Universe Scientific Publishing Pte. Ltd.
73 Upper Paya Lebar Road #07–02B–03 Centro Bianco Singapore 534818
Website: www.usp–pl.com
E–mail: contact@usp–pl.com

ISSN 2315-456X

2023 VOLUME 12 ISSUE 1

Advanced Emergency Medicine

Universe Scientific Publishing

1

2023 Volume 12 Issue 1
ISSN：2315–456X

Advanced Emergency Medicine

Universe Scientific Publishing

Editorial Board

Honorary Editor-in-Chief

Associate Editors

Editorial Board Members

Volume 12 Issue 1·2023
ISSN:2315-456X

Advanced Emergency Medicine

Universe
Scientific Publishing

Universe Scientific Publishing

2023 | Volume 12 | Issue 1

Advanced Emergency Medicine

http://aem.usp-pl.com/index.php/aem

Contents

Original Articles

Effectiveness of Ultrasound-Guided Minimally Invasive Spinotomy in the Treatment of Multiple Small Benign Breast Nodules

Zhu Wu, Zhuo Wang, Qingqing Ye, Rong Fan*
Jingzhou First People's Hospital, Jingzhou 434000, China.

Abstract: Objective: To observe the efficacy of different surgical protocols in the management of multiple benign breast nodules. Methods: Patients diagnosed with multiple benign breast nodules from 2021.4 to 2023.2 were divided into two groups, blank and study groups, each with 51 cases, and treated with conventional open and ultrasound-guided minimally invasive rotational surgery respectively. Results: The study group had better incision diameter and VAS score at 24h postoperatively than the blank group, with significant differences ($P < 0.05$). Regarding the postoperative complication rate index, the study group vs. the blank group was 3.92% vs. 21.57% ($P < 0.05$). Conclusion: Minimally invasive spinotomy under ultrasound guidance for the treatment of patients with multiple breast nodules is safe and effective and has the potential to be used universally.

Keywords: Small Benign Breast Nodules; Ultrasound Guidance; Minimally Invasive Rotational Surgery; Outcome Observation

Introduction

Nipple discharge and breast tenderness are common symptoms of multiple breast nodules, and tumours are a common causative factor for this disease. Although conventional surgery can remove the entire nodule, the operation is invasive and conceals a variety of factors that can increase the risk of post-operative complications and is not conducive to rapid recovery. Minimally invasive spinotomy effectively compensates for the shortcomings of the traditional procedure by applying a high-speed form of spinotomy to fully aspirate the diseased tissue of the lesion and extract the specimen intact, with the advantages of minimal trauma, minimal scarring and high precision [1]. In this paper, we compare the treatment of traditional open and minimally invasive spinotomy, and the medical records of 102 patients are extracted for the following analysis.

1. Data and methods

1.1 General information

The 102 patients included in this study were diagnosed according to preoperative imaging and postoperative histopathological examination, with clear indications for surgery, excluding those with pathological findings suggesting malignant nodules and those who withdrew midway. The selected patients were divided equally into two groups of 51 cases each, and the status of each group was as follows.

Blank group: age 19~51 (32.41±2.19) years, duration of disease 6~25 (15.24±2.09) months, nodule diameter size 0.5~2.3 (1.42±0.55) cm.

Study group: Age 18-54 (3.52±2.26) years, duration of disease 7-26 (15.58±2.22) months, nodule diameter 0.4-2.5 (1.55±0.61) cm.

The above information was comparable between the two groups of patients (P > 0.05). This subject was carried out after obtaining the approval of the ethics committee and the consent of the patients.

1.2 Methods

Traditional open surgery was used in the blank group. The lesion was located with colour ultrasound before surgery, and a 2~3 ㎝ incision was made above the diseased breast to remove the entire lesion according to the specific number of nodules to make the corresponding number of incisions. Traditional electrocoagulation was used to stop the bleeding, repair the subcutaneous tissue, close the incision with conventional sutures, and apply pressure bandages and antibiotics for 7 days after surgery.

The study group used minimally invasive spinotomy. The size, number and anatomical location of the nodules were clarified by ultrasound exploration before surgery and the surgical incision was marked. After local anaesthesia, an incision was made within 2 ㎝ of the nodule and an attempt was made to remove multiple tumours with one incision, and in exceptional cases through two incisions. The ultrasound instrument guides the stabbing of the rotary cutter up to the deep position of the nodule. The ultrasound image information is used with the rotary cutter system to effectively extract the breast nodule and perform the operations such as excision and rotary cut, clear away all the accumulated blood, stop the bleeding by means of local pressure, and disinfect the puncture site in strict accordance with the protocol. A sterile dressing was applied to treat the incision and the dressing was applied continuously for 5 to 7 d.

1.3 Observation indicators

(1) Surgery-related indicators: time spent on surgery, intraoperative blood loss, incision diameter, incision healing time, 24-h postoperative visual analogue (VAS) score.

(2) Post-operative complications.

1.4 Statistical processing

SPSS26.0 software processed the data, indicating surgery-related indicators, mean age, etc. The rate (%) indicated the complication rate, and X^2 was calculated. Test criteria: P < 0.05.

2. Results

2.1 Surgery-related indicators

The detection values of all surgery-related indexes in the patients of the study group were better than those of the blank group, and the data between the groups differed significantly and reached the level of significance (P < 0.05), Table 1.

Table 1 Comparison of surgery-related indicators between groups of patients $(\bar{x} \pm s)$

Group（n）	Surgery time（min）	Intraoperative blood loss（ml）	Incision diameter（mm）	Incision healing time（d）	VAS at 24h postoperatively（分）
Research Group（51）	18.79±1.59	5.31±1.07	2.58±0.44	2.84±1.09	2.59±0.46
Blank group（51）	33.06±5.17	12.11±1.59	27.14±6.04	4.69±1.34	4.22±1.01

2.2 Postoperative complications

The incidence of postoperative complications in the study group was lower than that in the blank group, and the difference was statistically significant ($P < 0.05$), as shown in Table 2.

Table 2 Comparison of postoperative complication rates between groups

Group（n）	Local haematoma	Infection	Skin pigmentation	Breast deformity	Total occurrence（%）
Research Group（51）	0	1	1	0	2（3.92）
Blank group（51）	3	4	2	2	11（21.57）

3. Discussion

Breast nodules are a common disease in the modern female population, most of them are benign, but a few are at risk of cancer. It is generally believed that there is a correlation between female endocrine disorders and the development of the disease, and that when the metabolism of progesterone and oestrogen is abnormally disturbed in the body, this can lead to breast hyperplasia. Breast nodules have become a physical and psychological disease that can have a huge impact on the patient's physical and mental state, inevitably reducing the quality of their daily life and work efficiency, and should therefore be treated symptomatically as soon as possible after diagnosis [2].

Currently, surgery is advocated for the treatment of multiple small breast nodules, but traditional open surgery, in which inspection, separation and excision are carried out under direct vision, rarely causes damage to other breast tissues, but the incision made under this procedure is long and the operations performed during surgery can cause greater damage to the patient. In this study, the time taken to perform the operation was less than one hour. In this study, the VAS scores for operative time, intraoperative blood loss, incision diameter, incision healing time and 24h postoperative were (18.79±1.59) min, (5.31±1.07) ml, (2.58±0.44) mm, (2.84±1.09) d and (2.59±0.46) respectively, while the values for the above indicators in the blank group were in the order of ((33.06±5.17) min, (12.11±1.59) ml, (27.14±6.04) mm, (4.69±1.34) d, (4.22±1.01) points, it is obvious that the patients in the study group had better treatment results. Minimally invasive spinotomy is a hollow-core biopsy tool that incorporates the principles of vacuum aspiration, electric cutting technology, the former allowing complete excision of the pathological tissue, and the latter removing the focal tissue with the assistance of a spinotomy knife and an internal jacket needle. In the specific cutting session, a vacuum suction pump extracts the pathological tissue in real time and transports it outside the body. Multiple lesions can be removed quickly, efficiently and safely using a single small incision under minimally invasive rotary incision [3]. Compared to traditional open surgery, the minimally invasive rotary incision is more discreet, has a smaller postoperative scar area, and has essentially no major impact on the appearance of the breast, gaining a high degree of certainty and acceptance among the patient population with breast nodules.

References

[1] Liao H, Fang ZH, Chen LLL. Clinical study of minimally invasive spinotomy technique for the treatment of multiple small breast nodules [J]. China Medical Innovation,2019,16(18):111-114.

[2] Tan BC. Clinical study of colour Doppler ultrasound to identify benign and malignant breast nodules[J]. Journal of Practical Medical Technology, 2021, 28(07): 879-881.

[3] Yang F, Yang QF. Effectiveness of ultrasound-guided minimally invasive spinotomy in the treatment of multiple

small benign breast nodules [J]. Journal of Contemporary Clinical Medicine, 2021, 34(02):32-33.

Author Bio:

First author.

Name: Wu zhut (1982.5.14-), Male, Han Nationality, Place of Origin: Xiangtan, Hunan, Master, Title: Attending Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main Research Interests: Comprehensive treatment of breast cancer, diagnosis and treatment of non-lactating mastitis, postoperative reconstruction of breast tumor.

Corresponding author.

Fan Rong (1980.1.10-), F, Han, Place of origin: Hubei. Jingzhou, Master, Title: Attending, Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care, Major research interests: chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension, ECMO life support, etc.

Second author.

Wang Zhuo (1968.10.10-), Male, Ethnicity: Han, Origin: Xiangyang City, Hubei Province, Highest Education: B.S., Title: Deputy Chief Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main Research Interests: Comprehensive diagnosis and treatment of breast diseases and breast tumors, post-operative breast reconstruction, minimally invasive treatment of breast diseases, etc.

Third author.

Ye Qingqing (1979.2.23-), Female, Ethnicity: Han, Place of origin: Nanning, Guangxi, Highest education: Master, Title: Deputy Chief Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main research interests: standard treatment of breast tumours, surgical management of breast cancer.

Research Progress of Abnormal Expression of LKB1/STK111 in Non-Small Cell Lung Cancer

Fengmei Cao[1], Jiayun Liu [1,2*]

1. School of Medical Technology, Shaanxi University of Chinese Medicine, Xianyang 712000, China.

2. Xijing Hospital, Forth Military Medical University, Xian 710032, China.

*** National Natural Science Foundation of China (81972026)**

Abstract: Non small cell lung cancer (NSCLC) is a kind of malignant tumor originated from bronchial mucosa, bronchial glands and alveolar epithelium. It has become the main cause of death of malignant tumors in our population. *STK11* is a common tumor suppressor gene, its encoded protein liver kinase B1 (LKB1) is an essential serine / threonine protein kinase. LKB1/*STK111* inhibits the occurrence and development of tumors through a variety of mechanisms and plays a key regulatory role in malignant tumors. The increased risk of cancer development is also associated with the absence of *STK11*. More and more studies have found that the abnormal expression of LKB1/*STK111* will affect the occurrence and development of lung cancer, especially in NSCLC. This paper reviews the tumor suppressive mechanism of LKB1/*STK111* in the occurrence and development of NSCLC, its relationship with NSCLC, and the prognosis and treatment.

Keywords: LKB1/*STK111*; Non Small Cell Lung Cancer; Tumor Suppressive Mechanism; Prognosis; Treatment

Introduction

Global epidemiological studies reveal that lung cancer is still the leading cause of cancer-related death worldwide. Lung cancer is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), while NSCLC can be further divided into three categories: lung adenocarcinoma, lung squamous cell carcinoma and large cell carcinoma, and lung adenocarcinoma accounts for about 50% of all lung cancer cases [1]. Lung cancer has become the primary factor threatening human life among malignant tumors. Faced with such a severe situation, Modern medicine should urgently improve the level of early diagnosis and treatment of lung cancer.

Liver kinase B1 (LKB1), also known as STK11(serine threonine protein kinase11), was sequenced from patients with Peutz-Jeghers syndrome. STK11 gene is considered to be an important tumor suppressor gene, and its mutation and deletion are involved in the occurrence and development of various malignant tumors. Some scholars have found that the top three mutation rates in non-small cell lung cancer are p53 mutation, K-ras mutation and STK11 somatic mutation. The mutation rate of STK11 has reached 15%-35% in non-small cell lung cancer. STK11 gene mutation or deletion promotes carcinogenesis mainly through the LKB1/AMPK/mTOR signaling pathway. With the deepening of research, people have a more thorough understanding of the relationship between LKB1/STK11 and tumors, but the relationship between LKB1/STK11 and the occurrence and development of non-small cell lung cancer needs to be further explored. This paper reviews the research progress of abnormal expression of LKB1/STK11 in non-small cell lung cancer in recent years.

1. LKB1/STK11 Summary

The protein LKB1 encoded by STK11 is an essential serine/threonine protein kinase and is considered as a tumor

suppressor. STK11 is inactivated in about 30% of lung cancer, and abnormal expression of STK11 is also found in other malignant tumors, such as gastric cancer, liver cancer, pancreatic cancer.In cancer cells with cancer-driving mutations (such as KRAS, EGFR or ALK), deletion or mutation of STK11 gene has been observed to accelerate the occurrence and progression of malignant tumors by inducing the metabolism of glucose, lipids, glutamine and serine [2]. In addition to regulating angiogenesis, lipogenesis and cardiac function, STK11 gene and liver kinase B1 are also involved in a variety of processes including cell polarity, cell cycle arrest,and metabolism. The inhibitory effect of LKB1/STK11 is mainly reflected in its ability to promote cancer cell apoptosis, inhibit cancer cell migration and tumor angiogenesis.

2. Relationship between abnormal expression of LKB1/STK11 and occurrence and development of non-small cell lung cancer

2.1 Abnormal expression of LKB1/STK11 is common in non-small cell lung cancer

STK11 is a major regulator of various processes, including metabolism, proliferation and immunity. About one-third of non-small cell lung cancers have STK11 mutations[3]. STK11 can be inactivated by somatic mutations, leading to susceptibility to sporadic cancers such as pancreatic and gastrointestinal cancers, especially lung cancer. Most non-small cell lung cancers are driven by gene defects such as EGFR, BRAF, ALK, and the abnormality of STK11 gene has also been shown to induce lung adenocarcinoma, which is the third most commonly mutated gene in NSCLC adenocarcinoma, accounting for about 30%[4]. In addition, the most common KRAS co-mutation partners found in non-small cell lung cancer are TP53 (40%), STK11 (32%), and CDKN2A (19.8%) [5]. In sporadic lung cancer, up to 80% of NSCLC cell lines have LOH loss at chromosome 19p, indicating a higher correlation between STK11 mutations and NSCLC. In recent years, some studies on LKB1/STK11 and non-small cell lung cancer confirmed that the expression of LKB1 protein decreased in the development process of lung adenocarcinoma. Results show that loss of LKB1 protein expression has been observed in severe dysplasia, suggesting that LKB1 inactivation occurs early in the development of this type of lung cancer. Obviously, these reports have revealed a fact that abnormal expression of LKB1/STK11 is closely related to the occurrence and development of non-small cell lung cancer.

2.2 LKB1/STK11 mutations promote the development of non-small cell lung cancer

In non-small cell lung cancer, lung cancer cells with STK11 mutation will show various abnormal forms, such as Golgi localization error and lamellar foot formation, and the ability to cooperate with MAP/MARK to maintain cell polarity after STK11 mutation is reduced [6]. It is speculated that STK11 deletion can promote the epithelial-mesenchymal transition (EMT), which is a complex phenomenon that forces differentiated cells to regain their stem-like properties. The generation of this phenomenon is closely related to the occurrence, development, migration and metastasis of malignant tumors. One study related to LKB1/STK11 used gene knockout technology to breed mice with STK11 gene deletion. It was found that the mice with LKB1 deletion had abnormal vascular development and significantly increased VEGF expression. This result indicated that LKB1 could down-regulate the expression level of VEGF, thus achieving the effect of inhibiting tumor occurrence and development. STK11 gene mutation has a negative impact on the tumor immune microenvironment. In particular, the accompanying activation of KRAS mutations may explain the reduced response to immunotherapy in STK11

mutant NSCLC. More and more studies have shown that downregulation of STK11 can affect the occurrence and development of non-small cell lung cancer, and is closely related to tumor size, lymph node metastasis and tumor differentiation, and lung cancer patients with low STK11 expression have worse prognosis and shorter overall survival compared with those with normal STK11 expression.

3. Progress and prospect of treatment of non-small cell lung cancer with abnormal expression of LKB1/STK11

In recent years, many studies have found that STK11 mutations have certain resistance to PD-L1 treatment [7]. So far, the methods available in non-small cell lung cancer, which are mainly represented by anti-PD-1 /PD-L1 inhibitors, have no prospect in the case of STK11 inactivation. In addition, STK11-negative tumors are highly aggressive and resistant to chemotherapy, targeted therapy and immune checkpoint inhibitors (ICIs) [8]. Studies have shown that the presence of STK11 mutation is significantly correlated with the shortening of OS, and the presence of STK11 mutation is significantly correlated with the increase of treatment failure. These latest data may explain the decreased response of STK11 mutant non-small cell lung cancer to immunotherapy [9]. In order to study the metabolism and immune microenvironment of lung adenoma, Best SA established a mouse model with LKB1/STK11 mutation and found that the increased glutamate abundance in the tumor microenvironment of STK11 mutant mice was correlated with the activation of CD8 T cells in response to anti-PD-1 [10]. Most clinical trials are currently looking at the safety and efficacy of glutaminase inhibitors (BeGIN trial, KEAPSAKE, NCT04471415), There are also several related clinical trials that are combining PD-L1 inhibitors with glutaminase inhibitors or mammalian target rapamycin inhibitors (BUNCH) [11], among which Devarakonda et al recently reported their Phase II study results, This study suggested that everolimus (a dual inhibitor of mTOR) could be a therapeutic agent for patients with solid malignancies carrying multiple mutations, including STK11 mutations [11]. In addition, the downstream signal transduction inhibitor benzoguanidine in combination with soapicotib, a potent mTOR inhibitor, also exhibited tumor inhibitory activity in human cell lines carrying KRAS/STK11 mutations and in mouse models of NSCLC [26]. Drugs targeting protein glycosylation, such as Tunimycin and the protein transport inhibitor Brefeldin A, as well as drugs targeting glycolytic and inducing metabolic stress, such as 2-deoxyglucose (2-DG), may induce synthetic lethality in cancers where LKB1 / AMPK activity is deficient. It is believed that the further exploration of LKB1/STK11 in the future will lead to a clearer relationship between LKB1/STK11 and non-small cell lung cancer, which will also provide new ideas and directions for the search for new therapeutic targets and cancer targeted therapeutic drugs.

References

[1] Agalioti T, Giannou A, Stathopoulos G. Pleural involvement in lung cancer[J]. Journal of thoracic disease, 2015, 7(6): 1021-30.

[2] Zhang Y, Meng Q, Sun Q, et al. LKB1 deficiency-induced metabolic reprogramming in tumorigenesis and non-neoplastic diseases[J]. Molecular metabolism, 2021, 44: 101131.

[3] Pons-Tostivint E, Lugat A, Fontenau J, et al. STK11/LKB1 Modulation of the Immune Response in Lung Cancer: From Biology to Therapeutic Impact[J]. Cells, 2021, 10(11).

[4] Adderley H, Blackhall F, Lindsay C. KRAS-mutant non-small cell lung cancer: Converging small molecules and immune checkpoint inhibition[J]. EBioMedicine, 2019, 41: 711-716.

[5] Lindsay C, Jamal-Hanjani M, Forster M, et al. KRAS: Reasons for optimism in lung cancer[J]. European journal of cancer (Oxford, England : 1990), 2018, 99: 20-27.

[6] Sumbly V, Landry I. Unraveling the Role of STK11/LKB1 in Non-small Cell Lung Cancer[J]. Cureus, 2022, 14(1):

e21078.

[7] Arbour K, Riely G. Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review[J]. JAMA, 2019, 322(8): 764-774.

[8] Ndembe G, Intini I, Perin E, et al. LKB1: Can We Target an Hidden Target? Focus on NSCLC[J]. Frontiers in oncology, 2022, 12: 889826.

[9] Rosellini P, Amintas S, Caumont C, et al. Clinical impact of STK11 mutation in advanced-stage non-small cell lung cancer[J]. European journal of cancer (Oxford, England : 1990), 2022, 172: 85-95.

[10] Best S, Gubser P, Sethumadhavan S, et al. Glutaminase inhibition impairs CD8 T cell activation in STK11-/Lkb1-deficient lung cancer[J]. Cell metabolism, 2022, 34(6): 874-887.e6.

[11] Devarakonda S, Pellini B, Verghese L, et al. TSC1, TSC2, NF1, NF2A phase II study of everolimus in patients with advanced solid malignancies with or mutations[J]. Journal of thoracic disease, 2021, 13(7): 4054-4062.

Progress in the Application of Gait Analysis in Orthopedics and Physical Rehabilitation

Juchuan Dong[1], Yiwen Yuan[2*], Shude Xian[2], Guitan Hu[2], Yongmei Li[3]

1. Department of Rehabilitation Medicine, The Second Affiliated Hospital of Kunming Medical University, Kunming 650000, China.

2. Department of orthopedics, The First People's Hospital of Yunnan Provience, Kunming 650000, China.

3. Department of Rehabilitation Medicine, The Second Affiliated Hospital of Kunming Medical University, Kunming 650000, China.

Abstract: Human walking function is the biggest characteristic that distinguishes other animals, and it needs the coordination of multiple parts of the body to complete the movement.Gait analysis is a new method to study walking function and state, and it is also a hot topic of medical researchers and medical workers in orthopedics, physical rehabilitation and other fields in recent years.After hundreds of years of development, the medical field has realized the accurate and objective measurement of gait, and developed a variety of gait analysis systems suitable for different needs, such as plantar pressure measurement system, unmarked gait analysis system, wearable sensor system, etc.In the context of the continuous progress of related hardware and software technology, the scope of application of gait analysis is also gradually expanding. This paper mainly combined with the research situation of gait analysis in orthopedics and physical rehabilitation in recent years, to review the new progress of related research.

Keywords: Gait Analysis; Orthopedics; Physical Rehabilitation; Application Progress

Introduction

Gait analysis is a hot research topic in the medical field in recent years. It belongs to the research direction of biomechanics. The research content covers human walking function and walking state, involving multidisciplinary knowledge of physiology, anatomy, mechanics, etc[1]. Gait analysis research has a long history, dating back to the early 17th century. At that time, some researchers proposed to apply the principles of geometry, mechanics and other disciplines to the study of the movement rules of the skeletal musculoskeletal system under human activities, laying the foundation for gait analysis research [2]. In the application of gait analysis, it is necessary to compare with the normal data to clarify the abnormal parameters of the intervention objects and the relevant change rules, so as to realize the precise and individualized analysis of the factors affecting gait, and provide strong support for clinical disease assessment, disease diagnosis, treatment decision, etc.[3] [4]. In the field of orthopedics and physical rehabilitation, the traditional diagnosis and evaluation of diseases depends on the judgment of specialists on gait characterization, symptoms and signs, and chief complaints, and auxiliary laboratory and imaging examination for diagnosis. In terms of objective assessment, there is a lack of precision and sensitivity indicators. However, the research and application of gait analysis can effectively get rid of the above predicament.To provide sensitivity index in objective evaluation, diagnosis and prognosis of disease.This paper summarizes the progress of clinical research and application of gait analysis in orthopedics and physical rehabilitation in recent years, as

follows.

1. Basic concepts and methods of gait analysis

1.1 Basic concepts of gait analysis

Gait analysis refers to the analysis of human gait. From A medical point of view, human gait can be divided into normal gait and abnormal gait, among which normal gait is the most natural walking gait that conforms to human characteristics and comfort level. Walking with normal gait can maintain proper length of steps and body stability[5]. Abnormal gait will show abnormalities from the changes in body stability, different step length, abnormal increase in energy consumption and other aspects during walking. The generation of abnormal gait is mainly related to the pathological changes in a certain part of the body and the changes in health degree and other factors, mainly involving the peripheral nervous system, central nervous system, skeletal muscle system and other systems and corresponding organs and tissues.For example, common arthritis, fracture and pelvic injury can lead to abnormal gait [6]. Gait analysis in the medical field is mainly through the application of multidisciplinary principle knowledge for abnormal gait analysis, through the acquisition of gait parameters to identify problems and analyze the reasons.A complete gait cycle involves support phase and swing phase, both of which are in a normal equilibrium state to ensure normal gait [7]. At present, various gait analysis systems can be applied to different scenes to meet different needs. The acquisition of gait parameters such as gait cycle, dynamic parameters and kinematic parameters is the basis of the gait analysis system, such as recording step size, gait cycle and large joint motion Angle. Through the acquisition and measurement of various parameters, precise parameters are provided for the evaluation of abnormal gait.

1.2 Gait analysis Method

Gait analysis methods are varied, including footprint method, three-dimensional dynamic analysis, visual gait analysis, etc. Different methods have different application scenarios and characteristics [8] [9]. Foot printing method is widely used, with advantages of simple operation and low price. After evenly applying dye to the sole of the tested person, the foot is naturally walked on the hard ground laid with extension paper, and the data such as step length and width are recorded. In the three-dimensional dynamic analysis, the quantitative analysis of walking rules using three-dimensional space can obtain parameters such as range of motion, speed and displacement, and realize the acquisition of biomechanical information of key muscle tissues during walking, which has high accuracy and objectivity, and the application scenario is much higher than that of footprinting method.Visual gait analysis method is to record and observe gait features by using camera technology. Compared with three-dimensional dynamic analysis, visual gait analysis method has higher professional requirements for the tester, and has certain empirical and subjective characteristics. It is mostly used for auxiliary diagnosis in clinical diagnosis and treatment, with high limitations.

2. Application of gait analysis in orthopedics

Fracture is the most common type of disease in orthopedic diagnosis and treatment, such as calcaneal fracture, hip fracture, etc., mostly caused by various accidents, clinical treatment for all kinds of fracture mainly to fracture reduction, external fixation, internal fixation, mainly divided into two categories of surgical treatment, conservative intervention, no matter what kind of treatment, the occurrence of dysfunction is the majority of patients faced with common problems,It can directly affect patients' motor function and reduce their quality of life.The application of gait analysis can effectively make up for the shortcomings of traditional imaging examination and laboratory examination, and provide objective and quantitative indicators for rehabilitation intervention.Foot pressure gait analysis system can obtain the pressure between the foot and the ground of fracture patients in walking, standing and other activities through computer technology. Domestic

doctors[10] applied this system to patients with calcaneal fracture. Through foot pressure analysis to clarify the focus of rehabilitation treatment and develop rehabilitation training plan in line with individual needs, compared with the traditional rehabilitation training found that the application of foot pressure gait analysis system can promote the improvement of motor function of fracture patients, help patients to return to normal life as soon as possible. In A related foreign study [11], gait analysis was applied to fracture patients, and plantar stress measurement was carried out on selected cases of intertrochanteric fracture of femur, showing that the application of this test can effectively evaluate the application advantages of different operations in postoperative rehabilitation.To provide reference for the development of clinical treatment.

3. Application of gait analysis in the field of physical rehabilitation

In recent years, rehabilitation medicine is one of the disciplines with rapid development, and physical rehabilitation is an important branch of it. Gait analysis plays an irreplaceable value in the field of physical rehabilitation, and the diversification of application value is its important characteristic. For example, gait analysis can be applied to the quantitative assessment of limb function, provide precise reference basis for the formulation of diagnosis, treatment and rehabilitation programs, evaluate the comfort and effectiveness of the application of treatment methods, and evaluate the effects of diagnosis, treatment and rehabilitation interventions [12]. Foreign doctors [13] analyzed the advantages of physical rehabilitation therapy in improving the results of gait analysis based on the data of some patients after horseshoe varus, and compared it with Ponseti method.The results show that the application of physical rehabilitation therapy can effectively avoid the situation of excessive correction, but there is a certain risk of deformity, so it is necessary to combine the actual situation of patients to choose the treatment method.Hemiplegia after stroke is a key lesion type in the field of physical rehabilitation. Affected by the high incidence of chronic diseases, the incidence base of hemiplegia cases is increasing globally, and related rehabilitation work has also become the focus of research in the field of physical rehabilitation.The measurement and acquisition of motion parameters, dynamic parameters, and electromyographic activity parameters in gait analysis can realize the individualized formulation of rehabilitation treatment programs. Meanwhile, gait analysis in the rehabilitation intervention process can help doctors timely grasp the mechanism of gait abnormality[14] .Adjust the rehabilitation program in time to ensure the rehabilitation effect.

4. Summary and Outlook

At present, with the rapid development of medicine, gait analysis technology is also constantly innovative, and its application in various clinical fields is gradually expanded. In the context of the development of precision medicine, gait analysis has irreplaceable value.In recent years, our country vigorously developed gait analysis technology. Some medical institutions and scientific research institutions introduced gait analysis system, which laid the better foundation for related scientific research.At present, the application of gait analysis technology in China is still in the early stage, with great progress and exploration space, and the research of related technology is expected to provide more favorable support for the development of orthopedics and physical rehabilitation related diagnosis and treatment work.

References

[1] Liang J, Lang S, Zheng Y, et al.The effect of antigravity treadmill training for knee osteoarthritis rehabilitation on joint pain, gait, and EMG: Case report[J]. Medicine, 2019,98(18): e15386.

[2] Gao MM, HE ZJ, Yun XP, et al. Comparison of Spatio-temporal Consistency of Gaitboter and Noraxon Gait Analysis Systems [J].Chinese Journal of Rehabilitation Theory and Practice, 2021, 27(2): 216-221.

[3] Zhu HQ. Design and Implementation of Human Lower Limb Gait Analysis System [D]. Dalian: Dalian University

of Technology, 2018.

[4] Tan YW, Zheng YX, Zhan HS, et al.Application of three-dimensional gait analysis in knee osteoarthritis [J].International Journal of Bone Sciences, 2014, 35(4): 215- 218.

[5] Turkmen A. Electrocardiogram interference:a thing of the past; Biomed Instrum Technol. 2012 Nov-Dec; 46 (6): 470-7[J]. Biomed Instrum Technol, 2013, 47(2):95.

[6] Protopapadaki A, Drechsler WI, Cramp MC, et al. Hip, knee, ankle kinematics and kinetics during stair ascent and descent in healthy young individuals[J]. Clin Biomech (Bristol, Avon), 2007, 22(2):203-210.

[7] Sung YH, Kim CJ, Yu BK, et al. A hippotherapy simulator is effective to shift weight bearing toward the affected side during gait in patients with stroke[J]. NeuroRehabilitation, 2013, 33(3)：407-412.

[8] Choi Jk, Cha Ej, Kim Ka, et al.Effects of custom-made insoleson idiopathic pes cavus foot during walking [J].Biomed Mater Eng,2015,26(2):705-715.

[9] Moerenthout K, Chopra S, Crevoisier X. Outcome of the modified Lapidus procedure for hallux valgus deformity during the first year following surgery:a prospective clinical and gait analysis study[J]. Clin Biomech,2019,61(7):205-210.

[10] Chen ZF, Li XC, Zhao HT, et al.Biomechanical study of self-made calcaneal anatomical Plate and breakable bolt system for calcaneal fracture fixation[J].China Bone Injury, 2009,22 (6):448-450.

[11] Pfeufer D, Zeller A, Mehaffey S, et al. Weight-bearing restrictions reduce postoperative mobility in elderly hip fracture patients[J].Arch Orthop Trauma Surg, 2019, 139(9):1253-1259.

[12] Abourezk MN, Ithurburn MP, McNally MP, et al. Hamstring strength asymmetry at 3 years after anterior cruciate ligament reconstruction alters knee mechanics during gait and jogging[J]. Am J Sports Med, 2017, 45 (1):97-105.

[13] El-Hawary R, Karol LA, Jeans KA, et al. Gait analysis of children treated for clubfoot with physical therapy or the Ponseti cast technique[J]. J Bone Joint Surg Am, 2008, 90(7):1508-1516.

[14] Erhart-Hledik JC, Chu CR, Asay JL, et al. Longitudinal changes in knee gait mechanics between 2 and 8 years after anterior cruciate ligament reconstruction[J]. J Orthop Res, 2018, 36 (5):1478-1486.

An Investigation of the Efficacy of Glycine Theophylline Sodium Extended-Release Tablets in the Treatment of Bronchial Asthma

Rong Fan, Wei Xiao, Weihua Hu, Wu Zhu*
Jingzhou First People's Hospital, Jingzhou 434000, China.

Abstract: Objective: To observe the effect of treatment with theophylline extended-release tablets in patients with bronchial asthma. Methods: The medical records of 76 asthma patients admitted from 2020.8 to 2022.9 were extracted. 38 cases in the reference group received conventional basic treatment and 38 cases in the observation group received conventional + sodium theophylline glycinate treatment, and the condition control of the patients in the two groups was compared. Results: The patients in the observation group all disappeared from the disease symptoms earlier than the reference group ($P < 0.05$). In terms of total effective rate, the difference between the reference group and the observation group was 65.79% vs 92.11% ($P < 0.05$). Conclusion: Oral treatment with sodium theophylline glycinate is recommended for asthma patients to better control their condition.

Keywords: Bronchial Asthma; Sodium Theophylline Glycinate; Effect Observation

Introduction

The prevalence of asthma within the adult population in China is roughly 4.2%, and the overall vacancy rate of asthma is low, around 28.5% in urban areas. The pathological characteristics of asthma include airway hyperresponsiveness and significant airflow restriction, and patients will experience varying degrees of wheezing and coughing, which can easily cause airway remodeling conditions during the progressive prolongation of the disease course and rapid progression during acute exacerbations, increasing the morbidity and mortality rate[1]. Theophylline extended-release tablets have anti-inflammatory properties, dilate the airways and strengthen the respiratory drive, and this paper focuses on their effectiveness in the treatment of asthma, as reported below.

1. Data and methods

1.1 General information

The 76 patients with asthma who participated in this study had clear diagnostic findings, normal cognition and tolerance to the drugs used, and were seen from 020.8 to 2022.9. They were divided into two groups according to the randomisation principle, and the groups were as follows.

Reference group (n=38): 21 males and 17 females each, minimum and maximum age 39 and 76 years respectively, mean (54.28±6.23) years, minimum and maximum duration of illness 2-11 years, mean (6.27±1.09) years.

Observation group (n=38): 19 males and 19 females, minimum and maximum age 37 and 78 years, mean (55.26±6.30) years, minimum and maximum duration of illness 3 to 13 years, mean (6.44±1.22) years.

The age and gender of the patients in the two groups were similar, and none of the differences were significant ($P > 0.05$).

1.2 Methods

Patients in each group were advised to take the initiative to quit smoking, eat a balanced diet, strengthen respiratory function exercise, and give conventional treatments such as oxygen therapy, correction of acid-base imbalance, cough suppression and anti-infection in accordance with the actual condition. In the observation group, glycine theophylline sodium extended-release tablets were added, 1 tablet/time, 2 times/d.

Continuous medication for 3 months as a course of treatment.

1.3 Observation index

Record the disappearance time of cough, wheezing, coughing sputum and croup in each group. The following criteria were formulated to determine the efficacy: ①clinical control: cough and croup disappeared completely, possibly with occasional attacks, but only to a mild level and able to relieve themselves; ②significant effect: the main symptom expression of the disease was significantly reduced; ③improved: some symptoms gained improvement compared with those before treatment with medication, but with frequent attacks.

(iv) Ineffective: the above criteria were not met, or the condition deteriorated. Total effective rate = [number of people in this group (n) - number of invalid] / n × 100%.

1.4 Statistical processing

SPSS28.0 software was used to process the data. When the measurement and counting data conformed to the law of normal distribution, the test with was used respectively. Criteria for judging differences: $P < 0.05$.

2. Results

2.2 Time to disappearance of symptoms

Compared with the reference group, the time of disappearance of asthma symptoms was earlier in all patients in the observation group, and the difference was confirmed to be statistically significant by analysis ($P < 0.05$), Table 1.

Table 1 Comparison of the time to disappearance of the main symptoms in the two groups ($\bar{x} \pm s, d$)

Group（n）	Cough	Gasping for breath	Coughing up sputum	rumbling sound
Observation group（38）	5.01±0.42	2.07±0.35	4.92±0.38	4.42±0.43
Reference group（38）	6.63±0.39	3.75±0.44	6.07±0.47	5.92±0.56

2.2 Clinical efficacy

In the observation group, 26 cases reached the clinical control assessment standard, with a total effective rate as high as 92.11%; in the reference group, the corresponding values of the above two indicators were 12 cases and 65.79%, and the effect of disease treatment was better in the observation group than in the reference group ($P < 0.05$), Table 2.

Table 2 Comparison of the efficacy of the two groups of patients[n，(%)]

Group（n）	Clinical control	Visible effect	Good turnaround	Invalid	Total validity

Observation group（38）	26	5	4	3	35（92.11）
Reference group（38）	12	7	6	13	25（65.79）

3. Discussion

The pathogenesis of asthma is still unclear, but scholars at home and abroad generally believe that the inflammatory response and airway hyperreactivity are involved in the development of the disease. During acute exacerbations, patients may experience increased airway inflammation, local smooth muscle contraction, mucosal oedema, epithelial damage and other pathological changes, which in turn cause abnormal ventilation, wheezing and other manifestations to gradually worsen, and may also be accompanied by hypoxia [2].

The clinical goals for patients with asthma include reducing the risk of acute exacerbations, inhibiting the deterioration of the disease and improving their quality of life. The mechanism of action of theophylline extended-release tablets is to inhibit the activity of phosphodiesterases (PDEs), which in turn regulates calcium levels in airway smooth muscle, resists the contractile force exerted by adenine on the airway, strengthens the contraction level of the diaphragm, etc., which in turn relaxes the smooth muscle in a pre-spastic state and significantly improves the patient's respiratory function. Theophylline also has anti-inflammatory properties, modulates the body's immune level and induces central excitation[3]. The slow release of theophylline after oral administration of extended-release tablets maintained the antiasthmatic effect for up to 12h after a single dose, which is the reason for the twice daily dosing in this study, and maintained the relative stability of theophylline blood levels in patients around the clock, thus controlling the symptoms of the disease more effectively. The time to resolution of cough, wheeze, sputum and rales was (5.01±0.42)d, (2.07±0.35)d, (4.92±0.38)d and (4.42±0.43)d in the observation group and (6.63±0.39)d, (3.75±0.44)d, (6.07±0.47)d and (5.92±0.56)d in the reference group, respectively. The difference was significant and the total effective rate of the observation group was also above that of the reference group, confirming the effectiveness of sodium theophylline glycinate in the treatment of asthma disease with multiple data sets, which is worth promoting.

References.

[1] Zhao H, Zhao J. Effectiveness of glycine theophylline sodium extended-release tablets in the treatment of bronchial asthma [J]. China Medicine Herald, 2022, 19(01): 106-109.

[2] Cao YJ. Efficacy and safety of theophylline extended-release tablets in the treatment of adult bronchial asthma[J]. Psychological Monthly,2020,15(08):52-53.

[3] Qi XF, Cao Y, Wan Ruixiang. Clinical observation of 54 cases of bronchial asthma treated with theophylline extended-release tablets [J]. Shandong Pharmaceutical Industry,2003(05):48-49.

Author Bio

First author.

Fan Rong (1980.1.10-), F, Han, Place of origin: Hubei. Jingzhou, MA, Title: Attending, Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care, Major research interests: Chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension, ECMO life support, etc.

Corresponding author.

Wu zhu (1982.5.14-), Male, Han Nationality, Place of Origin: Xiangtan, Hunan Province, Master's Degree, Title: Attending Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main Research Interests: Comprehensive treatment of breast cancer, diagnosis and treatment of non-lactating mastitis, postoperative reconstruction of

breast tumors, etc.

Second author.

Xiao Wei (1969.9.8-), Male, Ethnicity: Han, Origin: Jingzhou, Hubei Province, Highest Education: Master, Title: Chief Physician, Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care, Main research interests: chronic obstructive pulmonary disease; bronchial asthma; lung cancer; pulmonary embolism; interstitial lung disease, etc.

Third author.

Hu Weihua (1977.10.12-) Female, Ethnicity: Han, Place of origin: Jingzhou, Hubei, Highest education: Master, Title: Chief Physician

Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care Main research interests: chronic obstructive pulmonary disease; bronchial asthma; lung cancer; interstitial lung diseases, etc.

Effect of Doxorubicin Combined with Ipratropium Bromide on Pulmonary Function Indexes in the Treatment of Chronic Obstructive Pulmonary Disease

Rong Fan, Wei Xiao, Weihua Hu, Wu Zhu*
Jingzhou First People's Hospital, Jingzhou 434000, China.

Abstract: Objective: To observe the effect of different methods in the treatment of chronic obstructive pulmonary (COPD) disease. Methods: 86 COPD patients attending the clinic from 2020.7 to 2022.11 were divided into groups I and II according to the envelope method, 43 cases each were treated with theophylline extended-release tablets and group II was treated with ipratropium bromide, the lung function indexes of each group were tested and the total effective rate was calculated and compared between groups. Results: At the end of the treatment course, FEV1, FVC and FEV1/FVC levels in group II were higher than those in group I, and the difference reached a significant level ($P < 0.05$). The total effective rate in group I was 74.42%, which was lower than that in group II, which was 95.35%, forming a significant difference ($P < 0.05$). Conclusion: Treatment with doxorubicin combined with ipratropium bromide for those with COPD is effective and worthy of popular application.

Keywords:Chronic Obstructive Pulmonary Disease; Doxorubicin; Ipratropium Bromide; Pulmonary Function; Total Effective Rate

Introduction

Pulmonary function is one of the common clinical indicators to assess the level of lung function of the body, so early restoration of lung function in COPD patients can more effectively curb the progression of the disease, reduce symptoms and achieve early recovery. Doxorubicin is a commonly used bronchodilator with antispasmodic and antiasthmatic effects, which helps to reduce the symptoms of dyspnoea. ipratropium bromide does not produce large irritation after nebulised inhalation, and is effective in relieving wheezing and breathlessness[1]. Doxorubicin and ipratropium bromide have been reported more frequently in the monotherapy of COPD, and the combined use of the drugs has been reported more rarely. In this paper, 86 patients' data were included to compare single and combined drug treatment for COPD, and the following report contents were significantly made.

1. Data and methods

1.1 General information

This subject was conducted with the approval of the ethics committee and the consent of the patients. The data of 86 COPD patients were sampled, and the time of consultation was from 2020.7 to 2022.11. The above enrolled patients were divided into two groups of 43 cases each, and the situation of each group was as follows.

Group I: 25 males and 18 females, aged 36 to 76 (55.94±3.62) years, duration of disease 2 to 12 (6.12±2.35) years.

Group II: 22 males and 21 females, aged 35-74 (56.32±3.70) years, with a disease duration of 3-13 (6.32±2.40) years, respectively.

The above demographic data of patients in groups I and II were similar, i.e. no significant difference was formed (P > 0.05).

1.2 Methods

In Group I, 200 p.p.m. of doxorubicin (basic amount) + 25% glucose injection was administered intravenously twice a day, the interval between the two injections was controlled to be 12h, and the duration of each injection was controlled to be about 25min. The dose of the drug was adjusted according to the patients' condition, and the patients were instructed not to consume caffeine-based food during the drug administration period.

In group II, the treatment regimen of doxorubicin was the same as that of group I, combined with nebulized inhalation of ipratropium bromide 2.5ml, 5~10min/time, 2 times d.

All groups were treated with the drug continuously for 14d.

1.3 Observation indexes

The levels of the 1sts force expiratory volume (FEV1) and force spirometry (FVC) were measured before and after treatment in each group, and FEV1/FVC values were calculated. Determination of efficacy: after treatment, the white blood cell (WBC) count returned to the normal range, the disease symptoms disappeared and no recurrence was recorded as significant effect; if the WBC count decreased to above the upper limit of normal, the symptoms decreased and no recurrence was recorded as improvement; if the disease did not improve before and after treatment, or there was different degrees of aggravation or recurrence, the disease was recorded as ineffective. Total effective rate = significant rate + improvement rate.

1.4 Statistical processing

SPSS32.0 software was used to process the data, and the values of lung function index tests were expressed as, and the rate (%) indicated the total effective rate, which was calculated by X^2. An empirical calculation of P < 0.05 indicated that the difference reached the level of significance.

2. Results

2.1 Pulmonary function

After drug treatment, lung function was recovered in all groups of patients, and patients in group II recovered better than group I, i.e. FEV1, FVC and FEV1/FVC values were all above group I, which was statistically significant (P < 0.05).

Table 1 Comparison of the results of pulmonary function indicators between the two groups of patients $(\bar{x} \pm s)$

Group（n）	Time	FEV1（L）	FVC（L）	FEV1/FVC（%）
II（43）	Before treatment	2.02±0.38	1.75±0.48	54.62±2.39
	After treatment	2.98±0.34	2.99±0.56	68.07±3.56
I（43）	Before treatment	2.04±0.41	1.68±0.41	53.97±2.43
	After treatment	2.28±0.36	2.13±0.37	58.01±3.09

2.2 Clinical efficacy

The total effective rate in Group II vs Group I was 95.35% vs 74.42%, which shows that the overall treatment effect of patients in the observation group was better (P < 0.05), Table 1.

Table 2 Comparison of patient outcomes between groups

Group（n）	Visible effect	Good turnaround	Invalid	Total validity（%）
II（43）	34	7	2	41（95.35）
I（43）	22	10	11	32（74.42）

3. Discussion

COPD is a highly prevalent respiratory disease with a complex etiology, and belongs to the category of airway inflammatory response diseases. In the context of increasingly serious air pollution and an ageing society, the prevalence of COPD in the elderly is increasing, endangering their health and increasing the burden of healthcare on the country [2].

Doxorubicin is commonly used in the treatment of COPD, and its effects are mainly focused on bronchodilatation, which in turn inhibits the phosphodiesterase activity in the airway smooth muscle cells of the patients, resulting in relaxation of airway smooth muscle and decompression. In this study, after 14 d of drug treatment, the FEV1, FVC and FEV1/FVC test values in group I were (2.28±0.36)L, (2.13±0.37)L and (58.01±3.09)% respectively, which were lower than those in group II (2.98±0.34)L, (2.99±0.56)L and (68.07±3.56)%. The difference was significant, suggesting a better improvement in lung function in Group II patients after treatment. The mechanism of action is anticholinergic. It relaxes the bronchi, reduces wheezing and other symptoms, inhibits remodelling and promotes the rapid expulsion of sputum into the body. Nebulised inhalation is not only a safe process, but also transforms the substance into an aerosol that can be inhaled directly into the lower airways and lungs, acting directly on the lesion and reducing the irritation caused to other parts of the body to more significantly reduce the disease and control it. The combination of medication can have a superimposed effect and strengthen the effect of medication, which has many advantages such as rapid effect and longer lasting effect. In this study, the total effective rate of group II reached 95.35%, higher than that of group I at 74.42%, which is consistent with the results of some previous reports in China [3], further confirming the effectiveness of combination drug therapy.

In conclusion, clinicians faced with COPD, patients are recommended to receive doxorubicin in combination with ipratropium bromide, which can more significantly improve patients' lung function and enhance the efficacy compared with the past single-drug approach, and is worth popularizing. However, reviewing the course of this study, the author is aware of some shortcomings, such as the small number of patients enrolled and the lack of observation of drug side effects and long-term efficacy, which should be improved in subsequent studies to provide more reliable theoretical support for the combination of drugs.

References

[1] Deng ZG. Effectiveness of theophylline extended-release tablets in combination with inhaled ipratropium bromide in the treatment of chronic obstructive pulmonary disease[J]. Northern Pharmacology, 2022, 19(03): 160-162.

[2] Shen WH. Analysis of the efficacy of tonifying Zhong Yi Qi Tang combined with ipratropium bromide in the treatment of patients with chronic obstructive pulmonary disease [J]. Gansu Science and Technology, 2021,37(19):185-187.

[3] Shi HY. Efficacy of budesonide combined with ipratropium bromide in the treatment of chronic obstructive pulmonary disease[J]. Electronic Journal of Clinical Medicine Literature,2020,7(35):61-62.

Author Bio

First author.

Fan Rong (1980.1.10-), F, Han, Place of origin: Hubei. Jingzhou, MA, Title: Attending, Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care, Major research interests: Chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension, ECMO life support, etc.

Corresponding author.

Wu zhu (1982.5.14-), Male, Han Nationality, Place of Origin: Xiangtan, Hunan Province, Master's Degree, Title: Attending Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main Research Interests: Comprehensive treatment of breast cancer, diagnosis and treatment of non-lactating mastitis, postoperative reconstruction of breast tumors, etc.

Second author.

Xiao Wei (1969.9.8-), Male, Ethnicity: Han, Origin: Jingzhou, Hubei Province, Highest Education: Master, Title: Chief Physician, Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care, Main research interests: chronic obstructive pulmonary disease; bronchial asthma; lung cancer; pulmonary embolism; interstitial lung disease, etc.

Third author.

Hu Weihua (1977.10.12-) Female, Ethnicity: Han, Place of origin: Jingzhou, Hubei, Highest education: Master, Title: Chief Physician

Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care Main research interests: chronic obstructive pulmonary disease; bronchial asthma; lung cancer; interstitial lung diseases, etc.

The Value of Cefoperazone Sulbactam and Amiloride Hydrochloride in the Treatment of Chronic Obstructive Pulmonary Disease

Rong Fan, Wei Xiao, Weihua Hu, Wu Zhu*
Jingzhou First People's Hospital, Jingzhou 434000, China.

Abstract: Objective: To observe the effect of different drug regimens in the treatment of chronic obstructive pulmonary disease (COPD). METHODS: Sixty-two patients with COPD admitted from 2020.9 to 2022.12 were divided into two equal groups, group A and group B. Thirty-two patients each were treated with cefoperazone sulbactam, while group B was treated with ambroxol hydrochloride. Results: The total effective rate in Group B reached 93.55%, higher than 67.74% in Group A (X^2=5.063, P=0.024<0.05). The time to disappearance of disease symptoms and hospital stay were shorter in Group B than in Group A. The difference reached a significant level (P < 0.05). Conclusion: Clinical treatment of COPD patients with amiloride hydrochloride combined with cefoperazone sulbactam as early as possible is effective and worth promoting.

Keywords: Chronic Obstructive Pulmonary Disease; Cefoperazone Sulbactam; Ambroxol Hydrochloride; Effect Observation

Introduction

COPD is a common disease in respiratory medicine, and middle-aged and elderly people are the most prevalent group of this disease. The prevalence of COPD increases with age, and COPD is more likely to be complicated by lung infection. The quality of life is certainly reduced. The clinical treatment of COPD is often pharmacological. Ambroxol hydrochloride is a commonly used expectorant that not only promotes effective sputum excretion, but also improves lung function, which in turn reduces symptoms and controls the disease more significantly. In recent years, it has been reported that single-agent treatment is difficult to achieve the desired effect, so it is recommended that patients diagnosed with COPD be treated with a combination of drugs [1]. In this paper, data from 62 patients were included and grouped together to compare single and combination drug therapy, and the following analysis is reported.

1. Data and methods

1.1 General information

62 patients with COPD were selected as study subjects, admitted from 2020.10 to 2022.8. Inclusion criteria: ① meeting the diagnostic criteria of COPD, confirmed by imaging; ② clear consciousness, good compliance and signed informed consent. Exclusion criteria: ① those with organic lesions of liver, kidney and other organs; ② those with severe allergies; ③ those with incomplete clinical data. Divided into two groups according to the envelope method as follows.

Group A (n=31): (M/F, cases) 18/13, age range 51-82 years, mean (62.85±5.64) years, duration of disease 4-21 years, mean (8.96±2.26) years.

Group B (n=31): (M/F, cases) 16/15, age 50-84 years, median age (63.52±5.70) years, disease duration range 5-20 years,

mean (9.06±2.11) years.

The above information of the patients between the groups showed a balance, i.e. the differences did not reach the level of significance (P > 0.05) and were comparable.

1.2 Methods

Patients in all groups were given basic symptomatic treatment, including cough suppression, expectoration, anti-infection and respiratory function exercises. The following therapeutic measures were added to each group.

(1) Group A: 2g cefoperazone sulbactam + 100ml saline, intravenous, 2 times/d.

(2) Group B: In addition to the treatment in Group A, patients were treated with Ambroxol Hydrochloride, which was taken orally after meals, 1~2 tablets/time, 3 times/d.

Patients in all groups were treated continuously for 7d.

1.3 Observation index

The following criteria were used to determine the efficacy of the treatment: the symptoms and signs related to the disease disappeared completely after treatment, the X-ray examination indicated that the lung shadow was well absorbed, and the white blood cell (WBC) count returned to the normal range, which was regarded as effective. If the disease does not meet the criteria of significant or effective, or deteriorates after treatment, the disease is considered ineffective. The total effective rate is the proportion of the total number of effective and apparent cases in the group.

1.4 Statistical processing

SPSS26.0 software was used to process the data. The mean age and time were expressed as t-test; the effective rate was expressed as % and calculated by X^2. Conditions for comparable data to be met: P < 0.05.

2. Results

2.1 Clinical efficacy

After assessment and judgment, it was confirmed that there were 22 cases and 7 cases in Group B who met the judgment criteria of significant and effective respectively, and 13 cases and 8 cases in Group A in that order, and the overall treatment effect in Group B was better than that in Group A (P < 0.05), Table 1.

Table 1 Comparison of patient outcomes between groups[n,(%)]

Group（n）	Visible effect	Effective	Invalid	Total validity
Group B（31）	22（70.97）	7（21.88）	2（6.45）	29（93.55）
Group A（31）	13（41.93）	8（25.81）	10（32.26）	21（67.74）
X^2	4.199	0.000	5.063	5.063
P	0.040	1.000	0.024	0.024

2.2 Regression of symptoms and length of hospital stay

Patients in group A had earlier regression of all clinical symptoms and shorter hospital stay than group A. The data were significantly different (p < 0.05), Table 2.

Table 2 Comparison between groups in terms of resolution of disease symptoms and length of stay in hospital $(\bar{x} \pm s, d)$

Group（n）	Normal body temperature	Cough	Rales in the lungs	Hospitalisation
Group B（31）	3.11±1.25	1.13±0.34	2.54±0.81	10.25±2.09
Group A（31）	6.28±1.85	2.74±0.32	4.97±0.84	15.26±2.54
t	7.905	19.199	11.594	8.441
P	0.000	0.000	0.000	0.000

3. Discussion

Older people are generally less fit, have lower resistance and may have a combination of underlying conditions that put them at higher risk of developing COPD, reducing their own efficiency and placing a financial burden on their families and society. In addition, many COPD patients may have a combination of infections during the exacerbation period, which makes it more difficult to control the disease and increase medical costs, and causes more damage to the patient's body. In the case of COPD patients, specialist treatment seeks to relieve symptoms as soon as possible, curb the occurrence of pulmonary impairment, enhance self-care and improve quality of life [2].

In this study, the time to normalise body temperature, cough and rales disappeared in group B was (3.11±1.25) d, (1.13±0.34) d and (2.54±0.81) d respectively, which were earlier than those in group A (6.28±1.85) d, (2.74±0.32) d and (4.97±0.84) d. The difference was significant, suggesting that the symptoms of the disease improved in group B after the combined drug treatment. Patients obtained better improvement in disease symptoms after the combination treatment. Although spoperidone sulbactam belongs to the category of antibacterial drugs and has a broad spectrum of antibacterial properties, it can reduce patients' symptoms in the short term, but it is easy to be resistant to long-term use and its long-term efficacy is unsatisfactory, so its promotion is limited. Ambroxol hydrochloride is a commonly used expectorant drug whose mechanism of action is to dilute sputum, reduce its viscosity, improve the efficiency of coughing and expectoration, and reduce the adverse effects of airway obstruction on the respiratory status. This drug has the medicinal effect of restoring the damaged airway cilia function in COPD patients, enhancing the transport capacity and allowing greater sputum expulsion [3]. In addition, amiloride touches the human epidermal vesicular epithelium and induces the synthesis of surface active substances, which in turn better improves the lung function of COPD patients and reduces the risk of problems such as infections. The overall effective rate of treatment in group B reached 93.55%, higher than 67.74% in group A, further confirming the effectiveness of the combination with the data.

In conclusion, clinical treatment of COPD patients with amiloride hydrochloride combined with cefoperazone sulbactam as early as possible can alleviate patients' symptoms more rapidly and improve the efficacy, which is worth promoting.

References

[1] Peng GR, Wang SP. Correlation between sputum pathogenic bacteria analysis and BODE index in patients with acute exacerbation of chronic obstructive pulmonary disease[J]. Journal of Clinical Pulmonology,2021,26(09):1356-1359.

[2] He XP. Effect of nebulized inhalation of ambroxol hydrochloride on acute exacerbation of chronic obstructive pulmonary disease[J]. China Urban and Rural Enterprise Health,2022,37(01):131-132.

[3] Sun GH. Analysis of antimicrobial drug treatment during acute exacerbation of chronic obstructive pulmonary disease[J]. Electronic journal of clinical medicine literature,2019,6(93):63.

Author Bio

First author.

Fan Rong (1980.1.10-), F, Han, Place of origin: Hubei. Jingzhou, MA, Title: Attending, Unit: Jingzhou First People's

Hospital, Department: Department of Respiratory and Critical Care, Major research interests: Chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension, ECMO life support, etc.

Corresponding author.

Wu zhu (1982.5.14-), Male, Han Nationality, Place of Origin: Xiangtan, Hunan Province, Master's Degree, Title: Attending Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main Research Interests: Comprehensive treatment of breast cancer, diagnosis and treatment of non-lactating mastitis, postoperative reconstruction of breast tumors, etc.

Second author.

Xiao Wei (1969.9.8-), Male, Ethnicity: Han, Origin: Jingzhou, Hubei Province, Highest Education: Master, Title: Chief Physician, Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care, Main research interests: chronic obstructive pulmonary disease; bronchial asthma; lung cancer; pulmonary embolism; interstitial lung disease, etc.

Third author.

Hu Weihua (1977.10.12-) Female, Ethnicity: Han, Place of origin: Jingzhou, Hubei, Highest education: Master, Title: Chief Physician

Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care Main research interests: chronic obstructive pulmonary disease; bronchial asthma; lung cancer; interstitial lung diseases, etc.

Domain Ontology Construction in the Glioma

Lanxin Huang, Na Sun*

School of Public Health, Shaanxi University of Chinese Medicine, Xianyang 712046, China.

Abstract: **Objective** To construct a domain ontology for glioma, and to achieve knowledge sharing and reasoning in the field of glioma through reuse and sharing of knowledge. **Methods** A domain ontology for glioma was constructed using the Ontology Web Language as the description language and a seven-step approach with the help of the ontology construction tool Protégé 5.5.0 as a knowledge source. **Results** A more comprehensive knowledge system related to glioma was presented, with 35 classes, 85 instances, 8 object properties and 5 data properties constructed. **Conclusion** By integrating the glioma knowledge and establishing the corresponding domain ontology, it provides knowledge support and reasoning basis for sharing, reusing and building the knowledge base of glioma knowledge.

Keywords: Glioma; Ontology; Protégé; Domain ontology

Introduction

Glioma is a tumour arising from cancerous changes in the glial cells of the brain and spinal cord. Among neurological tumours, it is one of the most common primary tumours [1]. It accounts for 50-60% of all primary cranial tumours, 20% of all neurological tumours and 80% of central nervous system tumours [2]. Studying the causes, diagnosis and treatment of glioma, it is important to establish a knowledge system for the integration of glioma knowledge and the construction of a knowledge base, which is scattered in medical books, journals, etc. It is important to construct the corresponding ontology of these multi-source heterogeneous data in a knowledge-based manner to prepare for the future knowledge sharing and application. Ontology has its origins in Western philosophy and is an inquiry into the origin of everything in the world [3]. The Semantic Web aims to achieve a very sophisticated management system by using automated tools to extract knowledge in the conceptual space [4]. At the heart of the Semantic Web's knowledge representation are ontologies that better describe the structure of knowledge and the specification of concepts at a semantic level, and that offer the possibility of knowledge sharing by discovering hidden relationships through logical reasoning.

Guarino [5] divided ontologies into three layers according to the degree of domain ontology dependency: top-level ontology, domain and task ontology, and application ontology, which are specialized ontology describing the relationship between concepts and concepts in a particular domain. Ontology have become a research hot spot, and with the continuous development of ontology technology, they are also gradually applied to knowledge expression in the medical domain, and are widely used in the biomedical field, such as Gene Ontology (GO) [6], and various ontologies for independent diseases, such as diabetes ontology, etc [7]. Most of these independent disease ontologies are constructed in terms of patient condition, disease staging, symptoms, and treatment, which can better assist in supporting clinical decision making. However, no brain glioma ontology has been found in single disease ontology studies. Our study is to provide ideas for other disease ontologies by building a glioma ontology that is designed to better integrate knowledge of glioma and allow knowledge from different sources to be brought together in a single body of knowledge to provide support for subsequent more comprehensive focus on the diagnosis, treatment and other processes of the disease.

1. Ontology construction

1.1 Ontology construction methods

There are various methods of ontology construction, and different methods produce different results. The common ones are the seven-step method, the skeleton method, the TOVE method, the METHONTOLOGY method, etc. The seven-step method was proposed by Stanford University School of Medicine in 1995 for domain ontology, and it is also the most appropriate ontology construction method for the medical field [8]. In this study, the fifth and sixth steps of the seven-step method were combined as follows: (i) identify the domain and scope of glioma; (ii) examine the possibility of reusing existing disease ontologies; (iii) list the important terms of the glioma ontology; (iv) define the hierarchy between glioma classes; (v) set the properties and their constraints; and (vi) create glioma instances.

1.2 Ontology building languages and tools

The Ontology Web Language (OWL) is one of the ontology description languages published by the W3C (World Wide Web Consortium) in 2004, developed from a combination of DAML and OLL, and builds on RDF and RDFs, and adds more semantics to the description logic. It has a more comprehensive and accurate description of semantics than RDFs and RDFs, is more powerful and functional, and is reasonably efficient for reasoning [9]. The Ontology Editor is used to build, develop and maintain ontologies. There are more than 60 ontologies building tools available, commonly used are Protégé, OntoEdit and others. Among these tools, the most widely used and popular ontology editing tool is Protégé [10] developed by the Stanford University Medical Intelligence Research Group. It is developed in Java and supports a wide range of ontology formats through various plug-ins, and has good openness and compatibility, making it the current tool of choice for ontology development. We used Protégé 5.5.0 to build the glioma domain ontology.

2. Glioma domain ontology construction

2.1 Defining the glioma domain and scope

The first step includes issues such as the scope and purpose of the domain. The purpose of the domain, i.e. the domain of glioma, is to structure glioma knowledge and build a more comprehensive knowledge map of glioma. Maja Hadzic et al. [11] proposed a four-dimensional generic ontology framework for the disease, including disease type, phenotype, treatment and etiology, which basically covers the most important features of the disease. we added two concepts to this top-level category, and the final brain The top level of glioma was identified as Basic_Information_of_Patient, Cause, Diagnosis, Sympton, Therapeutic_Procedure, and Tumor_Classification in a total of six areas. Knowledge is derived from encyclopedic knowledge, expert experience, and clinical guidelines including (National Comprehensive Cancer Network,NCCN) Clinical Practice Guidelines (2020.v3), the patient guide Brain Tumors - Glioma (v2021), (American Brain Tumour Association, ABTA), About Brain tumors-a Primer for patients and caregivers, and a literature search of glioma-related literature through literature databases.

2.2 Examining the possibility of reusing existing disease ontologies

Reusing ontologies can improve the efficiency of building ontologies and reduce the waste of resources. We searched BioPortal for relevant disease ontologies and reused terms from Thyriod Cancer Ontology, TCO and Brain Tumour Ontology, BTO.

2.3 List of important terms for glioma ontology

By manually extracting the entities related to glioma from the above knowledge sources, we obtained the concepts, properties and other contents of them, but in our process of collecting terms, there existed this term with multiple meanings, by referring to (NCI Thesaurus OBO Edition, NCIt), (systematized nomenclature of medicine-clinical terms, SNOMED CT) the relevant standard terminology was expressed in a standardized way whenever possible.

2.4 Defining a hierarchy between glioma classes

Based on the conceptual terms generated from the above steps, the analysis was followed by hierarchical relationship building. The core of the domain ontology is the class, and the hierarchical relationship between classes is the hierarchical relationship between concepts, using a combination of top-down and bottom-up approaches. The top-level concepts have six major classes which are Basic_Information_of_Patient, Cause, Diagnosis, Sympton, Therapeutic_ Procedure, and Tumor_Classification.

2.5 Defining properties and facets of classes

The properties of ontology classes include Object property and Data property. Object property represents the relationship between classes and classes, while data property represents the relationship between instances and data value types. Protégé has its own basic relationships including part-of, kind-of, instance-of, attribute-of. We have created a total of eight Object properties, defined by range and domain, which allow classes to be related to each other by means of this property, laying the foundation for the application of knowledge inference. For example, the Object property "treatedBy" relates Anaplastic_oligodendroglioma in "Grade III" to Chemotherapy in "Chemotherapy". Chemotherapy_Administered_During_Radiation_Therapy" in "Chemotherapy". A total of 5 Data attributes are created including characterize, has_ICDO-3_Code, has_SNOMED_CT®_ConceptId, hasMeshID and requireCOST, e.g. "has_ICDO-3_Code " and "has_SNOMED_CT®_ConceptId" have Functional properties because different gliomas can only have one International Classification of Diseases for Oncology or SNOMED_CT®_ConceptId. Diseases for Oncology or SNOMED_CT® with the property value xsd:string. e.g. Pilocytic_astrocytoma has_ICDO-3_Code "9421" and has_SNOMED_CT ®_ConceptId "128854008".

2.6 Creating glioma instances

After building the upper ontology and defining the properties, the final step requires the creation of Individuals, instances are concretizations of concepts i.e. individuals, which cannot be subdivided and inherit the properties of the class. Individuals are set in the symptoms, such as Seizures, Fatigue, Double_vision, etc., considering the existence of concretization properties for terms related to symptoms (Sympton) of glioma.

3. Reasoning and testing of glioma ontology

The consistency of domain ontologies includes three types of consistency: syntactic consistency, semantic consistency and consistency of user-defined domain rules [12]. After the ontology is constructed, it is first manually verified and then reasoned by Protégé 5.5.0's own reasoning machine HermiT 1.4.3.456, an OWL-based ontology reasoning machine developed by the Computer Science Data and Knowledge Research Group at the University of Oxford, which finds hidden potential by the consistency of our previously defined relational properties and axioms relations and instances. The results of the inference are presented in pale yellow and if the wrong relationship is established, the system will report an error for you to make changes. As one of the glioma symptoms, Headache can then be automatically categorised by the reasoning machine,

as shown in Figure 1. Based on the semantic relations we have constructed, diseases such as Glioblastoma and Optic_nerve_glioma have Headache as a symptom, and the reasoning results will show what diseases have Headache as a symptom. The ontology we have constructed has passed the consistency test and has internal logical consistency.

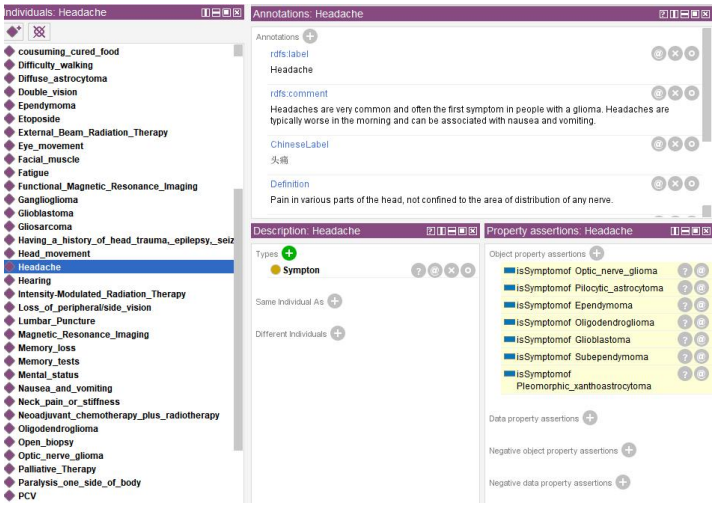


Figure 1. Example of ontology consistency reasoning

4. Graphical presentation of the glioma ontology

The glioma ontology constructed in this paper has 35 classes, 85 instances, 8 object properties and 5 data properties. This knowledge ontology is graphically presented using OntoGraf, a tool that comes with Protégé (Figure2). This figure shows the structure of the glioma ontology, with nodes representing semantic concepts, solid lines representing relationships between classes, and dashed lines representing different object properties connected by arrows, with different arrow colours representing different semantic relationships.

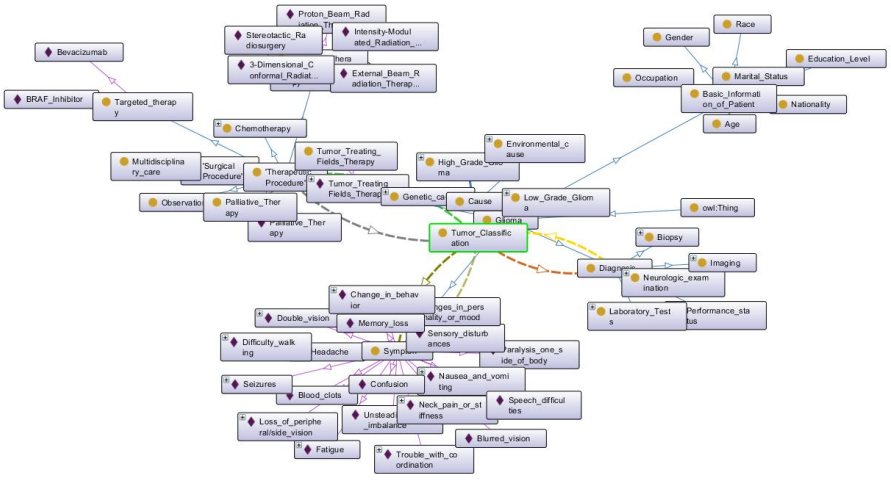


Figure 2. Structure of the glioma proper

Conclusion

A domain ontology is a description of the concepts and specific relationships between concepts in a relevant professional domain, which allows for a more effective and rational representation of knowledge. The combination of

medicine and ontology allows for more focused knowledge exploration and relationship discovery around glioma, which not only facilitates knowledge sharing and application, but also provides a reference for other disease ontologies. However, this ontology has some limitations, mainly in the following areas. Because the ontology was constructed manually, the constructed glioma domain ontology may not be complete and more domain experts are needed to participate in it. Future work will require more in-depth research and extensions, such as automated methods for building ontologies, adding conceptual terms related to glioma-related aspects, or building SWRL rule bases for reasoning.

References

[1] Ostrom QT, Gittleman H, Stetson L, Virk SM, Barnholtz-Sloan JS. Epidemiology of gliomas. Cancer Treat Res. 2015;163:1-14.

[2] Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol. 2012 Nov;14 Suppl 5(Suppl 5):v1-49.

[3] Li Shanping, Yin Qiwei, Hu Yujie, Guo Ming, Fu Xiangjun. A review of ontology research[J]. Computer Research and Development,2004(07):1041-1052.

[4] Antoniou G, Van F H . A Semantic Web primer[M]. MIT Press, 2004.

[5] Guo HY. Study on the construction of ontology model of disease domain [D]. Chinese People's Liberation Army Academy of Military Medical Sciences, 2011.

[6] Ashburner M, Ball C.A, Blake J. A, et al. Gene ontology: tool for the unification of biology[J]. The Gene Ontology Consortium. Nature Genetics, 2000, 25(1): 25-29.

[7] Shaker El-Sappagh, Farman Ali. DDO: a diabetes mellitus diagnosis ontology[J]. Applied Informatics, 2016, 3(1).

[8] Chen ZJ. Research on ontology-based knowledge retrieval system for diagnosis of digestive system diseases [D]. Chongqing University,2017.

[9] Yuan Y. Research on the construction of pathological ontology for colorectal cancer[D]. Zhejiang University, 2016.

[10] Rubin DL，Noy NF，Musen MA. Protege: a tool for managing and using terminology in radiology applications. Journal of Digital Imaging, 2007, 20 (Suppl 1): 34-46.

[11] Hadzic M, Chang E. Ontology-Based Support for Human Disease Study[C]// Hawaii International Conference on System Sciences. IEEE, 2005.

[12] Xu Y, Wang ZX, Li ZY. Consistency checking of domain ontologies[J]. Computer Engineering, 2009,35(01): 55-57+64.

Clinical Observation of External Fixation Stent Combined with Limited Open Reduction and Kirschner Wire Internal Fixation for Comminuted Distal Radius Fracture

Chaochao Ji, Xudong Sun

Department of Traumatic Orthopedics, Maanshan People's Hospital, Maanshan 243000, China.

Abstract: **Objective:** To investigate the clinical effect of external fixation stent combined with limited open reduction and Kirschner wire internal fixation in the treatment of comminuted distal radius fracture. **Methods:** A total of 40 patients with comminuted distal radius fractures from January 2018 to December 2021 were selected, including 15 males and 25 females. Age 35-74 years old; AO type: C2 type 26 cases, C3 type 14 cases. External fixation stent combined with limited open reduction and internal fixation with Kirschner wire were used for the surgery. Wrist function was evaluated by Dienst score at the last follow-up. **Results:** In this study, all patients were followed up for 6-12 months after surgery, with an average of 8.5 months. Bone union was achieved in all patients. Complications: 1 case of nail tract infection, 2 cases of Kirschner wire withdrawal, 1 case of traumatic arthritis; According to Dienst score of wrist joint function, 25 cases were excellent, 12 cases were good, and 3 cases were fair. The excellent and good rate of wrist joint function was 92.5% (37/40). **Conclusions:** External fixation stent combined with limited open reduction and Kirschner wire internal fixation for the treatment of comminted distal radius fracture can effectively fix, avoid the second incision and removal operation, can be performed according to the early stage of functional exercise, postoperative functional recovery of the wrist, providing an effective treatment method for the clinical treatment of this kind of fracture.

Keywords: Comminuted Fracture of the Distal Radius; External Fixation Bracket; Kirschner Wire

Introduction

Distal radius fractures are the most common type of fracture in the long dry bones of the extremities, accounting for approximately one in six emergency department fractures, and approximately 20% of these fractures are unstable fractures. With the aging of the population, the incidence of distal radius fracture is increasing. It is the third most common osteoporotic fracture[1]. In addition to low energy injuries, there are more and more patients with high energy injuries, mostly young people, most of them are intraarticular comminuted fractures. At present, about 32% of fractures are AO type C fracture.In the past, the preferred treatment was manual reduction plaster fixation or Kirschner wire fixation, but most unstable fractures will be displaced again in the later stage. With the continuous improvement of living standards and patients' functional requirements for the affected limb, surgery has gradually become the mainstream way to treat distal radius fractures. Restoring the smooth articular surface is very important to improve the functional effect of the wrist and improve patient satisfaction[2].In order to explore a better treatment plan, our department selected 40 patients with comminuted distal radius fractures from January 2018 to December 2021, and treated them with external fixation stent combined with limited open reduction and internal fixation with Kirschke wire. All of them achieved good short-term efficacy, and the analysis is reported as follows.

Materials and methods

Subjects

A total of 40 patients with comminuted distal radius fractures were included in this study from January 2018 to December 2021.There were 15 males and 25 females; The age range is 35-74, with an average age of 59. 25. AO type: C2 type 26 cases, C3 type 14 cases. Causes of injury: 17 cases were injured by car accident, 19 cases were injured by falling, 4 cases were injured by high fall. This study has been approved by the Ethics Committee of the hospital, and all patients signed informed consent.

Surgical methods

After the brachial plexus block anesthesia was satisfied, the patient was placed in the supine position, the forearm pronated 20° ~ 30°, the ulnar side was placed high, so that the wrist joint was ulnar offset and metacarpal flexion, 2 external fixation needles were placed vertically before the middle part of the second metacarpal body and the axis of the metacarpal, and then 2 external fixation needles were placed vertically at the proximal end of the fracture 3cm and 6cm from the fracture line, and attention was paid to the protection of the superficial branch of the radial nerve.The fracture was then reduced by manual traction along the long axis of the radius, assisted reduction of the palmar or dorsal incision was performed according to the fracture situation, bone grafting was performed at the fracture collapse if necessary, and 1 to 3 Kirschner wires were used to maintain the broken end of the fracture according to the fracture situation. After the fracture was confirmed to be well reduced by fluoroscopy with C-arm X-ray machine, the wrist joint was then maintained in the functional position of the affected limb to be connected with the external fixation rod and fixed.

Postoperative management

The active and passive functional exercise of interphalangeal joint and metacarpophalangeal joint was performed 24 h after the operation. Three weeks after surgery, the wrist joint was fixed in neutral position. Four weeks after surgery, the wrist joint was loosened. The patient was instructed to perform active flexion and extension training of the wrist with the assistance of external fixation bracket, 3-4 times a day, 15 minutes each time.The movable screw of the stent was released 6 weeks after operation, which was convenient for wrist flexion and extension function exercise. The external fixation stent was removed 8 weeks after surgery, and the Kirschner wire was removed 8 to 10 weeks after surgery, and the patients were instructed to carry out weight-bearing exercise.

Typical cases are shown in Pictures 1

Results

In this study, all patients were followed up for 6-12 months after surgery, with an average of 8.5 months. Bone union was achieved in all patients. Complications: 1 case of nail tract infection, 2 cases of Kirschner wire withdrawal, 1 case of traumatic arthritis, no other serious complications.According to Dienst score of wrist joint function, 25 cases were excellent, 12 cases were good, and 3 cases were fair. The excellent and good rate of wrist joint function was 92.5% (37/40).

Discussion

With the aging of the population and the increase of high-energy injuries such as traffic accident injuries and high fall injuries in modern society, distal radius fracture has gradually affected the elderly and young people[3], especially the

compostulated fractures of C2 and C3 distal radius, which means that the injury is more serious and the joint may face many serious complications in the later stage, such as wrist joint function limitation, traumatic arthritis, etc. Therefore. The surgical treatment of C2 and C3 fractures is difficult, because they involve articular surface separation, collapse, and comminuted displacement of metaphyseal fractures. Simple open palmar approach plate internal fixation may not be able to effectively fix all fractures, especially the collapsed articular surface, which cannot be adequately supported by screws.For patients with senile osteoporotic fractures, plate screws may not maintain effective reduction, and may easily lead to screw removal, aggravating the wear of the articular surface. For young patients with high-energy injuries, these fractures are associated with severe soft tissue damage, and open reduction plate internal fixation requires extensive dissection, which can aggravate soft tissue damage and increase the risk of wound infection[4].

External fixation scaffold has its advantages in the treatment of comminuted distal radius fracture. (1)External Fixator is a minimally invasive surgery, the main reduction principle is through ligament traction reduction[5];(2)It does not compress the surrounding soft tissue, small damage to the local hematoma and periostosis of the fracture, and maximally retains the blood supply at the fracture end, fast postoperative recovery, in line with the "BO" principle of modern fracture treatment;(3)The external fixation stent is elastic fixation, and early functional exercise can be performed after surgery, so the functional recovery is good, and the complications are far lower than the traditional plaster, splint and plate fixation;(4)Fixation was removed in vitro after fracture healing to avoid a second operation and reduce the chance of infection.

For C2 and C3 comminuted fractures, external fixation supports can provide some reduction and support, but auxiliary incisions and additional Kirschner wires are also necessary.Our own experience is that the conventional palmar-approach assisted small incision reduction of fracture blocks, prying up the collapsed articular surface, suggesting sufficient intraoperative bone grafting to prevent re-collapse, reduction of the remaining metaphyseal free and overturned fracture blocks, and multi-angle fixation with multiple Kirschler wires. Kirscher is extremely important for the adjustment and fixation of such fracture blocks, which can provide additional stability. To prevent small displacement of the fracture block, kapandji technique can be used to reduce the displacement of the dorsal fracture block during the operation. If the overall line of force and stability are seriously affected by the crushing of the dorsal fracture, the dorsal incision can be assisted and reduced and fixed under direct vision[6].

Conclusion

External fixation stent combined with limited open reduction and Kirschner wire internal fixation for the treatment of comminted distal radius fracture can effectively fix, avoid the second incision and removal operation, can be performed according to the early stage of functional exercise, postoperative functional recovery of the wrist, providing an effective treatment method for the clinical treatment of this kind of fracture.

References

[1] Li, H., Yan, K., Zhong, Z., Chen, J., & Zheng, Y. (2012). Journal of Southern Medical University, 32(11), 1680–1683.

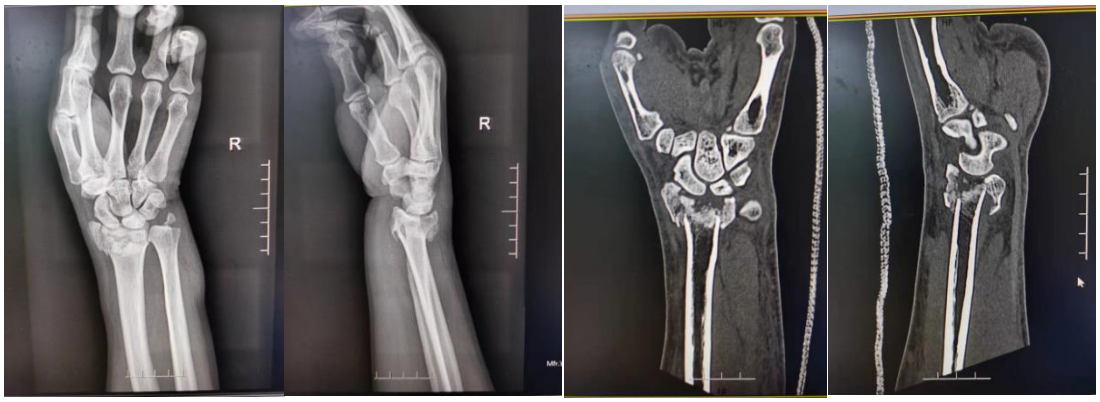
[2] Liu, Y., & Bai, Y. M. (2020). Efficacy of non-bridging external fixation in treating distal radius fractures. Orthopaedic surgery, 12(3), 776-783.

[3] Haddad, M., Rubin, G., Soudry, M., & Rozen, N. (2010). External fixation for the treatment of intra-articular fractures of the distal radius: short-term results. The Israel Medical Association journal : IMAJ, 12(7), 406–409.

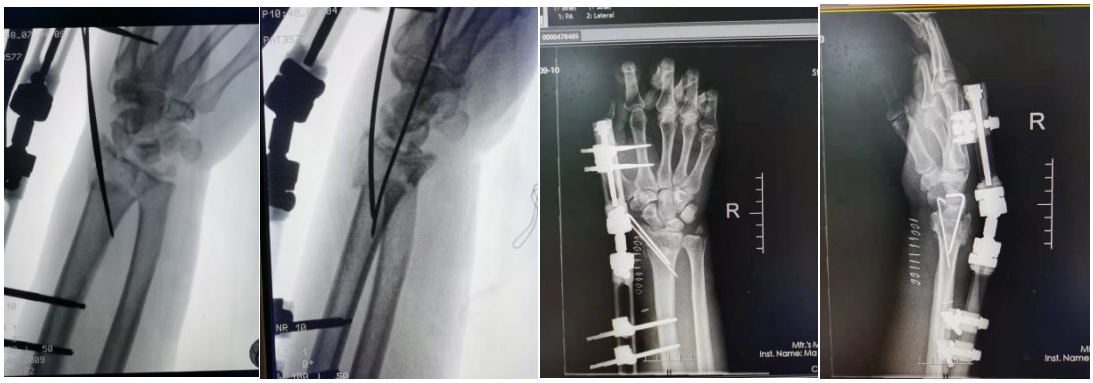
[4] Lin, C., Sun, J. S., & Hou, S. M. (2004). External fixation with or without supplementary intramedullary Kirschner wires in the treatment of distal radial fractures. Canadian journal of surgery. Journal canadien de chirurgie, 47(6), 431–437.

[5] Ermutlu, C., Mert, M., Kovalak, E., Kanay, E., Obut, A., & Öztürkmen, Y. (2020). Management of Distal Radius Fractures: Comparison of Three Methods. Cureus, 12(8), e9875.

[6] Mohamed, M. A., Abdel-Wanis, M. E., Said, E., Abdel-Aziz, I. A., Ahmed, A. M., & Addosooki, A. (2022). Dorsal bridge plating versus bridging external fixation for management of complex distal radius fractures. Injury, 53(10), 3344–3351.



a b c d



e f g h

Figure 1. The patient, a 50-year-old male, AO type C3;(a,b,c,d) Preoperative plain radiographs and three-dimensional CT showed comminuted fracture of the distal right radius; (e,f) Intraoperative reduction using kapandji technique; (g,h) Postoperative radiographs showed good fracture reduction.

Corresponding author :

Chaochao Ji , Department of Traumatic Orthopedics , Maanshan People's Hospital , No.45, Hubei Road , P.R.China

Exploration of Treatment in Patients with T3 Rectal Cancer with EMVI

Youzhong Ke, Yuan Liu , Hao Zhang, Houjun Jia*

The First Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing 400000, China.

Abstract: To explore the clinical efficacy of neoadjuvant chemoradiotherapy, combined with surgery and direct surgery in patients with stage T3 rectal cancer combined with EMVI. **Method:** The clinical data of patients with extragastrointestinal middle and low rectal cancer in the First Affiliated Hospital of Chongqing Medical University from January 2015 to May 2019 were retrospective reviewed, including 59 patients in the neoadjuvant treatment group (neoadjuvant chemoradiotherapy +surgical treatment) and 71 patients in the direct surgery group. Both groups underwent total rectal total membrane resection. **Data and Methods:**The concurrent chemotherapy regimens were all included in the XELOX regimen. The RT was performed by IMRT with D T 45 to 50.4 G y, from 1.8 to 2.0 G y each, for 25 to 28 sessions. Perioperative conditions, postoperative pathology and follow-up of the two groups were observed. **Results:** There was no significant difference in postoperative conditions (gastrointestinal function recovery time, postoperative drainage drainage, postoperative time of drainage removal) between the neoadjuvant treatment group and the direct surgery group (P> 0. 05); The length of postoperative hospital stay was significantly different (P <0.05); No significant operation time occurred between the neoadjuvant treatment group (264 min vs. 239 min) and the surgical group, (P> 0. 05)； The amount of intraoperative bleeding (85.7ml vs.110.0 ml), the number of lymph node dissection (11 vs. 13), the lymph node positive rate (27.12% vs.43.6%) betweenthe neoadjuvant treatment group and the direct surgery group had statistical significant (P＜0. 05); The 3-yearrecurrence-free survival (93.2 %) rate was higher in the neoadjuvant treatment group than in the direct surgery group (74.6 %), which was significant (P <0.05); The 3-year survival rate (98.30,% vs. 85.9 %) was significantly significant (P <0.05); There was no significant difference in the anal preservation rate (71.19% vs. 80.28%) (P> 0. 05). **Conclusion:** The neoadjuvant chemoradiotherapy improves the recurrence-free survival rate of locally advanced rectal cancer, and has no obvious effect on the postoperative complications rate, anal preservation rate and gastrointestinal function recovery.

Keywords: Rectal Cancer; Neoadjuvant Chemoradiotherapy; EMVI; Long-Term Efficacy

Introduction

At present, there are different controversies at home and abroad about the treatment of T3 patients with low rectal cancer. The American Association for Clinical Oncology for Treatment The treatment guidelines (NCCN) believe that patients with stage T3 rectal cancer (regardless of the presence of positive lymph nodes) will need preoperative new supplementation Aid, chemoradiotherapy, [1]. And the European Annual Cancer Conference believes that according to the patient risk grade, the risk grade is medium risk, can be directly advanced The surgical [2] was performed. Meanwhile, multiple studies suggest that MR suggests that positive EMVI may be considered a risk for rectal cancer metastasis One of the factors, the [3,4]. The latest version of the Society of Medical Oncology (ESMO) guidelines also see the mr-EMVI as an important one Risk factor, [2]. Therefore, 130 patients of medium and low rectal cancer with EMVI positive patients were

retrospectively studied Analysis, now the results are reported as follows.

1. Data and methods

1.1 General Information:

Inclusion criteria:(1) Preoperative colonoscopy biopsy suggested rectalcancer.; (2) Pre-hospital examination is excluded Tumors originating elsewhere outside the rectum;(3) Colonoscopy indicated that the tumor location was 10cm (4) with perfect rectal MR examination, and the stage was T3 / EMVI + / CRM-. Exclusion criteria:(1) Unable to tolerate surgery or neoadjuvant treatment for their own reasons; (2) the preoperative examination indicates distant metastasis or tumors at other sites, and it is

impossible to judge where the primary lesion is;(3) No rectal MR examination before surgery; (4) Hartmann surgery or palliative surgery. The Gastroenterology and intestinal Surgery Department of the First Affiliated Hospital of Chongqing Medical University was collected from January 2015 to May 2019 .according to the NCCN guidelines and the CSCO guidelines Patients underwent preoperative neoadjuvant therapy, requiring 71 direct surgical treatment and preoperative chemotherapy patients 59 human being,Sex, age, body mass index (BMI), history of abdominal surgery, and underlying disease and surgery None of the pre-stages were statistically different.

Table 1 Comparison of general data for one or two groups of rectal cancer patients [Case (%)]

Clinical parameters	The Direct Surgery Group（71）	New Auxiliary Group (59)	P
Age	59	57	0.925
Sex			0.413
Male	55	42	
Female	16	17	
BMI	23.7±3. 5	24. 4±3. 6	0. 595
History of abdominal surgery	17(23.9%)	13(22.1%)	0.797
Preoperative staging			0.872
II(cT3N0M0)	16	14	
III($cT_3N_{1-2}M0$)	55	45	

The tumor target area (GTV) is the primary lesion and metastatic lymph node determined on imaging, the clinical target area (CTV) is GTV + selective lymphatic drainage area, and the planned target area (PTV) is CTV expansion of 0. 5~1. 0 cm. All patients underwent surgery at 8-12 weeks after the completion of the neoadjuvant therapy.

1.2 Modus operandi:

The procedure was performed according to standard TME principles with routine lymph node dissection. According to the results of preoperative anal finger examination and colonoscopy, the patients with the distance from the lower edge of the tumor to the anal edge is within 4-10cm will undergo anal preservation surgery. For patients with tumors located at the lower edge of the anus, miles surgery is performed.

1.3 Follow-up visit:

To consult the inpatient medical records, outpatient review and regular telephone inquiry. If CT indicated recurrence, gastroenteroscopy or magnetic resonance examination was improved. The first postoperative year and once every 6 months from the second to the third postoperative year. Recurrence-free survival was defined as the time from surgery to the onset of local recurrence. Overall survival was defined as the deadline from surgery to patient death or follow-up.

1.4 Statistical method:

Data was processed with the SPSS 22 version. 0 software.χ 2 test is used for comparing count data, T test for normal distribution data and Mann-Whitney U test. Survival analysis was performed with the Kaplan parallel Log-r-rank method.

Table 2 Perioperative condition comparison of the patients in the two groups [Case (%)]

Clinical parameters	The Direct Surgery Group（71）	New Auxiliary Group (59)	P
Modus operandi			
Dixon	57	42	
Miles	14	17	
Protected ileostomy	12	27	0
Operation time	202 （201-209）	208（200-210）	0.021
Intraoperative bleeding volume (ml)	110 (79.5～ 200. 0)	85.7 0(50. 0～ 116. 3)	0. 013
Gastrointestinal function recovery time (D)	3	3	0. 988
Extubation time	7.0(6.3～8.9)	8.0 (6.8～ 9.4)	0. 312
length of stay (D)	18.0(10.5～ 24.3)	11.0(8.7 ～ 13.4)	0. 000

Dixon=anterior rectal resection; Miles=abdominoperineal resection；D=Day

2. Result

Perioperative and post-operative pathology conditions: an R0 resection was obtained in both groups. The intraoperative bleeding volume, and the proportion of protective ileostomy in the neoadjuvant treatment group were all significantly higher than that in the direct surgery group (P＜0.05); There was no significant difference in the postoperative recovery situation (postoperative drainage rate, gastrointestinal function recovery time, and extubation time between the two groups (P＞0. 05) ;

For 130 patients with low rectal cancer (tumor was 10 cm from the anal margin), dixon was performed in 42 out of 59 patients (71.19%) in the neoadjuvant treatment group,Dixon was performed in 57 (80.28%) of the direct surgery group.

The incidence of postoperative complications was significantly higher in the neoadjuvant treatment group than in the direct surgery group (46.3% vs. 25.3%, P = 0. 001). Perineal incision complications (including infection, dehiscence, delayed incision healing, etc.) in the neoadjuvant group (25.4% vs 5.6% P=0.006) were significantly higher than those in the direct surgery group.

Comparison of postoperative efficacy:The 3-year relapse survival period in the neoadjuvant chemoradiotherapy group was (11.3 ± 9.3) months in the direct surgery chemoradiotherapy group, and the 3-year relapse survival period was (22.7 ± 12.1),no significant difference between the two groups (P=0.095).Neoadjuvant recurrence-free survival rate (93.2%) was higher than that in the direct surgery group (74.6%),The difference was statistically significant (P＜0. 05) ,recurrence curves between the two groups are seen in Figure 1.The median time to death in the surgical group was 18 months, and the 3-year overall survival rate in the neoadjuvant chemoradiotherapy group was 98.30%,the 3-year overall survival rate in the direct surgery group was 85.9%,there were significant differences between the two groups (P＜0. 05),The survival curves between the two are shown in Figure 2.

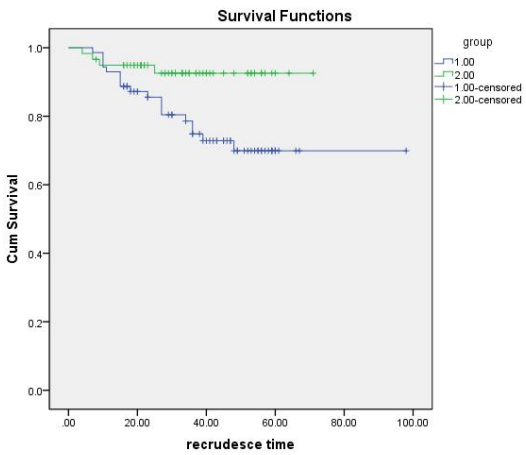
Table 3 Postoperative pathological data of both groups [case (%)]

Clinical parameters	The Direct Surgery Group（71）	New Auxiliary Group (59)	P
Number of lymph node dissection	13	11	0

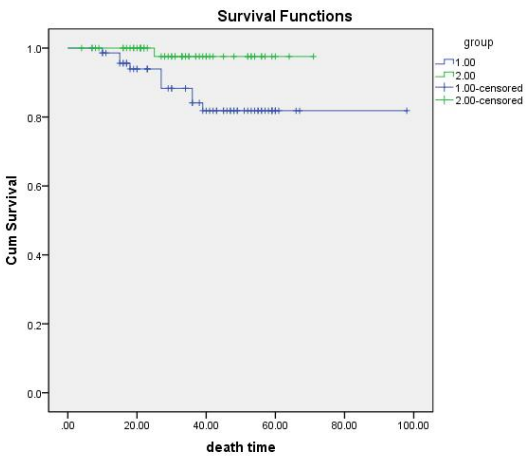
Number of positive lymph nodes	31 （43.6）	16（27.12）	0.037
Postoperative stage			0.002
0	0(0.00)	9(15.25)	
I pT1-2N0M0	4(5.60)	18(30.51)	
II pT3-4N0M0	57(80.28)	26(44.07)	
III pT2-4N1-2M0	10(14.08)	6(10.17)	

Table 4 Comparison of postoperative complications between the two groups [Case (%)]

Complication	The Direct Surgery Group（71）	New Auxiliary Group (59)	P
Anastomotic fistula	8 （11.27）	4（6.78）	0.375
Pneumonia	6 （8.45）	3（5.09）	0.685
Abdominal incision infection	5 （7.04）	2（3.39）	0.597
Abdominal infection	9 （12.68）	7（11.86）	0.888
Complications associated with the perineal incision	4 （5.6）	13 (22.0)	0.006



(Figure 1)



(Figure 2)

1= Direct surgery group ; 2= neoadjuvant chemotherapy group

3. Discussion

For patients with stage T3N0M0 intermediate and low rectal cancer, it is still controversial whether all such patients should receive neoadjuvant chemoradiotherapy or not in [5,6].Histopathological extrtramural vascular invasion (EMVI) is defined as tumor cell invasion of veins beyond the muscularis propria, suggesting a poor prognosis for patients with rectal cancer and attracting widespread attention to [7,8] in pathological reports of colorectal cancer.External vascular invasion in rectal cancer is a poor prognostic factor, with a 5-fold increase in the rate of synchronous metastasis and a nearly 4-fold increase in the persistent risk of developing metastasis during postoperative follow-up with [9]. Lack of confidence in the accurate detection of EMVI may be the reason not considered a mandatory treatment factor [10],meanwhile, because the prevalence of EMVI varies widely and the value is underestimated in histopathological specimens is used, [11] is also one of the clinical reasons for not treating EMVI as a therapeutic factor.Therefore, this study included low-grade rectal cancer, with

a stage of T3 / EMVI + / CRM-in patients.

In this study, 9 out of the 59 patients in the neoadjuvant chemotherapy group achieved pathological remission, with a PCR rate (15.2%), which basically matched the [12] with 16.5% to 22.8% in the NSABP R-04 clinical trials.At the same time, relevant studies showed that the diagnosis accuracy of T3 stage rectal cancer was 82.4% [13]. The postoperative pathological results of the surgical group in this study suggested that the proportion of patients with T3 rectal cancer was 80.28%, which was consistent with relevant studies.

The number of lymph node clearance and lymph node positive rate in the neoadjuvant group were lower than that in the surgical group.The neoadjuvant group can reduce the number of positive lymph nodes (on average of 3) and reduce the rate of positive lymph nodes, which is consistent with the results of relevant foreign studies: [14,15].The duration of surgery in the neoadjuvant group was not significant compared with the surgical group (264 min vs 239 min P=0.131), but the intraoperative bleeding volume was less than that in the surgical group (85.7 ml vs 110 ml P=0.013).The possible reason is that the pelvic tissue edema and fibrosis caused by preoperative radiotherapy make it difficult to judge the correct free level during the operation, which increases the difficulty of the operation. Therefore, it leads to more care during the main knife operation and more caution about intraoperative bleeding and other related problems, thus reducing the amount of intraoperative bleeding.

However, there are many studies on adverse reactions of neoadjuvant chemoradiotherapy, but there are few studies on neoadjuvant perioperative complications. It has been controversial whether preoperative neoadjuvant chemoradiotherapy can increase postoperative complications in [16]. The results of this study suggest that the postoperative complications (including: anastomotic fistula, incision infection, pneumonia, and abdominal cavity infection) in the neoadjuvant chemotherapy group were not statistically significant compared with the surgical group (P>0.05). However, perineal incision-related complications increased significantly compared with the surgical group, which was consistent with the findings of Hoare's et al.[17]. The results of this study suggest that the neoadjuvant chemoradiotherapy could not improve the anal preservation rate for the patients with low rectal cancer, and it was different from the relevant domestic research results in [18]. Large research institutions need to further improve the relevant research.

The relevant study results suggest that distant metastasis is the main cause of death in patients with colorectal tumors, [19], Liver metastasis is a common site of metastasis in such patients, and about one-third of CRC patients developed within three years [20,21], Even after radical resection of the primary lesion, the patient's liver metastasis rate was approximately 10–25% [22].In this study, the rate of postoperative liver metastasis in direct surgery within three years was 19.71%, which is consistent with the relevant study.However, the postoperative liver metastasis rate of the neoadjuvant chemotherapy group was 6.8%, which was statistically significant (P= 0.033), suggesting that the neoadjuvant chemoradiotherapy could improve the prognosis of such patients;At the same time, relevant foreign studies suggest that venous invasion can lead to a poor survival rate, [23],the results of this study suggest that there was a statistical significant difference between the three-year overall survival rate of 98.30% in the neoadjuvant group and 85.9% in the direct surgery group (P＜0. 05).It suggests that the neoadjuvant chemoradiotherapy has some effect on improving the long-term survival rate of such patients.

In conclusion, for patients with T3 medium and low rectal cancer combined with EMVI positive patients, preoperative neoadjuvant can reduce intraoperative bleeding and shorten the length of hospital stay, with no significant effect on postoperative complications.In terms of long-term efficacy, neoadjuvant chemotherapy can significantly improve the recurrence-free survival rate and the three-year overall survival rate of patients.Therefore, preoperative neoadjuvant chemoradiotherapy is recommended for such patients.

References

[1] You, Y. Nancy, et al. "The American society of colon and rectal surgeons clinical practice guidelines for the

management of rectal cancer." Diseases of the Colon & Rectum 63.9 (2020): 1191-1222.

[2] Glimelius, B., et al., Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 2013. 24: p. vi81-vi88.

[3] Sohn, B., et al., MRI-detected extramural vascular invasion is an independent prognostic factor for synchronous metastasis in patients with rectal cancer. European Radiology, 2015. 25(5): p. 1347-1355.

[4] Bugg, W.G., et al., The prognostic significance of MRI-detected extramural venous invasion in rectal carcinoma. Clinical Radiology, 2014. 69(6): p. 619-623.

[5] Yang,Li,Study on the Efficacy of Neoadjuvant Radiochemotherapy in the Treatment of T3 Mid-low Rectal Cancer.2016.Second Military Medical University,MA thesis.

[6] Glynne-Jones, Rob. "Do t3 rectal cancers always need radiochemotherapy?." Early Gastrointestinal Cancers II: Rectal Cancer (2014): 95-115.

[7] Smith, N.J., et al., Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg, 2008. 95(2): p. 229-36.

[8] Betge, J., et al., Intramural and extramural vascular invasion in colorectal cancer. Cancer, 2012. 118(3): p. 628-638.

[9] Siddiqui, M.R.S., et al., A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. British Journal of Cancer, 2017. 116(12): p. 1513-1519.

[10] Chand, M., et al., Adjuvant therapy decisions based on magnetic resonance imaging of extramural venous invasion and other prognostic factors in colorectal cancer. The Annals of The Royal College of Surgeons of England, 2014. 96(7): p. 543-546.

[11] Gray, R., et al., Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet, 2007. 370(9604): p. 2020-9.

[12] O'Connell, M.J., et al., Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol, 2014. 32(18): p. 1927-34.

[13] D,Y,Zhang.Application value of MRI and spiral CT in preoperative staging diagnosis of rectal cancer [J]. Modern MedicalIimaging,2018,27(02):441-443.

[14] Mechera, R., et al., Lymph node yield after rectal resection in patients treated with neoadjuvant radiation for rectal cancer: A systematic review and meta-analysis. European Journal of Cancer, 2017. 72: p. 84-94.

[15] Govindarajan, A., et al., Challenging the feasibility and clinical significance of current guidelines on lymph node examination in rectal cancer in the era of neoadjuvant therapy. J Clin Oncol, 2011. 29(34): p. 4568-73.

[16] Tang.C,H, Chu.S,B, Shuai.H,J, Clinical study of neoadjuvant chemoradiotherapy combined with surgery in the treatment of stage T_3N_ + / T_4N_x rectal cancer[J].Journal of Clinical Oncology,2019,24(03):242-246.

[17] Hoare, D., A. Maw and S. Gollins, Does pre-operative chemoradiotherapy cause wound complications after abdominoperineal excision for rectal cancer? An observational study. International Journal of Surgery, 2013. 11(5): p. 395-399.

[18] Wang FJ, Chi B, Lin HM, et al. Effect of neoadjuvant chemoradiotherapy on anal preservation rate of different highly low rectal cancer and its prognostic factors[J]. Chinese Journal of Surgery, 2016, 54(06):419-423.

[19] Kopetz, Scott, et al. "Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy." Journal of clinical oncology 27.22 (2009): 3677.

[20] Oshi, M., et al., Higher Tumor Burden Neutralizes Negative Margin Status in Hepatectomy for Colorectal Cancer Liver Metastasis. Annals of Surgical Oncology, 2019. 26(2): p. 593-603.

[21] Jing WJ, Zhu JQ. Risk factor analysis and prediction model construction of liver metastasis after colorectal cancer.Chinese Journal of Clinical Oncology,2022. 49(01): Pages 26-30.

[22] Eichler, K., et al., Hepatic Arterial Infusion with Irinotecan in Patients with Liver Metastases of Colorectal Cancer: Results of an Extended Phase I Study. Chemotherapy, 2013. 59(1): p. 66-73.

[23] Bokey, E. L., et al. "Factors affecting survival after excision of the rectum for cancer." Diseases of the colon & rectum 40.1 (1997): 3-10.

Application of Multi-State Markov Models to Alzheimer's Disease Data

Lin Qianwei and Deng Huiling
School of Public Health, Shaanxi University of Chinese Medicine, Xianyang 712046, China

Abstract: **Objective:** To explore the impact of the probability of metastasis between stages, mean residence time and APOE4 allele count on disease progression during the progression of Alzheimer's disease. **Methods:** 3191 patients initially diagnosed with Alzheimer's disease in the Uniform Data Set UDS maintained by the National Alzheimer's Collaborative Center (NACC) were selected, and a multi-state Markov model with death as the outcome was developed based on the MMSE standard cut-off point delineation criteria with three stages of Alzheimer's disease: mild, moderate and severe. **Results:** The metastatic intensity and probability of metastatic death gradually increased as the disease progressed through mild, moderate and severe stages; the mean length of stay in mild, moderate and severe Alzheimer's disease patients was 2.905, 1.875 and 1.819 years, respectively; with one APOE4 allele [HR 1.176, 95% CI (1.031,1.340)] and [HR 1.426, 95%CI(1.202,1.693)] were risk factors for mild to moderate transfer. **Conclusions:** Alzheimer's disease has a long course with multi-stage progression, risk factors affecting disease progression are more complex, the APOE4 allele is a risk factor for Alzheimer's disease, and having 2 APOE4 alleles is a greater risk than 1 APOE4 allele.

Keywords: Multi-State Markov Model; Alzheimer's Disease; APOE4 Allele; Disease Progression; Probability of Metastasis

Introduction

In recent years, as the average life expectancy increases, the world's population structure is shifting and the number of elderly people is gradually increasing, diseases of the elderly have become a serious public health problem worldwide. The number of people living with the disease is expected to reach over 100 million between 2040 and 2050[1], placing a heavy burden on healthcare and families. The risk of Alzheimer's disease is 60-80% dependent on genetic factors, with the APOE allele being the most strongly associated with the disease[2]. Among the APOE alleles, the APOE4 allele is the strongest genetic risk factor for sporadic Alzheimer's disease and is an important biomarker of Alzheimer's disease susceptibility[3]. Neuropsychological assessment is an important tool for early detection, monitoring disease progression and assessing the effectiveness of treatment. Clinically, Alzheimer's disease can be staged into "mild", "moderate" and "severe" according to the thresholds of neuropsychological scales such as the Brief Mental State Examination Scale (MMSE)[4] and the Clinical Dementia Rating Summation Scale (CDR-SB) [5]. Alzheimer's disease has an insidious and irreversible onset, with a complex multi-stage progression, and it is important to understand the impact of important risk factors on the various stages of Alzheimer's disease. Multi-state Markov models have many advantages in analysing longitudinal data of complex diseases with multi-stage progression [6,7]. First, multi-state Markov models allow for the simultaneous analysis of multiple outcome states in a single system. Secondly, the model is applicable to process data with arbitrary observation times and censored states. Third, multi-state Markov models can be used to determine the transfer probability between states, the transfer strength and the effect of each covariate on the two-state transfer rate. Fourth, multi-state Markov models can estimate the dwell times of different disease states. In recent years, multi-state Markov models have been widely used in medical research

to analyse the progression of various chronic diseases [8-12], such as hypertension, cervical disease, viruses and cells, breast cancer and childhood lupus nephritis. Therefore, in this study, a multi-state Markov model will be developed to assess the progression of different disease stages of Alzheimer's disease based on the standard cut-off point delineation of MMSE [13], and to investigate the effect of different APOE4 allele counts on disease progression in different stages of Alzheimer's disease.

1. Data and Methods

1.1 General information

The data for this study were obtained using the Uniform Data Set (UDS) maintained by the National Alzheimer's Coordinating Center (NACC) in the USA. The study cohort began in 2005 with a follow-up interval of approximately one year. The dataset contains information on demographics, neuropsychological measures, lifestyle, co-morbidities, medication use, and clinical diagnoses. A total of 3191 patients with an initial diagnosis of suspected Alzheimer's disease at baseline, with complete baseline data and two or more follow-ups, were included in this study from 2005-2013.

1.2 Methods

The number of APOE4 alleles was divided into two groups, i.e. one APOE4 allele and two APOE4 alleles. Patients with Alzheimer's disease were classified into mild, moderate and severe tertiary stages according to the MMSE score, i.e. 20≦MMSE≦30 as mild, 10≦MMSE≦19 as moderate and 0≦MMSE≦9 as severe [13]. With patient death as the outcome absorption state, a multi-state Markov model with 4 states was established, with state 1, state 2, state 3 and state 4 representing mild, moderate, severe and death of the disease respectively. As shown in Figure 1.

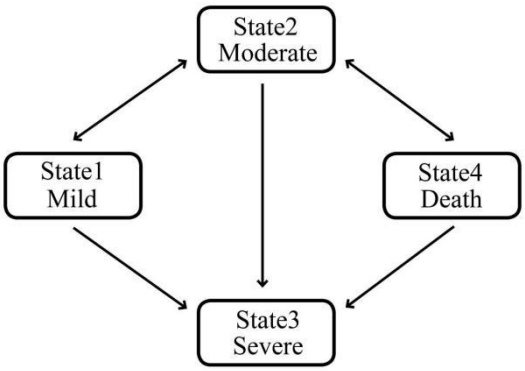


Figure 1. Structure of Alzheimer's disease staging transfer in a 4-state Markov model

1.3 Statistical analysis

R4.1.3 software was used to describe the data statistically, with measures expressed as mean ± standard deviation and counts expressed as frequency (composition ratio). Multi-state Markov models were performed in the MSM package in R software version 4.1.3.

2. Results

2.1 Basic information

Of the 3191 patients, 1520 (47.6%) were male and 1671 (52.4%) were female with a mean age of 74.87 ± 9.334 years, 1455 (45.6%) had one APOE4 allele and 420 (13.2%) had two APOE4 alleles.

In total, patients had 1143 metastases from mild to moderate and 431 from moderate to severe, with 201, 348 and 255 patients dying in mild, moderate and severe respectively. As shown in Table 1.

Table 1 Frequency of metastasis in Alzheimer's disease patients

	Mild	Moderate	Severe	Death
Mild	3646	1143	59	201
Moderate	214	1330	431	348
Severe	0	14	339	255

2.2 Transition intensity matrix

The model-estimated transition intensity matrix for patients with Alzheimer's disease by subperiod is shown in Table 2. Mild to moderate transfer is more likely than transfer to death (0.323>0.022), moderate to severe transfer is 1.858 (0.262/0.141) and 2.015 (0.262/0.130) times more likely than moderate reversion to mild and progression to death, and patients in severe highest likelihood of death (0.515). As shown in Table 2.

Table 2 Multi-state Markov model transition strength matrix (95% CI)

	Mild	Moderate	Severe	Death
Mild	-0.344(-0.364,-0.326)	0.323 (0.304, 0.342)	-	0.022(0.016,0.030)
Moderate	0.141 (0.123, 0.162)	-0.533(-0.568,-0.501)	0.262(0.238,0.288)	0.130(0.109,0.155)
Severe	-	0.035 (0.021, 0.059)	-0.550(-0.621,-0.487)	0.515(0.454,0.583)

2.3 Probability of metastasis and mean length of stay

The probability of death increased progressively with disease severity over 8 years, with the probability of death at severe being 0.970, and the probability of patients metastasising to moderate at mild being the highest (0.138) among those with adjacent stages of disease progression. As shown in Table 3. The mean length of stay for patients was 2.905 [95% CI (2.751,3.067)] years for mild, 1.875 [95% CI (1.760,1.998)] years for moderate and 1.819 [95% CI (1.610,2.022)] years for severe.

Table 3 Estimated transfer probabilities from multi-state Markov models

	Mild	Moderate	Severe	Death
Mild	0.140	0.138	0.087	0.636
Moderate	0.060	0.068	0.057	0.815
Severe	0.005	0.008	0.018	0.970
Death	0.000	0.000	0.000	1.000

2.4 Effect of different APOE4 allele numbers on disease metastasis

Model fitting results showed that having 1 APOE4 allele [HR 1.176, 95% CI (1.031,1.340)] and 2 APOE4 alleles [HR 1.426, 95% CI (1.202,1.693)] were both risk factors for transfer from mild to moderate in patients with Alzheimer's disease, with the risk of having 2 APOE4 alleles was higher, being 1.213 (1.426/1.176) times higher than 1 APOE4 allele. As shown in Table 4.

Table 4 Effect of different APOE4 allele counts on disease metastasis

Variable	Multivariable model [Hazard ratio (95% CI)]
One APOE4 allele	Multivariable model

Mild→Moderate	1.176* (1.031,1.340)
Mild→Death	0.649 (0.339,1.240)
Moderate→Mild	0.783 (0.586,1.046)
Moderate→Severe	0.929 (0.753,1.145)
Moderate→Death	0.936 (0.646,1.356)
Severe→Moderate	1.250 (0.407,3.844)
Severe→Death	0.945 (0.720,1.241)
One APOE4 alleles	
Mild→Moderate	1.426* (1.202,1.693)
Mild→Death	0.046 (0.000,8.431)
Moderate→Mild	0.628 (0.392,1.007)
Moderate→Severe	1.158 (0.876,1.531)
Moderate→Death	0.759 (0.424,1.357)
Severe→Moderate	0.554 (0.064,4.775)
Severe→Death	1.054(0.717,1.548)

Conclusion

In many longitudinal studies of clinical disease, the data are characterised by multi-state or multi-stage progression, with chronic disease being more distinctive and the data complex. Different disease types can be staged according to the diagnostic and stage classification criteria of the respective specialties. The multi-state Markov model is suitable for longitudinal data on complex disease stages. The model can estimate the probability of transition between states, calculate the effect of disease covariates on the probability of state shift, estimate the duration of disease stay in each disease stage and predict disease prognosis. The APOE4 allele is an important risk factor for the progression of Alzheimer's disease from mild to moderate, and the higher the number of APOE4 alleles, the greater the risk and the greater the clinical concern for having multiple APOE4 alleles. Patients with multiple APOE4 alleles need to be of high clinical concern. The multi-state Markov model has good application in the study of clinical disease staging, which can understand the dwell time and transition pattern of different disease stages, and dynamically estimate the disease progression, which is important for clinical decision making and guidance of therapeutic interventions, and has a clear use value in dynamically assessing disease stage progression.

References

[1] Cummings J, Lee G, Zhong K, et al. Alzheimer's disease drug development pipeline: 2021[J]. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2021, 7(1): e12179.

[2] Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease[J]. The Lancet, 2021, 397(10284): 1577–1590.

[3] Zhao J, Fu Y, Yamazaki Y, et al. APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer’s disease patient iPSC-derived cerebral organoids[J]. Nature communications, 2020, 11(1): 1-14.

[4] Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician[J]. Journal of psychiatric research, 1975, 12(3): 189-198.

[5] Hughes CP, Berg L, Danziger W, et al. A new clinical scale for the staging of dementia[J]. The British journal of psychiatry, 1982, 140(6): 566-572.

[6] Jackson C. Multi-state modeling with R：the msm package (version 1.0). 2011.

[7] Andersen, PK, Wandall, E.N.S. & Pohar Perme, M. Inference for transition probabilities in non-Markov multi-state

models. Lifetime Data Analysis (2022) 28:585–604.

[8] Zheng X, Xiong J, Zhang Y, et al. Multistate Markov model application for blood pressure transition among the Chinese elderly population: a quantitative longitudinal study[J]. BMJ open, 2022, 12(7): e059805.

[9] Taguchi A, Hara K, Tomio J, et al. Multistate markov model to predict the prognosis of high-risk human papillomavirus-related cervical lesions[J]. Cancers, 2020, 12(2): 270.

[10] Dessie ZG, Zewotir T, Mwambi H, et al. Modelling of viral load dynamics and CD4 cell count progression in an antiretroviral naive cohort: using a joint linear mixed and multistate Markov model[J]. BMC infectious diseases, 2020, 20(1): 1-14.

[11] Farahani MV, Dizaji PA, Rashidi H, et al. Application of Multi-State Model in Analyzing of Breast Cancer Data[J]. Journal of Research in Health Sciences, 2019, 19(4): e00465.

[12] Smith EMD, Eleuteri A, Goilav B, et al. A Markov Multi-State model of lupus nephritis urine biomarker panel dynamics in children: Predicting changes in disease activity[J]. Clinical Immunology, 2019, 198: 71-78.

[13] Wattmo C, Wallin AK, Minthon L. Progression of mild Alzheimer's disease: knowledge and prediction models required for future treatment strategies[J]. Alzheimer's research & therapy, 2013, 5(5): 1-15.

Correlation Analysis of Agricultural Injuries and Quality of Life Among Rural Residents in Hainan Province

Kang Lu, Qisheng Wu, Weiling Xu, Qiao Li*

International School of Public Health and One Health, Hainan Medical University, Haikou 571199, China.

Abstract: **Objective** To analyze the correlation between agricultural injuries and quality of life among rural residents in Hainan Province, and to provide a scientific basis for agricultural injury prevention in Hainan. **Methods** Using a multi-stage random sampling method, one city (county) was randomly selected in each of the five directions of Hainan: east, south, west, north and central. 1-2 towns (townships) were selected in each of the selected cities (counties), then 5-10 natural villages were selected in each town, and 20-30 households were randomly selected in each village (neighbourhood committee) to conduct a face-to-face survey of all permanent residents aged 15 or above in the selected households. **Results** In both the no agricultural injury group and the group with agricultural injury, there were statistically significant differences (P<0.05) in the six dimensions of Physical Functioning, Role-Physical, Bodily Pain, General Health, Social Functioning and Role-Emotional and in the total score between the two groups, all with the no agricultural injury group scoring higher than the agricultural injury group. The incidence of agricultural injuries showed an overall decreasing trend as the quality of life score increased (P<0.05). **Conclusion** The incidence of agricultural injuries among rural residents in Hainan is related to the quality of life, and relevant measures should be taken to reduce the incidence of agricultural injuries and improve the quality of life of rural residents in Hainan.

Keywords: Rural Residents of Hainan Province; Agricultural Injuries; Quality of Life; Correlation

Introduction

Hainan Province is the only tropical province in China and the most important area for modern agricultural development with tropical characteristics in China, with a rural practicing population increasing from 5.256 million in 2005 to 6.1958 million in 2018. Of these, 3.2398 million were directly engaged in agricultural production, and agricultural employment accounted for 53.95% of the total social employment (6.050 million) [1].Study showed that the overall incidence of work-related agricultural injuries in China was 30.6%[2]. Agricultural injuries remain a widespread social problem worldwide and can lead to an increased economic burden on society[3]. In rural areas of China, injuries cause direct medical costs of up to 65 billion yuan, and losses due to injury off work amount to more than 6 billion yuan[4],such huge economic losses and burdens have affected our economic development.Therefore, relevant measures should be taken to prevent and control the occurrence of injuries, so as to reduce the socio-economic burden caused by injuries.The occurrence of agricultural injury is related to many factors. This study intends to analyze the correlation between agricultural injury and quality of life in rural residents of Hainan, which will provide data reference for preventing the occurrence of agricultural injury in Hainan.

1. Objects and methods

1.1 Study population and sampling methods

Using a multi-stage random sampling method, one city (county) was randomly selected in each of the five directions of Hainan: east, south, west, north and central. 1-2 towns (townships) were selected in each of the selected cities (counties), then 5-10 natural villages were selected in each town, and 20-30 households were randomly selected in each village (neighbourhood committee) to conduct a face-to-face survey of all permanent residents aged 15 or above in the selected households. There were 1,893 surveys, 1,776 valid questionnaires, with an effective rate of 93.8%, and all survey respondents gave their informed consent.

1.2 Criteria for agricultural injury

Agricultural laborers are defined as agricultural injuries when they rest for more than one day due to injuries or go to medical institutions for disposal in engaging in agricultural production labo[r][5].

1.3 Research tools

The Chinese version of the SF-36 scale was used to measure the quality of life of the population. The scale has 36 entries and is divided into 8 dimensions: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental health (MH). Higher scale scores indicate a higher quality of healthy life.

1.4 Statistical Analysis

SPSS 26.0 software was applied for statistical analysis. General demographic information was described statistically and comparisons between groups were made using t-tests or chi-square tests. The test level was $\alpha=0.05$.

2. Results

2.1 General demographic data

Of the 1776 people investigated, 952 (53.6%) were male and 824 (46.4%) were female; 1182 (66.55%) were Han, 529 (29.79%) were Li, and 65 (3.66%) were other ethnic groups; the mean age was (45.1 ± 15.7) years; 274 (15.43%) were unmarried, 1426 (80.29%) were married, and 76 (4.28%) were divorced or widowed.

2.2 Correlation analysis of agricultural injuries and quality of life among rural residents in Hainan

In the non-agricultural injury group and the agricultural injury group, except that there was no significant difference in the scores of vitality (VT) and mental health (MH) between the two groups, there were significant differences in the scores of the other six dimensions and the total score between the two groups ($P < 0.05$), which were higher in the non-agricultural injury group than in the agricultural injury group, indicating that the occurrence of agricultural injury in residents was related to the quality of life.The results are presented in Table 1.

Table 1 Differences in Quality of Life Scores of Rural Residents in Hainan with or without Agricultural Injury Experience

$(\overline{X} \pm S)$

Dimension	Agricultural Injuries		*t*	*P*
	Yes（n=529）	No（n=1247）		
PF	88.85±17.12	94.73±13.72	-5.606	＜0.0001
RP	71.41±31.10	88.28±24.61	-9.946	＜0.0001
BP	77.12±21.30	87.99±18.34	-9.883	＜0.0001
GH	62.50±22.33	69.21±19.81	-3.999	＜0.0001
VT	73.24±16.42	74.70±14.18	-1.165	0.244
SF	79.77±18.44	84.24±15.88	-5.012	＜0.0001
RE	65.85±41.20	89.48±25.05	-13.623	＜0.0001
MH	72.17±16.50	71.03±14.47	0.566	0.571
Overall score	589.16±125.50	651.93±101.45	-7.571	＜0.0001

2.3 Changes in the incidence of agricultural injuries with quality of life among rural residents in Hainan

Rural residents in Hainan Province were divided into four groups based on quartiles of quality of life scores (The results are shown in Table 2). Chi-square trend test showed that there was a linear trend between the incidence of agricultural injuries and the scores of quality of life ($P < 0.05$), indicating that the incidence of agricultural injuries generally showed a decreasing trend with the increase of quality of life scores.

Table 2 Comparison of the incidence of agricultural injuries among different subgroups of rural residents in Hainan Province in terms of quality of life

Quality of Life Group	Agricultural Injuries		X^2	*P*
	Yes(n=529)	No(n=1247)		
Low Group (>P25)	211(39.9%)	223(17.9%)	114.818	<0.0001
Lower Middle Group (P25~P50)	140(26.5%)	312(25.0%)		
Upper Middle Group (P50~P75)	84(15.9%)	350(28.1%)		
High Group (<P25)	94(17.8%)	362(29.0%)		

3. Discussion

Rural residents who had not been injured in agriculture had higher scores on six dimensions of Physical Functioning, Role-Physical, Bodily Pain, General Health, Social Functioning, Role-Emotional and higher total quality of life scores than those who had been injured in agriculture. The analysis found that the incidence of agricultural injuries among rural residents in Hainan generally tended to decrease as the quality of life scores increased. This suggests that the quality of life of Hainan's rural residents is related to the incidence of agricultural injuries. Therefore, the relevant authorities need to develop some measures to reduce the occurrence of agricultural injuries among rural residents in Hainan in order to improve the quality of life of rural residents in Hainan.

Among rural residents in Hainan Province,those with agricultural injuries scored slightly higher on the mental health

dimension compared to those without agricultural injuries, but the difference was not statistically significant, which may be related to the prevalence of the Daddy tea culture among Hainan residents, making those who have experienced agricultural injuries less psychological trauma compared to other regions[6]. The current study showed a correlation between physical and mental health status and the occurrence of agricultural injuries, which is consistent with the results of foreign studies[7].

Agricultural injuries not only cause economic losses, but also endanger the health of rural residents[8]. Therefore, we need to strengthen the comprehensive management of the rural agricultural environment, as well as strengthen the education of rural residents on agricultural injuries to reduce the risk factors in rural agricultural production and effectively control the occurrence of agricultural injuries. In addition to reducing the incidence of agricultural injuries, we should also pay more attention to people who have experienced agricultural injuries, who have lower quality of life scores and may need more care and policy attention.

4. Acknowledgment

The Natural Sciences in Hainan Province in 2019 (grant no. 319QN221).

References

[1] Tang J. Current Situation, Problems and Countermeasures of Modern Agricultural Development with Characteristics in Hainan Province [J]. Guizhou Agricultural Science, 2020, 48 (06): 156-161.

[2] Zheng WJ. Effect of temperament type and family stress on the level of agricultural injury [D]. Chinese Center for Disease Control and Prevention, 2011.

[3] Scott, Erika E, and Deborah B Dalton. “Agricultural Fatalities in New York State from 2009-2018: Trends from the past Decade Gathered from Media Reports.” Journal of agromedicine vol. 26,2 (2021): 132-139.

[4] Wang JQ, Guan Baosheng, Zhang Yidian,et al. Effects of temperament type and family stress on the level of agricultural injury[J]. Journal of Mudanjiang Medical College,2016,40(3):136-138.

[5] The Fifth Standing Committee of the First Committee of Chinese Preventive Medicine Association on Injury Prevention and Control adopted a decision on criteria for injury definition to [J]. Chinese Journal of Disease Control, 2011, 15 (1): 9.

[6] Jiao LM, Li W, Zhang X, et al. Effects of "Dad's tea" on quality of life of local institutionalized elderly people in Hainan[J]. Chinese Journal of Gerontology, 2022, 42(04): 964-967.

[7] Voaklander Donald C et al. Farm work exposure of older male farmers in Saskatchewan.[J]. American journal of industrial medicine, 2010, 53(7) : 706-15.

[8] Luo YL. A survey on agricultural injuries among rural residents[J]. Anhui Agricultural Science, 2014, 42(19):6441-6443.

First Author: Kang Lu, Postgraduate student

Corresponding author: Qiao Li,Associate Professor

Research Progress on the Epidemiological Characteristics and Treatment of BP-Induced Melioidosis in China

Mingze Sui, Kecheng Wan
Department of Pediatrics, Hainan General Hospital, Haikou 570311, China.

Abstract: Burkholderia pseudomallei is a non-fermentative gram-negative bacterium that is positive for oxidase and enzyme, does not form spores and does not have metachromatic particles. It is the pathogen of human anthrax. Burkholderia melioides is easy to cultivate and has strong antimicrobial resistance. Although lipopolysaccharide (LPS) or capsular polysaccharide subunit vaccine can play a part of immune protection in mouse models, there is no effective vaccine for melioidosis. Melioidosis is a kind of zoonosis caused by Burkholderia melioides infection. In China, it is mainly prevalent in the southern region, with the focus of Hainan, Guangdong, Guangxi, Taiwan, etc. The main routes of infection include inhalation subcutaneous inoculation and skin damage infection, which are usually found in sewage, soil and paddy fields, and often caused by agricultural contact. It is estimated that there are about 165000 cases of people infected with melioidosis and 89000 deaths every year in the world, of which the incidence rate in South Asia, East Asia and the Pacific is 44%, 40%, and the mortality is 47% and 35% respectively [1]. Its lesions can involve all organs of the body, which is easy to cause high misdiagnosis rate and case fatality rate. As an endemic infectious disease, melioidosis has the characteristics of wide distribution, difficult diagnosis, strong latency, strong pathogenicity, and difficult treatment. Therefore, this article aims to improve the attention of Chinese medical workers to melioidosis, and makes a detailed review from the five aspects of pathogenic characteristics, epidemiological characteristics, clinical characteristics, diagnosis and treatment, and prevention and control measures of melioidosis. To understand the epidemiological characteristics and drug resistance of pathogenic bacteria in patients with blood flow infection of paragangrene, and provide data support for the prevention and control of blood flow infection of paragangrene

Keywords: Paragangrene; Epidemiological Characteristics; Burkholderia

Introduction

Anthrax is a zoonotic infectious disease caused by Burkholderia melioides. Burkholderia melioides is an environmental saprophytic bacterium, which widely exists in water, soil and other living environments, and has high pathogenicity to humans and animals. Burkholderia melioides mainly inhabits the soil, water and paddy fields in tropical areas. It is widely distributed in Southeast Asia and northern Australia. The damaged skin, digestive tract and respiratory tract can be infected. People and animals are infected by contact with contaminated soil or water. Therefore, people who are easily exposed to epidemic water or soil are high-risk groups, such as farmers, workers, fishermen, etc. The clinical manifestations of paragangrene are diverse, including acute bacteremic pneumonia, disseminated visceral abscess and local infection, and it is called "like a hundred diseases". In the acute phase, it often mainly invades the human lungs, causing refractory pneumonia, lung cavities, and rapidly causing septicemia. [2] In the chronic phase, it is mostly the suppurative performance of the affected organs and tissues. The disease is usually serious, and if it is not treated in time, the mortality rate is high. At present, the disease has become a major public health problem for people in tropical and subtropical areas.

1. Pathogenic characteristics of Burkholderia melioides

Burkholderia paragangrenoides is a short gram-negative bacterium with blunt round ends, strong staining at both ends, flagella, no spores and no capsule. The morphological characteristics of paragangrenous are relatively special. After 48 hours of culture on the blood plate, a slightly raised gray-white rough disk-shaped colony with strong metal texture and earthy smell can be formed, which can be used as the characteristics of clinical laboratory to identify the bacteria. In recent years, the research on the formation of biofilm of Burkholderia melioides has also become a hot spot. The formation of biofilm provides a shelter for pathogens. At the same time, the formation of biofilm has a certain relationship with the escape of pathogens from the body's immunity, the mechanism of drug resistance and the recurrence after cure [3].

2. Epidemiological characteristics of paragangrenosis

The disease is mainly distributed in tropical and subtropical regions between 20 ° north and south latitudes, such as Southeast Asia and northern Australia, and has also been reported in Central America, the Caribbean, the Middle East, Africa, Europe and other regions. China is mainly popular in southern regions, including Hainan, Guangdong, Guangxi, Fujian, Hong Kong and Taiwan. Hainan is the most important epidemic focus in China, and also the area with the highest isolation rate of Burkholderia pseudomallei. Hainan Province is a subtropical monsoon climate and also a high incidence area of typhoons. It has rainy season from May to October and typhoon season from June to October every year. [4] The specific microenvironment composed of various climatic factors in the coastal area may be more suitable for the survival and transmission of anthrax.

3. Clinical characteristics of paragangrenosis

The clinical features are "change-like" lesions, which are mainly divided into acute infection, chronic infection, subacute infection and recessive infection, which are mainly related to the immunity of the body and the amount of bacteria infected [5]. The patients with acute infection have a sudden and severe onset of disease, which often lead to acute sepsis, severe pneumonia, multifunctional multiple organ failure and other major clinical manifestations, such as shivering, high fever, dyspnea, abdominal pain, myalgia, cough and pus sputum, and can also form local abscess or necrosis, such as liver and spleen abscess, joint abscess, bone necrosis, etc. Localized paragangrenosis can be manifested as acute suppurative lesions, shallow and deep abscess, pericarditis, osteoarthritis, prostatic abscess, etc. The clinical manifestation of fulminant sepsis like gangrene is similar to that of other gram-negative bacterial sepsis. The main cause of death is severe sepsis and the resulting organ failure

4. Diagnosis and treatment of melioidosis

Bacterial isolation and culture is the "gold standard" for the diagnosis of paragangrene. For the population with high-risk occupation, susceptibility factors and infection that is difficult to control, multiple bacteriological examinations of relevant parts including blood culture should be carried out as soon as possible. The treatment plan of paragangrenosis is mainly divided into intensive and eradication treatment. During the treatment period, a sufficient amount of sensitive antibiotics can have better therapeutic effect and good prognosis. At present, there is no specific treatment and standard treatment plan for the treatment of patients with paragangrene. The clinical treatment is mostly empirical, including early effective antibiotic treatment, adequate nutrition supplement, and correction of hypovolemic shock caused by septicemia. Research shows that the vast majority of deaths are related to inadequate antibiotic treatment, and the uncured cases may be related to mistreatment and delayed treatment. [6] In clinical treatment, drug sensitivity test in vitro should be conducted, and appropriate drugs should be selected for early treatment with sufficient amount and duration

5. Prevention and control measures of paragangrenosis

The characteristics of paragangrene are not only low cure rate and high mortality, but also variable clinical manifestations and long treatment course. There is great pressure to do a good job in the detection, prevention and control of the disease. At present, there is no effective vaccine, so it is very important to do a good job of three-level prevention. In addition, we should strengthen the health education for doctors and the public at the grass-roots level. Corresponding publicity and education should be carried out for high-risk groups and doctors in the epidemic area, especially to improve the ability and awareness of clinicians to identify the disease and better improve the level of prevention, control and treatment of paragangrene. Conduct effective serological screening for high-risk groups in epidemic areas. Improve the accuracy of clinical diagnosis, and further develop detection methods for early and rapid diagnosis. Measures such as regular reexamination of cured patients and follow-up of patients' living environment and the incidence of human and animal diseases can improve the ability to prevent and control melioidosis. Regular monitoring should be strengthened, and the source of infection should be disinfection and sterilization to cut off its route of infection, so as to curb the spread of Burkholderia melioidosis.

Summary

At present, little is known about the global disease burden, epidemic distribution, and the pathogenic mechanism and molecular characteristics of Burkholderia melioides infection. At present, in the global case report data, the number of reported cases of anthrax in 46 countries that are known to be epidemic areas is seriously insufficient. For another 34 countries that have never reported the disease, anthrax may be a potential new epidemic [7, 8]. Anthrax like mostly occurs in the rainy season, especially in the tropical and subtropical regions of the world after heavy rains and typhoons. The clinical manifestations of paragangrene are complex and diverse, and blood flow infection is the most common type of infection reported in China. It can be manifested as asymptomatic infection, local skin abscess, acute or chronic pneumonia, joint infection or severe systemic sepsis, among which the mortality rate of infectious shock cases is higher than 90%. With the increase of reports of paragangrene, Burkholderia paragangrenoides is increasingly considered as one of the important pathogens for humans. Melioidosis has natural resistance to a variety of antibiotics. At present, Melioidosis in this region is still sensitive to the main antibiotics for clinical treatment. However, due to its rapid genomic variation, it is very easy to produce new drug resistance characteristics, which may cause difficulties or even failures in the treatment of conventional infections. Standardized and individualized antibiotic treatment programs for paragangrenosis are very important. Burkholderia paragangrenosis is most sensitive to tetracycline, imipenem, compound sulfamethoxazole and ceftazidime. These four antibiotics are also currently used as antibiotics for drug sensitivity analysis and targeted treatment in Hainan, China. Some studies have reported that Burkholderia paragangrene has emerged resistance to ceftazidime, compound sulfamethoxazole and other antibiotics, which has brought new challenges to the treatment. The disease of multiple tissues and organs can be caused by paragangrene, which is very easy to be misdiagnosed. However, there are some limitations in the current epidemic screening technology of paragangrenosis in China. Although paragangrenosis has been discovered for more than one hundred years, people generally lack full understanding of the disease. Because of its diverse clinical symptoms, the rate of missed diagnosis, misdiagnosis and mortality are high. Therefore, it is necessary to strengthen the monitoring of the status of Burkholderia melioides in the region, carry out more comprehensive epidemiological and ecological research from the genetic characteristics, and implement an effective disease monitoring and reporting system to improve people's understanding of the melioidosis, including the actual disease burden in the epidemic area, which is of great significance to the diagnosis and treatment of melioidosis. To sum up, the cure rate of paragangrene is low, and the mortality and recurrence rate are high, so medical staff should pay attention to it. Middle aged and old people, people in

contact with epidemic water and soil, coastal areas, summer and autumn are the high risk factors of melioidosis. In the future prevention and control work, we should strengthen the awareness of key groups and regions on melioidosis, and reduce its incidence rate.

References

[1] Limmathurotsakul D, Golding N, Dance DAB, et al.Predicted global distribution of Burkholderia pseudomallei and bur-den of melioidosis[J]. Nat Microbiol, 2016, 1: 15008.

[2] Mao XH. Strengthen the research of paragangrene [J] Journal of the Third Military Medical University, 2011,33 (13):1315-1317.

[3] Anutrakunchai C, Bolscher JGM, Krom BP, et al. Im-pact of nutritional stress on drug susceptibility and biofilm struc-tures of Burkholderia pseudomallei and Burkholderia thailandensisgrown in static and microfluidic systems[J]. PLoS One, 2018, 13(3):e0194946.

[4] Fu XH, Zheng YQ, Extreme weather events in Hainan Province and their impact analysis [J]. Southern Agriculture, 2018, 12 (18): 158162. The study found that typhoons had an impact on the incidence and epidemic trend of anthrax in Hainan.

[5] Xu JW, Deng WQ, Zhan LM, et al. A case report of chronic paragangrenosis and literature review [J]. China Tropical Medicine, 2019, 19 (7): 704-706.

[6] Wuthiekanun V, Amornchai P, Saiprom N, et al. Survey of antimicrobial resistance in clinical *Burkholderia pseudomallei* isolates over two decades in Northeast Thailand[J]. Antimicrobial Agents and Chemotherapy, 2011, 55(11): 5388 – 5391.

[7] Limmathurotsakul D, Golding N, Dance DAB, et al. Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis[J]. Nature Microbiology, 2016, 1(1): 15008.

[8] Almog Y, Yagel Y, Geffen Y, et al. A *Burkholderia pseudomallei* infection imported from Eritrea to Israel[J]. The American Journal of Tropical Medicine and Hygiene, 2016, 95(5): 997 – 998.

Author profile: Sui Mingze, male (August 18, 1993), Han nationality, Hohhot, Inner Mongolia, resident physician, master, pediatric intensive care. 19 Xiuhua Road, Xiuying District, Haikou, Hainan Province.

Corresponding author: Wan Kecheng, male (1992.01.08), Han nationality, Danzhou, Hainan, attending physician, master, pediatric blood and cancer. 19 Xiuhua Road, Xiuying District, Haikou, Hainan Province.

Development and Validation of a Predictive Model for the Prognosis of Complications of Supracondylar Fractures of The Humerus in Children

Qian Wang[1], Yu Wang[1], Man He[2], Haiying Cao[1] , Jingxin Zhao[1,*]

1. Department of orthopedics, Affiliated Hospital of Chengde Medical College, Chengde 067000, China.

2. Department of Rehabilitation, Affiliated Hospital of Chengde Medical College, Chengde 067000, China.

Abstract: Objective: Informing patient consultations and healthcare choices, clinical predictive models can offer patients tailored projections of the outcome. The most frequent elbow fractures in children are supracondylar humerus fractures, and clinical prediction models were still largely underutilized in these cases. By developing and verifying a prediction model to lower the risk of postoperative problems in children with supracondylar humerus fractures, this research sought to evaluate independent risk variables connected with the incidence of complications of supracondylar humerus fractures in children. Methods: We retrospectively studied 411 children with supracondylar humerus fractures treated surgically at our hospital from 2015 to 2019, and explored the independent risk factors affecting the prognosis of supracondylar humerus fractures in children in the study group using univariate and multifactorial Cox regression analysis, respectively. In addition, a prediction model based on the independent factors was constructed, a nomogram was made and data from the two cohorts were used to verify the feasibility and reliability of the model and visualize the data. Results: Height, older than eight years, weight, nerve damage, fracture type and with joystick technology of the child as independent risk factors influenced the prognosis of pediatric supracondylar humerus fractures in the modeling constructed by the training cohort, respectively. The results of the validation cohort were further screened for older than eight years, nerve injury and fracture type as independent prognostic factors. Conclusions: We were able to construct a predictive model based on a large genuine data sample, and clinical characteristics in this model could be used as independent predictors for reducing the occurrence of postoperative complications in supracondylar fractures. Combining basic vital signs and clinical risk factors into a simple and clear nomogram was more likely to result in the best treatment plan.

Keywords: Supracondylar Fracture of the Humerus In Children; Predictive Model; Independent Factors

1. Introduction

Supracondylar humeral fractures (SCHF) account for 18% of fracture types in children and reach 60% of elbow fractures in children. They usually occur in children aged 5 to 10 years[1,2]. According to epidemiological statistics, the majority of supracondylar fractures of the humerus are extension fractures, which account for about 97%-99%[3]. The rest are flexion fractures. In addition, supracondylar fractures of the humerus are also classified into three types in the Gartland classification according to the degree of displacement of the fracture. Type I and IIa fractures are stable fractures and can be fixed in a cast. Type II b and III fractures usually require surgical treatment[2,4].

Closed reduction and percutaneous pinning(CRPP) is used as the surgical method of choice for SCHF in children[4,5].

Short operative time, minor surgical side injuries, and low risk of surgical site infection are the advantages of this procedure. However, the occurrence of postoperative complications causes the time for fracture healing to be prolonged, making the postoperative recovery of the fracture different from the ideal situation. For this reason, this review analyzed the risk factors for postoperative fracture complications in children with SCHF admitted to the Affiliated Hospital of Chengde Medical College. The prediction model for multiple risk factors for postoperative supracondylar fractures of the humerus was constructed as a predictive model of independent factors for the prognosis of fractures in children with supracondylar fractures of the humerus, to explore the indicators affecting the prognosis of supracondylar fractures in children.

2. Objects and methods

2.1 Subjects

This study was a retrospective study analysis. A total of 411 children with supracondylar fractures of the humerus were included in the study, of whom 168 were male. All children underwent surgery at the Affiliated Hospital of Chengde Medical College from September 2015 to June 2019. Inclusion criteria: 1: those with complete medical history; 2: preoperative diagnosis of unstable supracondylar humerus fracture; 3: not accompanied by multiple fractures. Exclusion criteria: 1: the patient had a history of multiple fractures; 2: those with preoperative co-infection; 3: patients with chronic diseases. This study was approved by the Ethics Committee of the Affiliated Hospital of Chengde Medical College.

2.2 Study indicators

All children's general information were collected, and item-by-item univariate analysis and COX regression analysis were performed on this basis. The clinical information involved contained height, weight, gender, side, BMI, open fracture, older than eight years, time from injury to surgery, type of fracture, number of Kirschner, nerve damage, surgical method, and operation time.

2.3 Statistical analysis

SPSS 20.0 software was applied to statistically analyze the test data. Height, weight, age, BMI, and continuous variables such as time are converted into categorical variables. The single-factor analysis was carried out by binary logistic regression. The indexes with p-value less than 0.05 were summarized and analyzed by multivariate logistic regression analysis. The risk factors for the final prediction model were screened out. The prediction model was established using State software, and the independent risk factors that could influence the prognosis of fractures were screened using COX regression analysis. The consistency index (C-index) was calculated, with less than 0.05 being considered as a model without predictive ability, between 0.05 and 0.07 as a model with low discrimination, 0.07-0.09 as a model with moderate discrimination, and greater than 0.09 as a model with high discrimination, with C-index=1.0 indicating complete agreement between the model and the results. The effectiveness of the clinical prediction model was assessed using the Receiver operating characteristic curve (ROC) and the Area under the curve (AUC), and a p-value of less than 0.05 was considered a statistically significant difference.

3. Results

3.1 Comparison of basic information of collected data, see Table 1 for details.

Table 1 Comparison of basic information of collected data

A *p*-value＜0.05 was statistically significant.

	train		P	verification		*P*
	Out=0	Out=1		Out=0	Out=1	
n	192	95		88	36	
Height(cm)	110(96,120)	128(113,140)	＜0.001	110(103.5,125)	140(120.5,145)	0.642
Weight(kg)	20(15,25)	26(20,37)	＜0.001	20(16,28.7)	34(23,40.5)	0.324
Sex(male)	109(56.8%)	59(62.1%)	0.45	48(55%)	26(72%)	0.074
Left	103(53.6%)	47(49.5%)	0.53	45(51%)	25(69%)	0.074
BMI	16.53(14.87, 19.91)	15.98(14.86, 19.20)	0.51	16.56(15.10, 18.99)	17.98(14.79, 22.04)	0.280
Duration of injury(h)	4(3.9)	4(3,7)	0.74	4(3,10)	6(4.11)	0.200
Older than 8 years	5(3.6)	8(5,10)	＜0.001	6(4,7)	9(8.10.5)	＜0.001
Open	0(0.0%)	2(2.1%)	0.11	0(0.0)	0(0.0)	1
Type(III)	47(24.5%)	56(58.9%)	＜0.001	27(31%)	17(47%)	0.026
Nerve damage	21(10.9%)	22(23.2%)	0.008	8(9%)	6(17%)	0.028
Kirschner	190(99.0%)	93(96.8%)	0.34	85(97%)	36(100%)	0.560
Prying	21(10.9%)	22(23.2%)	0.008	13(15%)	5(14%)	1
Kirschner Less than2	29(15.1%)	10(10.5%)	0.36	33(38%)	8(22%)	0.140
Inone	4(2.1%)	5(5.3%)	0.16	1(1%)	0(0%)	1
external fixator	0(0.0%)	2(2.1%)	0.11	6(7%)	1(3%)	0.670
Surgery time(time)	51(34.5,95)	49(40,77)	0.61	48(28,72)	61.5(45.5,90.5)	0.042

As shown in Figure 1, the performance in the nomogram conventional scoring system achieved the ideal situation regardless of the threshold, both in the training cohort and in the validation verification cohort, which ensured that the maximum clinical benefit was obtained. Finally, decision curve analysis (DCA) demonstrated that our proposed nomogram mode can be used to make valuable and profitable decisions. These results were also validated in the validation cohort. (Figure 2).

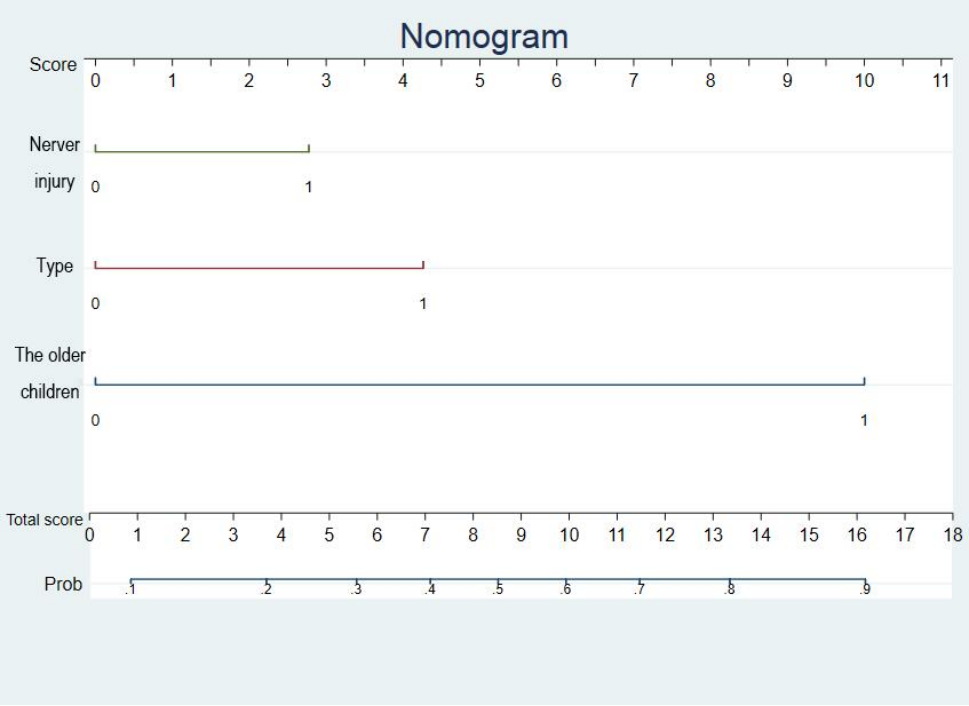


Figure 1 nomogram.

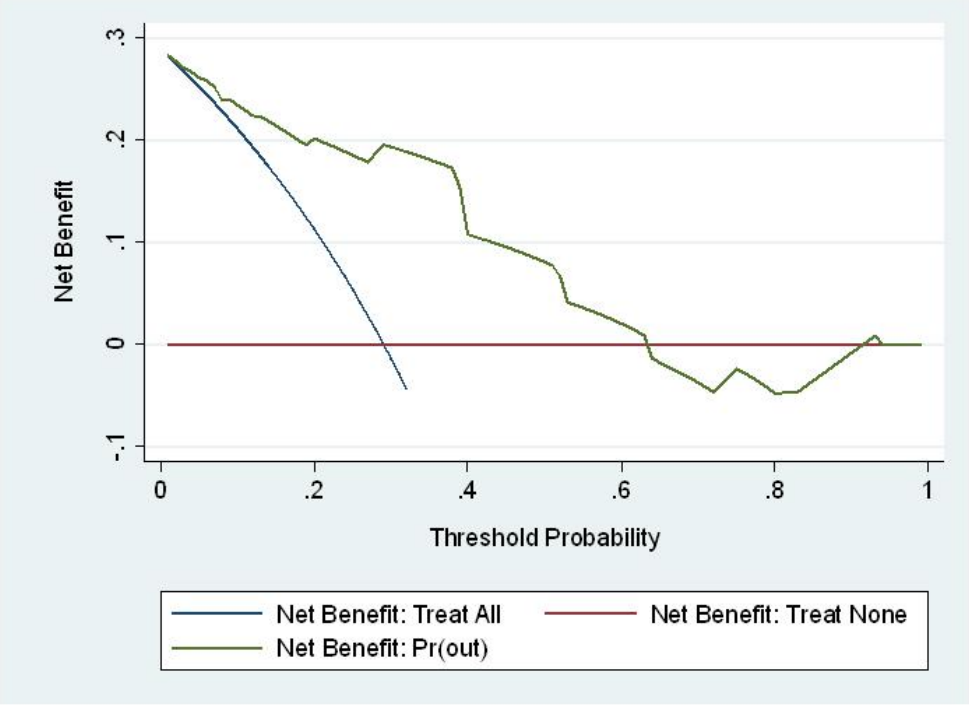


Figure 2 the decision curve analysis.

The established nomograms yielded C indices of 0.86 (95 % CI, 0. 81-0. 90) and 0. 86 (95% CI, 0. 79-0. 93) in the training and validation verification cohorts, respectively, using a study cohort of 411 (male, 242; female, 169) patients with supracondylar humerus fractures from the same dataset. Figures 3 and 4 are examples of this. Accordingly, the calibration curves showed that the probability of occurrence of postoperative complications predicted using the nomogram was consistent with the actual occurrence values (Figure 5).

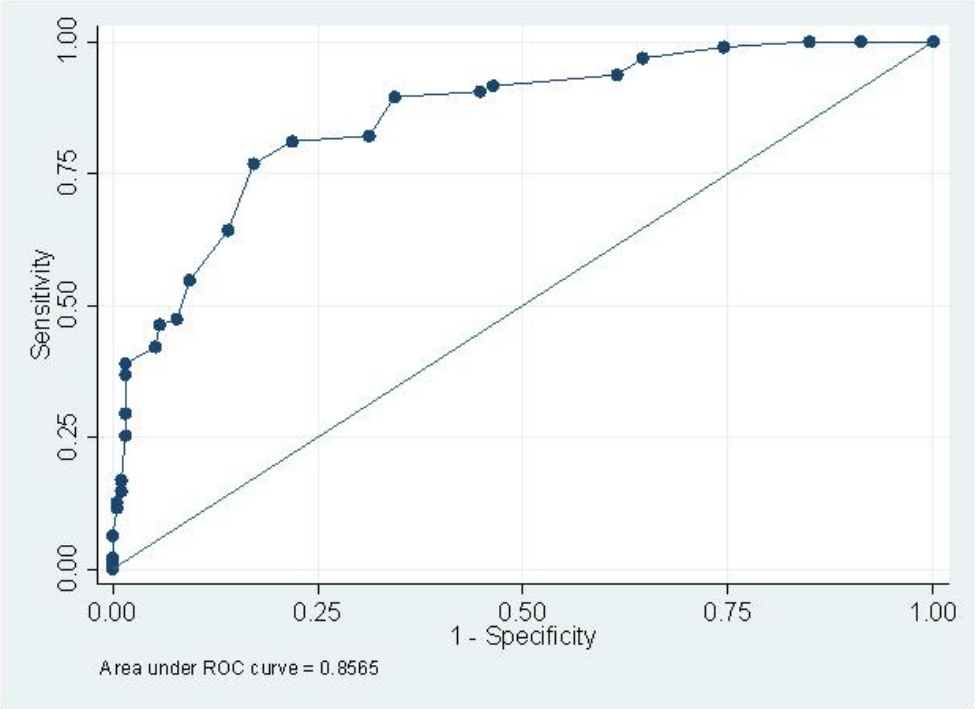


Figure 3 C indices of the training cohort.

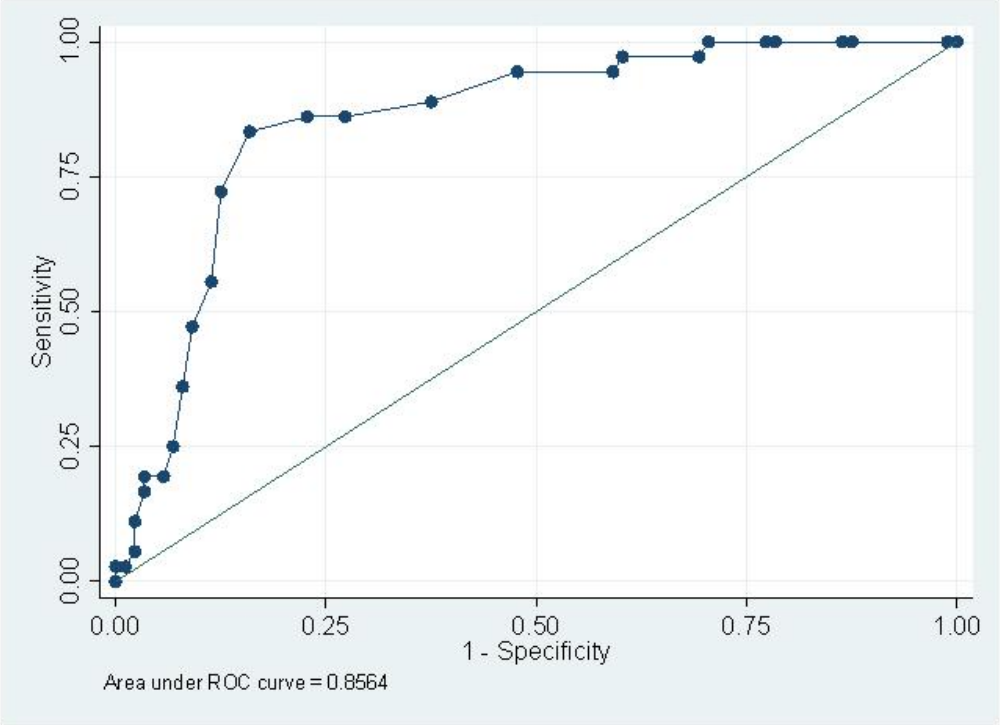


Figure 4 C indices of the validation verification cohort.

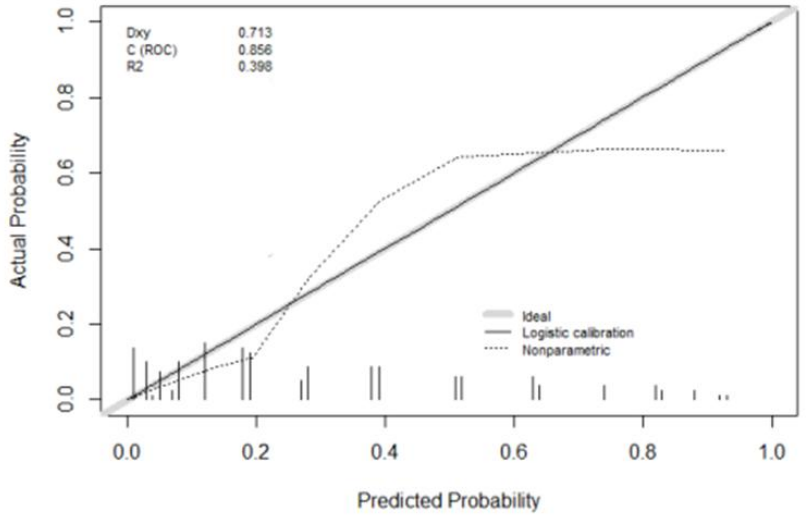


Figure 5 calibration curve

4. Discussion

The treatment of supracondylar fracture disease in children has been a hot topic in pediatric orthopedics. Among them, how to reduce the chance of postoperative complications of supracondylar humeral fractures is a hot study. To the best of our knowledge, predictive models have rarely been applied in the course of fracture studies in children. And we established a comprehensive prognostic score based on 16 variables related to general vital signs and surgical treatment in early childhood supracondylar humerus fractures. Our findings showed that risk factor scores were related to the outcome of postoperative complications and that risk factor scores can be used to guide patients in different risk groups. In addition, our study listed correlations regarding the relationship between general vital signs and postoperative complications. This risk factor prognostic model may accurately assess the likelihood of postoperative complications in children with preoperative supracondylar humerus fractures and provide increasing or downgrading systematic treatment for probable complications from a clinical standpoint. Future validation of this model was warranted.

Based on the risk factors screened by logistic regression, a nomogram model of the sample was constructed. Each risk factor degree had a corresponding score, and the total score was obtained by aggregating the scores of each risk factor. The corresponding linear predictor was found, together with the probability value, which was the probability of complications after a supracondylar fracture of the elbow in a particular child. This helped us to identify patients at "high risk" for supracondylar fractures and to focus attention and guidance on the prevention of related postoperative complications.

Because this is the most common fracture of the elbow joint in children[6-11], appropriate fracture therapy is critical. This is because inappropriate management may lead to fracture-related complications and secondary damage to the child's body, mind, and the child's family. Although there are many methods how to evaluate postoperative function in children with supracondylar humeral fractures, such as by Flynn score and modified Mayo score, differences that may stem from different definitional criteria, differences in study populations, and differences in the orientation of researchers' studies lead to gaps between the applicability of different assessment criteria in the clinical setting and the results of observational studies.

Among the possible complications after surgical treatment of supracondylar fractures of the humerus are nerve injury, pin tract infection, Varus or valgus deformity of the elbow, delayed fracture healing, osteofascial compartment syndrome, ischemic muscle contracture and secondary displacement[12]. Nerve injury can be caused by fracture displacement, where the fracture break can trap the nerve during fracture displacement and produce injury; it can also be due to inappropriate

treatment practices. Most of these nerve injuries are neurological disorders and recover completely. Therefore, surgical exploration of the nerve is rarely required. Valencia et al[13] reported that with long-term conservative treatment of supracondylar fractures of the humerus, the associated nerve injuries recovered completely, e.g., 100% of radial nerve injuries, 87.5% of median nerve injuries, and 25% of ulnar nerve injuries. The average time to recovery of nerve function was 3 months for the radial nerve, 2.5 months for the median nerve, and 5 months for the ulnar nerve. The literature reported postoperative pin tract infections in children with supracondylar humerus fractures in the range of 1% to >25%[14,15]. Most infections were superficial and could be relieved by the removal of the gristle pin and oral antibiotics[16-18]. In rare cases of deep infection or joint involvement, debridement and drainage and intravenous antibiotic therapy usually resolved the problem without significant sequelae[19]. Most authors considered elbow inversion to be the result of fracture deformity healing rather than growth arrest. Angular deformity and rotational deformity are considered to be the cause of elbow inversion. Posterior medial displacement showed higher Baumann values indicating elbow inversion deformity, while posterior lateral displacement showed lower Baumann values indicating elbow valgus [20]. Limb perfusion status can be used as the best reflector of vascular status. According to the presence of a pulse and limb perfusion, the pulse condition can be divided into three conditions: 1) good pulse and good limb perfusion (capillary filling distal to the pulse <3 seconds detected by eco doppler); 2) no pulse but good perfusion in the hand when the so-called pink pulseless hand (disappearance of the pulse, microvascular filling <3 seconds, no distal pulse); 3) disappearance of the pulse and poor perfusion in the hand when the so-called cold hand (pale, cold blood, capillary filling >3 seconds). Ischemia further progresses to necrosis and Volkmann ischemic contracture. There was no satisfactory clinical treatment for such complications[21]. A survey by the British Society for Paediatric Orthopaedic Surgery revealed that 60% of surgeons supported continued observation if the forearm remained pulseless but well perfused[21].

Predictive models were not widely used in fractures in children. We conducted a systematic and thorough analysis of general vital signs and related surgical treatment measures in the current study and discovered many main findings: 1) We obtained the imbalance status of age, fracture type, and nerve injury, which were the basic physical signs, may affect disease progression and lead to postoperative related complications. 2) In the prediction of the occurrence of postoperative complications in children with supracondylar humerus fractures, gender was used as a protective factor of the occurrence of postoperative complications. Consistent with the results of relevant studies. In a five-year follow-up study of more than 63,000 children with supracondylar humerus fractures, there was no statistically significant difference in the incidence of supracondylar fractures by gender[22]. 3) In previous studies in the literature, the use of a combination of preoperative radiographs and postoperative elbow function scores was found to be effective in the management of patients. Our current study showed that the type of fracture was an independent risk factor regarding postoperative complications. If a child developed a supracondylar humeral fracture, clinicians could use this visual scale to assess the risk of postoperative complications in combination with other relevant scores as well as X-rays to further prevent postoperative complications.4) The main finding of this study: independent prognostic factors identified using COX regression analysis in the training cohort contained six readily available clinical variables, and in the validation, the cohort contained three readily available clinical variables allowing for the prediction of the associated risk. The corresponding column line graph model was developed using COX regression, and validation of the nomogram confirmed the good risk prediction performance of the model. Interestingly, our study demonstrated that increasing age, as determined by the optimal cutoff value, was an important risk factor for the development of postoperative complications.

Medical nomograms provided predictive information tailored to the individual by creating a concise graph that generates numerical probabilities of clinical events[22-26], and in this study, we first identified independent predictors of the occurrence of postoperative fracture complications with parameters that suggested older than eight years, fracture type, and nerve injury.

The established nomogram showed moderate discriminatory power and was further externally validated. Overall, this predictive model allowed pediatricians to use the nomogram to assess the risk stratification of the probability of postoperative complications in children with supracondylar humeral fractures.

We acknowledged that this study had some limitations. First, the nature of this study was retrospective and there may be selection bias in the selection of the target population; second, a nomogram model based mainly on baseline levels of vital signs was established. Since these vital signs cannot be maintained at a certain level throughout the study period, this may lead to imprecise results compared to the normal range and may result in differences between predicted and observed values; third, all patients in this study were children who underwent surgery at the same hospital. To reduce error, a prospective trial with a large number of patients recruited from multiple institutions would help to address these limitations.

5. Conclusion

Taken together, the results suggested that clinical characteristics can be used as independent risk predictors for the development of complications after supracondylar fracture surgery. Combining vital signs and clinical risk factors into an easy-to-use nomogram was more likely to predict the probability of complications in patients after supracondylar fracture surgery, leading to more appropriate treatment modalities.

References

[1] Challa S, Agarwal-Harding KJ, Levy P, Barr-Walker J, Sabatini CS. Supracondylar humerus fractures in low- and lower-middle-income countries: a scoping review of the current epidemiology, treatment modalities, and outcomes. Int Orthop. 2020 Nov;44(11):2443-2448.

[2] Kropelnicki A, Ali AM, Popat R, Sarraf KM. Paediatric supracondylar humerus fractures. Br J Hosp Med (Lond). 2019 Jun 2;80(6):312-316.

[3] Berdis G, Hooper M, Talwalkar V, Walker J, Muchow R, Riley S, Iwinski HJ, Prusick V. Assessment of Lateral Rotation Percentage and Rotational Deformity of the Elbow in Type 3 Supracondylar Humerus Fractures: A Biomechanical Study. J Pediatr Orthop. 2021 Sep 1;41(8):e605-e609.

[4] Abzug JM, Herman MJ. Management of supracondylar humerus fractures in children: current concepts. J Am Acad Orthop Surg. 2012 Feb;20(2):69-77.

[5] Segal D, Cobb L, Little KJ. Fracture obliquity is a predictor for loss of reduction in supracondylar humeral fractures in older children. J Pediatr Orthop B. 2020 Mar;29(2):105-116.

[6] Lucas DE, Willis LM, Klingele KE. Factors predictive of early radiographic failure after closed reduction of Gartland type II supracondylar humeral fractures. J Orthop Trauma. 2013 Aug;27(8):457-61.

[7] Gaston RG, Cates TB, Devito D, Schmitz M, Schrader T, Busch M, Fabregas J, Rosenberg E, Blanco J. Medial and lateral pin versus lateral-entry pin fixation for Type 3 supracondylar fractures in children: a prospective, surgeon-randomized study. J Pediatr Orthop. 2010 Dec;30(8):799-806.

[8] De Pellegrin M, Fracassetti D, Moharamzadeh D, Origo C, Catena N. Advantages and disadvantages of the prone position in the surgical treatment of supracondylar humerus fractures in children. A literature review. Injury. 2018 Nov;49 Suppl 3:S37-S42.

[9] Erçin E, Bilgili MG, Baca E, Başaran SH, Bayrak A, Kural C, Avkan MC. Medial mini-open versus percutaneous pin fixation for type III supracondylar fractures in children. Ulus Travma Acil Cerrahi Derg. 2016 Jul;22(4):350-4.

[10] Uçar BY, Demirtaş A, Uçar DE. Treatment approaches and outcomes in childhood supracondylar humerus fractures. Eur Rev Med Pharmacol Sci. 2012 Jul;16(7):936-41.

[11] British Orthopaedic Association Trauma Committee. Supracondylar fractures of the humerus in children. Injury.

2021 Mar;52(3):376-377.

[12] Vaquero-Picado A, González-Morán G, Moraleda L. Management of supracondylar fractures of the humerus in children. EFORT Open Rev. 2018 Oct 1;3(10):526-540.

[13] Valencia M, Moraleda L, Díez-Sebastián J. Long-term Functional Results of Neurological Complications of Pediatric Humeral Supracondylar Fractures. J Pediatr Orthop. 2015 Sep; 35(6):606-10.

[14] Battle J, Carmichael KD. Incidence of pin track infections in children's fractures treated with Kirschner wire fixation. J Pediatr Orthop. 2007 Mar;27(2):154-7.

[15] Green SA. Complications of external skeletal fixation. Clin Orthop Relat Res. 1983 Nov;(180):109-16.

[16] Skaggs DL, Cluck MW, Mostofi A, Flynn JM, Kay RM. Lateral-entry pin fixation in the management of supracondylar fractures in children. J Bone Joint Surg Am. 2004 Apr;86(4):702-7.

[17] Gupta N, Kay RM, Leitch K, Femino JD, Tolo VT, Skaggs DL. Effect of surgical delay on perioperative complications and need for open reduction in supracondylar humerus fractures in children. J Pediatr Orthop. 2004 May-Jun;24(3):245-8.

[18] Battle J, Carmichael KD. Incidence of pin track infections in children's fractures treated with Kirschner wire fixation. J Pediatr Orthop. 2007 Mar;27(2):154-7.

[19] Sabharwal S, Tredwell SJ, Beauchamp RD, Mackenzie WG, Jakubec DM, Cairns R, LeBlanc JG. Management of pulseless pink hand in pediatric supracondylar fractures of humerus. J Pediatr Orthop. 1997 May-Jun;17(3):303-10.

[20] de Gheldere A, Bellan D. Outcome of Gartland type II and type III supracondylar fractures treated by Blount's technique. Indian J Orthop. 2010 Jan;44(1):89-94.

[21] Zorrilla S de Neira J, Prada-Cañizares A, Marti-Ciruelos R, Pretell-Mazzini J. Supracondylar humeral fractures in children: current concepts for management and prognosis. Int Orthop. 2015 Nov;39(11):2287-96.

[22] Iqbal M, Habib-ur-Rehman. Nerve injuries associated with supracondylar fracture of the humerus in children. J Pak Med Assoc. 1994 Jun;44(6):148-9.

[23] Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008 Mar 10;26(8):1364-70.

[24] Van Belle V, Van Calster B. Visualizing Risk Prediction Models. PLoS One. 2015 Jul 15;10(7):e0132614.

[25] Bonnett LJ, Snell KIE, Collins GS, Riley RD. Guide to presenting clinical prediction models for use in clinical settings. BMJ. 2019 Apr 17;365:l737.

[26] Martin GP, Sperrin M, Snell KIE, Buchan I, Riley RD. Clinical prediction models to predict the risk of multiple binary outcomes: a comparison of approaches. Stat Med. 2021 Jan 30;40(2):498-517.

Abbreviations

SCHF: Supracondylar humeral fractures.

CRPP: Closed reduction and percutaneous pinning.

ROC: the Receiver operating characteristic curve.

AUC: the Area under the curve.

DCA: decision curve analysis.

Fund Project

Supported by S＆T Program of Chengde NO. 202109A075 , S＆T Program of Chengde NO. 202204A063 and Medical Science Research Project of Hebei Province NO.20210846. The funding bodies have no responsibilities in study design, the collection, analysis, and interpretation of data, the writing of the report, and the decision to submit the manuscript.

The Value of Breast-Conserving Surgery Combined with Neoadjuvant Therapy for Breast Cancer

Zhu Wu, Zhuo Wang, Qingqing Ye, Rong Fan
Jingzhou First People's Hospital, Jingzhou 434000, China.

Abstract: Objective: To observe the efficacy of different methods in the treatment of breast cancer disease. Methods: A sample of 78 patients attending the clinic from 2020.8 to 2023.1 was randomly selected and divided into groups A and B. Thirty-nine patients each underwent conventional breast-conserving surgery and group B combined with neoadjuvant therapy to compare the effectiveness of treatment between the groups. Results: The overall efficiency of group B vs group A was 94.87% vs 71.79%, a significant difference ($P < 0.05$). Surgery-related indicators were better in Group B than in Group A ($P<0.05$).Conclusion: Early intervention with breast-conserving surgery combined with neoadjuvant therapy is recommended for patients with breast cancer and has demonstrated high clinical value.

Keywords: Breast Cancer; Breast-Conserving Surgery; Neoadjuvant Therapy; Value Analysis

Breast cancer is a malignant tumour disease originating from the epithelium of the breast, and women aged 40 to 55 are the most common group for this disease. The clinical research on the physiology and pathology of breast cancer is becoming more and more advanced, and it has been reported that breast-conserving surgery combined with neoadjuvant therapy can achieve better results in the treatment of this disease. In this paper, we now include data of 78 patients and compare them in groups to confirm the effectiveness of the above combined therapy treatment, which is reported as follows.

1. Data and methods

1.1 General information

The 78 patients included in the study were diagnosed with breast cancer, had definite indications for surgical treatment and cooperated actively with the study. They were divided into two groups of 39 cases each, with each group as follows.

Group A: age range 34-61 years, duration of disease 2-7 months, pathological stage: stage II and III in 14 and 25 cases respectively.

Group B: Age range 32-61 years, duration of disease 3-8 months, stage: 17 and 21 cases each of stage II and III.

The above baseline data of patients were compared between groups ($P > 0.05$).

1.2 Methods

Group A was treated with conventional breast-conserving surgery, i.e. local excision of the tumour site under general anaesthesia, and intraoperative pathological tissue examination was completed quickly. If a certain margin is positive, the resection area should be expanded by about 1 ㎝ to ensure that the cut edge of the lesion is negative.

In group B, the treatment method for breast-conserving surgery is the same as in group A, combined with neoadjuvant therapy, i.e. 75 p.m./㎡ + 600 p.m./㎡ epirubicin, d1. 550 p.m./㎡ cyclophosphamide d2, d8. 450 p.m./㎡, d2, d7. 1 week of continuous treatment as a course of treatment, usually about 3 courses of treatment.

1.3 Observation indicators

(1) Judgment of efficacy: ① remission: the symptoms of breast cancer disease were greatly relieved after treatment and the physical examination results were good; ② partial remission: the symptoms were partially relieved after treatment, but breast swelling and pain and overflow still existed; ③ invalid: the disease performance was not reduced before and after treatment, or the condition deteriorated. The percentage of the number of remission and partial remission in the total number of cases in the group was used to indicate the total effective rate.

(2) Surgery-related indicators: time spent on surgery, first time out of bed, extubation and hospitalization time.

1.4 Statistical processing

SPSS 21.0 software package was used to process the data. When the measurement and counting data conformed to the pattern of normal distribution, t and X^2 tests were used respectively. $P < 0.05$ was regarded as a statistically significant difference in the data.

2. Results

2.1 Clinical efficacy

In group B, 29 cases met the criteria for remission, with a total effective rate of 94.87%; in group A, the corresponding values of the above two indicators were 19 cases and 71.79%, respectively, and the clinical efficacy of group B was better than that of group A ($P < 0.05$), Table 1.

Table 1 Comparison of clinical outcomes between the two groups of patients

Group（n）	Relief	Partial relief	Invalid	Total validity（%）
Group B（39）	29	8	2	37（94.87）
Group A（39）	19	9	11	28（71.79）

2.2 Surgical indicators

Both in terms of surgical time spent and extubation time indicators, Group B outperformed Group A. The difference in data reached a significant level ($P < 0.05$), Table 2.

Table 2 Comparison of surgical index tests between the two groups of patients $(\bar{x} \pm s)$

Group（n）	Surgery time（min）	Getting out of bed for the first time（d）	Extubation time（d）	Length of stay in hospital（d）
Group B（39）	41.25±4.46	3.14±0.62	3.89±0.79	4.32±1.37
Group A（39）	84.27±18.52	4.63±1.33	7.92±1.36	7.85±1.40

3. Discussion

Traditional open surgery for the treatment of breast cancer involves the removal of a large amount of breast tissue, which is difficult to meet the requirements put forward by patients for the aesthetics of their breasts and is not conducive to maintaining their physical and mental health [2]. Breast-conserving surgical treatment preserves the patient's breast, allows selective removal of diseased breast tissue, and precisely clears the axilla and surrounding residual tissue lesions, significantly increasing the aesthetic appearance of the breast while ensuring the treatment effect. The combination of breast conservation and neo-adjuvant chemotherapy can facilitate early recovery without damaging the breast, using a combination

of chemotherapy treatments. Neoadjuvant therapy uses chemotherapy drugs to reduce the size of the breast lump, but in practice the duration of adjuvant treatment is set in relation to the patient's condition, for example, some patients are treated with breast-conserving surgery after 2 courses of chemotherapy, while some patients require longer chemotherapy. In patients with locally advanced breast cancer, neoadjuvant interventions can be downgraded to meet the indications for breast-conserving treatment and increase the safety of breast-conserving treatment [3].

In this study, the time spent on surgery, first time out of bed, extubation and hospital stay were (41.25±4.46) min, (3.14±0.62) d, (3.89±0.79) d, (4.32±1.37) d, respectively, compared to (84.27±18.52) min, (4.63±1.33) d, (7.92±1.36) d, ((7.85±1.40) d, a significant difference, and the total effective rate was higher in group B than in group A, confirming the effectiveness of the combination therapy with the data. The reason for this may be that the neoadjuvant chemotherapy stage allows for real-time assessment of lesion size, anatomical location and depth, etc., which can then be used to consider whether or not to electively operate, and after treatment, the residual tumour status can be assessed in combination with the patient's disease manifestations and imaging findings, which can then present a more objective picture of the treatment effect, reasonably predict the risk of recurrence, etc., and use more effective means to intervene.

In conclusion, early intervention with breast-conserving surgery combined with neoadjuvant therapy is recommended for patients with breast cancer, with definite results and demonstrating high clinical value.

References

[1] Yuan S. L.,Chen Y.,Wang Y. Recent efficacy and prognosis analysis of plastic breast-conserving surgery for early breast cancer [J]. Chinese aesthetic medicine, 2022,31(12):33-35.

[2] Wang L. Effectiveness of plastic breast-conserving surgery in the treatment of early breast cancer[J]. China Medical Guide,2022,20(28):45-48.

[3] Wang JB, Zheng RS. Advances in neoadjuvant endocrine therapy for breast cancer[J]. Journal of Bengbu Medical College,2009,34(11):1048-1050.

Author Bio:

First author

Name: Wu zhut (1982.5.14-), Male, Han Nationality, Place of Origin: Xiangtan, Hunan, Master, Title: Attending Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main Research Interests: Comprehensive treatment of breast cancer, diagnosis and treatment of non-lactating mastitis, postoperative reconstruction of breast tumor.

Corresponding author

Fan Rong (1980.1.10-), F, Han, Place of origin: Hubei. Jingzhou, Master, Title: Attending, Unit: Jingzhou First People's Hospital, Department: Department of Respiratory and Critical Care, Major research interests: chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension, ECMO life support, etc.

Second author

Wang Zhuo (1968.10.10-), Male, Ethnicity: Han, Origin: Xiangyang City, Hubei Province, Highest Education: B.S., Title: Deputy Chief Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main Research Interests: Comprehensive diagnosis and treatment of breast diseases and breast tumors, post-operative breast reconstruction, minimally invasive treatment of breast diseases, etc.

Third author

Ye Qingqing (1979.2.23-), Female, Ethnicity: Han, Place of origin: Nanning, Guangxi, Highest education: Master, Title: Deputy Chief Physician, Unit: Jingzhou First People's Hospital, Department: Breast Surgery, Main research interests: standard treatment of breast tumours, surgical management of breast cancer.

A Perplexing Case of a DUOX2 Mutation and Graves' Disease

Li Yuan, Hongping Sun, Xue Yang, Mingxue Zhang, Guofang Chen
Department of Endocrinology, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Traditional Chinese Medicine; Key Laboratory of TCM Syndrome & Treatment of Yingbing of State Administration of Traditional Chinese Medicine, Jiangsu Provincial Academy of Traditional Chinese Medicine, Nanjing 210028, China.

Abstract: It is commonly accepted that DUOX2 mutations may cause congenital hypothyroidism and thyrotropin resistance, thus its combination with Graves' disease would be unusual. In this case, our patient's serum thyroid function tests suggested a high probability of thyroid hormone resistance syndrome, but genetic testing did not suggest gene mutations of THRα or THRβ. This is a rare case report of thyroid hormone resistance.

Keywords: Graves' Disease; DUOX2 Mutations; Thyroid Hormone Resistance Syndrome

Introduction

The effects of the thyroid hormone are mediated by thyroid hormone receptors (TRs). There are two different subtypes of TR, TRα, and TRβ. Therefore, the syndrome of resistance to thyroid hormone (RTH), which is characterized by the reduced response to thyroid hormone in various tissues, should include RTH due to TRα mutation (RTHα) in addition to RTH due to TRβ mutation (RTHβ).

In this case, the patient's thyroid function level suggested a high probability of thyroid hormone resistance syndrome, but genetic testing did not suggest mutations in the THRα or THRβ genes. Interestingly, however, in previous studies, it was found that (1) the probability of patients with thyroid hormone resistance syndrome without THRα or THRβ gene mutations is about 15%, and (2) DUOX2 gene mutations are often likely to be nonsense mutations. Combining the above 2 points, we suspect that the mutation in this patient may be a nonsense mutation, and this patient belongs to the 15% non-mutation scenario.

Case report

In May 2009, a 15-year-old young woman presented to a local hospital with neck swelling, heat intolerance, sweating, excessive hunger, panic, and hand tremors with no apparent cause. Based on serum thyroid function testing, she was diagnosed with Graves' disease and treated with anti-thyroid drug therapy. However, her thyroid function remained uncontrolled, thus she was treated with three repeated doses of 131I (doses unknown) in January 2013, June 2013, and October 2014. The patient's hyperthyroidism recurred within six months after the first two 131I doses, then she became hypothyroid after completion of the third 131I dose.

The patient's father had a history of mild asymptomatic hyperthyroidism that was not treated with any medication.The patient then showed unexplained changes in her serum thyroid function tests starting in January 2016. Serum free triiodothyronine (FT3) and free thyroxine (FT4) values were both elevated when the serum thyrotropin (TSH) was normal; yet when the FT3 and FT4 levels were low, the TSH levels could be extremely high.

In August 2020, repeat serum thyroid function tests showed: FT3 4.26 pmol/L (reference, 3.1-6.8 pmol/L) , FT4 27.87 pmol/L (reference, 12-22 pmol/L) , TSH 23.38 μIU/ml (reference, 0.27-4.20 μIU/ml) , thyroglobulin antibody 137 IU/ml (reference, 0-115IU/ml) , thyroid peroxidase antibody 132 IU/ml (reference, 0-34IU/ml). She was confirmed to have a third pregnancy. She was depressed, weak, and dizzy, had a foreign body sensation in the neck, and reported paroxysmal pain in the abdomen. There was no heat intolerance, blurred vision, recent memory loss, weight loss, nor abnormal bowel movements. Physical examination revealed a normal-sized thyroid gland that was mobile and non-tender.

Considering that the patient's thyroid function abnormalities were difficult to explain, the patient and her immediate family were advised to have a thorough evaluation to include genetic testing. The patient's father remained asymptomatic and had no signs of hyperthyroidism. Her mother and brother had no abnormalities in their serum thyroid function tests.

Genetic testing suggested that the patient had a heterozygous mutation in the DUOX2 gene (c.127A>T), resulting in a pathogenic mutation (p.N43Y). Treatment was begun with levothyroxine (Eugenol) 175 μg once daily and hydrocortisone 10 mg once daily. She was also begun on calcium and vitamin D supplementation, progesterone, and dydrogesterone fetal preservation therapy. On this therapy, the patient was able to deliver a baby boy, who had a mildly elevated serum TSH on a heelstick blood screen and for which further follow-up will be needed.

Discussion

In this case, the patient had a foreign body sensation in the neck as the main clinical manifestation, and no enlargement of the thyroid gland was seen on physical examination, and the patient was treated with "hyperthyroidism" at the local hospital. However, from January 2016, all hospital tests of thyroid function suggested some kind of resistance relationship between TSH levels and FT3 and FT4, which was inconsistent with the common clinical regression of hyperthyroidism. The patient's father had mildly elevated serum FT3 and FT4, but had been in good health since childhood without any discomfort. Combining the patient's medical history, treatment history and family history, it was highly suggested that the patient had a combination of thyroid hormone resistance syndrome, so full gene sequencing was performed, which revealed that both the patient and his father had DUOX2 gene mutation.

This case reports a female patient who suffered from chronic thyroid function abnormalities. The following 3 points should be focused on in this case: (1) Cases of Graves Disease and resistance of thyroid hormone have been reported, but cases of Graves Disease and resistance of thyroid hormone combined with DUOX2 mutation has not been reported; (2) Most resistance of thyroid hormone has a genetic mutation, but there is a small percentage without a mutation; (3) Most reported DUOX2 mutations are associated with hypothyroidism, but whether DUOX2 is significant in this case needs to be further explored.

Our patient developed unexplained changes in thyroid function and was considered to be resistant for thyroid hormones after being hospitalized in our hospital. Further thyroid-related genetic testing did not reveal mutations in THRα and THRβ. The combination of Graves Disease, thyroid hormone resistance and DUOX2 mutation was thus considered, which has not been reported in the previous literature.

The earliest record of RTH, also known as syndrome of inappropriate TSH secretion (SITSH), was reported by Refetoff [1] et al. in an RTH genetic family presenting with elevated thyroid hormone with thyrotropin levels. Germline mutations in the TRβ gene were first identified in a patient with RTH in 1989 [2]. TRα mutations were first reported in 2012 [3] , and TRα mutations are not present in SITSH. In addition, mutations in TRβ and TRα are not found in some SITSH patients [4] , and these patients are in about 10-15% of RTH [5].

In 2010, Japanese scholar Sato[6] reported a case of hyperthyroidism combined with thyroid hormone resistance. Sato's case report suggests that Graves' disease combined with thyroid hormone resistance syndrome can be completely remitted by methimazole treatment, but there is no standardized control goal, which should be combined with clinical manifestations and

thyroid function levels, maintaining thyroid function at slightly high levels of FT4 and FT3 and normal or slightly high levels of TSH, and avoiding drug overdose as much as possible. If a patient with Graves' disease has normalized FT4 and FT3 after drug treatment but is hypothyroid, this is highly suggestive of a combination of thyroid hormone resistance syndrome.

The thyroid hormone resistance syndrome combined with Graves' hyperthyroidism has been rarely reported, with only 6 cases reported worldwide. There is no unified treatment guideline, and pharmacological treatment is the first choice. Hyperthyroidism can be well controlled, but the control goal should be combined with the patient's clinical performance and thyroid function level.

At present, it is believed that simple thyroid hormone resistance is not suitable for treatment with antithyroid drugs, surgery or radioactive iodine, because lowering the circulating level of thyroid hormone will weaken the negative feedback inhibitory effect of thyroid hormone on the secretion of pituitary TSH cells, resulting in further increase in serum TSH concentration, TSH cell hyperplasia, and even the development of pituitary tumors. However, it is interesting to note that a small number of thyroid hormone resistance syndromes do not have genetic mutations and the molecular mechanisms need to be further investigated.

Another aspect, Congenital primary hypothyroidism (CH) is a state of inadequate thyroid hormone production detected at birth, caused either by absent, underdeveloped or ectopic thyroid gland (dysgenesis), or by defected thyroid hormone biosynthesis (dyshormonogenesis)[7]. The gene DUOX2 or THOX2 encodes the human protein dual oxidase 2 (DUOX2), a member of the NADPH oxidase family. Hydrogen peroxide (H2O2) is essential for thyroperoxidase-mediated thyroid hormone synthesis in the follicular lumen of the thyroid gland. DUOX2 and its maturation factor and essential partner, DUOXA2, play a crucial role in H2O2 generation, necessary for the biological activation of TPO[8]. Previous studies have mostly reported on DUOX2 gene mutations causing hypothyroidism, but in this case, CH was not seen in the patient, nor was it seen in her immediate family. This situation still requires further discussion.

In this case report, the patient's father had a thyroid function presentation consistent with thyroid hormone resistance syndrome, but genetic testing suggested a DUOX2 mutation. This raises the suspicion that the DUOX2 mutation is a nonsense mutation and that in actual clinical studies there is a 15% probability that the thyroid hormone resistance syndrome does not have a mutation.

It is believed that a small proportion of thyroid hormone resistance syndromes are still free of genetic mutations, and the specific molecular mechanisms need to be further investigated.

References

[1] Refetoff S, Dewind L T, Degroot L J. Familial syndrome combining deaf-mutism, stuppled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone[J]. J Clin Endocrinol Metab. 1967, 27(2): 279-294.

[2] Sakurai A, Takeda K, Ain K, et al. Generalized resistance to thyroid hormone associated with a mutation in the ligand-binding domain of the human thyroid hormone receptor beta[J]. Proc Natl Acad Sci U S A. 1989, 86(22): 8977-8981.

[3] Bochukova E, Schoenmakers N, Agostini M, et al. A mutation in the thyroid hormone receptor alpha gene[J]. N Engl J Med. 2012, 366(3): 243-249.

[4] Weiss RE, Hayashi Y, Nagaya T, et al. Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptor alpha or beta genes may be due to a defective cofactor[J]. J Clin Endocrinol Metab. 1996, 81(12): 4196-4203.

[5] Dumitrescu AM, Refetoff S. The syndromes of reduced sensitivity to thyroid hormone[J]. Biochim Biophys Acta. 2013, 1830(7): 3987-4003.

[6] Sato H. Clinical features of primary hyperthyroidism caused by Graves' disease admixed with resistance to thyroid hormone (P453T)[J]. Endocr J. 2010, 57(8): 687-692.

[7] Kostopoulou E, Miliordos K, Spiliotis B. Genetics of primary congenital hypothyroidism-a review[J]. Hormones (Athens). 2021, 20(2): 225-236.

[8] Carvalho DP, Dupuy C. Role of the NADPH Oxidases DUOX and NOX4 in thyroid oxidative stress[J]. Eur Thyroid J. 2013, 2(3): 160-167.

Research Progress of Laboratory Diagnosis of TB

Mimi Zhang [1], Jiayun Liu [1,2*]

1. School of Medical Technology, Shaanxi University of Chinese Medicine, Xianyang 712000, China.

2. Xijing Hospital, Forth Military Medical University, Xi'an 710032, China.

Abstract: Early, rapid, and accurate identification of Mycobacterium tuberculosis is crucial to the treatment and management of the disease, and laboratory diagnosis is an important means for its diagnosis, treatment, and prevention control. Common methods include pathogenic methods based on bacterial smear and culture, molecular methods based on polymerase chain reaction (PCR), immunological methods such as tuberculin skin test and gamma-interferon (IFN-γ) release test, and the latest emergence of molecular methods, such as Xpert MTB/RIF and CRISPR technology have provided new perspectives for TB diagnosis. This review focuses on the main research advances in laboratory diagnosis of TB.

Keywords: TB; Mycobacterium Tuberculosis; Laboratory Diagnosis

Introduciton

Tuberculosis (TB) is a chronic wasting disease caused by Mycobacterium tuberculosis (M.tb). Due to its high incidence and mortality, TB has become one of the primary research objects in public health, infectious disease prevention and treatment[1]。Tuberculosis is one of the highest mortality rates from a single source currently, especially since the outbreak of novel Coronavirus in 2019, the shortage of medical resources make the increasing number of people infected with tuberculosis [2,3]。As a large country with tuberculosis infection, China has so great difficulties to the prevention and control of tuberculosis due to the epidemic of AIDS, mycobacterium tuberculosis drug resistance and the emergence of multi-drug-resistant tuberculosis bacteria.

Early, timely and effective treatment is crucial for TB patients, which relies on rapid and accurate diagnostic techniques. At present, the commonly used diagnostic methods in the laboratory include microscopic microscopy, bacterial culture, immunological examination, molecular biology examination and so on. Bacterial culture is the gold standard for tuberculosis diagnosis, but due to the slow growth of Mycobacterium tuberculosis, the isolation, identification and drug sensitivity testing of Mycobacterium tuberculosis usually take several weeks with a low sensitivity; although molecular diagnostic methods improve the detection sensitivity and specificity, most of them rely on large equipment and professional technicians; immunological diagnosis usually has poor specificity and high false positive rate due to the existing antigen or antibodies and other microorganisms[4]. None of these methods meet the clinical need for rapid and accurate detection. With the deepening of continuous research in recent years, the laboratory detection methods of tuberculosis have been continuously improved. This article reviews the current status and progress of laboratory tests for TB.

1. Bacteriological detection

1.1. Microscopy of traditional smear staining

Traditional microscopic detection of Mycobacterium tuberculosis after smear acid-fast staining is still a simple and

rapid method to confirm pulmonary tuberculosis. Cellule-Nielsen acid staining microscope as a classic MTB detection method is widely used, because of its simple, fast, high specificity, cheap, without special equipment and other advantages , but its also has the following disadvantages: such as low sensitivity, cannot distinguish between active and inactive tuberculosis, and also limited by sputum specimen is qualified or not and inspection personnel technical level[5].

In addition, there is also the fluorescent staining method represented by gold amine O-rhodamine. Compared with the traditional smear acid staining, this method makes the smear fluorescent staining fast, which greatly shortens the reading time, so is more suitable for the examination of a large number of specimens, and improves the sensitivity of microscopy[6]. Although used as a WHO-recommended highly specific method for detecting Mycobacterium tuberculosis, its difficult to use in poor area because the fluorescence microscopy is expensive[7].

1.2 Light-emitting diodes (LED) fluorescence microscopy

In recent years, some researchers combine fluorescence microscope technology with light-emitting diode (LED), developed a tool named LED fluorescence microscope, which compared with ordinary fluorescence microscope has many advantages, such as simple operation, long life, low price, no light and dark vision requirements, short reading time at the same time has high sensitivity and specificity[8]. This makes it have great application value in the basic hospitals. The WHO recommends using LED fluorescence microscope instead of conventional light microscope[9].

1.3 Culture of Mycobacterium tuberculosis

Isolation and culture of Mycobacterium remains the gold standard for detection of Mycobacterium tuberculosis. Its sensitivity is higher than smear staining microscopy, but due to the biological characteristics of the slow growth of Mycobacterium tuberculosis, the traditional solid culture method will take 4-8 weeks to detect the growth of Mycobacterium tuberculosis, but the positive rate is low and it is more difficult to distinguish whether it is Mycobacterium tuberculosis, so that it have to get the help of Mycobacterium species identification and drug sensitivity tests[10]. The principle of liquid culture of Mycobacterium is to use the liquid medium containing redox display agent for culture, when there is mycobacterial growth, the redox system reduces the colorless tetrazolium salt in the medium to a water-insoluble purple-red substance, which can be easily observed by visual observation. The subsequent development of liquid rapid culture systems, such as Mycobacterial growth indicator tube (MGIT) 960 system, which includes a growth system and an indicator system, has a higher degree of automation, a higher rate of positive isolation, a shorter time required for detection, and the ability to perform drug sensitivity tests. However, it is difficult to be widely used in developing countries with high prevalence of TB due to its high price[11].

2. Molecular biology testing

2.1 Polymerase chain reaction

Polymerase chain reaction PCR is the most common nucleic acid amplification method to determine whether infection is tuberculosis by testing the nucleic acid sequence specific to Mycobacterium tuberculosis. Compared with traditional examination methods, it has the advantages of speed, high sensitivity, strong specificity and no need for long bacterial culture. Some studies have shown that the positive rate of Mycobacterium tuberculosis by PCR is significantly higher than by smear microscopy. PCR amplification technology has been widely used since its inception in 1980, but it also has many disadvantages, such as high false positives, easy pollution, cumbersome operation, and the need for professional equipment and personnel[12].

2.2 Loop-Mediated Isothermal Amplification(LAMP)

Loop-mediated isothermal amplification(LAMP) is a novel isothermal amplification technique that allows nucleic acid amplification to detect MTB DNA fragments at 65℃ to achieve the diagnosis of TB. Based on this, another molecular detection method recognized by WHO named tuberculosis ring-mediated isothermal amplification (TB-LAMP) has been developed, and can even be used as an alternative method for smear microscopic examination, with high sensitivity, simplicity and speed[13,14].

2.3 Nucleic acid amplification of real-time rifampicin resistance

Mycobacterium tuberculosis and the rapid molecular detection system-Xpert MTB/RIF can directly detect the presence of Mycobacterium tuberculosis and the resistance to rifampin within 2h[15]. This method is based on semi-nested real-time PCR and uses the rpoB gene as the target gene. In recent years, Xpert has been widely used in MTB and rifampicin resistance testing in clinical specimens, with the advantages of simple operation, short time consuming, high sensitivity and specificity, and good biological safety, so it has been recommended by WHO as the preferred method for molecular drug susceptibility detection of MTB[16].

3. Immunological testing

3.1 Tuberculin skin test

Tuberculin skin test (TST) as a simple, low cost of mycobacterium tuberculosis infection diagnosis method is widely used in China, especially in the childhood tuberculosis diagnosis. However, due to the cross-reactivity of this method with the antigenic components of BCG (bacillus Calmette-Guérin, BCG) and non-tuberculous mycobacteria, its sensitivity and specificity are low, application in tuberculosis diagnosis is limited[17].

3.2 γ -interferon (IFN- γ) release test

The γ -interferon release assay (IGRA) utilizes that mycobacteria contain specific proteins, but BCG strains and most nontuberculous mycobacteria do not contain these proteins[18]. When the body is infected with tuberculosis, by adding polypeptide antigen of mycobacterium specific protein, it can stimulate the T cells infected with Mycobacterium tuberculosis to produce interferon γ, which can reflect the cell immune intensity of the cell, so as to determine whether infected with tuberculosis[19]. Including whole blood-based enzyme-linked immunosorbent assay and peripheral blood lymphocyte-based immune spot assay T-SPOT.TB. It has high specificity and sensitivity, and is not affected by body immunity and BCG vaccination. It has high diagnostic value for incubation period, atypical tuberculosis and extrapulmonary tuberculosis and HIV with tuberculosis infection[20].

In conclusion, there are so many laboratory methods for TB diagnosis currently, but all have their own advantages and disadvantages. Bacteriological method is the gold standard but long time consuming and low sensitivity; molecular diagnosis is fast and sensitive, which is the ideal clinical diagnostic method. Especially, with the development of CRISPR-Cas technology, more and more rapid diagnostic methods emerged, but also has the disadvantages of expensive instruments and reagents. At present, tuberculosis is still a global health problem, and the situation of tuberculosis prevention and control in China is very serious, so we need to complement various methods, in order to provide a strong basis for the diagnosis and treatment of tuberculosis.

References

[1] Natarajan A, Beena P M, Devnikar A V, et al. A systemic review on tuberculosis[J]. Indian J Tuberc, 2020, 67(3): 295-311.

[2] Visca D, Ong C W M, Tiberi S, et al. Tuberculosis and COVID-19 interaction: A review of biological, clinical and public health effects[J]. Pulmonology, 2021, 27(2): 151-165.

[3] Can Sarınoğlu R, Sili U, Eryuksel E, et al. Tuberculosis and COVID-19: An overlapping situation during pandemic[J]. J Infect Dev Ctries, 2020, 14(7): 721-725.

[4] Acharya B, Acharya A, Gautam S, et al. Advances in diagnosis of Tuberculosis: an update into molecular diagnosis of Mycobacterium tuberculosis[J]. Mol Biol Rep, 2020, 47(5): 4065-4075.

[5] Dzodanu EG, Afrifa J, Acheampong DO, et al. Diagnostic Yield of Fluorescence and Ziehl-Neelsen Staining Techniques in the Diagnosis of Pulmonary Tuberculosis: A Comparative Study in a District Health Facility[J]. Tuberc Res Treat, 2019, 2019: 4091937.

[6] Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review[J]. Lancet Infect Dis, 2006, 6(9): 570-81.

[7] Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review[J]. Lancet Infect Dis, 2006, 6(10): 664-74.

[8] Bhalla M, Sidiq Z, Sharma P, et al. Performance of light-emitting diode fluorescence microscope for diagnosis of tuberculosis[J], 2013, 2(3): 174-178.

[9] WHO Guidelines Approved by the Guidelines Review Committee, Fluorescent Light-Emitting Diode (LED) Microscopy for Diagnosis of Tuberculosis: Policy Statement, Geneva: World Health Organization Copyright © 2011, World Health Organization., 2011.

[10] Wallace E, Hendrickson D, Tolli N, et al. Culturing Mycobacteria[J]. Methods Mol Biol, 2021, 2314: 1-58.

[11] Kohli A, Bashir G, Fatima A, et al. Rapid drug-susceptibility testing of Mycobacterium tuberculosis clinical isolates to first-line antitubercular drugs by nitrate reductase assay: A comparison with proportion method[J], 2016, 5(4): 469-474.

[12] Maclean E, Kohli M, Weber S F, et al. Advances in Molecular Diagnosis of Tuberculosis[J]. J Clin Microbiol, 2020, 58(10).

[13] Yadav R, Daroch P, Gupta P, et al. Diagnostic accuracy of TB-LAMP assay in patients with pulmonary tuberculosis...a case-control study in northern India[J]. Pulmonology, 2022, 28(6): 449-453.

[14] Kamra E, Mehta PK. Current updates in diagnosis of male urogenital tuberculosis[J]. Expert Rev Anti Infect Ther, 2021, 19(10): 1175-1190.

[15] Umair M, Siddiqui SA, Farooq MA. Diagnostic Accuracy of Sputum Microscopy in Comparison With GeneXpert in Pulmonary Tuberculosis[J]. Cureus, 2020, 12(11): e11383.

[16] Saeed M, Iram S, Hussain S, et al. GeneXpert: A new tool for the rapid detection of rifampicin resistance in mycobacterium tuberculosis[J]. J Pak Med Assoc, 2017, 67(2): 270-274.

[17] Li Z, Hu J, Liu P, et al. Microarray-based selection of a serum biomarker panel that can discriminate between latent and active pulmonary TB[J]. Scientific Reports, 2021, 11(1): 14516.

[18] Wang S, Wu J, Chen J, et al. Evaluation of Mycobacterium tuberculosis-specific antibody responses for the discrimination of active and latent tuberculosis infection[J]. International Journal of Infectious Diseases, 2018, 70: 1-9.

[19] Kisuya J, Chemtai A, Raballah E, et al. The diagnostic accuracy of Th1 (IFN-γ, TNF-α, and IL-2) and Th2 (IL-4, IL-6 and IL-10) cytokines response in AFB microscopy smear negative PTB- HIV co-infected patients[J]. Scientific Reports,

2019, 9(1): 2966.

[20] Abebe F, Holm-Hansen C, Wiker HG, et al. Progress in serodiagnosis of Mycobacterium tuberculosis infection[J]. Scand J Immunol, 2007, 66(2-3): 176-91.

* National Natural Science Foundation of China (81972026)

Investigation and Fabrication of Micromotors for Biomedical Applications

Yu'ang Zhang
College of Chemistry and Materials Science, Jinan University, Guangzhou 510632, China.

Abstract: The research of micromotors have received extensive attention in recent years, and their iconic feature is the ability to utilize external energy to achieve autonomous motion then carry out various tasks. Micromotor for biological applications is a common type of micromotors, this specific type of micromotor is capable to be applied to drug delivery system and transportation of cells. The content of this article is to introduce examples, potential, and current problems of micromotors based on hydrogels or other kind of environment-friendly materials for cell culture and drug delivery, and to further explore the effects of hydrogels and micromotors on cells and drugs. In addition, methods and steps of the preparation of a four-sided, dual-power Sodium Alginate (SA) hydrogel micromotor is demonstrated and explicitized, the micromotor's ability to achieve independent movement and its potential applications are also explored.

Keywords: Micromotor; Bioengineering; Tissue Engineering; Hydrogel

Introduction

Inspired and influenced by natural biological motors, artificial micromotors, which can convert external energy into motion are considered as a new type of intelligent biomimetic materials. Because its function is similar to the motor in daily life, it is often referred to as micromotor by researchers. Micromotors have received extensive attention due to their wide range of applications. Since researchers first reported millimeter-scale chemically actuated motors in 2002, more and more researchers have proposed various types of novel micromotors with autonomous motion capabilities are developing rapidly. Due to the unique self-transforming ability of micromotors, they may revolutionize bioapplication fields, including active drug delivery, biological surgery, environmental remediation, and micro/nanoengineering.

However, due to the complexity and particularity of diseases in different parts of the human body, although the capability of active movement of micromotors can bring benefits and revolutionary changes to traditional disease treatments, the realization of many advantages of micromotors in disease treatment is still in its infancy and the actual micromotor-based drug delivery system for disease treatment *in vivo* is still far from clinical application. There are still many problems and limitations in the application and research of micromotors. At present, many major diseases (such as cancer, cardiovascular diseases, organ fibrosis, etc.) have limited therapeutic drugs and poor therapeutic effects due to their complex pathogenesis and environment of diseased tissue, thus the need for innovative therapeutics involving micro and nanotechnology is imminent.

Literature Review

In previous literature, a series of micromotors fabricated by different materials and different methods can successfully accomplish a large number of direct medical and biological tasks, such as biosensing, in vivo imaging, cancer therapy, diagnostic analysis, etc., among which drug delivery and cell encapsulation It is the relatively common and main application

of micromotors. (Figure 1).

Figure 1

Micromotor Based on Pine Pollen for Drug Delivery[1]

Taking a micromotor based on pollen as an example, the author developed a pollen based micromotor (PPBM) using natural pine pollen as material. After remove the lipid on the outer wall to improve its permeability, Fe_3O_4 magnetic nanoparticles (MNPs) and drugs are filled into the two cavities by vacuum loading. The resulting micromotor can realize the rolling, tumbling and spinning under the manipulation of the external magnetic filed (MF) (Figure 2), which has a great potential as a carrier applies to targeted drug delivery.

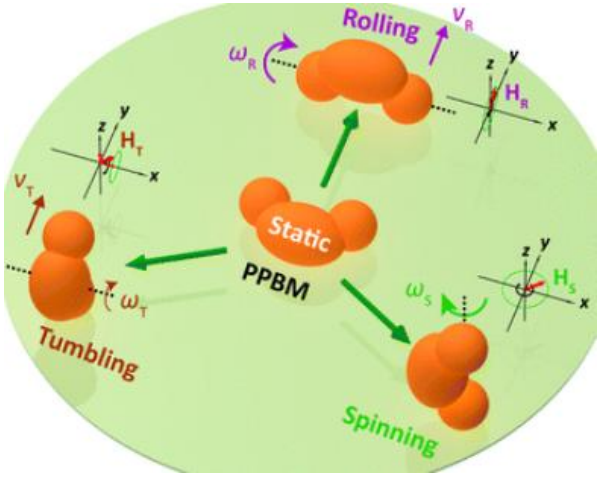


Figure 2

Micromotors for Pickup and Transportation of Circulating Tumor Cells (CTCs)[2]

In this article, The authors prepared a hollow tubular micromotor called microrocket and use H_2O_2 and catalase as a power source to provide traction to transport large cells, for example, CTCs. Antibodies were also attached to the surface of the micromotor, so that the microrocket is able to identify, grab, and transport CTCs (Figure 3) , thus could be applied to extract tumor cell samples for the early detection of cancer and to prevent its recurrence, and to reduce the chances of cancer metastases and recurrence. It can be a solution to efficiently separate cancer cells, diagnose cancer, and prevent cancer recurrence.

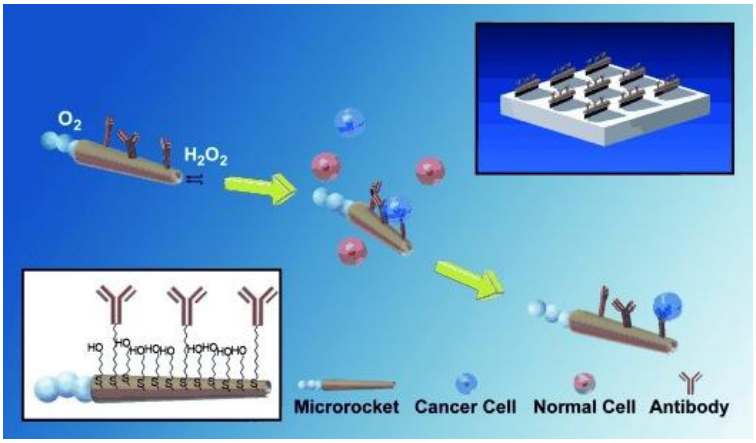


Figure 3

Bio-inspired Helical Micromotors as Cell Carriers[3]

The researchers who wrote this article, developed a SA hydrogel based spiral micromotor, and used as a dynamic cell microcarrier (Figure 4) , and then by further encapsulating MNPs in its raw materials, make the micromotor has high manipulation in the external moving MF, and can achieve rotation and linear movement. At the same time, because SA hydrogel is an environmental-friendly material with good biocompatibility, the micromotor prepared by this material has great potential as a cell carrier, and can be applied into the application of cell inoculation and cell planting. Because of this, the spiral micromotor can be further embedded into other natural structures, stacked together with each other to form cell blocks, which can be used in cell culture.

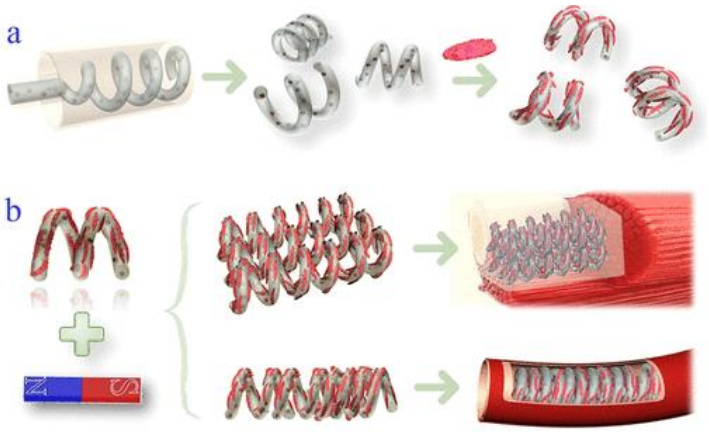


Figure 4

Eight-sided Dual-power Micromotors Fabricated via a Biocompatible Gas-shearing Strategy[4]

In this article, the authors propose an environmentally friendly method for manufacturing multifaceted micromotors with dual power sources, with no organic reagents required for the whole preparation process. The raw material that the author chooses is the biocompatible SA hydrogel, the power source is the Fe_3O_4 MNPs or catalase mixed into the raw material, and then the spherical micromotor is prepared through a specially customized eight-chamber needle. The resulting micromotor can carry out movements under the action of the magnetic field, including rotational motion, linear motion,

curve motion and circular motion.

Experimentation

Inspired by the above article, we decided to design and develop a spherical micromotor, with SA hydrogel as raw material, a special custom needle containing four smaller diameter needles for output mixed power source SA raw materials or pure SA hydrogel, and a slightly larger channel for gas to connect high pressure gas, adjust the size and size of micromotor production a solution containing $CaCl_2$ is placed below to help condense the SA hydrogel into a glue. The power source we designed for the micromotor is the Fe_3O_4 MNPs, equipped with MNPs micromotor can rotate on the magnetic stirrer and can be guided to perform other forms of motion; the another power source is the catalase. When the early micromotor and its related movement mode is explored, the cells will be add into part of pre-gel solution, make two of the four surfaces of magnetic motor has cells, and then let the micromotor move for a period of time, then study the cell migration during the period and explore the cell encapsulation of micromotor. (Figure 5).

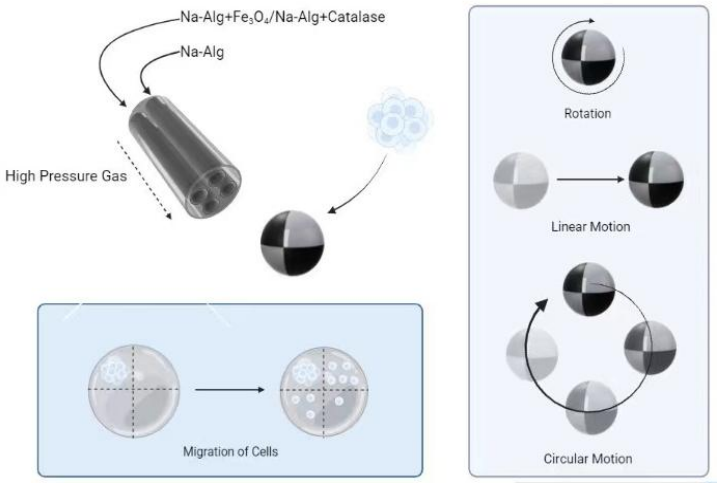


Figure 5

The experiment is divided into two parts. In the first stage (Figure 6) , we will first prepare micromotors equipped with MNPs or catalase, to explore the relationship between air flow and particle size, and to study their movement mode under different conditions. In the second stage(Figure 7) , the cells will be added to the raw material, and the cell migration in the micromotors will be further investigated and explored.

Figure 6

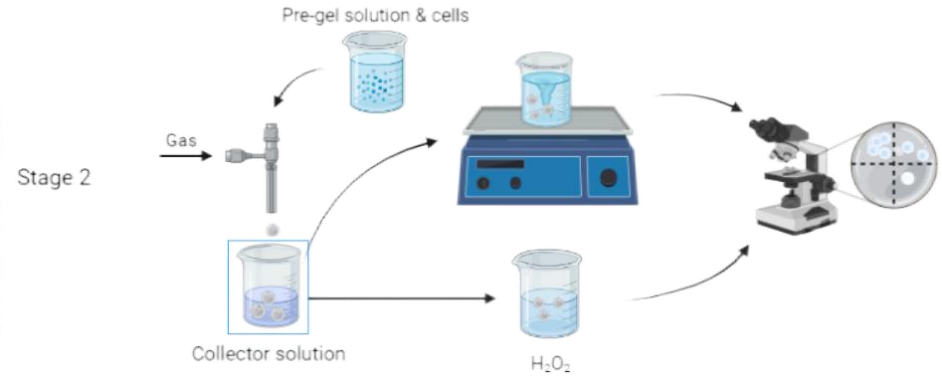


Figure 7

Result and Discussion

Through the experiments, We have successfully prepared bidynamic micromotors with a particle size of around 1mm, It can perform linear motion, rotation and circular motion under magnet guidance or on a magnetic agitator, Flow velocity reduces the particle size of the magnetic motor to some extent, However, if the air flow velocity exceeds a certain threshold value, The regional distribution of the magnetic motor is disrupted by the airflow, Since size is a key factor influencing micromotors in medical applications, The next step we hope is that by regulating the concentration and viscosity of the pre-gel solution, And regulating the viscosity of MNPs to avoid fine internal divisions of micromotors disrupted by airflow, Thus further reducing the diameter of the micromotors, If the particle size of the micromotor reaches a certain size requirement, The cell experiments will be performed very soon.

Conclusion

This research report introduces the inspiration of micro motor, development history and the current problems and the future development direction, in-depth study related to biological application of two categories of micro motor mechanism, use and preparation process, and prepared a double-powered micro motor, ready to further study its performance indicators, provide new ideas for micro motor research, increase its potential in biological applications.

References

[1] Sun M, Fan X, Meng X, et al, Magnetic biohybrid micromotors with high maneuverability for efficient drug loading and targeted drug delivery, Nanoscale, 2019, 11, 18382-18392.

[2] Balasubramanian S, Kagan D, Jack Hu CM, et al. Micromachine-enabled capture and isolation of cancer cells in complex media[J]. Angewandte Chemie, 2011, 123(18): 4247-4250.

[3] Yu Y, Guo J, Wang Y, et al. Bioinspired helical micromotors as dynamic cell microcarriers[J]. ACS applied materials & interfaces, 2020, 12(14): 16097-16103.

[4] Tang G, Chen L, Lian L, et al. Designable dual-power micromotors fabricated from a biocompatible gas-shearing strategy[J]. Chemical Engineering Journal, 2021, 407: 127187.

Mitochondria-Derived Peptides in Age-Related Diseases: A Review

Chuying Zhao, Ying Li
Department of Nephrology, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400042, China.

Abstract: Mitochondrial—derived peptides (MDPs) are new kinds of peptides, which are small open reading frames in circular mitochondrial DNA that encode a variety of microproteins, including humanin(HN), SHLPs 1-6, and MOTS-c. It is found that it can regulate mitochondrial bioenergy and mitochondrial metabolism, and has many biological effects such as helping to maintain mitochondrial function and cell viability under stress conditions, giving play to cell protection and improving metabolic markers.In this paper, we review recent research progress in MDPs, examines the biological effects of MDPs and focus on the role of MDPs in age-related diseases(ARDs), including mechanism of action and therapeutic potential.

Keywords: Mitochondria-Derived Peptides; Oxidative Stress; Genome; Mutation; Cell Aging

1. Introduction

Aging is usually accompanied by chronic degenerative diseases [1]. Mitochondria are important organelles involved in various human metabolisms and are a major source of reactive oxygen species (ROS) [2]. Mitochondrial dysfunction and increased production of ROS are considered to be one of the main markers of ARDs [1, 3, 4]. Therefore, mitochondrial modifications are considered an important target for the treatment of ARDs. Mitochondria-derived peptides (MDPs) are newly identified retrograde signaling entities from mitochondria[5]. Recent studies have found that the levels of MDPs are strongly associated with ARDs [6, 7]. We will review the functions and characteristics of MDPs and their relation with geriatric diseases in order to provide new ideas for diagnostic and therapeutic studies of age-related diseases.

2. MDPs in ARDs

2.1 humanin (HN)

HN is the first discovered member of the MDPs and the most studied of them.HN is a linear polypeptide encoding 24 amino acids.It has certain anti-inflammatory[8], anti-apoptosis [9] and neuroprotective effects [10], and regulates metabolism related to aging. HN also acts as a cell protective molecule in type 2 diabetes, cardiovascular disease, atherosclerosis and cancer[11], and its levels generally decline with age and is associated with increased healthspan and lifespan[12].

2.2 MOTS-c

MOTS-c is a linear polypeptide that is encoded by the mitochondrial 12SrRNA open reading frame[13].The main target of action of MOST-c is skeletal muscle, and it is thought to be the 1st peptide in MDP to regulate gene expression in the nucleus by interacting with transcription factors, leading to the production of retrograde signaling molecules[14]. Recent

studies have demonstrated that MOST-c exerts its effects by increasing glucose utilization, fatty acid oxidation, altering mitochondrial function and nucleotide metabolism in the organism, which in turn improves muscle metabolism, increases insulin sensitivity, and regulates lipid metabolism. Because of these important cellular functions, MOTS-c has been shown to be beneficial in ARDs.[15, 16].

2.3 SHLP1-6

SHLP1-6 is another six small peptides similar to HN found in HN's 16SrRNA gene.Among them, SHLP2 and SHLP3 have been extensively studied and have HN-like cytoprotective effects on apoptosis and metabolism.Current studies have shown that SHLP2 has an anti-oxidative stress effect and it improves insulin sensitivity in both central and peripheral systems. Moreover, circulating SHLP2 levels have been found to decrease with age, Indicate that it is associated with the progression of ARDs [17].

3. MDP and ARDs

3.1 Diabetes

The global incidence of diabetes is increasing year by year [2]. Oxidative stress is an important factor in the progression of diabetes [18]. Current studies have found that mitochondrial dysfunction is closely related to diabetes mellitus. MDPs improve the prognosis of diabetic patients by improving insulin resistance, suppresses inflammatory response and anti-apoptosis [19]. At present, MOTS-c and HN are the main MDPs associated with diabetes and its complications. Yang et al[20] found that MOTS-c regulates the expression of PGC-1α in mice through AMPK signaling pathway, reduces insulin resistance, promotes glucose metabolism and thus improves the clinical outcome of diabetic patients. MOTS-c also protects pancreatic β cells from streptozotocin mediated damage[21] . SHEN M et al. found that HN analogues (HNG) inhibited endothelial cell apoptosis induced by high glucose, providing a new direction for HN-related biologics to treat various types of diabetes-related vascular complications[22].

3.2 Cardiovascular disease

More and more research have shown that MOTS-c and HN in MDP are closely related to coronary artery disease (CAD). Patients with coronary artery disease (CAD) endothelial dysfunction have both low MOTS-c and HN levels[23]. Ya Wear, E. et al. found a strong correlation between MOTS-c level and CAD. Therefore, MOTS-c can help distinguish CAD patients for early preventive treatment[24]. And HN plays a key role in CAD. CAI et al. found that low circulating HN is an independent risk factor for CAD[25].

3.3 Neurodegenerative disease

HN has been increasingly studied in neurodegenerative diseases.Sandra et al. found in a rat model of surgical menopause that HN prevented synaptic loss in hippocampal neurons and reduced inflammation in astrocytes[26].Niikura et al. recently discovered the mechanism behind the antagonistic effect of HN on cognitive deficits - HN can directly promote neuronal regulation of exocytosis, thereby promoting improvement in cognitive function [27].Kelvin et al. found that ginsenosides improved metabolic health span parameters and reduced inflammatory markers in middle-aged mice treated with ginsenoside analogs (HNG) twice a week[12].

4. Conclusion

To sum up, we mainly introduce MDPs in ARDs, hoping to draw attention to the potential value of MDPs in the

diagnosis and treatment of ARDs. Although studies have proved that MDPs have the effects of anti-apoptosis, regulating metabolism and protecting cells in many diseases processes, and their possible mechanisms have been preliminarily explored, the existing studies are scattered and unsystematic, and most of them are limited to animal experiments, so there are still many gaps that need to be further explored.

References

[1] Conte M, Sabbatinelli J, Chiariello A, et al. Disease-specific plasma levels of mitokines FGF21, GDF15, and Humanin in type II diabetes and Alzheimer's disease in comparison with healthy aging [J]. GeroScience, 2021, 43(2): 985-1001.

[2] Wu Y, Sun L, Zhuang Z, et al. Mitochondrial-Derived Peptides in Diabetes and Its Complications [J]. Frontiers in endocrinology, 2021, 12(808120.

[3] Chen G, Kroemer G, Kepp O. Mitophagy: An Emerging Role in Aging and Age-Associated Diseases [J]. Frontiers in cell and developmental biology, 2020, 8(200.

[4] Natarajan V, Chawla R, Mah T, et al. Mitochondrial Dysfunction in Age-Related Metabolic Disorders [J]. Proteomics, 2020, 20(5-6): e1800404.

[5] Lee C, Yen K, Cohen P. Humanin: a harbinger of mitochondrial-derived peptides? [J]. Trends in endocrinology and metabolism: TEM, 2013, 24(5): 222-8.

[6] Qin Q, Delrio S, Wan J, et al. Downregulation of circulating MOTS-c levels in patients with coronary endothelial dysfunction [J]. International journal of cardiology, 2018, 254(23-7.

[7] Du C, Zhang C, Wu W, et al. Circulating MOTS-c levels are decreased in obese male children and adolescents and associated with insulin resistance [J]. Pediatric diabetes, 2018,

[8] Zaman F, Zhao Y, Celvin B, et al. Humanin is a novel regulator of Hedgehog signaling and prevents glucocorticoid-induced bone growth impairment [J]. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 2019, 33(4): 4962-74.

[9] Zuccato CF, Asad AS, Nicola Candia AJ, et al. Mitochondrial-derived peptide humanin as therapeutic target in cancer and degenerative diseases [J]. Expert opinion on therapeutic targets, 2019, 23(2): 117-26.

[10] Hashimoto Y, Ito Y, Niikura T, et al. Mechanisms of neuroprotection by a novel rescue factor humanin from Swedish mutant amyloid precursor protein [J]. Biochemical and biophysical research communications, 2001, 283(2): 460-8.

[11] Conte M, Martucci M, Chiariello A, et al. Mitochondria, immunosenescence and inflammaging: a role for mitokines? [J]. Seminars in immunopathology, 2020, 42(5): 607-17.

[12] Yen K, Mehta HH, Kim SJ, et al. The mitochondrial derived peptide humanin is a regulator of lifespan and healthspan [J]. Aging, 2020, 12(12): 11185-99.

[13] Lee C, Zeng J, Drew BG, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance [J]. Cell metabolism, 2015, 21(3): 443-54.

[14] Kim KH, Son JM, Benayoun BA, et al. The Mitochondrial-Encoded Peptide MOTS-c Translocates to the Nucleus to Regulate Nuclear Gene Expression in Response to Metabolic Stress [J]. Cell metabolism, 2018, 28(3): 516-24.e7.

[15] Kim SJ, Xiao J, Wan J, et al. Mitochondrially derived peptides as novel regulators of metabolism [J]. The Journal of physiology, 2017, 595(21): 6613-21.

[16] Mohtashami Z, Singh MK, Salimiaghdam N, et al. MOTS-c, the Most Recent Mitochondrial Derived Peptide in Human Aging and Age-Related Diseases [J]. International journal of molecular sciences, 2022, 23(19):

[17] Cobb LJ, Lee C, Xiao J, et al. Naturally occurring mitochondrial-derived peptides are age-dependent regulators of

apoptosis, insulin sensitivity, and inflammatory markers [J]. Aging, 2016, 8(4): 796-809.

[18] Sada K, Nishikawa T, Kukidome D, et al. Hyperglycemia Induces Cellular Hypoxia through Production of Mitochondrial ROS Followed by Suppression of Aquaporin-1 [J]. PloS one, 2016, 11(7): e0158619.

[19] Sequeira I R, Woodhead J S T, Chan A, et al. Plasma mitochondrial derived peptides MOTS-c and SHLP2 positively associate with android and liver fat in people without diabetes [J]. Biochimica et biophysica acta General subjects, 2021, 1865(11): 129991.

[20] Yang B, Yu Q, Chang B, et al. MOTS-c interacts synergistically with exercise intervention to regulate PGC-1α expression, attenuate insulin resistance and enhance glucose metabolism in mice via AMPK signaling pathway [J]. Biochimica et biophysica acta Molecular basis of disease, 2021, 1867(6): 166126.

[21] Yin Y, Pan Y, He J, et al. The mitochondrial-derived peptide MOTS-c relieves hyperglycemia and insulin resistance in gestational diabetes mellitus [J]. Pharmacological research, 2022, 175(105987.

[22] Shen M Y, Wang M, Liu Z, et al. [Gly14]-Humanin Ameliorates High Glucose-Induced Apoptosis by Inhibiting the Expression of MicroRNA-155 in Endothelial Microparticles [J]. Diabetes, metabolic syndrome and obesity : targets and therapy, 2021, 14(2335-47.

[23] Gong Z, Goetzman E, Muzumdar RH. Cardio-protective role of Humanin in myocardial ischemia-reperfusion [J]. Biochimica et biophysica acta General subjects, 2022, 1866(2): 130066.

[24] Yaşar E, Çakmak T, Bayramoğlu A, et al. MOTS-c as a predictor of coronary lesions and complexity in patients with stable coronary artery disease [J]. European review for medical and pharmacological sciences, 2022, 26(16): 5676-82.

[25] Cai H, Cao P, Sun W, et al. Circulating humanin is lower in coronary artery disease and is a prognostic biomarker for major cardiac events in humans [J]. Biochimica et biophysica acta General subjects, 2022, 1866(1): 130010.

[26] Zárate SC, Traetta ME, Codagnone MG, et al. Humanin, a Mitochondrial- Derived Peptide Released by Astrocytes, Prevents Synapse Loss in Hippocampal Neurons [J]. Frontiers in aging neuroscience, 2019, 11(123.

[27] Ikegawa N, Kozuka A, Morita N, et al. Humanin derivative, HNG, enhances neurotransmitter release [J]. Biochimica et biophysica acta General subjects, 2022, 1866(10): 130204.

Relationship Between ANCA-Associated Vasculitis and Infection: A Review

Yingxue Zhou, Qing Shen
Department of Nephrology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China.

Abstract: ANCA-associated vasculitis (AAV) is an autoimmune disease with multiorgan involvement of the entire body. And infection has been paid more and more attention in the course of treatment. As far as the current research is concerned, infection participates in the pathogenesis of AAV, interferes with the treatment of AAV, and affects the prognosis of AAV. This paper focuses on the role of pathogen infections in AAV pathogenesis. This review also elaborates on the types and prognosis of secondary infections in AAV patients. According to the current study, maintaining an appropriate BMI and vaccination is beneficial to the prevention of infection and the prognosis of AAV patients.

Keywords: ANCA; Infection; Pathogenesis; Complications.

Introduction

Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis (AAV) is characterized by inflammation of small vessels. It is an autoimmune disease that can affect a number of different systems of the body. The ANCA serotypes are PR3-ANCA, MPO-ANCA, and ANCA-negative. According to pathological classification, it is divided into Microscopic polyangiitis (MPA), Granulomatosis with polyangiitis (GPA), and Eosinophilic granulomatosis with polyangiitis (EGPA).[1] Although AAV is rare, the occurrence rate of AAV has been increasing over time.[2] And infection is involved in all stages of AAV. This review aims to illustrate the relationship between AAV and infection.

1. Pathogenesis

ANCA is an autoantibody that is in the neutrophils and monocytes. A case in 2009 reported that MPO-ANCA from a mother with MPA passed through the placenta into a preterm infant. Subsequently, the infant developed pulmonary hemorrhage and renal damage in a few days.[3] This report provides direct evidence that ANCA is pathogenic in humans. The main ANCA target antigens are Proteinase 3 (PR3) and Myeloperox-idase (MPO). Neutrophils and monocytes can be activated by MPO-ANCA and PR3-ANCA. Activated neutrophils undergo respiratory bursts and degranulation.[4] Similar responses were also observed in monocytes. [5] And then a series of inflammatory reactions happen and finally lead to vasculitis.

There are currently two hypotheses:

1) Molecular mimicry hypothesis: In a study, anti-human Lysosome-associated membrane protein 2 (LAMP-2) autoantibodies have also been found to participate in the pathogenesis of ANCA. There is 100% homology between bacterial adhesins FimH and LAMP-2, so FimH is considered to trigger autoimmunity to LAMP-2.[6]

2) Autoantigen complementation hypothesis: A study found antibodies against the complementary peptide of PR3 (cPR3) in some PR3-ANCA-positive patients.[7] Therefore, the initial immune response in AAV patients is not against the

self-antigen, but against the peptide complementary to the self-antigen epitope. In recent years, it has been found that neutrophils, Neutrophilextracellular traps (NETs), complement, and Lymphocytes all play a big part in AAV pathogenesis.

2. Infection induces AAV

According to the above two hypotheses, infectious factors are involved. The first hypothesis suggests that FimH is present in some Gram-negative bacteria. When humans are infected with FimH-bearing pathogens, it may lead to AAV. From the second hypothesis, pathogens with constitutive analogues of cPR3, such as Staphylococcus aureus and Ross River virus, could presumably act as exogenously introduced cPR3 to cause ANCA formation.

2.1 Staphylococcus aureus

In Stegeman's study, nasal S. aureus was present in 63% of patients with GPA in the experimental group. It was 25% in the control group. Meanwhile, there was a remarkably increased risk of GPA recurrence in the experimental one. [8] A 2017 study similarly confirmed that GPA patients with active nasal disease at admission were more likely to recur.[9] It has been demonstrated that superantigens, peptidoglycans, and fungal β-glucans derived from Staphylococcus aureus can induce the expansion of Th17 cells. [10] Th17 cells are considered central parts of the autoimmune response. [11] In addition, Staphylococcus aureus can induce NETs formation.[12] NETs destroy vascular endothelial cells. And they activate Lymphocytes to promote autoimmune responses.[13]

2.2 Viruses

It has been proposed that cytomegalovirus, HBV, HCV, etc., participate in the pathogenesis of autoimmune diseases.[14] Many studies have confirmed that SARS-CoV-2 can cause autoimmune diseases. The mechanism by which COVID-19 induces AAV is not clear. A theory suggests that COVID-19 could lead to an increase in proinflammatory cytokines and cytokine storm.[15] Another hypothesis is that COVID-19 causes transient immunosuppression and inappropriate immune reconstitution, causing the development of autoantibodies and the inability to correctly recognize self-antigens.[16]

3. Secondary infection

Immunosuppressive therapy can effectively improve the survival time and quality of life of AAV patients. But increased infection morbidity and mortality were found in AAV patients during immunosuppressive therapy. In a recent study, the cumulative rate of infection in AAV patients at 1 and 5 years was almost 50% and 65%. Serious infections were almost 20% and 25%. Respiratory tract infections were the most common. And Staphylococcus aureus was the highest proportion of pathogen cultures (41%).[17]

Another study found that the highest incidence of serious infection in AAV patients at 1 and 5 years was almost 20% and 10%, both lower than the rates in those studies. The study attributes this reduction to better long-term care, controlled long-term use of CYC, and limited initial prednisone use.[18] The 2021 KDIGO guidelines state that initial therapy for de novo AAV can be induction therapy with CYC or RTX plus glucocorticoids.[19] The happening of serious infections was found to be more in patients receiving CYC (20%) than RTX (11%) during the total induction treatment. The respiratory tract infections were 45%, followed by 24% herpes zoster.[18]

A Chinese study also found that lung infection was the most common type of infection (72%). Pathogens found during infection include bacteria, fungi, and viruses. the most common infections were bacterial (65%), particularly Acinetobacter baumannii and Staphylococcus aureus, followed by fungal (25%) and viral (10%) infections. These include cytomegalovirus and Pneumocystis.[20]

4. Prevention and prognosis

One study found that 14% of AAV patients who were infected during treatment died of severe pneumonia after immunosuppressive therapy.[18] In a large sample study in China, the cumulative survival rates at 1 and 5 years were almost 80% and 60%. Secondary infections were the major cause of death in the first year after diagnosis (40%).[21]

Kinds of literature has suggested that we should pay attention to the dose of immunosuppressive agents and the speed of dose reduction to avoid infection. For AAV patients treated with CTX or RTX ,trimethoprim-sulfamethoxazole is advised for the prophylaxis of Pneumocystis infection.[22] Guidelines recommend that most AAV patients receive vaccines, such as the influenza vaccine, pneumonia vaccine, and others.[23] A Japanese study found that malnutrition in patients at the time of AAV diagnosis may increase vulnerability to infection during immunosuppressive therapy.[24] Therefore, it is necessary to maintain an appropriate BMI in dealing with infection.

This review preliminarily elucidates the role of infection in the pathogenesis, progress, and prognosis of AAV. Now there are still no clear guidelines and norms for the treatment of AAV complicated with infection. There are still contradictions between immunosuppressive therapy and anti-infection therapy. Doctors can only make corresponding judgments according to the patient's individual condition and give the patient appropriate treatment measures.

References

[1] Jennette J, Falk R, Bacon P, *et al*. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides[J]. Arthritis & Rheumatology, 2012, 20(1).

[2] Mohammad AJ. An update on the epidemiology of ANCA-associated vasculitis. Rheumatology (Oxford). 2020 May 1;59(Suppl 3):iii42-iii50.

[3] Silva F, Specks U, Sethi S, *et al*. Successful Pregnancy and Delivery of a Healthy Newborn Despite Transplacental Transfer of Antimyeloperoxidase Antibodies From a Mother With Microscopic Polyangiitis[J]. American Journal of Kidney Diseases, 2009, 54(3):542-545.

[4] Falk RJ, Terrell RS, Jennette L, *et al*. Anti-Neutrophil Cytoplasmic Autoantibodies Induce Neutrophils to Degranulate and Produce Oxygen Radicals in vitro[J]. Proceedings of the National Academy of Sciences of the United States of America, 1990, 87(11):4115-4119.

[5] Jennette JC, Falk RJ. ANCAs Are Also Antimonocyte Cytoplasmic Autoantibodies[J]. Clinical Journal of the American Society of Nephrology Cjasn, 2014, 10(1):4-6.

[6] Kain R, Exner M, Brandes R, *et al*. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis[J]. Nature Medicine, 2008, 14(10): 1088-1096.

[7] Pendergraft WF, Preston GA, Shah RR, *et al*. Autoimmunity is triggered by cPR-3(105-201), a protein complementary to human autoantigen proteinase-3.[J]. Nature Medicine, 2004, 10(1):72-79.

[8] Stegeman CA, Tervaert JW, Sluiter WJ, *et al*. Association of Chronic Nasal Carriage of Staphylococcus aureus and Higher Relapse Rates in Wegener Granulomatosis[J]. Ann Int Med, 1994, 120(1):12-17.

[9] Salmela A, Rasmussen N, Tervaert JWC, *et al*. European Vasculitis Study Group. Chronic nasal Staphylococcus aureus carriage identifies a subset of newly diagnosed granulomatosis with polyangiitis patients with high relapse rate. *Rheumatology (Oxford)*. 2017;56(6):965-972.

[10] Li H, Nooh MM, Kotb M, *et al*. Commercial peptidoglycan preparations are contaminated with superantigen-like activity that stimulates IL-17 production[J]. Journal of Leukocyte Biology, 2008, 83(2): 409-418.

[11] Oukka, M. Th17 cells in immunity and autoimmunity[J]. Annals of the Rheumatic Diseases, 2008, 67 Suppl 3(Suppl 3):986789-986789.

[12] Bhattacharya M, Berends ETM, Chan R, *et al*. *Staphylococcus aureus* biofilms release leukocidins to elicit extracellular trap formation and evade neutrophil-mediated killing. *Proc Natl Acad Sci U S A*. 2018;115(28):7416-7421.

[13] Nakazawa D, Masuda S, Tomaru U, *et al*. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis [published correction appears in Nat Rev Rheumatol. 2019 Jan 17;:]. Nat Rev Rheumatol. 2019;15(2):91-101.

[14] Sfriso P, Ghirardello A, Botsios C, *et al*. Infections and autoimmunity: the multifaceted relationship. J Leukoc Biol. 2010;87(3):385-395.

[15] Henderson LA, Canna SW, Schulert GS, *et al*. On the alert for cytokine storm: Immunopathology in COVID-19[J]. Arthritis & Rheumatology, 2020, 72(7).

[16] Caas CA . The triggering of post-COVID-19 autoimmunity phenomena could be associated with both transient immunosuppression and an inappropriate form of immune reconstitution in susceptible individuals[J]. Medical Hypotheses, 2020, 145:110345.

[17] Mcgregor J, Negrete-Lopez R, Poulton C J, *et al*. Adverse events and infectious burden, microbes and temporal outline from immunosuppressive therapy in antineutrophil cytoplasmic antibody-associated vasculitis with native renal function[J]. Nephrology Dialysis Transplantation, 2015, 30(suppl_1): i171-i181.

[18] Thomas K, Argyriou E, Kapsala N, *et al*. Serious infections in ANCA-associated vasculitides in the biologic era: real-life data from a multicenter cohort of 162 patients[J]. Arthritis Research & Therapy, 2021, 23(1):1-9.

[19] Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021 Mar;99(3S):S1-S87.

[20] Yang L, Xie H, Liu Z, *et al*. Risk factors for infectious complications of ANCA-associated vasculitis: a cohort study[J]. Bmc Nephrology, 2018, 19(1):1-7.

[21] Lai QY, Ma TT, Li ZY, *et al*. Predictors for mortality in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a study of 398 Chinese patients.[J]. Journal of Rheumatology, 2014, 41(9):1849-55.

[22] Kronbichler A, Kerschbaum J, Gopaluni S, *et al*. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2018;77(10):1440-1447.

[23] Furer V, Rondaan C, Heijstek MW, *et al*. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2020;79(1):39-52.

[24] Sugiyama H, Yamaguchi M, Katsuno T, *et al*. Association between body mass index and severe infection in older adults with microscopic polyangiitis: a retrospective cohort in Japan[J]. BMC Geriatrics, 2021, 21(1):1-10.

High Flow Nasal Catheter (HFNC) for Sepsis Induced Respiratory Failure After Extubation Meta Analysis of Clinical Control Studies on Reintubation Rate and Mortality

Bo Li[1], Xuanguo Zhang[2], Gaojie Wang[3], Qiuzhen Yuan[1], Minjuan Shi1, Li Xi[4*]

1. Department of Pharmacy, Shaanxi Traditional Chinese Medicine Hospital, Xi'an 710003, China.

2. Intensive Care Unit, Shaanxi Traditional Chinese Medicine Hospital, Xi'an 710003, China.

3. Graduate School, Shaanxi University of Chinese Medicine, Xianyang 712046, China.

4. Editorial Department of Shaanxi Journal of Traditional Chinese Medicine, Shaanxi Academy of Traditional Chinese Medicine, Xi'an 710003, China.

Abstract: **Objective:** To analyze the reintubation rate and mortality of patients with sepsis complicated (or induced) respiratory failure after extubation, and to seek evidence-based basis for the efficacy of HFNC in the re intubation rate and mortality of sepsis induced respiratory failure after extubation. **Methods:** The databases of PubMed, EMBASE, Ovid, CNKI, CBM, VIP and Wanfang were searched to find the clinical studies of patients with sepsis and respiratory failure, and meta-analysis was carried out by Stata software. **Results:** Meta analysis showed that there was no significant difference between HFNC and noninvasive positive pressure ventilation (NPPV) in 72 hour reintubation rate, mortality during ICU and 28-day in hospital. **Conclusion:** The reintubation rate and mortality of HFNC after extubation in sepsis induced respiratory failure are equivalent to that of NPPV.

Keywords: Sepsis; Respiratory Failure; High Flow Nasal Catheter; Noninvasive Positive Pressure Ventilation

Introduction

Sepsis is a syndrome caused by a series of inflammatory reactions in the host and accompanied by organ failure, with critical condition and high mortality. A large number of studies have shown that sepsis can cause changes in respiratory muscles and respiratory patterns [1], and most sepsis can induce respiratory failure [2]; respiratory failure is also closely associated with increased sepsis mortality [3]. Necessary mechanical ventilation support for patients with sepsis complicated with respiratory failure is the main measure to improve a series of symptoms of insufficient ventilation, such as hypoxemia and respiratory distress. When the respiratory condition improves, it is necessary to take off-line extubation. After extubation, it is usually given sequential treatment of noninvasive positive pressure ventilation (NPPV), which can effectively reduce the rate of re intubation and mortality. In recent years, high flow nasal catheter (HFNC) has been widely used in respiratory support because of its comfort, convenience and providing high flow, high concentration, heated and humidified oxygen [4]. It has also been used in sequential treatment of sepsis induced respiratory failure after extubation. This study aims to provide evidence-based evidence for the clinical efficacy of HFNC in the treatment of sepsis induced respiratory failure after weaning from mechanical ventilation and extubation by meta-analysis of clinical control studies on the reintubation rate and mortality rate after weaning from mechanical ventilation and extubation.

1. Method

1.1 Literature inclusion criteria

We assessed studies including randomized controlled trials, clinical controlled trials, cohort studies, case-control studies, case series studies, and case reports about high flow nasal catheter and noninvasive positive pressure. The subjects met the diagnostic criteria of sepsis, and there was no significant difference in basic characteristics. The treatment group was high flow nasal catheter and the control group was noninvasive positive pressure ventilation. The routine treatment methods were the same. The outcome indicators included the rate of re intubation within 72 hours, ICU mortality, 28-day hospitalization mortality, adverse reactions, etc. There are no language restrictions.

1.2 Exclusion criteria

Other literatures that did not meet the inclusion criteria were excluded, such as no clinical reports, reviews, inconsistent research objectives, inconsistent interventions and repeated literatures.

1.3 Data extraction

According to the pre-established data extraction table, literature data were extracted and a unified data table was established using Excel 2013 (Microsoft, Redmond, Washington, USA), including author, year of publication, sample size, gender, age, underlying diseases, intervention measures, observation indicators, clinical results, etc.

1.4 Data processing

The re-intubation rate within 72 hours, ICU mortality and 28-day mortality were meta analyzed by Stata 13.0.

2. Result

2.1 Literature screening

The search scheme of nasal catheter / high flow nasal catheter + noninvasive positive pressure ventilation + sepsis is adopted. The search words include similar phrases expressing the same meaning, such as "sepsis" [title / Abstract] and "nasal" [title / Abstract] and "noninvasive" [title / Abstract] and "ventilation" [title / Abstract] in PubMed. The retrieval time is from the establishment of the database to January 3, 2022.We searched the literature and read the title and abstract.The literatures that did not meet the inclusion criteria were excluded, the full text of the remaining literatures was read, and the retrospective studies, repeated studies, studies with inconsistent intervention measures, non controlled studies and other literatures were excluded.Finally, two studies were included [5-6]. (Figure 1)

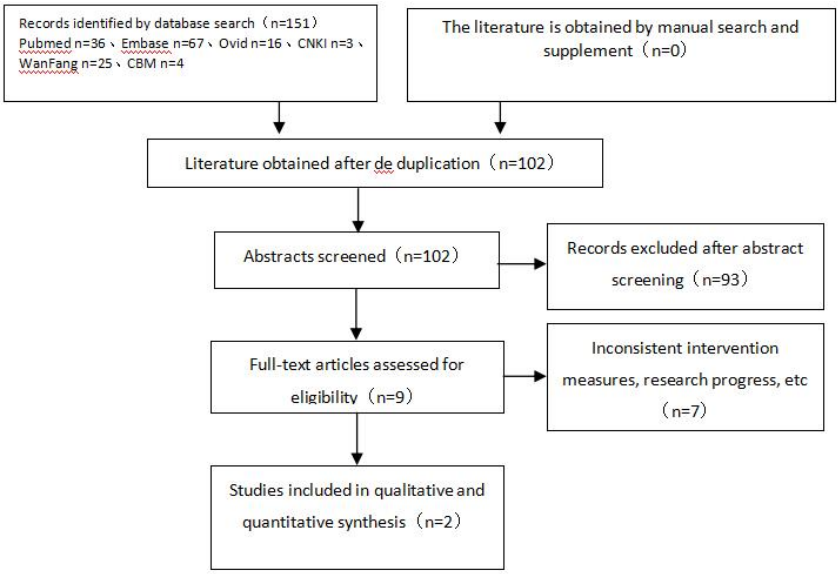


Figure 1. PRISMA flow chart of study selection.

2.2 Effectiveness evaluation of high flow nasal catheter and noninvasive positive pressure ventilation

Two controlled studies on the clinical efficacy of HFNC and NPPV after extubation in patients with purulent respiratory failure were included (Xuan LZ et al., 2021; Surat et al., 2021), one from China and the other from Thailand. A total of 505 people were included in the study population, 279 in HFNC group and 226 in NPPV group. There was no significant difference between the two groups in demographic characteristics (age, gender, BMI, etc.), general clinical status at ICU admission, arterial blood gas index at extubation and before sequential treatment, APACHE II score, SOFA score or invasive MV time before extubation.

Both studies reported 72 hour reintubation rate, mortality during ICU and 28-day mortality in hospital. Meta analysis of 72 hour reintubation rate showed that there was no significant difference between high flow nasal catheter and noninvasive positive pressure ventilation[OR = 0.94, 95% CI (0.53, 1.69), P > 0.05]. (Figure 2)

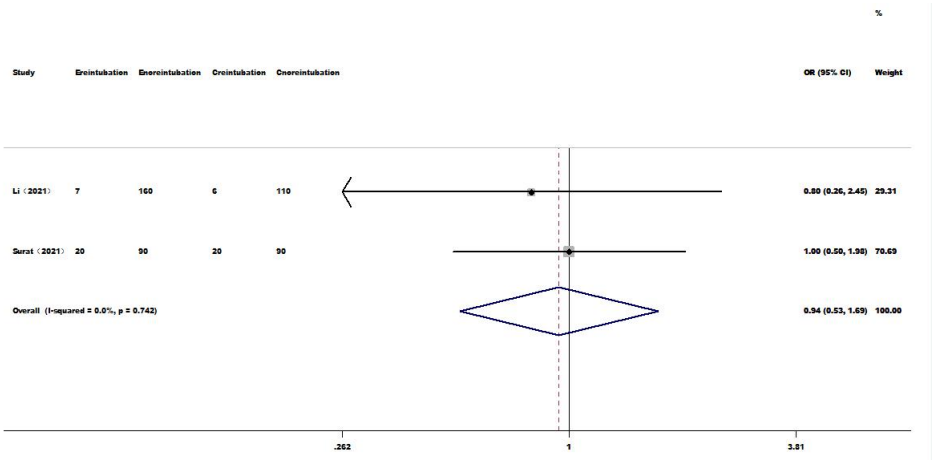


Figure 2 Meta analysis of 72h reintubation rate

Meta analysis of mortality during ICU showed that there was no significant difference between high flow nasal catheter and noninvasive positive pressure ventilation[OR = 1.21, 95% CI (0.49, 3.02), P > 0.05]. (Figure 3)

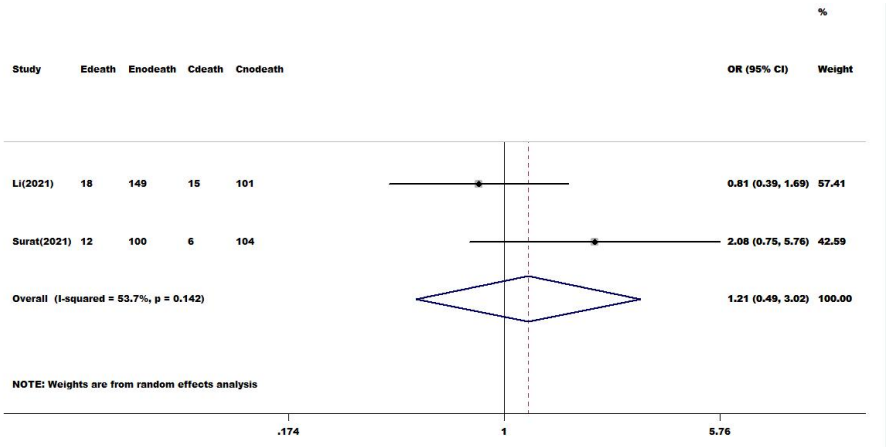


Figure 3 Meta analysis of mortality during ICU

Meta analysis of 28-day mortality in hospital showed that there was no significant difference between high flow nasal catheter and noninvasive positive pressure ventilation [OR = 0.96, 95% CI (0.55, 1.68), P > 0.05]. (Figure 4)

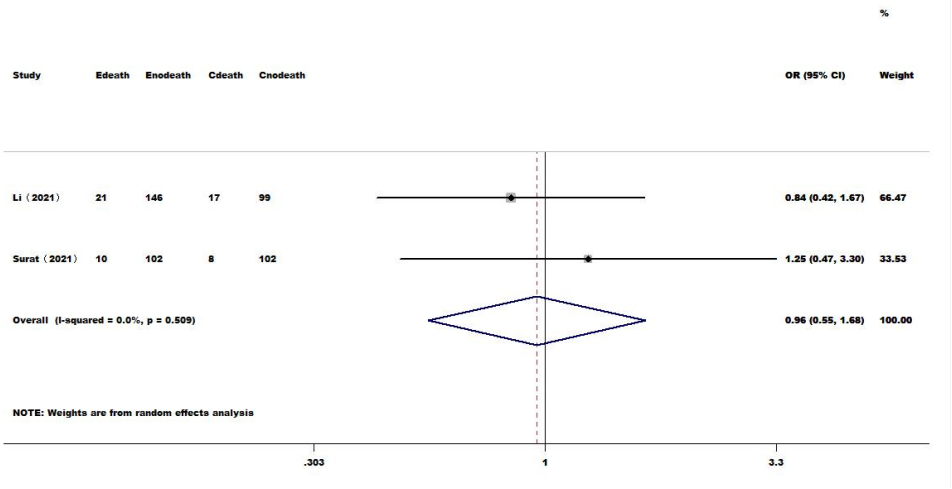


Figure 4 Meta analysis of mortality during ICU

So, there was no significant difference between HFNC and NPPV in the rate of reintubation 72 hours after extubation and the mortality 28-day after hospitalization in the treatment of sepsis induced respiratory failure.

3. Discussion

Respiratory support therapy is very important for the treatment of the patient who have sepsis induced respiratory failure after mechanical ventilation extubation. It can effectively reduce the rate of re intubation and mortality. The commonly used sequential respiratory support mode is NPPV. The research results of Stefano Nava [7] et al. in 2005, Miquel Ferrer [8] et al. in 2006 and Alexandre demoule [9] et al. in 2015 show that the use of NPPV can avoid respiratory failure after extubation and reduce mortality. However, due to the poor comfort of NPPV, the use is limited. In recent years, HFNC has been widely used because of its comfort, convenience and effectiveness. Salvatore Maurizio Maggiore [10] in 2014, Jean Pierre frat [11-12] in 2015 and Gonzalo Hern á ndez [13-14] in 2016 found that HFNC and NPPV can improve patients' shortness of breath and oxygenation index. HFNC is more comfortable than mask and patients have better tolerance. The expert consensus on the clinical standardized application of high flow nasal intubation oxygen therapy in adults published in 2020

[15] recommended that after weaning from mechanical ventilation and extubation, patients with a low risk of reintubation in the ICU, HFNC, patients with a high risk of reintubation in the ICU and weaning from mechanical ventilation after surgey，HFNC or NPPV. The campaign to save sepsis: international guidelines for sepsis and septic shock 2021[16], jointly released by the American Society of critical care medicine and the European Society of critical care medicine, suggests that for adults with hypoxic respiratory failure caused by sepsis, we recommend using high fow nasal oxygen on the basis of noninvasive ventilation. However, there is no recommendation on the application of weaning extubation in the follow-up treatment of sepsis induced respiratory failure.

Through meta-analysis, this study found that there was no significant difference between HFNC and NPPV in the rate of re intubation 72 hours after extubation, mortality and 28-day mortality after hospitalization in the treatment of sepsis induced respiratory failure, which provided evidence-based basis for the application of HFNC in the follow-up treatment of sepsis induced respiratory failure. Due to the influence of the number of included studies, randomized control and the etiology of sepsis, the accuracy of the results of this study needs to be further confirmed by more high-quality clinical studies.

References

[1] Xie J, Wang H, Kang Y, et al. CHinese Epidemiological Study of Sepsis (CHESS) Study Investigators. The Epidemiology of Sepsis in Chinese ICUs: A National Cross-Sectional Survey. Crit Care Med. 2020 Mar;48(3):e209-e218.

[2] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10.

[3] Genga KR, Russell JA. Update of Sepsis in the Intensive Care Unit. J Innate Immun. 2017;9(5):441-455.

[4] Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001 Jul;29(7):1303-10.

[5] Xuan LZ, Ma JF, Tao JL. et al. Comparative study of high flow nasal catheter device and noninvasive positive pressure ventilation for sequential treatment in sepsis patients after weaning from mechanical ventilation in intensive care unit[J], Ann Palliat Med, 2021, 10: 6270-6278.

[6] Tongyoo Surat, Tantibundit Porntipa, Daorattanachai Kiattichai et al. High-flow nasal oxygen cannula vs. noninvasive mechanical ventilation to prevent reintubation in sepsis: a randomized controlled trial[J], Ann Intensive Care, 2021, 11: 135.

[7] Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005 Nov;33(11):2465-70.

[8] Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006 Jan 15;173(2):164-70.

[9] Demoule A, Chevret S, Carlucci A, et al. oVNI Study Group; REVA Network (Research Network in Mechanical Ventilation). Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries. Intensive Care Med. 2016 Jan;42(1):82-92.

[10] Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014 Aug 1;190(3):282-8.

[11] Frat JP, Brugiere B, Ragot S, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. Respir Care. 2015 Feb;60(2):170-8.

[12] Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015 Jun 4;372(23):2185-96.

[13] Hernández G, Vaquero C, Colinas L, et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive

Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. JAMA. 2016 Oct 18;316(15):1565-1574.

[14] Hernández G, Vaquero C, González P, et al. Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. JAMA. 2016 Apr 5;315(13):1354-61.

[15] Xu JQ, Su LX, Yan P, et al. Pulmonary & Critical Care Medicine Group of Chinese Thoracic Society/ Pulmonary & Critical Care Medicine Committee of Chinese Association of Chest Physician. Expert consensus on clinical standardized application of high-flow nasal cannula oxygen therapy in adults. Chin Med J (Engl). 2020 Jun 5;133(11):1322-1324.

[16] Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143.

This work was supported by the Emergency launch of science and technology program during epidemic prevention and control in Shaanxi Province [grant number 2020LCZX-02].