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PROGRESS IN THE INVESTIGATION OF TRADITIONAL MEDICINE'S THERAPEUTIC EFFECTS ON HELICOBACTER PYLORI INFECTION

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Abstract: Helicobacter pylori infection is the main cause of gastric cancer, peptic ulcer, chronic gastritis, gastric mucosa-associated lymphoid tissue lymphoma and other diseases, and is related to some extra-gastrointestinal diseases such as iron deficiency anemia. Eradication therapy is the only effective way to cure Helicobacter pylori-related diseases, but the increase in drug resistance makes it increasingly difficult to eradicate Helicobacter pylori with chemical drugs and antibiotics. Finding active ingredients that inhibit and kill Helicobacter pylori from traditional medicine is an effective way to develop new Helicobacter pylori treatment drugs. This article reviews the current status of the application of traditional Chinese medicine, Tibetan medicine, Mongolian medicine, Yao medicine, Zhuang medicine and other traditional Chinese medicine methods in the treatment of Helicobacter pylori infection.
Keywords: Traditional medicine; Helicobacter pylori; Alternative therapy

1 TRADITIONAL CHINESE MEDICINE TREATMENT

Barry Marshall and Robin Warren of Australia first isolated Helicobacter pylori (Hp) in 1982 and found it to be the main pathogenic factor causing gastritis and peptic ulcer. For this great discovery, the two jointly won the Nobel Prize in Medicine in 2005 [1]. Later research findings confirmed that H. pylori infection is not only related to gastritis and peptic ulcer, but also the main cause of gastric cancer and gastric mucosa-as-sociated lymphoid tissue lymphoma (MALT) [2]. It may also be related to unknown diseases. It is related to the occurrence of extra-gastrointestinal diseases such as iron deficiency anemia and immune thrombocytopenic purpura [3]. Therefore, how to successfully eradicate Helicobacter pylori has always attracted the attention of medical workers at home and abroad. However, with the growth of drug-resistant strains in recent years, eradication treatment of H. pylori has become increasingly difficult. Unconventional therapy (Unconventional therapy) for Hp eradication treatment, that is, alternative therapy (Alternative therapy) or phytotherapy (Medicinal therapy), has gradually attracted widespread attention at home and abroad [4-6]. Medical workers in many countries are trying and evaluating the direct application of plants to treat pyloric screw [4, 7, 8]. my country's traditional medicine is extensive and profound, with a development history of thousands of years. In order to discover new therapeutic drugs for Hp, it is also necessary to delve deeply into the treasure trove of traditional medicine and explore possible alternative treatment options. This article provides a relatively comprehensive summary of the current clinical application status of traditional Chinese medicine, Tibetan medicine, Mongolian medicine, Yao medicine, Zhuang medicine and serotherapy in the treatment of Hp infection.

Traditional Chinese medicine has appeared since primitive society and was basically formed during the Spring and Autumn Period and the Warring States Period. It has a history of thousands of years. Its main theoretical basis is the theory of Yin and Yang and the Five Elements [9]. Wang Xuwu et al. conducted an in vitro bacteriostatic test on 200 Chinese herbal medicines that may be anti-Hp, and found 38 Chinese medicines with varying degrees of Hp inhibitory effects. Among them, the four drugs with strong inhibitory effects are Huangfang, Coptis, rhubarb, Phellodendron, other traditional Chinese medicines with inhibitory effects include cassia twig, ground bark, rose flower, smilax, galangal, black plum, mountain orange, Magnolia officinalis, etc. [10]. Wang Hengqi et al. studied the in vitro anti-Hp activity of 10 kinds of Chinese herbal medicines and found that Angelica dahurica and gallnut have strong effects. Mulberry bark, Malan, madder, and gentian also have certain anti-Hp effects [11]. Xu Yi et al. conducted an in vitro study on the anti-Hp activity of 136 single Chinese herbal medicines and 11 Chinese medicine prescriptions [12] and found that Coptis chinensis has a strong inhibitory effect on Hp, and those with moderate inhibitory effects include Huangfang, rhubarb, Salvia miltiorrhiza, Wu Rongmeng, Xuanhu, Daqingye, Licorice, Diyu. Huangbai is one of the Chinese herbal medicines that is more sensitive to Hp in the research of Wang Xuwu and others, but it is only a low-sensitivity drug in the research of Xu Yi and others [10, 12]. This inconsistency in research conclusions is likely to be related to the different extraction methods of active ingredients of traditional Chinese medicine used in the trials. The former uses alcohol extracts prepared by biochemical methods, while the latter uses traditional Chinese herbal medicine boiling and concentration methods in research [10, 12]. Zhang Jinyan et al. used decoctions of Coptis chinensis and Huangfang to study the in vitro antibacterial activity of four bacteria, and also found that Coptis chinensis and Huangfang had strong inhibitory activity against Helicobacter pylori [13]. The active ingredient of coptis is mainly berberine, and an analysis of the clinical treatment of Hp infection using berberine combined with Western medicine triple antibiotic eradication

program found that berberine can indeed significantly improve the eradication rate of Hp and reduce the incidence of adverse reactions [14].

In addition, Yang Xingtang found that other single drug ingredients, such as licorice, also have good anti-Hp activity, and their effects are equivalent to clarithromycin [15]. The main inhibitory and killing effects come from the glycyrrhizic acid and licorice flavonoids in licorice, both of which show equal inhibitory and killing effects on Hp in vitro [15]. Gu Shengqing and others used the prescription Gancao Xiexin Decoction containing licorice combined with quadruple therapy of Western medicine (rabeprazole, colloidal pectin spade, amoxicillin, clarithromycin) to treat Helicobacter pylori-related gastric ulcer, and found that the combined treatment of Chinese and Western medicine can eradicate it. The rate (90.32%) is significantly better than Western medicine treatment alone (64.52%) [16, 17]. Studies in recent years have found that Tianjihuang extract and extracts, patchouli alcohol, mastic gum, Hericium fermentum fermentation broth, and bitter melon aqueous extract all have varying degrees of inhibitory effects on Hp in vitro. However, the actual eradication efficacy remains to be determined. A large number of clinical practices are used to further verify [18, 19].

Gastritis, peptic ulcer and other diseases caused by Hp infection are classified as "stomach pain" and "fullness" in traditional Chinese medicine. Traditional Chinese medicine prescriptions are mostly treated with drugs that reduce qi, stop vomiting, warm the middle and dispel cold. Traditional Chinese medicine prescriptions and patent medicines such as semi-Xia Xiexin Decoction, Qingyou Jianzhong Decoction, Sanhuang Xiexin Decoction, Sihuang Tiaowei Decoction, Jinghua Weikang Capsules, Morodan, etc. all have such effects [20-22]. Xu Yi et al. conducted anti-Hp tests on 11 commonly used traditional Chinese medicine prescriptions and found that Zuojin Pills had a strong inhibitory effect, while Xianglian Pills and Qingyou Yangwei Pills had a moderate inhibitory effect. There are many similar TCM syndrome differentiation prescriptions for the treatment of gastritis and gastric ulcer caused by Hp infection. When combined with antibiotics to treat Hp infection, they can increase the eradication rate of Hp infection with conventional antibiotics to varying degrees and reduce adverse reactions.

2 TIBETAN MEDICINE TREATMENT

The systematic theory of Tibetan medicine was formed approximately in the fifth century BC. Tibetan medicine is a traditional medicine with a long history in my country and has a relatively complete theoretical system. Different from traditional Chinese medicine, Tibetan medicine theory believes that "Long, Triba, and Bacon" are the three major elements that make up the human body, which is called the "three causes" theory. This is the theoretical core and foundation of Tibetan medicine [23]. According to Tibetan medicine theory, both gastritis and ulcer are "Bacon's disease". Clinical studies have confirmed that simple Tibetan medicine treatment is highly effective in improving symptoms and promoting recovery. Patients' subjective symptoms can be quickly relieved, and the eradication rate of H. pylori infection is also relatively ideal. For example, Huaerjiang uses a combination of Renqing Mangjue Pills, Eryiwei Hanshuishi Pills, Xia Sadesi Pills, and Erwuwei Datang Powder to treat H. pylori, with an eradication rate of 87.5% [24]. Suojinlan treats patients with pyloric screw-related peptic ulcer using Western medicine combined with Tibetan medicine (Renqing Changjue Pills, Zhituo Jiebai Pills, Twenty-one-flavored Hanshuishi Pills, Thirteen-flavored Muxiang Pills, and Fifteen-flavored Black Pills). and simple western medicine triple therapy (omeprazole, amoxicillin, tinidazole) for 2 weeks of treatment. It was found that the eradication rate of Hp in the treatment group with Western medicine alone was 82.1%, while the eradication rate of Hp in the treatment group with Tibetan medicine combined with Western medicine and antibiotics reached 93% [25]. It shows that the combined application of Tibetan medicine can significantly improve the eradication rate of Hp infection with Western medicine [25]. If Tibetan medicine theory can be properly combined with the patient's condition for syndrome differentiation analysis, and Tibetan medicine and Western medicine can be combined for treatment, the result will be twice the result with half the effort.

3 MONGOLIAN MEDICINE TREATMENT

Mongolian medicine was formed in the late tenth century AD. Its main theoretical basis is the "Three Roots Theory", which believes that the human body is composed of three roots, seven elements, and three impurities [26]. When the three roots and seven elements are out of balance, diseases will occur, and the process of treating diseases is the process of restoring the balance between them. Modern Mongolian medicine attributes H. pylori infection to the Badagan parasite that lives in the stomach. Wang Wuyue et al. used Mongolian medicines such as Chagan Urel, Alatan Arula, and Xihe Riebisi-6-flavored pills to clinically treat patients with H. pylori infective gastritis. The total clinical effective rate (94.0%) was significantly higher than The control group (82.0%) received triple therapy with Western medicine (omeprazole, amoxicillin, and erythromycin) [27]. Hu Wenhua et al. used the method of syndrome differentiation and treatment of Mongolian medicine to classify Hp infectious gastritis into Heyi type, Shila type, Badagan type, and Baoru type. They applied Ruda-6 Wei Powder, Zhuang Xi-6 Wei Powder, and Alatan Arula -5 flavor powder, Zhamusa -4 flavor soup, Haododun Arula -10 flavor pills, Zhuangxi -21 flavor powder, Hadungaridi 13 flavor pills, Yourel -13 flavor Mongolian medicine prescriptions such as pills were used for treatment, while the control group was treated with standard quadruple therapy of ytoprazole, potassium amoxicillin, amoxicillin, and clarithromycin [28]. The results

showed that the total effective rate of the Mongolian medicine group (91.78%) was significantly better than the control group (82.19%) using quadruple therapy with Western medicine [28]. Suyilatu used the Mongolian medicine Bater-7 pills alone to treat gastric Hp infection, and the control group used triple therapy with Western medicine (potassium tetrafluorophosphate, clarithromycin, and metronidazole). After completing 2 weeks of treatment, the total number of patients in the Mongolian medicine group was The effective rate (95.5%) was significantly better than that of the Western medicine group (86.4%), and the clinical symptoms of patients were significantly improved [29]. In short, Mongolian medicines are all developed from natural herbal medicines. They are easy to take, have few side effects, and have significant clinical therapeutic effects, which are worthy of attention. Extensive clinical promotion should be carried out based on further in-depth study of the mechanism of action.

4 YAO MEDICINE TREATMENT

Yaoyi uses the break-even theory as the basis for syndrome differentiation and treatment, and pays attention to the "three-yuan harmony" [30]. There are various treatment methods. In addition to herbal medicine, there are also acupuncture, anesthesia, egg moxibustion, cupping, etc. Liu Xiaomei et al. used a shaking medical jar made of twelve kinds of herbs combined with Western medicine quadruple eradication therapy to treat patients with spleen and stomach damp-heat type Hp-related pneumonia, while the control group only used Western medicine standard quadruple eradication therapy (rabeprazole, colloidal pectin) spade, amoxicillin, clarithromycin) [31]. The results showed that the treatment group combined with shaking medical jar therapy achieved better results, with the treatment effective rate (96.77%) and eradication rate (93.54%) significantly better than the control group (82.75%, 89.65%). The recurrence of Hp infection was followed up for 6 months, and it was found that the recurrence rate of Hp infection treated with Yao medicine jar (9.67%) was lower than that of standard quadruple therapy (19.23%), achieving a more satisfactory effect [31]. It shows that Yao medicine medicine cup therapy is a treatment method worthy of promotion. However, there are currently no relevant reports on the therapeutic impact of Yao herbal medicine and other treatments on H. pylori eradication.

5 APHRODISIAC TREATMENTS

Zhuang medicine began in the pre-Qin period, and its theoretical basis is the natural view of heaven and man of "balancing qi and blood" and "synchronization of the three qi". The main treatment for peptic ulcer, gastritis and other diseases caused by Hp infection is overall treatment. According to reports by Qin Jiemei et al., the Zhuang Yao Yuyang Powder was used for experimental treatment of peptic ulcer patients with Hp infection. The results showed that the eradication rate of Hp infection reached 95.0%, which was better than the use of Western medicine triple eradication therapy (omeprazole, Metronidazole, clarithromycin) control group (82.1%) [32]. However, the number of cases in the study was small, with only 40 cases in each group. This is also the only current study that uses strong drugs to clinically kill Hp. Therefore, more clinical research verification is needed. In addition, in order to find cheap and efficient anti-Hp strong drugs, Zhang Yu et al. selected 50 commonly used strong drugs that may have anti-Hp effects from more than 2,000 kinds of strong drugs, and conducted in vitro screening studies on the anti-Hp effects [33]. It was found that 5 kinds of herbs have strong antibacterial effect on Hp, and they are in order: Huangteng > Kudingcha = Areca Nut > Golden Fruit Olive > Little Flying Grass, followed by Diofeng and Yizhijian. In addition, there are 8 kinds of herbs that have a mild inhibitory effect on HP, including Jiubing Ying, Gangbangui, Wuzhifeng, Jinzhan Yinpan, papaya, Jiujie tea, Shixiantao and Daliwang [33]. Although the antibacterial effect in vitro does not mean that it is effective in vivo, and the effect in vivo and in vitro is not necessarily disproportionate, it can provide good clues and basis for future research.

6 DONG MEDICINE TREATMENT

Dong medicine is a traditional medical treatment method based on herbal medicine and based on the theory of six natures and six flavors. It classifies diseases into 12 categories and 560 conditions. Wu Weihua and others from Hainan used a rat model infected with Helicobacter pylori to study the in vitro treatment effect of Dong medicine Xue Ma Bu (Guangdong Purple Pearl) on Hp. They found that Xue Ma Bu had no effect on gastric acid secretion, but had a dose-dependent significant effect on H pylori. The inhibitory effect is even better than that of clarithromycin, but there is still a lack of clinical research and research on the mechanism of action [34]. Zhang Xihe et al. used simple oral administration of compound Dong medicinal powders (Casicasia, Shui Haitang, Di Guniu, Mountain Ginger, Paddy Seven, baking soda) and decoctions (Roadside Yellow, White Leaf Herring Gall, Wei Qing Cao, Lonicera Lonicerae, Tianjin). (Qingdihong, Yuyejinhua) in the treatment of duodenal ulcers caused by Hp infection. The eradication rate of Hp after 2 weeks of treatment reached 91.5%, which was significantly better than the control group treated with triple therapy of cimetidine, metronidazole and amoxicillin. (76.2%), and the recurrence rate (8.4%) was also significantly lower than the control group (25.7%) [35]. Although the Western medicine triple therapy used is not a standard triple regimen, it is still a promising Dong medicine prescription and deserves further study on its pharmacological mechanism at the molecular level.

7 OUTLOOK

Although the current Western medicine standard triple and quadruple eradication therapies are still the classic and mainstream therapies for the treatment of H. pylori, the emergence of increasing drug-resistant strains and the toxic and side effects of drugs are two major problems that trouble people. It is undoubtedly the most ideal to discover safe, economical, effective and non-toxic drugs to eradicate H pylori. It is undeniable that traditional medicines may contain many unknown active ingredients that can effectively inhibit and kill HP. Especially in areas with backward economies and inconvenient transportation, traditional medicine still plays a huge role. Some people abroad have tried to use plant extracts to treat Hp infection and achieved certain results. Many cases of effective clinical treatment have also proven that in-depth exploration of therapeutic drugs for Hp infection-related diseases in traditional medicine is a shortcut to the development of new effective anti-Hp drugs. Because drug-resistant Hp strains are increasingly common in developing countries, the reinfection rate after eradication is much higher than in Western developed countries. All these require us to work hard to find more effective treatments with fewer side effects. Traditional medicine uses various herbal single and compound preparations to treat various diseases caused by Hp, and it has been confirmed that they contain ingredients with the activity of inhibiting and/or killing Hp. However, due to various reasons, the quantity and quality of clinical reports cannot be compared with Western medicine. On the one hand, this may be because medical workers who perform traditional ethnic therapies generally need to further strengthen their scientific research capabilities, and their clinical summary capabilities also need to be improved. On the other hand, many places where traditional treatments are performed have backward economic conditions, let alone scientific research environments. Therefore, there may still be a long way to go to carry out general and in-depth excavation, research and analysis of traditional medicine methods for treating various HP-related diseases, but it is undoubtedly a very meaningful work. The study of effective bacteriostatic and bactericidal ingredients in single drugs and prescriptions, and even the mechanism of action at the molecular level, is the focus of relevant research work in the future. We believe that through extensive and in-depth research on traditional medicine, safer and more effective anti-Hp drugs will emerge in the future.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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ASSESSMENT OF THE THERAPEUTIC EFFECTIVENESS OF NICORANDIL IN THE MANAGEMENT OF CORONARY HEART DISEASE

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Abstract: Coronary heart disease, as one of the common heart diseases, is also called coronary atherosclerotic heart disease. It is specifically characterized by myocardial ischemia or hypoxia caused by coronary atherosclerosis or dynamic vasospasm in patients. Myocardial necrosis and other conditions can cause patients to suffer from myocardial infarction, death, angina and other diseases. However, with the accelerated pace of people's life and unreasonable dietary structure, coronary heart disease appears in people of all ages, which can easily induce various cardiovascular and cerebrovascular complications and seriously threaten the life, health and safety of patients. This needs to be strengthened. Clinical trials of effective drugs for coronary heart disease to enhance the therapeutic effect of coronary heart disease.
Keywords: Nicorandil; Coronary heart disease; Clinical treatment progress; Evaluation

1 PROGRESS IN THE TREATMENT OF NICORANDIL IN STABLE ANGINA PECTORIS

In recent years, the incidence of coronary heart disease in our country has been increasing year by year. The reason is caused by the fast-paced life style and unreasonable dietary structure. In particular, diets high in fat and sugar content make the population at risk of coronary heart disease tend to become younger. Once the patient does not receive timely and effective clinical treatment, it will cause serious damage to the patient's life and health. It is imperative to strengthen the clinical drug treatment of patients. As an effective drug for various types of angina pectoris, nicorandil is a nitrate compound that can effectively reduce the risk of cardiovascular events [1-2]. Since its first launch in 1984, nicorandil has been widely used in the clinical treatment of stable angina pectoris and accumulated a large amount of clinical research data. At the same time, nicorandil is also a stable agent in the treatment of angina pectoris. Through experiments on Hospitalized patients with stable angina pectoris were tested for vascular classification and coronary prognosis risk factors such as non-fatal myocardial infarction to rule out the interference of patients with factors such as respiratory diseases and bad habits such as smoking. Finally, it was found that the difference between the test results between the two groups of patients was not significant and not statistically significant[3]. Later, a clinical trial was conducted on the oral treatment of nicorandil and the treatment of stable angina with isosorbide mononitrate. The final results proved that nicorandil can effectively reduce the incidence of angina in patients and the dosage of nitroglycerin, and its therapeutic effect is better than Far superior to isosorbide mononitrate, it can be said that nicorandil has become one of the main ways to treat angina pectoris[4-5].

2 PROGRESS IN THE TREATMENT OF NICORANDIL IN UNSTABLE ANGINA PECTORIS

According to relevant clinical treatment experiments and reference literature, the random number method was used to group the experimental subjects into an experimental group using nicorandil to treat unstable angina and a control group using isosorbide dinitrate injection, a controlled experiment was carried out with the consent of the patients[6]. The results showed that the probability of angina pectoris disappearing in the experimental group of patients who used nicorandil to treat angina pectoris was 76%, which was much higher than that of the patients in the control group who used isosorbide dinitrate injection to treat angina pectoris[7]. The probability of seizure disappearance was 53.6%, and the difference between the two groups' data was statistically significant; while the probability of adverse reactions in the experimental group treated with nicorandil after treatment was 2.4%, which was much lower than that of the group treated with nicorandil 7.6% of patients in the sorbitol ester injection group.

3 PROGRESS IN THE TREATMENT OF NICORANDIL IN ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

This study used a random grouping method to divide 366 experimental subjects with acute ST-segment elevation myocardial infarction into four groups: patients with prodromal symptoms who needed to be treated with nicorandil, patients with no prodromal symptoms, and patients who were treated with placebo. Patients with prodromal symptoms and patients without prodromal symptoms were treated with intravenous medication before performing coronary intervention. The final results showed that the degree of prevention of coronary microvascular damage in patients with prodromal angina and treated with nicorandil during surgery was very close to that of patients without prodromal angina, and the incidence of postoperative cardiovascular disease was the probability is extremely low and is higher in patients treated with placebo. Among them, 84.5% of nicorandil patients had grade 3 blood flow after thrombolysis for

myocardial infarction after surgery, and 81.9% of placebo patients. The patients with ST segment decrease greater than 50% accounted for 78.6% of the nicorandil group and 81.9% of the placebo group. 65.3%, indicating that intravenous injection of nicorandil has a positive protective effect on patients before percutaneous coronary intervention and can effectively improve the myocardial infarction status of patients.

4 PROGRESS OF NICORANDIL IN MYOCARDIAL PROTECTION DURING PERCUTANEOUS CORONARY INTERVENTION

Through the extensive practice of nicorandil in percutaneous coronary intervention, it has been proved that nicorandil has an important protective effect on the myocardium during and after percutaneous coronary intervention. It is shown in relevant literature , in order to verify the protective effect of nicorandil on the myocardium of patients during percutaneous coronary intervention surgery, 50 surgical patients were randomly divided into control group and nicorandil group. Among them, patients in the nicorandil group The patient maintained intravenous injection of nicorandil 24 hours before the operation, and then took nicorandil orally. At the same time, the patient's myosin, creatine kinase, and troponin levels were tested before and after the operation. Tests were conducted every 4 hours to check the patient's health status. The final results proved that nicorandil can effectively protect the patient's myocardial condition during percutaneous coronary intervention.

5 CONCLUSION

In summary, nicorandil, as an application of nitrate fat, has effectively improved the recovery rate of patients with coronary heart disease in clinical treatment experiments of coronary heart disease, especially in patients with stable angina, unstable angina, and acute ST. Myocardial protection plays an important protective role in segment elevation myocardial infarction and percutaneous coronary intervention, and has broad application prospects in the treatment of coronary heart disease.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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ADVANCEMENTS IN THE STUDY OF NON-CODING RNA'S ROLE IN MODULATING GLIOMA CHEMOTHERAPY RESISTANCE

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Abstract: Glioma represents the most frequently occurring malignant tumor of the human brain, constituting approximately 80% of all such cases. Its high malignancy, intense invasiveness, propensity for recurrence, and significant resistance to chemotherapy have significantly impacted the quality of life for patients affected by this disease. This article aims to provide a comprehensive overview of the research advancements made in understanding the mechanisms through which non-coding RNA regulates glioma's resistance to chemotherapy.
Keywords: Non-coding RNA; Glioma; Chemotherapy resistance

1 THE RESEARCH VALUE OF NON-CODING RNA

Among malignant central nervous system tumors, glioma is the most common type and one of the most malignant adult primary brain tumors with the worst prognosis. Treatment methods include surgery, radiotherapy and chemotherapy.. The growth location of glioma is very special, and its growth characteristics are mainly invasive. Current surgical treatment is difficult to remove completely, and it is easy to leave residual lesions, resulting in a high postoperative recurrence rate. Therefore, radiotherapy and chemotherapy have become important auxiliary treatments after surgery. However, during the treatment process, we often encounter another problem: resistance to chemotherapy drugs. Therefore, understanding the chemotherapy resistance process and its regulatory mechanisms from the molecular mechanism has become a research hotspot in the tumor community. With the application of shingled chips and new sequencing technologies, more than 90% of the proteins in the entire human genome sequence do not code but can be transcribed into RNA. These RNAs are non-coding RNAs [1]. It can regulate gene expression levels at multiple levels in the form of RNA. At the same time, the expression of non-coding RNA is different between normal tissues and tumor tissues, so it has become one of the targets of tumor gene therapy. This article collates recent research at home and abroad, and reviews the research value of non-coding RNA in glioma, the mechanism involved in chemotherapy resistance and the regulation of drug resistance, and the mechanism of chemotherapy resistance in glioma.

1.1 The Content of Non-Coding RNA is Higher than that of other Organs, which is Beneficial to Diagnosis and Prognosis Assessment

Compared with the content in other organs of the body, the expression content of non-coding RNA is higher in the central nervous system than in other peripheral organs. Because of this characteristic, glioma can be accompanied by differences in the expression of non-coding RNA during multiple development stages and multiple pathological changes. Li et al.[2] and Klein[3] mentioned that the expression content of Inc-RNA H19 is positively correlated with the grade of glioma. It is one of the key biological detection indicators for the progression of glioma, and it plays an important role in the progression of glioma. played a key role in its progress and invasion.

1.2 Non-Coding RNA is Involved in Multiple Biological Behaviors of Glioma Cells and is a Gene Target

The key to treatment lies in the cell proliferation, apoptosis and invasion of glioma cells. Non-coding RNA participates in the development of glioma through different transcriptional molecular mechanisms and signaling pathways. For example, CRNDE, another member of the non-coding RNA family, uses the mTOR signaling channel to play a regulatory role in glioma cell growth; in addition, Yin Shi et al.[4] also concluded through literature collection that ASLNC22381 and ASLNC20819 use IGF-1R to promote cell growth. Activation of proliferative signaling pathways.

1.3 Non-Coding RNA has Bidirectional Regulatory Function

The family of non-coding RNAs is very large, and each plays a different role. Some promote the occurrence and development of glioma, while others inhibit its proliferation and invasion. For example, Zhang et al. [5] found through experiments that in glioma patients, high expression of HOTAIR indicates a worse prognosis and survival rate; the expression levels of CRNDE in glioblastoma and astrocytoma are also higher than normal. Tissue is much higher. At the same time, this RNA also plays a role in promoting the proliferation and invasion of glioma.

2 MECHANISMS OF RESISTANCE TO CHEMOTHERAPY DRUGS IN GLIOMA

Currently, the chemotherapy drugs used for malignant glioma include cisplatin, temozolomide and nitrosourea drugs, as well as procarbazine, vinblastine and podophyllotoxin drugs, as well as molecular targeted drugs.

2.1 Cisplatin

Cisplatin is one of the most widely used chemotherapy drugs in clinical practice. It is often used in the chemotherapy treatment of solid tumors and is also used in the treatment of gliomas. However, cisplatin is prone to drug resistance during tumor treatment. Rabik et al. [6] The mechanism of drug resistance reaction discovered through clinical experiments is as follows: There is a drug transport system in cells, which can continuously transport drugs, so that the accumulated amount of cisplatin in the cells is continuously consumed; at the same time, tumor cells contain glutamine The expression of reducing substances such as thione can activate the drug detoxification system in the body. When the system is activated, the effective substances contained in the drug will be continuously removed; the repair of mismatches and cross-links occurs autonomously within the DNA. and other chain reactions, completely changing its mode of action and mechanism; apoptosis can also induce abnormalities in cell death pathways, etc.

2.2 Temozolomide

Temozolomide is a widely used chemotherapy drug in clinical practice. It is classified as a DNA alkylating agent. It can penetrate the blood-brain barrier and directly reach the tumor site. Its mechanism of action is to destroy DNA fragments in glioma cells and prevent them from carrying out DNA processing. Modification, causing tumor cells to undergo apoptosis or cause them to die. However, as the treatment process continues, patients will develop resistance to it, gradually reducing the sensitivity to the drug, making the treatment of the disease more difficult. Its drug resistance mechanism is related to the enhanced activity of methylguanine-DNA methyltransferase and nucleic acid mismatch repair protease; at the same time, its drug resistance mechanism is also a complex process involving multiple molecules.

2.3 Nitrosoureas

Nitrosourea drugs (Nus) are also one of the commonly used chemotherapy drugs for the treatment of glioma. They are alkylating agents. Its representative drugs are lomustine, carmustine, etc., which have the ability to penetrate the central nervous system. Highly lipid-soluble, it exerts anti-tumor effects mainly through alkylation damage to DNA. Jin Peng et al. [7] summarized the mechanisms of nitrosoureas chemotherapy resistance at home and abroad as follows: MGMT, BER, NER and MMR, which are involved in DNA damage repair in the human body and are involved in DNA damage repair, can also easily cause tumor chemotherapy resistance. Glutathione (GSH) and glutathione S-transferase (GST) present in the human body, in the process of protecting biological cells from damage by poisons (including cytotoxic drugs), also increase drug resistance during treatment.. But overall, Nus resistance is a very complex process.

3 CHEMOTHERAPY RESISTANCE MECHANISMS OF NON-CODING RNA

3.1 Regulatory Signaling Pathways and Tumor Chemotherapy Resistance

Non-coding RNA participates in important epigenetic processes such as genomic imprinting and chromatin remodeling, thereby changing the expression abundance of genes and affecting the expression of downstream drug resistance signaling pathways. At the same time, DNA epigenetic modifications also exist in non-coding RNA and mediate the regulation of other genes. Yang et al. [8] found through research that lncRNA AK126698 can promote the expression of NKD2 gene, and at the same time, NKD2 gene can inhibit Wnt/ The β-catenin signaling pathway allows non-small cell lung cancer cells to develop therapeutic resistance to cisplatin.

3.2 miRNA Interaction and Tumor Chemotherapy Resistance

For example, lncRNA ATB, a non-coding RNA, Shi et al.[9] found through research that it can become an endogenous competitive RNA (ceRNA) for miR-200c, and can promote the regulation of breast cancer cells by regulating related target genes. Lizumab forms a drug-resistant response and facilitates the invasion and migration of breast cancer cells in the body.

3.3 Regulating Drug Membrane Transport and Tumor Chemotherapy Resistance

Non-coding RNA can participate in regulating drug membrane transport by affecting the uptake and excretion of drugs, key metabolic enzymes and interfering with drug effects; research by Wang et al. [10] showed that knocking out lncR NAMRUL can promote doxorubicin and vincristine resistance. The drug increases the apoptosis of SGC7901/ADR and SGC7901/VCR in gastric cancer cell lines, allowing the drug to accumulate in cells. At the same time, it can also downregulate the expression of MRUL, thereby inhibiting the expression of ATP and subfamily B member 1 protein (ABCB1). Combined, it maintains the concentration balance of chemotherapy drugs in cells and dynamically regulates the sensitivity of tumor cells to chemotherapy drugs.

3.4 Apoptotic Proteins and Tumor Chemotherapy Resistance

During the course of chemotherapy, the adaptive changes of tumor cells, such as the transformation of epithelial cells into mesenchymal phenotype and the induction of CSC expansion, can cause chemotherapy resistance. In particular, EMT and CSC activation are closely related to drug resistance. Hang et al. [11] have shown that non-coding RNA has the potential to reverse EMT and regain the sensitivity of tumors to chemotherapy drugs. In addition, Wu et al. [12] found that since non-coding RNA does not undergo protein translation and mostly functions directly at the transcription level, it is also considered to have a more efficient "bridge regulatory effect".

4 CONCLUSION

The treatment of human brain glioma is one of the current treatment problems in the oncology community. How to find a drug with low resistance rate and good therapeutic effect is the direction that clinical oncologists have been working hard. With the deepening of clinical research and With the progress of non-coding RNA research, the mechanism of non-coding RNA in tumor drug resistance has gradually become clearer. However, currently, because the relationship between tumor chemotherapy resistance is complex and involves many pathways, it is difficult to discover its fundamental mechanism from the source. The mechanism of drug resistance and mechanism of action. The current mechanism of drug resistance of glioma chemotherapy is still debated by hundreds of schools of thought and is not very clear. At present, with the increasingly sophisticated research methods, the gradual discovery of non-coding RNA and its related regulatory signaling pathways will provide more effective methods for the treatment and diagnosis of glioma, and will also bring more hope to clinical patients. and the gospel.

COMPETING INTERESTS

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INVESTIGATIONS INTO THE UTILIZATION OF PLURIPOTENT STEM CELLS FOR EVALUATING NEURODEVELOPMENTAL TOXICITY

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Abstract: Induced pluripotent stem cells are a cell type similar to embryonic stem cells obtained by inducing mature somatic cells to express specific genes [1]. Both iPSCs and ESCs have the ability of unlimited proliferation and multi-lineage differentiation in vitro, and both play important roles in drug screening, cell therapy, etc. However, iPSCs come from a wide range of sources and are easy to obtain, and their acquisition can avoid medical ethical issues. Traditional developmental toxicity research methods not only require a large number of experimental animals, but also have long experimental cycles, cumbersome operations, and species differences. In 1981, Evans and Kaufman [2] first obtained mouse ESCs from the inner cell mass of mouse blastocysts. In 1997, Spielmann et al. [3] established an in vitro alternative model "embryonic stem cell test" by using the characteristics of mouse ESCs to differentiate into the three germ layers, and it became a classic method for in vitro developmental toxicity research. Subsequently, human ESCs and human iPSCs were obtained and used in in vitro surrogate models of developmental toxicity. The application of these human cells solved the problem of species differences [4-6]. The in vitro developmental toxicity model was initially used to evaluate the toxic effects of chemicals through the differentiation of pluripotent stem cells into myocardium. Later, the products of differentiation into other lineages were gradually applied to this model.
Keywords: Stem cells; Nerve; Neurodevelopment; Toxicity model

1 DIFFERENTIATION OF PLURIPOTENT STEM CELLS INTO NEURAL LINEAGE

The development process of the nervous system is highly spatiotemporal, and the sensitivity to toxic substances depends on the developmental stage. When in the sensitive stage, even a low level of exposure to toxic substances can cause irreversible brain damage [7]. This kind of brain injury sometimes does not show obvious clinical characteristics, but persistent changes in the nervous system, which is called "silent developmental toxicity" [8]. In addition to the vulnerability of the nervous system itself, humans are also increasingly exposed to developmental neurotoxicity (DNT) substances. According to statistics, from 2006 to 2013, the number of DNT substances increased from 6 to 12 [9]. Therefore, the DNT issue has attracted more and more attention. Currently, the use of pluripotent stem cells to establish in vitro cell models has become an important way to study DNT. Neural lineage cell types differentiated from pluripotent stem cells and DNT assessment methods have become important aspects of this research. This article reviews four aspects: differentiation of pluripotent stem cells into neural lineage, DNT detection indicators and applications, high-throughput technology applications, prospects and challenges.

The use of pluripotent stem cells to establish an in vitro cell model for DNT research relies on the development of technology for the differentiation of pluripotent stem cells into neural lineages. With the development of stem cell culture technology, more and more cell types of pluripotent stem cells have differentiated into the neural lineage. There are two main differentiation methods: adherent method and embryoid body (EB) method.

At present, the neural lineage cell types generated by differentiation of pluripotent stem cells are dopamine neurons, glutamatergic neurons, astrocytes, cochlear spiral ganglion cells, etc. [10-20]. Gradually, the spatial structure has also undergone a transformation from two-dimensional to three-dimensional. For example, Reichman et al. [19] induced human iPSCs to form retinal organs containing ultrastructured photoreceptors; Pamies et al. [21] used iPSCs to differentiate to form a three-dimensional structure similar to the human brain, which is composed of differentiated mature neurons and glial cells. It can simulate synapse formation, neuron spontaneous firing and myelination during neural development, and its myelination can reach 40%. In addition, Schwartz et al. [22] seeded neural progenitor cells differentiated from human ESCs on synthetic polyethylene glycol hydrogel for culture, and added endothelial cells and mesenchymal cells derived from ESCs at a certain proportion during the differentiation process. Mesenchymal stem cells and microglia/macrophage precursors ultimately form a three-dimensional neural structure containing different types of neurons, glial cell populations, and interconnected vascular networks.

In short, using different types of nerve cells generated from pluripotent stem cells is an important basis for in vitro DNT research. Different cell types can also be sensitive to chemicals of different properties. For example, neural progenitor cells are more sensitive to chemicals that induce apoptosis. [23], establishing a specific cell replacement model.

In addition, the three-dimensional neural structure generated by the differentiation of pluripotent stem cells can simulate the interaction between cells and is closer to the neural tissue in the body in structure and function. Application in DNT research can narrow the difference between the cellular level and the in vivo level, further improving Accuracy of DNT assessment.

2 DNT DETECTION INDICATORS AND APPLICATIONS

Neurodevelopmental processes include cell proliferation, apoptosis, differentiation, migration, synapse formation, neurite and network formation, gliogenesis, and myelination. Using pluripotent stem cells to simulate the neural development process and then evaluate the DNT of chemical substances can make up for the shortcomings of traditional experiments. However, how to comprehensively and accurately evaluate the DNT of chemical substances based on cell models is a difficulty in research. At present, the detection indicators for in vitro evaluation of DNT are roughly divided into three categories: nerve cell biological behavior, neuronal function and other indicators.

2.1 Biological Behavior of Nerve Cells

2.1.1 Proliferation and apoptosis

Proliferation and apoptosis occur throughout the entire neural development process. The DNT of chemical substances can be preliminarily evaluated based on the proliferation and apoptosis levels of the cell model. Commonly used related detection methods include cell counting, BrdU staining, CCK8, caspase3/ 7 activity, etc. [23-30].

2.1.2 Differentiation

The differentiation of pluripotent stem cells into neurons with different shapes, structures and functions is essentially the selective expression of genes. Quantitative real-time PCR (qPCR), immunostaining and other methods are usually used to detect the expression levels of specific markers such as glial acidic protein and myelin basic protein to evaluate the impact of toxic substances on the neural differentiation process. Impact [31-32].

2.1.3 Cell migration

Neural crest cell migration is one of the key processes in human fetal development. If this process is interfered with by the external environment or toxic substances, the fetus will develop abnormally. Cell scratch experiments are mainly used in vitro to evaluate the impact of toxic substances on the cell migration process [33-34].

2.1.4 Process growth

Neurons are connected to each other through neurites for information transmission. Ryan et al. [35] used neurons derived from human iPSCs to study and found that some chemicals did not cause cytotoxicity but only selectively inhibited neuronal process growth. It can be seen that protrusion growth can be used as an important indicator to evaluate DNT.

2.1.5 Myelination

The main function of myelin is to provide electrical insulation for axons and accelerate the transmission of electrical signals. Oligodendrocytes are an important cell source of myelin and can be indirectly detected by detecting their precursor cell differentiation, migration and other processes. Evaluate the effects of chemicals on myelination [24, 36-37].

2.2 Neuron Function

Existing research shows that conventional detection methods may not necessarily be able to detect the toxic effects of chemical substances. As the basic functional properties of neurons, electrophysiological properties can be used as functional terminals to evaluate DNT sensitivity. For example, Ylä-Outinen et al. [38] exposed neurons differentiated from human ESCs to 500 nmol/L methylmercury chloride for 72 hours. The electrophysiological signals of the neuronal network were significantly reduced, but cell proliferation and qPCR , immunostaining and other test results did not change.

2.3 Other Indicators

In addition to the above two types of detection indicators, DNT can also be evaluated through other indicators.

2.3.1 Generation of reactive oxygen species (ROS) and oxidative stress

Oxidative stress is an important mechanism by which chemicals cause DNT [39-40]. For example, arsenic, mercury, etc. can cause nerve cells to produce excessive ROS, leading to an imbalance in the oxidation-antioxidation system in the cell, that is, an increase in oxidative stress levels, which in turn can cause mitochondrial dysfunction and cell apoptosis [41-42]. Therefore, the DNT of chemical substances can be evaluated based on intracellular ROS levels, superoxide dismutase and other indicators during the neural differentiation process of pluripotent stem cells [43].

2.3.2 Metabolites

Pamies et al. [43] used non-targeted metabolomic analysis and found that the metabolites of three-dimensional neural structures formed by human iPSCs differentiation differed at different differentiation stages. At the same time, cell

metabolism after treatment with rotenone for 48 hours The product also changed significantly. Therefore, studying the metabolites of cells can help people discover subtle differences from a metabolic perspective and further identify the toxic effects of chemicals.

2.3.3 MicroRNA(miRNA)

miRNA is a small endogenous non-coding RNA molecule that regulates gene expression by targeting and binding to mRNA. At present, it is clear that more than 50% of miRNAs are expressed in the brain and are involved in regulating brain development [44]. Studies have shown that toxic substances can cause the abnormal expression of some miRNAs, and these miRNAs are closely related to the proliferation, migration, and myelination of nerve cells [45].

In short, the neural development process is extremely complex. When using pluripotent stem cells to establish an in vitro cell model to evaluate DNT, it is necessary to combine different detection indicators to make a correct assessment of the DNT of chemical substances. I believe that with the development of science and technology, more sensitive indicators will be Discovered and used in DNT research.

3 DNT HIGH-THROUGHPUT TECHNOLOGY APPLICATIONS

Although using pluripotent stem cells to establish an in vitro surrogate model to evaluate the chemical substance DNT has many advantages over traditional methods, it is also challenging to process and detect a large number of cell samples in different ways. The key to DNT research is to efficiently and accurately predict in vivo results based on in vitro models. Therefore, high-throughput technology is necessary for in vitro DNT research. Currently, there are also some high-throughput technology applications in the use of pluripotent stem cells to study DNT methods.

3.1 High Content Imaging Analysis (HCA) Technology

HCA is an important tool capable of high-throughput imaging and quantitative analysis of image information using multiple models, and can be used for toxicity detection of a large number of chemical substances [46] . For example, a study reported that 80 chemicals were applied to neurons derived from iPSCs for 72 hours, and then HCA technology was used to photograph them and analyze them from four parameters: cell activity, neurite length, neurite number, and branch number of neurons. Image information greatly improves the processing capabilities of image information [35].

3.2 Microfluidic Chip

Microfluidic chip is a micro-platform that integrates cell culture, differentiation, processing and detection and analysis. It can perform two-dimensional and three-dimensional stem cell culture methods, and can be combined with different detection systems to analyze cell samples. Carry out analysis of different indicators [47]. This platform is used in DNT research. It can not only realize the automatic processing of a large number of chemical substances, but also analyze the DNT of chemical substances from different indicators, improving the research efficiency and evaluation accuracy of DNT.

3.3 Microelectrode Array (MEA)

MEA is a non-invasive microelectrode extracellular electrical signal recording technology. It can be used to culture cells for a long time and record the electrical signals generated by different samples in real time. It is a high-throughput detection method for nerve cells. important tool for electrophysiological characterization [48-50].

Although high-throughput technology can detect and analyze a large number of samples to a certain extent, most high-throughput technologies cannot be widely used due to high equipment costs, complex operations, and the need for professional and technical personnel. However, with the advancement of science and technology, it is believed that more and more high-throughput technologies will be further developed and applied, thereby improving the research efficiency and evaluation accuracy of using pluripotent stem cells to evaluate DNT.

4 PROSPECTS AND CHALLENGES

At present, great progress has been made in pluripotent stem cell research. For example, the continuous optimization of pluripotent stem cell culture systems, that is, serum-free and feeder-free culture, has clearer ingredients and is conducive to the realization of standardized production. In addition, the use of pluripotent stem cells to differentiate in vitro to form the diversity of neural cell types, the diversity of DNT detection indicators, and the application of high-throughput detection technology, etc., all help to reduce research costs and shorten the time to a certain extent. DNT research cycle, improve prediction accuracy, etc. However, the use of pluripotent stem cells for DNT research also faces many problems, such as the high cost of stem cell culture, the long differentiation time of neural three-dimensional models, the lack of a standardized evaluation system for neural tissue (or cell) models, and the different exposure methods of chemical substances. (Concentration, action time, etc.), the cell types affected by chemical substances may not be sensitive; the detection system needs to be improved, etc. In addition, although the three-

dimensional model formed by the differentiation of pluripotent stem cells already has preliminary structure and function, there is still a big gap compared with the neural tissue in the human body. Moreover, the current in vitro detection system can only detect the toxic effects of the chemical substances themselves. The toxic effects of the chemical substances in the metabolic process in the body and the composite effects of the placental barrier and the blood-brain barrier in the body cannot be simulated in vitro. This will easily lead to overestimation or Underestimating the DNT of chemicals [51]. In short, although there are still many shortcomings in using pluripotent stem cells to establish cell models in vitro to study DNT, with the maturity and improvement of related technologies, it is believed that pluripotent stem cells, especially iPSCs, will play an irreplaceable role in the future application of DNT in vitro models.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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PREDICTIVE VALUE OF RCCEP IN THE OUTCOME OF PATIENTS WITH ADVANCED ESOPHAGEAL SQUAMOUS CELL CARCINOMA TREATED WITH CAMRELIZUMAB

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Abstract: To evaluate the predictive value of reactive cutaneous capillary endothelial proliferation (RCCEP) in the treatment outcome of patients with first-diagnosed advanced esophageal squamous cell carcinoma (ESCC) treated with camrelizumab in combination with chemotherapy. This is a single-center, retrospective, observational study of 76 patients who were first diagnosed with advanced ESCC and received Camrelizumab combination chemotherapy at our institution from January 2021 to December 2022, and were compared between those who had and those who did not have an RCCEP response to determine the predictive value of an RCCEP response for treatment outcomes in this patient population.The overall survival (OR) of patients with RCCEP response was 15.08 ± 6.35 months, which was better than that of patients without RCCEP response of 10.55 ± 4.68 months, and the difference was statistically significant (P=0.001). Twenty-eight cases (77.78%) of the patients who experienced partial response (PR), while the overall response rate (ORR) was 77.78%; while among the patients who did not experienced RCCEP response, only five cases (12.50%) experienced PR, and the ORR was 12.50%, which were statistically different in both cases (P<0.001; P<0.001). There was no difference in the occurrence of treatment-related adverse events between the two groups. Meanwhile, 88.89% of RCCEP patients experienced grade I response, 11.11% experienced grade II response, and no grade III-V response occurred. 66.67% of RCCEP patients showed red-nevus-like.The occurrence of RCCEP suggests therapeutic efficacy in patients with advanced ESCC treated with camrelizumab in combination with chemotherapy, indicating the prognostic value, and may serve as a potential predictor of treatment outcome in this patient population.

Keywords: Esophageal Squamous Cell Carcinoma; Reactive cutaneous capillary endothelial proliferation; Camrelizumab; Immune-related adverse events; Advanced esophageal carcinoma

1 PREAMBLE

In 2020, it is estimated that there will be more than 19.3 million new cancer cases and more than 10 million new cancer deaths in the world, and esophageal cancer has become one of the major cancers threatening human health, accounting for 3.1 percent of new cancer cases and 5.5 percent of new cancer deaths[1, 2]. The histological subtype of Esophageal carcinoma (EC) shows varying incidence depending on regional differences, although in some Western populations, the incidence of adenocarcinoma has surpassed that of squamous carcinoma. Esophageal Squamous Cell Carcinoma (ESCC) remains the dominant sub type in Asian populations[3-5]. With the optimization of surgical modalities and treatment strategies, although EC-related mortality and 5- year overall survival (OS) have improved, patients with advanced ESCC have an OS of only 8-11 months, and the prognosis remains poor[3, 6, 7].

Patients with EC are usually already advanced or metastasized at the time of diagnosis, and the current recommended first-line treatment for such advanced or metastasized ESCC is chemotherapy[8]. However, multiple prospective clinical studies have shown that overall survival remains low in patients receiving chemotherapy[9]. In recent years, Programmed cell death protein (PD-1) and Programmed cell death protein ligand 1(PD-L1) has shown remarkable efficacy and great promise in the treatment of a variety of cancers[10-13]. In the ATTRACTION-03 clinical trial,

Nivolumab for advanced ESCC showed prolonged OS (10.9 vs. 8.4 months) and a lower incidence of grade III or IV adverse events (18% vs. 63%) in the Nibolumab group compared with chemotherapy[14]. At the same time, immunotherapy combined with chemotherapy showed better outcomes in a variety of tumor types. The ESCORT study has demonstrated that in patients with advanced or metastatic ESCC, Camrelizumab combined with chemotherapy significantly improves overall survival and progression-free survival compared with placebo-plus chemotherapy[8].

Although immune-related adverse events (irAE) during immunotherapy have been shown to predict immunotherapy outcomes, few studies have been conducted in advanced ESCC. Especially reactive cutaneous capillary endothelial proliferation(RCCEP), which is a common occurrence of immune-related adverse events[15, 16]. Therefore, we conducted this retrospective study to evaluate the prognostic value of RCCEP in patients receiving Camrelizumab in combination with chemotherapy for advanced ESCC.

2 METHODS OF STUDY

2.1 Clinical Data

This study was a single-center, retrospective, observational study. The protocol was approved by the Institutional Review Board of our hospital, which waived the need for informed consent because it was a retrospective study. All methods were carried out in accordance with the Helsinki Principles. A total of 76 patients with advanced Esophageal Squamous Cell Carcinoma (ESCC) who were first diagnosed in our hospital between January 2021 and December 2022 and received Camrelizumab combined with chemotherapy were selected as the study subjects.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: Meet the diagnostic criteria for advanced esophageal cancer, clinical stage III b-IV; The pathological types were squamous cell carcinoma; Aged 30-80 years old; Have not had any previous treatment; Camrelizumab combined with chemotherapy was chosen; Patients were conscious and able to communicate normally. Exclusion criteria: other serious diseases, such as cardiovascular and cerebrovascular diseases; Combined with consciousness or cognitive impairment; Allergic reactions and contraindications to the drugs in this study; Patients with concurrent autoimmune disease or a history of chronic autoimmune disease; And a history of previous tumors other than esophageal cancer.

2.3 Methods

Control group: All patients agreed to receive and use the regimen recommended by the Clinical Oncology Collaborative Committee of the Chinese Anti-Cancer Association (CSCO) guidelines, mainly platinum combined with paclitaxel or fluorouracil or docetaxel. Observation group: On the basis of control group, patients received immunotherapy combined with Camrelizumab. Usage and dosage:Camrelizumab injection 200mg+250ml0.9% sodium chloride solution, intravenous infusion, 60min(90min for the first time), a treatment cycle of 3 weeks, a total of 2 cycles of treatment (clinical efficacy evaluation every 2-3 cycles, patients without disease progression continue to receive the next course of treatment).

2.4 Outcome Measures

(1) survival: overall survival (OS), which refers to the time from the start of treatment to the last follow-up or death from any cause; (2) anti-tumor effect: refer to the RECIST efficacy evaluation criteria (2000) to determine the anti-tumor effect of the patient. overall response rate (ORR)= complete response (CR)+ partial response (PR); stable disease (SD); progressive disease (PD); (3) treatment-related adverse reactions: nausea; Fatigue; Vomiting; Fever; Gastrointestinal reactions; Leukopenia; thrombocytopenia;(4) reactive cutaneous capillary endothelial proliferation (RCCEP) grade: Grade I (maximum nodule diameter ≤10 mm, with or without rupture and bleeding); Grade II (nodule maximum diameter >10 mm, with or without rupture and bleeding); Grade II (diffuse nodules throughout the body that may be complicated by skin infection); Grade IV (systemic and multiple nodules, and life-threatening); And Grade V

(death). RCCEP remission refers to regression of all RCCEP lesions. At the same time, according to the shape of RCCEP occurrence, it is divided into; Red nevus shape; Pearl-like; Mulberry; Patchy; Tumour-like.

2.5 Statistical Methods

SPSS 23.0 statistical software was used for analysis, measurement data were represented by($\bar{x} \pm s$), and T-test was performed; Counting data were represented by frequency and rate, and P<0.05 indicated statistical difference.

3 RESULTS

3.1 General Data Comparison

The mean age of patients with RCCEP reaction was 63.25 ± 9.40, and the mean age of patients without RCCEP reaction was 65.20 ± 8.23, with no statistical difference. Among the patients with RCCEP reaction, 32 (88.89%) were treated with paclitaxel + cisplatin combined with carrellizumab (Camrelizumab), and 4 (11.11%) were treated with docetaxel + cisplatin combined with Camrelizumab; Among the patients with no RCCEP response, 22 (55.00%) were treated with paclitaxel + cisplatin combined with Camrelizumab, and 18 (45.00%) were treated with docetaxel + cisplatin combined with Camrelizumab, with statistical differences (P<0.001; P<0.001). No statistically significant difference was found in other patients' general data, as shown in Table 1.

Table 1. Clinical characteristics of patients

	RCCEP(n=36)	Non-RCCEP (n=40)	P
age	63.25 ± 9.40	65.20 ± 8.23	0.338
Gender,male	35 (97.22)	35 (87.50)	0.117
BMI, kg/m2	22.14 ± 2.25	21.53 ± 4.65	0.468
ECOG rating			
0	26 (72.22)	30 (75.00)	0.784
1	10 (27.78)	8 (20.00)	0.426
2	0 (0)	2 (5.00)	0.174
Transfer parts			
lung	1 (2.78)	2 (5.00)	0.619
liver	0 (0)	1 (2.50)	0.340
bone	1 (2.78)	0 (0)	0.289
other	0 (0)	1 (2.50)	0.340
Treatment mode			
TP+Cam	32 (88.89)	22 (55.00)	0.001
DP+Cam	4 (11.11)	18 (45.00)	0.001

Note: Eastern Cooperative Oncology Group (ECOG) score; TP, Paclitaxel + cisplatin; DP,docetaxel + cisplatin; Cam, carelizumab; Metrological data were expressed with ($\bar{x} \pm s$) ; Counting data is expressed in frequency and rate.

3.2 Treatment-Related Adverse Reactions were Compared between the Two Groups

Treatment-related adverse reactions occurred: nausea, fatigue, vomiting, fever, gastrointestinal reactions, leukopenia, thrombocytopenia and hyperthyroidism, and there were no statistical differences between the two groups, as shown in Table 2.

Table 2. Comparison of treatment-related adverse reactions between the two groups

	RCCEP(n=36)	Non-RCCEP (n=40)	P
Nausea	9 (25.00)	5 (12.50)	0.160
Fatigue	5 (13.89)	7 (17.50)	0.666
Vomiting	5 (13.89)	6 (15.00)	0.891
Fever	3 (8.33)	5 (12.50)	0.555
Gastrointestinal reactions	4 (11.11)	6 (15.00)	0.617
Hyperthyroidism	1 (2.78)	1 (2.50)	0.940
Leukopenia	2 (5.56)	3 (7.50)	0.733
Thrombocytopenia	1 (2.78)	0 (0)	0.289

Note: Measurement data are represented by($\bar{x} \pm s$) ; Counting data is expressed in frequency and rate.

3.3 Comparison of Treatment Outcomes between the Two Groups

It was found in Table 3 that the overall survival of patients with RCCEP reaction was 15.08 ± 6.35 months, which was better than 10.55 ± 4.68 months without RCCEP reaction, and the difference was statistically significant (P=0.001). There were no patients with complete response in either group. A total of 28 patients (77.78%) with RCCEP response had partial response, which was better than 5 patients (12.50%) without RCCEP response, and the difference was statistically significant (P<0.001). Disease progression occurred in 1 case (2.78%) with RCCEP reaction, and in 3 cases (7.50%) without RCCEP reaction, with no statistical difference (P=0.357). It can be observed by follow-up CT that the length and thickness of follow-up CT with RCCEP reaction were 3.52 ± 2.07cm and 0.98 ± 0.48cm, respectively, which were smaller than those without RCCEP reaction (4.87 ± 1.67cm; 1.54 ± 0.70cm), the difference was statistically significant (P=0.002; P<0.001).

Table 3. Comparison of treatment outcomes between the two groups

	RCCEP(n=36)	Non-RCCEP (n=40)	P
Lifetime			
Overall survival,OS	15.08 ± 6.35	10.55 ± 4.68	0.001
Complete remission,CR	0 (0)	0 (0)	
Partial remission,PR	28 (77.78)	5 (12.50)	<0.001
Disease stable,SD	7 (19.44)	32 (80.00)	<0.001
Disease progression,PD	1 (2.78)	3 (7.50)	0.357
Objective response rate,ORR	28 (77.78)	5 (12.50)	<0.001
CT(before treatment)			
Length,cm	5.84 ± 2.14	5.39 ± 1.87	0.335
Thickness,cm	1.73 ± 0.85	1.68 ± 0.62	0.766
CT(Last follow-up)			
Length,cm	3.52 ± 2.07	4.87 ± 1.67	0.002
Thickness,cm	0.98 ± 0.48	1.54 ± 0.70	<0.001

Note: Measurement data are indicated by($\bar{x} \pm s$) ; Counting data is expressed in frequency and rate.

3.4 RCCEP Response

Among the 36 patients with RCCEP reaction, 32 patients (88.89%) had grade I reaction, 4 patients (11.11%) had grade II reaction, and no patients had grade III-V reaction. According to the morphological observation of RCCEP reaction, a total of 24 patients (66.67%) showed red nevus, 5 patients (13.89%) showed pearl, 1 patient (2.78%) showed mulberry, 4 patients (11.11%) showed patellar and 2 patients(5.56%) showed nodular. Among the 36 patients with RCCEP, 1 (2.78%) had oral mucosal lesions, 2 (5.56%) had conjunctival lesions, and 1 (2.78%) had nasal mucosal lesions.

4 DISCUSS

Esophageal carcinoma (EC) is a malignant tumor occurring in the esophageal epithelium with various etiology and can be caused by alcohol abuse, smoking, bad diet and other factors. China is one of the countries with high incidence of esophageal cancer in the world[17]. In China, the most common subtype of Esophageal Squamous Cell Carcinoma (ESCC), and EC because of the early clinical symptoms are not obvious, usually when the doctor is already in the late stage or metastasis, the prognosis is poor, 5-year survival rate is only 15%-25%[18]. In the past, the first-line treatment for advanced EC is mainly the use of systemic chemotherapy containing fluorouracil and platinum drugs, but the traditional chemotherapy has poor efficacy, large side effects, and the after-line treatment after chemotherapy failure is not good[19]. In recent years, with a large number of clinical studies on PD-1/PD-L1 treatment of a variety of tumors, and achieved gratifying results, but also for the treatment of advanced EC has brought opportunities and challenges.

A number of clinical trials at home and abroad have confirmed that immunotherapy in patients with advanced or metastatic EC, compared with traditional chemotherapy, can bring better safety and effectiveness for patients. In addition to being effective on tumor cells, Immune checkpoint inhibitors (ICIs) may also cause autoimmune toxicity and immune-related adverse events (irAE)[20-22]. Although the exact mechanism of irAE is unknown, autoantibody stimulation, overactivation of T cells and increased cytokine levels may explain this phenomenon[21, 23]. Although irAE is an adverse drug reaction, several studies have found that the occurrence of irAE may be associated with better clinical outcomes[24]. IrAE is an immune reaction involving multiple organs in the whole body, especially the skin reaction. Reactive cutaneous capillary endothelial proliferation (RCCEP) is the irAE with the highest incidence during Camrelizumab treatment[15, 25, 26]. The objective of this study was to explore the predictive value of RCCEP in treatment outcomes of patients with first diagnosed advanced ESCC treated with Camrelizumab combined with chemotherapy.

In a study of RCCEP, Camrelizumab may promote vascular proliferation by activating CD4+T cells and increasing the release of cytokine IL-4, thereby stimulating macrophage differentiation and releasing VEGF-A[15]. In this study, the incidence of RCCEP was 47.37%(36/76). However, in one nasopharyngeal carcinoma patient receiving Camrelizumab combined with apatinib, the incidence of RCCEP was only 12.1%(4/33), and Apatinib, as a VEGFR 2 inhibitor, was considered to be related to the inhibition of RCCEP by blocking downstream proteins after Apatinib binding to VEGF[27]. These results suggest that RCCEP may not be appropriate for predicting the occurrence of RCCEP in all tumors treated with Camrelizumab, as other agents may affect the occurrence[28] of RCCEP. Meanwhile, in the present study, RCCEP occurred mainly in the skin of the head, face and trunk and was mainly red nevus (66.67%). Among all the grades of RCCEP, 88.89%(32/36) were in grade I patients and 11.11%(4/36) were in grade II patients. No III-V RCCEP was observed, and no RCCEPrelated death events were observed. Most RCCEP usually did not require special management, and most lesions resolved spontaneously within 2 months of discontinuation of Camrelizumab. When nodules need to be treated, the ruptured and bleeding nodules should be stopped and mupirocin ointment should be administered to prevent infection; In patients with larger nodules, some may also be surgically removed. Of the 36 patients who developed RCCEP, 1 had oral mucosal lesions, 2 conjunctival lesions, and 1 nasal mucosal lesions. No mucosal lesions of the trachea or digestive tract (esophagus and gastrointestinal tract) were observed, and therefore none of the patients was at risk of hemoptysis or gastrointestinal bleeding.

Several studies have shown that the occurrence of cutaneous irAE can predict the efficacy of PD-1/PD-L1 in some tumors[16, 29]. Also, in our study, we found that the group that developed an RCCEP response had an increased overall

survival relative to the group that did not develop an RCCEP response (15.08 ± 6.35 months vs. 10.55 ± 4.68 months). In terms of antitumor effect, although there was no difference between the two groups in patients with complete response, the RCCEP group had better partial response and objective response rate than the group without RCCEP response. In addition, in a study of Camrelizumab for hepatocellular carcinoma, patients who responded to RCCEP had a higher rate of objective response than those who did not respond to RCCEP (19.3% vs. 5.6%)[16, 29]. This suggests that patients who respond to RCCEP during Camrelizumab therapy may have a better prognosis.Therefore,RCCEP may be a clinical indicator for predicting the efficacy of Camrelizumab.

In conclusion, RCCEP can predict the outcome of advanced ESCC patients treated with Camrelizumab combined with chemotherapy to some extent, but it needs to be confirmed by larger prospective clinical trials. At the same time, more monitoring and follow-up of patients with RCCEP should be conducted to prevent the occurrence of severe and life-threatening RCCEP.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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THE TRANSFORMATION OF AXILLARY SURGERY FOR BREAST CANCER

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Abstract: Breast cancer surgery treatment has a century of development from extended radical mastectomy to modified radical mastectomy and then to breast-conserving surgery. Breast cancer surgery tends to be more and more minimally invasive. Axillary surgery is an important part of breast cancer surgery. Sentinel lymph node biopsy (SLNB) is a common surgical procedure, and axillary lymph node dissection (ALND) is the most common choice for patients with positive sentinel lymph nodes. However, ALND has many sequelae for breast cancer patients, such as postoperative lymphedema, abnormal limb sensation and movement, etc. In the past decade, evidence has shown that it is feasible to avoid ALND in breast cancer with positive sentinel lymph nodes. Some scholars have studied that SLNB combined with axillary radiotherapy is equivalent to ALND. In short, axillary surgery is increasingly tending to be minimally invasive and narrow in scope. This study aims to explore the transformation and future development direction of axillary surgery for breast cancer.

Keywords: Breast cancer; Axillary surgery; SLNB; ALND

1 INTRODUCTION

At the end of the 19th century, Halsted proposed radical mastectomy, which significantly extended the survival time of patients, followed by extended radical mastectomy and modified radical resection, which continued for decades, and both performed axillary lymph node dissection. Axillary lymph node dissection can make a clear pathological stage of lymph nodes for breast cancer and guide subsequent treatment, but after axillary lymph node dissection, patients may have complications such as lymphatic return disorders, paresthesias, and mobility disorders of the affected limb. At the end of the twentieth century, sentinel lymph node biopsy was introduced into breast cancer surgery, followed by a series of clinical trials showing that sentinel lymph node negative patients[1]. The overall survival rate and disease-free survival rate were similar in the Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) groups. Now, in challenging the traditional notion of tumor-free, the Z0011 trial has shown that sentinel node-positive patients are safe and feasible to be exempt from ALND under certain conditions[2]; There have also been studies on the applicability of sentinel lymph node biopsy after neoadjuvant chemotherapy. The current management of axillary surgery is still in a transitional stage, and it is necessary to find an appropriate balance between reducing the recurrence rate, maintaining tumor safety, and performing staged surgery, but the overall trend of surgical development is to ensure safety while reducing surgical complications. This paper reviews the development status and development trend of axillary surgery for breast cancer.

2 HISTORY OF SENTINEL LYMPH NODE BIOPSY

Since the advent of Halsted surgery, ALND has been the standard axillary surgery for breast cancer patients, and ALND still plays an important role in breast cancer surgery, mainly including: 1. Assessing lymph node status, 2. Preventing axillary recurrence, and 3. Removing positive lymph nodes may improve survival. However, the role of ALND has been gradually changed by several randomized clinical trials, and ALND does not reduce systemic recurrence or improve survival. 1985, American Study Group on Adjuvant Breast and Intestinal Surgery (NSABP) B-04 Clinical Trial.

The results of the 10-year study showed that immediate ALND in clinically axillary node-negative patients did not improve survival[3]; A 25-year follow-up study also confirmed that ALND did not reduce systemic recurrence rates or improve survival [4]. SLNB was introduced into the surgical treatment of breast cancer by Krag et al. in 1993 [5], and then NSABP B-32 large randomized clinical trial randomized 5611 patients were randomly divided into ALND group and ALND group only when the sentinel was positive, and there was no difference in the 8-year overall survival rate and disease-free survival rate between the two groups, indicating that SLNB only for SLN-negative patients was safe [1]. Then the ALMANAC clinical study enrolled 1031 patients with clinical axillary node-negative breast cancer were randomly divided into SLNB and ALND groups, and were followed up for 1 year, and the results showed that the SLNB group could reduce the incidence of upper limb complications and improve the quality of life[6]. Based on a series of similar findings, the 2005 ASCO guidelines recommend that early breast cancer patients with clinically negative axillary lymph nodes can be exempted from ALND if SLN is negative, and routine SLNB is recommended for patients with clinically negative axillary lymph nodes [7]. The results show that more and more breast cancer patients undergo SLNB in recent years, and a 2016 study by the Breast Center of Heidelberg University in Germany showed that the proportion of SLNB increased from 10.3% in 2003 to 76.4% in 2016 [8]. Even though SLNB has been widely used, the false negative rate of SLNB is objective, so how can we minimize the false negative rate of SLNB? Related tests such as ALMANAC Trialists, in this experiment, blue staining and radioisotope double tracing method was used to perform SLNB. The results showed that the false negative rate of patients with one SLN removed was 10.1%, and that of two SLN was 8.5%, while that of patients with more than or equal to three SLN was 1.1%. In addition, Bonneau et al surveyed 144517 breast cancer patients who underwent SLNB from the SEER database in 2014 and concluded that removal of at least three SLNs could reduce the false negative rate and had a higher 5-year survival rate [9,10]， Therefore, the false-negative rate of SLNB is related to tracer, number of SLNs, and surgical experience of surgeons. At present, guidelines have also put forward requirements for the diagnosis and treatment of SLNB, the detection rate of SLNB should not be less than 90%, and the false negative rate should not be higher than 10%. Therefore, surgeons are advised to use double tracer method for SLNB [11]. SLNB has been accepted and recognized by clinicians after 20 years of development. About internal mammary SLNB, studies have shown that the metastasis rate of the internal mammary SLNs is as follows 18.0% ~ 33.0%, of which 90.0% ~ 98.0% of patients had axillary lymph node metastasis and 2.0% ~ 10.0% had only internal mammary lymph node metastasis [12-14]. Therefore, SLNB can evaluate the lymph node status of most breast cancer patients, and internal mammary lymph node biopsy has been abandoned by most surgeons, and SLNB has become the standard surgical method for clinically negative patients with early-stage breast cancer.

3 AXILLARY SURGERY FOR SENTINEL NODE-POSITIVE BREAST CANCER

The NSABP B-32 trial has demonstrated that it is safe and feasible for sentinel node-negative breast cancer patients not to undergo ALND, but for patients who are clinically axillary negative but pathological sentinel lymph node positive, especially those with less than two positive lymph nodes, the need for axillary lymph node dissection is currently controversial.The International Breast Cancer Research Group IBCSG23-01 trial was designed to address the question of whether patients with single or multiple sentinel lymph node micrometastases (≤2 mm without extracapsular extension) could avoid ALND [15]. In this study, 934 breast cancer patients with SLN biopsies with micrometastases were randomly assigned to either no longer undergo surgery or continue with ALND. After 5 years, the disease-free survival rates in the SLN biopsy group and ALND group were 87.8% and 84.4%, respectively. Similarly, the AATRM trial randomly divided patients with clinically negative axillary but micrometastases on SLNB into the observation group or the ALND group, with a median follow-up of 5 years, and there was no significant difference in disease-free survival between the two groups (Observation group: 2.5%; in the; ALND group: 1%) [16]. The data from the IBCSG23-01 trial and the

AATRM trial provide evidence for the safety of exempting axillary lymph node dissection for early breast cancer patients with micrometastasis of sentinel lymph nodes. For patients with macrometastasis of sentinel lymph nodes, the ACOSOG-Z0011 trial enrolled 891 breast cancer patients with clinically negative axillary lymph nodes and positive sentinel lymph nodes 1-2. 446 patients underwent SLNB only and 445 underwent ALND. The median follow-up was 6.3 years. The 5-year overall survival rates of the SLND group and the ALND group were 92.5% and 91.8%, respectively; the 5-year disease-free survival rates were 83.9% and 82.2%, respectively; and the 5-year local recurrence rates were 1.6% and 3.1%, respectively. There was no statistically significant difference in the 5-year overall survival rate, disease-free survival rate, and local recurrence rate between the two groups [2]. Based on the above data, the 2015 ASCO guidelines recommend that axillary lymph node dissection can be waived for breast cancer patients who meet the Z0011 trial criteria (breast-conserving surgery, T1 or T2, clinically negative axillary nodes, and 1-2 sentinel lymph node metastases) [9]. The Z0011 trial has revolutionized the traditional concept that ALND should be performed routinely on SLN-positive patients. Although the current guidelines suggest that ALND can be exempted if the Z0011 trial conditions are met, there are still many controversies. In actual application, there are not many breast cancer patients who meet the Z0011 trial criteria. A multicenter retrospective clinical study in the Netherlands analyzed 11,031 patients with early invasive breast cancer, of whom only 558 met the Z0011 criteria and could be exempted from ALND, accounting for only 5.1% of the total number of breast cancer patients [17]. The above clinical trials were all conducted on patients with clinically negative axillary early breast cancer, and no studies were conducted on cases with clinically positive axillary disease. In 2018, the TAXIS clinical trial conducted a study on patients with clinically positive axillary breast cancer (18). The clinical trial aimed to study the effect of tailored axillary surgery (TAS) surgery. Tailored axillary surgery refers to SLNB & removal of all suspicious lymph nodes & axillary radiotherapy, and its therapeutic effect is no less than ALND. The first case was enrolled in the trial in August 2018, and the final results are yet to be announced. However, for most breast cancer patients, the current standard treatment for patients with clinically positive axillary disease or SLN-positive breast cancer is still ALND, and there is still no unified standard and consensus.

4 ALTERNATIVE TREATMENT FOR AXILLARY SURGERY

At present, the majority of sentinel node-positive breast cancer patients still need to undergo ALND, although ALND can completely remove lymph node lesions and assess lymph node metastasis status. However, it also has side effects such as lymphedema of the upper extremities and motor sensory dysfunction, reduced quality of life for breast cancer patients. Now that there is a lot of evidence that adjuvant therapy can heal some of the remaining metastatic lymph nodes, is reducing the scope of surgery a trend in axillary surgery in the future? The success of the ACOSOG-Z0011 trial is unquestionable, however the trial has been questioned for several reasons [18]**.** One reason for this is that many cases in the SLNB observation group received radiation therapy, but the SLNB group in the trial was defined as "no further axillary treatment", which can be understood as "No axillary dissection and no axillary radiation therapy" [19]. There are many scholars who believe that the Z0011 trial can do so well because the patients in the SLNB observation group are undergoing breast radiation therapy. The armpits were also accidentally treated with radiotherapy[20-22]. But when Reshma Jagsi tried to collect radiotherapy records from 891 patients in the Remodeling Z0011 trial, only 29% of the cases were well documented[23]. Therefore, we do not know the specific radiotherapy data for Z0011. The EORTC AMAROS clinical trial and the OTOASOR clinical trial complement this shortcoming [24,25], both of these trials investigating clinically axillary-negative but sentinel-positive breast cancer randomized to ALND group or SLNB and axillary radiotherapy group. There was no significant difference in the 5-year axillary recurrence rate between the two groups, suggesting that total axillary radiation therapy is an effective alternative to ALND. The ALND group of these two trials had about 32.8% of cases and 38.5% of positive nonsentinel lymph nodes, respectively, and we can

extrapolate that the axillary radiotherapy group also had such a high proportion of positive lymph node residuals. And the local recurrence rates were similar in the ALND and axillary radiotherapy groups, and there is no doubt that residual positive axillary lymph nodes are sensitive to axillary radiotherapy. Although, we cannot ignore the role of systemic adjuvant therapy, which has been shown to achieve an axillary pathological complete response (pCR) rate of about 20% to 50% in patients with node-positive breast cancer[26,27]. Perhaps the combination of the adjuvant therapy and axillary radiation therapy will be more effective in controlling the local recurrence rate of the axilla. In summary, further research is still needed to confirm how to choose the appropriate treatment regimen for sentinel node-positive breast cancer patients, and from the current research, the direction of axillary radiotherapy as an alternative to ALND is promising.

5 AXILLARY SURGERY AFTER NEOADJUVANT CHEMOTHERAPY

SLNB is the gold standard for axillary lymph node staging in early-stage breast cancer, and neoadjuvant chemotherapy (NAC) is the standard treatment option for patients with locally advanced and inflammatory breast cancer. But now NAC can be used not only for patients with locally advanced disease, there is also an increasing use of NAC, as it can make breast-conserving patients who cannot conserve breast. However, most current guidelines are based on surgical pathology prior to adjuvant therapy. Preoperative NAC poses a challenge to clinicians, especially for axillary surgery. For patients with clinical axillary lymph node negative (cN-) before NAC, studies have shown that the detection rate and false negative rate of SLNB before and after NAC are consistent. Moreover, SLNB after chemotherapy can reduce the number of SLN positives, reduce unnecessary axillary dissection, and reduce complications after ALND, and the recurrence rate and survival rate are similar[28,29]. At present, most experts believe that SLNB after NAC is safe and feasible, and the 2016 ASCO clinical practice guidelines have also been updated to provide SLNB for early breast cancer patients receiving preoperative NAC [30]. For patients with clinical axillary positive (cN+) before NAC, studies have shown that NAC can increase the pCR rate of axillary positive lymph nodes from 20% to 50%. In theory, these patients do not need axillary dissection, but what is the false negative rate of SLNB in patients with axillary positive breast cancer after NAC? In the ACOSOGZ1071 trial, 701 breast cancer patients with axillary lymph node metastasis and NAC were enrolled in this trial, and the false negative rate of SLNB was 12.6% [31]; Similar trails, such as the SENTINA trails, had a false-negative rate of 14.2% for SLNB [32]; Compared with the false negative rate of SLNB in early breast cancer patients without NAC, a 2016 Meta analysis of sentinel lymph node biopsy by Niebling showed that the false negative rate of double tracer SLNB was 2.6% [33]. The false negative rate of these two trials is relatively high, and the high false negative rate will inevitably leave out many breast cancer patients who must implement ALND. Therefore, at present, there is a great controversy about whether to perform SLNB with axillary lymph nodes positive before NAC. However, in order to reduce the false negative rate of SLNB after neoadjuvant chemotherapy, Anderson proposed a new technique-targeted axillary dissection (TAD), that is, puncture biopsies of all suspected metastatic lymph nodes before neoadjuvant chemotherapy. Radioactive iodine 125 particles were placed in the lymph nodes with pathologically confirmed metastasis. after the completion of NAC, patients underwent axillary surgery with X-ray films to selectively remove the lymph nodes labeled by iodine-125 particles [34]. This is a new technique that can be used to remove all suspicious lymph nodes in a targeted manner and reduce the false-negative rate of SLNB. One study recruited 208 breast cancer patients who underwent NAC with TAD before operation, and then the false negative rate of SLNB decreased from 10.1% to 1.4%. [35].

6 PROSPECTS FOR FUTURE AXILLARY SURGERY

SLNB has opened a new era for axillary surgery for patients with early-stage breast cancer, and the development direction of breast cancer surgery is minimally invasive and aesthetic, and so is axillary surgery. Nowadays, there are many screening methods, and more and more early breast cancer patients are being detected. There are also many systemic adjuvant treatments for breast cancer, and the treatment effect is also very obvious. Since systemic adjuvant treatment is also effective for the axilla, too much surgery will only reduce the patient's quality of life. It is worth discussing whether the scope of axillary surgery can be further reduced, even for patients with clinically negative axillary findings, can SLNB be abandoned based solely on negative imaging findings [36]. Perhaps even if the axillary tumor is clinically positive, the same therapeutic effect as ALND can be achieved by simply removing all suspicious lymph nodes and receiving systematic and standardized treatment. The TAXIS trial is currently conducting a phase III clinical study on clinically axillary-positive breast cancer, and the results will take some time to verify. But we hope that TAS surgery and axillary radiotherapy can bring similar therapeutic effects to ALND, and have a higher quality of life.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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EFFECT OF PATERNAL AGE ON EMBRYONIC DEVELOPMENT IN MOTHERS AGED 31-35 YEARS OLD

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Abstract: Most studies on embryo development have considered female factors, and few studies have introduced the influence of paternal age on embryo development. In this study, to explore the influence of paternal age on the development of offspring embryos, women aged 31-35 years old and their husbands aged 22-42 years old were selected from the assisted reproductive cycle. Their eggs were fertilized by intracytoplasmic sperm injection, the normal fertilization rates, normal cleavage rates, effective embryo rates, high-quality embryo rates, blastocyst formation rates of their embryos were statistically analyzed to assess the effects of paternal sperm on embryonic development at different ages. The results showed that for mothers between 31 -35 years old, when fathers were between 28 -36 years old, the embryo development were better, indicating that the sperm quality of fathers in this age group may be the best, and the most conducive to embryo development. When paternal age were more than 36 years old, the normal fertilization rates, effective embryo rates, high-quality embryo rates, blastocyst formation rates all decreased with age increased. This finding suggested that men should have children no later than the age of 36.
Keywords: Embryonic development; Paternal age; Male factor infertility

1 INTRODUCTION

Currently, approximately 10%-15% couples of reproductive age worldwide are affected by infertility[1]. The main factors affecting fertility are environmental factors and parental factors[2]. Among them, the most important factors for both parents are age[3]. Most studies have explored the effect of maternal age on embryonic development, including multicenter studies[4-10]. However, there are fewer studies on the influence of paternal age[11, 12]. Some studies have explored the influence of genetic factors such as sperm genes and chromosomes on the development of embryos, but have not described the influence of sperm from different paternal ages on embryonic development[13]. In addition, there are some studies showed conflicting results[14, 15].

In order to further clearly explore the influence of paternal age on embryo development, this study selected 31-35 years old females which are the main infertility group to explore the influence of their partner's age on the outcome of embryo development. The fertilization method was selected by intracytoplasmic sperm injection, excluding donor patients and patients with less than 3 mature eggs, as well as patients undergoing PGT cycle due to genetic or chromosomal factors. The influence of paternal age on the outcome of embryo development was determined by analyzing five indexes, normal fertilization rates, normal cleavage rates, effective embryo rates, high-quality embryo rates and blastocyst formation rates.

2 RESULTS

2.1 Effect of Paternal Age on Normal Fertilization of Ovum

Among women in 31-35 age group, the fertilization rates of eggs are highest when their husbands aged between 28-30 years old (Figure 1). When fathers older than 30 years old, the fertilization rates of eggs showed a slow decline trend with age increased (Figure 1). The result suggests that the optimal age of fertilization for male sperms may be between 28-30 years old.

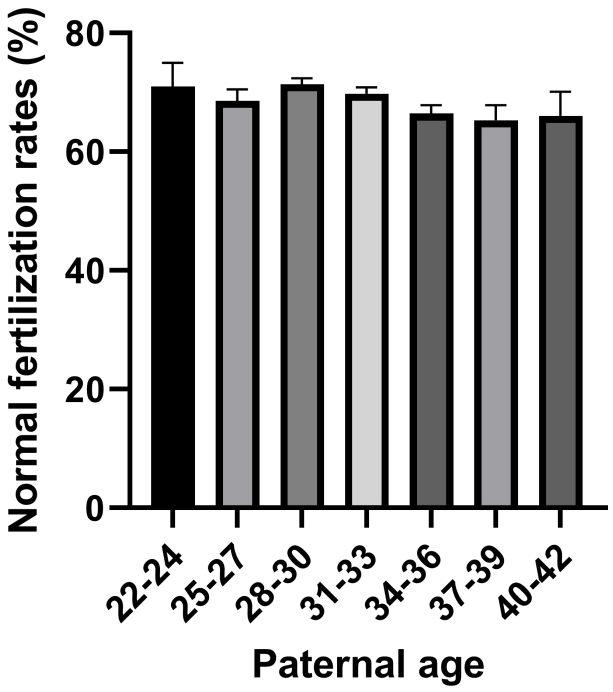

Figure 1 Effect of Paternal Age on Normal Fertilization of Ovum

The influence of paternal sperm from different age group on normal fertilization of eggs was statistically analyzed when the mothers were between 31-35 years old. (22-24, n=26. 25-27, n=117. 28-30, n=364. 31-33, n=390. 34-36, n=192. 37-39, n=65. 40-42, n=31)

2.2 Effect of Paternal Age on Normal Cleavage of Fertilized Eggs

In Figure 2, the results showed that the normal cleavage rates are almost not affected by paternal age. Normal cleavage rates of paternal age between 40-42 years old (95.9032%) are slightly lower than that of other groups, the normal cleavage rates of paternal age between 22-24 years old (97.8846%) are slightly higher than that of other groups, and the overall normal cleavage rates remains above 95% (Figure 2). The result indicates that paternal age had little effects on normal cleavage rates.

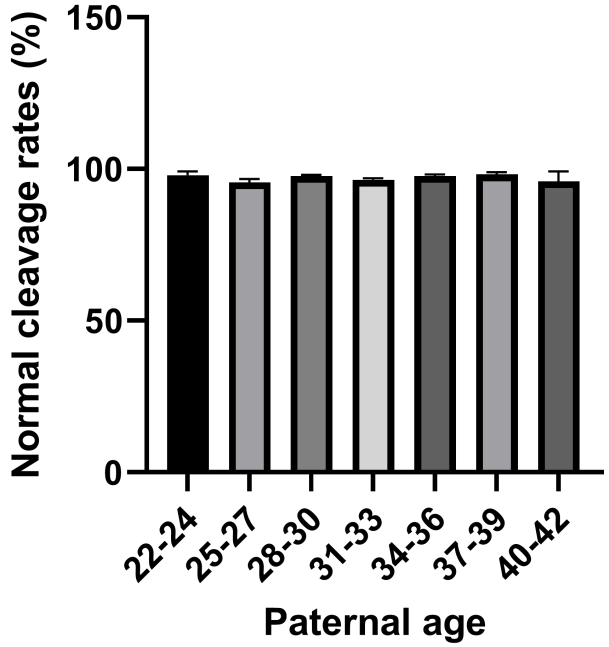

Figure 2 Effect of Paternal Age on Normal Cleavage

The influence of paternal sperms from different age group on normal cleavage of fertilized eggs was statistically analyzed when the

mothers were between 31-35 years old. (22-24, n=26. 25-27, n=117. 28-30, n=364. 31-33, n=390. 34-36, n=192. 37-39, n=65. 40-42, n=31)

2.3 Effect of Paternal Age on Effective Embryo Formation

For paternal age, before 28 years old, the effective embryo rates increased with age (Figure 3). After 30 years, with the increase of age, the effective embryo rates gradually decreased (Figure 3). Although there is a peak of effective embryo rates in male aged 37-39 years old, this may be due to the smaller sample size (n=65) (Figure 3). We speculate that this peak should disappear when the sample size is large enough. This data suggests that the sperms of males aged between 28-30 years old may be most conducive to embryo formation.

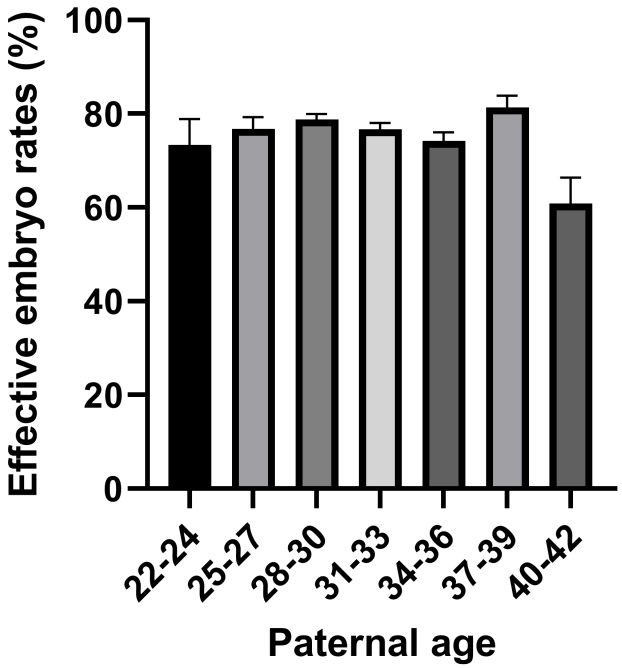

Figure 3 Effect of Paternal age on Effective Embryo Formation

The influence of paternal sperms from different age group on effective embryo formation was statistically analyzed when the mothers were between 31-35 years old. (22-24, n=26. 25-27, n=117. 28-30, n=364. 31-33, n=390. 34-36, n=192. 37-39, n=65. 40-42, n=31)

2.4 Effect of Paternal Age on the Formation of High-Quality Embryos

When paternal ages were younger than 31 years old, the rates of high-quality embryos gradually increased with age (Figure 4). When paternal ages were older than 33 years old, the rates of high-quality embryos gradually decreased with the increase of age (Figure 4). Although the data in figure 4 showed a peak in the rates of high-quality embryos between the ages of 25-27 and 37-39 years old, we also suspected that it was due to the smaller sample sizes (25-27, n=117. 37-39, n=65) (Figure 4). When the sample sizes are large enough, the two peaks above may be disappeared. This result suggests that the paternal age between 31-33 years old is most conducive to the formation of high-quality embryos.

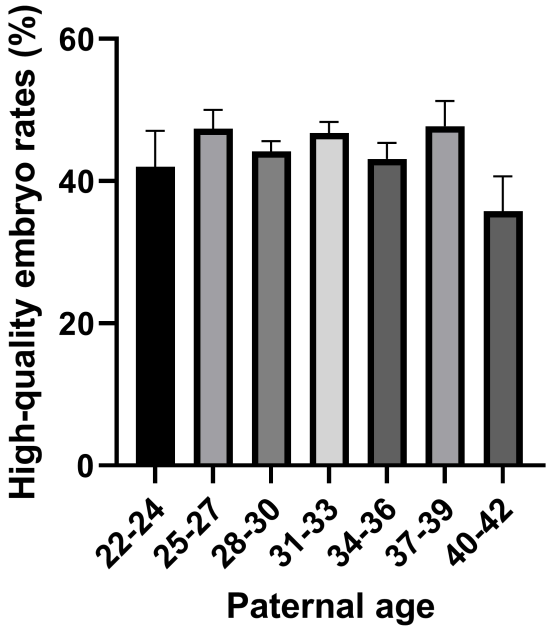

Figure 4 Effect of Paternal Age on the Formation of High-Quality Embryos
The influence of paternal sperms from different age group on the formation of high-quality embryos was statistically analyzed when the mothers were between 31-35 years old. (22-24, n=26. 25-27, n=117. 28-30, n=364. 31-33, n=390. 34-36, n=192. 37-39, n=65. 40-42, n=31)

2.5 Effect of Paternal Age on Blastocyst Formation

When paternal ages were older than 36 years old, the rates of blastocyst formation gradually decreased with the increase of age (Figure 5). But the rates of blastocyst formation were not affected when paternal ages young than 34 years old (Figure 5). The trough in 28-30 years old group was also suspected to be due to the insufficient sample size (n=364) (Figure 5). The result indicates that the paternal age less than 36 years old is conducive to blastocyst formation.

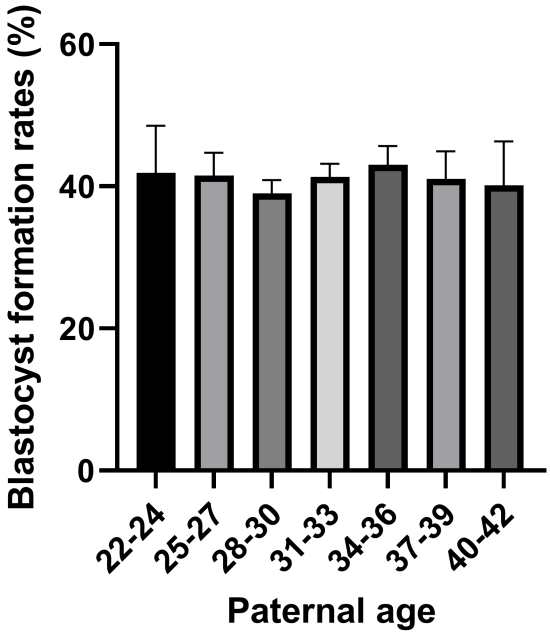

Figure 5 Effect of Paternal Age on Blastocyst Formation
The influence of paternal sperms from different age group on blastocyst formation was statistically analyzed when the mothers were between 31-35 years old. (22-24, n=26. 25-27, n=117. 28-30, n=364. 31-33, n=390. 34-36, n=192. 37-39, n=65. 40-42, n=31)

3 DISCUSSION

In this study, we investigated the influence of paternal age on the outcome of embryonic development. Eligible women aged 31-35 years old with infertility were selected from author's reproductive medicine center, which is also the peak age of infertile women in modern society. Exploring the effect of their husbands' age on embryo development can better reflect the influence of male reproductive age on embryo development and the overall fertility in modern society.

In this study, we found that although maternal age shows very important impact on the outcome of embryonic development, paternal age also plays a role. By comparing the data of normal fertilization rates, normal cleavage rates, effective embryo rates, good embryo rates and blastocyst formation rates, we found that the best age of male reproduction may be between 28-36 years old. This result will be helpful to guide the public how to choose the best male childbearing age, so that the majority of men can reasonably arrange their own birth plan.

The shortcomings of this study including that the data volume is not large enough, and it does not extend the age of paternal to whole age group also due to the limitation of data volume. If conditions permit, the author will continue to expand the sample size and the age range of paternal in order to obtain more realistic and useful results.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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INVESTIGATION OF OCCULT HEPATITIS B VIRUS INFECTION AMONG VOLUNTARY BLOOD DONORS IN HARBIN AREA

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Abstract: Objective To understand the situation of occult hepatitis B virus infection among voluntary blood donors in Harbin City, analyze its epidemiological characteristics, and assess the risk of transfusion-transmitted hepatitis B virus infection. Methods The results of hepatitis B surface antigen (HBsAg) ELISA double reagent negative and hepatitis B virus nucleic acid (HBV DNA) positive tests from 1,020,943 voluntary blood donors at the Harbin Blood Center from January 2016 to December 2022 were analyzed. Statistical analysis was performed on the total positive rate of occult HBV infection among voluntary blood donors, in relation to gender and whether it was their first time donating blood. Results Among the 1,020,943 voluntary blood donors at the Harbin Blood Center from January 2016 to December 2022, the overall positive rate of HBV infection was 0.032%, with little difference between genders, which was not statistically significant. However, there was a difference between first-time and repeat donors, which was statistically significant ($P < 0.05$). Conclusion The positive rate of HBV among voluntary blood donors in the Harbin area is related to whether they are repeat donors. Therefore, it is necessary to strengthen the promotion of knowledge about voluntary blood donation and infectious diseases, to avoid high-risk behaviors. It is important to scientifically compile recruitment guidelines and conduct health consultations before blood donation. Developing a low-risk group of voluntary blood donors can reduce transfusion risks and improve blood safety quality.

Keywords: HBV DNA nucleic acid testing (NAT); Blood screening; Occult hepatitis B virus infection (OBI); Transfusion risk

1 INTRODUCTION

In the process of patient rescue in medical institutions, blood transfusion has gradually become an important treatment method, playing a significant role in improving the efficiency of patient rescue. In recent years, with the rapid development of China's medical industry, the status of blood transfusion treatment has increased, and medical institutions have seen a corresponding increase in the demand for blood. Unsafe blood can endanger patients' lives and health. Therefore, it is of great importance to widely promote the significance of voluntary blood donation, popularize scientific knowledge about blood donation, carry out education on the prevention and control of diseases transmitted through blood, consult and examine donors to ensure the safety and effectiveness of the collected blood. At the same time, in terms of blood testing, using advanced testing equipment and high-quality reagents, continuously improving the testing level of staff, can issue accurate test reports, ensure blood quality, and provide safe and effective blood products for clinical use. However, looking at the qualified rate of blood tests, the qualified rate of repeat blood donors is often higher than that of first-time donors. In response to this situation, this study focuses on analysis, analyzes the correlation factors of the accuracy of blood tests for voluntary blood donors, and lays a good foundation for the subsequent work of voluntary blood donation.

Hepatitis B is a disease that can be transmitted through blood. Hepatitis B virus (HBV) infection is a worldwide epidemic and one of the important public health issues[1]. According to the World Health Organization, about one-third of the world's population has been infected with HBV, and its prevalence characteristics vary by region[2]. China is located in a high and medium prevalence area of HBV infection, with an average infection rate of 8%. Among them, hepatitis B surface antigen (HBsAg) serological testing is negative, but molecular biology testing HBV DNA is positive, this special infection mode has attracted widespread attention, and thus developed the concept of occult hepatitis B virus infection (OBI). With the continuous improvement of the sensitivity of HBV serological testing methods, most

HBV infections have been excluded among voluntary blood donors through screening for hepatitis B surface antigen (HBsAg), and the risk of transmitting HBV through blood transfusion has been reduced to a lower level. However, at present, the risk of transmitting HBV through blood transfusion mainly comes from HBsAg-negative but infectious blood donors, some of whom are in the serological transformation window period after HBV infection, and others are from occult HBV infection donors. Using ELISA alone for HBsAg testing cannot eliminate the risk of post-transfusion infection with HBV caused by the hepatitis B window period and OBI. Using nucleic acid testing (NAT) technology to detect HBV can effectively screen for occult hepatitis B virus infection in blood donors and reduce the risk of HBV. To understand the situation and population characteristics of occult hepatitis B virus infection among voluntary blood donors in Harbin from January 2016 to December 2022, a retrospective analysis was conducted on 1,020,943 voluntary blood donors in Harbin. The report is as follows:

2 MATERIALS AND METHODS

2.1 Research

subjects selected from 1,020,943 voluntary blood donor specimens collected by the Harbin Blood Center database from January 2016 to December 2022. Three samples were taken from each blood donor, one 5ml sample was taken with an EDTA-K3 vacuum collection tube (produced by VACUETTE Greiner Bio-One) for serological testing; two 5ml samples were taken with an EDTA-2K vacuum collection tube (produced by BD Pharmingen) for nucleic acid testing. All specimens were collected and stored according to the requirements of the "Blood Station Technical Operation Procedures (2015 Edition)". The age of blood donors ranged from 18 to 60 years old, and all voluntary blood donors met the health standards in the current "Blood Station Management Methods".

2.2 Method

Firstly, colloidal gold immunochromatography was used for rapid detection of HBsAg before donation. After passing the test, specimens were collected for two enzyme-linked immunosorbent assays (ELISA), and after both results were negative, one nucleic acid test (NAT) was performed. Nucleic acid testing was first performed in a combined form of 6 mixtures, and reactive specimens from combined testing were then subjected to individual identification experiments.

2.3 Reagents and Instruments

2.3.1 Serological testing system

ELISA reagents were from Zhuhai Livzon Reagent Co., Ltd. and France BioRad; using TECAN freedom evo fully automatic sampler (Switzerland Tecan Company) and Microlab FAME24/30 (Switzerland Hamilton Company) fully automatic enzyme immunoassay system for specimen testing.

2.3.2 Nucleic acid testing system

Nucleic acid testing reagents were from cobas TaqScreen MPX Test, cobas TaqScreen MPX Control Kit (ROCHE); using MICRLOAB STAR fully automatic sampler, Roche Cobas s 201 nucleic acid testing system (cobas AmpliPrep nucleic acid extraction instrument and cobas TaqMan nucleic acid amplification detector). All reagents were tested and qualified by the Chinese Drug Biological Products Identification Institute, within the validity period and strictly operated according to the reagent kit instructions.

2.4 Judging Rules for HBsAg

ELISA double reagent negative specimens, HBV/HCV/HIV (hepatitis B virus/hepatitis C virus/human immunodeficiency virus) nucleic acid joint detection was performed in a combined form of 6 mixtures. Reactive specimens from combined testing were then subjected to individual identification experiments for HBV/HCV/HIV, screening out HBV DNA reactive specimens, which were determined as HBV-DNA positive specimens.

2.5 Statistical Treatment

The organization of data in this study relied on SPSS20.0 statistical software to complete, % as the manifestation of counting data, using X^2 test for analysis, when the difference between groups meets the requirement of $P < 0.05$, it is considered statistically significant.

3 Results

3.1 From January 2016 to December 2022, a total of 1,020,943 voluntary blood donors had overall positive results for HBV screening, as shown in Table 1.

Table 1 Overall positive results for HBV screening among voluntary blood donors from January 2016 to December 2022.

Year	Number of Voluntary Blood Donors	OBI	Positive Rate（%）
2016	141917	44	0.031
2017	148648	54	0.036
2018	156701	62	0.040
2019	167254	68	0.041
2020	138808	41	0.030
2021	143234	30	0.021
2022	124381	27	0.022
Total	1020943	326	0.032

3.2 HBV Screening Results

Among Blood Donors of Different Genders: From January 2016 to December 2022, among the 1,020,943 voluntary blood donors, 604,944 male donors were tested, with 201 cases positive for HBV DNA, resulting in a positivity rate of 0.033%. In contrast, out of 415,999 female donors, 125 cases were positive for HBV DNA, yielding a positivity rate of 0.030%. The detection rate of HBV DNA positivity was slightly higher in males than in females, as shown in Table 2.

Table 2 Gender Proportion in Positive HBV Screening Results Among Voluntary Blood Donors

Year	Male			Female		
	Number of Voluntary Blood Donors	OBI	Positive Rate（%）	Number of Voluntary Blood Donors	OBI	Positive Rate（%）
2016	82311	26	0.032	59606	18	0.030
2017	90675	34	0.037	57973	20	0.034
2018	92465	38	0.041	64236	24	0.037
2019	91989	40	0.043	75265	28	0.037
2020	74956	23	0.031	63852	18	0.028
2021	92545	21	0.023	50689	9	0.018
2022	80003	19	0.024	44378	8	0.018
Total	604944	201	0.033	415999	125	0.030

3.3 HBV Detection in First-Time and Repeat Blood Donors:

From January 2016 to December 2022, among the 1,020,943 voluntary blood donors, 571,782 first-time donors were tested, with 246 cases positive for HBV DNA, resulting in a positivity rate of 0.043%. In contrast, out of 449,161 repeat donors, 80 cases were positive for HBV DNA, yielding a positivity rate of 0.018%. Statistical analysis indicates that the positivity rate among first-time donors is higher than that of repeat donors ($P<0.05$). See Table 3.

Table 3 Comparison of Positivity Rates Between First-Time and Repeat Blood Donors

Year	First time blood donor			Repeat blood donor		
	Number of Voluntary Blood Donors	OBI	Positive Rate（%）	Number of Voluntary Blood Donors	OBI	Positive Rate（%）
2016	78054	37	0.047	63863	7	0.011

2017	87702	43	0.049	60946	11	0.018
2018	81484	44	0.054	75217	18	0.024
2019	90317	48	0.053	76937	20	0.026
2020	77732	33	0.042	61076	8	0.013
2021	80602	20	0.025	62632	10	0.016
2022	75891	21	0.028	48490	6	0.012
Total	571782	246	0.043	449161	80	0.018

4 DISCUSSION

Voluntary blood donation, advocated by the World Health Organization and the International Red Cross, is a form of safe blood donation and an important indicator of a society's level of civilization. With the rapid development of China's medical and health care services and the continuous increase in promotional efforts for voluntary blood donation by blood collection agencies, ensuring the safety of clinical transfusions has become a focal concern. Before nucleic acid testing (NAT) technology was applied to screening in voluntary blood donation, most Chinese blood collection agencies used two different reagents for parallel ELISA testing. Although the sensitivity and specificity of ELISA kits have been continually improved, they still cannot avoid missed detections due to factors such as the window period of viral infection, viral mutation, and immunological silencing. In 2008, a case was reported where a recipient developed typical HBV infection after being transfused with HBsAg-negative, HBV DNA-positive blood during a 12-month window period, highlighting OBI (occult HBV infection) and the window period as two major challenges to transfusion safety[3]. In developed countries, 0.007%-0.05% of HBsAg-negative blood donors test positive for HBV DNA[4. 5. 6]. As China is a high-incidence area for hepatitis B, domestic research reports also show that the proportion of OBI among Chinese blood donors ranges from 0.03%-0.2%, significantly higher than in Western developed countries[7. 8. 9]. Since 1992, China has initiated a comprehensive vaccination program against hepatitis B, which has reduced the risk of transmission to some extent. The survey results indicate a significant difference between first-time and repeat blood donors, with the latter often having higher awareness and trust in voluntary blood donation [10]. Screening blood donors from a pool of regular voluntary donors is crucial for ensuring the safety and sufficient supply of clinical blood use. For first-time donors, it is necessary to strengthen education on blood donation and infectious diseases, focusing on pre-donation consultation and assessment.

Voluntary blood donation is a commendable social welfare activity primarily used for the treatment of clinical diseases. With the rapid development of China's medical and health care services and the increasing promotional efforts for voluntary blood donation by blood collection agencies, obtaining high-quality blood products requires stringent testing of donor blood parameters. To ensure the authenticity and reliability of blood tests, careful selection of reagents and automated testing equipment is essential. Fully leveraging the functional characteristics of testing equipment can improve the accuracy of blood tests, reduce errors, and lower the probability of missed detections. Moreover, considering the risk of transfusion-transmissible diseases, adequate protective measures should be taken to minimize potential hazards during blood collection. Therefore, effective strategies should be adopted to address the issue of "window period" infections, as different testing methods and reagents have varying window periods. Thus, the rational use of NAT technology can shorten the "window period," significantly reducing the safety risks associated with clinical transfusions. The current study shows that, from the perspective of infectious disease infection rates in blood donation, the occurrence rate among repeat donors is significantly lower than that among first-time donors, thus improving the safety level of blood donation; repeat donors are considered a low-risk group for voluntary blood donation. Additionally, undergoing multiple blood tests and health consultations during each donation process means that this group faces a lower risk of transfusion safety issues related to the "window period." Compared to first-time donors, repeat donors have a certain level of understanding about blood donation, can accurately identify risky behaviors, and significantly reduce safety risks in blood collection work. Therefore, maintaining repeat donors and establishing a strong team of regular voluntary blood donors is crucial. Nowadays, China's health administrative departments strictly supervise and manage blood collection agencies, with blood quality being a top priority. To provide patients with sufficient blood products, expanding the team of repeat donors, using modern testing equipment, and high-quality testing reagents to

offer safe and high-quality blood donation services are essential. By collecting blood from low-risk groups, the quality of blood products can be ensured. From the perspective of the "window period," repeat donors have a lower probability of being in this phase, correspondingly reducing safety risks and minimizing blood wastage. This also presents a substantial advantage in terms of cost investment for blood collection agencies.

It is evident that the blood provided to patients is of higher safety, making clinical use more reliable. Before blood collection, medical staff should conduct health consultations, assessments, and examinations on donors, as well as explain relevant knowledge about blood donation, enhancing their understanding of the purpose and significance of voluntary blood donation. This encourages regular, voluntary, unpaid donations and ensures the quality and reliability of the collected blood for better use in the rescue and treatment of patients. Blood collection personnel must take precautions at work, promptly disposing of used equipment to prevent injuries. Voluntary blood donation reflects the selfless spirit of our people, where individuals willingly donate blood without seeking rewards, fulfilling patient needs for blood products. However, everyone's physical condition varies, and with the fast-paced lifestyle nowadays, people's dietary habits and living environments are undergoing significant changes. To ensure the effective implementation of voluntary blood donation efforts, improving blood quality has become a focal point for blood collection agencies. Hepatitis B, C, syphilis, and AIDS are all diseases transmitted through blood. Therefore, every step in the donation process must be handled with caution, with increased control over blood quality. With the aid of modern, intelligent testing equipment, donors' blood indicators can be tested, results analyzed, and health consultations, assessments, and examinations completed to provide effective prevention and control measures for ensuring the safety of clinical blood use. For repeat donors, having donated multiple times, they have received more information about voluntary blood donation, significantly enhancing their awareness of blood testing. They know how to avoid risks and protect their safety when hazards approach. Thus, compared to first-time donors, repeat donors have a lower probability of transmitting infectious diseases, ensuring better blood quality and safety. Furthermore, in the process of carrying out various tasks related to blood donation, the interaction between staff and donors, as well as guidance on health education and other matters, takes up significantly less time for repeat donors, greatly improving efficiency and quality, reducing time wastage, and decreasing costs, benefiting the development of China's blood service and health care industry.

In recent years, the Harbin Blood Center has collaborated with universities to regularly organize mobile blood collection vehicles visiting campuses, providing convenience for college students to donate blood and achieving positive results. College students, being physically healthy and culturally educated, possess a strong sense of social responsibility and enthusiasm for public welfare. Their blood quality and safety are relatively high, making them a reliable and stable source of voluntary blood donations in our country. Developing and consolidating a sufficiently large team of low-risk voluntary blood donors, encouraging more first-time donors to become repeat donors, meeting the growing demand for blood use, and reducing transfusion risks are crucial for promoting the sustainable and healthy development of voluntary blood donation efforts.

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META-ANALYSIS OF STATINS IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH PULMONARY HYPERTENSION

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Abstract: Objective To systematically evaluate the meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH). Methods: Systematically searching PubMed,CBM, VIP and Wanfang databases, and comprehensively collecting randomized controlled trials (RCT) of statins in the treatment of chronic obstructive pulmonary disease with pulmonary hypertension. According to the inclusion and exclusion criteria, literatures were screened, Meta were extracted and methodological quality was evaluated, and meta-analysis was performed by RevMan 5. 0 software. Results: Seven RCTs were included, with a total of 356 patients. Including 2 placebo-controlled trials and 5 non-placebo-controlled trials. Meta-analysis showed that: ① statin could improve the mean pulmonary arterial pressure (mPAP) [MD=-3. 83 mmHg, 95% ,CI(-5. 2, -2. 43)}, and the pulmonary arterial systolic pressure (PASP) [MD =-5. 66 mmhg, 95%, cl (-7 ... ②statin can significantly reduce the endothelin -1(ET-1) value [MD =-3. 51 pg/m1, 95% Cl, (-4. 77,-2. 55)] and increase the nitric oxide (NO) value [SMD = 1. 06,95%, CI (0 .. ③statin can improve the percentage of forced expiratory volume in the first second (FEV,%) [MD = 2. 92,95%, CI (-2.83,8.68)]. Conclusion: Statins can significantly improve pulmonary artery pressure, pulmonary function and clinical efficacy in COPD patients with PH.
Keywords: Chronic obstructive pulmonary disease; Statins; Meta analysis

Pulmonary hypertensionStatins, that is, 3- hydroxy -3- methylglutaryl-coenzyme A [3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)] reductase inhibitors, mainly inhibit the conversion of HMG-CoA to mevalonic acid, MVA) competitively, thus blocking cholesterol synthesis and lowering blood cholesterol levels. Large-scale clinical trials 4s, LIPID, CARE, WOSCOPS, AF CAPS/TEX CAPS and HPS have proved that statins can significantly reduce the incidence and mortality of coronary heart disease and play an important role in primary and secondary prevention of cardiovascular diseases. At present, statins are widely used in clinic: simvastatin, atorvastatin, lovastatin, pravastatin, fluvastatin, rosuvastatin and pitavastatin. After cerivastatin was approved for listing in 1998, it was delisted in 2001 because of the high incidence of fatal rhabdomyolysis. With the incidence of hyperlipidemia increasing year by year [1-2], the utilization rate of statins is also rising rapidly. In 2011, simvastatin became the second largest prescription drug in the United States. Many studies have shown that besides lowering blood lipid, statins have many clinical effects, which are called pleiotropic effects of statins, mainly including: reducing or eliminating inflammatory reaction, anti-oxidative stress, improving endothelial cell function, inhibiting smooth muscle cell proliferation, inhibiting tumor cell proliferation, regulating immunity, anticoagulation, stabilizing plaque, promoting bone anabolism, promoting angiogenesis, etc. The multiple effects of statins provide a new way to prevent and treat many clinical diseases, such as cardiovascular diseases, respiratory diseases, diabetes, kidney diseases, multiple sclerosis, malignant tumors and osteoporosis, and its role in chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension. PH) has become the focus of clinical attention in recent years.

Statins are very important drugs for the prevention and treatment of hypercholesterolemia and atherosclerotic diseases at present, and their adverse reactions include myopathy, elevated liver enzymes and increased risk of diabetes. With the increasing incidence of coronary heart disease and the discovery of the pleiotropic effects of statins, the usage and clinical application range of statins are also expanding, and the safety of statins has increasingly attracted the attention of clinicians and academic circles. In recent years, people began to explore the role of meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) [3-6]. Statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) is one of the most popular studies. At present, many studies have reported the Meta-analysis relationship of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH), but the results are quite different. In this study, the related studies were comprehensively collected and quantitatively analyzed by systematic evaluation and meta-analysis, so as to provide statins for the treatment of COPD complicated with pulmonary hypertension.

Chronic obstructive pulmonary disease (COPD) is a common disease that seriously endangers human health. It is characterized by incomplete reversible airflow restriction and has a high mortality. An epidemiological survey involving seven regions in China shows that the total prevalence of COPD among people over 40 years old is 8.2%, and the prevalence rate in rural areas is even higher, reaching 8.8%. It is estimated that it is currently the fourth leading cause of death in the world, and it is expected to become the third leading cause of death in the world by 2025. When COPD

patients are complicated with pulmonary hypertension, the survival rate and quality of life deteriorate rapidly, and the prognosis becomes worse [4]. Studies have shown that the risk of death will increase by more than 4 times for every 1OmmHg increase in average pulmonary artery pressure. Therefore, effective control of pulmonary hypertension plays an important role in delaying the progression of COPD and improving the survival rate of patients. The conventional treatment of COPD complicated with PH is mainly aimed at the primary disease, improving symptoms, including continuous low-flow oxygen inhalation through nasal catheter, controlling respiratory tract infection, relieving spasm and asthma, relieving cough and phlegm, diuresis, anticoagulation, etc. These methods can't prevent the progress of PH from getting worse, so new treatment methods need to be studied. Many studies at home and abroad have shown that statins can inhibit the inflammatory reaction of COPD patients, reduce the risk of all-cause mortality and acute exacerbation, and improve the quality of life. A large number of animal experiments have found that statins can improve cardiopulmonary vascular remodeling and reduce pulmonary artery pressure. At present, domestic and foreign studies have explored the therapeutic effect and possible mechanism of these drugs on COPD complicated with PH, but the sample size is small, the methodological quality is low, and the research results are not consistent. At present, for the treatment of COPD-related PH, the role and choice of drugs are limited. Statins, that is, 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors, have the functions of anti-inflammation, anti-oxidation, improving endothelial function, stabilizing plaque, reducing the activation of neuroendocrine, improving myocardial remodeling, anticoagulation, anti-platelet, stimulating endothelial progenitor cell differentiation, etc. [5-7], and their role in PH has been paid more and more attention. Up to now, many clinical trials have observed the efficacy and safety of statins in the treatment of COPD complicated with PH, but most of them have small sample size, low methodological quality and inconsistent research results. In recent years, more and more evidences show that statin can dilate blood vessels, inhibit the proliferation of smooth muscle cells, improve endothelial function, promote angiogenesis, and inhibit inflammatory reaction, which are independent of their lipid-lowering effects, thus improving the remodeling of cardiopulmonary blood vessels and reducing pulmonary artery pressure. They may be promising drugs for treating PH, inhibiting the development of cor pulmonale and improving the prognosis of cor pulmonale. Most of the existing related studies are non-randomized controlled clinical studies, and the sample size is small, and the clinical efficacy is not completely consistent. There is insufficient evidence that statins can reduce the pulmonary artery pressure and improve the therapeutic effect in patients with stable COPD and PH. Therefore, it is necessary to make a systematic and quantitative comprehensive analysis of the existing research results by using meta-analysis method, so as to guide clinical rational drug use and provide reliable evidence for its efficacy and safety.

With the continuous expansion of drug use, the safety of statins has been paid more and more attention. Generally speaking, these drugs are well tolerated, with fewer adverse reactions, and liver transaminase elevation and myotoxicity are recognized adverse reactions at present. Large-scale randomized controlled clinical trials show that the incidence of the increase of alanine aminotransferase, ALT) and aspartate aminotransferase,AST) in the lowest dose treatment is about 0.1 %~0.2%, even in the approved high dose range, it is only 2%~3%[8~11]. The results of such experiments and observational studies also show that the increase of liver enzymes in patients taking statins will not exceed 3 times of the upper limit of normal value. Myotoxicity is the most typical and serious adverse reaction of statins, mainly manifested as myalgia, myositis and rhabdomyolysis with or without elevated serum creatine kinase, CK). The criteria and incidence of muscle adverse reactions reported in different studies are also different. A systematic review of 21 clinical trials indicates that the incidence of mild myalgia, myopathy and rhabdomyolysis caused by statin therapy is 190,5,1.6/100,000 person-years, respectively. In observational studies, the incidence of mild adverse reactions related to statin is much higher than that of experimental studies (about 5%~10%). Studies have pointed out that about 25%~50% of patients with coronary heart disease stop taking statins for one year. Although there are many factors influencing drug withdrawal, most of them think that adverse reactions are the main reason for their non-compliance. The mechanism of statin-induced muscle adverse reactions has not been fully clarified. Studies have found that factors such as advanced age, women with low body mass index, strenuous physical exercise, high-dose use of statins and combined use with drugs that interfere with the distribution and metabolism of statins may increase the risk of statin adverse reactions. In addition, the adverse reactions of statins also showed obvious individual differences.

Systematic evaluation is a comprehensive literature research method, which systematically and comprehensively collects the existing research results according to the research purpose, screens out the documents that meet the standards according to strict quality evaluation principles and methods, and scientifically synthesizes them qualitatively or quantitatively, and finally draws comprehensive and reliable conclusions. Meta-analysis is a quantitative synthesis method in systematic evaluation, which can avoid the limitation of single small sample study, enlarge the sample size, increase the efficacy of statistical test, quantitatively estimate the average level of research effect and evaluate the inconsistency of research results. Sub-group analysis includes a small number of studies, which may lead to unstable merger results.

In this study, evidence-based medicine systematic review and meta-analysis were used to study the correlation of meta-analysis polymorphism of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH), so as to provide scientific basis for clinical application of statins in respiratory system, prediction of statins toxicity, guidance of individualized medication, reduction of adverse reactions and improvement of drug compliance.Through systematic evaluation and Meta-analysis, the best current research evidence can be produced to solve the problems in disease prevention, diagnosis, treatment and prognosis,This study focuses on the changes of indexes before and after treatment, refers to "Impacting standard deviations for changes from baseline" recommended by Cochrane's manual, and estimates the Meta value and standard deviation of the changes of indexes in

the two groups thus promoting rational drug use and scientific health decision [12], and the shortcomings of the original research can also be found, providing new ideas and directions for future research.

COPD is a chronic respiratory disease that seriously harms human health, and can cause systemic adverse effects. Long-term hypoxia, high inflammatory level, oxidative stress, etc. lead to the injury and abnormal proliferation of pulmonary vascular endothelium, resulting in a decrease in the production and release of nitric oxide, NO), and an increase in the synthesis and secretion of endothelin-1 (ET-1), which leads to pulmonary vascular contraction and remodeling: inflammation [such as interleukin-6 (IL-6) Combined with pulmonary arteriole microthrombosis, pulmonary circulation resistance continues to increase, eventually leading to pH. When the patient is complicated with PH, the survival rate and quality of life deteriorate rapidly, and the prognosis becomes worse. At present, the treatment of COPD-related PH, drug action and choice are quite limited. Statins have been paid more and more attention because of their pleiotropic effects in pH. Up to now, many clinical trials have explored the role and possible mechanism of statins in CO PD complicated with PH, but the sample size is small and the clinical effects are not consistent [13-16]. This study explored the effects and safety of statins on the quality of life, dyspnea symptoms, pulmonary function, pulmonary artery pressure, vasoactive substances and inflammatory factors of COPD patients with PH by systematic evaluation and Meta-analysis, in order to provide scientific basis for developing new treatment methods.

1 DATA AND METHODS

Literature search computer search PubMed, embase, the Cochrane library, web of science, CBM, CNKI, VIP and WanFang Data, and trace the references included in the research. The key words include statins, COPD and PH-related words. Statin-related drugs: "hydroxymethylglutaryl CoA reductase inhibitor, statin, HMG-CoA reducer inhibitor, statin, simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, rosuvastatin, cerivastatin, mevastatin". Related to COAD: "Chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, chronic airway obstruction, chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, chronic ie, Obstructive Airway Disease、ChronicAirflow Obstruction、Pulmonary Disease，Chronic Obstructive"[17-20]. PH correlation: "Pulmonary hypertension; Pulmonary hypertension; Pulmonary hypertension; Pulmonary hypertension; Lung; Hypertension; pulmonary hypertension; pulmonary arterial hypertension; pulmonary vascular disease; PH; PA H; Hypertension,Pulmonary "。 Search by combining free words with subject words. Some search terms are connected by the logical symbol OR, AND the three search terms are connected by the logical symbol AND. The retrieval time is from the database establishment to March 23, 2017.

The research subjects have published prospective randomized controlled studies or well-designed non-randomized controlled studies on the efficacy of statin alone or in combination with conventional therapy in the treatment of stable COPD patients with PH.

1.1 Types of Patients

The types of patients are in line with the relevant diagnostic criteria of COPD Diagnosis and Treatment Guide formulated by COPD Group of Respiratory Branch of Chinese Medical Association in 2007 and the definition of American Thoracic Association. Patients diagnosed as COPD are all in the stable stage of the disease, and no acute exacerbation occurred in the first half year of the trial. The diagnostic criteria of pulmonary hypertension are mPAP≥25mmHg measured by right heart catheter at sea level rest or MPAP ≥ 30mmhg during exercise [21-23]. If there is no data of right cardiac catheter, Doppler ultrasound showed PASP≥40 mmHg.

1.1.1 Inclusion criteria

(1) The original data are published original documents, and the content is about the study of the curative effect of statin alone or in combination with conventional treatment on stable COPD patients with PH. (2) The original literature is a prospective randomized controlled study or a well-designed non-randomized controlled study. (3) There are clear counting data at the end of follow-up in the original literature. (4) The follow-up rate of the study is over 95%.

1.1.2 Outcome indicators

① Pulmonary function: forced expiratory volume in the first second (FEV),FEV, the percentage of the expected value (FED %}, forced vital capacity (FVC) and FEV,/FVC; ② Pulmonary artery pressure: sPAP and mPAP; ③ Borg dyspnea score; ④ Exercise endurance: 6 min walking distance (6 MWD); ⑤ Adverse reactions.

Exclusion criteria (1) Studies with inaccurate or unclear diagnostic criteria for unreported cases were excluded, and studies with pulmonary hypertension caused by primary PH and other types and heart diseases (including rheumatic heart disease, valvular heart disease, congenital heart disease, history of cardiothoracic surgery [24-25], autoimmune diseases, severe liver and kidney dysfunction, malignant tumor, asthma and active tuberculosis) were reported. (2) No available raw data is provided and the request is fruitless; (3) Repeatedly published literatures, and only the studies with the most complete data are collected; (4) The original data is not a study that directly compares the curative effect of patients with stable COPD and PH with statin and conventional treatment. (5) At the same time, it is accompanied by heart diseases such as valvular heart disease and congenital heart disease, autoimmune diseases, malignant tumors, abnormal liver function, kidney diseases and systemic inflammatory diseases, and the selected persons have not taken statins for nearly 3 months. (6) The original literature data cannot be used.

1.2 Methods

1.2.1 Interventions

This study is to analyze the published papers with the method of systematic evaluation to obtain the final results and quantify them. The quality of the original data directly affects the credibility of this study. The final concern of this study is whether conventional therapy combined with statin can improve pulmonary artery pressure in stable COPD patients with PH compared with conventional therapy alone [26] and improve clinical efficacy. Treatment group: atorvastatin (20 mg /dqd) or simvastatin (4mg/d qd) or fluvastatin (40mg/d qd) or pravastatin (40mg/d qd)+ conventional treatment. Control group: Conventional treatment or conventional treatment plus placebo. Conventional treatment includes low-flow oxygen inhalation through nasal catheter, control of respiratory tract infection, relieving cough, relieving asthma and eliminating phlegm.

1.2.2 Data sources

Data sources used in data retrieval (1)Pubmedo(2) China Biomedical Literature Database (CBM) o③ VIP information resource system. (4) Wanfang Data Knowledge Service Platform. Search strategy: keyword search and keyword search, combined with literature tracing and manual search. COPD, chronic obstructive pulmonary disease, pulmonary hypertension and statins were used as key words. The related literatures were searched with obstructive pulmonary disease, chronic pulmonary hypertension [27-28] and statins as key words. The English key words are: pulmonary disease, chronic, pulmonary hvperten-sion, statin. The language is limited to Chinese or English. The original literature sample size and follow-up years are not limited. According to the inclusion and exclusion criteria, the literature is screened and cross-checked. The screening process is as follows: first, read the title; if it meets the inclusion criteria, further read the abstract; if it meets the inclusion criteria, continue to read the full text; if it meets the inclusion criteria, it will be included.

1.2.3 Literature screening

Before the formal screening, two researchers randomly selected 10 literatures from the search results independently, and pre-screened them according to the pre-established screening criteria, so as to discuss whether the screening criteria are appropriate, and at the same time train the researchers to use the selection criteria uniformly and normatively. During the formal screening, two evaluators independently screen and cross-check according to the final inclusion and exclusion criteria. In case of disagreement, an agreement can be reached through discussion or reference to the opinions of a third party. First of all, read the titles and abstracts of the literature for preliminary screening, search for the full text of the literature retained in the preliminary screening and those that can't be determined whether or not to be excluded, then screen the full text for the second time, and list the excluded literature and its reasons during the full text screening.

1.2.4 Data extraction

Before starting data extraction, select several representative literatures, and use the pre-established data extraction table for pre-test to check whether it has some defects such as missing some important items, too many items, etc., and further revise and improve them. Two researchers independently extracted the information included in the study and cross-checked, and any disagreement was resolved through discussion or third-party arbitration. The extracted contents mainly include: ① Basic information included in the study: the title of the literature, the first author, the publication time, the country of publication and the source of the literature, etc. ② Research methods and possible bias: grouping method, whether grouping method is hidden, whether blind method is adopted, and whether withdrawal and withdrawal are described; ③ Characteristics of research subjects: number of cases, age, sex ratio, research location, diagnosis criteria of cases, inclusion and exclusion criteria of research subjects, COPD stage and whether there are any complications, etc. ④ Intervention measures: drug name, administration route, dosage, treatment time, control mode, etc. ⑤ Measurement data information of various outcome indicators before and after treatment; Mean and its standard deviation, the number of adverse reactions (any adverse reactions occurring during the trial, including gastrointestinal reactions, elevated transaminase and CK, etc., are included in this paper, excluding those who can be relieved by themselves without special treatment, drug reduction or withdrawal); Including research methods of key elements of quality evaluation, basic data of patients in experimental group and control group [29], intervention measures and methods, and observation time; Before and after treatment, pulmonary arterial pressure, endothelin -1, nitric oxide, improvement of pulmonary function (FEV, 0o) and adverse reactions during treatment were observed.

1.3 Data Extraction

Before starting data extraction, select several representative literatures, and use the pre-established data extraction table for pre-test to check whether it has some defects such as missing some important items and too many items, and further revise and improve them. Two researchers independently extracted the information included in the study and cross-checked, and any disagreement was resolved through discussion or third-party arbitration. The extracted contents mainly include: ① Basic information included in the study: the title of the literature, the first author, the publication time, the country of publication and the source of the literature, etc. ② Research methods and possible bias: grouping methods, whether grouping methods are hidden, whether blind methods are adopted, and whether withdrawal and withdrawal are described; ③ Characteristics of research subjects: number of cases, age, sex ratio, research place, diagnosis criteria of cases, inclusion and exclusion criteria of research subjects, COPD stages and complications, etc. ④

Intervention measures: drug name, administration route, dosage, treatment time, control mode, etc. ⑤ Measurement data information of various outcome indicators before and after treatment: mean and its standard deviation, the number of adverse reactions (any adverse reactions during the trial, including gastrointestinal reactions, elevated transaminase and CK, etc., are included in this paper, excluding those who can be relieved by themselves without special treatment, drug reduction or withdrawal).

1.4 Evaluation Index of Curative Effect

the most important outcome variables in the original literature involved in this study are the improvement of pulmonary artery pressure (including PASP and mPAP) and pulmonary function [the first second forced expiratory volume (FEV) or the percentage of the first second forced expiratory volume to the expected value (FEV%)]; Secondary outcome: the improvement of blood endothelin -1(ET-1) and nitric oxide (NO).

1.5 Statistical Analysis

(1) First, clinical and statistical homogeneity analysis is conducted to find out whether there are factors that affect clinical heterogeneity. At the same time, P-value and I-value are used to judge whether there is heterogeneity among the studies. P < O.10 is taken as the standard of heterogeneity; I ≤ 50% indicates that the heterogeneity is acceptable, and I ≥ 75% indicates that the heterogeneity is obvious, so it cannot be combined for analysis. If there is no obvious statistical and clinical heterogeneity in the included study, the fixed effect model is used for analysis; Otherwise, the source of heterogeneity should be analyzed. If there is no obvious clinical heterogeneity, the random effect model can be carefully combined and analyzed. The continuous variables PASP, mPAP, FEV% are expressed by mean standard deviation, and the effect quantity is expressed by 95%. RevMan 5.0 software is used for statistics. Sub-group analysis is carried out when necessary. (2) You can also use Revman5.3 software provided by Cochrane Collaborative Network for Meta-analysis. The data were analyzed by the changes of indexes before and after treatment. Since all the original studies included only reported the average and standard deviation of indexes before and after treatment, the following formula was used to calculate the average and standard deviation of the changes before and after treatment.

$$M_{change} = M_{final} - M_{baseline}$$

$$SD_{change} = \sqrt{SD^2_{baseline} + SD^2_{final} - (2 \times Corr \times SD_{baseline} \times SD_{final})}$$

The formula is from "impacting standard deviations for changes from baseline" in Cochrane handbook for systematic reviews of interventions (version 5.1.0), 16.1.3.2, and the value of Corr is set to 0.5, which is substituted into the formula for calculation. Mean difference (MD) or standardized mean difference, SMD) and its 95% confidence interval < confidence interval, CI) are used as the combined statistics of measurement data, and odds ratio, OR) and its 95% CI are used as the combined statistics of counting data. Yin test was used to test the heterogeneity among the included research results. When the heterogeneity test results are P > 0.10, I < 50%, it can be considered that there is homogeneity among multiple studies. Meta-analysis is carried out by using the fixed effect model, whereas statistics are combined by using the random effect model. To explore the source of heterogeneity, subgroup analysis was carried out according to the type, dosage and treatment time of statins, and sensitivity analysis was carried out by switching effect model, eliminating low-quality studies and only including stable patients. Begg rank correlation method and Egger linear regression method were used to test publication bias (Stata I 2.0). All p values are bilateral tests, and P ≤0.05 is considered statistically significant [30-35].

2 RESULTS

2.1 A Total of 115 Related Literatures were Retrieved

By reading the titles and abstracts, obviously irrelevant literatures were excluded, followed by reviews, conference reports and repeatedly published literatures. A total of 15 literatures were collected. Read the full text carefully one by one to further screen, and exclude the literature with blank research, non-clinical trials, different intervention methods and incomplete data. Finally, 7 articles were included, totaling 356 patients (see Figure 1). Seven papers are randomly grouped, only two of them specifically describe the random allocation method [5,9], and the rest are not clearly described; A double-blind, well-hidden, placebo-controlled study was used in one study, and the rest of the control groups were treated with routine treatment. See Table 1 for the general situation of literature inclusion and Table 2 for methodological evaluation of literature quality.

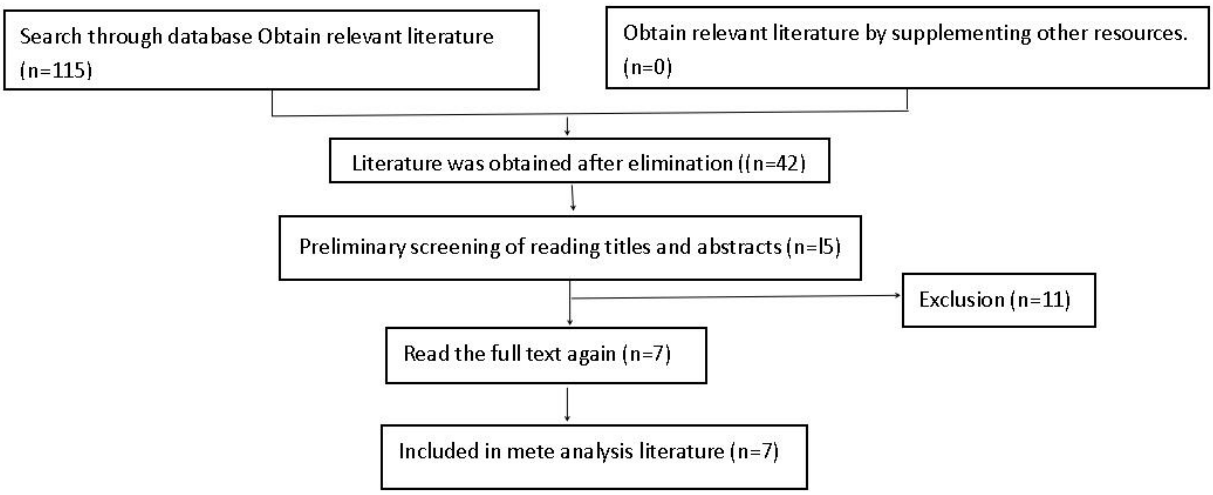

Figure 1 The Progres and Results of Researches Included and Excluded

Table 1 The General Data of Inclusive Researches

document	case load(T/C)	Gender (male/female)	Age (years)	complication	Smoking situation	Intervention measure treatment group	control group	Observation time (months)	adverse effect
Yu Fengxia (2012)	78/78	128/38	64.8 ± 6.7	without	mention	Statin ten others	other	12	Unmentioned
Zhang Yuqing(2010)	27/28	47/8	67 ± 4.0	without	mention	Statin ten others	other	6	have
Wang Lingling(2011)	35/56	46/24	63 ± 45.2	without	mention	Statin ten others	other	6	Unmentioned
LeeTMC(2009)	27/26	39/14	71±6	without	mention	Statin ten others	Ten other placebos	3	without
Cao Yanhong(2012)	18/18	24/12	66 ± 7.0	without	Unmentioned	Statin ten others	other	3	Unmentioned
Tang yanfen(2010)	18/17	23/12	65 ± 6.0	without	Unmentioned	Statin ten others	Ten other placebos	3	Unmentioned
Liu yunli(2010)	31/31	52/10	67 ± 4.0	without	Unmentioned	Statin ten others	other	6	Unmentioned

Table 2 The Quality Evaluation on the Research Methods

document	Random method	Allocation hidden	Blind line	Baseline comparison
Yu Fengxia(2012)	Undescribed	Undescribed	Undescribed	be comparable
Zhang Yuqing(2010)	Undescribed	Undescribed	Undescribed	be comparable
Wang Lingling(2011)	Undescribed	Undescribed	Undescribed	be comparable
LeeTM(2012)	Computer random number	be	Double blind	be comparable
Cao Yanhong(2012)	table of random number	Undescribed	Undescribed	be comparable
Tang yanfen(2010)	Undescribed	Undescribed	Undescribed	be comparable
Liu yunli(2010)	Undescribed	Undescribed	Undescribed	be comparable

2.2 Results of Meta-analysis

2.2.1 Improvement of mPAP

4 literatures[6~9] studied the improvement of mpap by statin, a total of 156 patients, and the longest follow-up period was 6 months. The statistical heterogeneity among studies (P = 0. 93, I = 0%), using the fixed effect model, the mean difference of combined effects (MD) was-3. 83 mmHg, the 95% confidence interval (CI) was (-5. 22,-2. 43), and the overall test efficiency was Z = 5. 37 (Therefore, it can be considered that the difference between the statin group and

the control group is statistically significant, and the stain treatment significantly improves mPAP compared with the control group.

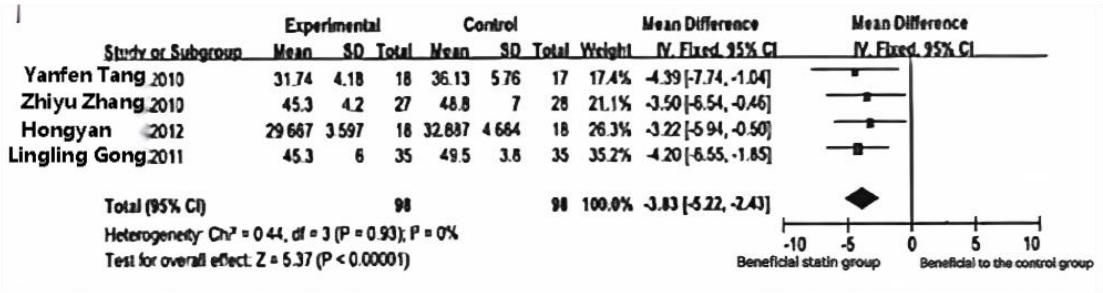

Figure 2 Mets Analysis of the Effect of STALIN on mPAP in Stable COPD Patients Compared with Conventional Treatment

2.2.2 Improvement of PASP

3 literatures[5,8,10] studied the improvement of pasp by statin, with a total of 200 patients, and the longest follow-up period was 12 months. There was no statistical heterogeneity among the studies (P = 0.22, I = 34%), and the fixed effect model was adopted. The mean difference of combined effects (MD) was-5.66mm Hg, the 95% confidence interval (CI) was (-7.15,-4.56), and the overall test efficiency was Z = 7.43 (P < Therefore, it can be considered that there is a significant difference between the statin group and the control group, and statin treatment significantly improves PASP compared with the control group.

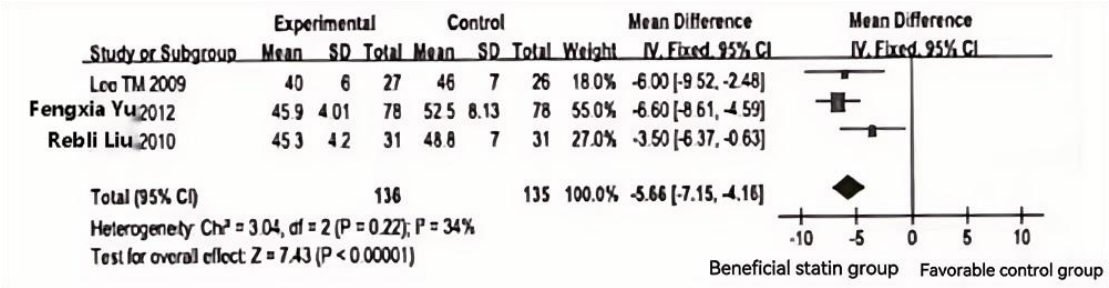

Figure 3 Mets analysis of the effect of STALIN on PASP in stable COPD patients compared with conventional treatment

2.2.3 Improvement of ET-1

5 articles[3-6,9] studied the improvement of ET-1 by statin, with a total of 184 patients, and the longest follow-up period was 6 months. There is no statistical heterogeneity among the studies (P = 0. 91, I = 0%), and the fixed effect model is adopted. The mean difference of combined effects (MD) is-3. 51 mmHg, the 95% confidence interval (CI) is (-4. 66,-2. 55), and the overall test efficiency Z = 7. 8 (Therefore, it can be considered that there is a significant difference between the statin group and the control group, and statin treatment significantly improves ET-1 compared with the control group.

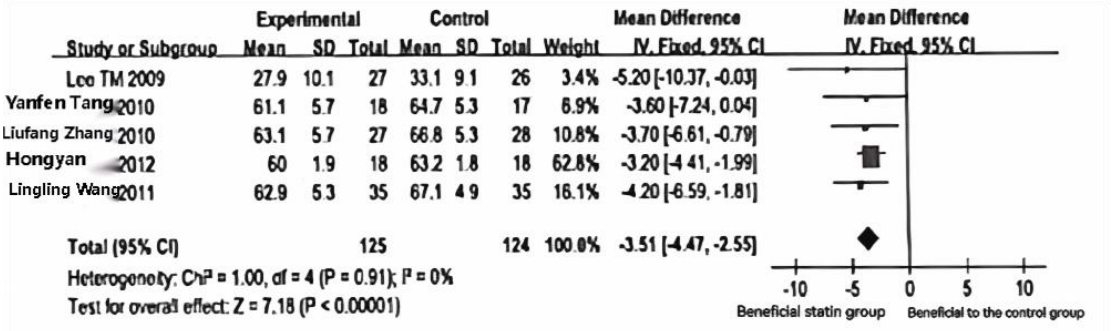

Figure 4 Mets Analysis of the Effect of STALIN on ET-1 in Stable COPD Patients Compared with Conventional Treatment

2.2.4 Improvement of NO

3 literatures[8-10] studied the improvement of no by statin, with a total of 235 patients, and the longest follow-up period was 12 months. There was no statistical heterogeneity among the studies (P = 0. 28, I = 34%), and the fixed effect model was adopted. The standard mean difference (SMD) of combined effects was 1. 39, the 95% confidence interval (CI) was (0. 86,1. 91), and the overall test efficiency was Z = 8. 25 (P < Therefore, it can be considered that the

difference between the statin group and the control group is statistically significant, and the statin treatment significantly improves the NO level compared with the control group.

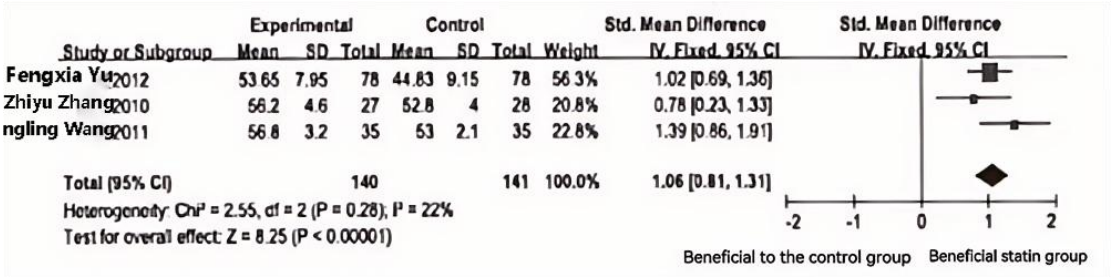

Figure 5 Mets Analysis of the Effect of STALIN on NO in Stable COPD Patients Compared with Conventional Treatment

2.2.5 Improvement of FEV%

6 literatures[5, 9, 13-15, 18,] studied the improvement of fev% by statin, with a total of 174 patients, and the longest follow-up period was 12 months. Test the heterogeneity p = 0. 0002, I = 79%, and use the random effect model to analyze. The mean difference (MD) of combined effects is 2.92, the 95% confidence interval (CI) is (-2.83,8.68), and the overall test efficiency Z = 0.99 (P < 0.0001, see Figure 6). It can be considered that there is a significant difference between the statin group and the control group. Compared with the control group, statin treatment improves FEV,% by%.

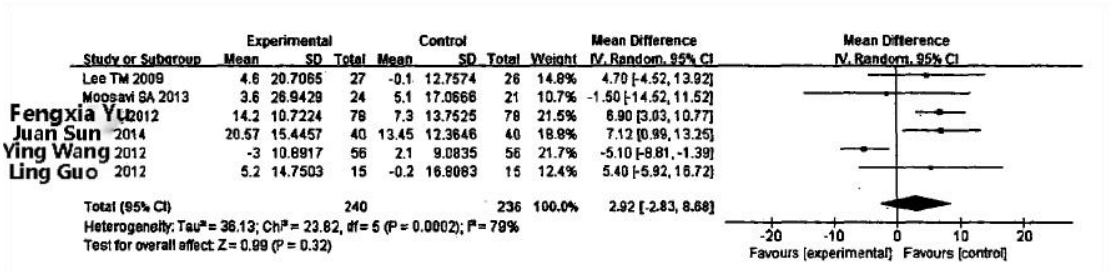

Figure 6 Weta Analysis of the Improvement of FEV,% between Statins and Control Group

2.2.6 Adverse reactions included in the study

Only one document [5] reported a slight increase of alanine aminotransferase after oral atorvastatin (no specific value was provided), and other documents mentioned related adverse reactions.

3 DISCUSSION

In recent years, there have been a lot of reports on the treatment of COPD complicated with PH with statins. Li Min et al. [44] and Ge Xiaoyan [30] respectively made a M eta analysis of them and concluded that statins can significantly reduce pulmonary arterial pressure and improve pulmonary function. Compared with this study, this study has the following characteristics: ① This study collected the related literature published by PubMed, Embase, Web of Science, The Cochrane Library and four Chinese databases as of February 2015. The research of Li Min et al. and Ge Xiaoyan did not search EMBASE before September 2013, and then a large number of original studies were published with different results, so the literature included in this paper is more comprehensive; ② The outcome indicators are more comprehensive. This paper evaluates the curative effect from five aspects: quality of life, dyspnea symptoms, exercise endurance, pulmonary arterial pressure and pulmonary function, and discusses the possible mechanism from four aspects: NO, ET-1, IL-6 and hs-CRP. Besides, the occurrence of adverse reactions is compared, and the curative effect, safety and possible mechanism of statins on COPD complicated with PH are comprehensively evaluated. However, previous studies only reported several indicators, but did not evaluate the safety. ③ The published meta-analysis compares the indexes of the experimental group and the control group after treatment, regardless of whether the baseline is comparable. This study focuses on the changes of indexes before and after treatment, refers to "Impacting standard deviations for changes from baseline" recommended by Cochrane's manual, and estimates the Meta value and standard deviation of the changes of indexes in the two groups before and after treatment by consulting relevant literature to determine the parameter values in the formula, so as to compare whether there are differences in the changes of the two groups' outcomes, which is more comparable.

Statins are widely used in primary and secondary prevention of hyperlipidemia and coronary heart disease in clinic because of their effect of lowering plasma LDL cholesterol concentration. Generally speaking, statins are well tolerated, but adverse reactions such as muscle toxicity and hepatotoxicity may occur in some patients, which leads to the decrease of treatment compliance, thus increasing the risk of cardiovascular events in patients to some extent. In recent

years, the safety of statins has attracted wide attention from all walks of life [36-42], and a large number of studies have explored the relationship between genes and adverse reactions. Meta-analysis is a quantitative synthesis method in systematic evaluation, which can avoid the limitation of single small sample study, enlarge the sample size, increase the efficacy of statistical test, quantitatively estimate the average level of research effect and evaluate the inconsistency of research results.Among them, the meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) has become a research hotspot, but the results are controversial. In order to avoid the limitation of a single study, this study comprehensively collected the published meta-analysis literature about statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) at home and abroad, and through strict methodological quality evaluation and meta-analysis method, more comprehensive and objective evaluation provided the basis for clinical individualized medication.

In the treatment of COPD patients with PH, reducing pulmonary artery pressure is the most important part of treatment. According to the recommendations of the existing guidelines, it is difficult to fundamentally prevent the progression of PH from getting worse in the treatment of COPD complicated with pH. Statins, independent of lipid-lowering effects, have many effects such as anti-inflammation, anti-oxidation, anti-apoptosis and improvement of vascular endothelial function, which can reduce pulmonary artery pressure [43]. They may be promising drugs for treating PH, suppressing the development of cor pulmonale and improving the prognosis of cor pulmonale.

COPD is the key pathological link in the development of pulmonary heart disease, which is very common in clinic. Finding, preventing or lowering PH in time is of great significance for delaying the occurrence and development of right heart failure and reducing mortality. In the past, antihypertensive drugs, such as A receptor blocker, potassium channel opener, calcium antagonist, angiotensin-converting enzyme inhibitor, leukotriene receptor antagonist, prostacyclin and its analogues, endothelin receptor antagonist, etc., often caused a significant decrease in systemic circulation pressure when reducing pulmonary arterial pressure, and the therapeutic effect was not ideal, so they were rarely used clinically.

The results of this study also suggest that compared with the control group, statins can improve the dyspnea of COPD patients with PH (MD=-3. 37, 95%, CI:-4. 61~-2. 14,P <0.000 O1), but the results are unstable due to the small number of included studies (2), so the conclusion needs to be further confirmed. 6MWD is an important index to evaluate exercise endurance, which is mainly used to evaluate the therapeutic effect of patients with moderate and severe heart and lung diseases. It is one of the endpoint observation indexes of clinical trials and one of the prediction indexes of patient survival rate. Meta-analysis showed that simvastatin and atorvastatin could significantly increase 6 MWD of patients [44-45], suggesting that they could improve exercise endurance, cardiopulmonary function and quality of life of patients. In addition, there is only one study to discuss the therapeutic effect of pravastatin and rosuvastatin on COPD complicated with PH, so the curative effect of pravastatin and rosuvastatin can't be confirmed. There are few reports of adverse reactions in the included literature, so they can't be combined with Meta-analysis. The existing research results show that there is no significant difference in the incidence of adverse reactions of statins in COPD complicated with PH compared with the control group, and the safety is acceptable. This may be related to the short observation time and the absence of adverse reactions, which suggests that the future research should extend the treatment time, pay attention to the observation of adverse reactions, and make detailed records, so as to provide real and reliable information for the evaluation of drug safety. This study shows that compared with the control group, short-term application of statin in stable COPD patients with PH can improve the pulmonary artery pressure. However, the heterogeneity of FEV% was not completely accepted (P = 0.12, I = 58%), which may be related to the basic condition of patients, infection and control, nutritional support, airway spasm control, data acquisition methods, instruments and subjective factors. Considering that there is no obvious clinical heterogeneity, random effect model analysis was adopted. The results showed that the statin group was effective in improving FEV%. The above results are consistent with those of Lee et al.

FEV,% is a good index to evaluate moderate and severe airflow restriction in pulmonary function examination, which is easy to operate and has little variability. FEV can detect mild airflow restriction, and these two indexes are of great significance to evaluate the diagnosis, treatment and prognosis of COPD patients. Meta-analysis of this study showed that there was no significant difference in FEV% between the statin treatment group and the control group, but when the following sensitivity analysis was carried out, the results changed substantially: ① When the low-quality studies were excluded, the combined results showed that compared with the control group, the FEV% of patients in the statin group decreased more obviously; ② Only those studies that reported stable patients were included in sensitivity analysis, and the hMetaerogeneity among studies was significantly reduced (I = 0%). The results showed that statins could significantly improve the lung function of patients, which was consistent with the meta-analysis results of Li Min et al. (FEV%: MD=9.79,95%CI: 6.05, 13.53). The above sensitivity analysis results all indicate that the original meta-analysis results are unstable. There has been controversy about whether statins can delay or improve the changes of pulmonary function in COPD patients, which may be related to the severity of the patients' illness and the length of follow-up. For example, a meta-analysis [22] which integrated 12 RCTs showed that statins could significantly improve FEV% of COPD patients, while another meta-analysis which only included stable COPD patients found that the treatment group had no significant improvement on FEV% [31]. According to the drug types and doses, subgroup analysis and sensitivity analysis by switching effect model within subgroups showed that the effects of different types and doses of statins on pulmonary function indexes of COPD patients complicated with PH were unstable, and the existing research failed to draw reliable conclusions. Statins are very important drugs for the prevention and treatment of hypercholesterolemia and atherosclerotic diseases at present, and their adverse reactions include myopathy, elevated liver enzymes and increased risk of diabetes. With the increasing incidence of coronary heart disease and the discovery

of the pleiotropic effects of statins, the usage and clinical application range of statins are also expanding, and the safety of statins has increasingly attracted the attention of clinicians and academic circles. In recent years, people began to explore the role of meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension.According to the sub-group analysis and sensitivity analysis within the group, we found that statins can significantly improve FEV% of moderate and severe airflow restriction index when the treatment time is less than or equal to 3 months, but this improvement effect has no statistical significance after a long time of treatment. In addition, no matter whether the treatment time exceeds 3 months, FEV index has no statistical significance. In the literature screening, four studies were excluded because they failed to report the diagnostic criteria and could not contact the authors, which may lead to data omission. We speculate that long-term statin therapy may not reverse the lung function damage in patients. Because the number of studies divided into some subgroups is small, the reliability of the combined results is affected. It is suggested that large-scale randomized controlled clinical trials with multiple doses and drugs should be carried out in the future to compare the curative effects of different doses and different kinds of statins, so as to obtain more specific and reliable results.

The follow-up time of all the included studies was at least 3 months and at most 12 months. The follow-up time was relatively short, and the long-term curative effect of statin, such as disability rate and mortality rate, could not be given, so the long-term curative effect could not be concluded. All the included trials reported the improvement of pulmonary artery pressure, and 7 trials (2 placebo and 5 open trials) with 356 cases showed that statin therapy could improve pulmonary artery pressure and benefit COPD patients with PH. Among them, a placebo-controlled trial adopted strict randomization, hidden allocation and double-blind, with high methodological quality and reliable results. Among all the included studies, only one study reported adverse reactions, with slight increase of ALT, drug reduction or withdrawal, which decreased to normal. The rest of the studies did not mention adverse reactions, which should be paid attention to and improved in future research and treatment reports. According to the report of the American Lipid Society (NI,A) Statin Safety Evaluation Working Group, liver transaminase elevation occurred in 0. 5%~2. 0% of cases [46], and it was dose-dependent. The ratio of liver enzymes < ALT or AST > 3 times the upper limit of normal (ULN) was < 1% after the initial dose and moderate dose of statin treatment.

All the documents included in this paper are published documents, most of which are in China, and the lack of grey documents and research data in other countries limits the universality of the application of this research conclusion. In the literature screening, four studies were excluded because they failed to report the diagnostic criteria and could not contact the authors, which may lead to data omission. The sample size of the original studies included is all small, only two studies have used the correct random allocation method and blind method, and the result data are complete. The methodological quality of other studies is generally low, and the correct random allocation method is rarely used, and the blind method is not clear, which leads to the possibility of selection bias, measurement bias and implementation bias, which weakens the credibility of the systematic evaluation results. Only two of the included studies reported the readmission rate, fatality rate or the incidence of cardiopulmonary events, while the rest of the studies mainly observed laboratory indicators. Therefore, there is not enough evidence to prove that statins can improve the readmission rate, fatality rate, the incidence of cardiopulmonary events and other clinical endpoints of COPD complicated with PH. At present, the clinical trial time is mostly 3 or 6 months, and the long-term curative effect of drugs cannot be observed. Therefore, the treatment time should be extended to evaluate its long-term curative effect. The indexes included in this paper are basically quantitative data. Although the difference between the two groups is statistically significant, its clinical value remains to be verified [47-48], and its clinical significance needs to be further explored. In addition, in data analysis, the standard deviation of the mean difference of each index before and after treatment in a single study was estimated by using Cochrane's recommended method and the coefficients in other related studies, which may be slightly different from the real value, but will not have a substantial impact on the results. Sub-group analysis includes a small number of studies, which may lead to unstable merger results.

In this study, evidence-based medicine systematic review and meta-analysis were used to study the correlation of meta-analysis polymorphism of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH), so as to provide scientific basis for clinical application of statins in respiratory system, prediction of statins toxicity, guidance of individualized medication, reduction of adverse reactions and improvement of drug compliance.

To sum up, simvastatin can improve FEV,FEV,% ,FVC levels, reduce mPAP and increase 6MWD in COPD patients with PH, but the current evidence is not enough to prove that it can reduce sPAP in patients, and there is no effective evidence to judge its influence on FEV, /FVC. Atorvastatin can effectively reduce the levels of sPAP and mPAP and increase 6M WD, but the current evidence is not enough to prove that it can improve the indexes of lung function. Fluvastatin can significantly reduce patients' sPAP, but there is no effective evidence to judge its effect on lung function. The safety of statins in the treatment of COPD complicated with PH remains to be studied. Therefore, a series of high-quality, large-sample, multi-center randomized controlled trials are still needed to further confirm the efficacy and safety of statins in the treatment of COPD complicated with PH [49], in order to draw more reliable conclusions to guide clinical practice.

4 CONCLUSION

Statins can obviously improve exercise endurance and reduce pulmonary artery pressure in COPD patients complicated with PH, and its mechanism may be related to statins increasing NO, decreasing ET 1 and inflammatory factors IL-6,.

hs-CRP levels in circulating blood. However, the results of improving dyspnea, lung function and its safety, and whether there are differences in statin treatment effects of different drug types, doses and treatment time are unstable, and it is still necessary to carry out a randomized controlled trial with strict design and standardized implementation of large samples to make it clear. Meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH). The current research is not enough to prove that statins can increase the incidence of adverse reactions of other statins, but the reliability of the results may be affected due to the small number of original studies involving other statins. It is suggested that more large-scale multi-ethnic population and well-designed epidemiological studies should be carried out to study the correlation of meta-analysis of statins in the treatment of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) [50-51] and the role of genes and environmental factors.

Generally speaking, statins can significantly increase 6MWD and reduce pulmonary arterial pressure in COPD patients complicated with PH, and its mechanism may be caused by increasing circulating NO, decreasing ET-1 and decreasing the levels of inflammatory factors IL-6 and HS-CRP, but there is still no clear conclusion on the quality of life, dyspnea symptoms, lung function and its safety. There may be differences in curative effects among different statins: simvastatin and atorvastatin can significantly increase the patient's 6MWD and reduce the pulmonary artery pressure, while fluvastatin can significantly reduce the pulmonary artery pressure. Other therapeutic indexes of these three drugs and those of other statins need to be confirmed by further research. Different doses of statins may have different therapeutic effects: 10mg/d and 20mg/d statins can significantly increase patients' 6MWD and reduce pulmonary arterial pressure, but the effect on pulmonary function can't be confirmed. 40mg/d statins can significantly reduce patients' pulmonary arterial pressure [52-53], but the effect on 6MWD and pulmonary function still needs further study. There may be differences in the therapeutic effects of statins in different treatment time: when the treatment time is less than or equal to 3 months, statins can significantly increase 6MWD, improve FEV% of moderate and severe airflow restriction index and reduce pulmonary artery pressure, but the effect on FEV 1/FVC still needs further research to confirm. When the treatment time is more than 3 months, 6MWD increases significantly, but it is not enough to prove that it can improve lung function. Different types, doses and treatment time of statins may have no significant difference in the improvement mechanism and safety of PH in COPD patients. The reliability of this system evaluation is affected to some extent due to the limitation of the quality of research methodology.

Based on the current evidence, statins can effectively improve pulmonary arterial pressure and respiratory function in COPD patients with PH, but its effect on long-term death and disability needs further study.

5 SUGGESTIONS

According to the conclusion of this study and the limitations in the process of systematic evaluation and Meta-analysis, the following suggestions are put forward: ① The pleiotropic effects of statins can be used clinically to improve the PH of COPD patients, but the monitoring of adverse reactions should be strengthened. In the future, more strictly designed, large-sample, multi-center randomized controlled trials should be carried out, and the dose-effect relationship of statins other than simvastatin and atorvastatin should be increased, and the treatment time should be appropriately prolonged, so as to evaluate the long-term therapeutic effect of statins in COPD complicated with PH. ② When conditions permit, the meta-analysis polymorphism of chronic obstructive pulmonary disease (COPD) complicated with pulmonary hypertension (PH) should be detected before using statins, so as to evaluate and avoid possible serious adverse reactions, and at the same time reduce the probability of non-compliance with statins for fear of toxic and side effects. It is hoped that in the future, more epidemiological studies with strict design, large sample size, multi-drug types involving people other than Europeans will be carried out, and information such as treatment time and drug dosage will be reported in detail, so as to further study the interaction between gene-gene and gene-environment.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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