mice	2012	6.86	**2012**	2018	
phosphorylation	2012	5.91	**2012**	2015	
free radical	2012	5.84	**2012**	2018	
derivative	2012	6.2	**2013**	2015	
growth inhibition	2014	6.53	**2014**	2017	
cancer cell	2011	10.59	**2015**	2017	
lipid peroxidation	2012	6.26	**2015**	2019	
dietary phytochemical	2013	6.78	**2016**	2018	
stem bark	2016	6.35	**2016**	2019	
vivo	2016	6.19	**2016**	2020	
system	2019	7.27	**2019**	2023	
secondary metabolite	2018	6.98	**2019**	2023	
green synthesis	2017	7.38	**2020**	2023	
functional food	2020	6.34	**2020**	2023	
degradation	2013	5.81	**2020**	2023	

Figure 7 (A) Keyword co-occurrence mapping and clustering (different colors in the Figure represent different clusters and nodes). (B) Top20 keywords strength and time of occurrence with most citation bursts.

Table 6 Top15 co-occurring keywords by centrality

Rank	Count	Centrality	Year	Keyword
1	79	0.06	2010	alkaloid
2	63	0.06	2010	chemotherapy
3	84	0.05	2012	antitumor activity
4	67	0.05	2012	ellagic acid
5	408	0.04	2010	flavonoid
6	162	0.04	2010	glycoside
7	102	0.04	2012	lung cancer
8	88	0.04	2012	bioavailability
9	74	0.04	2012	rat
10	72	0.04	2012	model
11	48	0.04	2012	alpha
12	39	0.04	2012	binding
13	30	0.04	2013	cisplatin
14	434	0.03	2010	constituent
15	324	0.03	2010	leave

4. Discussion

Currently, with the incidence and mortality of cancer rising globally, how to overcome the toxic side effects as well as multidrug resistance (MDR) caused by conventional treatments, and develop safe therapeutic strategies has become a major problem for clinicians. Natural phytochemicals have demonstrated great therapeutic potential for a variety of chronic conditions, particularly in the chemoprevention and co-treatment of cancer. However, there are still several issues that need to be resolved before phytochemicals widely used, including the proper concentration, application methods, in vivo mode of action, and safety, etc. For these reasons, this study is the first bibliometric examination of the connection between phytochemicals and tumors, allowing researchers to easily grasp the research advances, hotspots, and frontiers.

General Information

Oncology and phytochemicals-related papers totaling 6523 were searched for and extracted from the WOSCC between 2010 and 2023, as the foundation for this bibliometric study. A time-series analysis of the annual NP and AAC is beneficial to understand the dynamic research progress in a field. In terms of annual NP, tumor-related phytochemicals have shown a general upward trend. Without a doubt, the two most noTable dates are 2012 and 2022. 2012 witnessed the beginning of research on tumor-related phytochemicals, and since then, both the annual NP and the average citations per year have grown rapidly. The NP peaked in 2022 with 1,032 articles appearing and increased by more than twice as much as in 2012. After 2020, however, the average annual citations decreased dramatically, which may be related to the delay in citations of newly published papers. Following 2012, a large number of studies clarified the chemopreventive and therapeutic potential of phytochemicals against preclinical models of a variety of cancers[21, 22], including the EGCG[23-25], Resveratrol[26, 27], and Curcumin[28]. In terms of mechanistic investigations, it has been demonstrated that phytochemicals inhibit tumor proliferation, invasion, and metastasis by down-regulating multiple pathways. Examples include PI3K/ Akt / mTOR[29, 30] , IL - 6 / JAK/ STAT3[31], NF - κB[11, 32], MAPK/ ERK[33]. These studies have contributed to the peak of publications, and the available evidence suggests that the research on tumor-related phytochemicals will continue to increase in the future.

China has the highest NP and TC in tumor-related phytochemicals research which is reflected in the country/region analysis (Table 1), which examines the popularity and output of a study in various nations and regions. This characteristic is also demonstrated in Figure 4A, where the authors of high-impact publications are virtually exclusively Chinese, with varying numbers of papers produced from 2012 onwards. This may be related to China's long history of dietary and traditional Chinese medicine culture. There is a strong cooperation between high-publishing countries, with Saudi Arabia and Iran being the most frequent partners, followed by China and the United States. Saudi Arabia is also the nation with the most co-authors of various nationalities. Surprisingly, SYRIA, SWEDEN, and the U.S are the top3 nations with the greatest average article citations internationally, with China and India being left out of the Top20. This indicates that the quality of papers from China and India needs to be improved, and more cross-national or cross-nationality collaborations should be carried out in the future. Statistics demonstrate a significant correlation between population density and the burden of tumors in China, India, and the United States, which may be one of the explanations for why these nations are more active in tumor-related phytochemical study.

When we used local citations to evaluate the influence of authors, Prof. Liu, Rui Hai from Shenyang Agricultural University attracted our attention the most, focusing on the antioxidant and antiproliferative activities of different phytochemicals in cancer. For example, Ursolic Acid inhibits the growth of breast cancer cells and induces death via the Nrf2 or p231/MAPK signaling pathways[34, 35]. Efferth Thomas from Johannes Gutenberg University of Mainz and Kumar Shashank from Central University of Punjab, both of Germany. The most publications about tumor-related phytochemicals are published in MOLECULES. The first open-access journal of MDPI, MOLECULES was established in 1996, which includes two main columns, "Materials Chemistry" and "Nanochemistry", and contains a wide range of articles in the fields of materials chemistry, biomedicine and nanomaterials. Food Chemistry (IF=8.8) in the subject of food science and technology in the United Kingdom, launched in 1976 and published as a semimonthly by Elsevier Press, has the highest H-index and TC. It offers complete open access and publishes a wide variety of original research papers in the fields of food chemistry and biochemistry. Although this journal does not appear in the Top10 journals in terms of number of articles issued (Figure 5), it has the most TC. Indicating that its excellent academic caliber

has attracted greater attention and citations from scholars.

Knowledge Base

A reference's or a keyword's centrality is a reliable sign of how significant it is to the wider network. In this bibliometric analysis, we evaluated the Top15 references with the highest centrality (Table 4) to understand the research base of tumor-related phytochemicals. Along with the global cancer incidence and mortality rates provided by GLOBALCAN, the Global Cancer Burden Statistics published by Siegel RL et al. in 2021 had the highest centrality and number of citations, which underlined the necessity of antitumor research[12, 36]. A range of phytochemicals exert chemopreventive effects on cancer by lowering oxidative stress were reviewed by Chikara S[12, 36]. Natural phytochemicals still play a significant role in antitumor research due to their antioxidant properties. For instance, SAW CL et al. showed that Quercetin, Kaempferol, and Pterostilbene exert a synergistic antioxidant stress effect by activating the Nef2-ARE pathway and reducing intracellular levels of reactive oxygen species (ROS)[37]. In addition, the four highly centrality literature reviewed phytochemicals as anticancer medicines successfully applied in the clinic or in clinical trials[14, 38-40]. These phytochemicals are the cornerstone of research and keep advancing practically in fresh studies. For instance, in 2012, the FDA approved the use of sphingomyelin/cholesterol (SM/Chol) liposome vincristine (Marqibo®) for the treatment of relapsed acute lymphoblastic leukemia in adults[41]. Since then, novel pathways for the clinical use of Paclitaxel[42], Vincristine[43] and Homoharringtonine[44, 45] have been discovered, highlighting the enormous potential of phytochemicals for medical uses. Shukla S et al. revealed how plant chemicals can modify epigenetics to mediate anticancer effects[15]. In 2016, Anantharaju PG et al. introduced phenolic compounds to regulate vascular endothelial factors, cell cycle proteins, transcription factors, epigenetics and other effects[46]. The Top15 centrality keywords in Table 6 can also assist us in swiftly summarizing the fundamental information of studies on tumor-related phytochemicals. These keywords primarily include alkaloid, chemotherapy, antitumor activity, flavonoid, glycoside, lung cancer, and bioavailability, among others. Global cancer burden, processes of phytochemicals in carcinogenesis and development, and clinical applications make up the majority of the fundamentals on phytochemicals associated with tumors.

Hot Topics and Frontiers

Reference and keyword citation bursts are frequently used to highlight trending themes over time. We can understand the research hotspots of tumor-associated phytochemicals by combining the keywords bursts (Figure 7B) with the corresponding clustering maps. Between 2012 and 2016, the impacts of cancer chemotherapy were incredibly prevalent in citation bursts. For instance, Nitidine, a STAT3 pathway inhibitor, inhibits Janus kinase 2 / STAT3 signaling and STAT3 DNA binding activity in endothelial cells to mediate angiogenesis suppression and apoptosis[47]. SHAN et al. demonstrated for the first time that Sulforaphane (SFN) mediates EMT inhibition in bladder cancer through the mir-200c/ZEB1 pathway[48]. Picrasidine induces apoptosis in cholangiocarcinoma cells by activating mitochondria-dependent pathways through induction of Cystatinase activation, regulation of bcl2/Bax expression and inactivation of the PI3K/AKT pathway[49]. According to these research, phytochemicals, as modulators of important cell signaling pathways, interact with cancer targets to have chemopreventive. Interestingly, Sulforaphane and Nitisin, two chemical compounds with nitrogen, are included in the most centrality term "Alkaloid" that are frequently found in nature. Subsequently, new findings on the regulation of epigenetics by phenolic chemicals continue to emerge. For instance, EGCG induces RKIP expression by histone modification in AsPC-1 pancreatic cancer cells, which reduces invasive and metastatic activities[23]. Resveratrol reduces the risk of breast tumors caused by exposure to aromatic hydrocarbon receptor agonists (AhR) during pregnancy by inhibiting CpG methylation of the BRCA-1 gene[26]. The keywords "in vivo" and "mice" have the longest time span between 2012 and 2020, since in vivo animal experiments, such as nude mouse transplanted tumor models, may better imitate the complex in vivo environment and are one of the most widely used techniques for anticancer drug screening. Between 2015 and 2019, lipid peroxidation got a lot of attention, particularly in anticancer investigations involving oxidative stress and Ferroptosis. For instance, colon cancer cells treated with Saffron extracts CST and CTA dramatically reduced hydrogen peroxide-induced ROS generation and MDA levels (a recognized LPO marker)[50]. In 2017, Tamara Y et al. showed that strawberry extracts enriched with anthocyanin fractions modulated lipid metabolism, modulated ROS and Thiobarbituric Acid (TBARs) production to improve the redox status of HepG2 cells[51]. Ferroptosis is primarily triggered by LPO, which has three primary stages: initiation, propagation, and termination[52]. Numerous phytochemicals have been demonstrated to have anticancer effects when they target NRF2 to induce LPO and iron-deficiency anemia[53]. In present, some keywords from 2019 continue to have a large

audience, including secondary metabolite, green synthesis, functional food, and degradation.

In addition, some other hotspots also deserve our attention. Withaferin A (WFA) is one of the most important herbs in Ayurvedic system in India[54]M.</author></authors></contributors><auth-address>School of Systems Biology, George Mason University, Manassas, VA, United States.</auth-address><titles><title>Evaluating anticancer properties of Withaferin A-a potent phytochemical</title><secondary-title>Front Pharmacol</secondary-title></titles><periodical><full-title>Front Pharmacol</full-title></periodical><pages>975320</pages><volume>13</volume><edition>2022/11/08</edition><keywords><keyword>Ashwagandha</keyword><keyword>Withaferin A</keyword><keyword>Withania somnifera</keyword><keyword>apoptosis</keyword><keyword>cancer</keyword><keyword>cancer treatment</keyword><keyword>withanolides</keyword><keyword>commercial or financial relationships that could be construed as a potential</keyword><keyword>conflict of interest.</keyword></keywords><dates><year>2022</year></dates><isbn>1663-9812 (Print, and it has the most linked articles in the cluster mapping of literature co-citation network. Several preclinical studies have shown that it has potent anticancer action[55]. For example, WFA, for example, reduced tumor growth in 80% of ovarian epithelial carcinomas when combined with cisplatin[56]. The combination of phytochemicals and chemotherapeutic drugs, which ranked second in the cluster mapping, has long been used to reverse MDR and chemotherapeutic sensitization. Teng et al. (2016) revealed that β-carotene inhibited P-gp transcription by stimulating ATPase activity in a variety of drug-resistant tumor cells and improved doxorubicin, paclitaxel, and mitoxantrone chemosensitivity[57]. Allicin and 5-FU can exert a synergistic effect in a variety of cancers, including lung, liver, and colorectal cancers, promoting tumor cell morphology transformation and inhibiting tumor cell invasion and migration[58]. After 2015. New approaches to tumor therapy are made possible by the quick development of materials chemistry. In 2017, Javid et al. created Nanoparticles made from PLGA/PEG copolymers for the first time to construct nanoparticles with a combination of Curcumin and Chrysin, which successfully reduced hTERT expression, sped up the inhibition of caco-2 cells, and lessened harmful side effects[59].

Table 5 shows that the research interest in oncology-related phytochemicals from 2021-2023 is focused on drug development based on naturally derived phytochemicals[60], computer model assessment of pharmacokinetics and drug similarities[19], and clinical application of phytochemicals in cancer therapy[20]. Surprisingly, these topics are extremely similar to the research base and the drugability and clinical translation may become a central topic for future research.

Limitation

Since we used the WOSCC database to gather all the data for this research, it's possible that we left out certain articles. Additionally, our analysis only included English-language articles, some non-English writing, reviews, and other kinds of studies were omitted. Due to word count restrictions, there are only a limit number of graphs and Tables that can be provided in the bibliometric analysis.

4. Conclusion

In oncology, phytochemicals have important research value and clinical application potential. Since 2012, the NP and the average annual citations have been rising quickly, peaking in 2012, which has drawn significant interest from academics and institutions all around the world. Although China has the greatest NP and TC in the world, there is still room to improve international collaborations. The closest collaborations are between Saudi Arabia and Egypt, with Saudi Arabia having the most publications written with authors of other nationalities. The author with the most scientific contributions is LI Y, whereas Prof. RH Liu has the most local citations. The journal with the greatest H-index and most referenced articles was Food Chemistry, however Molecules had the most papers published in it. Chemoprevention, anti-tumor mechanisms, and clinical applications are the key topics of interest in the development of phytochemicals related to tumors. We should combine computational and materials chemistry approaches with fundamental research in the future to promote additional therapeutic applications of anti-tumor phytochemicals.

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and language. Dr. Falin Wang was extremely helpful in writing and proofreading the article.

Conflict of interest

Authors declare that no conflicts of interest are declared in this study.

References

[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries [J]. CA Cancer J Clin, 2021, 71(3): 209-49.

[2] Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023 [J]. CA Cancer J Clin, 2023, 73(1): 17-48.

[3] Islam A, Yang YT, Wu WH, et al. Capsaicin attenuates cell migration via SIRT1 targeting and inhibition to enhance cortactin and beta-catenin acetylation in bladder cancer cells [J]. Am J Cancer Res, 2019, 9(6): 1172-82.

[4] Bi S, Liu JR, Li Y, et al. gamma-Tocotrienol modulates the paracrine secretion of VEGF induced by cobalt(II) chloride via ERK signaling pathway in gastric adenocarcinoma SGC-7901 cell line [J]. Toxicology, 2010, 274(1-3): 27-33.

[5] Li Y, Sun WG, Liu HK, et al. gamma-Tocotrienol inhibits angiogenesis of human umbilical vein endothelial cell induced by cancer cell [J]. J Nutr Biochem, 2011, 22(12): 1127-36.

[6] Ranjan A, Ramachandran S, Gupta N, et al. Role of Phytochemicals in Cancer Prevention [J]. Int J Mol Sci, 2019, 20(20).

[7] Ng CY, Yen H, Hsiao HY, et al. Phytochemicals in Skin Cancer Prevention and Treatment: An Updated Review [J]. Int J Mol Sci, 2018, 19(4).

[8] Wang P, Long F, Lin H, et al. Dietary phytochemicals targeting Nrf2 for chemoprevention in breast cancer [J]. Food Funct, 2022, 13(8): 4273-85.

[9] Lee J, Han Y, Wang W, et al. Phytochemicals in Cancer Immune Checkpoint Inhibitor Therapy [J]. Biomolecules, 2021, 11(8).

[10] Liu K, Sun Q, Liu Q, et al. Focus on immune checkpoint PD-1/PD-L1 pathway: New advances of polyphenol phytochemicals in tumor immunotherapy [J]. Biomed Pharmacother, 2022, 154: 113618.

[11] Ding Y, Fan J, Fan Z, et al. Gamma-Tocotrienol reverses multidrug resistance of breast cancer cells through the regulation of the gamma-Tocotrienol-NF-kappaB-P-gp axis [J]. J Steroid Biochem Mol Biol, 2021, 209: 105835.

[12] Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021 [J]. CA Cancer J Clin, 2021, 71(1): 7-33.

[13] Chikara S, Nagaprashantha LD, Singhal J, et al. Oxidative stress and dietary phytochemicals: Role in cancer chemoprevention and treatment [J]. Cancer Lett, 2018, 413: 122-34.

[14] Seca AML, Pinto D. Plant Secondary Metabolites as Anticancer Agents: Successes in Clinical Trials and Therapeutic Application [J]. Int J Mol Sci, 2018, 19(1).

[15] Shukla S, Meeran SM, Katiyar SK. Epigenetic regulation by selected dietary phytochemicals in cancer chemoprevention [J]. Cancer Lett, 2014, 355(1): 9-17.

[16] Lee KW, Bode AM, Dong Z. Molecular targets of phytochemicals for cancer prevention [J]. Nat Rev Cancer, 2011, 11(3): 211-8.

[17] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation [J]. Cell, 2011, 144(5): 646-74.

[18] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin, 2018, 68(6): 394-424.

[19] Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules [J]. Sci Rep, 2017, 7: 42717.

[20] Choudhari AS, Mandave PC, Deshpande M, et al. Phytochemicals in Cancer Treatment: From Preclinical Studies to Clinical Practice [J]. Front Pharmacol, 2019, 10: 1614.

[21] Katiyar SK, Singh T, Prasad R, et al. Epigenetic alterations in ultraviolet radiation-induced skin carcinogenesis: interaction of bioactive dietary components on epigenetic targets [J]. Photochem Photobiol, 2012, 88(5): 1066-74.

[22] Weng CJ, Yen GC. Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives [J]. Cancer Treat Rev, 2012, 38(1): 76-87.

[23] Kim SO, Kim MR. Epigallocatechin 3-gallate inhibits invasion by inducing the expression of Raf kinase inhibitor protein in AsPC-1 human pancreatic adenocarcinoma cells through the modulation of histone deacetylase activity [J]. Int J Oncol, 2013, 42(1): 349-58.

[24] Moseley VR, Morris J, Knackstedt RW, et al. Green tea polyphenol epigallocatechin 3-gallate, contributes to the degradation of DNMT3A and HDAC3 in HCT 116 human colon cancer cells [J]. Anticancer Res, 2013, 33(12): 5325-33.

[25] Saldanha SN, Kala R, Tollefsbol TO. Molecular mechanisms for inhibition of colon cancer cells by combined epigenetic-modulating epigallocatechin gallate and sodium butyrate [J]. Exp Cell Res, 2014, 324(1): 40-53.

[26] Papoutsis AJ, Selmin OI, Borg JL, et al. Gestational exposure to the AhR agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin induces BRCA-1 promoter hypermethylation and reduces BRCA-1 expression in mammary tissue of rat offspring: preventive effects of resveratrol [J]. Mol Carcinog, 2015, 54(4): 261-9.

[27] Wu ML, Li H, Yu LJ, et al. Short-term resveratrol exposure causes in vitro and in vivo growth inhibition and apoptosis of bladder cancer cells [J]. PLoS One, 2014, 9(2): e89806.

[28] Bao B, Ali S, Banerjee S, et al. Curcumin analogue CDF inhibits pancreatic tumor growth by switching on suppressor microRNAs and attenuating EZH2 expression [J]. Cancer Res, 2012, 72(1): 335-45.

[29] Khan K, Quispe C, Javed Z, et al. Resveratrol, curcumin, paclitaxel and miRNAs mediated regulation of PI3K/Akt/mTOR pathway: go four better to treat bladder cancer [J]. Cancer Cell Int, 2020, 20(1): 560.

[30] Chen X, Tian F, Lun P, et al. Curcumin Inhibits HGF-Induced EMT by Regulating c-MET-Dependent PI3K/Akt/mTOR Signaling Pathways in Meningioma [J]. Evid Based Complement Alternat Med, 2021, 2021: 5574555.

[31] Sun M, Liu C, Nadiminty N, et al. Inhibition of Stat3 activation by sanguinarine suppresses prostate cancer cell growth and invasion [J]. Prostate, 2012, 72(1): 82-9.

[32] Wang Y, Park N Y, Jang Y, et al. Vitamin E gamma-Tocotrienol Inhibits Cytokine-Stimulated NF-kappaB Activation by Induction of Anti-Inflammatory A20 via Stress Adaptive Response Due to Modulation of Sphingolipids [J]. J Immunol, 2015, 195(1): 126-33.

[33] Fan Y, Patima A, Chen Y, et al. Cytotoxic effects of beta-carboline alkaloids on human gastric cancer SGC-7901 cells [J]. Int J Clin Exp Med, 2015, 8(8): 12977-82.

[34] Jiang X, Li T, Liu RH. 2alpha-Hydroxyursolic Acid Inhibited Cell Proliferation and Induced Apoptosis in MDA-MB-231 Human Breast Cancer Cells through the p38/MAPK Signal Transduction Pathway [J]. J Agric Food Chem, 2016, 64(8): 1806-16.

[35] Zhang X, Li T, Gong ES, et al. Antiproliferative Activity of Ursolic Acid in MDA-MB-231 Human Breast Cancer Cells through Nrf2 Pathway Regulation [J]. J Agric Food Chem, 2020, 68(28): 7404-15.

[36] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012 [J]. Int J Cancer, 2015, 136(5): E359-86.

[37] Saw CL, Guo Y, Yang AY, et al. The berry constituents quercetin, kaempferol, and pterostilbene synergistically attenuate reactive oxygen species: involvement of the Nrf2-ARE signaling pathway [J]. Food Chem Toxicol, 2014, 72: 303-11.

[38] Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010 [J]. J Nat Prod, 2012, 75(3): 311-35.

[39] Newman DJ, Cragg GM. Natural Products as Sources of New Drugs from 1981 to 2014 [J]. J Nat Prod, 2016, 79(3): 629-61.

[40] Greenwell M, Rahman PK. Medicinal Plants: Their Use in Anticancer Treatment [J]. Int J Pharm Sci Res, 2015, 6(10): 4103-12.

[41] FDA approves liposomal vincristine (Marqibo) for rare leukemia [J]. Oncology (Williston Park), 2012, 26(9): 841.

[42] Bernabeu E, Cagel M, Lagomarsino E, et al. Paclitaxel: What has been done and the challenges remain ahead [J]. Int J Pharm, 2017, 526(1-2): 474-95.

[43] Yoshihara H, Yoshimoto Y, Hosoya Y, et al. Infantile fibrosarcoma treated with postoperative vincristine and dactinomycin [J]. Pediatr Int, 2017, 59(3): 371-4.

[44] Li X, Yin X, Wang H, et al. Correction: The combination effect of homoharringtonine and ibrutinib on FLT3-ITD mutant acute myeloid leukemia [J]. Oncotarget, 2019, 10(61): 6641-2.

[45] Chen J, Mu Q, Li X, et al. Homoharringtonine targets Smad3 and TGF-beta pathway to inhibit the proliferation of acute myeloid leukemia cells [J]. Oncotarget, 2017, 8(25): 40318-26.

[46] Anantharaju PG, Gowda PC, Vimalambike MG, et al. An overview on the role of dietary phenolics for the treatment of cancers [J]. Nutr J, 2016, 15(1): 99.

[47] Chen J, Wang J, Lin L, et al. Inhibition of STAT3 signaling pathway by nitidine chloride suppressed the angiogenesis and growth of human gastric cancer [J]. Mol Cancer Ther, 2012, 11(2): 277-87.

[48] Shan Y, Zhang L, Bao Y, et al. Epithelial-mesenchymal transition, a novel target of sulforaphane via COX-2/MMP2, 9/Snail, ZEB1 and miR-200c/ZEB1 pathways in human bladder cancer cells [J]. J Nutr Biochem, 2013, 24(6): 1062-9.

[49] Zhang Y, Sun S, Chen J, et al. Oxymatrine induces mitochondria dependent apoptosis in human osteosarcoma MNNG/HOS cells through inhibition of PI3K/Akt pathway [J]. Tumour Biol, 2014, 35(2): 1619-25.

[50] Menghini L, Leporini L, Vecchiotti G, et al. Crocus sativus L. stigmas and byproducts: Qualitative fingerprint, antioxidant potentials and enzyme inhibitory activities [J]. Food Res Int, 2018, 109: 91-8.

[51] Forbes-Hernandez TY, Gasparrini M, Afrin S, et al. Strawberry (cv. Romina) Methanolic Extract and Anthocyanin-Enriched Fraction Improve Lipid Profile and Antioxidant Status in HepG2 Cells [J]. Int J Mol Sci, 2017, 18(6).

[52] Yin H, Xu L, Porter NA. Free radical lipid peroxidation: mechanisms and analysis [J]. Chem Rev, 2011, 111(10): 5944-72.

[53] Dodson M, Castro-Portuguez R, Zhang DD. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis [J]. Redox Biol, 2019, 23: 101107.

[54] Atteeq M. Evaluating anticancer properties of Withaferin A-a potent phytochemical [J]. Front Pharmacol, 2022, 13: 975320.

[55] Dutta R, Khalil R, Green R, et al. Withania Somnifera (Ashwagandha) and Withaferin A: Potential in Integrative Oncology [J]. Int J Mol Sci, 2019, 20(21).

[56] Kakar SS, Ratajczak MZ, Powell KS, et al. Withaferin a alone and in combination with cisplatin suppresses growth and metastasis of ovarian cancer by targeting putative cancer stem cells [J]. PLoS One, 2014, 9(9): e107596.

[57] Teng YN, Sheu MJ, Hsieh YW, et al. beta-carotene reverses multidrug resistant cancer cells by selectively modulating human P-glycoprotein function [J]. Phytomedicine, 2016, 23(3): 316-23.

[58] Tigu AB, Toma VA, Mot AC, et al. The Synergistic Antitumor Effect of 5-Fluorouracil Combined with Allicin against Lung and Colorectal Carcinoma Cells [J]. Molecules, 2020, 25(8).

[59] Lotfi-Attari J, Pilehvar-Soltanahmadi Y, Dadashpour M, et al. Co-Delivery of Curcumin and Chrysin by Polymeric Nanoparticles Inhibit Synergistically Growth and hTERT Gene Expression in Human Colorectal Cancer Cells [J]. Nutr Cancer, 2017, 69(8): 1290-9.

[60] Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review [J]. Biotechnol Adv, 2015, 33(8): 1582-614.

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Clinical Observation on the Treatment of Chronic Hypertrophic Rhinitis with Endoscopic Nasal Dilatation

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Abstract: Objective: To observe the clinical effect of endoscopic nasal dilatation in the treatment of chronic hypertrophic rhinitis. Methods: A total of 100 patients who received treatment in the Department of Otolaryngology of our hospital from January 2019 to January 2021 were selected as the study subjects. Patients were divided into a control group and an experimental group using the method of numerical random allocation. There are 50 patients in each group. Patients in the control group were treated with medication, while patients in the experimental group were treated with endoscopic nasal dilatation. Compare the differences in the efficacy, nasal congestion symptoms, and nasal resistance between the two groups of patients after treatment. Results The total effective rate of treatment in the experimental group (98.00%) was higher than that in the control group (69.00%), with a statistically significant difference ($P<0.05$); The visual analogue scale (VAS) scores, nasal resistance, and nasal endoscopy scores of the two groups of patients after treatment were lower than those before treatment, and the VAS scores, nasal resistance, and nasal endoscopy scores of the experimental group were lower than those of the control group after treatment, with a statistically significant difference ($P<0.05$); There was no statistically significant difference in the total incidence of complications between the two groups ($P>0.05$). Conclusion The treatment of chronic hypertrophic rhinitis with endoscopic nasal dilatation can achieve good results.

Keywords: Endoscopic Nasal Dilatation; Chronic Hypertrophic Rhinitis; Effect Analysis

1. Data and Methods

1.1 General information

A total of 100 patients with chronic hypertrophic rhinitis who were treated in the Department of Otolaryngology of our hospital from January 2019 to January 2021 were selected as the study subjects. The patients were divided into a control group and an experimental group based on a digital random allocation method, with 50 patients in each group. Inclusion criteria: Patients identified as having symptoms of nasal congestion and other diseases, underwent nasal cavity examination, and found that the surface of the nasal mucosa was uneven, thick, and mulberry shaped. The patients understood the experimental content and voluntarily accepted the study. Exclusion criteria: Patients who have received nasal surgery and are accompanied by intellectual and mental disorders, as well as patients with other major diseases, refuse to cooperate with this researcher. In the experimental group, there were 32 males and 18 females; Age: 19-69 years old, with an average age of (35.12 ± 3.25) years; The course of disease ranged from 1 to 7 years, with an average of (4.03 ± 0.12) years. In the control group, there were 23 males and 27 females; Age: 17-68 years old, with an average age of (38.12 ± 3.26) years; The course of disease ranged from 1 to 8 years, with an average of (4.20 ± 0.53) years. Compared with the general data of the two groups of patients, the difference was not statistically significant ($P>0.05$) and was comparable. This study has been approved by the Hospital Medical Ethics Committee.

1.2 Method

The patients in the control group were treated with a mixture of Xiaozhiling and procaine in a ratio of 1:1. During treatment, the patients were injected bilaterally at the same time, with a dose of 2ml per side for 7 days each time. Three times were used as a course of treatment, and a total of 2 courses of treatment were implemented.

Patients in the experimental group were treated with endoscopic nasal cavity dilatation.

The external fixation of the inferior turbinate is performed using a nasal endoscope (0 °), a cutting suction device, and the patient's inferior turbinate mucosa is planed to reduce the hypertrophy of the inferior turbinate, thereby achieving the effect of volume expansion. If the patient has hyperosteogeny of the inferior turbinate, the submucosal portion of the bone is removed. After inferior turbinate surgery, the patient's posterior nostrils should be fully exposed and the total nasal tract width ≥ 5mm. During the reduction of the inferior turbinate, try to preserve the relevant integrity of the mucosa of the turbinate.

During nasal septoplasty and nasal septum three line tension reduction surgery, try to preserve the relevant supporting effects of cartilage and bone scaffolds, and process the relevant curves that exhibit abnormal tension during growth (which can lead to deviation of the nasal septum), so as to restore the biomechanical effects of the nasal septum. If the patient has a simple spinous process of the nasal septum, an incision should be made in front of the deviation, and the deviation spinous process should be removed without suturing the incision.

Internal fixation of the middle turbinate Under endoscope, the root of the patient's middle turbinate is peeled off, pressed inward for displacement, and an expanded sponge is filled in the patient's middle nasal meatus to promote the expansion of the middle nasal meatus. After middle turbinate surgery, ensure that the distance between the lateral wall of the patient's nasal cavity and the lower edge of the turbinate is ≥ 5mm.

Treatment of uncinate process and ethmoidal vesicle If a patient with chronic hypertrophic rhinitis has uncinate process and ethmoidal vesicle, the uncinate process should be removed and the ethmoidal vesicle should be opened to widen the middle nasal tract, thereby promoting the increase in the relevant ventilation area of the nasal cavity.

After the surgery is completed, an inflatable sponge is used for tamponade, and antibiotic intervention is routinely performed to prevent infection. After 48 to 72 hours, the tamponade is removed, and nasal irrigation is performed 2 weeks later.

1.3 Observation indicators and evaluation criteria

To observe and analyze the treatment effects of two groups of patients with chronic hypertrophic rhinitis, and compare the differences in nasal congestion symptoms, nasal resistance, and nasal endoscopy scores between the two groups before and after treatment, while analyzing the occurrence of complications in the two groups.

Treatment effect: The nasal cavity is well ventilated, and the middle turbinate can be seen. The distance between the lower turbinate and the nasal floor and septum is ≥ 5mm, which is a significant effect; The nasal ventilation has improved, and it can be seen that the middle turbinate is effective if the distance between its lower turbinate and the nasal floor and septum is less than 5mm; Compared with before treatment, the nasal ventilation and physical signs of the patient have no significant changes, which is considered invalid. Total effective rate of treatment= (significant+ effective) cases/total cases × 100%.

1.4 Statistical methods

SPSS21.0 statistical software was used to analyze the data. The measurement data were expressed as mean ± standard deviation ($x \pm s$), using t-test, and the counting data were expressed as rate (%), using χ In the 2-test, the difference was statistically significant with $P<0.05$.

2. Results

2.1 Comparison of total treatment effectiveness between two groups of patients

The total effective rate of treatment in the experimental group (98.00%) was higher than that in the control group (69.00%), with a statistically significant difference ($P<0.05$).

2.2 Comparison of VAS scores, nasal resistance, and nasal endoscopy scores between the two groups of patients before and after treatment

There was no statistically significant difference in VAS score, nasal resistance, and endoscopic score between the two groups before treatment ($P>0.05$); The VAS score, nasal resistance, and nasal endoscopy score of the two groups after treatment were lower than those

before treatment, and the VAS score, nasal resistance, and nasal endoscopy score of the experimental group after treatment were lower than those of the control group, with a statistically significant difference ($P<0.05$).

3. Discussion

Chronic hypertrophic rhinitis is one of the most common clinical diseases. In clinical treatment, the common treatment method is drug treatment. In order to ensure the treatment effect, most patients currently choose to receive surgical treatment, and different treatment methods have differences in treatment efficacy. The traditional surgical treatment for chronic hypertrophic rhinitis used to be to cut a portion of the patient's inferior turbinate, which is simple and can damage the integrity of the patient's inferior turbinate mucosa, thereby affecting the physiological function of the nasal cavity. "Nasal cavity expansion surgery, including external fixation of inferior turbinate, internal fixation of middle turbinate, and three line tension reduction plasty of nasal septum, can remove the lesion according to the specific disease situation of the patient, better preserve the normal structure, anatomy, and function of the patient's nasal cavity, effectively expand the nasal sinus and nasal cavity, improve ventilation volume, reduce ventilation resistance in the patient's nasal cavity, and alleviate symptoms such as upper airway obstruction."

For small nasal septal nodules in the nasal cavity, treatment may not be required. If the nodules are large, equal interventions such as cutting, suction, and planing may be implemented. The middle turbinate is the main site through which gas is inhaled, and its size and shape can directly affect the relative patency of the middle nasal tract. If the middle turbinate is inverted and bubbly, it can cause compression and obstruction of the middle nasal tract. However, the implementation of middle turbinate internal displacement and fixation intervention can solve the above problems, which can maximize the preservation of the mucosa on the outside and inside of the patient's middle turbinate, and the operation is simple to avoid affecting the patient's sense of smell, And there will be no postoperative adhesion. After surgery, it should be ensured that the distance between the lateral wall of the patient's nasal cavity and the lower edge of the middle turbinate is $\geq$ 5mm, and the middle nasal tract with physiological curvature should be widened. If the patients with chronic hypertrophic rhinitis have severe middle turbinate reflexes and vesicular middle turbinates, they can undergo middle turbinate plasty intervention. It is worth noting that during the surgery, it is necessary to ensure the symmetry of the physiological functions of both sides of the patient's nasal cavity to avoid the occurrence of compensatory hypertrophy caused by asymmetric expansion.

4. Summary

In summary, the application of endoscopic nasal dilatation in the treatment of patients with chronic hypertrophic rhinitis can achieve better results, which can better improve the nasal congestion symptoms of patients, reduce their nasal resistance, and improve the prognosis of patients with chronic hypertrophic rhinitis. The application value is high, and it is worth promoting and applying.

References

[1] Jiang N. "Clinical observation of endoscopic nasal dilatation in the treatment of chronic hypertrophic rhinitis [J]. Chinese Journal of Metallurgical Industry Medicine, 2021 (02)".

[2] Luo LH, Liu ZJ, Zhou XL. Effects of different surgical procedures on nasal healing in patients with nasal septum deviation and chronic hypertrophic rhinitis [J]. Journal of Clinical and Experimental Medicine, 2021 (03).

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Effects of Ginsenosides on Cardiomyocytes and NF in Type 2 Diabetes Rats- κ B Expression

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Abstract: Objective: To explore the clinical medicinal value of ginsenosides. Methods: 24 male type 2 diabetes rats aged 7 weeks were taken as the research object, and the myocardial cell morphology, inflammatory factor content and NF in each group were observed by grouping them with different doses- κ B expression. Result: The swelling degree of cells in the CP+Rg50 group was alleviated most significantly, with a significant reduction in deep staining of the nucleus, a significant reduction in cell shrinkage, and a basic trend towards normal cell morphology. Meanwhile, compared to the control group, the CP+Rg50 and CP+Rg25 groups showed significant differences in IL-1 levels β/ IL-6, TNF- α It also significantly decreased horizontally ($P<0.05$); NF of CP+Rg25 Group and CP+Rg50 Group- κ The expression level of B protein was also lower than that of CPCG Group ($P=0.02$) and close to that of NCG Group ($P>0.05$). Conclusion: Ginsenoside Rg1 has significant effects in the treatment of cardiomyopathy and is worth promoting in clinical practice.

Keywords: Ginsenoside Rg1; Type 2 Diabetes Rats; Myocardial Cells; NF- κ B

1. Introduction

The main pharmacological active ingredients of ginsenosides include ginsenoside Rg1, ginsenoside RH2, Rg3, and ginsenoside G-Rg3. Among them, ginsenosides RH2, Rg3, and PDL1 have significant effects in the mechanism of action in gastric cancer, while Rg3 treatment can regulate the expression of matrix metalloproteinase-2 (MMP-2) and MMP-9 and inhibit the expression of epithelial mesenchymal transition (EMT) related transcription factors, which has a significant effect on inhibiting the migration and invasion activity of nasopharyngeal carcinoma (NPC) cells.

In addition, some studies have pointed out that ginsenoside Rg1 may also inhibit tumor cell proliferation and induce tumor cell apoptosis by regulating pathways and immune functions, possessing good anti-tumor ability and broad clinical application prospects. In order to further explore the effect of ginsenoside on cardiomyocytes, this paper will take type 2 diabetes rats as an example to study it and explore the transcription factor NF- κ The expression of B.

2. Materials and Methods

2.1 Research materials

Twenty four male type 2 diabetes rats aged 7 weeks were used in the experiment. These animals do not have specific pathogens and are kept in separate cages, each containing six mice. The environmental conditions, including temperature, relative humidity, and light/dark cycle, all comply with standard procedures. Domesticate the rats for a week and provide standard rat food and water at will. The program used in this experiment was approved by the Animal Ethics Committee of the School of Basic Medicine, Guangxi Medical University. In addition, strict adherence to the guidelines of the National Institutes of Health's "Guidelines for the Care and Use of Experimental Animals" (NIH Publication No. 8023, revised in 1978).

2.2 Experimental Plan

All animals were divided into the following groups: normal control group (NCG), model group (CPCG), low-dose ginsenoside group (CP+Rg25), and high-dose ginsenoside group (CP+Rg50). Rats in the NCG and CPCG groups were given 5% Tween 80 daily for 5 weeks. At the same time, rats in the Rg25+CP group and Rg50+CP group were given 25 and 50mg/kg of ginsenoside, respectively, for 5 weeks.

Starting from the second week of treatment, all rats, except for the NCG group, received weekly intraperitoneal injection of CP (100mg/kg) for 4 weeks. An overview of the experimental design is shown in Figure 1. The CP and Rg concentrations used in this study were based on early studies. At the end of the experiment, all rats were anesthetized with thiopental sodium and blood was collected directly through cardiac puncture. The serum obtained from whole blood after centrifugation is used to analyze the levels of cardiac natriuretic peptide in heart tissue.

After euthanasia, the rat heart tissue was dissected, washed with distilled water, and weighed. Afterwards, the heart tissue was homogenized in phosphate buffered saline (pH7.4) at 6000rpm at 4 ℃ for 30 minutes, and the supernatant collected after centrifugation was stored at -80 ℃ until further analysis.

2.3 Organizational analysis

H&E staining was performed on fixed heart tissue with 10% buffered monomerrin. The heart tissue is dehydrated in a graded alcohol solution and waxed with paraffin. The staining procedure follows the standard H&E staining scheme.

2.4 Detection of inflammatory factor content in myocardial tissue

Approximately 50mg of myocardial tissue was taken from each rat and prepared into a 10% homogenate at 3000r/min, centrifuged at 4 ℃ for 10 minutes. The supernatant was collected and detected for interleukin-1 in the supernatant using an ELISA kit β (IL-1 β)\ Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) Content. Measure the OD value using an enzyme-linked immunosorbent assay (Thermo Fisher Scientific China) at 450nm. To ensure quality, all the above experimental processes need to be repeated 3 times.

2.5 Statistical Analysis

Analyze the data using one-way AVONA and Newman Keuls post test using Graph Pad Prism (5th edition). The results are displayed as mean ± standard deviation. $P<0.05$ is statistically significant

3. Results

3.1 Comparison of cell morphology of myocardial tissue in each group

By using an optical microscope to observe the collected samples, the results are shown in Figure 1:

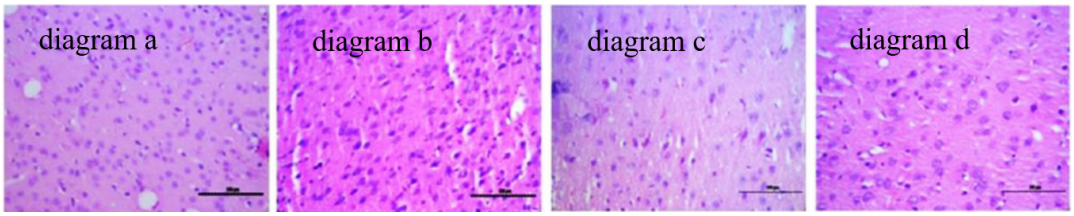

Figure 1 Comparison of the morphology of myocardial tissue cells in each group

As shown in the above figure, the morphology of myocardial tissue cells in the NCG group (Figure a) was normal, arranged neatly, with intact cell nuclear membranes and clearly visible nucleoli, without obvious nuclear pyknosis; In the CPCG group (Figure b), the cell volume of myocardial tissue in rats was significantly reduced, with obvious nuclear pyknosis and deep staining. Cell edema was evident, and there was significant cell infiltration in the intercellular space, with obvious necrotic cells visible; The edema status of myocardial tissue cells in the CP+Rg25 group (Figure c) and CP+Rg50 group (Figure d) of rats was improved compared to the CPCG group, and the edema status of cells showed varying degrees of reduction. Among them, the swelling degree of cells in the CP+Rg50 group was alleviated most significantly, with a significant reduction in nuclear staining, a significant reduction in cell shrinkage, and a basic trend towards normal cell morphology.

3.2 Comparison of inflammatory factor content in myocardial tissue of each group

As shown in Table 1, compared with the NCG group, the CPCG group, CP+Rg25 group, and CP+Rg50 group showed significant dif-

ferences in IL-1 β、 IL-6, TNF- α The levels were significantly elevated, and the differences were statistically significant (P<0.05).

Table 1 Comparison of inflammatory factor content in myocardial tissue of rats in each group

Group	IL-1β	IL-6	TNF-α
NCG Group(n=6)	0.64±0.17	13.78±2.45	4.36±0.09
CPCG Group(n=6)	7.98±0.28 ①	283.52±20.56 ①	86.24±3.51 ①
CP+Rg25 Group(n=6)	6.31±0.41 ①②	220.85±15.76 ①②	63.55±3.40 ①②
CP+Rg50 Group(n=6)	4.26±0.53 ①②③	114.39±15.12 ①②③	36.51±4.25 ①②③

Note: P<0.05, statistically significant. ① Compared to NCG Group, ② compared to CPCG Group, and ③ compared to CP+Rg25 Group.

Based on the above table, it can be seen that compared with the CPCG group, the CP+Rg25 group and the CP+Rg50 group have IL-1 β、 IL-6, TNF- α The level has significantly decreased. P<0.05 indicates statistical significance. Meanwhile, compared with the CP+Rg50 group and the CP+Rg25 group, in IL-1 β、 IL-6, TNF- α There is also a significant decrease in level. P<0.05 indicates statistical significance.

3.3 NF of myocardial tissue in each group- κ B expression

As shown in Figure 2, the NF of CPCG Group- κ The expression level of B protein is significantly higher than that of NCG Group, while the NF of CP+Rg25 Group and CP+Rg50 Group is significantly higher- κ The expression level of B protein was also lower than that of CPCG Group (P=0.02) and close to that of NCG Group (P>0.05).

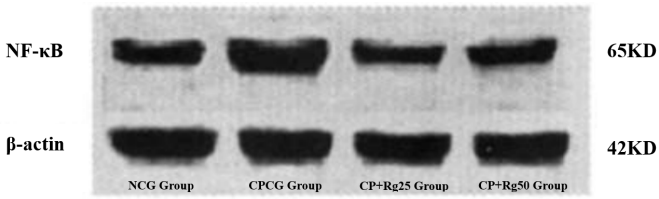

Figure 2 NF of myocardial tissue in each group- κ B expression

4. Conclusion

Ginsenoside, as a multi ion channel blocker, can reduce the self-discipline of damaged myocardium, reduce the formation and conduction of abnormal impulses, and play an anti arrhythmic role. This article takes rats as an example, and studies have shown that ginsenosides can alleviate cell damage caused by hypoxia and reoxygenation. The reason for this is the occurrence of myocardial ischemia-reperfusion injury, which is essentially caused by deficiency of qi and blood, deficiency of blood vessels, inability to nourish the myocardium, causing myocardial damage, chest pain, palpitations, and other symptoms. The research results of this article are similar to previous theories. Based on this, it is concluded that ginsenoside Rg1 has the effect of restoring qi and blood, promoting myocardial regulatory ability, maintaining normal blood and myocardial function, and reducing myocardial damage in clinical practice. Therefore, it is worth promoting in clinical practice.

References

[1] Qiong L, Yu Z, Yonghua X,et al.Deciphering the transcriptomic response of Ilyonectria robusta in relation to ginsenoside Rg1 treatment and the development of ginseng rusty root rot[J].FEMS Microbiology Letters, 2022(1):1.

[2] Estrin SI, Kravchenko TV, Kovalchuk AO. The Effect of Mesenchymal Stem Cells Transplantation on Cardiac Functioning and Contractility in Experimental Myocardial Infarction[J]. Ukrainian Journal of Cardiovascular Surgery, 2021, 1(42):28-37.

[3] Cao L, Wang S, Zhang L, et al. mPEG-b-P(Glu-co-Phe) nanoparticles increase gastric retention time and gastric ulcer treatment efficacy of 20(S)-ginsenoside Rg3[J]. Biomedicine & pharmacotherapy =: Biomedecine & pharmacotherapie, 2022(14):6.

[4] Chen C, Xia J, Ren H, et al. Effect of the structure of ginsenosides on the in vivo fate of their liposomes[J].Asian Pharmaceutical

Science, 2022, 17(2):11.

[5] Kim Y, Cho SH. The effect of ginsenosides on depression in preclinical studies: A systematic review and meta-analysis.[J].Elsevier, 2021(3).

[6] Ling XB, Wang J, Qi MM, et al. Effect of hypoxia/reoxygenation on the viability expression of ROS and MAPKs in myocardial cells[J].Journal of Hainan Medical University, 2021, 27(7):1-5.

[7] Meng W, Guo HD. Small Extracellular Vesicles Derived from Induced Pluripotent Stem Cells in the Treatment of Myocardial Injury[J].International Journal of Molecular Sciences, 2023, 24(1).

[8] Pan YM, Shao CY, Zhang LH, et al. The effect of Guanxin Shutong capsule on alleviating the myocardial fibrosis in heart failure rats[J]. Journal of Ethnopharmacology: An Interdisciplinary Journal Devoted to Bioscientific Research on Indigenous Drugs, 2021, 275(1).

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Investigation and Analysis of the Relationship Between Gastric Disorders and Gluten Disorders Among Residents of Yushe County, Shanxi.

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Abstract: Celiac disease, wheat and gluten allergies, and non-celiac gluten sensitivity are the three types of conditions belonging to gluten-related disorders. While already a popularly known issue in developed countries, both medical professionals and the general populace in China lack basic knowledge of gluten-related disorders. However, previous studies have found that gluten-related disorders are possibly pervasive in China. This study targets the rural areas of Yushe, Shanxi, where wheat-based foods are the main staple. It confirms the relationship between gastric disease occurrences and nut-and-grain allergies through a logistic regression model, with wheat and gluten being the most dominant foods in the local diet under this category. Therefore, gluten disorders may actually have the greatest impact on gastric diseases in villagers. Well-designed prospective studies are needed to establish the causality between gluten-related disorder and gastric disease.

Keywords: Gluten-Related Disorder; Wheat and Gluten Allergy; Gastric Disease; China

1. Introduction

1.1 Research Background

A county in northeastern China, Yushe, Shanxi, has a population of around 35 million, with an area of about 60,500 square miles, of which 80% are mountains and hills. The area is located inland in the mid-latitude zone and has a temperate continental monsoon climate (Shanxi Provincial Bureau of Statistics 2023). From various noodles to buns and dumplings, foods made from wheat flour constitutes a major part of the local diet (Wank 2015).

During on-site visits, a high prevalence of gastric diseases was found among the villagers living in the area. 8 out of 10 households have at least one member who suffers from chronic stomachache, bloating, or nausea. Moreover, people die of stomach cancer every year. Based on their symptoms and dietary habits, we suspect that gluten-related disorders coupled with continuous gluten intake could be associated with their gastric diseases.

1.2 Literature Review

Gluten-related disorders, including celiac disease, wheat and gluten allergies, and non-celiac gluten sensitivity, are emerging as a progressively prevalent issue, what once believed to be relatively rare is now estimated to affect nearly 10% of the population (Sapone et al. 2012). It incurs a range of symptoms, with digestive symptoms being the most prominent, and if left uncured, could even result in cancer in the most extreme of cases (Catassi, Italo Bearzi, and Holmes 2005).

While gluten-related disorders have garnered significant attention in developed nations such as the United States, Canada, and various European countries, there exists a notable dearth of knowledge and awareness regarding these conditions among both medical professionals and the general populace in China (NPD Group 2013).

Small sample studies find that amongst Chinese adults and children with chronic diarrhea, the presence of celiac disease-related antibodies ranges from 1.77% to 12% (Wang et al. 2011). Examining 1,952 patients with severe allergic reactions, another study shows that wheat is the primary food factor causing anaphylactic shock in Chinese people (Jiang et al. 2016). Furthermore, there is a noteworthy prevalence of irritable bowel syndrome in China, ranging from 4.4% to 11.8% (Zhang et al. 2014). Given its frequent misdiagnosis alongside gluten sensitivity, and considering wheat's status as China's second largest staple, it is plausible that China may have a substantial population

with gluten sensitivity (Rubio–Tapia et al. 2009).

1.3 Significance

This study contributes to the literature in two ways. First, there are currently close to none existing academic papers on gluten-related disorders in China, and none looks at the correlation between gastric disease and gluten-related disorders. This paper therefore presents new findings, offering unique insight into gluten-related disorders in China.

Secondly, by looking at the correlation between the prevalence of gluten-related disorders and incidence of gastric disease, I can propose gluten-related disorders as a possible cause for the villagers' gastric diseases if the variables are strongly correlated or rule out the possibility if the correlation is low. This will provide a foundation upon which studies on the causality between gluten-related disorders and gastric disease can be conducted in further depth.

The results of this investigation will bring to light the often-overlooked pervasiveness of gluten-related disorders in China, provide a basis for further research, and serve as a reference for policymakers pertaining public health. For these reasons, this investigation is worth conducting.

2. Objects and Methods

2.1 Questionnaire

In July 2023, a random sample of 150 survey respondents was selected from the villages of Nanhedi and Xihe, both situated within Yushe County. Yushe County is situated within Jinzhong City, Shanxi Province, which was chosen as the study's research site. This investigation distributed a total of 150 questionnaires, of which 127 were collected, with 119 valid responses, resulting in a 93.7% response rate.

The investigation was conducted with responses obtained through random sampling of the self-designed questionnaire "Shanxi Gastric Disease and Chronic Food Allergy Survey Questionnaire". The survey consisted of 15 questions, comprising 11 single-choice and 4 multiple-choice questions. These questions encompassed various aspects including respondents' demographic information (gender and age), dietary habits, gastric disease conditions (symptoms, onset time, severity), and their level of awareness regarding food allergies. The collected survey data was inputted into Microsoft Forms and subsequently verified. Descriptive analysis of the questionnaire was then carried out using Microsoft Excel.

2.2 Food-Specific IgG Antibody Assessment

A test was conducted on the total immunoglobulin G (IgG) antibodies of the villagers using finger-tip blood samples from 37 random villagers at the Nanhedi and Xihe villages. Proteins from 22 different food items, including wheat and gluten, were used in the test, revealing the test subjects' immune response towards the foods. In other words, this test tests for non-celiac wheat and gluten sensitivity amongst the villagers at Yushe County, Shanxi Province. We obtained finger-tip blood samples from villagers, utilizing a testing kit, and forwarded them to a Shanghai-based laboratory within the CTI Testing Group for analysis.

2.3 On-site Interviews

On-site interviews were also conducted, in which we communicated directly with villagers to understand their dietary habits, symptoms, and coping attitudes towards gastric disease as well as reasons behind them.

3. Results and Discussion

3.1 Gastric Disease

Of the respondents surveyed, 49 are male (41%), 70 are female (59%); the number of people with ages 20 or below, 21 to 40, 41 to 60,

and 61 or above are 0, 6, 31, and 82 respectively; most of the respondents are at ages 61 or above, with 42 (35%) who is from 61 to 70, and 31 (26%) who is from 71 to 80.

Results show that 84 (71%) of the resident villagers of the two villages studied have experienced chronic gastric discomfort. Among them, 1 person (1%) finds their symptoms neglectable, 41 people (49%) rated them as mild, 17 (20%) as moderate, 22 (26%) as somewhat severe, and 3 (4%) as severe.

According to those surveyed, 31 exhibit bloating, 53 experience stomachache, 37 show nausea, 3 suffers from diarrhea, 51 display indigestion, 10 report constipation, and 23 exhibit vomiting. It can be seen that stomachache and indigestion are notably common among the symptoms.

3.2 Gluten Disorder

Apart from symptoms of gastric disease, results from the survey also revealed that the majority of the villagers (62%) have experienced headache and dizziness, a common symptom of wheat and gluten sensitivity. In addition, 2 have experienced rhinitis and regular sneezes, 2 have experienced itchiness and rashes.

From the food-specific IgG antibody assessment, a combined total of 14 out of the 37 (38%) tested villagers are found to be sensitive to wheat and gluten, with 10 sensitive to wheat and 4 sensitive specifically to gluten. Of those with wheat sensitivity, 8 are mild and 2 are moderate, and of those with gluten sensitivity, 2 are mild and 2 are moderate.

Among the 14 people with wheat and gluten sensitivity, 14 (100%) have reported to having chronic gastric symptoms. The number of people experiencing indigestion, headache/dizziness, bloating, stomachache, nausea, and vomiting are 8, 8, 3, 5, 3, and 3 respectively.

3.3 Relationship Between Gastric Disease and Food Allergy

In order to further analyze whether gastric diseases in villagers are related to food allergies, this study used 37 villagers who underwent antibody testing as research samples to establish a logistic regression model for validation. Logistic regression analysis requires a sample size of 10 times the number of independent variables. In this model, the independent variable is various types of food allergies (such as nut and grain food allergies, egg milk food allergies, seafood food allergies, etc.), and the dependent variable is whether the residents have gastric diseases.

Firstly, assign the dependent variable Y of logistic regression to 0 and 1, where 0 represents no symptoms of gastric disease and 1 represents symptoms of gastric disease.

The independent variables X of logistic regression are also assigned values of 0 and 1, where 0 indicates that villagers are not allergic to this type of food and 1 indicates that villagers are allergic to this type of food.

We establish a logistic regression model as follows:

$$Y = a + b1X1 + b2X2 + \cdots + bnXn$$

Firstly, describe the distribution of dependent variables in the sample (Table 1) : 70.27% of villagers suffer from gastric diseases, and 29.73% of villagers have no symptoms of gastric diseases.

The model evaluation results(Table 2) show that the Likelihood-ratio chi-square test results of the model show a significance P-value of 0.011 * * , showing significance at the horizontal level, rejecting the original hypothesis, thus the model is effective.

Table 1 Distribution of dependent variables

Y	Option	Frequency	percentage (%)
Suffering from gastric diseases	Yes	26	70.27
	No	11	29.73
	Total	37	100

Table 2 Model evaluation results

Likelihood-ratio chi-square	P	AIC	BIC
28.457	0.011**	42.457	53.733

Note: * * *, * *, * represent significance levels of 1%, 5%, and 10%, respectively

The results of binary logistic regression show that:

The significance P-value of Nuts & grains is 0.060 *, showing significant significance at the level. Therefore, nuts and grains allergies will have a significant impact on patients with gastric diseases.

The significance P value of other food all more than 0.1, which is not significant at the level, so other food will not have a significant impact on patients with gastric diseases.

Table 3 Logistic regression results

Experimental group=is		Error	Wald	P	OR	95% confidence interval of OR value	
						upper limit	lower limit
	-0.479	0.522	0.843	0.359	0.619	0.222	1.723
Nuts & grains	2.546	1.356	3.526	0.060*	12.751	0.894	181.787
Meat	23.518	82263.125	0	1.000	16356527437.254	0	-
Seafood	-0.29	292547.699	0	1.000	0.749	0	-
Egg & milk	23.599	45276.976	0	1.000	17744477233.402	0	-
Vegetable	-1.152	1.891	0.371	0.542	0.316	0.008	12.865
Fruit	1.641	1.689	0.945	0.331	5.162	0.189	141.307
Dependent variable: Suffering from gastric disease							

Note: * * *, * *, * represent significance levels of 1%, 5%, and 10%, respectively

In summary, there is a significant correlation between gastric diseases and chronic food allergies among residents in Yushe County, Shanxi Province. Especially, allergies to nuts and grains have a real and significant impact on residents suffering from gastric diseases (p=0.060 *). Among them, gluten food such as wheat, as a staple food in the daily lives of local residents, cannot be underestimated in their impact on gastric diseases.

4. Cause Analysis

4.1 Dietary Habits

Residents of Yushe County, Shanxi Province have been eating foods made from wheat flour for generations. The iconic Daoxiaomian, Youmian Jin, and Shuijiao are just examples. According to “Shanxi Gastric Disease and Chronic Food Allergy Survey Questionnaire”, 107 out of 119 people eat millet gruel, 108 eat various noodles or other food made from wheat flour, and 89 eat buns every day, showing that wheat flour constitutes a major part of people’s diet at Yushe. The reasons behind such a diet encompass a wide spectrum: traditional, geographic, and economic factors.

The people in Shanxi have a recorded two thousand years of history of wheat foods. In fact, it is known as “The Root of World Noodles”, with origins tracing back to the dawn of the Ancient Chinese civilization (Tang et al. 2018). With generations of exposure and consumption of wheat foods, people at Shanxi have become accustomed to and dependent on eating wheat foods.

As an area located in northeastern China, Shanxi Province mainly produces wheat, maize etc., as staple crops, while economic crops include ginseng, hemp, apples, walnuts, persimmons, peppers, cotton, soybeans, ferns, etc. (Shanxi Provincial Bureau of Statistics 2023).

Due to its location, Shanxi has a more arid climate compared to southern provinces, with an average yearly rainfall of about 508.8 mm (Shanxi Provincial Bureau of Statistics 2023). In contrast, the province with the highest rice output, Sichuan, has an average yearly rainfall of 1070.5 mm, which is more than double the rainfall at Shanxi (The People’s Government of Sichuan Province 2020). As a result, the average rice output for Sichuan has exceeded 14 million tons since 2013 (Xu, Wu, and Ge 2018), while only slightly over 2000 tons for Shanxi (Shanxi

Provincial Bureau of Statistics 2023).

Moreover, as 80% of the land in Shanxi are mountains and hills (Shanxi Provincial Bureau of Statistics 2023), transportation is difficult, low in efficiency, and costly. Considering these factors, therefore, the price for rice in Shanxi is notably higher than that of wheat flour, with an average of 6.43 RMB per kilogram and 5.06 RMB per kilogram for rice and wheat respectively (Shanxi Economic Daily 2023). Thus, the economically poor villagers would opt for wheat and not its immediate substitute rice, resulting in a diet comprised mainly of wheat flour.

4.2 Wheat Foods as a Main Staple

From 3.3 it can be observed that the significance P-value for the Nuts & grains category is 0.060*, while it is 1.000, 1.000, 0.542, and 0.331 for Meat, Seafood, Egg & milk, Vegetable, and Fruit respectively. This indicates that while there is a high correlation between gastric disease and chronic food allergies among residents in the Yushe County, allergies to nuts and grains specifically have a real and significant impact.

Wheat foods are the main staple of Shanxi, and it is a major part of the local diet. Of the 119 survey samples collected, 108 (over 90%) include wheat-based foods in their thrice-daily meals. This makes wheat foods far more common than corn, the second most consumed grain under the category, which only 68 (57%) of the respondents reported eating every day. Therefore, the effect of wheat and gluten allergies on the villagers' gastric symptoms may in fact be the most significant.

A possible explanation for the results obtained in 3.3 is the leaky gut syndrome, in which a weakening of the intestinal walls allows partially digested food to enter the bloodstream. consistent ingestion of high quantities of gluten protein elicits inflammation, worsening leaky gut and thus causing autoimmune responses on a wider range of food molecules, making villagers allergic to a variety of other foods like soy, potatoes, pineapples, milk, edamame, spinach etc. (Giacomo Caio et al. 2020). The fact that these foods are rarely, if ever consumed by residents at the remote villagers of Yushe, Shanxi, coupled with the sheer diversity of the allergens makes the first notion reasonable.

4.3 Cognitive Level

While it is undeniable that education overall has become more accessible in recent years, people at Yushe still lacked the level of cognition that allows them to know the concept of gluten and associated gluten disorders.

From survey results, it can be seen that 90 out of 119 respondents (76%) were not aware of food intolerance, and of those 29 (24%) who knew of some cases of food intolerance, none knew about the possibility of being intolerant to wheat or gluten. At the same time, 0 reported to knowing many people with food intolerance, demonstrating that food intolerance alone mostly remains an unknown concept, not to mention wheat and gluten intolerance.

Responses to the survey reveals that 33 (35%) people believe that their gastric symptoms are caused by stomach cold, 23 (24%) people think of eating spoiled food, and only 3 (3%) believe the reason to be food intolerance. These responses show that people still tend to resort to traditional and stereotypical causes for gastric disease.

However, 35 (37%) people have noted that they feel like "other" factors have contributed to their gastric symptoms. This might imply that some people have already begun to have the notion that their gastric symptoms cannot simply be explained by stomach cold and eating spoiled food.

4.4 Coping Attitude

Interviews revealed that in response to their gastric symptoms, villagers often do not visit the hospital, which, according to them, is due to a lack of financial ability. Villagers are not clear on the coverage which their medical insurance provides, and when they consult medical staff at local hospitals, the staff would respond saying that they do not know as well. Another reason for not visiting the hospital is that when they were younger, they believed their symptoms to be neglectable and nothing major.

However, as time passes by, symptoms intensify in severity, and diseases develop further. When the symptoms become unbearable, they would take their last resort: to visit the hospital. Often times diseases have developed to a point where it is incurable. At this point, simi-

larly, villagers will refuse to receive treatment, as the expenses are entirely unaffordable.

Many tragedies resulted, including a mother telling me of her daughter who passed away at 45 years old because of stomach cancer, which is a severe extreme of gastric diseases. According to the villagers, three brothers also passed out one by one from stomach cancer, and these are mere examples of the great many who died from the disease.

To sum up, their lack of financial ability resulted in their reluctance in visiting the hospital, which caused a passive coping attitude, which caused diseases and conditions to worsen. In addition, the medical insurance system is not entirely mature, and its coverage not sufficiently transparent, so that villagers would often spend more money at hospitals than what is affordable.

5. Conclusion and Suggestions

The study was designed to explore the relationship between gastric disease and chronic food allergies. The logistic regression model found that there was a high positive correlation between chronic food allergies and gastric disease occurrences, with nut-and-grain allergies being the most significant. Due to the dominance of gluten foods in the local diet, wheat and gluten allergy, a type of gluten disorder, may actually have the greatest impact on gastric diseases in villagers. Moreover, this study speculates that gluten disorders may be the root cause of other food allergies, but the accuracy of this speculation needs to be further confirmed in the future.

Based on results of this study, it is suggested that there should be more advertisement and public education on gluten disorders, and accessibility for gluten allergy tests should be promoted. Improvement in these two aspects could potentially enhance public health and well-being, increasing overall social welfare.

Future studies on the topic could focus on the causality between gluten disorder and gastric disease, as this study merely looks at the correlation between the variables.

References

[1] Catassi, Carlo, Italo Bearzi, and Geoffrey Holmes. 2005. “Association of Celiac Disease and Intestinal Lymphomas and Other Cancers.” Gastroenterology 128 (4): S79–86.

[2] Giacomo Caio, Lisa Lungaro, Nicola Segata, Matteo Guarino, Giorgio Zoli, Umberto Volta, and Roberto De Giorgio. 2020. “Effect of Gluten-Free Diet on Gut Microbiota Composition in Patients with Celiac Disease and Non-Celiac Gluten/Wheat Sensitivity.” Nutrients 12 (6): 1832–32.

[3] Jiang, Nannan, Jie Yin, Liping Wen, and Hong Li. 2016. “Characteristics of Anaphylaxis in 907 Chinese Patients Referred to a Tertiary Allergy Center: A Retrospective Study of 1,952 Episodes.” Allergy, Asthma and Immunology Research 8 (4): 353–53.

[4] Lionetti, Elena, Salvatore Leonardi, Chiara Franzonello, Margherita Mancardi, Martino Ruggieri, and Carlo Catassi. 2015. “Gluten Psychosis: Confirmation of a New Clinical Entity.” Nutrients 7 (7): 5532–39.

[5] NPD Group. 2013. “Percentage of U.S. Adults Trying to Cut down or Avoid Gluten in Their Diets Reaches New High in 2013.” NPD. 2013. https://www.npd.com/news/press-releases/percentage-of-us-adults-trying-to-cut-down-or-avoid-gluten-in-their-diets-reaches-new-high-in-2013-reports-npd.

[6] Rubio–Tapia, Alberto, Robert A Kyle, Edward L Kaplan, Dwight R Johnson, William F Page, Frederick J Erdtmann, Tricia L Brantner, et al. 2009. “Increased Prevalence and Mortality in Undiagnosed Celiac Disease.” Gastroenterology 137 (1): 88–93.

[7] Sapone, Anna, Julio C Bai, Carolina Ciacci, Jernej Dolinšek, Peter, Marios Hadjivassiliou, Katri Kaukinen, et al. 2012. “Spectrum of Gluten-Related Disorders: Consensus on New Nomenclature and Classification.” BMC Medicine 10 (1).

[8] Shanxi Economic Daily. 2023. “Grain Market Prices across the Province.” Shanxi.gov.cn. The People’s Government of Shanxi Province. 2023. http://www.shanxi.gov.cn/ywdt/sxyw/ 202308/t20230830_9224998.shtml.

[9] Shanxi Provincial Bureau of Statistics. 2023. “Overview of Provincial Conditions.” Shanxi.gov.cn. The People’s Government of Shanxi Province. 2023. http://www.shanxi.gov.cn/ zjsx/zlssx/sqgk/202007/t20200724_6045048.shtml?eqid=9189b-78d00002e9500000003643d333d.

[10] Miao T, Wang XY, Hou K, and Hou LL. 2018. “Carbon and Nitrogen Stable Isotope of the Human Bones from the Xiaonanzhuang Cemetery, Jinzhong, Shanxi: A Preliminary Study on the Expansion of Wheat in Ancient Shanxi, China.” Acta Anthropologica Sinica 37 (02): 318.

[11] The People’s Government of Sichuan Province. 2020. “Overview of Sichuan Province - the People’s Government of Sichuan Province.” Sc.gov.cn. 2020. https://www.sc.gov.cn/10462/ 10703/11250/.

[12] Wang XQ, Liu W, Xu CD, Mei H, Gao Y, Peng HM, Yuan L, Xu JJ. Celiac Disease in Children With Diarrhea in 4 Cities in China. Journal of Pediatric Gastroenterology and Nutrition 53(4): p 368-370, October 2011.

[13] Wank, D.L. (2015). Knife-Shaved Noodles Go Global: Provincial Culinary Politics and the Improbable Rise of a Minor Chinese Cuisine. In: Farrer, J. (eds) The Globalization of Asian Cuisines. Palgrave Macmillan, New York.

[14] Xu CC, Wu WX, and Ge QS. 2018. “Impact Assessment of Climate Change on Rice Yields Using the ORYZA Model in the Sichuan Basin, China.” International Journal of Climatology 38 (7): 2922–39.

[15] Zhang L, Duan L, Liu Y, Leng Y, Zhang H, Liu Z, Wang K. [A meta-analysis of the prevalence and risk factors of irritable bowel syndrome in Chinese community]. Zhonghua Nei Ke Za Zhi. 2014 Dec;53(12):969-75. Chinese.

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To Explore the Brain-Gut Interaction Pathway of Intestinal Flora Based on Traditional Chinese and Western Medicine

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Abstract: There is no direct anatomical relationship between the brain and the gut, but there is a close correlation in clinical manifestations, which is called "brain-gut axis". With the breakthroughs made in the treatment of Parkinson's disease, depression, Alzheimer's disease and other fields based on the brain-gut axis theory, more and more studies have been conducted on the mechanism of brain-gut axis. The current research status mainly defines the basic concept of brain-gut axis from the perspective of traditional Chinese and western medicine, expounds and analyzes the related mechanism and modern clinical application of brain-gut axis. Therefore, the following review summarizes the understanding and research progress of "brain-gut axis".

Keywords: Brain-Gut Axis; Gut Microbiota; Mechanism of Action; Traditional Chinese and Western Medicine Dimensions

Introduction

The brain-gut axis (brain-gut axis) is the bidirectional communication between the enteric nervous system (ENS) and the central nervous system (CNS). In recent years, scientific studies have pointed out that intestinal dysfunction can increase the risk of central nervous system diseases, such as neurodegenerative diseases and other mental diseases. The small intestine can not only influence brain activity by using microbiota, but also interact with the human brain through the nervous system, immune and endocrine pathways of the "brain-gut axis". The close relationship between them has gradually attracted people's attention. This article reviews the interaction pathways between the gut and the brain, mainly based on intestinal flora, so as to provide reference for revealing the nature of the "brain-gut axis".

1. Understanding of brain-gut axis in western medicine

The brain-gut axis is composed of brain, gut and intestinal microorganisms, and is jointly participated by the central neuroendocrine system, enteric nervous system, autonomic nervous system and hypothalamic-pituitary-adrenal axis system [1]. The central nervous system modulates the signals of the brain-gut axis and transmits them down to the gastrointestinal tract to express their functions, while the enteric nervous system can regulate the brain-gut interaction through this bidirectional regulation process, also known as brain-gut interaction [2].

2. Explore the brain-gut interaction pathway based on intestinal flora from the perspective of western medicine

An important part that makes up the brain-gut axis is the content of gut bacteria. Relevant literature reports that brain-gut interaction is involved in the pathogenesis of Parkinson's disease, depression, Alzheimer's disease and other diseases [3-5], most of which are accompanied by precursors such as intestinal flora imbalance, digestive system diseases, and brain-gut axis dysfunction. Moreover, studies have shown that intestinal flora may affect neurogenesis [6] and myelination [7], the normal function of hypothalamic-pituitary-adrenal cortex and endocrine system [8], and intestinal flora has a certain maintenance effect on the formation of blood-brain barrier and can promote the maturation of immune system [9]. Intestinal flora is mainly responsible for regulating the physiological, behavioral and cognitive functions of the brain It is accomplished by neural, endocrine and immune pathways.

2.1 Regulation of gut microbiota-neuroendocrine pathways

The hypothalamic-pituitary-adrenal axis jointly affects the brain, gastrointestinal nervous system and endocrine system [10]. The signal transmission of the stress sympathetic nerve to the enteric nervous system is the main path for the axis to directly affect various functions

in the stomach. Intestinal flora also has a huge negative impact on various sensory and endocrine functions in the stomach. Similarly,when gastrointestinal absorption function is disturbed, gastrointestinal inflammatory factors and gastrointestinal bacteria act on the axis, which will also affect the cognitive and behavioral functions of the brain.

2.1.1 Gut microbiota-nervous system interaction

Gut microbiota can affect the production of neurotransmitters by regulating the function of intestinal epithelial cells or directly synthesizing and secreting GABA, 5-HT, Na, dopamine and other neurotransmitters. Studies have found that gut microbiota can play a role in the central nervous system and is closely related to 5-HT, with bilateral effects [11]. 5-HT is stimulated and regulated by abundant specific intestinal flora and metabolites, binds to receptors, and participates in hypothalamic-pituitary-adrenal regulation under the action of various receptor subtypes, stimulating the secretion of adrenocorticotropic hormone (ACTH), cortisol and other axis regulating hormones. If the gut microbiota is dysregulated, neurotransmitters enter the HPA axis through the peripheral blood vessels, bind to 5-cranial nerves and receptors, and interfere with cortisol and CRH secretion, attenuate the activity of 5-HT neurons, leading to complete axis disorder and brain abnormalities. In addition, some scientists have studied that brain-produced neurotrophic factors can affect neuronal activation [12], and when intestinal flora changes in infectious disease models, it will change the expression of certain proteins, which will have an impact on the increase in anxiety [13].

2.1.2 Interaction between gut microbiota and endocrine system

Intestinal flora can control intestinal endocrine cells to produce adrenocorticotropic hormone releasing factor (CRF), adrenocorticotropic hormone (ACTH), adrenocortical corticosterone (CORT) and other hormones, activate the function of HPA axis [14], and release Glucocorticoid (GC), which is involved in the growth of neurons , differentiation and apoptosis, can regulate the state of neurons and glial cells, and then affect the plasticity of neurons, leading to the functional changes of the central nervous system [15]. Similarly, the composition of gut microbiota is regulated by the stress response and the HPA axis [16]. Several studies have suggested that the activation of the HPA system and the release of CRF and GC may protect the gastrointestinal mucosa during chronic stress [17].

2.2 Intestinal microbiota-Immune regulation

The combination of host and cells develops for a long time to form a relatively balanced environment of the digestive tract microbiome, which participates in important biological processes including host metabolites, nutrient products and immunity, especially plays a crucial role in the construction and improvement of the host immune system. Relevant studies have confirmed that the intestinal flora in the host directly or indirectly affects the host immune system [18], and the intestinal flora promotes the development of the immune system and also affects the differentiation process of immune cells. The immune pathway is also one of the ways to connect the gastrointestinal tract and the brain through the bidirectional interaction of the brain-gut axis.

2.2.1 Intestinal barrier interaction

The gastrointestinal barrier composed of the intestinal mucosa plays a crucial role in the brain-gut axis pathway. Disruption of the integrity of the intestinal mucosal barrier can easily cause inflammation and affect intestinal motility, sensation and hormone secretion [19]. This is because the destruction of the intestinal mucosal barrier will make the molecular structure bound to the intestinal mucosal surface release immunoactive substances such as proteases, and produce some inflammatory cytokines that pass through the intestinal mucosal barrier. The intestinal epithelial barrier is closely related to the homeostasis of the internal environment [20]. The entry of macromolecules and microorganisms into the gut and lymphoid tissues is controlled by microbiotic cells in the intestinal epithelial barrier. The outer layer of mucus is tightly distributed with a dynamic barrier composed of glycoproteins called biofilm. This glycoprotein biofilm is broken down by microorganisms during low dietary fiber and increases sensitivity to pathogen recognition.

2.2.2 Blood-brain barrier interaction

The diffusion barrier between the central nervous system and the cerebrospinal fluid is usually formed by clathrin [21], which builds up the endothelial cells of the cerebral blood vessel wall. Permeability to this barrier, in turn, is determined by organic factors released by the intestinal bacterial population that control connexin expression. Recent studies have shown that an important signal metabolite affecting the blood-brain barrier may be short-chain unsaturated fatty acids [22]. Short-chain unsaturated fatty acids act on the blood-brain barrier through

genetic modification. Microglia, the immune cells in the central nervous system, can be activated by intestinal microbes to release immune factors that regulate the function of the nervous system, thereby affecting the physiological activities of the brain.

3. Understanding of brain-gut axis in traditional Chinese medicine

In traditional Chinese medicine, the role of "brain" in the brain-gut axis is interpreted as the regulation of cerebrovascular diseases and emotional disorders, and the regulation of "intestinal tract" can be interpreted as the regulation of visceral function related to digestion. The term "brain-gut axis" is not mentioned in traditional Chinese medicine, but modern medicine has confirmed that the brain-gut axis is closely related to the spleen, liver and kidney [23-25]. The normal life activities of the human body depend on the five zang organs, and the brain, as the original spirit, dominates the spiritual consciousness and sensory movement of the whole body. At the same time, the meridian system connects the five zang organs, qi and blood, Yin and Yang of the human body, and its circulation and syndromes are also closely related to the brain.

3.1 Integration of heart and brain sensing

The theory of traditional Chinese medicine believes that the generation of emotion originates from the brain and originates from the heart, and gradually forms the concept of "the heart and brain induction integration". People often say "using the brain" as "heart". "Suwen-Linglan Secret classic" says: "The heart, the official of the monarch, God out of the Yan". The Medical Classic Jingyi says, "All things enter the brain through the eye, through the ear, and through the heart." Zhang Xichun's Yi Xue Zhong zhong shen Xilu (Medical Zhongzhongshen Xilu) of the Qing Dynasty wrote, "The human deity is originally located in the heart and the brain, and the function of the deity is supplemented by the heart and the brain. The brain for the original god, the heart for the god.If a man wants to use his God, he will reach his heart from his head. If he does not use his god, he will return from his heart to his head." Referring to the textbook Basic Theory of Traditional Chinese Medicine, the functions of heart and brain are described as "heart governs mind" and "brain assists heart in regulating human spirit, consciousness, thinking, and functional activities of zangfu organs." It can be seen that ancient and modern doctors generally believe that the brain and heart are connected and perceive external things together.

3.2 Heart-gut relationship

The theory of "the exterior and interior of the heart and the small intestine" was first put forward in the Benshu (Shu of Miraculous Pivot), "the heart connects the small intestine". From the theory of meridians, in the book Meridians of Miraculous Pivot, it is written: "The heart and hand are shaoyin vessels, which originate from the heart, originate from the heart system, and are lower than the diaphragm and small intestine". The relationship between the heart and the small intestine can also be reflected from the physiological function. For example, Zhu bing Yuan hou Lun (Theory of All Diseases, Sources and Syndromes) believes that the small intestine has the function of helping the heart to discharge water. "The heart of the small intestine is also, its water and qi descending to the small intestine is the Ao stool, then the heart has no stop drinking, and the body fluid and water drink stop accumulation, forced by the heart, so that the heart is not smooth, so the pain and more saliva also"; According to the pathological manifestations, the heart fire is transferred to the small intestine, and the water is injected into the bladder through the three jiao, causing difficulty in urination. And the small intestine has heat can also follow the meridian inflammation in the heart, visible upset, tongue red erosion and so on. Therefore, the heart and small intestine are exteriors and exteriors of each other, and cooperate, influence and connect with each other in physiology, pathology and meridians.

4. Explore the brain-gut interaction pathway based on intestinal flora from the perspective of traditional Chinese medicine

It has been found that the balance of Yin and Yang in the internal environment system of the body is determined by the circulation movement mechanism of "Qi ascending and descending" of the whole body function of the viscera, and the functional ascending and descending and constitutive mechanism are determined by the characteristics of qi ascending and descending of the corresponding viscera, re-

spectively. Under the support of the theory of brain-gut axis, the combination of spleen, liver and kidney is the main cause and pathogenesis of the human body, and the three can also interact.

4.1 Qi of spleen and stomach and Yin-Yang-intestinal flora

As the driving force of the brain-gut axis system, gut microbiota is involved in the regulation of brain-gut axis pathways. The imbalance of intestinal flora will affect the balance of the internal environment, such as the normal physiological function of the digestive, nervous, endocrine and immune systems, thus affecting the overall function [26]. Yin and Yang change with the rise and fall of middle qi, which is the qi of the spleen and stomach, and the rise and fall of middle qi is the driving force for the growth and change of all things. Through qi, blood, meridian-collateral and other systemic auxiliary substances, its imbalance will also affect the dysfunction of the whole body. There is no term "gut microbiota" in traditional Chinese medicine. Therefore, in traditional Chinese medicine, the intestinal flora can be understood as the qi of the spleen and stomach and the Yin and Yang of the spleen and stomach. Maintaining the homeostasis between probiotics and pathogens in the gut microbiota plays a key role in the proper functioning of the body. Under physiological conditions, maintaining a stable intestinal microecology is an important part of the normal rise and fall and smooth circulation of human qi, which can mainly reflect the function of the spleen and stomach.

4.1.1 Brain, spleen and intestine related

The relationship between the spleen and stomach and the brain is extremely close, and there is a relationship between meridian-qi and substance. The meridian system is an important bridge of the brain-gut axis in traditional Chinese medicine. The stomach meridian runs into the brain in foot-yangming, and the stomach and brain meridian are connected by qi. In the Wu Long Jin Ye bie of Miraculous Pivot, it says, "When the body fluids of the five grains are combined and become an ointment, they penetrate into the bone cavity and replenish the brain." The blood and essence of the spleen and stomach nourishments the normal physiological function of the brain, and the transport of blood and semen depends on the promotion of the spleen and stomach qi. On the one hand, the imbalance of Yin and Yang of spleen and stomach qi can lead to insufficient brain bone marrow and insufficient qi and blood, which affects brain function. On the other hand, the brain has the role of dominating life activities and directing whole body functions. If the perception ability of the brain decreases, the brain loses contact with the spleen and stomach, and the spleen and stomach cannot receive and transport normally, followed by abdominal distension, diarrhea, poor stool and other digestive problems. If the brain is damaged, it will damage the spirit and cannot drive the reception and transportation of the spleen and stomach, resulting in the loss of the movement function of the spleen and stomach, abnormal rise and fall of qi, insufficient blood gas and biochemistry, damage to the function of the main spleen muscles and limbs, muscle weakness, fatigue and other symptoms. [27]

4.1.2 Liver, spleen and brain related

Traditional Chinese medicine proposes that the liver plays a key role in the relationship between the rise and fall of the spleen and stomach. Liver-qi disharmony inevitably affects the laxative function of the liver. Liver against spleen and stomach, resulting in loss of temperament, qi stagnation, qi and blood discord. The body temperature is low, qi and blood are insufficient, and the stomach can not eat, which aggravates the lack of liver blood and stagnation of liver qi, resulting in the loss of mental nutrition. In addition, TCM proposes that the normal functions of spleen, stomach and consciousness are closely related to the unobstructed liver. According to the Miraculous Pivot: Meridian, "The vessel of liver foot Jueyin reaches the lower abdomen, clamp the stomach and leaves the forehead, and meets the governor vessel at the top." It can be seen that the liver meridian runs down to the gastrointestinal tract and up to the top of the roof, which is an indispensable channel for brain-gut communication. The brain also has the function of regulating emotions and splenic anxiety. Lack of spirit, excessive use of the brain, mental stress or depression, it is easy to cause spleen deficiency. Lu Dianqiang et al. [28] believed that the normal rise of middle coke can ensure normal emotional activity. Spleen blood, blood and heart; Spleen dysfunction, mental and nutritional deficiencies, and mood disorders are the result of the absence of the spirit in the spleen

4.1.3 Spleen, kidney and brain related

Huangdi Neijing (Yellow Emperor's Internal Classic) once put forward the theory that "the kidney hides the essence and the essence generates the marrow", which means that the brain bone marrow is produced by the congenital kidney essence. The governor vessel and the

bladder meridian form the channel between the kidney and the brain. From a physiological point of view, the spleen meridian and the governor vessel are connected between the mouth and the heart, and Yang qi should be injected into the governor vessel by the stomach meridian. The governor vessel regulates the Yang qi of the whole body, circulates along the meridians and the brain, and strengthens the connection between the spleen, stomach, the governor vessel and the brain. The meridians of the spleen are connected to those of the bladder, which pass through the abundant muscles on both sides of the spine. Thus, it depends on the function of the splenic innervating muscles and the spleen and stomach as the basis for acquiring acquired postnatal. In terms of pathology, the kidney loses its shuttering function, the kidney Yin cannot converge, the kidney Yang and spleen Yang cannot be attributed to the kidney house, the kidney Yang is deficient, the promotion is weak, the evaporation and gasification function is lost, and the water metabolism is abnormal. Kidney water insults spleen soil, conditioning weakness, aggravation of systemic gasification dysfunction [29]. Based on the above discussion, the brain-gut axis pathway in modern medicine can be generally understood as the relationship between spleen, brain and intestine in traditional Chinese medicine.

5. Summary and Prospect

In the 21st century, the pace of life is getting faster and faster, science and technology and medicine are developing rapidly, but we still face many medical problems. Brain-gut axis is a turning point for human beings to understand and break through the difficult problems of mental or gastrointestinal diseases. Modern scientific research [30] points out that gut microbiota can affect individuals to improve brain and gut functions through the microbiota-gut-brain axis. The heart and small intestine are the outer and inner parts of each other, mainly reflecting the function of helping the small intestine digest food. Learning from the perspective of the heart is from the perspective of the brain. Based on this, under the framework of the disease treatment function of modern clinical traditional Chinese medicine and western medicine combined with the theoretical basis of internal correlation in clinical research, this paper systematically and in detail discusses the mechanism of disease regulation by the bacteria-brain-gut axis, analyzes and construct the relationship between neuropsychiatric diseases and gastrointestinal diseases from multiple angles, and provides new ideas for the development of related drugs and the treatment plan of coupling diseases of nerves and gastrointestinal Road. At present, in view of the fact that there is no unified understanding of the mechanism and prognosis of brain-gut axis system in regulating gastrointestinal diseases among many domestic and foreign basic researchers and scholars, many researches are focused on the basic problems of dynamic monitoring and management of intestinal flora balance function. The future research direction should focus on exploring the biological dynamic mechanisms of the brain-brain-gut axis system in the cooperative regulation of brain-gut diseases and the development of brain-gut diseases, and expounds the various biological mechanisms of how the body automatically realizes the simultaneous treatment and regulation of stomach, brain, and gut functions.

References

[1] Wang LD, Du XJ, Liu JH, et al. Research ideas of soothing the liver and strengthening the spleen in the treatment of functional dyspepsia based on brain-gut interaction [J]. Chinese Medicine Research,2019,32(04):1-3.

[2] Howard R Mertz. Overview of functional gastrointestinal disorders: dysfunction of the brain-gut axis[J]. Gastroenterology Clinics of North America,2003,32(2).

[3] Liu LJ. Study on the correlation between constipation and depression in Parkinson's disease based on the theory of "brain-gut axis" [D]. Anhui University of Traditional Chinese Medicine, 2017.

[4] Qu Y, Hu JQ, Wu S, Wang CC, Rong Fei. Treatment of Alzheimer's disease with spleen based on the theory of brain-gut axis [J/OL]. World Traditional Chinese Medicine:1-9[2022-07-10].

[5] Xiang YY, Shi HY, Tan AH, Xie GJ, Ran SM, Wang P. Treatment of vascular dementia with brain and intestine in traditional Chinese medicine based on the theory of "brain-gut axis" [J]. Shizhen Traditional Chinese Medicine and Chinese Medicine, 2021, 32(09): 2231-2233.

[6] Ogbonnaya ES, Clarke G, Shanahan F, Dinan TG, Cryan JF, O'Leary OF. Adult Hippocampal Neurogenesis Is Regulated by the Microbiome. Biol Psychiatry. 2015 Aug 15;78(4):e7-9.

[7] Hoban, A., Stilling, R., Ryan, F. et al. Regulation of prefrontal cortex myelination by the microbiota. Transl Psychiatry 6, e774 (2016).

[8] Sudo N. Microbiome, HPA axis and production of endocrine hormones in the gut. Adv Exp Med Biol. 2014;817:177-94.

[9] Honda, K., Littman, D. The microbiota in adaptive immune homeostasis and disease. Nature 535, 75–84 (2016).

[10] Bonaz BL, Bernstein CN. Brian - gut interaction in inflammatory bowl diseases [J]. Gastroenterology, 2013144 (1).

[11] Ning HJ. Research progress on the relationship between intestinal microecology and digestive system diseases [J]. Chinese Medicine Guide, 2019, 17(19):17-19.

[12] Zhan TY, Cai ZL. Research progress of acupuncture and moxibustion regulating neuroendocrine function in chronic fatigue syndrome [J]. Jiangxi Traditional Chinese Medicine, 2012, 53(01): 68-72.

[13] Mary Bates. Gut Feeling: Researchers Are Discovering a Link Between Depression and Gut Bacteria[J]. IEEE Pulse, 2017,8(6).

[14] Liu RT. The microbiome as a novel paradigm in studying stress and mental health.[J]. The American Psychologist, 2017 regulation (7).

[15] Lyte M. Microbial endocrinology in the microbiome-gut-brain axis: how bacterial production and utilization of neurochemicals influence behavior[J]. PLoS pathogens, 2013, 9(11).

[16] Javad Barouei, Mahta Moussavi, Deborah M Hodgson. Effect of maternal probiotic intervention on HPA axis, immunity and gut microbiota in a rat model of irritable bowel syndrome[J]. PLoS ONE, 2017,7(10).

[17] Kieran Rea, Timothy GD, John F. Cryan. The microbiome: A key regulator of stress and neuroinflammation[J]. Neurobiology of Stress,2016,4(C).

[18] Zhao YF, Qu HB. Effect of enteral microecological nutrition support on platelet parameters, intestinal flora and immune system function in children with ITP [J]. General Nursing, 2021,20(24):3404-3406.

[19] Qin, J., Li, R., Raes, J. et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65 (2010).

[20] Li YC, Wang CF, Yang GL. Animal gastrointestinal epithelial barrier role in the stable control of intestinal environment [J]. Chinese journal of veterinary, 2015, 35 (6): 1031-1036.

[21] Jiang S. Dyrk1a regulates LAG3 gene methylation in the pathogenesis of Parkinson's disease [D]. Xinjiang medical university, 2021.

[22] Carlezon WA Jr, Mague SD, Parow AM, Stoll AL, Cohen BM, Renshaw PF. Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. Biol Psychiatry. 2005 Feb 15;57(4):343-50.

[23] Feng WL, Wu HT. A study on the pathogenesis of irritable bowel syndrome from "porta purpura is also the causative agent of five zang organs" [J]. China Journal of Basic Medicine of Traditional Chinese Medicine,2016,22(10):1314-1316.

[24] Lin XY, Cai GX, Tan YS. Discussion on the theory of "spleen and kidney correlation" from the brain-gut axis [J]. Shizhen Medical Sinopharm, 2015,26 (9): 2210-2211.

[25] Tran N, Zhebrak M, Yacoub C, Pelletier J, Hawley D. The gut-brain relationship: Investigating the effect of multispecies probiotics on anxiety in a randomized placebo-controlled trial of healthy young adults. J Affect Disord. 2019 Jun 1;252:271-277.

[26] Quigley EMM. Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. Curr Neurol Neurosci Rep. 2017 Oct 17;17(12):94.

[27] Sudo N. Microbiome, HPA axis and production of endocrine hormones in the gut. Adv Exp Med Biol. 2014;817:177-94.

[28] Wei XM, Liao L, Hu ZP, Xie CG. Analysis of blood glucose fluctuation in diabetes mellitus from the theory of "One breath flow" [J]. Chinese Journal of Traditional Chinese Medicine,2020,61(16):1463-1465. (in Chinese)

[29] Huang XQ, Liao XP. Research progress on the correlation between gut microbiota and depression [J]. Chinese Journal of Applied Neurology, 2019,22 (1): 112-116.

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Analysis of Abnormal Gait in the Diagnosis of Early Neurodegenerative Diseases: A Review

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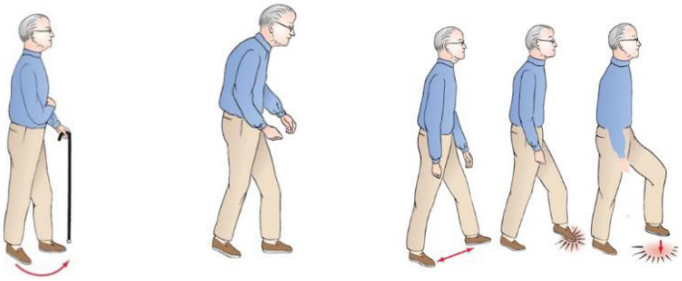
Abstract: Early detection of neurodegenerative diseases can increase the possibility to access to treatment, and assist in advance care planning. At present, most of the gait researches focus on the design and application of recognition tools for disease diagnosis, such as recording the walking and movement status through wearable sensor devices, while, relatively less non-contact machine vision is used to measure gait. The non-contact gait detection method is characterized by the advantages, including the absence of human cooperation, non-invasive nature and so on, which is also suitable for long-distance perception. In this paper, we focused on some non-contact analysis methods for abnormal gait, and it is hoped that it can provide guidance for the diagnosis of neurodegenerative diseases.

Keywords: Neurodegenerative Diseases; Early Diagnosis; Abnormal Gait; Non-Contact Detection

1. Introduction

With the aggravation of the aging of the population, neurodegenerative diseases suffered by the elderly have gradually evolved into a significant social problem. Some of most known and serious neurodegenerative diseases are Parkinson's (PD), S.L.A., Alzheimer's (AD), Huntington Korea (HD) and Dementias (DD).The pathological changes associated with the onset of neurodegenerative diseases are irreversible. When patients show cognitive impairment, the course of disease is often in the middle or late stage. By that moment, treatment is only available for slowing down the development of the disease, instead of fundamental reversion of the damage of neural network. The conventional diagnosis of neurodegenerative diseases largely depends on the subjective measures obtained from observations and questionnaire of the clinicians to require a UPDRS score. These descriptive symptoms may cause misclassification and low efficiency. To formulate appropriate treatment protocols, and improve patient care during rehabilitation, it is important to promptly and accurately identify gait abnormalities[1]. By the time neurodegenerative diseases are diagnosed, sufficient neuronal injury has occurred to the extent that reversal of the disease is unlikely Gait(see Fig.1) is regarded as a complex task requiring higher control of cognitive processing that involves attention, planning, memory and other motor, perceptual and cognitive processes and is shown to have a robust relationship with cognition.So early diagnosis is facing great challenges.



(a) (b) (c)

Fig.1 The abnormal gait due to neurodegenerative diseases. (a)Hemiplegic gait (b) Parkinson's gait (c) Ataxic gait [2]

Patients with hemiplegic gait(Fig.1(a)), always have the leg is stiff, and with each step is rotated away from the body, then toward it, forming a semicircle(without flexion of knee and ankle,). Patients with Parkinson's gait often present with abnormal posture and hands shake(Fig.1(b)). Patients with ataxic gait, often have the deformity seen with foot drop(Fig.1(c)).

However, the cost of these analysis systems is extremely high, and the fixed installation set-up is needed. Meanwhile, traditional disease detection methods are difficult to eliminate the impact of subjective differences among diversified testers, which is not conducive to

longitudinal observation of patients' condition, and the evaluation of disease progression. Gait abnormalities associated with neurodegenerative diseases are due to protein aggregates in different brain regions, which may lead to cell dysfunction or death . More advanced diagnostic techniques such as computed tomography scans that measure brain function, can be cost prohibitive and may expose patients to radiation and other harmful effects. Increasing gait-based detection technologies are proposed as alternative, fast, low-cost and non-invasive detection methods. So it's trend that cooperating with medical institutions to diagnose early neurodegenerative diseases in a non-intrusive way.

2. Abnormal gait analysis in the early diagnosis of neurodegenerative diseases

Many previous studies have analyzed the gait variables in neurodegenerative diseases, including Parkinson's disease, for various applications. these tests is that they may not be efficient at early-stages of cognitive impairment. Recent studies have demonstrated that some gait abnormalities may appear particularly early in neurodegenerative diseases, although these early features remain to be elucidated fully [3]. According to the research of Ríona McArdle of Newcastle University, by studying the unique walking patterns of patients with cognitive impairment, clinicians can accurately diagnose whether they are suffering from Alzheimer's disease or Lewy body dementia. The results showed that these two special gait characteristics were enough for the identification of 60% of dementia subtypes. The research of Panyakaew et al. illustrates that patients with early Parkinson's disease may not complain about gait difficulties, however, when they are confronted with dual tasks, subtle gait abnormalities may be revealed as part of "preclinical gait syndrome". To maintain the speed, patients with early Parkinson's disease develop compensatory mechanism by increasing beat, and reducing swing time and cycle time. In addition, temporal gait variability and arm kinematics are also promising markers of preclinical Parkinson's disease. As per the research of Mole [4], the clinical symptoms of early neurodegenerative dementia have impact on the movement disorder or human gait cycle to a great extent. The experimental results suggest that this method is available for the effective distinguishing of the gait dynamics characteristics of pathological group and healthy control group. Barrett Blake [5] et al. described the changes of gait and the balance ability caused by cognitive decline in the early stage of dementia, and pointed out that early detection of gait changes and centralized intervention would reduce mortality. Amyotrophic lateral sclerosis (ALS) is characterized by gradual muscle atrophy, difficulty in autonomous movement, and cognitive dysfunction due to the damage of motor neurons in the cerebral cortex, brain stem and spinal cord. Literature proposed a method for early diagnosis of this disease, and abnormal gait was proved to be effective.In addition, certain early neurological symptoms show the characteristics, including some gait disorders, such as Alzheimer's disease, isolated adrenocortical hormone deficiency, hemophilia, early childhood ataxia or developmental coordination disorder , Huntington's disease, rheumatoid arthritis [6], etc.

In conclusion, gait is of guiding significance for the early diagnosis of neurodegenerative diseases, especially Parkinson's disease. At present, in most cases, the mature gait analysis methods are suitable for the detection and analysis of moderate and severe frozen gait. Besides, the method of characterizing gait disorder has irreplaceable advantages for the early diagnosis of neurodegenerative diseases.

3. Abnormal gait detection method

Currently, most of the gait researches for disease diagnosis focus on the design and application of recognition tools which use wearable sensor systems to record gait dynamics characteristics, including force contact sensors (such as foot switch and sole pressure insole) , accelerometers, gyroscopes and inertial measurement units. In recent studies, motion sensors (dedicated to smart phones) are also utilized to determine the characteristics of the disease, usually by ensuring that the waist and legs and other parts of the sensor, which are integrated into a wearable device. But assessment techniques based on behavioral tests such as rotarod, grip strength or scoring systems are characterized by several limitations. Some sensors will be limited by non-physiologic test conditions, while some devices will depend on the users and motivational factors. As a non-contact measurement tool, the depth camera is employed for the collection of the gait data of the elderly in the room, which can identify the walkers without interference, and the generation of the probability method of automatic gait estimation over time. Besides, it can also provide the residents with fall risk assessment data based on gait parameters at home. Diagnostic techniques and treatment optimization are of important academic theory and practical application value. Balaji E. [7]proposed gait classification framework with several classifiers (i.e DT, SVM, EC and BC), and utilized the vertical ground reaction force (VGRF) gait dataset, the minimal feature

vector using the statistical analysis. The results reveal that the proposed method outperforms several other PD classification methods.

The monitoring of gait parameters collected in the above-mentioned literatures involves highly accurate but expensive systems, such as three-dimensional gait analysis, infrared camera, photoelectric system and force sensor. As non-mobile devices, these sensory systems are only operable in controlled environment, therefore, it is difficult to analyze the continuous gait cycle of long-term application, especially in the case of free walking. In contrast, non-contact measurement methods, such as depth camera are more suitable for home measurement, unfortunately, there is no evaluation on early diagnosis of related diseases.

Conclusion

At present, there is a lack of effective methods to detect gait disorders in early degenerative diseases from the perspective of visual cognition. This is due to the fact that the extracted abnormal motion features can not only have a good "distinguishing" description for the behavior types of different diseases, but also have a good 'invariance' description for the same behavior under various complex conditions. Human vision can easily capture the key areas in walking gait, it is therefore very important to model the human behavior and key point feature extraction mechanism in the process of visual cognition, starting from the characteristics of human visual attention and the individual processing mechanism.

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References

[1] Joshi D, Khajuria A, Joshi P. An automatic non-invasive method for Parkinson's disease classification. Comput Methods Programs Biomed. 2017 Jul;145:135-145.

[2] Examination of Gait, Available from: https://epomedicine.com/clinical-medicine/ physical-examination-gait/.

[3] Ghoraani B, Boettcher LN, Hssayeni MD, Rosenfeld A, Tolea MI, Galvin JE. Detection of Mild Cognitive Impairment and Alzheimer's Disease using Dual-task Gait Assessments and Machine Learning. Biomed Signal Process Control. 2021 Feb; 64: 102249.

[4] Mole SSS, Sujatha K. An efficient Gait Dynamics classification method for Neurodegenerative Diseases using Brain signals. J Med Syst. 2019 Jun 25;43(8):245.

[5] Barrett B, Schultz SK, Luther SL, Friedman Y, Cowan L, Bulat T. Mortality and Associated Risk Factors in Community-Dwelling Persons With Early Dementia. Alzheimer Dis Assoc Disord. 2020 Jan-Mar;34(1):40-46.

[6] Aşuroğlu, T., Açıcı, K., Erdaş, Ç. B., Toprak, M. K., Erdem, H., Oğul, H. Parkinson's disease monitoring from gait analysis via foot-worn sensors. Biocybernetics and Biomedical Engineering, 38(3) (2018)760-772.

[7] Balaji E., Brindha D., Balakrishnan R. Supervised machine learning based gait classification system for early detection and stage classification of Parkinson's disease. Applied Soft Computing Journal. 94(2020)1-15.

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Comparative Study on the Costs of Treating Diabetic Foot, Necrotizing Fasciitis, and Stage IV Pressure Ulcers

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Abstract: Objective: To compare the total treatment costs for patients with diabetic foot with osteomyelitis, necrotizing fasciitis, and stage IV pressure ulcers in Dalian city, to explore the economic burden of different types of chronic wounds. Methods: A retrospective analysis design was used, collecting data from 18 patients (6 of each wound type) from the electronic medical record system of a large hospital in Dalian. One-way ANOVA and Tukey's HSD post-hoc tests were applied to compare the treatment costs of different wound types. Results: The treatment costs for the necrotizing fasciitis group were significantly higher than those for the stage IV pressure ulcer group, while the costs for the diabetic foot group did not show significant differences from the other two groups. This finding highlights the impact of chronic wound types on treatment costs and the importance of early intervention. Conclusion: The results provide data support for the optimized allocation of medical resources, especially in a context of limited resources. They emphasize the necessity of early identification and management of chronic wounds and provide a basis for establishing cost-effective treatment strategies.

Keywords: Chronic Wound; Socio-Economic Factors; Treatment Costs

Introduction

In the fields of medicine and public health, chronic wounds, including diabetic foot, necrotizing fasciitis, and stage IV pressure ulcers, have always been a problem of significant clinical and socio-economic importance1. These complex clinical conditions require highly personalized treatment strategies and often long-term care, which undoubtedly increase overall medical costs. With the exacerbation of global population aging, these issues are expected to grow, making the exploration of chronic wound treatment costs an urgent issue to be addressed.

In China, with the rapid development of the economy and changes in population structure, the incidence of chronic diseases is on the rise, and the increasing costs of chronic wound treatment are posing a significant burden on families and socio-economic development2. The treatment costs of diabetic foot, necrotizing fasciitis, and stage IV pressure ulcers, as three major types of chronic wounds, and their impact on patients' financial status have not been fully studied. Especially in specific cities like Dalian, the specifics and comparisons of these costs are not clear.

In recent years, the healthcare services and medical insurance system in Dalian have undergone significant changes, which may affect the treatment costs of patients with chronic wounds. Therefore, studying the treatment costs of patients with chronic wounds in Dalian is not only important for local medical decision-making and resource allocation but may also provide valuable experience and reference for other similar cities3.

The purpose of this study is to compare the total costs incurred during the treatment of patients with diabetic foot, necrotizing fasciitis, and stage IV pressure ulcers in Dalian. Through this comparison, we aim to explore the economic burden of different types of chronic wounds and analyze how these burdens reflect the specific medical resource allocation and disease management strategies of Dalian city. Additionally, this study will discuss the impact of these costs on the financial status of patients' families and the potential significance of these findings for optimizing medical resource allocation and improving disease prevention and early intervention4.

Association Between Chronic Wound Treatment Costs and Socio-economic Factors

The treatment costs of chronic wounds and their association with socio-economic factors is a multi-dimensional and complex issue. In China, this issue is particularly concerning due to significant disparities in economic development levels, medical resource distribution, and

social security systems across different regions5. These disparities not only affect patients' access to medical services but also determine the extent to which they bear medical expenses.

Firstly, the high costs of chronic wound treatment pose a particular challenge for low-income groups. These patients may not be able to afford optimal treatment plans, such as the use of modern wound care technologies and advanced biomaterials, potentially leading to poor treatment outcomes and chronicity of the disease6. Moreover, due to financial pressure, these patients might delay seeking medical care, leading to the exacerbation of their condition, increasing the ultimate treatment costs and socio-economic burden7.

Materials and Methods

This study employed a retrospective analysis design to compare the total treatment costs of three different types of chronic wounds in Dalian city—diabetic foot with osteomyelitis, necrotizing fasciitis, and stage IV pressure ulcers.

Study Subjects:

The study sample included patients treated from January to December 2022 at a large hospital in Dalian city. Inclusion criteria included: 1) Patients diagnosed with diabetic foot with osteomyelitis, necrotizing fasciitis, or stage IV pressure ulcers; 2) Aged between 45 and 85 years; 3) Treated surgically and recovered. Exclusion criteria included: 1) Patients with necrotizing fasciitis and stage IV pressure ulcers who also had diabetes; 2) Patients needing parenteral nutrition, or whose vital signs were poor requiring rescue and ICU treatment. In the end, 6 patients were included in each group, equally divided between male and female.

Data Collection:

Data collection included patients' basic information (age, sex, condition, etc.) and treatment-related costs. Treatment costs included hospitalization fees, surgical fees, medication fees, material fees, and other related costs. All data were obtained from the hospital's electronic medical record system.

Statistical Analysis:

One-way ANOVA was used to compare the treatment costs of the three groups of patients. Subsequently, post-hoc multiple comparison tests were conducted to determine the specific cost differences between different types of chronic wounds. Tukey's HSD test was used for post-hoc comparisons. All statistical analyses were completed using GraphPad Prism statistical software. The significance level in the results was set at $p < 0.05$.

Results

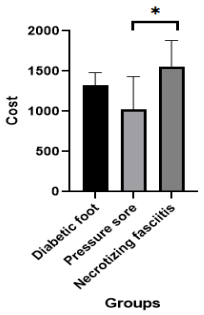
The statistical analysis of this study was based on the treatment cost data of three different groups of chronic wound patients in Dalian city: diabetic foot with osteomyelitis, necrotizing fasciitis, and stage IV pressure ulcers. One-way ANOVA was performed on 18 samples (6 samples per group) to assess whether there were statistically significant differences in the average treatment costs between the three groups, as shown in Table 1.

Necrotizing fasciitis				Diabetic foot				Stage iv pressure sore			
gender	Days	Cost	Cost/Day	gender	Days	Cost	Cost/Day	gender	Days	Cost	Cost/Day
F	20	31714.52	1585.73	F	21	24182.64	1151.55	F	15	15955.67	1063.71
M	18	22204.62	1233.59	M	15	22513.44	1500.90	M	13	23193.08	1784.08
M	5	9352.27	1870.45	M	15	17324.07	1154.94	F	9	8789.03	976.56
F	23	26782.77	1164.47	F	12	17620.43	1468.37	M	48	31058.46	647.05
F	7	10780.32	1540.05	M	15	19512.04	1300.80	F	16	15338.77	958.67
M	7	13708.02	1958.29	F	14	19504.05	1393.15	M	37	27281.86	737.35
Average cost/day	1558.76			Average cost/day	1328.28			Average cost/day	1027.90		

Table 1: The table shows three groups of patients, with the data for each patient group from left to right being sex, hospitalization days, treatment costs, and average daily treatment costs. The last column for each group shows the average daily treatment costs for that group.

Descriptive statistics showed that the average treatment cost for the diabetic foot group was 19,090.42 yuan, with a standard deviation of 9,177.12 yuan. The average treatment cost for the pressure ulcer group was 20,109.44 yuan, with a standard deviation of 2,722.02 yuan. The necrotizing fasciitis group had the highest average treatment cost of 20,269.48 yuan, with a standard deviation of 8,352.77 yuan.

The ANOVA results showed (as seen in Figure 1) that the F-value for the variance analysis between the treatment groups was 4.414, with a p-value of 0.0311, indicating that there were statistically significant differences in average treatment costs between at least two groups. The R-squared value was 0.3705, meaning that the type of treatment could explain about 37.05% of the total variance.



Further post-hoc multiple comparisons using Tukey's HSD test yielded the following results: the average difference between the diabetic foot and pressure sore groups was 300.4 yuan, with a 95% confidence interval (CI) of -165.0 to 765.8 yuan, and an adjusted p-value of 0.2462, indicating no significant statistical difference between the two groups. The average difference Figure 1: The X-axis represents the three groups, and the Y-axis represents the treatment costs. The bars marked with an asterisk indicate statistically significant differences between them.

between the diabetic foot and necrotizing fasciitis groups was -230.5 yuan, with a 95% CI of -695.9 to 234.9 yuan, and an adjusted p-value of 0.4240, also indicating no significant difference between the two groups. The average difference between the pressure sore and necrotizing fasciitis groups was -530.9 yuan, with a 95% CI of -996.3 to -65.45 yuan, and an adjusted p-value of 0.0247, indicating a significant difference between the two groups.

In conclusion, these results suggest that, in Dalian city, the treatment costs for patients with necrotizing fasciitis are on average higher compared to those with stage IV pressure ulcers. However, the treatment costs for patients with diabetic foot did not show significant differences from the other two groups.

Discussion

The purpose of this study was to compare the treatment costs for patients with diabetic foot with osteomyelitis, necrotizing fasciitis, and stage IV pressure ulcers in Dalian. The results revealed differences in the treatment costs of these three types of chronic wounds, especially between necrotizing fasciitis and stage IV pressure ulcer patients8.

When interpreting these differences, we must consider a variety of possible influencing factors. Necrotizing fasciitis, due to its rapid progression and high mortality rate, typically requires urgent and invasive medical interventions, including but not limited to extensive surgical debridement and long-term antibiotic treatment. This may explain why the average treatment cost for this group was the highest. In contrast, although stage IV pressure ulcers also require long-term management and costly care, their treatment costs are lower compared to necrotizing fasciitis. This may be partly due to differences in treatment methods and strategies, as well as the disease course and recovery speed of different wound types9.

The treatment costs for patients with diabetic foot did not show significant differences from the other two groups. This may be related to the standardized degree of treatment. Patients with diabetic foot typically receive standardized multidisciplinary treatment, including blood sugar control, local wound management, and appropriate foot protection10. Nevertheless, this result may hide underlying complexities, as the treatment costs for diabetic foot may be influenced by a variety of factors, including the control of diabetes, the occurrence of complications, and the possibility of readmission.

Furthermore, our study results emphasize the importance of early and proactive intervention for patients with chronic wounds. In clinical practice, adherence to evidence-supported treatment methods can effectively control treatment costs. For instance, for patients with pressure ulcers, regular position changes and the use of pressure-distributing mattresses might prevent the worsening of pressure ulcers, reducing the number of patients requiring expensive treatment.

When analyzing the study results, we must also acknowledge the limitations of the study. The small sample size may affect the generalizability of the statistical results, and future research should include a broader patient population to validate these findings. Additionally, this study only focused on direct medical costs and did not consider indirect costs, such as loss of work capacity and family care expenses, which

may significantly impact the overall economic burden of chronic wounds.

Another limitation of the study is that it did not consider differences in the severity of the condition, which may affect treatment costs. Future research should incorporate the severity of the condition as a covariate to more comprehensively assess treatment costs11.

Lastly, our findings have potential implications for medical decision-making and policy formulation. A deep understanding of the treatment costs of chronic wounds can help health policy makers optimize resource allocation, especially in situations with limited budgets. Moreover, this information is crucial for developing cost-effective treatment plans that help improve patients' treatment outcomes and quality of life.

Conclusion

This study compared the treatment costs for patients with diabetic foot with osteomyelitis, necrotizing fasciitis, and stage IV pressure ulcers. The results showed that although there are differences in the treatment strategies and costs of these three chronic wound types, the average treatment costs for patients with necrotizing fasciitis were significantly higher than those for stage IV pressure ulcer patients. Meanwhile, the treatment costs for diabetic foot patients did not show significant differences from the other two groups.

Future research should focus on a broader patient group, consider the severity of the condition, and include indirect costs to fully understand the economic burden of chronic wounds.

References

[1] Adeyemi, A. & Waycaster, C. Cost-minimization Analysis of Negative Pressure Wound Therapy in Long-term Care Facilities. Wounds : a compendium of clinical research and practice 30, E13-e15 (2018).

[2] Brain, D. et al. Cost-effectiveness analysis of an innovative model of care for chronic wounds patients. PloS one 14, e0212366, doi:10.1371/journal.pone.0212366 (2019).

[3] Carter, M. J. et al. Chronic wound prevalence and the associated cost of treatment in Medicare beneficiaries: changes between 2014 and 2019. Journal of medical economics 26, 894-901, doi:10.1080/13696998.2023.2232256 (2023).

[4] Chan, B. et al. Cost-of-illness studies in chronic ulcers: a systematic review. Journal of wound care 26, S4-s14, doi:10.12968/jowc.2017.26.Sup4.S4 (2017).

[5] Gethin, G., Probst, S., Stryja, J., Christiansen, N. & Price, P. Evidence for person-centred care in chronic wound care: A systematic review and recommendations for practice. Journal of wound care 29, S1-s22, doi:10.12968/jowc.2020.29.Sup9b.S1 (2020).

[6] Graves, N., Phillips, C.J. & Harding, K. A narrative review of the epidemiology and economics of chronic wounds. The British journal of dermatology 187, 141-148, doi:10.1111/bjd.20692 (2022).

[7] Kapp, S. & Santamaria, N. The financial and quality-of-life cost to patients living with a chronic wound in the community. International wound journal 14, 1108-1119, doi:10.1111/iwj. 12767(2017).

[8] Samsell, B. et al. Health economics for treatment of diabetic foot ulcers: a cost-effectiveness analysis of eight skin substitutes. Journal of wound care 28, S14-s26, doi:10.12968/jowc.2019.28. Sup9.S14 (2019).

[9] Sen, C. K. Human Wound and Its Burden: Updated 2020 Compendium of Estimates. Advances in wound care 10, 281-292, doi:10.1089/wound.2021.0026 (2021).

[10] Sibbald, R.G. et al. Wound Bed Preparation 2021. Advances in skin & wound care 34, 183-195, doi:10.1097/01.ASW.0000733724.87630.d6 (2021).

[11] Wilkins, R.G. & Unverdorben, M. Wound cleaning and wound healing: a concise review. Advances in skin & wound care 26, 160-163, doi:10.1097/01.Asw.0000428861.26671.41 (2013).

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Risk Factors for Death in Patients with Atrial Fibrillation

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Abstract: With the aging society and increasing risk factors for cardiovascular diseases, the incidence of atrial fibrillation is gradually increasing, seriously affecting human health. Previous studies have shown that hypertension, diabetes, heart failure, chronic kidney disease, etc, increase the risk of death of patients with atrial fibrillation. Research has shown that cardiac pathological remodeling is the fundamental pathophysiological mechanism for atrial fibrillation, which is closely related to thromboembolism and death in patients with atrial fibrillation. At present, there is limited research on the risk factors for increased mortality in patients with atrial fibrillation. Therefore, this article will review the related factors that increase the risk of death in patients with atrial fibrillation.

Keywords: Atrial Fibrillation; Death; Risk Factors

Introduction

Atrial fibrillation (AF) is a common supraventricular arrhythmia, characterized by abnormal atrial electrical stimulation and systolic dysfunction.It can lead to cardiac dysfunction. AF not only reduces the quality of life of patients, but also increase the all-cause mortality rate of patients with metabolic cardiovascular disease by 1.5-1.9 times [1, 2]. The ion channels of myocardial cells alter the excitability of atrial muscles, forming a reentrant loop, leading to the ccurrence of AF, activating the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS), promoting myocardial fibrosis, and leading to cardiac pathological remodeling and dysfunction[3]. Research has shown that AF is closely related to adverse outcomes such as thromboembolism and increased mortality [4, 5]. Currently, there is relatively little research on the risk factors for increased mortality in patients with AF, so this article provides a review of this research.

1. Atrial fibrillation and death

The study found that the incidence rate of ischemic stroke in patients with AF was higher and more serious, the cerebrovascular mortality increased [6]. AF can lead to hemodynamic abnormalities, cardiac endothelial dysfunction, platelet aggregation, and coagulation factor release, promote left atrial thrombosis, and increase the incidence rate of thromboembolic stroke[7]. Toshimi et al[8]found that without cardiovascular risk factors, AF is also an independent risk factor for stroke related death. In addition, research has confirmed that with the use of oral anticoagulants, the cerebrovascular mortality rate in patients with AF has decreased, but there is still a higher risk of cardiovascular death[9]. Especially among the elderly, there is a significant increase in cardiovascular mortality [10]. The mechanism of increased mortality in patients with AF is closely related to the pathological remodeling of the heart caused by various cardiovascular diseases and fatal arrhythmias caused by cardiac dysfunction [4, 11].

2. The death risk factors of AF

2.1 Women

Research has found that elderly female with AF have a higher risk of thromboembolism related stroke, and have a higher all-cause mortality rate[1, 12]. Women with AF have a 2.5 times higher cardiovascular mortality rate than men[13]. In a meta-analysis of 30 studies, it was found that female AF patients had an all-cause mortality rate 12% higher than male[14]. At present, there is no mechanism to clearly explain the gender differences in AF mortality, which may be related to insufficient treatment in female AF patients, differences in anticoagulant drug responsiveness, and a high risk of fatal adverse events caused by antiarrhythmic drugs [15, 16].

2.2 Smoking

Smoking is a risk factor for AF, and research has confirmed that smoking is associated with a high risk of thromboembolism and death in AF patients[17]. Kwon et al.[18] found that AF patients who smoke are more prone to ischemic stroke and cardiovascular death. Lee et al.[19] found through follow-up of newly diagnosed patients with AF that patients who did not quit smoking had a significantly higher risk of cerebrovascular death compared to those who quit smoking. Alanna M Chamberlain et al. [20]also found that smokers with AF have a higher risk of all cause death compared to non-smokers. Smoking can increase the risk of death in patients with AF by promoting catecholamine secretion, increasing cardiac contraction, leading to myocardial ischemia .It can also by affecting blood lipids, promoting oxidative stress response, damaging vascular endothelial function, accelerating atherosclerosis, increasing the risk of myocardial infarction and heart failure[17] .

2.3 Obesity

Obesity can lead to the transition from paroxysmal to persistent AF[21]. Obese patients often have an increase in epicardial adipose tissue. Currently, research has found that epicardial adipose tissue has metabolic activity, which can induce myocardial fibrosis and cardiac dysfunction[22]. It was found that obesity can prolong the QT gap and increase the risk of sudden cardiac death[23]. However, the impact of obesity on the mortality of AF patients is controversial. Research has found that high body mass index (BMI) is the main risk factor for death in patients with AF[24]. However, some studies have found a reverse relationship between BMI and mortality in patients with AF. Compared with patients with normal BMI, low-weight patients have higher all-cause mortality, while overweight and obese patients have lower all-cause mortality [25]. The “obesity paradox” has also appeared in recent studies. When BMI is less than 30kg/m2, all-cause mortality is negatively correlated with BMI [26]. This may be related to the fact that patients with higher BMI are often younger, with fewer comorbidities, and that rhythm control and anticoagulant therapy are more commonly used in patients with AF in higher BMI.

2.4 Inflammation

Inflammation plays an important role in the progression of cardiovascular diseases, and participate in cardiac remodeling, leading to the persistence of AF[27]. Inflammation is an important response for the body’s immune defense, but sustained or inappropriate inflammation can also cause damage to the body. Research has confirmed that inflammation can increase the risk of death in AF patients. Aulin et al. [28]found that the levels of interleukin-6 are positively correlated with all-cause mortality in AF patients. Hermida et al. confirmed that high levels of hypersensitive C-reactive protein are independent risk factors for all cause and cardiovascular death in AF patients[29]. Some studies have also found that AF patients have a higher proportion of CD4+CD28- T cells compared to non-atrial fibrillation patients, and CD4+CD28- T cells are significantly correlated with cardiovascular mortality in AF patients[30]. Inflammation can increase the risk of thromboembolism in AF patients, leading to cerebrovascular mortality. It is related to the hypercoagulable state, platelet activation, and endothelial dysfunction. Inflammation can also promote cardiac remodeling and increase cardiovascular mortality in AF patients[31, 32].

2.5 Hypertension

Research has confirmed that hypertension is the risk factor of AF[33]. In addition, studies have also confirmed that hypertension can increase the risk of death in AF patients. Wang Jianping et al.[34] found that hypertension above grade 2 is a high-risk factor for all-cause mortality in non-valvular atrial fibrillation patients. G A Dan et al. [35]also found that when AF and hypertension coexist, the all-cause mortality rate is higher than in patients with AF alone. The activation of the RAAS, inflammation, and oxidative stress in the long-term hypertensive state of the body can lead to myocardial fibrosis and ischemia, which can lead to the occurrence of arrhythmias, increase the risk of ventricular arrhythmias in AF patients, and increase the risk of sudden cardiac death[33]. Moreover, the increase in left ventricular volume load caused by hypertension can develop into hypertensive heart disease and congestive heart failure, leading to a significant increase in cardiogenic death in AF patients.

2.6 Chronic kidney disease

Chronic kidney disease (CKD) often coexists with AF, leading to an increased all-cause mortality rate in AF patients[36, 37]. Research has confirmed that CKD can increase the risk of thromboembolic events in AF patients by affecting coagulation function, leading to an increased risk of cerebrovascular death[37]. Research has found that in AF patients, as the glomerular filtration rate decreases, all-cause and cardiovascular mortality rates are increase [38]. The hemodynamic changes in the heart caused by AF can promote the development of end-stage kidney disease by reducing renal perfusion[39]. In addition, AF can further damage renal function through increasing fibrosis in myocardial and renal tissues, upregulation of fibrinogen, and renal micro thrombosis formation[40]. The disorder of calcium and phosphorus metabolism, vascular calcification caused by CKD, and the decrease in coronary blood flow caused by AF can lead to insufficient coronary blood supply, myocardial ischemia, increasing risk of coronary heart disease and susceptibility to acute myocardial infarction and sudden cardiac death. In summary, the correlation between AF and CKD promotes a significant increase in the risk of death.

2.7 Diabetes

Diabetes is one of the risk factors of AF. Many studies have confirmed that the death of AF patients with diabetes is significantly increased. Polovina et al.[41] found through a median 5-year follow-up of 1803 AF patients with T2DM, the all-cause mortality rate was 56% higher than that of non T2DM AF patients, and the cardiovascular mortality rate was 48% higher. Karayiannides S et al. [42]found that the effect of diabetes and AF increased the all-cause mortality rate by twice compared with the general population. A recent meta-analysis of 21 studies confirmed that diabetes is associated with a higher risk of cardiovascular and all-cause death in AF patients [43]. The mechanism of the impact of diabetes on the survival of AF patients has not been completely clear, and the following reasons are mainly considered. First, insulin resistance exists in patients with diabetes, which leads to abnormal lipid metabolism of myocardial cells, leading to heart “lip toxicity”; Secondly, diabetes can lead to cardiac electrical, structural and autonomic nerve remodeling, make AF recur and continue, and affect the stability of hemodynamics; Third, diabetes can promote the development of cardiomyopathy and heart failure through systemic inflammation, microvascular dysfunction and oxidative stress, and increase the risk of cardiovascular death[23, 42, 44].

2.8 Heart failure

Heart failure (HF) and AF often occur together, promoting each other and leading to poor prognosis. Cardiovascular death of AF is closely related to HF. Marijon et al.[45] followed up 18113 AF patients for a median of 2 years and found that cardiovascular death accounted for 37.4% of the total deaths, HF being the strongest predictor of cardiovascular death. In Framingham’s study, it was found that AF patients with HF have an increased risk of all-cause death[46]. In another study, it was found that HF is the main death cause after one year of new onset AF [47]. AF is mainly characterized by irregular contraction of the atrium. Changes in the excitation contraction coupling of myocardial cells and myocardial fibrosis can lead to abnormal atrioventricular node conduction, leading to an increase in the occurrence of ventricular arrhythmias. In AF patients with HF, cardiac remodeling is more significant, and the stress between myocardial cells also undergoes significant changes. Under the influence of ventricular arrhythmias, sudden cardiac death is more likely to occur[11, 48]. HF is often accompanied by various diseases such as diabetes, hypertension, metabolic syndrome, renal insufficiency, etc. In patients with AF and HF, the above diseases are also often accompanied. The combined effect of these diseases significantly increases the all-cause mortality of patients with AF[49].

3. Summary

AF as a common arrhythmia in clinical practice, can seriously affect the quality of life of patients and significantly increase the risk of death. Studies have found that many factors are closely related to the death of patients with AF, including women, smoking, obesity, inflammation, hypertension, diabetes, CKD, HF, etc. Clarifying the impact of various factors on the death of AF patients is of great significance for their diagnosis and treatment. According to the impact of risk factors on the death of AF patients, risk stratification management can be carried out for the prognosis of AF patients, and active prevention and treatment of risk factors may reduce the death of AF patients. Currently,

research has shown that the impact of certain factors such as gender and obesity on mortality in AF patients is still controversial, and further clinical research is needed to clarify.

References

[1] Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98(10):946-952.

[2] Antikainen RL, Peters R, Beckett NS, et al. Atrial fibrillation and the risk of cardiovascular disease and mortality in the Hypertension in the Very Elderly Trial. J Hypertens 2020; 38(5):839-844.

[3] Andrade J, Khairy P, Dobrev D, et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res 2014; 114(9):1453-1468.

[4] Staerk L, Sherer JA, Ko D, et al. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circ Res 2017; 120(9):1501-1517.

[5] Kamel H, Okin PM, Elkind MS, et al. Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. Stroke 2016; 47(3):895-900.

[6] Vinding NE, Kristensen SL, Rorth R, et al. Ischemic Stroke Severity and Mortality in Patients With and Without Atrial Fibrillation. J Am Heart Assoc 2022; 11(4): e022638.

[7] Gomez-Outes A, Suarez-Gea ML, Garcia-Pinilla JM. Causes of death in atrial fibrillation: Challenges and opportunities. Trends Cardiovasc Med 2017; 27(7):494-503.

[8] Sairenchi T, Yamagishi K, Iso H, et al. Atrial Fibrillation With and Without Cardiovascular Risk Factors and Stroke Mortality. J Atheroscler Thromb 2021; 28(3):241-248.

[9] Proietti M, Laroche C, Nieuwlaat R, et al. Increased burden of comorbidities and risk of cardiovascular death in atrial fibrillation patients in Europe over ten years: A comparison between EORP-AF pilot and EHS-AF registries. Eur J Intern Med 2018; 55:28-34.

[10] Xia Z, Dang W, Jiang Y, et al. Association Between Atrial Fibrillation and the Risk of Cardiovascular Mortality Among Elderly Adults With Ischemic Stroke in Northeast China: A Community-Based Prospective Study. Front Aging Neurosci 2022; 14:836425.

[11] Waldmann V, Jouven X, Narayanan K, et al. Association Between Atrial Fibrillation and Sudden Cardiac Death: Pathophysiological and Epidemiological Insights. Circ Res 2020; 127(2):301-309.

[12] Poli D, Antonucci E. Epidemiology, diagnosis, and management of atrial fibrillation in women. Int J Womens Health 2015; 7:605-614.

[13] Roquer J, Rodriguez-Campello A, Gomis M, et al. Comparison of the impact of atrial fibrillation on the risk of early death after stroke in women versus men. J Neurol 2006; 253(11):1484-1489.

[14] Emdin CA, Wong CX, Hsiao AJ, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ 2016; 532:h7013.

[15] Humphries KH, Kerr CR, Connolly SJ, et al. New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome. Circulation 2001; 103(19):2365-2370.

[16] Roden DM, Kannankeril P, Darbar D. On the relationship among QT interval, atrial fibrillation, and torsade de pointes. Europace 2007; 9 Suppl 4(Suppl 4):iv1-3.

[17] Albertsen IE, Rasmussen LH, Lane DA, et al. The impact of smoking on thromboembolism and mortality in patients with incident atrial fibrillation: insights from the Danish Diet, Cancer, and Health study. Chest 2014; 145(3):559-566.

[18] Kwon Y, Norby FL, Jensen PN, et al. Association of Smoking, Alcohol, and Obesity with Cardiovascular Death and Ischemic Stroke in Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS). PLoS One 2016; 11(1):e0147065.

[19] Lee SR, Choi EK, Jung JH, et al. Smoking Cessation after Diagnosis of New-Onset Atrial Fibrillation and the Risk of Stroke and

Death. J Clin Med 2021; 10(11).

[20] Chamberlain AM, Alonso A, Gersh BJ, et al. Multimorbidity and the risk of hospitalization and death in atrial fibrillation: A population-based study. Am Heart J 2017; 185:74-84.

[21] Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011; 123(14):1501-1508.

[22] Wong CX, Ganesan AN, Selvanayagam JB. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. Eur Heart J 2017; 38(17):1294-1302.

[23] Homan EA, Reyes MV, Hickey KT, et al. Clinical Overview of Obesity and Diabetes Mellitus as Risk Factors for Atrial Fibrillation and Sudden Cardiac Death. Front Physiol 2018; 9:1847.

[24] Dai H, Zhang Q, Much AA, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes 2021; 7(6):574-582.

[25] Wang L, Du X, Dong JZ, et al. Body mass index and all-cause mortality in patients with atrial fibrillation: insights from the China atrial fibrillation registry study. Clin Res Cardiol 2019; 108(12):1371-1380.

[26] Yang D, Ye S, Zhang K, et al. Association between obesity and short- and medium-term mortality in critically ill patients with atrial fibrillation: a retrospective cohort study. BMC Cardiovasc Disord 2023; 23(1):150.

[27] Zhou X, Dudley SC, Jr. Evidence for Inflammation as a Driver of Atrial Fibrillation. Front Cardiovasc Med 2020; 7:62.

[28] Aulin J, Hijazi Z, Siegbahn A, et al. Serial measurement of interleukin-6 and risk of mortality in anticoagulated patients with atrial fibrillation: Insights from ARISTOTLE and RE-LY trials. J Thromb Haemost 2020; 18(9):2287-2295.

[29] Hermida J, Lopez FL, Montes R, et al. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). Am J Cardiol 2012; 109(1):95-99.

[30] Sulzgruber P, Koller L, Winter MP, et al. The impact of CD4(+)CD28(null) T-lymphocytes on atrial fibrillation and mortality in patients with chronic heart failure. Thromb Haemost 2017; 117(2):349-356.

[31] Hu YF, Chen YJ, Lin YJ, et al. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015; 12(4):230-243.

[32] Lip GY, Patel JV, Hughes E, et al. High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis. Stroke 2007; 38(4):1229-1237.

[33] Aune D, Mahamat-Saleh Y, Kobeissi E, et al. Blood pressure, hypertension and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol 2023; 38(2):145-178.

[34] JanPing Wang, QiQiang Jie, Chang Pan. The effect of hypertension on short-term hospital mortality in patients with non valvular atrial fibrillation after anticoagulation therapy. Journal of Clinical Military Medicine2021; (12):1337-1339.

[35] Dan GA, Badila E, Weiss E, et al. Arterial hypertension in patients with atrial fibrillation in Europe: A report from the EURObservational Research Programme pilot survey on atrial fibrillation. Int J Cardiol 2018; 254:136-141.

[36] Bansal N, Xie D, Sha D, et al. Cardiovascular Events after New-Onset Atrial Fibrillation in Adults with CKD: Results from the Chronic Renal Insufficiency Cohort (CRIC) Study. J Am Soc Nephrol 2018; 29(12):2859-2869.

[37] Ru Wang, JunLu Zhang, AiJun Xing,et al. The effect of chronic renal dysfunction on cardiovascular and cerebrovascular death in patients with atrial fibrillation. Chinese Journal of Cardiac Pacing and Electrophysiology 2016; (03):242-245.

[38] Liampas E, Kartas A, Samaras A, et al. Renal function and mortality in patients with atrial fibrillation. J Cardiovasc Med (Hagerstown) 2022; 23(7):430-438.

[39] Chen SC, Su HM, Hung CC, et al. Echocardiographic parameters are independently associated with rate of renal function decline and progression to dialysis in patients with chronic kidney disease. Clin J Am Soc Nephrol 2011; 6(12):2750-2758.

[40] Burstein B, Qi XY, Yeh YH, C et al. Atrial cardiomyocyte tachycardia alters cardiac fibroblast function: a novel consideration in atrial remodeling. Cardiovasc Res 2007; 76(3):442-452.

[41] Polovina M, Lund LH, Dikic D, et al. Type 2 diabetes increases the long-term risk of heart failure and mortality in patients with atrial fibrillation. Eur J Heart Fail 2020; 22(1):113-125.

[42] Karayiannides S, Lundman P, Friberg L, et al. High overall cardiovascular risk and mortality in patients with atrial fibrillation and diabetes: A nationwide report. Diab Vasc Dis Res 2018; 15(1):31-38.

[43] Xu J, Sun Y, Gong D, et al. Impact of preexisting diabetes mellitus on cardiovascular and all-cause mortality in patients with atrial fibrillation: A meta-analysis. Front Endocrinol (Lausanne) 2022; 13:921159.

[44] Goudis CA, Korantzopoulos P, Ntalas IV, et al. Diabetes mellitus and atrial fibrillation: Pathophysiological mechanisms and potential upstream therapies. Int J Cardiol 2015; 184:617-622.

[45] Marijon E, Le Heuzey JY, Connolly S, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation 2013; 128(20):2192-2201.

[46] Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003; 107(23):2920-2925.

[47] Healey JS, Oldgren J, Ezekowitz M, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet 2016; 388(10050):1161-1169.

[48] Packer M. Neurohormonal Antagonists Are Preferred to an Implantable Cardioverter-Defibrillator in Preventing Sudden Death in Heart Failure. JACC Heart Fail 2019; 7(10):902-906.

[49] Triposkiadis F, Giamouzis G, Parissis J, Set al. Reframing the association and significance of co-morbidities in heart failure. Eur J Heart Fail 2016; 18(7):744-758.

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Revolutionizing Health Management: An Insight into the Impact of AI and Big Data

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Abstract: This article explores the opportunities and challenges of artificial intelligence (AI) and big data for health management. It argues that AI and big data can revolutionize health management by enabling personalized, preventive, and predictive medicine; enhancing health research and innovation; and transforming health systems and policies. However, it also acknowledges that AI and big data pose ethical, legal, social, and technical challenges and risks that need to be addressed and mitigated. It proposes that ethical and governance frameworks for AI and big data for health should be based on human values and principles. The article provides an overview of the main aspects of health management that can be revolutionized by AI and big data, as well as some recommendations or suggestions for future research or practice in this field.

Keywords: Artificial Intelligence; Big Data; Health Management; Personalized Medicine

Introduction

Health management is a broad and interdisciplinary field that encompasses the planning, organization, coordination, and evaluation of health services and resources at different levels and settings, such as individual, community, national, and global[1]. The main goal of health management is to improve the health outcomes and well-being of individuals and populations by ensuring the availability, accessibility, quality, and efficiency of health services and resources[2]. Health management also involves addressing the social, economic, environmental, and political determinants of health that affect the health needs, demands, and expectations of different individuals and groups[3].

In the 21st century, health management faces many complex and dynamic challenges that require innovative and effective solutions. Some of these challenges are:The increasing demand for health services and resources due to the growing and aging population, the changing burden of diseases, the rising prevalence of chronic and non-communicable diseases, and the emergence and re-emergence of infectious diseases[4]. The rising costs of health services and resources due to the advancement of medical technologies, the expansion of health coverage, the inflation of health expenditures, and the inefficiency and wastage of health resources[5]. The aging population that poses a higher risk of developing multiple chronic conditions, requiring more long-term care and support, and consuming more health resources[6]. The changing lifestyles that influence the health behaviors and choices of individuals and groups, such as physical activity, nutrition, smoking, alcohol consumption, etc., which can have positive or negative impacts on their health status and outcomes[7]. The emerging diseases that pose new threats to public health and security, such as COVID-19, Ebola, Zika, etc., which can cause outbreaks, epidemics, or pandemics that can overwhelm the health systems and disrupt the social and economic activities[8]. The health inequities that exist within and between countries and regions, as well as among different individuals and groups based on their gender, age, ethnicity, income, education, location, etc., which can result in unequal access to health services and resources, as well as unequal health status and outcomes[9].

To address these challenges, health management needs to leverage the potential of new technologies that can enhance the delivery and utilization of health services and resources. Among these technologies are artificial intelligence (AI) and big data.

AI is a branch of computer science that aims to create machines or systems that can perform tasks or reasoning processes that normally require human intelligence. AI can be classified into two types: narrow AI or weak AI, which is designed to perform specific tasks or functions; and general AI or strong AI, which is capable of performing any tasks or functions that humans can do[10]. AI can also be categorized into three levels: artificial narrow intelligence (ANI), which is focused on one domain or area; artificial general intelligence (AGI), which is equivalent to human intelligence across domains or areas; and artificial superintelligence (ASI), which surpasses human intelligence across domains or areas.

Big data is a term that refers to large, complex, and high velocity datasets that are generated from various sources and formats. Big data can be characterized by four dimensions: volume (the amount of data), variety (the types of data), velocity (the speed of data generation and processing), and veracity (the quality and reliability of data)[11]. Big data can also be analyzed using different methods: descriptive analytics (what happened), diagnostic analytics (why it happened), predictive analytics (what will happen), prescriptive analytics (what should happen), or cognitive analytics (how to make it happen).

AI and big data are closely related technologies that complement each other. AI requires a large amount of data to learn from and improve its performance. Big data analytics leverages AI techniques to process complex data more efficiently and effectively[12]. Together, AI and big data can provide powerful tools for health management.

The aim of this article is that AI and big data can revolutionize health management by enabling personalized, preventive, and predictive medicine; enhancing health research and innovation; and transforming health systems and policies. The article will discuss how AI and big data can impact each of these aspects of health management, as well as the benefits and limitations of their applications. The article will also provide some recommendations for future research or practice in this field.

Applications and Impacts of AI and Big Data in Health Care Delivery

One of the main aspects of health management that can be revolutionized by AI and big data is health care delivery, which refers to the provision of health services and resources to individuals and groups who need them[13]. Health care delivery involves various processes and functions, such as diagnosis, treatment, prevention, monitoring, evaluation, and education. The quality and efficiency of health care delivery depend on various factors, such as the availability and accessibility of health services and resources, the competence and communication of health care professionals, the satisfaction and engagement of patients, and the coordination and integration of health care systems[14].

AI and big data can improve the quality and efficiency of health care delivery by enabling personalized, preventive, and predictive medicine. These are three types of medicine that aim to provide more customized, proactive, and anticipatory health care services and interventions for patients based on their individual characteristics and needs.

Personalized medicine refers to the tailoring of medical treatments and interventions to the individual characteristics and needs of each patient. Personalized medicine takes into account various factors that influence the health status and outcomes of patients, such as their genetic makeup, medical history, lifestyle, environment, preferences, values, etc. Personalized medicine can improve the effectiveness and safety of treatments and interventions by reducing adverse effects,increasing compliance, and enhancing outcomes[15].

Preventive medicine refers to the actions taken to prevent diseases or reduce their severity and complications[16]. Preventive medicine can be classified into three levels: primary prevention (avoiding the occurrence of diseases), secondary prevention (detecting and treating diseases at an early stage), and tertiary prevention (reducing the disability and mortality caused by diseases). Preventive medicine can improve the health status and well-being of individuals and populations by reducing the burden of diseases, lowering the costs of health care, and increasing the quality of life. Predictive medicine refers to the use of data and models to forecast the likelihood and outcomes of diseases and conditions. Predictive medicine can help identify individuals or groups who are at high risk of developing or worsening certain diseases or conditions,as well as provide recommendations for interventions or actions that can prevent or mitigate them. Predictive medicine can improve the health status and outcomes of individuals and groups by enabling early detection, diagnosis, prognosis, and treatment of diseases and conditions[17].

AI and big data can help diagnose, treat, and monitor diseases, as well as identify risk factors and recommend interventions for personalized, preventive, and predictive medicine. For example, AI and big data can help analyze medical images, such as X-rays, CT scans,and MRI scans, to detect abnormalities and signs of diseases, such as cancer, fractures, or infections.

AI and big data can also help interpret natural language, such as speech and text, to understand the symptoms and complaints of patients, as well as the notes and reports of health care professionals. AI and big data can also help provide clinical decision support systems, which are tools that assist health care professionals in making evidence-based decisions for diagnosis and treatment.

AI and big data can also help monitor the health status and behavior of patients using wearable devices, such as smart watches, sensors,

or implants, which can collect and transmit data on vital signs, physical activity, medication adherence,etc.

Some examples of AI and big data applications in health care delivery are:IBM Watson Health: a cognitive computing system that uses natural language processing and machine learning to analyze large volumes of structured and unstructured health data, such as medical records, clinical trials, research papers, etc., to provide insights and recommendations for diagnosis and treatment. Google DeepMind Health: a deep learning system that uses neural networks to process complex data, such as medical images, genomic data, electronic health records, etc., to improve disease detection, diagnosis, prognosis, and treatment. Babylon Health: a digital health service that uses natural language processing and machine learning to provide online consultations with doctors and nurses,as well as symptom checkers and health assessments. AliveCor: a mobile device that uses electrocardiogram (ECG) sensors to measure the electrical activity of the heart and detect irregular heart rhythms, such as atrial fibrillation. Medtronic: a medical device company that uses sensors and algorithms to monitor glucose levels in diabetic patients and adjust insulin delivery accordingly[18-20].

These applications show how AI and big data can enhance health care delivery by providing more accurate, timely, convenient, and personalized services for patients and health care professionals.

However, AI and big data also pose ethical, legal, social, and technical challenges and risks that need to be addressed and mitigated. These challenges and risks include: The protection of privacy and confidentiality of health data: AI and big data rely on large amounts of personal and sensitive health data that may be collected, stored, shared, or used without proper consent or authorization from patients or providers. This may expose patients or providers to potential breaches or misuse of their data by unauthorized parties or malicious actors. The assurance of quality and safety of AI systems: AI systems may have errors or limitations in their design, development, deployment, or use that may compromise their accuracy, reliability, validity, or performance. This may lead to incorrect or harmful decisions or actions for patients or providers. The prevention of bias and discrimination in AI systems: AI systems may reflect or amplify existing biases or inequalities in health data or algorithms that may affect their outcomes or impacts for different individuals or groups based on their gender, age, ethnicity, income, education, location, etc. This may lead to unfair or unjust treatment or outcomes for patients or providers. The accountability and responsibility for AI systems: AI systems may have complex or opaque processes or mechanisms that may challenge the attribution or explanation of their decisions or actions for patients or providers. This may raise questions about who is liable or accountable for the consequences or harms caused by AI systems. The regulation and governance of AI systems: AI systems may operate across different jurisdictions or domains that may have different laws or standards for their development, deployment, or use. This may create conflicts or gaps in the regulation or governance of AI systems.

These challenges and risks require ethical and legal frameworks for AI and big data for health that are based on human values and principles. These frameworks should involve the collaboration and consultation of all relevant stakeholders. These frameworks should also be adaptable and responsive to the changing needs and contexts of health care delivery in the 21st century.

Applications and Impacts of AI and Big Data in Health Research and Innovation

Another aspect of health management that can be revolutionized by AI and big data is health research and innovation, which refers to the generation and application of new knowledge and solutions for health problems. Health research and innovation are essential for advancing the scientific understanding and developing new treatments and interventions for diseases and conditions that affect the health and well-being of individuals and populations[21]. Health research and innovation also involve various processes and functions, such as data collection, analysis, sharing, dissemination, translation, and evaluation.

AI and big data can enhance health research and innovation by facilitating data collection, analysis, and sharing. Health research and innovation require a large amount of data from various sources and formats, such as clinical data, genomic data, environmental data, behavioral data, etc. However, health research and innovation face many challenges and barriers in accessing and utilizing these data, such as the complexity and diversity of data types and structures, the ethical and legal issues of data privacy and consent,the lack of interoperability and standardization of data formats and platforms, and the scarcity of resources and expertise for data management and analysis.

AI and big data can help overcome these challenges and barriers by providing more powerful, efficient, and scalable methods for data

collection, analysis, and sharing.

For example, AI and big data can help automate and streamline the data collection process by using sensors, mobile devices,or online platforms to capture and transmit data from different sources and locations.

AI and big data can also help process and analyze large volumes of complex and heterogeneous data by using machine learning, deep learning,or natural language processing to extract and synthesize information, knowledge,or insights. AI and big data can also help share and disseminate the data and findings by using cloud computing, blockchain, or open access platforms to store and distribute data or publications.

AI and big data can also help generate new insights, discoveries, and solutions for health problems, as well as accelerate the development and testing of new drugs and devices. For example, AI and big data can help analyze genomic data, which is the information encoded in the DNA of living organisms, to understand the genetic basis of diseases, identify biomarkers, and design personalized therapies. AI and big data can also help discover new drugs and devices by screening large libraries of compounds or materials, predicting their properties and interactions, and optimizing their synthesis and formulation. AI and big data can also help conduct clinical trials, which are experiments that test the safety and efficacy of new drugs and devices on human subjects, by recruiting participants, monitoring their outcomes, and analyzing their data.

Some examples of AI and big data applications in health research and innovation are:

Deep Genomics: a biotechnology company that uses deep learning to analyze genomic data and discover new therapies for genetic diseases. Benevolent AI: a pharmaceutical company that uses machine learning to discover new drugs for various diseases, such as Parkinson's disease, Alzheimer's disease, and COVID-19. Verily: a life sciences company that uses machine learning to develop new devices for health monitoring, diagnosis,and treatment,such as smart contact lenses, glucose-sensing implants, and surgical robots. Antidote: a digital health company that uses natural language processing to match patients with clinical trials based on their eligibility criteria. WHO: a global health organization that uses AI and big data to support its health research and innovation activities,such as conducting systematic reviews, developing clinical guidelines,monitoring global health trends,responding to public health emergencies,etc[22-23].

These applications show how AI and big data can enhance health research and innovation by providing more powerful,efficient,and scalable methods for data-driven discovery and development. However, AI and big data also pose ethical,legal, social, and technical challenges and risks that need to be addressed and mitigated. These challenges and risks include: The protection of intellectual property rights of health data or innovations: AI and big data may create or use health data or innovations that may be subject to intellectual property rights or claims by different parties or entities. This may create conflicts or disputes over the ownership or use of these data or innovations. The assurance of quality and validity of health research or innovations: AI and big data may produce or use health research or innovations that may have errors or limitations in their design, development, deployment, or use. This may compromise their quality or validity for scientific or clinical purposes. The prevention of bias and discrimination in health research or innovations: AI and big data may reflect or amplify existing biases or inequalities in health research or innovations that may affect their outcomes or impacts for different individuals or groups based on their gender, age, ethnicity, income, education, location, etc. This may lead to unfair or unjust research or innovations for different individuals or groups. The accountability and responsibility for health research or innovations: AI and big data may have complex or opaque processes or mechanisms that may challenge the attribution or explanation of their research or innovations for different stakeholders. This may raise questions about who is liable or accountable for the consequences or harms caused by these research or innovations.

These challenges and risks require ethical and legal frameworks for AI and big data for health research and innovation that are based on human values and principles. These frameworks should involve the collaboration and consultation of all relevant stakeholders. These frameworks should also be adaptable and responsive to the changing needs and contexts of health research and innovation in the 21st century.

Applications and Impacts of AI and Big Data in Health Systems and Policies

A third aspect of health management that can be revolutionized by AI and big data is health systems and policies, which refer to the structures and processes that govern the organization, financing, and delivery of health services and resources to achieve health goals and

objectives. Health systems and policies involve various actors and stakeholders, such as governments, health care providers, researchers, technology companies, civil society organizations, and patients and communities. Health systems and policies also involve various functions and dimensions, such as governance, regulation, financing, planning, monitoring, evaluation, and accountability[24].

AI and big data can transform health systems and policies by enabling data-driven decision making and resource allocation. Health systems and policies require a large amount of information and evidence to support the formulation, implementation, and evaluation of health strategies and interventions. However, health systems and policies face many challenges and barriers in accessing and utilizing this information and evidence, such as the lack of timely, accurate, relevant, and actionable data; the difficulty of integrating and synthesizing data from different sources and levels; the complexity of measuring and comparing health outcomes and impacts;and the resistance of changing existing practices and behaviors.

AI and big data can help overcome these challenges and barriers by providing real-time information, feedback, and recommendations. For example,AI and big data can help monitor and evaluate the health status and outcomes of populations and subgroups, as well as the performance and impact of health programs and interventions. AI and big data can also help detect and respond to public health threats, such as infectious diseases,epidemics,or bioterrorism. AI and big data can also help manage and allocate health resources and services,such as human resources, financial resources, medical supplies, or health facilities.

Some examples of AI and big data applications in health systems and policies are: BlueDot: a public health company that uses machine learning and natural language processing to analyze global data sources, such as news reports, social media, flight records,etc.,to track and predict the spread of infectious diseases. Health Catalyst: a data analytics company that uses machine learning to provide data-driven insights and solutions for health system improvement,such as reducing costs,improving quality,enhancing patient safety,etc. . Wadhwani AI: a non-profit research institute that uses machine learning to develop AI solutions for social good,such as improving maternal and child health,reducing tuberculosis burden,enhancing crop yields,etc. . PATH: a global health organization that uses digital technologies,such as sensors, mobile devices,cloud computing,etc.,to improve health system strengthening, such as improving supply chain management,enhancing data quality and use, increasing access to essential medicines, etc. WHO: a global health organization that uses AI and big data to support its health system and policy activities, such as developing ethical and governance frameworks for AI for health[1], providing technical guidance and assistance for digital health[1],monitoring global health trends and indicators, responding to public health emergencies,etc[25-26]. These applications show how AI and big data can transform health systems and policies by providing more timely,accurate,relevant,and actionable information for decision making and resource allocation.

However, AI and big data also pose ethical,legal,social,and technical challenges and risks that need to be addressed and mitigated. These challenges and risks include: The protection of human rights and dignity of patients and communities: AI and big data may affect the autonomy, privacy, consent, or participation of patients or communities in their health care or research. This may undermine their rights or interests in their health or well-being. The respect for professional values and norms of health care providers and researchers: AI and big data may challenge the roles, responsibilities, or competencies of health care providers or researchers in their practice or conduct. This may affect their values or norms, such as trust, empathy, or integrity. The prevention of harm or abuse of AI systems: AI systems may have vulnerabilities or weaknesses that may expose them to potential harm or abuse by unauthorized parties or malicious actors. This may compromise their security, reliability, or performance. The promotion of equity and justice in health systems and policies: AI systems may create or exacerbate existing disparities or inequalities in health systems or policies that may affect the access, quality, or outcomes of health services or resources for different individuals or groups. This may lead to unfair or unjust distribution of benefits or burdens of AI systems. These challenges and risks require ethical and legal frameworks for AI and big data for health systems and policies that are based on human values and principles. These frameworks should involve the collaboration and consultation of all relevant stakeholders. These frameworks should also be adaptable and responsive to the changing needs and contexts of health systems and policies in the 21st century.

Conclusion

AI and big data are powerful technologies that can revolutionize health management by enabling personalized, preventive, and predic-

tive medicine; enhancing health research and innovation; and transforming health systems and policies. These technologies can provide more accurate, timely, convenient, and personalized health services and interventions for patients and health care professionals; generate more powerful, efficient, and scalable methods for data-driven discovery and development of new solutions for health problems; and provide more timely, accurate, relevant, and actionable information for decision making and resource allocation for health systems and policies. AI and big data can improve the health outcomes and well-being of millions of people around the world.

However, AI and big data also pose ethical, legal, social, and technical challenges and risks that need to be addressed and mitigated. These challenges and risks include the protection of human rights and dignity, the respect for privacy and consent, the prevention of bias and discrimination, the assurance of safety and quality, the accountability and responsibility, the regulation and governance, and the promotion of equity and justice. These challenges and risks are transnational in nature, as capturing, sharing, and using data generated or used by these technologies goes beyond national boundaries. Moreover, these challenges and risks are dynamic in nature, as these technologies are constantly evolving and changing.

Therefore, it is essential to develop and implement ethical and governance frameworks for AI and big data for health that are based on human values and principles. These frameworks should involve the collaboration and consultation of all relevant stakeholders. These frameworks should also be adaptable and responsive to the changing needs and contexts of health management in the 21st century.

Some of the main points that have been discussed in this article are:AI and big data can improve the quality and efficiency of health care delivery by enabling personalized, preventive, and predictive medicine. These are three types of medicine that aim to provide more customized, proactive, and anticipatory health care services and interventions for patients based on their individual characteristics and needs. AI and big data can enhance health research and innovation by facilitating data collection, analysis, and sharing. These are essential processes for generating and applying new knowledge and solutions for health problems. AI and big data can also help generate new insights, discoveries, and solutions for health problems, as well as accelerate the development and testing of new drugs and devices. AI and big data can transform health systems and policies by enabling data-driven decision making and resource allocation. These are crucial functions for supporting the formulation, implementation, and evaluation of health strategies and interventions. AI and big data can also help monitor and evaluate the health status and outcomes of populations and subgroups, as well as the performance and impact of health programs and interventions. AI and big data also pose ethical, legal, social, and technical challenges and risks that need to be addressed and mitigated. These challenges and risks include the protection of human rights and dignity, the respect for privacy and consent, the prevention of bias and discrimination, the assurance of safety and quality, the accountability and responsibility, the regulation and governance, and the promotion of equity and justice.

Some of the recommendations or suggestions that have been provided in this article are:Conduct more empirical studies and evaluations on the impact and outcomes of AI and big data applications in health management, especially in low- and middle-income countries or marginalized populations. Develop more inclusive or representative data sets or algorithms that reflect the diversity or complexity of health needs, preferences, or values of different individuals or groups. Establish more standards or guidelines for the development, deployment, or use of AI or big data for health that ensure ethical compliance, quality assurance, data security, or user feedback. Foster more education or awareness on the benefits or risks of AI or big data for health among health care professionals, researchers, policy makers, technology developers, or the general public. Create more platforms or mechanisms for dialogue or collaboration among different stakeholders to share best practices, address challenges, or promote innovation in AI or big data for health.

AI or big data have the potential to improve the health outcomes or well-being of millions of people around the world. However, this potential can only be realized if ethics or human rights are put at the heart of their design, deployment, or use. By following these recommendations or suggestions, we can ensure that AI or big data work for the public interest in all countries.

References

[1] Swarthout, M., & Bishop, M. A. (2017). Population health management: Review of concepts and definitions. American Journal of Health-System Pharmacy, 74(19), 1493–1498.

[2] Penman-Aguilar, A., Talih, M., Huang, D., Moonesinghe, R., Bouye, K., & Beckles, G. (2016). Measurement of health disparities,

health inequities, and social determinants of health to support the advancement of health equity. Journal of Public Health Management and Practice, 22(Suppl 1), S33-S42.

[3] Braveman, P., & Gottlieb, L. (2014). The social determinants of health: it's time to consider the causes of the causes. Public Health Reports, 129(Suppl 2), 19-31.

[4] Figueroa, C. A., Harrison, R., Chauhan, A., & Meyer, L. (2019). Priorities and challenges for health leadership and workforce management globally: a rapid review. BMC Health Services Research, 19(1), 239.

[5] Dangal, G. (2021). Essentials of health care management: challenges and way forward. Journal of Nepal Health Research Council, 19(1), I-III.

[6] Krumholz, H.M., & Dharmarajan, K. (2021). Management opportunities and challenges after achieving universal health coverage: lessons from the US Veterans Health Administration. BMJ Quality & Safety, 30(8), 623-626.

[7] Alkhenizan, A., & Shaw, C. (2011). Impact of accreditation on the quality of healthcare services: a systematic review of the literature. Annals of Saudi Medicine, 31(4), 407-416.

[8] Bazzoli, G. J., Dynan, L., Burns, L. R., & Lindrooth, R. (2004). Is provider capitation working? Effects on physician-hospital integration and costs of care. Medical Care, 42(3), 297-305.

[9] Bloomfield, G. S., Vedanthan, R., Vasudevan, L., Kithei, A., Were, M., & Velazquez, E. J. (2014). Mobile health for non-communicable diseases in Sub-Saharan Africa: a systematic review of the literature and strategic framework for research. Globalization and Health, 10(1), 49.

[10] Russell, S. J., & Norvig, P. (2016). Artificial intelligence: a modern approach. Pearson Education Limited.

[11] Bostrom, N. (2014). Superintelligence: paths, dangers and strategies. Oxford University Press.

[12] Trtica Majnarić, L., Babič, F., O'Sullivan, S., & Holzinger, A. (2021). AI and big data in healthcare: towards a more comprehensive research framework for multimorbidity. Journal of Clinical Medicine, 10(4), 766.

[13] Donabedian, A. (2005). Evaluating the quality of medical care. The Milbank Quarterly, 83(4), 691-729.

[14] Ngiam, K. Y., Khor, I. W., & Holzinger, A. (2019). Big data and machine learning algorithms for health-care delivery. The Lancet Oncology, 20(5), e262-e273.

[15] Delpierre, C., & Lefèvre, T. (2023). Precision and personalized medicine: what their current definition says and silences about the model of health they promote. Implication for the development of personalized health. Frontiers in Sociology, 8, 1112159.

[16] Clarke, E. A. (1974). What is preventive medicine? Canadian Family Physician, 20(11), 65-68.

[17] Gómez-Restrepo, C., & Gómez-Restrepo, C. (2019). Predictive, personalized, preventive and participatory (4P) medicine in telemedicine and ehealth: a systematic review. Telemedicine and e-Health, 25(7), 555-564.

[18] Ahmed, M. N., Toor, A. S., O'Neil, K., & Friedland, D. (2017). Cognitive computing and the future of health care: the cognitive power of IBM Watson has the potential to transform global personalized medicine. IEEE Pulse, 8(3), 4-9.

[19] Powles, J., & Hodson, H. (2017). Google DeepMind and healthcare in an age of algorithms. Health and Technology, 7(4), 351-367.

[20] Bhatia, S., & Abhishek, K. (2019). Babylon Health: a digital health service that uses natural language processing and machine learning to provide online consultations with doctors and nurses, as well as symptom checkers and health assessments. Retrieved from https://www. babylonhealth. com/

[21] World Health Organization. (2021, May 26). Using big data to inform health care: opportunities, challenges and considerations.

[22] Stark, Z., Dolman, L., Manolio, T. A., Ozenberger, B., Hill, S. L., Caulfield, M. J., Levy, Y., Glazer, D., Wilson, J., Lawler, M., Boughtwood, T., Braithwaite, J., Goodhand, P., Birney, E., & North, K. N. (2019). Integrating genomics into healthcare: a global responsibility. The American Journal of Human Genetics, 104(1), 13-20.

[23] Ahmed, M. N., Toor, A. S., O'Neil, K., & Friedland, D. (2017). Cognitive computing and the future of health care: the cognitive power of IBM Watson has the potential to transform global personalized medicine. IEEE Pulse, 8(3), 4-9.

[24] Cozzoli, N., Salvatore, F. P., Faccilongo, N., & Milone, M. (2022). How can big data analytics be used for healthcare organization management? Literary framework and future research from a systematic review. BMC Health Services Research, 22(1), 809.

[25] Coursera. (2023, May 17). AI in health care: Applications, benefits, and examples. https://www.coursera.org/articles/ai-in-healthcare

[26] Daley, S., & Velazquez, R. (2023, March 24). AI in healthcare & medical AI examples to know. Built In. https://builtin.com/artificial-intelligence/artificial-intelligence-healthcare

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Application of Modern Trace Examination Techniques In Forensic Science and Their Legal Aspects

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Abstract: In the process of case investigation, trace examination and forensic examination and identification can provide reliable evidence information, laying a good foundation for case detection. So in the process of case investigation through the application of modern trace inspection technology, at the same time the application of modern trace inspection technology to forensic science can effectively improve the efficiency and quality of case investigation. But the modern trace inspection technology applied to forensic science there are certain legal issues, the need for relevant personnel to take appropriate measures to deal with. In this paper, the application of modern trace inspection technology in forensic science and related legal issues are explained.

Keywords: Modern Trace Inspection Technology; Forensic Science; Application; Legal Issues

Introduction

Modern trace inspection technology is through the trace of the relevant theories and methods of verification of science applied to the case of various traces of physical evidence in the test, through the traces of the case as well as the case of human and material relations to be analyzed. So the trace examination technology for the apprehension of criminals, to protect social security has a very important significance. At the same time, forensic identification analysis is also an important part of the case analysis process, so the application of modern trace inspection technology in forensic science is of great significance, can provide more comprehensive and accurate information for the detection of cases. But the application of modern trace inspection technology in forensic science will involve certain legal issues. In this paper, we will analyze the role of forensic science in the application of modern trace inspection technology, and the existence of legal issues for research.

1. Modern trace inspection technology and forensic science links

Although forensic science and modern trace inspection technology belongs to different disciplines, but the two in the practice of research in the process of the way and method there is a certain connection. So forensic science and modern trace inspection technology can be essentially summarized as a trace of the discipline, but the object of the two studies are different. Forensic science will be external forces on the object produced by the physical evidence known as damage, and modern trace inspection technology will be external forces on the object produced by the physical evidence known as traces, can be seen that there is a relatively close link between the two. Usually, traces are suspects in the process of leaving clues, contains a lot of information, through the trace examination and forensic science can effectively analyze the suspect's criminal motives, criminal process, criminal tools and escape routes, for the detection of the case to provide powerful information to effectively enhance the efficiency and quality of the case detection.

2. The significance of modern trace inspection technology applied to forensic science

First of all, in the process of rapid development of science and technology, modern trace inspection technology has been rapid development, can better carry out the relevant trace inspection work. Its application to the case detection process can help public security organs to improve the efficiency and quality of case detection, to provide better conditions for combating crime, and effectively improve the quality of social security. Secondly, through the application of trace inspection technology can effectively innovate the program of case detection, so as to better protect the human rights of criminals. Third, due to the case investigation process, will be affected by a variety of factors that lead to the suspect's information can not be determined, through the application of trace inspection technology in forensic science can better de-

termine the suspect's relevant information, thus enhancing the reasonableness and accuracy of forensic science testing and analysis, improve the level of forensic science testing and analysis, and better promote the detection of cases. Finally, China's trace inspection technology and forensic science technology has been rapid development, but there are still technical incompleteness, by applying trace inspection technology to forensic science can effectively make up for the shortcomings of the two technologies, can better analyze the case information, to help the case handler for the detection of the case.

3. Forensic trace inspection technology classification

Usually, forensic science in trace examination technology can be divided into direct traces and related traces according to the actual needs of forensic science perspective, can provide direct evidence and indirect evidence for the detection of cases. One of the direct traces refers to the forensic science examination process through the visual observation of the body to grasp the shape of the tools left behind and related physical traces and damage. Through these direct traces can effectively determine the suspect used in the process of crime tools. Trace inspection is mainly used in the case of time, location and location of the body is not clear, through the relevant traces of the test can be on the time of the crime, the location of the crime and the location of the body and other relevant information to determine the case to provide relevant references to promote the development of the case for the case to create stronger conditions for the detection of the case.

4. The application of modern trace examination techniques in forensic science

4.1 Direct Trace Inspection

Forensic science through modern testing techniques for direct trace inspection is mainly fingerprint inspection and footprint inspection. One of the fingerprint test is also known as the handprint test, is one of the most commonly used trace inspection techniques. Because each person's fingerprints or palm prints are unique, through chemical or physical methods to extract the fingerprints and handprints left by the suspect information can effectively determine the number of suspects, so as to determine the number of crimes. At the same time, by comparing the collected fingerprint information and palm print information with the information in the fingerprint information database, the suspect can be locked with high accuracy. Footprint inspection technology is to extract and analyze the footprints left by the suspects, which can judge the physiological characteristics of the suspects. Although the footprint information does not have uniqueness, but through the footprint information can be on the suspect's gender, height and weight and other physiological information can be analyzed to effectively narrow the scope of the suspect, to create favorable conditions for the detection of the case. At the same time, the human foot has a more developed sweat gland system, forensic medicine can be extracted from the suspect's footprints to the suspect's sweat, so as to be able to obtain the suspect's biological information, and further lock the suspect, to help the detection of the case.

4.2 Relevant trace examination

Relevant trace examination refers to the way in the case of criminal suspects can not be examined through the body and the traces left behind. Relevant trace test mainly refers to the teeth test, tool trace test, vehicle trace test and disconnection trace test. First of all, dental impression refers to the traces left by human teeth when biting objects, dental impressions most often appear in food, but also may appear in the human body. Typically, a normal adult has 32 teeth, including 8 central incisors, 4 cuspids, 8 premolars and 12 molars. The teeth will also be arranged in an arch shape that is symmetrical between the upper and lower jaws. Each person's teeth shape, size, tooth direction, as well as the shape and size of the arch of the teeth have certain characteristics, so through the dental seal test can be the same identification of the person, to provide clues for the detection of the case. Secondly, tool marks. Tool traces refers to the criminal suspect in the process of the use of tools left behind by the traces, including traces of blowing, cutting traces and prying traces, etc., through the tool traces can be analyzed to effectively determine the suspect's modus operandi, the process of the crime and the tools, so as to provide a certain direction for the detection of the case. The third is the break away from the trace, break away from the trace is the crime process occurs in the break and separation of traces, common break away from the trace including fabric tearing traces and broken knife tip traces, etc., through the break away from

the trace of the examination and analysis can be further judged by the crime process. Through the relevant trace examination can effectively determine the crime time, location and tools, etc., to help the public security organs for case detection.

5. Modern trace examination techniques used in forensic science legal considerations

First of all, the Criminal Procedure Law clearly stipulates that in the process of women's physical examination needs to be carried out by female staff or physicians. So in the actual inspection process needs to be strictly in accordance with the provisions of the law to carry out, to avoid violations of human rights and illegal forensics in the inspection process. So the public security organs need to configure a certain number of female forensic doctors and trace examiners, so that better forensic examination in the modern trace examination techniques. Secondly, the "Criminal Procedure Law" clearly stipulates that the investigation and examination of the situation need to be written into a transcript, and by the investigation, examination and witnesses to sign or seal. So in the forensic examination in the application of modern trace examination techniques need to invite witnesses to witness. At the same time in the choice of witnesses need to pay attention to: (1) do not have the appropriate ability to identify or can not be expressed correctly as a witness; (2) and the case has an interest in the case, may affect the impartiality of the case can not be used as a witness; (3) for the investigation, inspection, search and seizure of staff can not be used as a witness. If in the objective circumstances can not find the conditions of the person as a witness, in accordance with the "People's Republic of China Criminal Procedure Law" in the relevant provisions of the transcript material, and retain the relevant activities for video. Finally, the need to do a good job of investigation and identification of separation. Forensic application of modern trace inspection technology process, personal examination records is one of the types of legal evidence, but the examination records and forensic identification results can not be taken between the equivalent relationship. So in the process of forensic examination need to do a good job of forensic examination process and forensic identification results of separation. Strictly in accordance with the "Criminal Procedure Law" and "Public Security Organs Handling Criminal Cases Procedural Provisions" of the relevant requirements, and effectively do a good job of investigation and identification of separation, to enhance the legitimacy of evidence collection.

Conclusion

In summary, the application of modern trace inspection technology in forensic science testing is of great significance. Through the modern trace inspection technology and forensic examination for effective combination of evidence can be better analyzed for the detection of cases to provide favorable evidence to enhance the efficiency and quality of the detection of cases. However, need to pay attention to trace inspection technology used in forensic science need to pay attention to the legal issues, in strict accordance with the relevant legal basis for forensic science testing to carry out the relevant test work, and effectively enhance the legal effect of the test results.

References

[1] Hou Q, Xu JB. The legal status of forensic medicine in personal examination and the matters that should be noted [C]. 2013:602-605.

[2] Zhai LP. On the use of trace science in forensic examination[J]. Guizhou police vocational college journal,2005,17(5):64-65.

[3] Tang L. Research on the utilization of trace-based science in forensic science examination[J]. Legal system and society, 2016(27): 267-268.

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The Follow-up Report of MRI After Transforaminal Endoscopic Surgery of Lumbar Disc Herniation with Spinal Stenosis

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Abstract: Objective: To observe the imaging changes of MRI in the responsible disc area after modified TESSYS foraminal scopy in patients with lumbar disc herniation (LDH), and to explore the postoperative repair time of the responsible disc area, so as to provide imaging reference for the rehabilitation plan of the patients. Materials: To investigate the VAS score and MRI imaging of patients with lumbar disc herniation and spinal stenosis after transforaminal endoscopic surgery, which to lay the foundation for the rehabilitation plan. Methods: Ten patients with lumbar disc herniation (L4/5, L5/S1) with spinal stenosis were collected and followed up by MRI and the VAS score on 1 week, 1 month, 4 months and 6 months after transforaminal endoscopic surgery. Results: The VAS score were significantly lower than those before operation ($P < 0.01$) on 1 week, 1 month, 4 months and 6 months after transforaminal endoscopic surgery. There was no statistical significance in the VAS score ($P > 0.05$) on 1 month and 6 months after operation. The high signal could be seen around the intervertebral foramen and nerve roots on the operation site on 1 week, 1 month and 4 months after operation Which disappeared at 6 months after operation. Conclusion: The symptoms of low back and leg pain in patients with lumbar disc herniation and spinal canal stenosis disappeared after 1 month, while the inflammatory reaction symptoms of intervertebral foramen and nerve root were disappeared on 6 months.

Keywords: Lumbar Disc Herniation; Spinal Stenosis; Transforaminal Endoscopic Surgery; MRI

Introduction

Lumbar disc herniation (LDH) is one of the main causes of lumbar and leg pain in modern people [1]. At present, due to the gradual trend of minimally invasive spinal surgery, foraminoscopy has become one of the mainstream minimally invasive surgical methods for LDH due to its remarkable efficacy and low trauma. At present, the most widely used TESSYS technology is created by Yeung et al [2] and Hoogland[3]. The improved TESSYS technology is formed on the basis of TESSYS technology by improving the puncture point, adjusting the puncture Angle, decompression range, etc. Its advantage is to reduce the incidence of postoperative complications while taking into account the stability of the spine [4]. At present, although there are various scoring scales to evaluate the recovery of patients, there is a lack of criteria for judging the postoperative recovery of the responsible disc area [5]. Therefore, this study conducted MRI examination of the responsible disc area after lumbar disc herniation through foraminoscopy to observe the changes in the signal of the responsible disc area, so as to provide imaging data for the postoperative repair time of the responsible disc area.

1. Material and Method

Thirty patients with lumbar disc herniation accompanied with spinal stenosis hospitalized in our department from January 2019 to January 2021 were selected as the study objects, including 16 males and 14 females, with the minimum age being 30, the maximum age being 45, and the average age being 35. All patients had L5/S1 disc herniation, VAS scores and MRI examinations were performed at 1 week, 1 month, 4 months and 6 months after surgery as required.

Inclusion criteria: Reference was made to the relevant diagnostic criteria of Practical Osteology [6] and Clinical Diagnosis and Treatment Guidelines. Branch of Orthopedics [7]:

① Typical clinical manifestations: low back pain with radiative leg pain (root pain), leg numbness, waist stiffness, limited movement, and occasional changes in urination and defecation function in severe cases;

② Physical examination: lumbar tenderness with radiating pain of lower limbs, positive for straight leg elevation test or Lasegue sign or straight leg elevation enhancement test Bragard sign, abnormal neurological function (sensory, muscular, reflex).

③ Related imaging examination: The diagnosis can be confirmed according to the anterolateral and lateral lumbar spine, hyperextension and flexion film, lumbar disc CT scan and lumbar MRI scan.

Exclusion criteria [8] : ① degenerative slip or instability; ② Congenital spinal stenosis; ③ Have a history of lumbar surgery, fracture, tumor, infection, diabetes and vasculitis; ④ Pregnant women and people with mental illness.

2. Surgical methods [9]

All patients were treated with German Maxmorespine foraminal lens equipment, and modified TESSYS technology was adopted in the surgical methods.

Postoperative treatment: bed rest, wake up with waist protection after 24h, no bending, 3-7 days without any abnormal discharge. Waist circumference protection for 4 weeks after discharge, heavy physical labor is prohibited for 6 months.

Follow-up: All patients underwent MRI examination at 1 week, 1 month, 4 months and 6 months after discharge.

3. Statistical methods

Data were analyzed by SPSS 18.0 statistical software, expressed as mean ± standard deviation ($\bar{X}\pm sd$), and one-way analysis of variance was used for inter-group comparison. $P < 0.05$ would have significant statistical significance, $P < 0.01$ would have extremely significant statistical significance.

4. Results

The average operation time was 70min, the average blood loss was 20 ml, and the average postoperative hospitalization was 5 days. Follow-up was 6 months.

The VAS scores of the 30 patients were shown in Table 1.The results showed that the VAS scores of 30 patients at 1 week, 1 month, 4 months and 6 months after surgery were all lower than those before surgery, with significant statistical significance ($P < 0.01$). The VAS score at 1 month, 4 months and 6 months after the operation was significantly improved compared with that at 1 week after the operation ($P < 0.05$), while the VAS score at 1 month, 4 months after the operation and that at 6 months after the operation was not statistically significant ($P > 0.05$). None of the 30 patients had dural sac tears during the operation. There were no serious complications such as intervertebral space infection and permanent nerve root injury.

Time	Number of patients	VAS score
Pre-operation	30	6.15±0.324
1 week after surgery	30	3.20±0.041 *
1 M after surgery	30	1.43±0.021 * Δ
4 M after surgery	30	1.41±0.031 * Δ
6 M after surgery	30	1.21±0.019 * Δ ★

Table 1

Compared with pre-operation, * $p < 0.01$, which had significant statistical significance; The $\Delta p < 0.05$ was statistically significant at 1 month, 6 months and 1 week after surgery. 6 months after surgery and 1 month after surgery, ★ $p > 0.05$, no statistical significance.

MRI findings of patients (Fig. 1-Fig. 4)

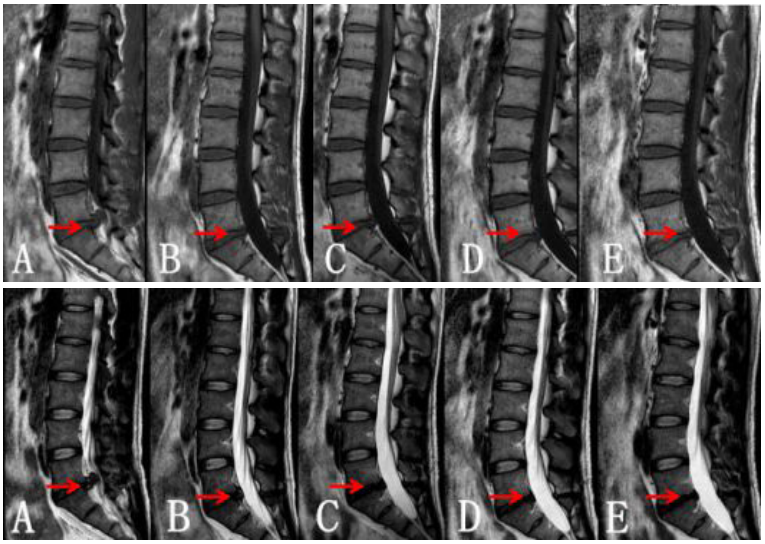

Fig. 1 MRI T1 image and Fig.2 MRI T2 imge (red arrow represents the operative area)

A: Before surgery; B: 1 week after surgery; C: 1 month after surgery; D: 4 months after surgery; E: 6 months after surgery;

A: Preoperative MRI showed that the L5/S1 intervertebral disc was prolapsed and free, and the spinal canal was obviously occupied.

B-E: From 1 week to 6 months after surgery, MRI showed that the protruded free disc with L5/S1 was removed surgically, the vertebral canal occupied disappeared, and no new disc herniation was observed.

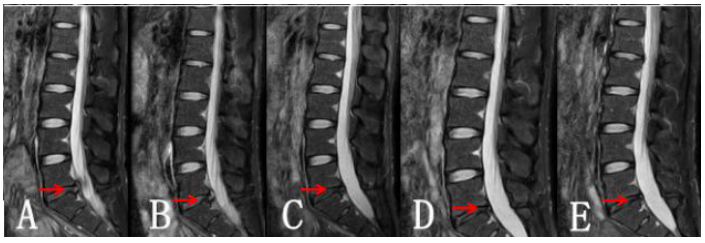

Figure 3 MRI SPAIR(red arrow indicates the operative area)

A: Before surgery; B: 1 week after surgery; C: 1 month after surgery; D: 4 months after surgery; E: 6 months after surgery;

A: Preoperative MRI showed that the L5 ~ S1 intervertebral disc was prolapsed and free, and the spinal canal was obviously occupied.

B-E: From 1 week to 6 months after surgery, MRI showed that L5-S1 prolapsed free discs were surgically removed,vertebral canal occupying disappeared, no new disc herniation, and the signal at the posterior margin of the intervertebral space was equal or low.

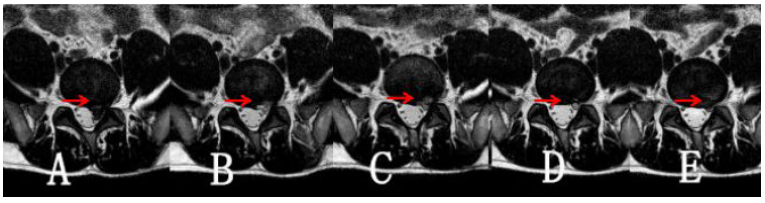

Fig. 4 MRI cross section (red arrow indicates the operative area)

A: Before surgery; B: 1 week after surgery; C: 1 month after surgery; D: 4 months after surgery; E: 6 months after surgery;

A: Preoperative MRI showed that the L5/S1 intervertebral disc was prolapsed and free, and the spinal canal was obviously occupied.

B-D: From 1 week to 4 months after surgery, high signals can still be seen in the operating area of the duty disc.

E: 6 months after surgery, the high signal in the operating area of the duty disc disappeared, presenting equal or low signal.

5. Discussion

LDH is a kind of fibrous annulus injury and rupture caused by lumbar intervertebral disc degeneration, inflammation and abnormal

stress in different degrees. As a result, the intervertebral disc, nucleus pulposus and cartilaginous endplate protrude in the spinal canal and come into contact with the blood environment, stimulating or oppressing adjacent spinal nerve roots [10] and provoking human immune response. Spinal lesions causing a range of symptoms such as back and leg pain.

In 2002, the TESSYS technology proposed by Professor Hoogland [11] in Germany expanded the surgical path from the Kambin safety triangle to the formed foramen. Zhu Kai et al. [12] summarized the steps as puncture, placement of working channels and endoscopic operation. Since then, many surgeons have improved surgical methods in terms of puncture point selection, puncture Angle, puncture needle location and other aspects based on the basic principles of TESSYS technology of predecessors. For example, Bai Yibing et al. [13,14] proposed "Broad Easy Immediate Surgery". This is to replace targeted disc removal with complete relief of nerve root compression. Among them, the modified TESSYS technology adopted in this study has significant advantages in terms of anesthesia risk, traction damage to nerve roots and dural sac, and postoperative scar tissue formation.

In order to study the repair of intraoperative wound, the VAS score and MRI findings of lumbar disc herniation were observed after foraminioscopy. The results showed that the VAS scores of all patients were lower before surgery, 1 week after surgery, 1 month after surgery, 4 months after surgery, and 6 months after surgery, with statistically significant comparison ($P < 0.01$). There was no statistical significance in VAS scores at 1 month, 4 months and 6 months after the operation ($P > 0.05$), indicating that the clinical symptoms of the patient were significantly relieved immediately after the operation, and basically disappeared 1 month after the operation. MRI sagittal T1, T2 and lipid-pressure sequences showed L5-S1 prolapse from 1 week to 6 months after surgery, free intervertebral disc disappeared, vertebral canal space disappeared, and no new intervertebral disc herniation. Transsectional MRI scan showed that T2 hypersignal was still visible in the operating area of the responsible disc from 1 week to 4 months after surgery, and the hypersignal disappeared in the operating area of the responsible disc 6 months after surgery, indicating that the inflammatory response around the foramen and nerve roots disappeared 6 months after surgery.

The study showed that the VAS score showed that the clinical symptoms of the patient tended to be stable 1 month after the operation, while MRI showed that the operative area signal of the patient was stable 6 months after the operation, and the patient avoided strenuous activities and carried out effective rehabilitation exercises within 6 months to prevent the recurrence of the disease.

However, there are some shortcomings in this study. First, there is a lack of long-term follow-up studies with large samples, which may lead to the bias of research results. Secondly, the follow-up time of this study is limited, and longer follow-up may be required to comprehensively and accurately evaluate the recovery time and intensity of patients with modified TESSYS after surgery. Finally, with the further development of spinal foraminoscopy, evidence-based medicine is also needed for the stability of postoperative spinal biomechanics.

References

[1] Tanaka M, Arataki S, Mehta R, et al. Transtubular Endoscopic Posterolateral Decompression for L5-S1 Lumbar Lateral Disc Herniation[J]. Journal of visualized experiments: JoVE. 2022.

[2] Yeung AT, Tsou PM. Posterolateral endoscopic excision for lumbar disc herniation: Surgical technique, outcome, and complications in 307 consecutive cases. Spine (Phila Pa 1976). 2002 Apr 1;27(7):722-31.

[3] Hoogland T, Schubert M, Miklitz B, Ramirez A. Transforaminal posterolateral endoscopic discectomy with or without the combination of a low-dose chymopapain: a prospective randomized study in 280 consecutive cases. Spine (Phila Pa 1976). 2006 Nov 15;31(24):E890-7.

[4] Yan H, Sun LM. Clinical study on improved TESSYS technology [J]. World Latest Medical Information Abstracts (Continuous Electronic Journal),2021,(11th issue): 48-49.(In Chinese)

[5] Ostelo RW, Costa LO, Maher CG, de Vet HC, van Tulder MW. Rehabilitation after lumbar disc surgery: an update Cochrane review. Spine (Phila Pa 1976). 2009 Aug 1;34(17):1839-48.

[6] Bredow J, Oppermann J, Scheyerer MJ, et al. Lumbar lordosis and sacral slope in lumbar spinal stenosis: standard values and measurement accuracy[J].Arch Orthop Trauma Surg, 2015,35(5):607-612

[7] Li ZF, Yan H. Clinical study of modified TESSYS technique in the treatment of lumbar spinal stenosis [J]. Massage and Rehabilitation Medicine, 2018,9(19):45-48. (In Chinese)

[8] Practical Osteology II [M]. Beijing: People's Military Medical Publishing House, 2012:2047-2050.(In Chinese)

[9] Chinese Association of Traditional Chinese Medicine. Clinical Diagnosis and Treatment Guide · Department of Orthopedics [M]. Beijing: People's Medical Publishing House.(In Chinese)

[10] Bredow J, Oppermann J, Scheyerer MJ, et al. Lumbar lordosis and sacral slope in lumbar spinal stenosis: standard values and measurement accuracy[J]. Arch Orthop Trauma Surg, 2015,35(5):607-612.

[11] Li ZF and Yan H. Clinical study of modified TESSYS technique for treatment of lumbar spinal stenosis [J]. Massage and Rehabilitation Medicine, 2018,9(19):45-48. (In Chinese)

[12] Li XJ, Tan D, Li SB. Percutaneous foraminal TESSYS technique for treatment of elderly lumbar disc herniation [J]. Chinese Journal of Bone and Joint Injury, 2019,35(7):724-726. (In Chinese)

[13] Hoogland T, Schubert M, Miklitz B, et al. Transforaminal postero-lateral endoscopic discectomy with or without the combination of a low-dose chymopapain:a prospective randomized study in 280 consecutive cases[J]. Spine,2006,31(24):E890-897.

[14] Zhu K, Tan J, Zhang YF. Progress of endoscopic decompression under percutaneous posterolateral foraminal approach in the treatment of lumbar spinal stenosis [J]. Chinese Journal of Spinal Cord, 2017, 27 (3): 268-271. (In Chinese)

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