

Clinical Neuroscience Research

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Clinical Neuroscience Research

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Research Progress on the Treatment of Depression with Chinese Herbal Medicine

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Abstract: Depression is a common affective disorder characterized by significant and persistent low mood. Traditional Chinese medicine (TCM) attributes depression to emotional disturbances, classifying it as a mood disorder. Chinese herbal formulas have unique advantages and higher safety profiles in treating depression, despite challenges such as complexity in herb combinations, varying efficacy, and potential side effects. Currently, Chinese patent medicines and decoctions are widely used in the clinical treatment of depression, yielding positive results. This article summarizes recent research on the pharmacological effects of Chinese herbal formulas and single herbs with antidepressant properties, analyzing them from three aspects: chemical composition, pharmacological mechanism, and adverse reactions. The aim is to provide references for the clinical application of Chinese herbal formulas in treating depression and to suggest directions for future research.

Keywords: Depression; Chinese herbal medicine treatment; Yixinshu capsule

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1. Introduction

Depression, also known as depressive disorder, is a common mental illness characterized by low mood, slowed thinking, and reduced volitional activities. The WHO has listed it as a global cause of disability. According to statistics, in 2023, approximately 340 million people worldwide suffered from depression, and about 800,000 people died by suicide every year. Modern medicine believes that depression is caused by various factors such as genetic factors, neuroendocrine dysfunction, and psychosocial factors. Its clinical manifestations include poor mood, lack of interest, anhedonia, sleep disorders, fatigue, and weakness ^[1]. The understanding of depression in traditional Chinese medicine began with the “Yellow Emperor’s Inner Canon.” It is believed that “the heart governs the mind”, and emotions such as “happiness, anger, worry, contemplation, sadness, fear, and surprise” can all lead to abnormalities in human consciousness ^[2]. Clinically, traditional Chinese medicine considers depression

a category of emotional disorders. The etiology and pathogenesis are caused by emotional dysregulation. Prolonged illness can lead to the formation of phlegm and turbidity, qi and blood stagnation, and the development of symptoms such as abdominal masses. The disturbance of qi movement can cause liver dysfunction, affecting the spleen. Prolonged illness can also harm the kidneys, leading to kidney yang deficiency, abnormal fluid metabolism, and endogenous phlegm turbidity, resulting in symptoms of blood stagnation and depression. For patients with depression, not only is effective drug treatment needed, but also emphasis on self-emotion regulation to restore the body to a state of yin-yang balance. Traditional Chinese medicine has a long history of treating depression. Doctors of past generations have accumulated rich experience in long-term clinical practice and summarized a series of prescriptions for the treatment of depression, such as Xiaoyao powder, Si Junzi decoction, Chaihu Shugan powder, Suanzaoren decoction, Ganmai Dazao decoction, Zhuru Daotan decoction, Yueju Pill, and Longdan Xiegan pill ^[3]. Additionally, traditional Chinese medicine can exhibit antidepressant effects by improving patients' cognitive function, enhancing their motor abilities, reducing pain symptoms, and alleviating anxiety ^[4]. However, there are issues such as repeated medicinal flavors, unreasonable drug combinations, and unstable efficacy in compound prescriptions of traditional Chinese medicine ^[5-7]. In recent years, with the continuous improvement of scientific research, many scholars have begun to pay attention to the clinical treatment effects of traditional Chinese medicine compounds on depression and have achieved good results, but there are still some limitations. This article mainly introduces the research achievements of traditional Chinese medicine monomers and compounds in the treatment of depression in recent years, aiming to provide references for the further development of traditional Chinese medicine in the treatment of depression in the future.

2. The role of traditional Chinese medicine in depression

Depression is a disease caused by multiple etiologies, primarily manifesting as a low mood. It can be classified into unipolar depression and bipolar depression, and is often treated with medication in clinical practice ^[8]. Traditional Chinese medicine (TCM) is an essential component of traditional Chinese medical science. Its long history, significant efficacy, low toxicity and side effects, no drug resistance, and low dependence have made it widely used in modern medical fields ^[9].

According to TCM theory, depression is caused by injury from the seven emotions (happiness, anger, worry, contemplation, sadness, fear, and surprise), leading to an imbalance of qi, blood, yin, and yang in the internal organs. The disease originates in the heart and is closely related to the liver, spleen, and kidneys ^[10]. The main pathological characteristics of depression include “irregular qi in the early stages of the disease, improper diet, excessive labor or leisure, and external and internal aggressions” ^[11]. Based on different causes, depression can be classified into three syndrome types: liver qi stagnation, phlegm-heat accumulation, and blood stasis obstructing the collaterals ^[12]. Starting treatment from the pathogenesis can achieve better results. TCM has unique advantages in treating depression. Compared with Western medicine, TCM emphasizes holistic concepts and syndrome differentiation and treatment, emphasizing the idea of “preventing disease before it occurs.” Through non-drug treatment methods such as psychological counseling, emotional regulation, and dietary adjustment for patients, it can significantly improve patients' depressive state ^[13]. Additionally, due to its multi-target and multi-pathway effects, traditional Chinese medicine has been increasingly studied. In recent years, many researchers have dedicated themselves to developing safe and effective antidepressant traditional Chinese medicines.

3. Antidepressant mechanisms of traditional Chinese medicine

TCM exhibits multi-target and multi-pathway characteristics, exerting antidepressant effects through mechanisms such as regulating neurotransmitter systems and antioxidant stress.

3.1. Plant extracts

Yu Xiaowen's research found that flavonoids from *Schizonepeta tenuifolia* could increase brain-derived neurotrophic factor (BDNF) and glutamate receptor protein levels in the hippocampus of chronically stressed rats, improving depressive-like behaviors^[14]. Genistein significantly increased the expression of BDNF and CREB in rat brain tissue induced by D-galactose, promoting synapse growth^[15]. Hang Huaqian et al. observed the treatment of a rat model of depression with coptisine extracts. The results showed that the treatment group had better heart rate variability and physical function recovery than the control group, indicating that coptisine extracts have good prospects in treating depression^[16].

3.2. Compound preparations of traditional Chinese medicine

The Chinese Pharmacopoeia lists Chaihu Shugan powder as a commonly used formula for treating symptoms caused by liver qi stagnation, such as chest and hypochondriac discomfort, irritability, or menstrual disorders, and it has a clear antidepressant effect. Bai Limin used a self-made Chaihu Shugan powder to treat depression and found that it could effectively relieve depressive symptoms and improve patients' hemorheological indicators and dyslipidemia, indicating that this compound has good efficacy and safety in treating depression^[17]. Chaihu decoction consists of four herbs: Bupleurum, *Paeoniae Radix Alba*, ginger, and jujube, and can be used to treat liver qi stagnation and spleen deficiency type depression. Li Yue et al. randomly divided Chaihu decoction combined with Xiangfu Shugan powder into two groups: Chaihu decoction and Xiangfu tablets. They compared changes in the Hamilton Depression Rating Scale (HAMD) scores, physical function, and cerebral blood flow after treatment in each group. The results showed that Chaihu decoction combined with Xiangfu tablets significantly improved HAMD scores, physical dysfunction, and reduced cerebral blood flow in a depressive state, indicating that this compound preparation of traditional Chinese medicine has an antidepressant effect^[18]. Furthermore, Li Dongfang believes that Chaihu Shugan powder has the effects of improving anxiety-like behaviors, regulating glucocorticoid secretion, and improving immune function and central nervous system function^[19].

3.3. Single herbs

3.3.1. Trazodone hydrochloride

Trazodone hydrochloride is a benzothiazole compound extracted from the roots of the leguminous plant *Viola yedoensis*, which exhibits high analgesic activity. It acts on the dorsal root ganglion (DRN) of the spinal cord, inhibiting the release of norepinephrine, dopamine, and 5-hydroxytryptamine, thereby achieving an antidepressant effect. Studies have found that trazodone hydrochloride has a protective effect on intestinal mucosal damage caused by trichloroacetic acid in rats, indicating its good gastric mucosal protective effect and ability to prevent intestinal damage caused by aluminum trichloride^[20]. Cai Congcong studied a mouse model of chronic unpredictable mild stress induced by D-galactose and found that trazodone hydrochloride has certain antidepressant effects, as well as various pharmacological effects such as anti-inflammatory, anti-oxidative stress, and improving microcirculation^[21]. Ding Meiling and others reported the protective effect of trazodone hydrochloride on a mouse model of acute poisoning induced by carbon tetrachloride, showing that the drug has good antioxidant effects^[22]. In summary, trazodone hydrochloride has demonstrated beneficial effects in areas

such as anti-oxidative stress and neuroprotection.

3.3.2. Yixinshu capsule

Yixinshu capsule is a traditional Chinese medicine primarily used as an adjuvant treatment for cardiovascular diseases. However, its ingredients, such as ginseng, danshen, and schisandra, have the effects of nourishing qi and restoring pulse, promoting blood circulation and removing blood stasis, and calming the nerves. In recent years, research on its use in the treatment of depression has gradually gained attention. The ingredients of the Yixinshu capsule may improve depressive symptoms through multiple pathways. For example, studies have found that Yixinshu capsule can treat depression by regulating neurotransmitters, mainly due to ingredients like danshen and schisandra that may adjust levels of 5-HT (serotonin), DA (dopamine), and NE (norepinephrine), thereby improving neurotransmitter concentrations in the synaptic cleft^[23]. Research has shown that patients with depression often suffer from chronic inflammation and oxidative stress, and components like tanshinone and ginsenoside have anti-inflammatory and free radical scavenging effects. Studies have found that Yixinshu capsule can reduce stress responses by inhibiting the excessive activation of the hypothalamic-pituitary-adrenal axis (HPA axis)^[24]. Additionally, it promotes the expression of brain-derived neurotrophic factor (BDNF), protecting neuronal function^[25]. Research indicates that Yixinshu capsule, when combined with conventional antidepressants (such as SSRIs), can enhance treatment efficacy, improve symptoms such as low mood and fatigue, and has fewer adverse reactions^[26]. For depression patients with comorbid cardiovascular diseases (like coronary heart disease), Yixinshu capsule may exert a synergistic effect through the “simultaneous treatment of heart and brain.” Studies have shown its significant effect on symptoms associated with depression, such as insomnia, palpitations, and shortness of breath^[27]. In chronic stress depression models, Yixinshu capsule can reduce depressive-like behaviors (e.g., immobility time in forced swimming tests), and its mechanism may be related to regulating gut microbiota and inhibiting the TLR4/NF- κ B inflammatory pathway^[28]. Through ingredient-target-pathway prediction, it has been found to potentially act on inflammatory factors like IL-6 and TNF- α , as well as pathways related to neural plasticity. Yixinshu capsule demonstrates certain potential in the treatment of depression, particularly in subtypes associated with comorbid cardiovascular diseases or inflammation, although its clinical application still requires more high-quality evidence to support it.

4. Adverse reactions

Currently, the compound Chinese medicines used clinically to treat depression are mainly Chinese patent medicines. According to statistics from the National Center for Monitoring Adverse Drug Events (cde-center.org), there have been 594 reported cases of adverse events related to Chinese patent medicines for depression since 2016. Among them, adverse events related to nervous system drugs have the highest incidence, followed by cardiovascular, digestive, psychoactive, and respiratory system drugs. This is related to the complex composition and multiple herb combinations in the compounds^[29]. For example, Chaihu Shugan powder, which contains herbs such as white peony root, angelica, atractylodes, and licorice, has the effect of dispersing stagnated liver qi and relieving qi stagnation, so it is prone to cause gastrointestinal adverse reactions^[30]. Mahuang Fuzi Xixin decoction contains herbs such as aconite, asarum, and ephedra, which have serious toxic and side effects. In particular, aconite can cause arrhythmia and even death^[31]. Xiaoyao Powder contains angelica, poria, atractylodes, bupleurum, mint, ginger, platycodon, cape jasmine, alismatis, and licorice, which may cause liver damage,

abnormal liver function, or aggravated liver injury^[32]. Additionally, some compound Chinese medicines contain aristolochic acid, which can produce reactive metabolites such as dihydroxyaristolochic acid during metabolism in the body^[33]. These reactive substances can cause renal toxicity, neurotoxicity, carcinogenicity, and mutagenic effects, leading to diseases such as renal failure, neural deafness, bladder cancer, and liver cancer^[34].

The adverse reactions of the aforementioned Chinese medicines are closely related to their dosage, and as the treatment course increases, the adverse drug reactions show a gradual decreasing trend. Therefore, selecting the appropriate dosage and treatment course is an important measure to reduce adverse drug reactions. In addition, most Chinese patent medicines are currently extracted and prepared manually, with a simple process that is prone to contamination. Production management is not standardized, and drug quality is difficult to ensure^[35]. Moreover, most Chinese patent medicines have complex components and too many medicinal flavors, which brings difficulties to clinicians in differential treatment based on syndrome differentiation, thereby affecting patient compliance with medication^[36]. Therefore, it is necessary to strengthen the standardization of Chinese medicine pharmaceutical technology to ensure the production of safe and effective Chinese medicine preparations.

5. Conclusion

This article summarizes the research progress on the treatment of depression with Chinese medicine as follows: The therapeutic mechanism of compound Chinese medicines mainly includes alleviating depressive symptoms by regulating neurotransmitters, brain-derived neurotrophic factor (BDNF), and 5-hydroxytryptamine (5-HT) levels; inhibiting monoamine neurotransmitter receptors, dopamine transporters, and acetylcholinesterase, and promoting monoamine oxidase activity; affecting the balance between excitation and inhibition of the central nervous system; and reducing the production of oxidative stress products and inflammatory cytokines.

In summary, compound Chinese medicines for the treatment of depression have advantages such as fewer side effects and low cost, but clinical research is still needed. Due to differences in age, gender, and etiology of depression patients, a single prescription or compound Chinese medicine cannot meet the needs of all patients, and combination therapy has become a new trend in antidepressant drug development at home and abroad. Therefore, individualized treatment should be adopted for the treatment of depression, and the best treatment plan should be formulated after a comprehensive analysis based on the patient's physical condition, course of disease, and past history. At the same time, when selecting appropriate medicinal materials, strict quality standards should be implemented to ensure efficacy. With the development of modern science and technology, continuous research on compound Chinese medicines will bring opportunities for the development of traditional Chinese medicine in China.

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Disclosure statement

The authors declare no conflict of interest.

References

- [1] Li W, Li ZY, 2024, Theory of Stagnation Syndrome in Traditional Chinese Medicine. People’s Medical Publishing House, Beijing, 538.
- [2] Peng QH, 2024, Self-study Encyclopedia of Traditional Chinese Medicine. Chemical Industry Press, Beijing, 477.
- [3] Tang QS, 2024, Clinical Application of Stone Medicines. People’s Medical Publishing House, Beijing, 652.
- [4] Liang WY, He HL, Jia HY, 2025, Relationship between Diversified Application of Chinese Herbal Medicines and Long-term Rehabilitation Quality of Patients with Neurological Sequelae. Journal of Traditional Chinese Medicine Management, 33(5): 109–111.
- [5] Zhou SY, Zhang KR, Yin Q, et al., 2016, Exploring the Syndrome Differentiation and Medication Rules of Traditional Chinese Medicine Combined with ICIs in the Treatment of Lung Cancer Based on Data Mining. Journal of Liaoning University of Traditional Chinese Medicine, 2016(8): 1–11.
- [6] Qiu XJ, 2024, Evaluation of the Influence of the Quality of Chinese Herbal Medicine Dispensing on the Rationality of Chinese Medicine Prescriptions and the Safety of Clinical Medication. Sichuan International Medical Exchange Promotion Association. Medical Nursing Innovation Academic Exchange Conference Proceedings (Smart Medicine). Navy Qingdao Special Service Sanatorium Department of Traditional Chinese Medicine, 425–427.
- [7] Wang J, Zhu XN, Wang XD, et al., 2025, Current Status, Challenges, and Potential Strategies of traditional Chinese Medicine in the Treatment of Primary Hepatocellular Carcinoma. Journal of Southwest Medical University, 48(2): 111–115.
- [8] Zhao Y, 2024, Analysis of Medication Rules of Professor Jiang Lihong in Treating Hypertension Complicated with Anxiety/depression Based on Data Mining Technology, thesis, Changchun University of Traditional Chinese Medicine.
- [9] Gong HT, Ruan JB, Wang YQ, 2024, Pharmaceutical Administration and Regulations. Chemical Industry Press, Beijing, 282.
- [10] Li Y, 2024, Theory of “Yin and Yang of Heart” and the Occurrence of Heart-related Insomnia, thesis, Zhejiang Chinese Medical University.
- [11] Hao QY, Li P, He QY, et al., 2022, Treatment of Depression from the Perspective of Shaoyin Disease. China Journal of Traditional Chinese Medicine Information, 11(3): 1–6.
- [12] Wang W, 2023, Three-Factor Theory of Syndromes in Traditional Chinese Medicine. People’s Medical Publishing House, Beijing, 202.
- [13] Fan CX, Li PF, Yu DH, 2025, Exploration of the “Five Discriminations” Theory in Preventive Treatment of Disease in Traditional Chinese Medicine. Shanghai Journal of Traditional Chinese Medicine, 59(1): 28–32.
- [14] Yu XW, 2019, Exploring the Syndrome Differentiation and Medication Rules of Depression Based on the Theory of Stagnation Syndrome in Traditional Chinese Medicine, thesis, Shandong University of Traditional Chinese Medicine.

- [15] Zhao HQ, Feng PC, Zhang X, et al., 2023, Effects of Genistein on Microglia Activation and HMGB1/TLR4 Pathway in Stroke Rats. *Chinese Journal of Gerontology*, 43(18): 4504–4508.
- [16] Hang HQ, Yu MS, Ye Y, et al., 2024, Pharmacokinetic Analysis of Total Alkaloids from *Corydalis saxicola* in a Depression Model Rat. *Chinese Journal of Experimental Traditional Medical Formulae*, 30(14): 175–183.
- [17] Bai LM, 2024, Observation on the Therapeutic Effect of Chaihu Shugan Powder Combined with Ear Acupuncture in Treating Post-stroke Depression with Liver Qi Stagnation Syndrome. *Journal of Practical Traditional Chinese Medicine*, 40(11): 2134–2136.
- [18] Li Y, Wang JD, Yao J, 2025, Clinical Observation on the Effect of Chaihu-like Prescriptions in Treating Dry Eye Patients with Anxiety and Depression. *Chinese Journal of Ophthalmology of Integrative Medicine*, 35(3): 219—224 + 231.
- [19] Li DF, 2024, Research on the Characteristics of Traditional Chinese Medicine Syndrome Elements and Clinical Intervention of Chronic Heart Failure with Depression based on Data Mining, thesis, Beijing University of Traditional Chinese Medicine.
- [20] Ma LB, 2021, Basic Theory and Application of Plant Extracts. Chemical Industry Press, Beijing, 277.
- [21] Cai CC, 2023, Study on the Regulatory Effect of Yulangshan Polysaccharide on Metabolism and Gut Microbiota in Chronically Stressed Depressed Rats, thesis, Shanxi University.
- [22] Ding ML, Gao M, Bao YW, et al., 2024, Protective Effect of Jingfang Granules on Alcoholic Liver Injury in Mice Based on the p62-Keap1-Nrf2 Signaling Pathway. *Chinese Traditional and Herbal Drugs*, 55(19): 6588–6598.
- [23] Zhang ML, 2024, Effect of Yixinshu Capsule on SAQ, SDS, and SAS Scores in Patients with Coronary Heart Disease and Depression. *Cardiovascular Disease Prevention and Control Knowledge*, 14(11): 60–62.
- [24] Gao JB, Li YD, Yang SZ, et al., 2017, Effects of Yixinshu Capsule on Quality of Life and Anxiety and Depression in Patients after Percutaneous Coronary Intervention. *Chinese Journal of New Drugs*, 26(10): 1148–1151.
- [25] Gao JB, Li YD, Yang SZ, 2017, Effects of Yixinshu Capsule on Anxiety, Depression, and Quality of Life after Acute Myocardial Infarction. *World Chinese Medicine*, 12(5): 1068–1071.
- [26] Li C, Jiang J, 2017, Effects of Yixinshu Capsule on Quality of Life and Anxiety and Depression in Patients after PCI. *Journal of Nanjing University of Traditional Chinese Medicine*, 33(3): 242–244.
- [27] Qin ZL, Li RQ, Tan C, et al., 2024, Network Meta-analysis of Chinese Patent Medicines for the Treatment of Cardiac Neurosis. *Journal of Integrated Traditional Chinese and Western Medicine for Cardiocerebrovascular Diseases*, 22(15): 2696–2707.
- [28] Cai XS, 2024, SIK2/CRTC1 Pathway Reduces Hippocampal Synaptic Plasticity and Participates in the formation of Liver Stagnation Syndrome during Perimenopausal Syndrome, thesis, Fujian University of Traditional Chinese Medicine.
- [29] Fang LZ, Du XP, 2024, Clinical Practice of Geriatrics in General Practice. People's Medical Publishing House, Beijing, 1020.
- [30] Luo N, Wang SL, Li M, et al., 2025, Exploring the Pathogenesis and Treatment Ideas of Gastric Cancer after Surgery Based on “Deficiency, Stagnation, Toxicity, and Stagnation”. *Journal of Basic Theory of Chinese Medicine*, 1–8.
- [31] Liu J, 2022, Practical Handbook of Chinese Materia Medica. Chemical Industry Press, Beijing, 848.
- [32] Pang Q, 2022, Clinical Observation and Related Mechanism Discussion on the Treatment of Graves' Disease with Syndrome Differentiation Combined with Sequential Syndrome Differentiation, thesis, China Academy of Chinese Medical Sciences.
- [33] Liang S, Sun H, Ding Y, et al., 2024, Simultaneous Determination of Aristolochic Acid I and Aristolochic Acid II in

Tongdi Capsules by UPLC-MS/MS. *Modern Chinese Medicine*, 26(8): 1307–1311.

- [34] Chen XP, Xia LF, Li XM, et al., 2024, Application of Zebrafish Experimental Model in Biological Activity Evaluation. *Today's Pharmacy*, 34(5): 387–400.
- [35] Yu ZY, 2024, *Pharmaceutical Service Technology*. Chemical Industry Press, Beijing, 261.
- [36] Xia JG, Yuan MX, Cai XL, et al., 2025, Chinese Expert Consensus on Comprehensive Management of Patients with Cardiovascular-Kidney-Metabolic Syndrome. *Chinese Journal of Cardiovascular Research*, 23(3): 193–228.

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Evaluation of the Therapeutic Effect of Cerebrospinal Fluid Replacement in Subarachnoid Hemorrhage and Study on the Endpoint of Replacement Volume

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Abstract: *Objective:* To evaluate the therapeutic effect of cerebrospinal fluid (CSF) replacement in subarachnoid hemorrhage (SAH) and analyze the endpoint of replacement volume. *Methods:* 36 patients with spontaneous or traumatic SAH and intracerebral hemorrhage breaking into the subarachnoid space received by the hospital from August 2024 to April 2025 were selected. Different volumes of CSF were replaced with routine operation, and the clinical efficacy was analyzed. *Results:* All 36 patients were effective without any complications. In terms of replacement volume, the patients in the clear CSF replacement group had a greater decrease in VAS scores immediately and at 48 hours, and their symptom relief was more significant. The difference was statistically significant by *t*-test. Regarding the average frequency of CSF replacement, the control group had a higher average frequency than the clear group, but there was no statistical difference by the rank sum test. *Conclusion:* CSF replacement therapy can effectively improve clinical symptoms in patients with SAH. In terms of replacement volume, patients in the clear CSF replacement group had a greater decrease in VAS scores immediately and at 48 hours, with more significant symptom relief. Therefore, CSF replacement should be thorough, has high safety, and is worthy of clinical promotion.

Keywords: Subarachnoid hemorrhage; Cerebrospinal fluid replacement; Different replacement volumes; Clinical efficacy

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1. Introduction

Subarachnoid hemorrhage (SAH) is a severe neurological disease primarily caused by the rupture of intracranial aneurysms. It manifests as a sudden and severe headache, often accompanied by consciousness disorders, intense headache, nausea and vomiting, meningeal irritation, and increased intracranial pressure. In severe cases, it can

also be complicated by cerebral vasospasm, hydrocephalus, delayed cerebral ischemia, and other complications, which seriously affect the prognosis and quality of life of patients ^[1]. Currently, the treatment of SAH includes surgical clipping of aneurysms or interventional therapy targeting the etiology, cerebrospinal fluid (CSF) replacement therapy, drug therapy, and combination therapy for subarachnoid hemorrhage. CSF replacement therapy is a commonly used method for the clinical treatment of SAH in China. It reduces the incidence of SAH complications by replacing the accumulated blood in the subarachnoid space, which is a practical and effective method.

This article mainly focuses on 36 patients with spontaneous or traumatic subarachnoid hemorrhage and cerebral hemorrhage breaking into the subarachnoid space admitted to the hospital from August 2024 to April 2025 as data collection subjects. The study subjects were selected based on inclusion and exclusion criteria. Both the patients and their families were informed of the study content and signed informed consent forms. This study was reviewed and approved by the medical ethics committee of the hospital. Inclusion criteria: patients diagnosed with subarachnoid hemorrhage and cerebral hemorrhage breaking into the subarachnoid space through cranial CT, magnetic resonance imaging, and other examinations, as well as patients who meet the indications for cerebrospinal fluid replacement surgery. Exclusion criteria: patients with combined liver and kidney dysfunction, spontaneous subarachnoid hemorrhage without interventional or craniotomy surgery, patients with expandable intracranial hypertension, and patients with respiratory and circulatory failure, thrombocytopenia, and coagulation dysfunction. The analysis was conducted, and the main contents are reported as follows.

2. Materials and methods

2.1. General information

During the period from August 2024 to April 2025, 36 patients with spontaneous or traumatic subarachnoid hemorrhage and cerebral hemorrhage breaking into the subarachnoid space admitted to the hospital were selected. They were divided into a control group and a study group (clear group) according to the random number method. Among them, the control group consisted of 9 males and 12 females, with a minimum age of 23 years, a maximum age of 84 years, and an average age of 64.0 years. The observation group consisted of 9 males and 5 females, with a minimum age of 43 years, a maximum age of 79 years, and an average age of 62.7 years.

Research method: Both groups received conventional treatment, including interventional or craniotomy surgery, infusion of mannitol, reduction of intracranial pressure, spasmolysis, antibiotics, hemostatic agents, blood pressure control, maintenance of acid-base balance, and bed rest. Cerebrospinal fluid replacement therapy was performed after the acute phase of bleeding.

2.2. VAS score

VAS pain scale was used to evaluate patients five times before surgery, immediately after surgery, 24 hours after surgery, 48 hours after surgery, and at the end of the entire replacement cycle. VAS is one of the commonly used pain scoring criteria, and its full name is Visual Analog Scale. A 10 cm horizontal line is drawn on paper, with one end marked as 0, indicating no pain; the other end marked as 10, indicating severe pain; and the middle section representing varying degrees of pain. Patients are asked to mark on the line according to their perceived level of pain. **Table 1** shows the VAS scoring criteria.

Table 1. VAS scoring criteria

Description of pain	Score	Patient's rating
Minor pain, tolerable	0–3 points	
Moderate pain affecting sleep, but still tolerable	4–6 points	
Severe pain strongly felt by the patient, affecting appetite and sleep	7–10 points	

2.3. Cerebrospinal fluid replacement therapy

Based on the amount of subarachnoid hemorrhage and the shade of bloody color in the cerebrospinal fluid, replacement was performed once every 1–2 days until the hemorrhage was basically cleared.

In the control group, lumbar puncture was performed on the patients to measure intracranial pressure. Cerebrospinal fluid was slowly released in 5~10 mL aliquots for testing, and 0.9% sodium chloride injection was slowly infused in 10 mL aliquots. This was followed by another slow release of 10 mL of cerebrospinal fluid. This process was repeated, with a total replacement volume of 40 mL.

In the experimental group, lumbar puncture was similarly performed to measure intracranial pressure. Cerebrospinal fluid was also slowly released in 5~10 mL aliquots for testing, followed by slow infusion of 10 mL of 0.9% sodium chloride injection. This was repeated until the cerebrospinal fluid became clear or significantly lighter in color, with a maximum total replacement volume of 120 mL. Observations were made after the completion of the entire cerebrospinal fluid replacement cycle.

2.4. Observation indicators

(1) Comparison of efficacy between the two groups. Complete recovery: Clinical symptoms such as vomiting, dizziness, and headache disappear, intracranial pressure returns to normal, consciousness recovers, and there is no recurrence of bleeding or other complications; Improvement: Clinical symptoms such as vomiting, dizziness, and headache show significant improvement, intracranial pressure returns to normal, and complications are controlled after intervention; Ineffective: No significant improvement in clinical symptoms such as vomiting and dizziness, and there are complications such as recurrence of bleeding. Total effective rate of treatment = (Number of complete recoveries + Number of improvements) / Total number of cases × 100% (2) Comparison of the number of treatments required between the two groups. (3) Comparison of the degree of headache relief within 48 hours between the two groups. (4) Comparison of the incidence of complications between the two groups.

3. Results

3.1. Statistical methods

Statistical analysis was performed using SPSS 22.0 software. Quantitative data conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using the *t*-test. For non-normally distributed data, the rank sum test was used for comparison. Qualitative data were expressed as rates or proportions and compared using the chi-square test. The significance level was set at 0.05.

3.1.1. Comparison of replacement frequency between the two groups

The average frequency in the control group was 2.10, and the average frequency in the clear group was 1.53. There was no statistically significant difference between the two groups according to the rank sum test ($z = 1.32$, $P = 0.187$) (**Figure 1**).

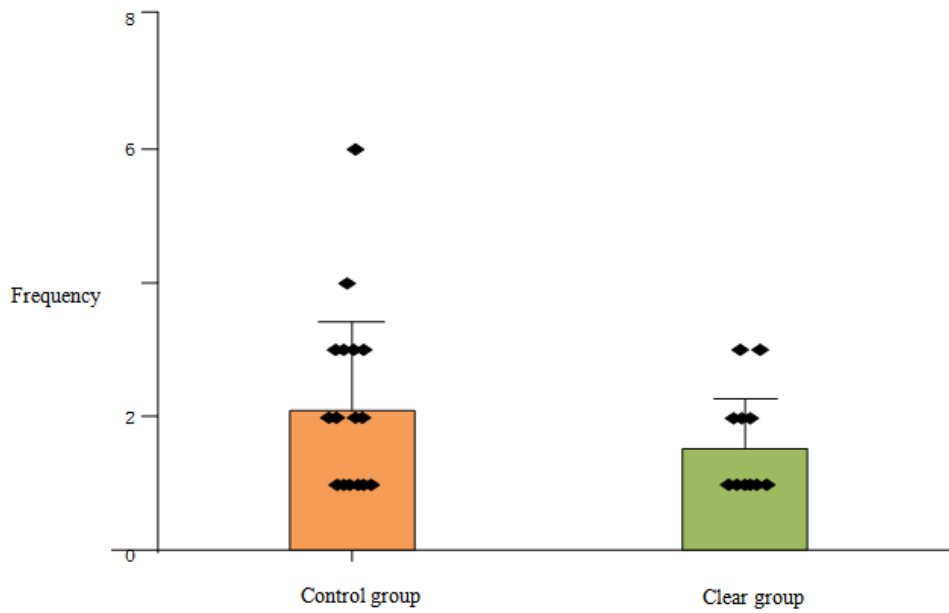


Figure 1. Comparison of frequencies between two groups

3.1.2. Comparison of immediate VAS score reduction between the two groups

The VAS score reduction in the control group was 1.41 ± 0.57 , while the VAS score reduction in the clear group was 2.75 ± 0.58 . The difference was statistically significant according to the *t*-test ($t = 6.28$, $P < 0.001$) (**Figure 2**)

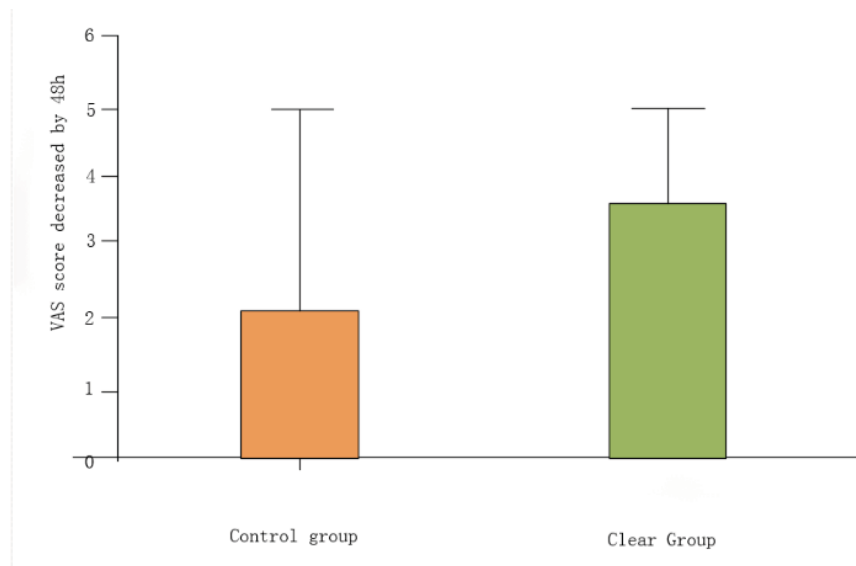


Figure 2. Comparison of immediate VAS score reduction between the two groups

3.1.3. Comparison of VAS score reduction at 48h between the two groups

The VAS score reduction at 48 hours in the control group was 2.17 ± 1.04 , while the VAS score reduction at 48 hours in the clear group was 3.67 ± 1.23 . The difference was statistically significant according to the *t*-test ($t = 3.59$, $P = 0.001$) (**Figure 3**).

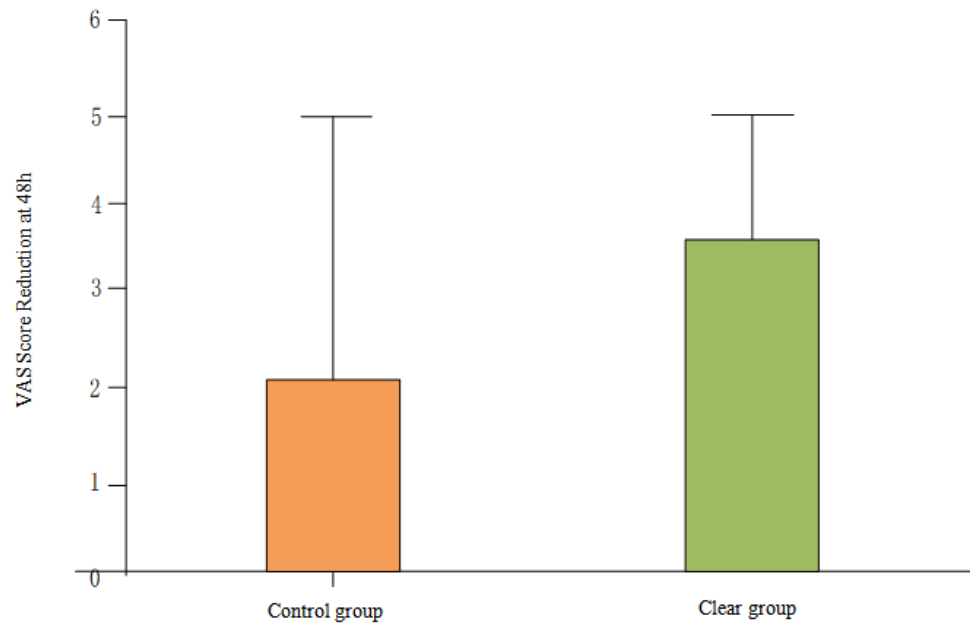


Figure 3. Comparison of VAS score reduction at 48h between the two groups

3.1.4. Comparison of average VAS score reduction at 48h between the two groups

The average VAS score reduction at 48 hours in the control group was 2.15 ± 0.95 , while the average VAS score reduction at 48 hours in the clear group was 3.36 ± 1.47 . The difference was statistically significant according to the *t*-test ($t = 2.75$, $P = 0.01$) (**Figure 4**).

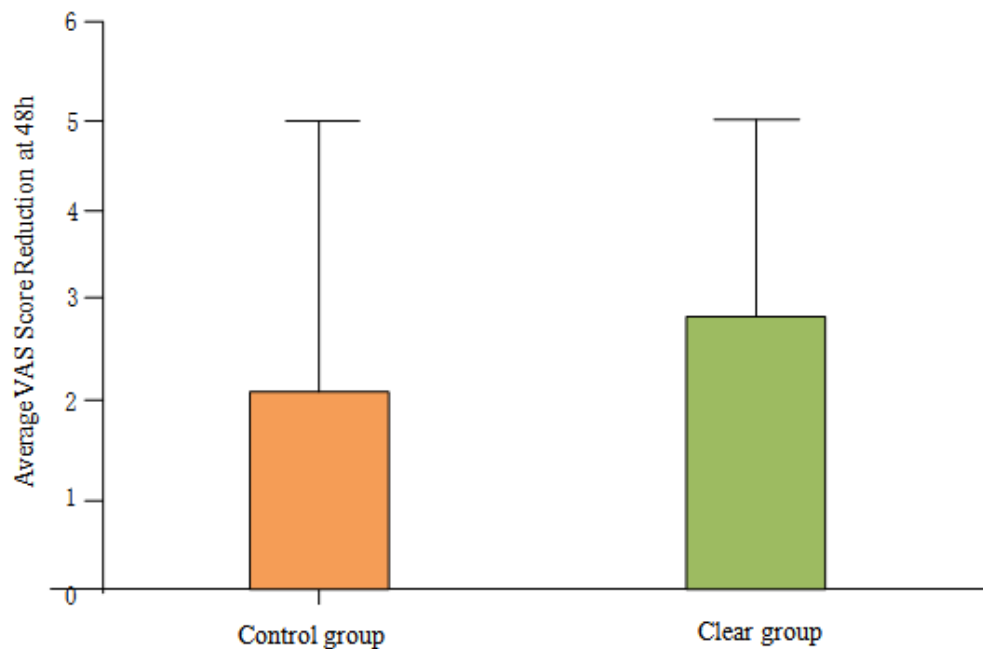


Figure 4. Comparison of average VAS score reduction at 48h between the two groups

3.2. SPSS calculation results

3.2.1. Comparison of replacement frequency between two groups

The comparison of replacement frequency between the two groups is shown in **Tables 2** and **3**.

Table 2. The comparison of replacement frequency between the two groups

Rank				
group		N	Mean rank	Sum of ranks
Frequency	Control group	21	20.31	426.50
	Clear group	15	15.97	239.50
	Total	36		

Table 3. Summary of the independent sample Mann-Whitney U test

Total N	36
Mann-Whitney U	119.500
Wilcoxon W	239.500
Test statistic	119.500
Standard error	28.777
Standardized test statistic	-1.320
Asymptotic significance (2-tailed test)	.187
Exact significance (2-tailed test)	.226

3.2.2. Comparison of VAS score reduction between the two groups

The comparison of VAS score reductions between the two groups is shown in **Tables 4** and **5**.

Table 4. Comparison of VAS score reduction between the two groups

Group statistics					
	Group	N	Mean	Standard deviation	Standard error of the mean
Decrease in VAS score	Control group	18	1.4074	.56656	.13354
	Clear group	12	2.7500	.58387	.16855

Table 5. Independent samples test

Independent samples test											
Levene's test for equality of variances				t-test for equality of means							
Significance										95% confidence interval of the difference	
		F	Significance	t	Degrees of freedom	One-tailed P-value	Two-tailed P-value	Mean difference	Standard error of the difference	Lower limit	Upper limit
Decrease in VAS score	Assuming equal variances	.097	.758	-6.283	28	<.001	<.001	-1.34259	.21370	-1.78034	-.90484
	Not assuming equal variances			-6.243	23.223	<.001	<.001	-1.34259	.21504	-1.78720	-.89799

3.2.3. Comparison of VAS score reduction at 48 hours between the two groups

The comparison of VAS score reduction at 48 hours between the two groups is shown in **Tables 6** and **7**.

Table 6. Comparison of VAS score reduction at 48 hours between the two groups

Group Statistics					
	Group	N	Mean	Standard deviation	Standard error of the mean
VAS score reduction at 48 hours	Control group	18	2.1667	1.04319	.24588
	Clear group	12	3.667	1.23091	.35533

Table 7. Independent samples test

Independent samples test										
Levene's test for equality of variances				t-test for equality of means						
Significance										95% confidence interval of the difference
	F	Significance	t	Degrees of freedom	One-tailed P-value	Two-tailed P-value	Mean difference	Standard error of the difference	Lower limit	Upper limit
VAS score reduction at 48 hours	Assuming equal variances	.168	.685	28	<.001	.001	-1.50000	.41766	-2.35553	-6.4447
	Not assuming equal variances			20.948	.001	.002	-1.50000	.43211	-2.39876	-6.0124

3.2.4. Comparison of the average reduction in VAS scores at 48 hours between the two groups

The comparison of the average reduction in VAS scores at 48 hours between the two groups is shown in **Tables 8** and **9**.

Table 8. The comparison of the average reduction in VAS scores at 48 hours between the two groups

Group statistics					
	Group	N	Mean	Standard deviation	Standard error of the mean
VAS score reduction at 48 hours	Control group	18	2.1481	.95296	.22461
	Clear group	12	3.3611	1.47339	.42533

Table 9. Independent samples test

Independent samples test										
Levene's test for equality of variances			t-test for equality of means							
Significance									95% Confidence interval of the difference	
	F	Significance	t	Degrees of freedom	One-tailed P-value	Two-tailed P-value	Mean difference	Standard error of the difference	Lower limit	Upper limit
VAS score reduction at 48 hours	Assuming equal variances	2.344	.137	28	.005	.010	-1.21296	.44162	-2.11758	-.30834
	Not assuming equal variances			17.129	.001	.022	-1.21296	.48100	-2.22720	-.19873

4. Discussion

Subarachnoid hemorrhage (SAH) includes spontaneous SAH and traumatic SAH, with traumatic brain injury being the main cause of traumatic SAH (tSAH). Traumatic vasoconstriction observed in animal models can lead to secondary ischemic injury, as well as changes in intracranial pressure and mean arterial blood pressure, which largely explain the clinical course of tSAH and may ultimately result in neurological deterioration, increased morbidity, and mortality ^[3]. Approximately 85% of non-traumatic SAH cases are typically associated with the rupture of intracranial aneurysms, with nearly 500,000 patients worldwide suffering from aneurysmal SAH (aSAH) each year ^[4-5]. The main symptom of aSAH is sudden severe headache, often described as “the worst headache of my life,” which may be accompanied by transient loss of consciousness, nausea or vomiting, pseudomeningocele, and epileptic seizures ^[6]. During aSAH, blood accumulates between the arachnoid and pia mater layers, leading to rapid increases in intracranial pressure and deprivation of oxygen to brain tissue, ultimately causing brain tissue damage and neurological dysfunction. Additionally, neurotoxins released from the hematoma can also cause cell death ^[7]. Blood breakdown products in the cerebrospinal fluid (CSF) can also block the arachnoid villi, leading to hydrocephalus and vasospasm, which can exacerbate neurological dysfunction ^[1]. The 30-day mortality rate for aSAH is approximately 20%, and up to 50% of survivors may become functionally dependent ^[8]. Currently, the etiology of SAH remains unknown for 10% of patients, making it impossible to determine the correct source of bleeding. This condition is known as angiographically negative SAH (naSAH), which has a more benign prognosis and better outcome compared to aSAH ^[9]. Therefore, for the clinical treatment of spontaneous SAH, rapid clearance of subarachnoid hematoma is key after addressing the underlying causes, such as aneurysms or vascular malformations, through craniotomy clipping or interventional therapy ^[10]. Conventional treatment cannot quickly clear the subarachnoid hematoma within a short period, while combined CSF replacement therapy for aneurysmal SAH can effectively control the disease and improve prognosis ^[11-12, 15]. In terms of efficacy and safety, both groups in this study were effective. Comatose patients were evaluated by head CT, showing a significant reduction in subarachnoid or ventricular hematoma, resulting in a 100% effectiveness rate. Regarding safety, lumbar puncture is a routine procedure in neurosurgery ^[2]. The safety of CSF replacement was assessed through preoperative evaluation (including medical history, physical examination, laboratory tests, and imaging

studies), strict aseptic techniques during surgery, lateral puncture techniques, strict control of CSF release and 0.9% sodium chloride injection rates, maintenance of intracranial pressure stability, and postoperative monitoring and care (including vital signs, neurological function, and CSF pressure). There were no complications in this group, demonstrating safety and efficacy. Currently, CSF replacement therapy is widely used to treat SAH due to its advantages of minimal trauma and rapid recovery. It can effectively improve clinical symptoms without increasing the risk of adverse reactions, exhibiting high safety^[13–14]. Regarding replacement volume, patients in the clear CSF replacement group showed a greater decrease in VAS scores immediately and at 48 hours, with more significant symptom relief. The difference was statistically significant, indicating the importance of thorough CSF replacement^[10]. This finding is consistent with previous literature reports. Regarding the average frequency of CSF replacement, the control group had a higher average frequency than the clear group, but there was no statistical difference, possibly due to the small sample size, necessitating further large-scale studies.

5. Conclusion

In summary, patients with SAH and hypertensive intracerebral hemorrhage with ventricular rupture who receive CSF replacement therapy can effectively improve clinical symptoms. In terms of replacement volume, patients in the clear CSF replacement group showed a greater decrease in VAS scores immediately and at 48 hours, with more pronounced symptom relief. Therefore, thorough CSF replacement is crucial and demonstrates high safety, making it worthy of clinical promotion.

Disclosure statement

The authors declare no conflict of interest.

References

- [1] Zhou YX, Wang YP, 2024, Comparison of the Effects of Continuous Lumbar Cistern Drainage and Cerebrospinal Fluid Replacement Therapy in Patients with Spontaneous Subarachnoid Hemorrhage. *China Medicine and Health*, 36(5): 142–145.
- [2] Tian MH, 2024, Observation on the Therapeutic Effect of Lumbar Puncture Cerebrospinal Fluid Replacement Therapy for Subarachnoid Hemorrhage. *Chinese and Foreign Medical Research*, 3(8): 23–25.
- [3] Griswold DP, Fernandez L, Rubiano AM, 2022, Traumatic Subarachnoid Hemorrhage: A Scoping Review. *Journal of Neurotrauma*. 39(1–2): 35–48.
- [4] Claassen J, Park S, 2022, Spontaneous Subarachnoid Haemorrhage. *Lancet (London, England)*, 400(10355): 846–862.
- [5] Zhang ZY, Fang YJ, Lenahan C, et al., 2021, The Role of Immune Inflammation in Aneurysmal Subarachnoid Hemorrhage. *Experimental Neurology*, 2021(336): 113535.
- [6] Cao Y, Li Y, He C, et al., 2021, Selective Ferroptosis Inhibitor Liproxstatin-1 Attenuates Neurological Deficits and Neuroinflammation After Subarachnoid Hemorrhage. *Neuroscience Bulletin*, 37(4): 535–549.
- [7] Ran KR, Wang AC, Nair SK, et al., 2023, Acute Multidisciplinary Management of Aneurysmal Subarachnoid Hemorrhage (aSAH). *Balkan Medical Journal*, 40(2): 74–81.
- [8] Geng Y, Jia J, Liu X, et al., 2023, Clinical Outcome and Prognostic Factors of Patients with Non-traumatic

Angiography-negative Subarachnoid Hemorrhage. *Frontiers in Neurology*, 2023(14): 1157845.

- [9] Wang W, Jiang B, Sun H, et al., 2017, Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480,687 Adults. *Circulation*, 135(8): 759–771.
- [10] Li TK, Yan J, Jin XL, et al., 2020, Effect of Cerebrospinal Fluid Replacement Therapy in Patients with Subarachnoid Hemorrhage. *China Medicine and Health*, 32(22): 27–29.
- [11] Zheng KP, Wang MQ, Zhang JW, et al., 2021, Clinical Observation of Aneurysm Embolization Combined with Cerebrospinal Fluid Replacement in the Treatment of Aneurysmal Subarachnoid Hemorrhage. *China Journal of Pharmaceutical Sciences*, 30(S02): 93–94.
- [12] Luo WK, Cheng HR, Chen YJ, et al., 2023, Effects of Cerebral Aneurysm Rupture Vascular Intervention Embolization Combined with Lumbar Puncture Cerebrospinal Fluid Replacement and Nimodipine on the Prevention of Cerebrovascular Spasm. *Practical Integration of Traditional Chinese and Western Medicine*, 23(13): 10–13.
- [13] Li HK, Liao J, Zhou KS, 2022, Effect of Cerebrospinal Fluid Replacement Therapy in the Treatment of Subarachnoid Hemorrhage with Cerebrovascular Spasm. *Chinese and Foreign Medical Research*, 20(4): 142–144.
- [14] Gan N, Wu RF, Xu ZJ, et al., 2023, Effect of Cerebrospinal Fluid Replacement Combined with Endovascular Interventional Embolization in the Treatment of Patients with Aneurysmal Subarachnoid Hemorrhage. *Chinese Scientific Journal Database, Medicine and Health*, 2023(4): 41–44.
- [15] Zhen Z, 2023, Effect of Cerebrospinal Fluid Replacement Combined with Endovascular Interventional Embolization in the Treatment of Patients with Aneurysmal Subarachnoid Hemorrhage. *China Medicine and Health*, 35(2): 4–7.

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Study on the Clinical Effect and Safety of Ginkgo Dipyrindamole Injection Combined with Hyperbaric Oxygen in the Treatment of Ischemic Optic Neuropathy

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Abstract: *Objective:* To analyze the effect of combining Ginkgo Dipyrindamole Injection with hyperbaric oxygen in the treatment of patients with ischemic optic neuropathy, and to study the safety of this combined therapy. *Methods:* Sixty eligible patients were selected from the hospital as samples, with a fixed time period and randomized grouping. The control group received only Ginkgo Dipyrindamole Injection as a therapeutic intervention, while the observation group received hyperbaric oxygen therapy in addition to Ginkgo Dipyrindamole Injection. The effects of different treatment regimens were compared and analyzed. *Results:* The effective rate of treatment in the observation group was higher than that in the control group. After treatment, there were significant changes in visual field-related indicators compared to before treatment. In addition to a higher MS index in the observation group than in the control group, LV and MD indicators were lower in the observation group. The differences mentioned above were statistically significant ($P < 0.05$). There was no statistically significant difference in adverse reactions between the two groups ($P > 0.05$). *Conclusion:* Combining Ginkgo Dipyrindamole Injection with hyperbaric oxygen can help patients with ischemic optic neuropathy achieve better treatment outcomes. Patients' visual fields improved significantly after combined therapy, highlighting the effectiveness of this treatment approach. The safety of the combined therapy can be guaranteed, demonstrating the significant value of this treatment plan.

Keywords: Ginkgo Dipyrindamole injection; Hyperbaric oxygen; Ischemic optic neuropathy; Adverse reactions; Visual field changes

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1. Introduction

Ischemic optic neuropathy is a fundus disease that is relatively common among elderly people, especially those over 60 years old^[1]. Analysis of this disease reveals a strong correlation between optic nerve ischemia and hypoxia, which can cause optic nerve damage, leading to negative developments in patients' vision and visual

fields, and further increasing the probability of disease occurrence. Clinically, this disease is often classified as anterior ischemic optic neuropathy and posterior ischemic optic neuropathy, which can occur in one or both eyes [2]. In addition to being common in elderly populations, the disease is more prevalent among women than men [3]. Affected patients may experience a gradual decline in vision. The onset of the disease is often sudden, with early optic disc swelling, a reddish appearance, and visual field defects limited to a specific quadrant of the optic disc [4]. It is essential to pay attention to this disease, recognize its negative impact on patients' vision, and actively correct and improve the condition to ensure patients' vision. Although there is no specific treatment for this disease, drug therapy can improve optic nerve blood circulation and enhance patients' visual function [5]. Some researchers have pointed out that using Ginkgo Dipyridamole Injection for the treatment of ischemic optic neuropathy can yield positive results [6]. However, there is still room for improvement in the efficacy of this monotherapy. Focusing on patient needs and striving to further enhance treatment effectiveness, the hospital proposes combining Ginkgo Dipyridamole injection with hyperbaric oxygen therapy based on clinical experience and relevant literature. This combined approach aims to improve the overall treatment effect for patients. To analyze the safety and practical effects of this combined therapy, the following study was conducted.

2. Materials and methods

2.1. General information

Patients with ischemic optic neuropathy admitted to our hospital from January 2020 to January 2023 were screened, resulting in a sample size of 60 cases. The patients were divided into a control group and an observation group using the envelope method, with equal numbers in each group. Statistical software analysis confirmed that the samples were balanced and comparable ($P > 0.05$). The data is shown in **Table 1**.

Table 1. Comparison of basic information (n , Mean \pm SD)

Group	Number of cases	Female	Male	Age range (years)	Average age (years)
Control group	30	18	12	46~70	58.63 \pm 2.74
Observation group	30	19	11	45~72	58.77 \pm 2.85
χ^2/t		0.070		-	0.194
P		0.791		-	0.846

Inclusion criteria: (1) Patients were diagnosed with ischemic optic neuropathy; (2) Patients were informed of the study details.

Exclusion criteria: (1) Presence of drug allergies or resistance to treatment methods; (2) Unable to provide accurate personal information.

2.2. Methods

All patients received basic treatment, which included glucocorticoid intervention and the use of neurotrophic drugs based on the specific conditions of the patients. In addition to the basic treatment, the two groups received different treatment regimens.

2.2.1. Control group

Only Ginkgo Dipyridamole Injection was used for treatment. Ginkgo Dipyridamole Injection (Shanxi Pude Pharmaceutical Co., Ltd., National Medical Approval Number H14023516) was administered intravenously by mixing 20 mL of the injection with 250 mL of normal saline. The infusion was performed once daily. The treatment course consisted of 12 days, with a 6-day interval between courses, for a total of 3 courses.

2.2.2. Observation group

In addition to the treatment received by the control group, the observation group also received hyperbaric oxygen therapy. Before hyperbaric oxygen therapy, patients were informed of the necessary precautions. They were guided into the hyperbaric oxygen chamber, given 0.5 mg of Nitroglycerin Tablets (Beijing Yimin Pharmaceutical Co., Ltd., National Medical Approval Number H11021022) to be taken sublingually, and instructed to wear an oxygen mask for pressurized air administration. The chamber pressure was set to 0.25 MPa, and the pressurization process lasted for 25 minutes. Patients inhaled pure oxygen twice, with each session lasting for 30 minutes. Between the two sessions, patients inhaled chamber air for 10 minutes, followed by a 25-minute decompression, for a total duration of 120 minutes. This treatment was performed once daily, with the same treatment course and interval as the control group.

2.3. Observation indicators

- (1) Analyze and compare the efficacy of patient treatment. Evaluate the efficacy based on the recovery of visual acuity and changes in visual fields. If the patient's visual acuity returns to normal levels and the visual field is normal after treatment, it is considered as effective treatment; if the patient's visual acuity improves significantly and the scope of visual field loss is reduced by more than 50% compared to before treatment, it is considered as partially effective; all other situations are considered as ineffective treatment.
- (2) Evaluate and compare visual field-related indicators before and after treatment. Key indicators include mean sensitivity (MS), loss variance (LV) of anterior and posterior visual fields, and mean defect (MD) of the visual field.
- (3) Record and compare the adverse reactions caused by the treatment in terms of probability.

2.4. Statistical methods

Statistical software SPSS 24.0 was used to analyze and process the data. The measurement data and count data (%) of the patients were tested using *t* and chi-square tests, respectively. A *P*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Comparison of treatment efficacy

The effective rate of treatment in the observation group was higher than that in the control group ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of treatment efficacy [n(%)]

Group	Number of cases	Markedly effective	Effective	Ineffective	Effective rate
Observation group	30	19 (63.33)	11 (36.67)	0 (0.00)	30 (100.00)
Control group	30	17 (56.67)	9 (30.00)	4 (13.33)	26 (86.67)
χ^2					4.285
<i>P</i>					0.038

3.2. Comparison of visual fields

After treatment, the patients' visual fields showed a significant improvement trend. Compared with the pretreatment values, both groups showed significant changes after treatment. Specifically, the MS in the observation group was higher than that in the control group, while the other indicators were lower than those in the control group ($P < 0.05$). The details are shown in **Table 3**.

Table 3. Comparison of visual fields (Mean \pm SD)

Group	MD (dB)		MS (dB)		LV (dB)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group ($n=30$)	11.78 \pm 1.15	5.34 \pm 0.55	14.86 \pm 1.49	19.87 \pm 2.01	24.54 \pm 2.47	15.41 \pm 1.56
Control group ($n=30$)	11.49 \pm 1.13	7.48 \pm 0.72	14.92 \pm 1.53	16.88 \pm 1.67	24.77 \pm 2.53	18.95 \pm 1.80
<i>t</i>	0.985	12.936	0.153	6.266	0.356	8.140
<i>P</i>	0.324	0.000	0.878	0.000	0.722	0.000

3.3. Comparison of adverse reactions

There was no statistically significant difference in adverse reactions between the two groups ($P > 0.05$). The details are shown in **Table 4**.

Table 4. Comparison of adverse reactions [n(%)]

Group	Number of cases	Metabolic disorder	Infection	Insomnia	Incidence rate
Observation group	30	1 (3.33)	0 (0.00)	1 (3.33)	2 (6.67)
Control group	30	1 (3.33)	1 (3.33)	1 (3.33)	3 (10.00)
χ^2					0.218
<i>P</i>					0.640

4. Discussion

Ischemic optic neuropathy is a relatively common ocular fundus disease in ophthalmology, mainly manifesting as sudden vision loss and a sense of visual obscuration^[7]. Relevant scholars believe that its occurrence has a certain correlation with the presence of corresponding underlying diseases in patients^[8]. Some studies have pointed out that if patients have common diseases such as hypertension, diabetes, and cardiovascular diseases, long-term pathologies can

lead to a decrease in optic nerve artery perfusion pressure and an imbalance in intraocular pressure^[9]. In this situation, ischemic optic nerve fibers can easily cause optic nerve atrophy, resulting in permanent visual impairment. To treat this disease, clinical interventions often involve the use of Western medications^[10]. Attempting hyperbaric oxygen therapy in addition to standard treatment theoretically can produce better treatment results^[11–12]. The principle of hyperbaric oxygen therapy is to improve the blood oxygen content of patients through pressurized oxygen administration, leading to positive changes in tissue oxygen saturation^[13]. This treatment method effectively enhances tissue oxygen uptake capacity and improves patients' nerve cell repair function, which can further enhance the treatment effect when applied to patients with ischemic optic neuropathy.

The Ginkgo Dipyridamole injection used in the study has antioxidant properties, participates in vasodilation and vasoconstriction regulation, and plays a significant role in improving erythrocyte aggregation and regulating blood viscosity^[14]. Simultaneously, ginkgolides in the medication can inhibit vascular endothelial damage, providing better control and intervention for microthrombus formation and platelet aggregation^[15]. Currently, the use of this drug for the treatment of ischemic optic neuropathy has gained clinical recognition. Therefore, adding hyperbaric oxygen therapy on this basis can yield better results^[16].

The study results indicate that both treatment groups demonstrated good safety performance. The reasonable control of adverse reactions suggests that the combination of hyperbaric oxygen and Ginkgo Dipyridamole injection does not produce a high incidence of adverse effects, highlighting its positive clinical significance. Regarding the actual treatment effect, the effective treatment rate reflects the positive outcomes of the therapies. The results indicate that the combined treatment is highly effective, suggesting that the treatment approach used in the observation group can further improve patients' conditions. In terms of changes in visual field-related indicators, the implementation of hyperbaric oxygen combined with Ginkgo Dipyridamole treatment can further enhance these indicators, leading to positive developments. Although both groups showed positive feedback, the numerical performance suggests that the observation group's actual treatment effect is more prominent, indicating the value of combined therapy.

5. Conclusion

In summary, the combined use of hyperbaric oxygen and Ginkgo Dipyridamole for the treatment of ischemic optic neuropathy offers outstanding overall treatment effects and safety. The necessity and enthusiasm for implementing this combined therapy are more fully reflected.

Disclosure statement

The author declares no conflict of interest.

References

- [1] Wang YG, Wang BY, Zhang DC, 2021, Clinical Effect of Puerarin Glucose Injection Combined with Vincamine Sustained-release Capsules in the Treatment of Anterior Ischemic Optic Neuropathy. *Drug Evaluation Research*, 44(1): 116–121.
- [2] Lv Y, Wang Q, 2022, Clinical Observation on the Effect of Compound Xueshuantong Capsule Combined with Compound Anisodine Injection in The Treatment of Non-Arteritic Anterior Ischemic Optic Neuropathy. *Chinese*

Journal of Modern Drug Application, 16(15): 45–48.

- [3] Liao L, Wang Y, Wei QP, 2022, Meta-analysis of the Efficacy and Safety of Compound Anisodine Injection in the Treatment of Anterior Ischemic Optic Neuropathy. *Chinese Journal of Experimental Ophthalmology*, 40(7): 645–650.
- [4] Chou YY, Ma J, Zhong Y, 2022, Neuroprotective and Nerve Regeneration Treatment Strategies for Non-Arteritic Anterior Ischemic Optic Neuropathy. *Chinese Journal of Experimental Ophthalmology*, 40(7): 675–679.
- [5] Guo LJ, Chen Y, 2022, Effects of Different Doses and Administration Methods of Glucocorticoids on Non-Arteritic Anterior Ischemic Optic Neuropathy. *Chinese Journal of Ocular Trauma and Occupational Eye Disease*, 44(11): 813–819.
- [6] Yang YQ, Ye JR, Bu SY, et al., 2022, Clinical Observation on the Effect of Self-Made Buqi Tongmu Decoction in the Treatment of Non-Arteritic Anterior Ischemic Optic Neuropathy of Qi and Blood Deficiency Type. *Sichuan Journal of Traditional Chinese Medicine*, 40(1): 164–167.
- [7] Zhang M, Wang XL, 2021, Exploring the Mechanism of Ginkgo Biloba in the Treatment of Non-Arteritic Anterior Ischemic Optic Neuropathy Based on Network Pharmacology. *Recent Advances in Ophthalmology*, 41(11): 1037–1042.
- [8] Liu M, Zheng YX, 2021, Effect of Modified Xuefu Zhuyu Decoction Combined with Acupuncture on Acute Anterior Ischemic Optic Neuropathy and its Influence on Vision, Visual Field, and Visual Evoked Potential. *Modern Journal of Integrated Traditional Chinese and Western Medicine*, 30(24): 2704–2707.
- [9] Sun WY, Liao X, Wang Y, et al., 2021, Systematic Evaluation of the Effectiveness of Glucocorticoids in the Treatment of Non-Arteritic Anterior Ischemic Optic Neuropathy. *Chinese Journal of Fundus Diseases*, 37(3): 224–230.
- [10] Ren Q, Li YF, Sun CB, et al., 2021, Clinical Observation of Hydrobromide Anisodine Injection in the Treatment of Non-Arteritic Anterior Ischemic Optic Neuropathy. *China Pharmacist*, 24(4): 709–712.
- [11] Shen L, Shi L, 2021, Observation on the Curative Effect of Compound Anisodine Combined with Mouse Nerve Growth Factor Injection in the Treatment of Ischemic Optic Neuropathy. *Zhejiang Clinical Medicine*, 23(6): 865–866.
- [12] Chen F, Gao F, Wang M, et al., 2021, Observation on the Curative Effect of Oral Glucocorticoids in the Treatment of Acute Non-Arteritic Anterior Ischemic Optic Neuropathy. *Chinese Journal of Fundus Diseases*, 37(10): 758–762.
- [13] Zhou WM, Cao WB, Chu JT, et al., 2021, Clinical Efficacy of Hyperbaric Oxygen Therapy in Patients with Non-Arteritic Anterior Ischemic Optic Neuropathy. *Chinese Journal of Navigation Medicine and High Pressure Medicine*, 28(1): 87–91.
- [14] Wu YB, Zhou ZB, Zhuo N, 2021, Clinical Efficacy of Injectable Mouse Nerve Growth Factor Combined with Traditional Medication in the Treatment of Anterior Ischemic Optic Neuropathy. *Journal of Clinical Rational Drug Use*, 14(3): 81–83.
- [15] Duan G, Xu XB, 2021, Clinical Efficacy and Safety Analysis of Ginkgo Biloba and Dipyridamole Injection Combined with Hyperbaric Oxygen Therapy in the Treatment of Ischemic Optic Neuropathy. *Hainan Medical Journal*, 32(21): 2779–2782.
- [16] Wang Y, 2021, Tongqiao Huoxue Decoction Combined with Deproteinized Calf Blood Extract Injection in the Treatment of 32 Cases of Anterior Ischemic Optic Neuropathy. *Fujian Journal of Traditional Chinese Medicine*, 52(2): 55–56.

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Application of De-escalation Techniques in Intervening Violent Behaviors of Mental Disorder Patients in Outpatient Clinics

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Abstract: *Objective:* To analyze the impact of de-escalation techniques in reducing violent behaviors in the nursing management of mental disorder patients in outpatient clinics. *Methods:* A total of 214 mental disorder patients who visited the clinic from June 2024 to November 2024 were selected as samples. 107 patients admitted from June to August were assigned to the control group, and 107 patients admitted from September to November were assigned to the study group. The study group received de-escalation intervention, while the control group received routine intervention. Both groups were evaluated using the Chinese version of the Brøset Violence Checklist (BVC) to compare the incidence of violent attack behaviors, BVC risk proportion, and the satisfaction of escort unit staff towards outpatient clinic staff before and after intervention. *Results:* The incidence of violent attack behaviors in the study group was lower than that in the control group, but there was no significant difference ($P > 0.05$). There was no difference in BVC risk level between the study group before intervention and the control group ($P > 0.05$). The BVC risk level in the study group after intervention was lower than that in the control group ($P < 0.05$). The BVC risk level in the study group after intervention was lower than that before intervention ($P < 0.05$). The satisfaction of the escort unit staff in the study group was higher than that in the control group ($P < 0.05$). *Conclusion:* The application of de-escalation techniques in the nursing management of mental disorder patients in outpatient clinics, combined with targeted management based on BVC assessment, can effectively reduce violent behaviors and lower the risk of violence occurrence.

Keywords: Mental disorders; De-escalation techniques intervention; Violent behaviors; BVC

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1. Introduction

During the onset of mental disorders, patients may exhibit destructive behaviors towards themselves, others, or other targets. Inappropriate handling of violent behaviors by medical staff can increase the incidence of medical

disputes and even affect the operation of medical institutions. Violent behaviors of mental disorder patients often occur in medical workplaces, commonly manifesting as physical attacks, verbal violence, and other forms. These behaviors not only harm the physical health of medical staff but also lead to anxiety and fear, reducing their enthusiasm for treating and caring for mental disorder patients. How to reduce violent behaviors in outpatient mental disorder patients and how to handle violent incidents that have already occurred remain key focuses of psychiatric outpatient management ^[1]. Routine outpatient management relies on the experience of medical staff, which has limitations. De-escalation techniques, as modern nursing measures, consist of risk assessment, communication, self-monitoring, and maintaining the safety of both parties. They can be used to prevent concealed violent events, effectively reducing violent behaviors in mental disorder patients and lowering the usage rate of coercive management measures such as protective restraint. Based on this, this article explores the value of de-escalation intervention using a sample of 214 mental disorder patients who visited the clinic from June 2024 to November 2024.

2. Materials and methods

2.1. Materials

A total of 214 mental disorder patients who visited the clinic from June 2024 to November 2024 were selected as samples. 107 patients admitted from June to August were assigned to the control group, and 107 patients admitted from September to November were assigned to the study group. There was no statistically significant difference in baseline characteristics between the two groups ($P > 0.05$). The details are shown in **Table 1**.

Table 1. Analysis of baseline data of patients with mental disorders

Group	n	Gender (%)		Age (years)		Type of mental disorder (%)						
		Male	Female	Range	Mean \pm SD	Undiagnosed	Agitated state	Bipolar disorder	Schizophrenia	Depressive State	Hallucinatory-paranoid state	Mental retardation
Study group	107	66 61.68	41 38.32	20-70	39.50 \pm 8.82	7 (66.66)	8 (7.48)	2 (1.87)	7 (6.54)	6 (5.61)	10 (9.35)	3 (2.80)
Control group	107	75 70.09	32 29.91	19-71	38.76 \pm 8.79	58 (54.21)	12 (11.21)	3 (2.80)	8 (7.48)	8 (7.48)	16 (14.95)	2 (1.87)
χ^2/t	-	1.6841		0.6147		0.6204						
P	-	0.1944		0.5394		0.5288						

2.2. Inclusion and Exclusion Criteria

Inclusion criteria: (1) Meet the criteria for mental disorders in the “Practice of Chinese Classification and Diagnostic Criteria for Mental Diseases” ^[2]; (2) Informed consent; (3) Normal organ function.

Exclusion criteria: (1) Pregnant women; (2) Severe physical illness; (3) Severe respiratory infection.

2.3. Methods

2.3.1. The control group received routine intervention

The Brøset violence checklist (BVC) was used to assess whether patients showed signs of violent behavior and to identify violence risk. A BVC score of 0 indicated a low risk of violence, and patients were closely monitored for fluctuations in their condition. A score of 1–2 indicated a moderate risk of violence, and prompt implementation of

emergency prevention and control measures was required, reporting to a physician, restraining one hand and one foot on the opposite side of the patient while in bed, assessing the patient's emotional state and blood circulation in the restrained area, and adopting appropriate methods to guide patients to vent their emotions, inducing them to talk about their needs, and satisfying their reasonable demands. A score of 3–6 indicated a high risk of violence, requiring both hands and feet to be restrained while in bed, and immediately implementing targeted measures to deal with aggressive behavior.

2.3.2. The observation group received a de-escalation intervention

Risk assessment: The BVC was used to assess patients for signs of violent behavior and to identify violence risks, promptly intervening with de-escalation techniques to avoid escalation of violence. The BVC consists of six sub-items (noise, chaos, destruction of property, injury, irritation, verbal threats, etc.). If any of these behaviors are present, 1 point is awarded; if not, 0 points are awarded. The BVC score ranges from 0–6, and the score is directly proportional to the risk of violent attacks in the next 24 hours.

Clinical communication: Healthcare workers should maintain a calm demeanor, communicate with patients from a distance of >1 m, use gentle movements, avoid direct eye contact but maintain appropriate eye contact, use a gentle and euphemistic tone to comfort patients, and listen carefully when patients talk. Based on the patient's family status and past medical history, deeply analyze the causes of violent behavior, guide patients to trust medical staff, analyze possible influencing factors of violent behavior with patients, and discuss solutions with them.

Self-regulation: Different mentally ill patients have different causes of violent behavior. It is necessary to analyze the causes of violent behavior from the patient's perspective, making patients feel respected and understood. Additionally, assign staff that patients trust or can maintain emotional stability to serve them, carry out self-supervision education, guide patients to master methods of venting negative emotions and relaxation techniques, such as guiding patients to accept their own illnesses and teaching them correct abdominal breathing, or meditation, imagining a better life after returning to society with improved health.

Maintaining the safety of both parties: **Environmental safety:** Enrich clinic facilities, maintain a quiet state in the consultation room, improve patient comfort, minimize agitation during patient visits, avoid potential hazards in the consultation room, such as flammable and explosive materials, sharp objects, etc., install anti-collision soft packs and anti-slip floors in the consultation room to reduce the harm of accidents, and scientifically plan the consultation space to reduce patient behavioral obstacles. **Team atmosphere:** Healthcare workers should support each other, take consistent action when patients exhibit violent behavior, and create a sense of awe in patients to reduce violent behavior in clinics. Additionally, the consultation room should be equipped with multiple staff members, such as nursing assistants and security guards, to facilitate emergency response. **Level of violence:** Based on the BVC score, analyze whether to take coercive measures against mentally ill patients, avoid excessive restraint, and if the patient's emotions are stable, the restraints can be removed, and their emotions can be appropriately comforted.

2.4. Observation indicators and statistical analysis of violence risk in patients with mental disorders

2.4.1. Observation indicators

Violent behavior: Record instances of patients with mental disorders engaging in unarmed confrontation with

individuals or objects.

Violence risk indicator: Document the BVC score, and categorize patients into low, medium, and high risk levels based on their scores.

2.4.2. Statistical analysis

Data was processed using SPSS 25.0. Enumeration data was tested using the χ^2 test (% recorded), and measurement data was analyzed using the t -test (Mean \pm SD recorded). Significant differences were observed at $P < 0.05$.

3. Results

3.1. Incidence of violent behavior

The incidence of violent behavior in the study group was lower than that in the control group, but there was no significant difference ($P > 0.05$). The details are shown in **Table 2**.

Table 2. Comparison of violent behavior incidence (n,%)

Group	Violent behavior occurrence	No violent behavior
Study group ($n=107$)	4 (3.74)	103 (96.26)
Control group ($n=107$)	10 (9.35)	97 (90.65)
χ^2	2.7514	
P	0.0972	

3.2. Violence risk rate

There was no difference in BVC risk rates between the study group before intervention and the control group ($P > 0.05$). However, the BVC risk rate in the study group after intervention was lower than that in the control group ($P < 0.05$) and lower than that in the study group before intervention ($P < 0.05$). The details are shown in **Table 3**.

Table 3. Comparison of violence risk rates (n,%)

Group	Low risk (0)	Medium risk (1–2)	High risk (3–6)
Control group ($n=107$)	21 (19.63)	53 (49.53)	33 (30.84)
Study group pre-intervention ($n=107$)	27 (25.23)	48 (44.86)	32 (29.91)
Study group post-intervention ($n=107$)	51 (19.63)	56 (52.34)	0 (0.00)
χ^2/P (Study group post-intervention)	0.9669/0.3255	0.4688/0.4936	0.0221/0.8818
χ^2/P (Control vs. post-intervention)	18.8380/0.0000	0.1683/0.6816	39.0166/0.0000
χ^2/P (Pre- vs. post-intervention)	11.6199/0.0007	1.1972/0.2739	37.6264/0.0000

4. Discussion

Patients with mental disorders are highly prone to violent behavior and often have poor physical and mental health status, making them a marginalized group among the healthy population ^[3–4]. During diagnosis and treatment, if

they receive coercive medical intervention, they are more likely to engage in impulsive destruction of property or violent harm to medical staff. Therefore, effective management measures should be implemented for these patients. Conventional interventions rely on the experience of medical staff and often yield unsatisfactory results in managing violent behavior. De-escalation techniques, as a modern and novel management strategy, include modules such as risk assessment, communication, self-regulation, and maintaining the safety of both parties. These techniques guide patients to reasonably vent their emotions and can reduce violent incidents ^[5-6].

The data presented in this paper suggest that the incidence of violent attacks in the study group was lower than that in the control group, although there was no significant difference ($P > 0.05$). This could be attributed to the effective implementation of de-escalation techniques, which include risk assessment using the BVC to assess patients' violence risk levels and implement appropriate management measures to contain violent incidents in their infancy stage. The communication module requires medical staff to maintain a distance of over 1 m from patients, avoiding resistance to medical treatment, and inquiring about patients' actual needs in a tactful manner. By analyzing the causes of violent incidents and exploring solutions from the patients' perspective, the communication module helps patients feel respected. The self-regulation module teaches patients relaxation and anger management techniques, and interventions such as meditation, education, and abdominal breathing enable patients to view their illnesses more positively, thereby reducing violent incidents. The module for maintaining the safety of both parties focuses on improving the comfort of the medical environment to prevent patients' excessive behavior and negative emotions, further reducing the risk of violent incidents ^[7-8]. Another set of data presented in this paper indicates that the BVC risk rate in the study group after intervention was lower than that before intervention ($P < 0.05$). This suggests that the BVC can predict the risk of violent incidents in patients with mental disorders within the next 24 hours. By identifying high-risk patients and promptly implementing protective isolation measures, coupled with de-escalation techniques to soothe patients' emotions, the BVC score can be reduced ^[9]. The standardized application of the BVC during de-escalation intervention effectively manages violent behavior and provides a basis for subsequent patient treatment ^[10].

5. Conclusion

In summary, the implementation of de-escalation techniques for patients with mental disorders can reduce the risk of violent behavior and decrease its incidence, making it worthy of promotion.

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Disclosure statement

The authors declare no conflict of interest.

References

- [1] Luo GQ, Feng ZM, 2024, The Effect of Emotional Control Intervention on Improving Violent Behavior in Male Patients with Mental Disorders. Chinese Scientific and Technological Journal Database (Citation Edition) Medicine

and Health, 2024(12): 21–24.

- [2] Xu SH, Gao ZX, Xu BX, 1993, Practice of Classification and Diagnostic Criteria of Mental Disorders in China. Chinese Journal of Neurology and Psychiatry, 19(1): 59–60.
- [3] Peng AQ, Wang L, Zhang Y, 2022, Application of Violence De-escalation Skills Training Based on the Violence De-escalation Technology Model in Psychiatry. Modern Nurse (Late Edition), 29(8): 155–159.
- [4] Xiang L, Lin CQ, Lu WY, et al., 2023, Observation on the Application Effect of the Chinese Version of the Broset Violence Risk Assessment in Receiving Stray Patients with Mental Disorders. Frontiers in Medicine, 13(5): 10–12.
- [5] Guo J, Wang Y, 2024, Application of Graded Intervention Based on Violence Risk Assessment Combined with Cognitive Behavioral Therapy in Patients with Mental Disorders. Nursing of Integrated Traditional Chinese and Western Medicine (Chinese and English), 10(8): 112–114.
- [6] Pan ZJ, Li SR, Shi CX, 2019, Validity and reliability of the Chinese version of the Broset Violence Risk Assessment Scale for Evaluating Severe Mental Disorders in Children and Adolescents. Chinese Journal of Mental Health, 33(8): 618–622.
- [7] Yang QH, Xiao Y, Liao YN, et al., 2019, Analysis of the Application Effect of the Chinese Version of the Attack Risk Screening Scale in Community Patients with Mental Disorders. Chinese Journal of Modern Nursing, 25(15): 1909–1913.
- [8] Liu Q, Li XL, 2024, A Retrospective Study on the Effects of Risk Assessment and Targeted Nursing on the Psychological State and Incidence of Violent Events in Hospitalized Patients with Mental Disorders. Guide of China Medicine, 22(10): 146–148.
- [9] Xiang F, Zheng SF, Feng MM, et al., 2023, Analysis of the Effect of Applying Violence Skills Training to Improve the Violence Prevention and Response Ability of Psychiatric Nurses. Medical Theory and Practice, 36(3): 532–534.
- [10] Zhao P, Gao LN, Li J, et al., 2023, Application Effect of Standard Violence Handling Operating Procedures in Patients with Violent Behavior in Psychiatric Hospital Outpatient Clinics. Chinese Community Doctors, 39(19): 135–137.

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Comparative Study on the Post-treatment Stability of Impacted Wisdom Tooth Extraction and Non-extraction Orthodontics in Different Age Groups

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Abstract: *Objective:* To analyze the post-treatment stability of impacted wisdom tooth extraction and non-extraction orthodontics in different age groups. *Methods:* 83 patients undergoing orthodontic treatment in the hospital from January 2021 to June 2024 were selected as the study subjects. All patients received orthodontic treatment with the straight wire appliance technique. They were divided into groups according to whether they received a tooth extraction. The control group ($n=39$) did not undergo impacted tooth extraction, while the observation group ($n=44$) underwent impacted tooth extraction. The PAR index, changes in inflammatory response factors PGE2, IL-6, and TNF- α , and the incidence of complications were compared between the two groups. *Results:* Before treatment, there was no difference in the PAR index between the two groups ($P>0.05$). However, after nearly 2.5 years of follow-up orthodontic treatment, there was a significant difference ($P<0.05$), with the observation group having a lower PAR index than the control group. Before treatment, $P>0.05$ for both groups. Within 7 days after tooth extraction, the levels of PGE2, IL-6, and TNF- α in the observation group were significantly higher than those in the control group, with a statistically significant difference ($P<0.05$). After nearly 2.5 years of follow-up treatment, the incidence of complications was found to be lower in the observation group. *Conclusion:* For patients with impacted wisdom teeth, orthodontic treatment after tooth extraction can maintain the teeth in normal dentition, adjust the relationship between the upper and lower jaws, improve occlusion function, and reduce the rebound phenomenon and complications after orthodontic surgery.

Keywords: Impacted wisdom tooth extraction; Non-extraction of impacted wisdom teeth; Inflammatory response; Post-orthodontic stability; Complications

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1. Introduction

Impacted wisdom teeth refer to the last molars in the mouth, which are partially or completely covered by gums due to obstruction from adjacent teeth, jaws, and soft tissues. The lower third molars are the most common ^[1].

Impacted wisdom teeth can cause many problems, such as pericoronitis, marginal osteomyelitis of the jaw, caries damage to the impacted wisdom teeth and adjacent teeth, and even the formation of cysts or tumors, which can lead to occlusal deformities in the mouth. Currently, whether the presence and eruption of third molars affect the formation of malocclusion and the recurrence after orthodontic treatment is a focus of attention in the orthodontic field. In orthodontic treatment, doctors usually need to make comprehensive judgments based on the specific conditions of patients and consider the management of third molars from the perspective of what is most beneficial to the patients^[2]. Tooth extraction can effectively avoid various symptoms and complications caused by impacted wisdom teeth. For certain orthodontic patients, extracting impacted wisdom teeth is the best choice^[3]. However, non-extraction orthodontic treatment methods also have their rationality. Among them, although tooth extraction is effective, it may also bring complications, such as bleeding, swelling, pain, fear, infection, and dry socket problems that may occur after the procedure. In addition, the choice of extraction or non-extraction of impacted wisdom teeth also affects the stability of orthodontic treatment. In this study, 83 patients undergoing orthodontic treatment in our hospital from January 2021 to June 2024 were selected as the study subjects to analyze the post-treatment effects of impacted wisdom tooth extraction and non-extraction on orthodontic patients. The report is as follows.

2. Materials and methods

2.1. General information

Eighty-three patients undergoing orthodontic treatment in the hospital from January 2021 to June 2024 were selected as study subjects. All patients received the straight-wire appliance technique for orthodontic treatment. They were grouped based on whether they underwent tooth extraction. The control group ($n=39$) consisted of patients aged 15–23 years, with a mean age of 19.47 ± 1.92 years, and a male-to-female ratio of 21:18. The observation group ($n=44$) consisted of patients aged 14–24 years, with a mean age of 20.32 ± 1.96 years, and a male-to-female ratio of 24:20. There were no significant differences in general information between the two groups ($P>0.05$).

2.2. Methods

The observation group underwent orthodontic treatment with the extraction of impacted wisdom teeth. The specific steps were as follows: ensuring the patient's comfort and central position, using a non-invasive technique, applying a high-speed handpiece, extraction burs, elevators, forceps, and ultrasonic bone scalpels, and slowly extracting the teeth in the direction of the long axis of the tooth through elevation, forceps extraction, or sectioning with a high-speed handpiece (ultrasonic bone scalpel). During the extraction process, the goals were to minimize operative time and trauma, and to avoid fracture of the extraction socket and tooth roots. After extraction, an oral cleanser was used for local cleaning. Once the wound healed, a specific and reasonable orthodontic treatment plan was developed based on the patient's age, gender, relationship between the upper and lower jaws, relationship between facial features and facial shape, and the condition of the dentin and alveolar bone.

The control group underwent orthodontic treatment while preserving the impacted wisdom teeth. The specific steps were as follows: directly developing a reasonable orthodontic treatment plan based on the patient's age, gender, relationship between the upper and lower jaws, relationship between facial features and facial shape, and the condition of the impacted wisdom teeth and adjacent teeth, as well as the alveolar bone. Fixed orthodontic appliances were used to move the teeth, improving tooth alignment and occlusion. During the orthodontic process,

patients received painless treatment, regular follow-up and adjustments, and regular cleaning and disinfection of the impacted wisdom teeth in their oral cavity.

2.3. Evaluation indices and criteria

(1) The PAR index before and after treatment was compared, including measurements of tooth malposition, posterior occlusion, midline, overjet, and overbite, with scores ranging from 0 to 6. Higher scores indicated more severe dental deformities ^[4]. (2) Inflammatory markers, including prostaglandin E2 (PGE2), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) concentrations, were compared before and after treatment to evaluate the patient's postoperative physical response and recovery. (3) Complications were compared between the two groups, including dry socket, pericoronitis, caries of impacted wisdom teeth or adjacent teeth, and recurrence of crowded or maloccluded dentition.

2.4. Statistical methods

Statistical analysis was performed using SPSS 22.0 software. Measurement data were expressed as mean and standard deviation (Mean \pm SD). Count data were analyzed using the chi-square test and expressed as percentages (%). A *P*-value less than 0.05 indicated a statistically significant difference between the two groups.

3. Results

3.1. Comparison of the PAR index before and after orthodontic treatment with wisdom tooth extraction

There was no difference in the PAR index between the two groups before treatment (*P*>0.05). However, after approximately 2.5 years of follow-up orthodontic treatment, there was a significant difference (*P*<0.05), with the observation group having a lower PAR index than the control group. The details are shown in **Table 1**.

Table 1. Compares the PAR index after treatment

Group	Anterior teeth alignment		Posterior teeth alignment		Posterior occlusion		Overjet		Midline		Overbite	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control Group (n=39)	4.86 \pm 3.22	0.63 \pm 0.25	5.20 \pm 1.26	2.10 \pm 0.19	4.76 \pm 1.10	1.52 \pm 0.22	3.44 \pm 1.20	0.39 \pm 0.14	3.81 \pm 1.26	1.22 \pm 0.25	4.06 \pm 1.11	1.08 \pm 0.25
Observation Group (n=44)	4.63 \pm 2.15	0.31 \pm 0.14	5.31 \pm 1.08	0.93 \pm 0.15	4.81 \pm 1.18	1.43 \pm 0.15	3.52 \pm 1.34	0.20 \pm 0.05	3.84 \pm 1.03	0.63 \pm 0.14	4.12 \pm 1.19	0.82 \pm 0.41
<i>t</i>	0.387	7.300	0.428	31.304	0.199	2.198	0.285	8.422	0.119	13.460	0.237	3.433
<i>P</i>	0.700	0.001	0.670	0.001	0.843	0.031	0.776	0.001	0.905	0.001	0.814	0.001

3.2. Comparison of inflammatory factors before and after extraction of impacted wisdom teeth

Before treatment, the *P* value for both groups was >0.05. Within 7 days after tooth extraction, the levels of PGE2, IL6, and TNF α in the control group were significantly lower than those in the observation group, with a statistically significant difference (*P* < 0.05). The details are shown in **Table 2**.

Table 2. Comparison of inflammatory factors (\pm s)

Group	PGE2 (pg/mL)		IL-6 (μ g/L)		TNF- α (μ g/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group ($n=39$)	76.42 \pm 5.47	112.63 \pm 9.74	1.27 \pm 0.21	5.78 \pm 0.64	2.49 \pm 0.43	5.12 \pm 1.01
Observation group ($n=44$)	75.73 \pm 5.35	148.77 \pm 10.32	1.31 \pm 0.22	8.63 \pm 0.79	2.52 \pm 0.41	10.55 \pm 1.73
t	0.580	16.378	0.845	17.911	0.325	17.172
P	0.563	<0.001	0.401	<0.001	0.746	<0.001

3.3. Comparison of complication rates

In terms of the incidence of complications after the extraction of impacted wisdom teeth for orthodontic purposes, after nearly 2.5 years of follow-up observation, it was found that the observation group was significantly better than the control group, with a statistically significant difference ($P < 0.05$). The details are shown in **Table 3**.

Table 3. Comparison of complications (n/%)

Group	Dry socket (Cases)	Pericoronitis (Cases)	Impacted wisdom teeth and adjacent caries (Cases)	Recurrent crowding/malalignment (Cases)	Total incidence (%)
Control group ($n=39$)	0 (0.00)	7 (17.95)	5 (12.82)	5 (12.82)	17 (43.59)
Observation group ($n=44$)	3 (6.82)	1 (2.27)	0 (0.00)	0 (0.00)	4 (9.09)
χ^2	-	-	-	-	13.019
P	-	-	-	-	<0.001

4. Discussion

The third molar is the tooth with the highest impaction rate in the dentition among impacted wisdom teeth, and the impaction rate varies among different populations. There are many factors that can cause third molar impaction, mainly related to insufficient eruption space and excessively oblique eruption angles ^[5]. When the third molar is impacted, food debris can easily get trapped locally, causing a large accumulation of plaque. If the factors causing impaction persist, it can lead to pericoronitis of the wisdom tooth and decay of the tooth itself and adjacent teeth, and even cause temporomandibular joint pain. Studies have shown that when the third molar erupts, it exerts a forward thrust, which aggravates the crowding of the anterior segment of the dental arch, thereby affecting the maintenance of orthodontic alignment after treatment ^[6]. Given the harms caused by impacted wisdom teeth, some scholars believe that early extraction of the third molars is advisable, while another viewpoint favors keeping the third molars for future orthodontic treatment or restoration. For some orthodontic patients who have already had four premolar teeth extracted, keeping the third molars can avoid the psychological impact of having eight teeth extracted ^[7]. In this study, the authors analyzed the effects of orthodontic treatment with and without the extraction of impacted wisdom teeth on orthodontic patients.

The PAR index, developed at the British Orthodontic Standards Working Conference in 1987, is an index used to record occlusal features. It is an objective indicator that can effectively evaluate the occlusal index and has been widely used domestically and internationally. It can effectively reflect the situation after successful treatment

and can effectively evaluate the degree of improvement and treatment methods for different types of malocclusions. Therefore, it is suitable for evaluating the results of all types of occlusions, treatment methods, and cases with and without tooth extraction^[8-9]. Specifically, the PAR index can assess the overall effectiveness of treatment, including changes in tooth position, adjustment of jaw relationships, improvement in occlusal function, and evaluation of aesthetic effects. Thus, the PAR index is not only used to evaluate treatment effectiveness but also to assess treatment stability, providing an important reference for clinical orthodontic treatment^[10-11]. In this study, by observing the PAR index before and after treatment in the observation and control groups, it was found that the observation group had a significantly lower PAR index than the control group after treatment. This data effectively reflects that orthodontic treatment after the extraction of impacted teeth can effectively improve the occlusal relationship of orthodontic patients, bringing their dental indices closer to normal values. Conversely, in the control group, due to the forward thrust caused by the impacted wisdom teeth, the anterior segment of the dental arch becomes crowded, resulting in insignificant improvement in occlusion after orthodontic treatment. Therefore, the improvement effect is lower than that of the observation group. Simultaneously, this reflects the better stability of the observation group after treatment. This article also compares the level of decay in the wisdom teeth themselves and adjacent teeth before and after orthodontic treatment with and without the extraction of impacted wisdom teeth. The results suggest that the observation group had a lower decay level after extraction treatment compared to the control group.

By comparing the frequency of complications between the two groups, it was observed that the observation group had a significant reduction in the occurrence of pericoronitis, decay of impacted wisdom teeth and adjacent teeth, and recurrence of crowded and misaligned dentition. This suggests that after tooth extraction, the stability of orthodontic treatment in the observation group was better. The reason for this is that although patients in the control group did not experience the pain associated with tooth extraction, some of them experienced a rebound effect of crowded and misaligned teeth after the completion of orthodontic treatment, when the impacted wisdom teeth continued to erupt or partially erupt, exerting a forward thrust. This resulted in poor stability of tooth alignment, and some patients who had undergone orthodontic treatment may require additional treatment. However, patients in the observation group who underwent tooth extraction experienced minimal rebound effects after the completion of orthodontic treatment, particularly in the lower anterior teeth region, where there was almost no recurrence of crowding and misalignment. Therefore, the risk of pericoronitis and decay of wisdom teeth and adjacent teeth was significantly reduced^[12]. Simultaneously, this phenomenon further demonstrates the positive and profound impact of tooth extraction on the overall effectiveness of orthodontic treatment. By reducing the risk of rebound effects, it enhances the long-term stability of teeth after orthodontic surgery, reduces treatment uncertainties and potential complications, and brings greater benefits to patients' oral health. Additionally, when observing the levels of inflammatory factors after treatment in both groups, the results showed no significant difference in PGE2, IL6, and TNF α levels between the observation group and the control group before treatment. However, after tooth extraction treatment, the levels of PGE2, IL6, and TNF α were higher in the observation group compared to the control group, especially for PGE2 and TNF α , which showed a more significant increase. This suggests that the inflammatory response increases after the extraction of impacted wisdom teeth, affecting the levels of inflammatory factors. This not only increases the risk of dry socket syndrome in some patients but also increases fear and anxiety, leading some patients to choose orthodontic treatment without tooth extraction.

5. Conclusion

In summary, the impact of orthodontic treatment with and without the extraction of impacted wisdom teeth

is significant for patients. Therefore, it is essential to conduct comprehensive preoperative assessments and accurately diagnose the condition. When the treating physician identifies adverse factors related to impacted wisdom teeth that may affect the postoperative recovery process after orthodontic treatment, early extraction of the affected teeth should be performed to avoid any negative impact on the recovery of the teeth after the completion of orthodontic treatment.

Disclosure statement

The author declares no conflict of interest.

References

- [1] Mu MK, Lu XL, Zhan W, et al., 2008, Evaluation of the Orthodontic Effect of Extraction and Non-Extraction Treatment for Angle's Class III Malocclusion Using the PAR Index. *Journal of Harbin Medical University*, 42(2): 174–175 + 178.
- [2] Zou H, Peng YJ, 2024, Comparison of Clinical Efficacy between Invisalign Appliance and Damon Q Self-Ligating Bracket in Non-Extraction Treatment of Dental Crowding. *Chinese Journal of Aesthetic Medicine*, 33(1): 125–129.
- [3] Zhou XR, Yang QQ, Feng H, et al., 2022, Study on the Effect of Invisalign Appliance in Non-Extraction Treatment of Dentition Defect with Malocclusion. *Chinese Journal of Aesthetic Medicine*, 31(12): 153–156.
- [4] Lai SY, Hou JX, 2020, Progress in the Application of Alveolar Ridge Preservation at Extraction Sites of Non-Periodontal and Periodontal Teeth. *Chinese Journal of Stomatology*, 55(4): 266–270.
- [5] Chai A, Lei RC, Jiang ZS, et al., 2023, Overview of Methods for Assessing the Difficulty of Extracting Mandibular Third Molars. *International Journal of Stomatology*, 50(6): 718–722.
- [6] Liu JY, Liu C, Pan J, et al., 2021, Application of Distal Triangular Flap in the Extraction of Impacted Mandibular Third Molars. *West China Journal of Stomatology*, 39(5): 598–604.
- [7] Li TT, Wang CF, Cai Y, et al., 2024, Study on the Effect of Residual Dental Follicle after Extraction of Impacted Mandibular Third Molars on the Periodontal Health of Adjacent Teeth. *Chinese Journal of Stomatology*, 59(8): 784–790.
- [8] Xing JH, Chen H, Chen M, et al., 2023, Study on Tooth Drift after Orthodontic Treatment Interruption Following Tooth Extraction. *Journal of Prevention and Treatment of Stomatological Diseases*, 31(10): 727–732.
- [9] Liu L, Dong T, Yuan LJ, et al., 2019, Preliminary Morphological Study of the Temporomandibular Joint before and after Orthodontic Tooth Extraction. *Chinese Journal of Orthodontics*, 26(4): 209–214.
- [10] Ouyang D, Hu DS, Yang JX, et al., 2021, Study on the Efficacy of Orthodontic Treatment Combined with Implant Anchorage for Dental Deformities and its Impact on the PAR Index. *People's Military Surgeon*, 64(4): 352–355.
- [11] Wang YN, Chang L, Liu HY, 2016, Analysis of Influencing Factors in Evaluating the Orthodontic Treatment Effect of 80 Patients Using the PAR Index. *Journal of Practical Stomatology*, 32(2): 263–267.
- [12] Li XR, Chen B, Li M, et al., 2023, Preliminary Application of PAR Index Combined with Cephalometric Measurement in Evaluating the Efficacy of Skeletal Class III Malocclusion. *Shanghai Journal of Stomatology*, 32(4): 417–421.

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A Real-world Study of the Adverse Effects of Tizanidine Based on Mining the FAERS Database

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Abstract: *Objective:* Tizanidine is a medication commonly used to relieve muscle spasms and has a wide range of clinical applications. However, as its use has increased, reports of related adverse reactions have also risen. In-depth analysis of tizanidine's adverse reaction patterns and potential safety risks through data mining is of great significance for guiding clinical decision-making and patient management. *Methods:* This study is based on the FAERS database, retrieving data from 2004 Q1 to 2025 Q1. The primary suspect drug was grouped, and the proportional imbalance method (ROR method) was used for signal detection of adverse drug events. *Results:* The adverse reactions of tizanidine are diverse and involve multiple systems, with nervous system diseases being the most common type of adverse event, accounting for 16.18% of the total reports. The proportion of adverse events reported by female and elderly patients is relatively high, and in terms of the outcome of adverse events, the proportion of hospitalizations is high, accounting for 30.31%, indicating a significant likelihood that tizanidine's adverse events require hospitalization. Additionally, hypotension, drowsiness, drug ineffectiveness, and completed suicide are common adverse events, suggesting that the medication can cause significant central nervous system, cardiovascular, and mental health-related issues during its use. Signal mining using the ROR method shows high ROR values for adverse events such as potassium-losing nephropathy and decerebrate rigidity, indicating a potential causal relationship with tizanidine usage. Furthermore, the median time to the occurrence of adverse events after administration is 3 days, revealing that tizanidine-related adverse events often manifest shortly after administration, particularly within the first few days. *Conclusion:* The potential adverse reactions of tizanidine in clinical use, particularly those related to the nervous system, mental health, and cardiovascular aspects, warrant significant attention. Enhanced drug safety monitoring, especially individualized treatment and close monitoring in high-risk patient groups, can maximize the safety of medication use.

Keywords: Tizanidine; FAERS; Adverse reactions; Signal mining; ROR

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1. Background

Tizanidine is an α_2 adrenergic receptor agonist widely used clinically to alleviate skeletal muscle spasms and other symptoms^[1]. With the expansion of its clinical application and the increasing number of users, reports of its adverse events have gradually attracted attention^[2]. Although traditional clinical trials can reveal adverse reactions to the drug to a certain extent, they may not fully cover the adverse reactions of the drug in the real world due to the strict control of the trial environment, relatively limited sample sizes, and shorter study periods. The FAERS database, as an important source of real-world data, collects a large number of spontaneous reports on adverse drug events, with advantages such as large sample sizes and diverse populations. In the context of real-world research, a systematic analysis of tizanidine adverse event data in the FAERS database is expected to supplement and improve the existing understanding of the drug's safety. This can provide valuable data support for subsequent drug development improvements and updates to clinical medication guidelines, thereby promoting the in-depth development of pharmacoepidemiology and drug safety research, and ensuring the safety of medication for patients.

2. Data processing and statistical methods

2.1. Data source

The raw data were downloaded from the FAERS database on the official FDA website (<https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>). The data retrieval range for this study spans from 2004 Q1 to 2025 Q1.

2.2. Target drug

The drug of interest is identified by searching for `BaseName_EN="TIZANIDINE"`.

2.3. Target population

Patients in the database whose primary suspected drug is the target drug are included in the target drug population, while other patients are included in the other drug population.

2.4. Data

Processing and analysis duplicates were removed according to the FDA's recommended de-duplication method. Statistical analysis was conducted using SAS 9.4.

2.5. Signal detection methods and calculation

The proportional reporting ratio (PRR) method was used for signal detection of adverse drug events. The reporting odds ratio (ROR) method was employed to detect adverse event signals.

3. Results

3.1. Basic characteristics of adverse event reports

Table 1 shows that reports from female patients accounted for 62.60% (1389 cases) of the total, males accounted for 27.36% (595 cases), and reports with unspecified gender accounted for 10.04% (218 cases), indicating room for improvement in data collection and reporting. In terms of age distribution, reports for patients under 18 years old

were few, comprising only 2.86% (67 cases). Reports from patients aged 18–64 were more numerous, with those aged 18–44 accounting for 19.25% (427 cases) and those aged 45–64 accounting for 29.34% (651 cases). Reports from patients aged 65 and above accounted for 14.40% (330 cases), but a significant proportion of reports (33.78%) had unspecified age (690 cases). From the perspective of the report year, the number of adverse event reports for Tizanidine has fluctuated annually since 2004, peaking in 2019 with 7.80% (167 cases) and followed closely by 2018 with 7.74% (166 cases). There has been a noticeable increase in reports since 2010, indicating the ongoing importance and continuity of monitoring this drug. Regarding the identity of reporters, consumers (Consumer) submitted the most reports, accounting for 31.55% (699 cases). This was followed by other health professionals (Other health professional) at 14.70% (326 cases), pharmacists (Pharmacist) at 21.70% (481 cases), and physicians (Physician) at 22.53% (483 cases). In terms of adverse event outcomes, hospitalization (Hospitalization: Initial or Prolonged) had a high proportion at 30.31% (658 cases), indicating a significant likelihood of requiring hospital treatment for adverse events related to Tizanidine. Life-threatening events (Life-threatening) were reported in 6.13% (133 cases), death in 1.40% (30 cases), and disability (Disability) in 2.32% (78 cases), reflecting the severity of certain adverse events.

Table 1. Characteristics of AEs reports

Characteristics	Case (%)
Sex	
Female (%)	1359 (62.60)
Male (%)	594 (27.36)
Not specified (%)	218 (10.04)
Age	
<18 (%)	62 (2.86)
18-44 (%)	426 (19.62)
45-64 (%)	637 (29.34)
≥65 (%)	356 (16.40)
Not specified (%)	690 (31.78)
Report year	
2004 (%)	105 (4.84)
2005 (%)	75 (3.45)
2006 (%)	53 (2.44)
2007 (%)	46 (2.12)
2008 (%)	54 (2.49)
2009 (%)	83 (3.82)
2010 (%)	80 (3.68)
2011 (%)	74 (3.41)
2012 (%)	57 (2.63)
2013 (%)	56 (2.58)
2014 (%)	103 (4.74)

Table 1 (Continued)

Characteristics	Case (%)
2015 (%)	131 (6.03)
2016 (%)	165 (7.60)
2017 (%)	103 (4.74)
2018 (%)	166 (7.65)
2019 (%)	125 (5.76)
2020 (%)	113 (5.20)
2021 (%)	150 (6.91)
2022 (%)	126 (5.80)
2023 (%)	113 (5.20)
2024 (%)	134 (6.17)
2025 (%)	59 (2.72)
Reporter	
Consumer (%)	685 (31.55)
Lawyer (%)	2 (0.09)
Not specified (%)	222 (10.23)
Other health professional (%)	308 (14.19)
Pharmacist (%)	471 (21.70)
Physician (%)	483 (22.25)
outcome	
Life-Threatening (%)	133 (6.13)
Hospitalization: Initial or prolonged (%)	658 (30.31)
Disability (%)	72 (3.32)
Death (%)	304 (14.00)
Congenital anomaly (%)	3 (0.14)
Required intervention to prevent permanent impairment/damage (%)	31 (1.43)
Other (%)	879 (40.49)

3.2. Proportion of adverse events by system organ class

As shown in **Figure 1**, nervous system disorders are the most common tizanidine-related adverse events, accounting for 16.18% (1417 cases) of the total reports. Special attention should be paid to related symptoms such as dizziness and drowsiness. General disorders and administration site conditions are the second most common category, accounting for 14.46% (1267 cases). Reports related to psychiatric disorders account for 12.28% (1076 cases), including hallucinations and depression. Adverse events related to investigations account for 8.32% (729 cases), suggesting that frequent health monitoring and laboratory tests may be necessary during the use of this medication. Injury, poisoning, and procedural complications account for 7.79% (682 cases), indicating that tizanidine may increase the risk of injury or poisoning complications, necessitating enhanced prevention and

monitoring. Gastrointestinal adverse events account for 6.31% (553 cases), showing that the use of tizanidine may cause gastrointestinal discomfort such as nausea and vomiting. Cardiac disorders-related adverse events account for 5.51% (483 cases), indicating that attention should be given to the drug's impact on the cardiovascular system, such as arrhythmias. Other relatively common adverse reactions include vascular disorders (4.59%, 402 cases), musculoskeletal and connective tissue disorders (4.34%, 380 cases), and respiratory disorders (3.04%, 266 cases). Less common adverse event categories include skin and subcutaneous tissue disorders (2.98%, 261 cases), renal and urinary disorders (1.87%, 164 cases), and eye disorders (1.82%, 159 cases). Although these events are less frequently reported, they still require attention. Even rarer adverse reactions, such as blood and lymphatic system disorders, ear and labyrinth disorders, and endocrine disorders, have fewer reports but should not be overlooked.

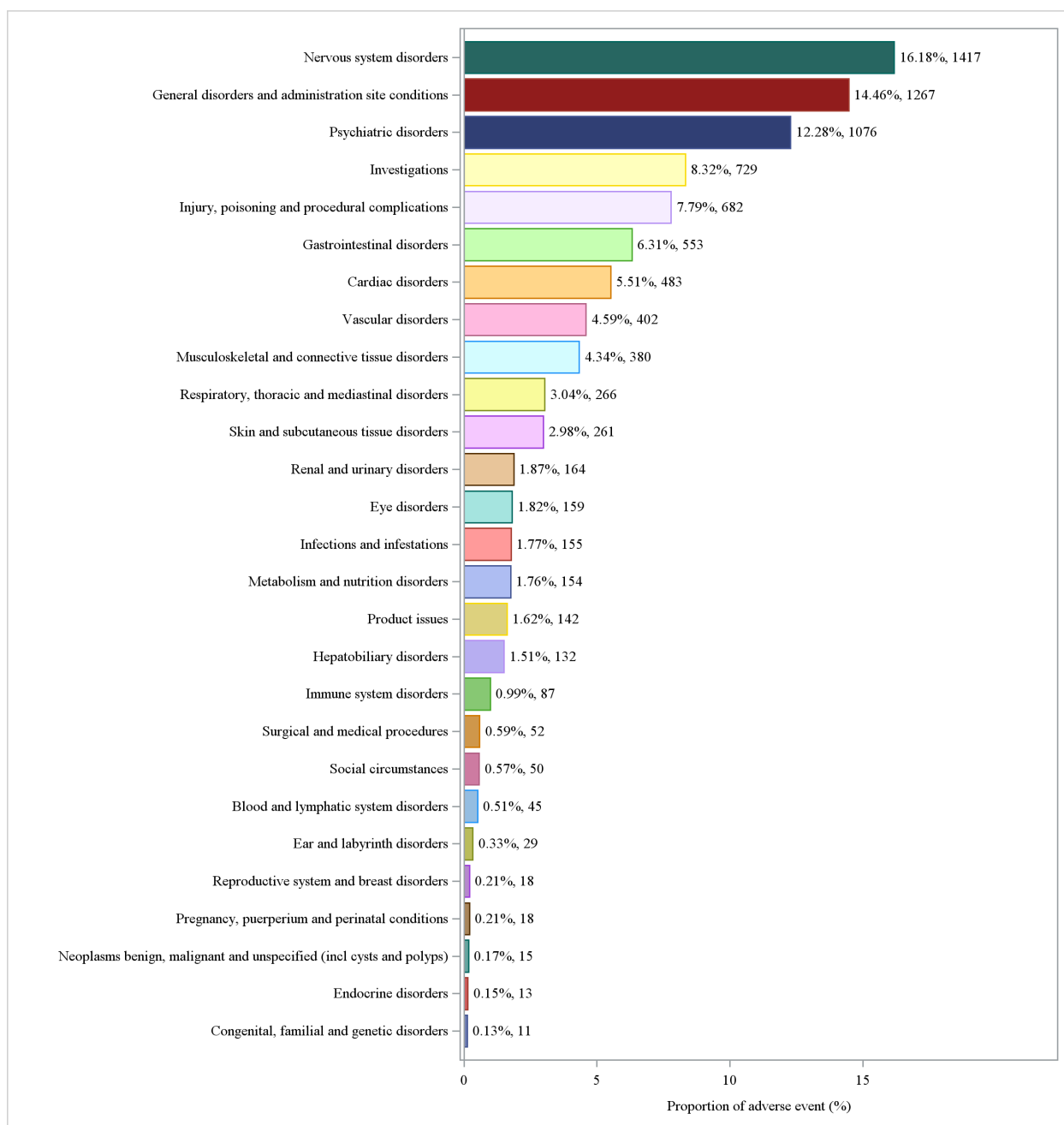


Figure 1. Proportion of adverse events by SOC's

3.3. Proportion of adverse events categorized by preferred terms

Figure 2 shows that hypotension is the most common adverse event, accounting for 2.31% (202 cases); somnolence accounts for 2.15% (188 cases); reports of drug ineffectiveness account for 2.09% (183 cases), indicating that some patients failed to achieve the expected therapeutic effect with tizanidine; reports of completed suicide account for 1.83% (160 cases), suggesting a potential association between the drug and suicide risk; dizziness accounts for 1.72% (151 cases); drug interaction accounts for 1.58% (138 cases), indicating that the concomitant use of tizanidine with other drugs may increase the risk of adverse events. Nausea accounts for 1.23% (108 cases), bradycardia for 1.13% (99 cases), reports of overdose for 1.02% (89 cases), and vomiting for 1.02% (89 cases). Other relatively common adverse events include hallucination (0.88%, 77 cases), toxicity to various agents (0.88%, 77 cases), confusional state (0.84%, 74 cases), and fatigue (0.84%, 74 cases). These symptoms further illustrate the effects of tizanidine on the central nervous system and its comprehensive reactions. Relatively less common but noteworthy adverse events include muscle spasms (0.80%, 70 cases), intentional overdose (0.80%, 70 cases), and pain (0.80%, 70 cases).

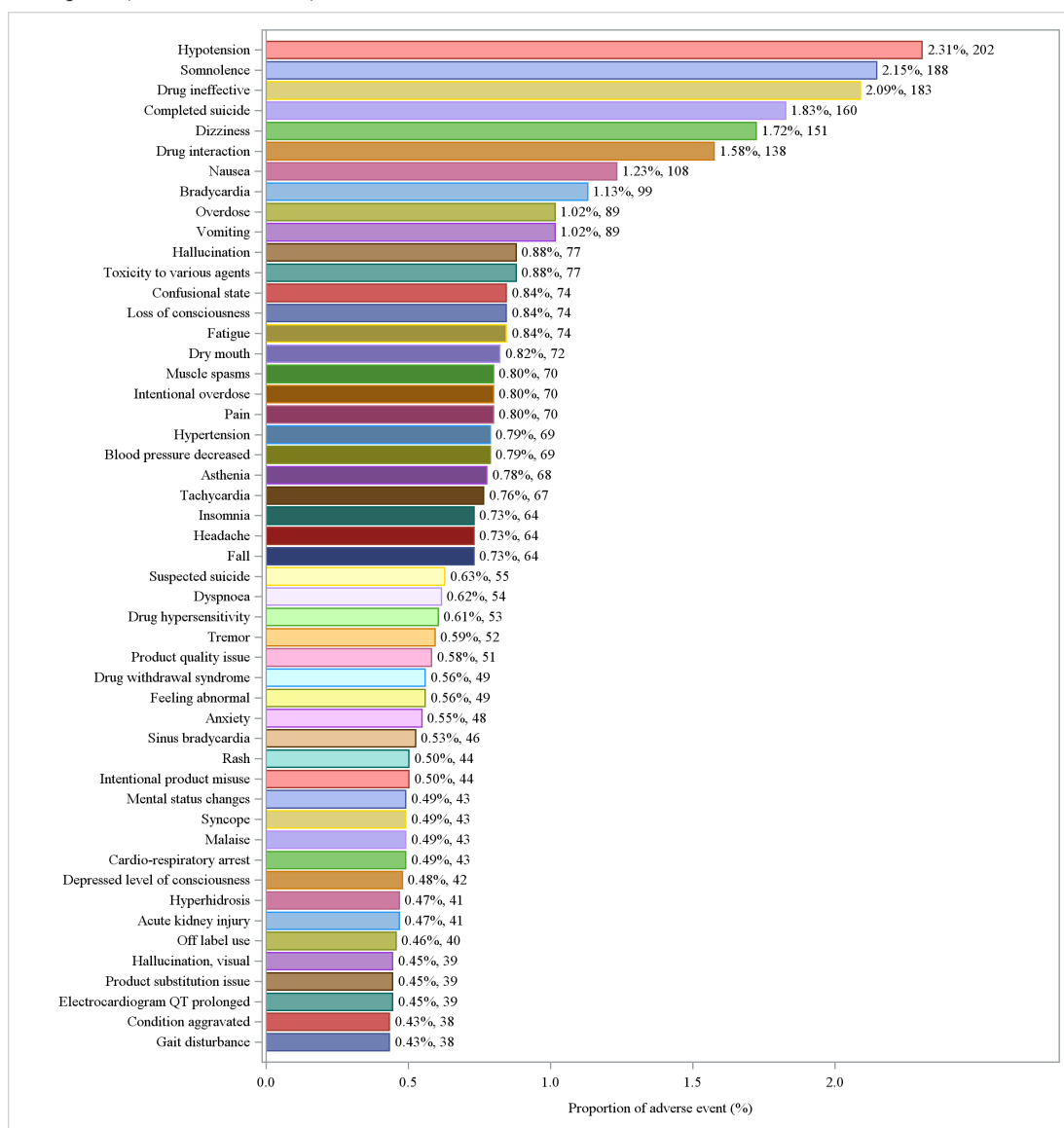


Figure 2. Proportion of adverse events by PTs

3.4. Forest plot of ROR signal strength

A higher ROR value indicates a stronger association between a specific drug and an adverse event. A higher ROR value suggests that this adverse event is more common in patients using the drug and implies a possible causal relationship. **Figure 3** shows that the ROR value for Potassium Wasting Nephropathy is 2396.32 (95% CI: 1349.30–4255.81), suggesting that tizanidine use may significantly increase the risk of kidney-related issues. The ROR value for Decorticate Posture is 454.89 (95% CI: 211.29–979.36); for Electrocardiogram U-wave Abnormality, the ROR value is 273.67 (95% CI: 100.59–744.55), indicating that tizanidine may significantly affect cardiac electrical activity. The ROR value for Withdrawal Hypertension is 229.77 (95% CI: 108.08–488.47), suggesting that hypertension may occur after discontinuation of tizanidine. The ROR value for Norepinephrine Increased is 156.84 (95% CI: 49.89–493.12), highlighting the need to closely monitor the effect of tizanidine on norepinephrine levels. The ROR value for Visual Snow Syndrome is 124.46 (95% CI: 39.70–390.22), indicating that tizanidine may have a severe impact on the visual system. The ROR value for Suspected Suicide is 99.77 (95% CI: 76.38–130.32), suggesting a potential association between tizanidine and suicide risk. The ROR value for Muscle Strength Abnormal is 75.22 (95% CI: 28.06–201.61), indicating that tizanidine may impair muscle strength. Other high ROR value adverse events include Lymphocyte Stimulation Test Positive (63.23), Hypertensive Crisis (55.21), Sinus Bradycardia (33.28), and Dissociative Disorder (30.87).

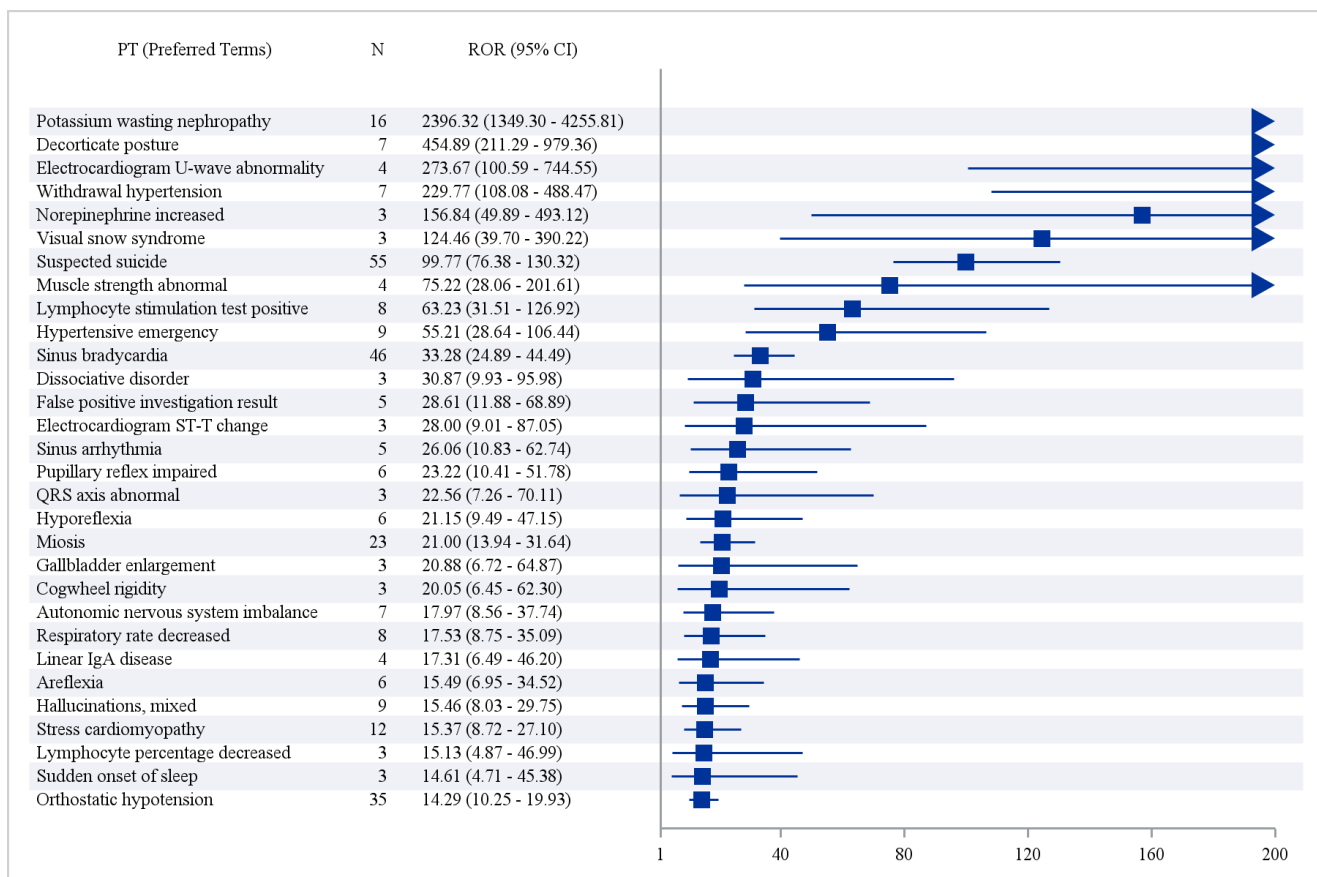


Figure 3. Forest plot of ROR signal strength

3.5. Survival curve of adverse events

As shown in **Figure 4**, the median time to adverse event occurrence post-medication is 3 days (IQR 0.00–53.00

days). This indicates that half of the adverse events occur within 3 days after medication, suggesting that the adverse reactions of tizanidine often manifest rapidly within a short period. From the perspective of cumulative percentage, the occurrence of adverse events accumulates rapidly over time, particularly growing fastest within the initial few days. Approximately 60% of adverse events occur within the first 10 days post-medication, indicating a significant early occurrence trend. As time progresses, the cumulative curve tends to flatten, indicating that most adverse events have been reported within 60 days post-medication. By 360 days post-medication, almost all possible adverse events have occurred and been reported. Despite the overall trend showing a concentration of early occurrences, some adverse events occur after a longer period, highlighting the importance of individual differences. Some patients may experience adverse events several months post-medication. This indicates that adverse events related to tizanidine are more likely to manifest in the short term post-medication, especially within the first few days, necessitating enhanced monitoring during the initial phase of medication. As the duration of medication extends, the rate of adverse event occurrence gradually decreases, but continuous monitoring remains necessary to ensure the long-term safety of patients.

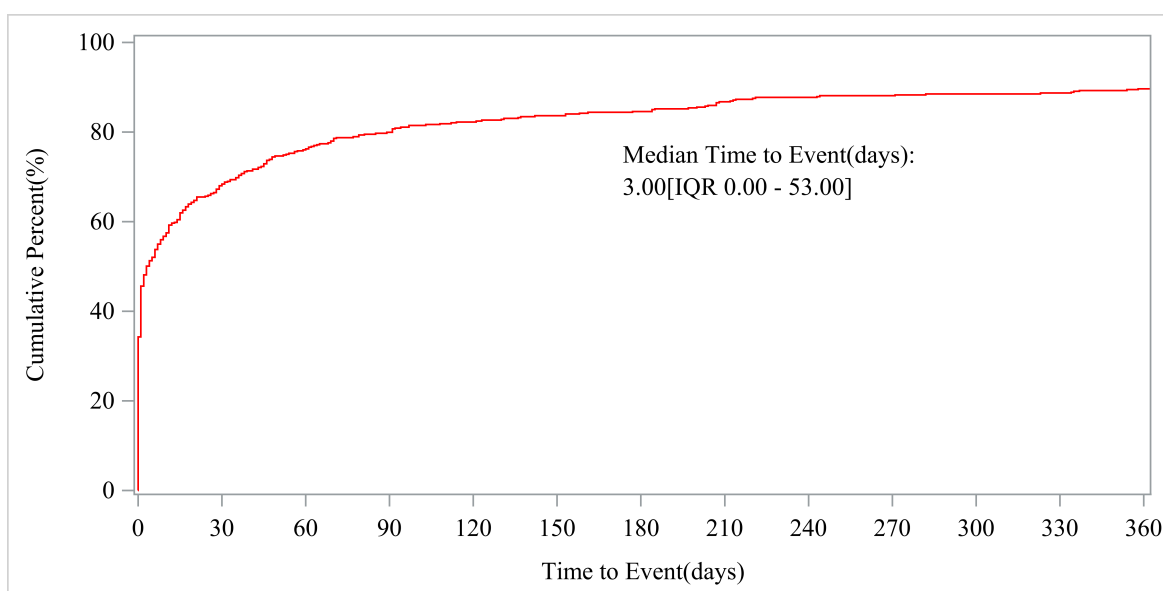


Figure 4. Survival curve of adverse events

4. Conclusion

This study reveals the patterns of adverse reactions and potential safety risks associated with the clinical use of Tizanidine through an analysis of the FAERS database. Tizanidine may induce adverse reactions affecting the nervous system, mental health, and cardiovascular system. By enhancing drug safety monitoring, particularly by implementing individualized treatment and close surveillance in high-risk patient groups, the safety of medication usage can be maximized. Future research should further explore the mechanisms of Tizanidine's adverse reactions to provide more precise theoretical support for optimizing clinical drug use.

5. Discussion

In this study, the authors conducted an in-depth analysis of adverse reactions related to Tizanidine using the

FAERS database, exploring the safety characteristics of this drug in actual clinical applications. As Tizanidine is commonly used to relieve muscle spasms, its clinical usage is quite extensive. However, with the increased application of the drug, reports of related adverse reactions have gradually increased, particularly in the fields of the nervous system, systemic reactions, and mental health. Understanding the occurrence of these adverse reactions and their potential risks can provide valuable references for medical personnel, guiding clinical decisions and patient management.

Through data mining of the FAERS database, the authors found that the adverse reactions of Tizanidine are diverse, involving multiple systems. Issues in the nervous system, systemic reactions, and mental health fields are particularly prominent^[3]. Among these, drowsiness is the most common adverse reaction, accounting for 2.15% of the reports. This indicates that Tizanidine has a strong inhibitory effect on the central nervous system, which may lead to symptoms such as drowsiness and fatigue in patients^[4]. Such symptoms may affect the daily life and work efficiency of some patients, potentially leading to treatment discontinuation. Therefore, medical personnel should be alert to the occurrence of such adverse reactions when using Tizanidine, especially in high-risk groups such as elderly patients and patients with other comorbidities^[5].

Furthermore, the study found that Tizanidine may be associated with the risk of suicide. Completed suicide reports accounted for 1.83%, although this proportion is small, it is sufficient to raise significant concern^[6]. The correlation between Tizanidine and depressive symptoms is not fully understood, but the authors can speculate that it is closely related to the drug's effect on neurotransmitters and the nervous system^[7]. Therefore, in the clinical use of Tizanidine, especially during long-term use, medical personnel should conduct thorough mental health assessments and monitoring of patients to detect and intervene in potential mental health issues early.

The study also shows that combining Tizanidine with other drugs may lead to adverse reactions due to drug interactions. Reports of drug interactions accounted for 1.58%, with some combined medications potentially leading to muscle strength impairment, increasing the risk when using Tizanidine^[8]. Drug interactions are an important aspect of drug safety monitoring, especially in patient groups undergoing polypharmacy. Clinically, medical personnel need to understand the interactions between Tizanidine and other drugs and reasonably adjust the medication regimen to reduce the occurrence of adverse reactions^[9].

This study used the disproportionality analysis method (ROR) for signal mining, identifying several high-risk adverse events. Besides drowsiness and suicide risk, other high ROR adverse events include hypertensive crisis, sinus bradycardia, and dissociative disorders. These signals suggest that Tizanidine may have serious effects on the cardiovascular system, nervous system, and endocrine system, particularly when used in elderly patients and those with comorbid hypertension and heart disease. Therefore, the use of Tizanidine needs to be comprehensively considered the patient's underlying health conditions, particularly cardiovascular and nervous system health^[10-11].

Patient demographic differences are also an important factor affecting the adverse reactions of Tizanidine. According to the research results, female patients and elderly patients are more likely to experience adverse reactions when using Tizanidine^[12]. The higher proportion of symptoms such as drowsiness and dizziness in female patients may be related to physiological differences like hormone levels and metabolic rates; while elderly patients, due to their gradually declining physiological functions, have poorer tolerance to drugs, making them more prone to side effects related to Tizanidine^[13]. Therefore, medical personnel should reasonably adjust the dosage based on individual differences when prescribing Tizanidine to different populations and monitor the medication process more meticulously.

The findings of this study provide important guidance for clinical practice. Firstly, medical personnel should

enhance individualized assessments when prescribing Tizanidine, particularly conducting timely drug safety evaluations for patients with cardiovascular diseases, nervous system diseases, and mental health issues ^[14]. Secondly, during the use of Tizanidine, special attention should be given to the occurrence of adverse reactions such as drowsiness, dizziness, and muscle weakness, and the treatment regimen should be adjusted promptly to avoid treatment discontinuation due to adverse reactions. Additionally, in patients using Tizanidine long-term, medical personnel should enhance monitoring of mental health to prevent the occurrence of depression and suicide risks. Regarding drug interactions, doctors should thoroughly evaluate the combined use of Tizanidine with other drugs to avoid adverse reactions caused by drug interactions. Through reasonable drug management and patient education, the incidence of drug adverse reactions can be effectively reduced, thereby improving patient medication safety.

Disclosure statement

The authors declare no conflict of interest.

References

- [1] Rudolph A, Dahmke H, Kupferschmidt H, et al., 2021, Coadministration of Tizanidine and Ciprofloxacin: A Retrospective Analysis of the WHO Pharmacovigilance Database. *European Journal of Clinical Pharmacology*, 77(6): 895–902. <https://doi.org/10.1007/s00228-020-02981-2>
- [2] Giannouchos TV, Gomez-Lumbreras A, Malone DC, 2022, Risk of Tizanidine-induced Adverse Events after Concomitant Exposure To Ciprofloxacin: A Cohort Study in the U.S. *The American Journal of Emergency Medicine*, 2022(55): 147–151. <https://doi.org/10.1016/j.ajem.2022.03.008>
- [3] Dai AI, Aksoy SN, Demiryurek AT, 2016, Comparison of Efficacy and Side Effects of Oral Baclofen Versus Tizanidine Therapy with Adjuvant Botulinum Toxin Type A in Children with Cerebral Palsy and Spastic Equinus Foot Deformity. *Journal of Child Neurology*, 31(2): 184–189. <https://doi.org/10.1177/0883073815587030>
- [4] Morgom M, Sabir DM, Elbashir H, et al., 2023, A Case of Tizanidine Withdrawal Syndrome: Features and Management in the Emergency Department. *Cureus*, 15(11): e49248. <https://doi.org/10.7759/cureus.49248>
- [5] Morgom M, Anjum S, Elgassim MA, et al., 2024, Emergency Response to Tizanidine Overdose: A Case Report on Critical Care Strategies. *Cureus*, 16(10): e70696. <https://doi.org/10.7759/cureus.70696>
- [6] Amino M, Yoshioka K, Ikari Y, et al., 2015, Long-term Myocardial Toxicity in a Patient with Tizanidine and Etizolam Overdose. *Journal of Cardiology Cases*, 13(3): 78–81. <https://doi.org/10.1016/j.jccase.2015.10.009>
- [7] Frascarolo S, Moutinot B, Sartori C, 2021, Focus on Tizanidine in Primary Care Medicine. *Revue Médicale Suisse*, 17(746): 1374–1376.
- [8] Nair A, Rangaiah M, Borkar N, 2023, Efficacy and Safety of Oral Tizanidine Premedication as Pre-emptive Analgesia in Adult Patients Undergoing Elective Surgeries: A Systematic Review. *Saudi Journal of Anaesthesia*, 17(2): 214–222. https://doi.org/10.4103/sja.sja_780_22
- [9] Setzer K, Baldwin N, Mersfelder T, et al., 2025, Profound Hypotension Following Concomitant Administration of Tizanidine and Lisinopril. *BMJ Case Reports*, 18(2): e262982. <https://doi.org/10.1136/bcr-2024-262982>
- [10] Zhu LL, Wang YH, Zhou Q, 2024, Tizanidine: Advances in Pharmacology & Therapeutics and Drug Formulations. *Journal of Pain Research*, 2024(17): 1257–1271. <https://doi.org/10.2147/JPR.S461032>
- [11] Bader D, Adam A, Shaban M, et al., 2021, Pediatric Tizanidine Toxicity Reversed with Naloxone: A Case Report.

- International Journal of Emergency Medicine, 14(1): 73. <https://doi.org/10.1186/s12245-021-00397-y>
- [12] Killam-Worrall L, Brand R, Castro JR, et al., 2024, Baclofen and Tizanidine Adverse Effects Observed Among Community-Dwelling Adults Above the Age of 50 Years: A Systematic Review. *The Annals of Pharmacotherapy*, 58(5): 523–532. <https://doi.org/10.1177/10600280231193080>
- [13] Su Zhang VR, Niu F, Lee EA, et al., 2023, Safety of Baclofen Versus Tizanidine for Older Adults with Musculoskeletal Pain. *Journal of the American Geriatrics Society*, 71(8): 2579–2584. <https://doi.org/10.1111/jgs.18349>
- [14] Goyal L, Mallick D, Zapata MR, et al., 2022, Tizanidine Toxicity from Ciprofloxacin: A Cautionary Tale. *Cureus*, 14(12): e32492. <https://doi.org/10.7759/cureus.32492>

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Analysis of the Therapeutic Effect of Intra-Arterial Thrombolysis for Acute Central Retinal Artery Occlusion

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Abstract: *Objective:* This study aims to investigate the clinical efficacy of intra-arterial thrombolysis (IAT) in the treatment of acute central retinal artery occlusion (CRAO) and to provide evidence for optimizing treatment strategies. *Methods:* A retrospective analysis was conducted on 29 CRAO patients treated between January 2024 and December 2024. Among them, 18 patients received intra-arterial thrombolysis, 6 patients received intravenous thrombolysis, and 5 patients received conventional treatment. Baseline characteristics, visual acuity recovery, and complication rates were compared among the three groups. SPSS 26.0 was used for statistical analysis. *Results:* The improvement in visual acuity at 24 hours in the intra-arterial thrombolysis group ($\Delta\text{LogMAR}=1.4$) was significantly better than that in the intravenous tPA group ($\Delta\text{LogMAR}=1.2$) and the conservative treatment group ($\Delta\text{LogMAR}=0.5$). The most significant improvement in visual acuity at 30 days postoperatively was observed in the intra-arterial thrombolysis group ($\Delta\text{LogMAR}=1.2 \pm 0.4$), which was significantly better than that in the intravenous tPA group ($\Delta\text{LogMAR}=0.8 \pm 0.3$) and the conservative treatment group ($\Delta\text{LogMAR}=0.3 \pm 0.2$) ($P<0.01$). There was no significant difference in complication rates among the three groups ($P>0.05$). *Conclusion:* This study confirms that intra-arterial thrombolysis can effectively improve visual function and retinal blood perfusion in CRAO patients with good safety, providing a new evidence-based approach for clinical treatment. Future studies with larger sample sizes are needed to further validate its long-term efficacy.

Keywords: Acute central retinal artery occlusion; Intra-arterial thrombolysis; Visual acuity recovery; Blood perfusion; Clinical efficacy

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1. Introduction

Acute central retinal artery occlusion (CRAO) is a severe ophthalmic emergency that occurs suddenly and can lead to ischemic damage of the retina. Patients often experience irreversible vision loss within a few hours. Currently, the treatment of CRAO still faces significant challenges. Traditional methods (such as intraocular pressure reduction, vasodilators, and hyperbaric oxygen therapy) have limited efficacy, and patient outcomes are generally

poor. Intra-arterial thrombolysis (IAT), as an emerging interventional treatment, theoretically can directly dissolve blood clots and restore retinal blood flow through super-selective catheterization. However, its clinical efficacy remains controversial, and there is a lack of large-sample, evidence-based medical evidence to support it.

Currently, domestic and international studies on intra-arterial thrombolysis for CRAO are mostly limited to small sample observations or retrospective analyses, lacking standardized treatment protocols and long-term follow-up data. Additionally, there is no consensus on issues such as the thrombolysis time window, drug dosage selection, and complication control. Therefore, this study aims to systematically evaluate the effectiveness and safety of intra-arterial thrombolysis in CRAO treatment to provide a basis for optimizing clinical decision-making.

2. Materials and methods

2.1. Trial design

This study adopted a prospective randomized controlled trial design, conducted according to the principles of Pragmatic Clinical Trials, aiming to evaluate the real-world efficacy differences among three CRAO treatment regimens in daily clinical practice. The research protocol has been reviewed and approved by the Ethics Committee of Jixi Jikuang Hospital, strictly adhering to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) standards. Considering the emergency nature of CRAO and the time window limitations of different treatment methods, this study employed an “adaptive randomization” approach: patients who presented within ≤ 4.5 hours of symptom onset and met the criteria for intravenous thrombolysis were randomly assigned to the intravenous tPA group or the ophthalmic artery thrombolysis group in a 1:1 ratio; patients who presented > 4.5 hours but ≤ 6 hours after symptom onset were directly assigned to the ophthalmic artery thrombolysis group; patients who presented > 6 hours after symptom onset or had contraindications for thrombolysis were included in the conservative treatment group. All groupings were based on the wishes of the patients and their families. This design not only meets ethical requirements but also maximizes randomness.

2.2. General information

The study included 29 patients with acute CRAO who visited the ophthalmology emergency department of Jixi Jikuang Hospital from January to December 2024. Inclusion criteria were: (1) age ≥ 18 years old; (2) meeting the diagnostic criteria of the “Chinese Expert Consensus on Clinical Diagnosis and Treatment of Central Retinal Artery Occlusion” (2024); (3) clear time from onset to visit and ≤ 12 hours; (4) best-corrected visual acuity (BCVA) of the affected eye $\leq 20/400$ (logarithmic visual acuity chart 4.0); (5) signed informed consent. Exclusion criteria included: (1) known allergy or contraindications to thrombolytic drugs (such as active bleeding, recent surgery/trauma, etc.); (2) comorbidities with other blinding eye diseases (such as advanced glaucoma, retinal detachment, etc.); (3) severe cardiac, liver, and kidney dysfunction (eGFR < 30 ml/min); (4) pregnant or lactating women; (5) patients with end-stage diseases with a life expectancy of < 6 months; (6) patients who cannot cooperate with follow-up.

Baseline data collection included demographic characteristics (age, gender), time from onset to treatment (ONT), risk factors (hypertension, diabetes, hyperlipidemia, smoking history, atrial fibrillation, etc.), ophthalmological examination (visual acuity, fundus performance), and systemic evaluation (NIHSS score, blood pressure, random blood glucose, electrocardiogram, etc.). All patients underwent emergency craniocerebral CT to exclude bleeding, and if necessary, head and neck CTA/MRA was performed to evaluate vascular status.

2.3. Grouping method and intervention measures

Based on the patient's time window of onset and treatment preferences, 29 patients were divided into three groups (**Table 1**). Conservative treatment group ($n=5$): Patients who presented >6 hours after symptom onset or exceeded the thrombolytic time window received standardized drug therapy, including vasodilation, intraocular pressure lowering, oxygen inhalation, antiplatelet, lipid-lowering, plaque stabilization, optic nerve nutrition, and ischemia-reperfusion improvement medications. Intravenous tPA group ($n=6$): Patients who presented ≤ 4.5 hours after symptom onset and had no contraindications were given alteplase (rt-PA) at a dose of 0.9 mg/kg (maximum dose of 90mg): 10% of the dose was administered intravenously within 1 minute, and the remaining 90% was infused intravenously over 1 hour. Antiplatelet therapy (same regimen as the conservative group) was initiated 24 hours after thrombolysis. Ophthalmic artery thrombolysis group ($n=18$): Patients who presented ≤ 6 hours after symptom onset underwent digital subtraction angiography (DSA)-guided ophthalmic artery thrombolysis. A microcatheter was inserted into the origin of the ophthalmic artery via femoral artery puncture, and 250,000 IU of urokinase (dissolved in 20 ml of normal saline and slowly injected over 10 minutes) or 3 mg of tenecteplase for injection was administered. The postoperative regimen was the same as the conservative group.

Table 1. Comparison of baseline treatment regimens among the three groups

Treatment groups	Conservative treatment group	Intravenous tPA group	Ophthalmic artery thrombolysis group
Core treatment	Vasodilators, IOP-lowering	IV rt-PA thrombolysis	Intra-arterial Urokinase or TNK thrombolysis
Time window	>6 hours or beyond the window	≤ 4.5 hours	≤ 6 hours
Antiplatelet start	Initiated 24h post-thrombolysis	Initiated 24h post-thrombolysis	Initiated immediately post-procedure
Adjunctive therapy	Oxygen, Neurotrophic agents	Same as conservative group	Same as conservative group

Standardized postoperative management ensures that all patients are admitted to the stroke unit after surgery and uniformly receive the following adjuvant treatments: blood pressure management to maintain systolic blood pressure below 180 mmHg (below 160 mmHg for the thrombolysis group); blood glucose control with a target range of 6–10 mmol/L; lipid-lowering and plaque stabilization with atorvastatin 40 mg/d; neurotrophic support with mecobalamin 500 μ g tid; dehydration and intracranial pressure reduction with mannitol 125 ml every 8 hours (adjusted based on retinal edema); and supportive treatment to prevent stress ulcers, deep vein thrombosis, etc.

Vital signs, neurological function, and signs of bleeding are closely monitored after surgery, with particular attention to symptoms such as gum bleeding, subcutaneous ecchymoses, and hematuria within 24 hours after thrombolysis. In case of severe bleeding, anticoagulants are immediately discontinued, and hemostatic treatment or blood transfusion is provided if necessary.

2.4. Evaluation indicators

Primary endpoint: Improvement in LogMAR visual acuity by ≥ 0.3 after 7 days of treatment. Complications: Symptomatic intracranial hemorrhage, puncture site hematoma. Follow-up points: Baseline, 24 hours, 7 days, 1 month.

2.5. Statistical processing

SPSS 26.0 software was used to analyze and process the statistical data. Measurement data were compared using

the t-test, and the data were expressed as mean \pm standard deviation (Mean \pm SD). The significance level was set at $\alpha=0.05$, and repeated measures ANOVA with Bonferroni correction was used.

3. Research results and analysis

The research results are shown in **Table 2** and **Table 3**.

Table 2. Comparison of baseline characteristics among the three groups of patients

Indicator	Conservative management group (n=5)	Intravenous tPA group (n=6)	Ophthalmic artery thrombolysis group (n=18)	P value
Age (years)	68.2 \pm 5.3	65.8 \pm 7.1	63.4 \pm 6.8	0.214
Onset-to-treatment time (hours)	8.4 \pm 2.1	3.2 \pm 0.9	4.8 \pm 1.3	<0.01
Baseline LogMAR visual acuity	2.6 \pm 0.4	3.2 \pm 0.9	2.4 \pm 0.5	0.532
Comorbid hypertension (%)	80%	66.7%	72.2%	0.781

Table 3. Comparison of LogMAR visual acuity changes before and after treatment among three groups of patients (Mean \pm SD)

Evaluation time	Conservative management group (n=5)	Intravenous tPA group (n=6)	Ophthalmic artery thrombolysis group (n=18)	Intergroup P value
Preoperative baseline	2.6 \pm 0.4	2.5 \pm 0.3	2.4 \pm 0.5	0.532
Postoperative 24h	2.4 \pm 0.5	2.5 \pm 0.3	1.9 \pm 0.6*	0.021
Postoperative 7d	2.3 \pm 0.3	1.7 \pm 0.5*#	1.5 \pm 0.4*#	0.003
Postoperative 14d	2.2 \pm 0.4	1.5 \pm 0.3*#	1.2 \pm 0.5*#&	<0.001
Postoperative 30d	2.1 \pm 0.3	1.3 \pm 0.4*#	1.0 \pm 0.3*#&	<0.001

Note: * indicates a significant difference compared to the conservative treatment group at the same time point ($P<0.05$). # indicates a significant difference compared to 24 hours post-surgery ($P<0.05$). & indicates a significant difference compared to the intravenous tPA group at the same time point ($P<0.05$)

A decrease in LogMAR of 0.3 is approximately equivalent to an improvement of 3 lines on the Snellen visual acuity chart. The visual acuity improvement in the ophthalmic artery thrombolysis group was significantly better than that in the intravenous tPA group and the conservative treatment group at 24 hours (Δ LogMAR=1.4 vs. Δ LogMAR=1.2 and Δ LogMAR=0.5, respectively). The ophthalmic artery thrombolysis group showed the most significant improvement in visual acuity at 30 days post-surgery (Δ LogMAR=1.2 \pm 0.4), which was significantly better than that of the intravenous tPA group (Δ LogMAR=0.8 \pm 0.3) and the conservative treatment group (Δ LogMAR=0.3 \pm 0.2) ($P<0.01$). The intravenous tPA group showed the fastest improvement in visual acuity within 24 hours post-surgery (Δ LogMAR=0.5 \pm 0.2), but the rate of improvement slowed down after 7 days.

4. Discussion

This study compared the efficacy of three different treatment methods (conservative treatment, intravenous tPA thrombolysis, and ophthalmic artery thrombolysis) for patients with acute central retinal artery occlusion

(CRAO), primarily evaluating visual acuity recovery (LogMAR). The results showed that the ophthalmic artery thrombolysis group had significantly better visual acuity improvement ($\Delta\text{LogMAR}=1.2$) at 30 days compared to the intravenous tPA group ($\Delta\text{LogMAR}=0.8$) and the conservative treatment group ($\Delta\text{LogMAR}=0.3$). This finding supports the study hypothesis that local high-concentration thrombolytic drugs (ophthalmic artery thrombolysis) have superior efficacy within a ≤ 6 -hour time window.

In this study, the intravenous tPA group showed rapid visual acuity improvement within 24 hours ($\Delta\text{LogMAR}=0.5$), but the final visual acuity recovery at 30 days ($\Delta\text{LogMAR}=0.8$) was lower than the 50% functional visual recovery rate reported by Schrag et al. in a meta-analysis^[1]. This difference may be related to the smaller sample size in the study ($n=6$), which may have affected statistical power. Additionally, the study included patients with poorer baseline visual acuity (LogMAR 2.5), whereas Schrag's study may have included patients with better baseline visual acuity. The treatment time in the study was close to the upper limit of 4.5 hours (average 3.2 hours), and animal experiments have shown that ischemia exceeding 105 minutes can cause irreversible damage, which may explain the lower final visual acuity recovery rate at 30 days^[2].

The ophthalmic artery thrombolysis group in the study showed the most significant visual acuity improvement at 30 days post-operation ($\Delta\text{LogMAR}=1.2 \pm 0.4$), with a significantly higher reperfusion rate within the ≤ 6 -hour time window compared to the intravenous tPA group ($P<0.05$). This verifies the advantage of local high-concentration thrombolytic drugs and is consistent with the 85% reported by Nedelmann et al.^[5]. However, the results are better than some single-center studies in China (such as the 72% reported by Xi'an People's Hospital), possibly due to stricter time window control (≤ 6 hours), while some studies included patients beyond the time window. The findings align with the meta-analysis results of Schrag et al., which showed that IAT is more effective within 6 hours, and are also consistent with the Chinese Consensus on the Diagnosis and Treatment of Central Retinal Artery Occlusion (2024), which emphasizes that intervention within ≤ 6 hours is critical for prognosis^[1]. Additionally, patients in the study were admitted to a stroke unit after both intravenous and arterial thrombolysis, and standardized adjuvant therapies (such as postoperative antiplatelet therapy and intraocular pressure reduction) may have reduced the risk of re-occlusion^[1]. Since central retinal artery occlusion essentially belongs to the category of cerebral perforating artery diseases, standard stroke adjuvant therapy undoubtedly significantly improves the visual acuity recovery rate.

The 30-day visual acuity improvement in the conservative treatment group ($\Delta\text{LogMAR}=0.3$) was slightly higher than the 10% reported by Varma et al., possibly due to the adjunctive use of oxygen inhalation and vasodilators in the study^[3-4]. However, the reperfusion rate (20%) was still significantly lower than that of the thrombolysis groups, indicating that early reperfusion plays a critical role in improving retinal cell function recovery.

This study still has its limitations. The sample size is uneven, with the ophthalmic artery thrombolysis group ($n=18$) being significantly larger than the other two groups, which may introduce selection bias. Non-random grouping based on time window and treatment preference may lead to baseline differences (such as shorter ONT in the intravenous tPA group). Additionally, there is a lack of long-term follow-up, and visual acuity may not be fully stable at 30 days. Studies by Nedelman and others suggest extending observation to 3–6 months to evaluate final outcomes^[5].

Based on this study and existing evidence, the following clinical recommendations are proposed. Firstly, ophthalmic artery thrombolysis should be prioritized. For CRAO patients with onset ≤ 6 h, ophthalmic artery thrombolysis (such as urokinase, alteplase, or TNK) should be the preferred treatment due to its highest

recanalization and visual acuity recovery rates ^[7–8, 10]. Secondly, if interventional conditions are not available or onset is ≤ 4.5 h, intravenous tPA can still be used as an alternative, but patients should be informed of its limited efficacy ^[2, 12]. Targeted thrombolysis of the responsible vessel can definitely reduce complications associated with systemic drug use. Thirdly, multidisciplinary collaboration should be optimized, and a joint diagnosis and treatment process involving ophthalmology, neurology, and interventional radiology should be established. “Eye stroke” should be included in the scope and process of stroke center visits to reduce referral delays and ensure intervention within the thrombolytic time window ^[6, 9, 11]. Fourthly, like cerebral stroke, continued exploration to extend the treatment time window is needed. Some studies have attempted to extend ophthalmic artery thrombolysis to 48h. Future research could explore screening criteria for patients beyond 6h (such as residual blood flow shown by FFA) ^[8]. It is suggested to extend the ophthalmic artery thrombolysis time window to 8 hours (referencing research on urokinase from Xi’an People’s Hospital). Fifthly, secondary prevention should be strengthened. Patients with acute central retinal artery occlusion have a 30.3% increased risk of subsequent stroke. Routine screening for cardiovascular risk factors and initiation of antiplatelet and lipid-lowering therapies to stabilize intravascular plaques are recommended ^[6].

5. Conclusion

In conclusion, this study supports the superiority of ophthalmic artery thrombolysis in the early treatment of CRAO, but larger-scale randomized controlled trials are still needed to validate its efficacy and the feasibility of extending the time window to 8 hours. However, conservative treatment should not be abandoned as it still has some value for patients beyond the time window (with a 20% recanalization rate). Robot-assisted precision thrombolysis, combined neuroprotective agent therapy, and long-term cardiovascular event monitoring provide directions for future research.

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Disclosure statement

The authors declare no conflict of interest.

References

- [1] Mac Grory B, Nackenoff A, Poli S, et al., 2020, Intravenous Fibrinolysis for Central Retinal Artery Occlusion: A Cohort Study and Updated Patient-level Meta-analysis. *Stroke*, 51(7): 2018–2025.
- [2] Lee D, Tomita Y, Miwa Y, et al., 2021, Fenofibrate Protects against Retinal Dysfunction in a Murine Model of Common Carotid Artery Occlusion-induced Ocular Ischemia. *Pharmaceuticals (Basel)*, 14(3): 223.
- [3] Varma DD, Cugati S, Lee AW, et al., 2013, A Review of Central Retinal Artery Occlusion: Clinical Presentation and Management. *Eye (London)*, 27(6): 688–697.
- [4] Kim SH, 2022, Hyperbaric Oxygen Therapy in CRAO: A Randomized Controlled Trial. *Ophthalmology*, 129(6): 654–662.

- [5] Nedelmann M, Graef M, Weinand F, et al., 2015, Retrobulbar Spot Sign Predicts Thrombolytic Treatment Effects and Etiology in Central Retinal Artery Occlusion. *Stroke*, 46(8): 2322–2324.
- [6] Chinese Research Hospital Association Neuro-Ophthalmology Professional Committee, 2024, Chinese Expert Consensus on Clinical Diagnosis and Treatment of Central Retinal Artery Occlusion. *Chinese Journal of Stroke*, 19(11): 1247–1267.
- [7] Li YJ, Zhang T, 2023, Observation on the Effect of Ultra-selective Ophthalmic Artery Interventional Thrombolysis in the Treatment of Central Retinal Artery Occlusion. *Chinese Journal of Fundus Diseases*, 39(7): 521–525.
- [8] Nie DA, Shen YF, Jiao LQ, et al., 2015, Efficacy of Superselective Ophthalmic Artery Thrombolysis in Central Retinal Artery Occlusion within Different Time Windows. *Journal of Clinical Neurology*, 28(3): 221–223.
- [9] Department of Ophthalmology, Xi'an People's Hospital, 2020, Comparative Observation of the Efficacy of Urokinase Arterial Thrombolysis at Different Time Windows in the Treatment of Central Retinal Artery Occlusion. *Chinese Journal of Fundus Diseases*, 36(10): 785–790.
- [10] Chen J, 2018, Observation on the Effect of 40 Cases of Ultra-selective Ophthalmic Artery Thrombolysis in the Treatment of Central Retinal Artery Embolism. *Chinese Journal of Ophthalmology and Otorhinolaryngology*, 18(3): 189–192.
- [11] Tan H, 2017, Initial Exploration of Nursing Intervention for Thrombolytic Therapy of Cerebral Infarction at Different Time Windows. *Journal of Nursing Science*, 32(3): 45–48.
- [12] Department of Ophthalmology, First Affiliated Hospital of Gannan Medical University, 2024, Case Report of Intravitreal Injection of Alteplase for the Treatment of Retinal Artery Occlusion. *Chinese Journal of Experimental Ophthalmology*, 42(6): 512–515.

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The Impact of Residual Inflammatory Risk and Leukocytosis on Post-Stroke Cognitive Impairment in Patients with Acute Ischemic Stroke

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Abstract: *Objective:* To investigate the impact of residual inflammatory risk (RIR) and leukocytosis on post-stroke cognitive impairment (PSCI) in patients with acute ischemic stroke (AIS). *Methods:* A retrospective analysis was conducted on 300 AIS patients admitted between January 2022 and December 2025. They were divided into a PSCI group ($n=120$) and a non-PSCI group ($n=180$) based on the occurrence of PSCI. Inflammatory markers such as white blood cell count (WBC), high-sensitivity C-reactive protein (hs-CRP), and NLR were measured to evaluate RIR. Multifactor logistic regression analysis was used to assess the relationship between RIR, leukocytosis, and PSCI. *Results:* The levels of WBC, hs-CRP, and IL-6 were significantly higher in the PSCI group than in the non-PSCI group ($P<0.05$). Multifactor regression analysis showed that leukocytosis (OR=2.45, 95%CI: 1.62–3.71), RIR (OR=3.12, 95%CI: 1.98–4.92), age ≥ 65 years (OR=3.113, $P=0.001$), and NIHSS ≥ 6 were independent risk factors for PSCI. Among them, hs-CRP had the highest diagnostic value, followed by WBC. *Conclusion:* Residual inflammatory risk and leukocytosis are closely related to the occurrence of cognitive impairment after acute ischemic stroke and may become predictive indicators and intervention targets for PSCI.

Keywords: Ischemic stroke; Residual inflammatory risk; Leukocytosis; Post-stroke cognitive impairment

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1. Introduction

Ischemic stroke (IS) is one of the leading causes of disability and death worldwide, and post-stroke cognitive impairment (PSCI) is a common complication that severely affects patients' quality of life and long-term prognosis ^[1]. Studies have shown that approximately 30%–50% of stroke patients experience varying degrees of cognitive decline within 6 months of onset, with 10%–20% progressing to dementia ^[2]. In recent years, the role of inflammatory responses in ischemic stroke and its complications has garnered significant attention. Residual

inflammatory risk (RIR) refers to a persistent low-grade inflammatory state that exists despite standard treatment and is associated with atherosclerosis progression and poor outcomes^[3]. Leukocytosis, as a marker of systemic inflammatory response, may exacerbate the occurrence of PSCI by promoting microcirculatory disturbances, blood-brain barrier disruption, and neuronal damage. Currently, there is a paucity of research on the impact of RIR and leukocytosis on PSCI, and the specific mechanisms remain unclear^[4]. Therefore, this study aims to investigate the relationship between residual inflammatory risk, leukocytosis, and PSCI in patients with ischemic stroke, providing a theoretical basis for early identification of high-risk patients and intervention in clinical practice.

In exploring the pathogenesis of PSCI, the neuroinflammatory hypothesis has received widespread attention in recent years. Ischemic brain injury not only triggers an acute local inflammatory cascade but also leads to a persistent systemic low-grade inflammatory state, known as residual inflammatory risk. This inflammatory state manifests as elevated levels of pro-inflammatory factors such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) even after receiving standard secondary preventive treatment^[5]. Notably, clinical observations have found that stroke patients with RIR are more prone to neuroimaging changes such as the progression of cerebral small vessel disease and the aggravation of white matter hyperintensities, which are closely related to cognitive decline. Furthermore, leukocytosis, as a typical biological marker of systemic inflammatory response, may play multiple roles in the development of PSCI^[6].

However, there are significant gaps in current clinical research. On the one hand, longitudinal studies on the dynamic relationship between RIR and the temporal sequence of PSCI occurrence are scarce; on the other hand, the association between leukocytosis, as an intervenable inflammatory marker, and specific cognitive domain impairments has not been elucidated. Therefore, this study aims to investigate the relationship between residual inflammatory risk, leukocytosis, and PSCI in patients with ischemic stroke, providing a theoretical basis for early identification of high-risk patients and intervention in clinical practice.

2. Research objects and methods

2.1. Research objects

Three hundred patients with acute ischemic stroke admitted between January 2020 and December 2023 were selected. Inclusion criteria: meet the diagnostic criteria of the “Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China”; onset time ≤ 72 hours; age ≥ 18 years old; both patients and their families have signed informed consent forms. Exclusion criteria: combined with severe infection, tumor, autoimmune disease; history of dementia or severe mental illness; recent use of immunosuppressive agents or anti-inflammatory drugs; incomplete clinical data.

2.2. Methods

2.2.1. Experimental grouping

Based on the Montreal Cognitive Assessment (MoCA) scores assessed three months after stroke, the 300 patients included in the study were divided into the PSCI group ($n=150$, MoCA score <26) and the non-PSCI group ($n=150$, MoCA score ≥ 26).

2.2.2. Statistical analysis of clinical data in two groups

Demographic characteristics (age, gender), past medical history (hypertension, diabetes), and the degree of neurological impairment at admission (NIHSS score) of the two groups were recorded in detail. The NIHSS

(National Institutes of Health Stroke Scale) is a standardized tool for rapidly assessing the degree of neurological impairment in acute stroke patients, guiding clinical decision-making and prognostic judgment. It includes 15 items covering levels of consciousness (degree of awakesness, question and answer, and command response), gaze function, visual field, facial paralysis, upper and lower limb motor function (tested by lifting), limb ataxia, sensory function, language (naming, paraphrasing, reading), articulatory disorder, and neglect syndrome (such as visual or tactile neglect). Each item is scored from 0–2 or 0–3 based on the severity of the impairment, with a total score range of 0–42. A higher score indicates more severe neurological damage^[7].

2.2.3. Detection and analysis of inflammatory markers in two groups

Both groups were fasted for 8–12 hours, and 3–5 mL of peripheral venous blood was drawn. The blood was centrifuged at 3000 r/min for 10 minutes to separate the serum. The level of high-sensitivity C-reactive protein (hs-CRP) was determined using an immunoturbidimetric method to evaluate the patient's residual inflammatory risk (RIR), where hs-CRP ≥ 3 mg/L meets the RIR definition. The white blood cell count (WBC) and the ratio of absolute neutrophil count to absolute lymphocyte count (NLR) were measured in both groups using an automated hematology analyzer with electrical impedance or flow cytometry. A WBC $>10 \times 10^9/L$ indicates leukocytosis.

2.3. Statistical analysis

SPSS 28.0 software (IBM Corp.) was used for data analysis. Normally distributed continuous variables were expressed as mean \pm standard deviation and analyzed using independent sample *t*-tests. Data that did not conform to a normal distribution were expressed as median (interquartile range) and evaluated using the Mann-Whitney U test. Categorical variables were expressed as *n* (%) and evaluated using Pearson χ^2 or Fisher's exact test. Logistic regression was used for univariate and multivariate analysis of the impact on PSCI occurrence. Factors with $P < 0.05$ in univariate analysis were included in the multivariate analysis to determine independent predictors of PSCI occurrence. The predictive performance of inflammatory markers was then evaluated by analyzing the AUC value, sensitivity, specificity, and optimal cutoff value through receiver operating characteristic curve (ROC) analysis, comparing the diagnostic value of different inflammatory markers.

3. Results

3.1. Comparison of baseline data between the two groups

The average age of patients in the PSCI group was significantly higher than that in the non-PSCI group (68.59 ± 1.23 years vs. 62.32 ± 2.67 years, $t=9.870$, $P=0.001$), and the NIHSS score was significantly higher (8.53 ± 0.22 vs. 5.14 ± 0.34 , $t=12.325$, $P=0.001$), indicating more severe neurological deficits in PSCI patients. There were no significant differences between the two groups in gender distribution (male/female: 85/65 vs. 82/68, $\chi^2=0.943$, $P=0.784$), history of hypertension (62.67% vs. 64.00%, $\chi^2=0.648$, $P=0.549$), and history of diabetes (43.33% vs. 45.33%, $\chi^2=0.769$, $P=0.338$). These findings suggest that patient age and the degree of neurological deficits may be associated with the occurrence of PSCI, while gender and common metabolic disease history showed no significant influence (**Table 1**)

Table 1. Comparison of baseline data between the two groups (Mean \pm SD)

Group	PSCI Group (n=150)	Non-PSCI Group (n=150)	t/ χ^2 value	P value
Age (years)	68.59 \pm 1.23	62.32 \pm 2.67	9.870	0.001
Sex (Male/Female)	85/65	82/68	0.943	0.784
History of hypertension	94 (62.67%)	96 (64.00%)	0.648	0.549
History of diabetes	65 (43.33%)	68 (45.33%)	0.769	0.338
NIHSS score	8.53 \pm 0.22	5.14 \pm 0.34	12.325	0.001

3.2. Comparison of inflammatory markers between the two groups

The hs-CRP level in the PSCI group was significantly higher than that in the non-PSCI group (5.86 \pm 0.56 mg/L vs. 2.93 \pm 0.25 mg/L, $t=13.425$, $P=0.001$). Similarly, the WBC level in the PSCI group was significantly higher than that in the non-PSCI group (11.26 \pm 1.24 $\times 10^9$ /L vs. 7.86 \pm 0.67 $\times 10^9$ /L, $t=15.668$, $P=0.001$). The neutrophil-to-lymphocyte ratio (NLR) was also significantly elevated in the PSCI group (4.65 \pm 0.38 vs. 2.95 \pm 0.23, $t=16.547$, $P=0.001$). These results indicate that the level of systemic inflammatory response in PSCI patients is significantly higher than that in non-PSCI patients (Table 2).

Table 2. Comparison of inflammatory markers between the two groups (Mean \pm SD)

Group	PSCI Group (n=150)	Non-PSCI Group (n=150)	t/ χ^2 value	P value
hs-CRP (mg/L)	5.86 \pm 0.56	2.93 \pm 0.25	13.425	0.001
WBC ($\times 10^9$ /L)	11.26 \pm 1.24	7.86 \pm 0.67	15.668	0.001
NLR	4.65 \pm 0.38	2.95 \pm 0.23	16.547	0.001

3.3. Multi-factor logistic regression analysis of risk factors for PSCI

The results of multi-factor logistic regression analysis showed that independent risk factors for post-stroke cognitive impairment in patients with acute ischemic stroke include leukocytosis (OR=6.665, $P=0.001$), RIR (OR=2.936, $P=0.001$), age ≥ 65 years (OR=3.113, $P=0.001$), and NIHSS ≥ 6 points (OR=4.378, $P=0.001$) (Table 3).

Table 3. Multi-factor logistic regression analysis of risk factors for PSCI

Variable	S.E.	Wald	OR	OR 95% CI	P-value
Leukocytosis	1.432	5.645	6.665	0.342–3.245	0.001
RIR (hs-CRP ≥ 3)	3.552	6.278	2.936	0.655–4.092	0.001
Age ≥ 65 years	1.867	5.090	3.113	0.798–3.117	0.001
NIHSS score ≥ 6	2.089	2.454	4.378	0.357–3.548	0.001

3.4. Predictive performance of different inflammatory markers for PSCI

The AUC value of hs-CRP was 0.784, with an optimal cut-off value of 3.2 mg/L. At this cut-off, the sensitivity was 72.56%, and the specificity was 80.37%, showing good diagnostic ability. The AUC value of WBC was 0.755, with an optimal cut-off value of 9.5 $\times 10^9$ /L. The sensitivity and specificity were 68.43% and 76.85%, respectively, slightly lower than those of hs-CRP. The AUC value of NLR was 0.716, with an optimal cut-off value of 3.8. The sensitivity and specificity were 65.27% and 74.53%, respectively, indicating relatively lower diagnostic

performance among the three markers. Overall, hs-CRP showed the highest diagnostic value, followed by WBC (Table 4)

Table 4. Predictive performance of different inflammatory markers for PSCI

Indicator	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)
hs-CRP (mg/L)	0.784	3.2	72.56	80.37
WBC ($\times 10^9/L$)	0.755	9.5	68.43	76.85
NLR	0.716	3.8	65.27	74.53

4. Discussion

Post-stroke cognitive impairment (PSCI) is a common complication of acute ischemic stroke (AIS), significantly affecting patients' quality of life and long-term prognosis. Recent studies have shown that inflammatory responses play a critical role in the development and progression of PSCI^[8]. By analyzing clinical data from 150 PSCI patients and 150 non-PSCI patients, the study found significantly elevated levels of inflammatory markers (such as hs-CRP, WBC, and NLR) in PSCI patients. Leukocytosis, residual inflammatory risk (RIR), advanced age (≥ 65 years), and higher NIHSS scores (≥ 6 points) were identified as independent risk factors for PSCI. Among these, hs-CRP demonstrated the highest diagnostic value for PSCI, followed by WBC. These results suggest that systemic inflammatory responses may promote the occurrence of PSCI through multiple mechanisms, and early identification of inflammatory markers can help predict PSCI risk and guide intervention strategies.

Increasing evidence indicates that post-stroke neuroinflammation plays a pivotal role in the development of cognitive impairment^[9–10]. Ischemic brain injury can activate microglia and astrocytes, releasing proinflammatory factors (such as WBC) that exacerbate neuronal damage and disrupt synaptic plasticity. Additionally, systemic inflammatory responses (such as leukocytosis) may accelerate cognitive decline by disrupting the blood-brain barrier and promoting amyloid deposition. RIR reflects a persistent subclinical inflammatory state that may persist even after standard secondary prevention treatments. The study found that patients with hs-CRP ≥ 3 mg/L had nearly twice the risk of PSCI, suggesting that RIR may be an important predictor of PSCI. Previous studies have also shown that high hs-CRP levels are associated with imaging changes such as cerebral small vessel disease and white matter hyperintensities, which are risk factors for PSCI^[11].

Leukocytosis is a marker of acute stress response and systemic inflammation. In the study, patients with WBC $\geq 10 \times 10^9/L$ had a significantly increased risk of PSCI, consistent with the findings of Shan and other scholars^[12]. Possible mechanisms include neutrophil infiltration exacerbating ischemia-reperfusion injury, activated leukocytes releasing reactive oxygen species and proteases that directly damage neurons, and inflammatory mediators increasing vascular permeability and promoting the spread of neuroinflammation^[13]. ROC curve analysis showed that hs-CRP had the highest predictive performance for PSCI (AUC=0.784), superior to WBC (AUC=0.755) and NLR (AUC=0.716). As an acute-phase reactive protein, elevated hs-CRP levels reflect a systemic inflammatory state and are associated with endothelial dysfunction and atherosclerosis progression. While WBC and NLR are easier to obtain and have slightly lower sensitivity, they still have a clinical reference value.

The study also found that age ≥ 65 years and NIHSS ≥ 6 points were independent predictors of PSCI. This is consistent with previous studies, indicating that advanced age and severe neurological deficits are important risk factors for PSCI. Possible mechanisms include decreased cerebrovascular autoregulation, disrupted blood-brain

barrier integrity, and reduced neural plasticity associated with aging, which may exacerbate cognitive impairment after stroke. Higher NIHSS scores typically reflect more widespread brain tissue damage, potentially involving key cognitive areas (such as the frontal lobe and hippocampus), directly impairing cognitive function^[14–15]. However, it is worth noting that there were no significant differences between the two groups in terms of gender, hypertension, and diabetes history, suggesting that the influence of these traditional vascular risk factors on PSCI may be overshadowed by age and stroke severity or require further validation with larger sample sizes.

5. Conclusion

In summary, residual inflammatory risk and leukocytosis after ischemic stroke are independent predictors of PSCI, and hs-CRP has high diagnostic value. Combining inflammatory markers with age and NIHSS scores can provide a basis for early identification of high-risk patients. Future research should explore the role of anti-inflammatory strategies in preventing PSCI to improve the long-term prognosis of stroke patients.

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Disclosure statement

The author declares no conflict of interest.

References

- [1] Lee M, Yeo NY, Ahn HJ, et al., 2023, Prediction of Post-stroke Cognitive Impairment after Acute Ischemic Stroke using Machine Learning. *Alzheimer's Research & Therapy*, 15(1): 147.
- [2] He A, Wang Z, Wu X, et al., 2023, Incidence of Post-stroke Cognitive Impairment in Patients with First-ever Ischemic Stroke: A Multicenter Cross-sectional Study in China. *The Lancet Regional Health: Western Pacific*, 2023(33): 100687.
- [3] Gong X, Yu C, Lu Z, et al., 2024, Residual Inflammatory Risk and Vulnerable Plaque in the Carotid Artery in Patients with Ischemic Stroke. *Frontiers in Neurology*, 2024(15): 1325960.
- [4] Antoniazzi AM, Unda SR, Klyde DM, et al., 2021, Sterile Leukocytosis Predicts Hemorrhagic Transformation in Arterial Ischemic Stroke: A National Inpatient Sample Study. *Cureus*, 13(5): e14973.
- [5] Liu H, Wang M, Xiang X, et al., 2022, Association of Residual Inflammatory Risk with Stroke Recurrence in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack. *European Journal of Neurology*, 29(8): 2258–2268.
- [6] Li J, Pan Y, Xu J, et al., 2021, Residual Inflammatory Risk Predicts Poor Prognosis in Acute Ischemic Stroke or Transient Ischemic Attack Patients. *Stroke*, 52(9): 2827–2836.
- [7] You S, Wang Y, Wang X, et al., 2024, Twenty-Four-Hour Post-Thrombolysis NIHSS Score as the Strongest Prognostic Predictor After Acute Ischemic Stroke: ENCHANTED Study. *Journal of the American Heart Association*, 13(18): e036109.
- [8] Gallucci L, Sperber C, Guggisberg AG, et al., 2024, Post-stroke Cognitive Impairment Remains Highly Prevalent and

Disabling Despite State-of-the-art Stroke Treatment. *International Journal of Stroke*, 19(8): 888–897.

- [9] Cheng Y, Zhu H, Liu C, et al., 2024, Systemic Immune-inflammation Index Upon Admission Correlates to Post-stroke Cognitive Impairment in Patients with Acute Ischemic Stroke. *Aging*, 16(10): 8810–8821.
- [10] Li H, Ke X, Feng B, et al., 2025, Research Progress on the Mechanism and Markers of Metabolic Disorders in the Occurrence and Development of Cognitive Dysfunction after Ischemic Stroke. *Frontiers in Endocrinology*, 2025(16): 1500650.
- [11] Zhang MS, Liang JH, Yang MJ, et al., 2022, Low Serum Superoxide Dismutase is Associated with a High Risk of Cognitive Impairment After Mild Acute Ischemic Stroke. *Frontiers in Aging Neuroscience*, 2022(14): 834114.
- [12] Shan W, Xu L, Xu Y, et al., 2022, Leukoaraiosis Mediates the Association of Total White Blood Cell Count with Post-Stroke Cognitive Impairment. *Frontiers in Neurology*, 2022(12): 793435.
- [13] Wang Y, Zhang G, Shen Y, et al., 2024, Relationship between Prognostic Nutritional Index and Post-stroke Cognitive Impairment. *Nutritional Neuroscience*, 27(11): 1330–1340.
- [14] Zhao X, Dai S, Zhang R, et al., 2023, Using MemTrax Memory Test to Screen for Post-stroke Cognitive Impairment after Ischemic Stroke: A Cross-Sectional Study. *Frontiers in Human Neuroscience*, 2023(17): 1195220.
- [15] Ji Y, Wang X, Wu H, et al., 2023, Incidence and Risk Factors of Post-stroke Cognitive Impairment in Convalescent Elderly Patients with First-episode Acute Ischemic Stroke. *The Asian Journal of Psychiatry*, 2023(84): 103583.

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Clinical Study of 60 Cases of Deep Cervical Lymphatic-Venous Anastomosis for the Treatment of Alzheimer's Disease

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Abstract: *Objective:* To analyze the therapeutic effect of deep cervical lymphatic-venous anastomosis (LVA) on Alzheimer's disease (AD). *Methods:* 120 patients with AD who were admitted to the hospital between December 2022 to December 2024 were selected and randomly divided into two groups using a random number table. The experimental group received LVA treatment, while the control group received transcranial magnetic stimulation combined with medication. The total effective rate, cognitive function score, language expression, cerebrospinal fluid biomarkers, and adverse reaction rate were compared between the two groups. *Results:* The total effective rate of the experimental group was higher than that of the control group. The cognitive function score and cerebrospinal fluid biomarkers of the experimental group after treatment were better than those of the control group ($P < 0.05$). The adverse reaction rate in the experimental group was similar to that in the control group ($P > 0.05$). *Conclusion:* LVA can improve the clinical efficacy of patients with AD, enhance their cognitive function and language expression, regulate the level of cerebrospinal fluid biomarkers, and has high surgical safety.

Keywords: Deep cervical lymphatic-venous anastomosis; Alzheimer's disease; Transcranial magnetic stimulation; Medication

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1. Introduction

Alzheimer's disease (AD) is a highly concealed neurological disease characterized by progressive degeneration. Its symptoms include decreased executive function, memory impairment, and behavioral changes, which can easily lead to diseases such as senile dementia^[1-3]. The commonly used treatments for this disease are oral medications such as donepezil and sodium oligomannate, which can nourish nerves and have a strong regulatory effect on

the microbiome-gut-brain axis, thereby reducing disease symptoms ^[4-5]. Transcranial magnetic stimulation is a physical therapy for this disease that can electromagnetically stimulate brain tissue to enhance neuronal activity and improve patients' cognitive function. However, the above therapies have limitations in terms of radical treatment ^[6-8]. LVA is a novel microsurgical procedure that involves anastomosing deep cervical lymphatics and jugular veins to promote lymphatic circulation and clear waste, pathogenic factors, and toxins from the brain, such as A β protein and Tau protein, thereby controlling the disease ^[9]. Based on this, 120 patients with AD were selected for this study to evaluate the therapeutic effect of LVA.

2. Materials and methods

2.1. General information

A total of 120 patients with AD admitted to the hospital between December 2022 to December 2024 were selected and randomly divided into two groups using a random number table. The control group consisted of 60 patients, including 33 males and 27 females, with ages ranging from 50 to 78 years old and a mean age of 62.18 ± 3.78 years. The experimental group also consisted of 60 patients, including 34 males and 26 females, with ages ranging from 48 to 77 years old and a mean age of 62.31 ± 3.82 years. There was no significant difference between the two groups ($P > 0.05$).

Inclusion criteria: Age <90 years old; normal liver and kidney function; newly diagnosed patients; meeting the indications for drug therapy, physical therapy, and surgical treatment; complete basic information; and informed consent for the study. Exclusion criteria: The etiology of cognitive impairment is cerebrovascular disease, etc.; Other neurological diseases such as Parkinson's disease; Combined with severe infection; Difficult to tolerate lumbar puncture; Withdrawal in the middle of the study.

2.2. Methods

The control group received transcranial magnetic stimulation combined with drug therapy. A transcranial magnetic stimulator was used, targeting the bilateral prefrontal lobes with a coil diameter of 12 cm and a frequency of 10 Hz. Stimulation was applied for 5 seconds, followed by a 25-second rest, with 30 repetitions per session. Treatment was administered 5 days per week for a total of 12 weeks. Additionally, patients received oral administration of donepezil hydrochloride at a dose of 5 mg once daily, which was increased moderately after 4 weeks of treatment, with a maximum daily dose of 10 mg. They also took sodium oligomannate at a dose of 450 mg twice daily. Both medications were continued for 12 weeks.

The experimental group underwent LVA treatment. Patients were positioned in a supine position, and marks were made along the anterior and posterior borders of the sternocleidomastoid muscle. High-frequency ultrasound was used to scan the deep cervical lymph nodes at the marked sites, evaluate the branching and course characteristics of the external jugular vein, and measure the specific caliber of the external jugular vein. Under general anesthesia, bilateral LVA treatment was performed. An incision of approximately 5cm was made in the middle of the posterior border of the sternocleidomastoid muscle. Indocyanine green (3 ml) was injected into the subcutaneous tissue behind the ear, the root of the mastoid process, and the angle of the jaw for lymphangiography. The platysma muscle was incised along the incision, and dissection was performed deep to expose the superficial cervical plexus nerve and external jugular vein. On the basis of protecting the great auricular nerve, the posterior border of the sternocleidomastoid muscle was identified, and the muscle was separated. The muscle tissue was

lifted forward appropriately, and the carotid sheath was dissected to expose the lymph nodes in zone III outside the lateral region of the internal jugular vein. The specific morphology of the lymph nodes and the characteristics of the lymphatic vessel course were evaluated. The platysma muscle was dissected, and the anterior border of the sternocleidomastoid muscle was identified. After separating the anterior border of the sternocleidomastoid muscle, the muscle was lifted backward to expose the lymph nodes (zone III) in the medial region of the vein. Dissection was performed toward the head to fully expose the lymph nodes in zone II. A fluorescence microscope was used to observe the lymph node development area and make clear markings. The external and internal jugular veins were dissected, and the lymph nodes (zone III) were also dissected while protecting the thick lymphatic vessels. The developed lymph nodes were moderately resected, and a cross-section was made to drain the lymph fluid. If the lymph fluid was clear, it indicated that the lymph node function was normal. The internal jugular vein or adjacent veins were taken, and the veins at both ends were clamped using venous clamps (the internal jugular vein was directly clamped on the lateral wall using a bulldog clamp). The vein was longitudinally incised with a length equivalent to the diameter of the lymphatic vessel. The outer membranes of the vein and lymph node cross-section were sutured with nylon sutures (single strand, 11-0), and end-to-side anastomosis was performed. The venous clamps were removed, and the anastomotic stoma was checked for leakage. Additional indocyanine green (0.1 ml) was injected behind the ear, and the shunt situation of the lymph fluid was evaluated under a fluorescence microscope. Due to the small movable range and large volume of lymph nodes in zone II, puncture was performed using a 16-gauge needle. The branch of the internal jugular vein and the outer membrane of the hole were sutured with nylon sutures (11-0), and end-to-end anastomosis treatment was performed. The wound was irrigated, and the bleeding was stopped. A drainage tube was placed, and the incision and platysma tissue were sutured in layers with tension reduction. Low molecular weight heparin was continuously administered for anticoagulation for 48 hours, and the patient's signs were monitored. The drainage tube could be removed 48 hours after surgery.

2.3. Observation indicators

2.3.1. Cognitive function scores

Mini-mental state examination (MMSE): Including orientation, recall, and language ability, with a total score of 30, and cognitive function is positively scored; Montreal cognitive assessment (MoCA): Including memory, executive function, and visual-spatial skills, with a total score of 30, and cognitive function is positively scored; Neuropsychiatric inventory (NPI): Including 12 items such as delusions, hallucinations, and anxiety, with a total score of 144 (each item scores 12), and cognitive function is negatively scored.

2.3.2. Cerebrospinal fluid biomarkers

Lumbar puncture was performed on an empty stomach, and 6 ml of cerebrospinal fluid was taken. The fluid was centrifuged for 15 minutes at 2000 r/min and placed at 4°C for 1 hour. The supernatant was taken, and the levels of beta-amyloid protein 1-40 (A β 1-40), A β 1-42, phosphorylated tau protein (P-tau), and total tau protein (T-tau) were evaluated by enzyme-linked immunosorbent assay.

2.3.3. Adverse reaction rate

The incidence of nausea, vomiting, dizziness, infection, diarrhea, hematoma, and poor wound healing was observed.

2.4. Therapeutic effect evaluation criteria

Significant effect means significant improvement in symptoms/signs, normal social skills, and ability to live independently; Effective means improvement in symptoms/signs, recovery of social skills, but poor self-care ability; Ineffective means no improvement in symptoms/signs, social skills, or self-care ability.

2.5. Statistical analysis

The data was processed by SPSS 28.0 software. Measurement values were compared/tested by t-value, and count values were compared/tested by chi-square value. Statistical significance was considered when the *P*-value was less than 0.05.

3. Results

3.1. Comparison of the total effective rate between the two groups

The total effective rate of the experimental group was higher than that of the control group ($P < 0.05$), as shown in Table 1.

Table 1. Comparison of total effective rate between the two groups [n/%]

Group	Number of cases	Markedly effective	Effective	Ineffective	Total effective rate
Experimental group	60	35 (58.33)	24 (40.00)	1 (1.67)	98.33 (59/60)
Control group	60	33 (55.00)	20 (33.33)	7 (11.67)	88.33 (53/60)
χ^2					4.821
<i>P</i>					0.028

3.2. Comparison of cognitive function scores between the two groups

Before treatment, there was no difference in cognitive function scores between the two groups ($P > 0.05$). After treatment, the cognitive function score of the experimental group was better than that of the control group ($P < 0.05$), as shown in Table 2.

Table 2. Comparison of cognitive function scores between the two groups [Mean \pm SD, points]

Group	Number of cases	MMSE score		MoCA score		NPI score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	60	20.15 \pm 2.65	26.95 \pm 3.12	11.53 \pm 2.15	25.04 \pm 2.91	92.53 \pm 7.15	52.98 \pm 5.07
Control group	60	20.11 \pm 2.62	24.02 \pm 3.10	11.51 \pm 2.13	23.01 \pm 2.88	92.48 \pm 7.11	57.13 \pm 5.18
<i>t</i>		0.083	5.160	0.051	3.841	0.038	4.435
<i>P</i>		0.934	0.000	0.959	0.000	0.969	0.000

3.3. Comparison of cerebrospinal fluid biomarkers between the two groups

Before treatment, there was no difference in cerebrospinal fluid biomarkers between the two groups ($P > 0.05$). After treatment, the cerebrospinal fluid biomarkers of the experimental group were better than those of the control group ($P < 0.05$), as shown in Table 3.

Table 3. Comparison of cerebrospinal fluid biomarkers between the two groups [Mean \pm SD]

Group	Number of cases	A β 1-40 (ng/ml)		A β 1-42 (ng/ml)		P-tau (pg/ml)		T-tau (ng/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	60	7.98 \pm 1.25	7.35 \pm 0.41	0.26 \pm 0.08	0.35 \pm 0.10	77.53 \pm 6.48	50.48 \pm 4.26	0.55 \pm 0.10	0.23 \pm 0.08
Control group	60	7.96 \pm 1.27	7.72 \pm 0.45	0.25 \pm 0.09	0.30 \pm 0.07	77.51 \pm 6.42	55.13 \pm 4.31	0.54 \pm 0.11	0.37 \pm 0.06
<i>t</i>		0.087	4.708	0.643	3.173	0.017	5.944	0.521	10.844
<i>P</i>		0.931	0.000	0.521	0.002	0.986	0.000	0.603	0.000

3.4. Comparison of adverse reaction rates between the two groups

The adverse reaction rate in the experimental group was similar to that in the control group ($P > 0.05$), as shown in Table 4.

Table 4. Comparison of adverse reaction rates between the two groups [n/%]

Group	Number of cases	Nausea and vomiting	Dizziness	Infection	Diarrhea	Hematoma	Poor wound healing	Incidence rate
Experimental group	60	0	0	1 (1.67)	0	1 (1.67)	1 (1.67)	5.00 (3/60)
Control group	60	1 (1.67)	1 (1.67)	1 (1.67)	1 (1.67)	0	0	6.67 (4/60)
χ^2								0.152
<i>P</i>								0.697

4. Discussion

Alzheimer's disease (AD) is a cognitive impairment disease with a high incidence rate. Its early stage is asymptomatic, making diagnosis challenging^[10–11]. The pathogenesis of AD is complex, involving genetic factors and neurotransmitter disorders, and conventional treatment often involves oral medication^[12–13]. Donepezil, a commonly used cholinesterase inhibitor, effectively inhibits acetylcholinesterase in brain tissue, promoting acetylcholine hydrolysis and improving cognitive and motor functions^[14]. Sodium oligomannate, a novel drug for AD, targets the brain-gut axis, corrects intestinal flora imbalance, and enhances cognitive function^[15–16]. Combined with transcranial magnetic stimulation, it can stimulate the cerebral cortex, improve brain metabolism, enhance interaction between subcortical nuclei and the cerebral cortex, restore the original structure of nerve cells, and alleviate disease symptoms^[17]. These therapies, based on traditional pathogenic mechanisms of AD, can stabilize the condition but often have limited long-term efficacy^[18–20].

In recent years, clinical medicine has deeply explored the pathological basis of AD, identifying abnormal meningeal lymphatic function as a risk factor^[21]. Improving meningeal lymphatic function could potentially slow disease progression^[22]. Additionally, lymphatic plexus degeneration is another etiological factor. The nasopharyngeal region, rich in lymphatic plexuses, facilitates cerebrospinal fluid (CSF) outflow. Degeneration of these plexuses can impede CSF outflow. Based on these theories, this study implemented lymphovenous anastomosis (LVA) for AD patients^[23–25]. LVA involves anastomosing deep cervical lymph nodes to the internal jugular vein, enabling lymph fluid to flow back into the vein. This utilizes the pressure difference between lymph

fluid and venous blood to clear amyloid-beta protein and tau protein from the lymph fluid. LVA safely and effectively drains lymph fluid through deep cervical lymphatics, removing toxic proteins.

Results showed that the experimental group had a higher total effective rate than the control group. After treatment, the experimental group had higher MMSE and MoCA scores and a lower NPI score. Additionally, the experimental group had lower levels of A β 1-40, P-tau, and T-tau, and higher levels of A β 1-42 ($P < 0.05$). The adverse reaction rate in the experimental group was similar to the control group ($P > 0.05$). During LVA surgery, high-frequency ultrasound is used to observe the lymphatic system's functional status, revealing its location, structure, and size. This helps assess the internal jugular vein's course and variability, enabling surgical plan design^[26]. Lymphangiography involves injecting indocyanine green into the lymphatic system, facilitating visualized anastomosis and assessing CSF patency post-surgery, ensuring clinical efficacy^[27–29]. LVA's brain drainage mechanism lowers intracranial lymphatic pressure, effectively anastomosing cervical lymph nodes and regional veins, thereby alleviating symptoms and improving cognitive function. Furthermore, guided by high-frequency ultrasound and lymphangiography, LVA boasts high precision and minimal intraoperative damage, reducing postoperative complications like hematoma^[30]. Studies have shown that meningeal lymphatic function correlates with age, with older individuals experiencing more significant decline, strongly linked to AD. Currently, LVA therapy is being clinically explored to reduce cognitive impairment and alleviate AD symptoms^[31]. According to cell research, LVA involves a clear mechanistic loop: meningeal lymphatics \rightarrow interleukin-6 \rightarrow synapses \rightarrow cognition. Future research could integrate LVA surgery with brain lymphatic imaging and cognitive assessment, aiming to rebuild the brain microenvironment, delay cognitive decline, and achieve optimal therapeutic outcomes.

5. Conclusion

In summary, LVA is highly effective in treating AD patients, improving cognitive function, restoring CSF patency, and not increasing postoperative adverse reactions, highlighting its surgical advantages.

Disclosure statement

The authors declare no conflict of interest.

References

- [1] Lu HR, Tan YF, Xie QP, 2022, Preliminary Observation on the Efficacy of Deep Cervical Lymphatic-venous Shunt Surgery under 3D Glasses-free Environment in the Treatment of an Elderly Patient with Cognitive Impairment. *Chinese Journal of Microsurgery*, 45(5): 570–574.
- [2] Gooty VD, Reddy SRV, Greer JS, et al., 2021, Lymphatic Pathway Evaluation in Congenital Heart Disease using 3D Whole-heart Balanced Steady State Free Precession and T2-weighted Cardiovascular Magnetic Resonance. *Journal of Cardiovascular Magnetic Resonance*, 23(1): 16.
- [3] Welker JL, Hardie RJ, Weber KA, et al., 2024, Anastomosis of the Caudal Thoracic Duct and Intercostal Vein using a Microvascular Anastomotic Coupler Device: Experimental Study in Six Dogs. *Veterinary Surgery*, 53(7): 1248–1255.
- [4] Xie PA, Liao H, Zhang YM, et al., 2022, Effects of miR-146a Tail Intravenous Injection on Cognitive Ability, Th17/Treg Distribution, and Inflammatory Factor Levels in Alzheimer's Disease Rats. *Shandong Medical Journal*, 62(20): 46–49.

- [5] Jang S, Lee CU, Hesley GK, et al., 2022, Lymphatic Mapping Using US Microbubbles before Lymphaticovenous Anastomosis Surgery for Lymphedema. *Radiology*, 304(1): 218–224.
- [6] Uyulmaz S, Grunherz L, Giovanoli P, et al., 2024, Primary Lymphovenous Anastomosis After Extended Soft Tissue Resection in the Medial Thigh for Reduction of Lymphocele and Lymphedema. *Annals of Plastic Surgery*, 93(2): 8.
- [7] Hattori Y, Hino H, Niu A, 2021, Surgical Lymphoedema Treatment of Morbihan Disease: A Case Report. *Annals of Plastic Surgery*, 86(5): 547–550.
- [8] Li K, Wen K, Ai ST, et al., 2025, Preliminary Clinical Observation on the Treatment of Alzheimer's Disease with Lymphatic/node-venous Shunt Surgery in Neck Zone II/III. *Journal of Tissue Engineering and Reconstructive Surgery*, 21(1): 10–13.
- [9] Fu XX, Liu XX, Fu MX, 2024, Application of 20 Hz Repetitive Transcranial Magnetic Stimulation in Improving Cognitive Function of Patients with Alzheimer's Disease and its Effect on Serum Inflammatory Factors. *Sichuan Journal of Physiological Sciences*, 46(3): 484–486 + 496.
- [10] Xia T, Cakmakoglu C, Kwiecien G, et al., 2023, ASO Author Reflections: Prophylactic Lymphaticovenous Anastomosis Performed with Lymphadenectomy is Oncologically Safe for Melanoma. *Annals of Surgical Oncology*, 30(3): 1.
- [11] Song MJ, Ahn JH, Han EJ, 2023, EP336/#874 Semiquantitative Lymphoscintigraphy in Gynecologic Cancer Patients with Lower Extremity Lymphedema: Prediction of Short-term Outcome after Lymphaticovenous Anastomosis. *International Journal of Gynecological Cancer*, 33(Sup4): 1.
- [12] Cakmakoglu C, Gastman B, Xia T, et al., 2022, Prophylactic Lymphaticovenous Bypass Performed during Complete Lymphadenectomy is Oncologically Safe. *Journal of Clinical Oncology*, 40(16): 9557.
- [13] Xu Y, Wang H, Zhang JG, 2020, The Role and Biological Significance of the GSK-3 β Signaling Pathway in Alzheimer's Disease. *Medicine Guide*, 39(12): 1716–1720.
- [14] Li DM, 2023, The Effect of Transcranial Magnetic Stimulation Combined with Medication on Improving Cognitive Function, Psychiatric Symptoms, and Neurotransmitters in Patients with Alzheimer's Disease. *Chinese Journal for Clinicians*, 51(10): 1183–1185.
- [15] Vaiyani D, Ford B, Gupta M, et al., 2023, Abstract 16011: Lymphatic Intervention Following Superior Cavo-Pulmonary Anastomosis Potentially Allows for Successful Fontan Completion. *Circulation*, 148(Sup1): 2.
- [16] Tolksdorf K, Hohberger FS, Ernst C, et al., 2024, First Experience using a Novel Microsurgical Robotic Device for Free Flap Surgery in Cranio- and Maxillofacial Surgery. *Journal of Cranio-Maxillofacial Surgery*, 52(6): 704–706.
- [17] Onoda S, Tsukura K, Taki K, et al., 2024, Teaching of Microsurgery and Supermicrosurgery for Residents. *Journal of Craniofacial Surgery*, 35(3): 3.
- [18] Jia WL, Xu DY, Zhou GP, 2024 A Case of Sodium Oligomannate Combined with Antiepileptic Drugs in the Treatment of Alzheimer's Disease with Epilepsy and Dementia Behavioral and Psychiatric Symptoms. *Journal of Brain and Nervous Diseases*, 32(9): 580–583.
- [19] Ding Y, Yue L, Wang JH, et al., 2023, A Randomized Double-blind Controlled Study of High-frequency Repetitive Transcranial Magnetic Stimulation of the Left Frontal Lobe to Improve Psychiatric Symptoms in Alzheimer's Disease. *Geriatrics & Health Care*, 29(5): 997–1001.
- [20] Qi S, Wang Y, Zhu Y, et al., 2023, NIR-II Fluorescence Lymphatic Imaging and Intraoperative Navigation Based on the "Isolated Cage" Monodisperse Strategy. *Nano Today*, 2023(49): 11.
- [21] Boyages J, Koelmeyer LA, Suami H, et al., 2020, The ALERT Model of Care for the Assessment and Personalized Management of Patients with Lymphoedema. *British Journal of Surgery*, 107(3): 238–247.

- [22] Sbitany H, 2022, Abstract ES8-1: Options for Reducing Risk for Lymphedema when ALND/regional Nodal XRT are Needed. *Cancer Research*, 82(4-Sup): 2.
- [23] Chen Y, 2023, “Study on the Effects of Different Antipsychotic Drugs on the Behavior and Psychiatric Symptoms of Patients with Alzheimer’s Disease. *Primary Medical Forum*, 27(31): 18–20.
- [24] Mo YW, Lee SJ, Lee DW, et al., 2024, Contrast-enhanced Ultrasonography as an Adjunctive Method to ICG Lymphography for Functional Lymphaticovenous Anastomosis. *Journal of Surgical Oncology*, 129(5): 965–974.
- [25] Chung JH, Kim DJ, Yoon ES, et al., 2023, First Experience of Lymphaticovenular Anastomosis using BHC RobotiScope: A Case Report. *Medicine*, 102(20): 3.
- [26] Jakub JW, Boughey JC, Hieken TJ, et al., 2024, Lymphedema Rates Following Axillary Lymph Node Dissection with and without Immediate Lymphatic Reconstruction: A Prospective Trial. *Annals of Surgical Oncology*, 31(11): 11.
- [27] Janani V, Robert CK, Ryan B, et al., 2023, Western Diet-induced Transcriptional Changes in Anastomotic Tissue is Associated with Early Local Recurrence in a Mouse Model of Colorectal Surgery. *Annals of Surgery*, 278(6): 954–960.
- [28] Mulken TJMV, Schols RM, Scharmga AMJ, et al., 2020, First-in-human Robotic Supermicrosurgery Using a Dedicated Microsurgical Robot for Treating Breast Cancer-related Lymphedema: A Randomized Pilot Trial. *Nature Communications*, 11(1): 757.
- [29] Awwad A, 2021, Editorial for: “Noncontrast MR Lymphography in Secondary Lower Limb Lymphedema”. *Journal of Magnetic Resonance Imaging*, 53(2): 467–468.
- [30] Alsaied T, Ashfaq A, 2021, From Other Journals: A Review of Recent Articles in Pediatric Cardiology. *Pediatric Cardiology*, 42(2): 469–473.
- [31] Kim K, Abramishvili D, Du S, et al., 2025, Meningeal Lymphatics-Microglia Axis Regulates Synaptic Physiology. *Cell*, S0092-8674(25): 00210-7.

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Application Status and Prospect of Craniocerebral Ultrasound in Neurodevelopment of Premature Infants

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Abstract: The purpose of this paper is to review the current status and future direction of the application of Cranial Ultrasonography (CUS) in the monitoring of brain development in preterm infants. A systematic search of the relevant literature and a comprehensive analysis of the data in these literatures indicate that CUS can provide real-time information about the structural and hemodynamic changes in the brain of preterm infants, which can help to identify neurodevelopmental abnormalities at an early stage, and that the application of new technologies, such as ultrasound elastography, ultrasound microfluidics, and ultrasonography, has further enhanced the assessment capability of CUS. Although the use of artificial intelligence algorithms such as deep learning in monitoring the neurodevelopment of preterm infants is still in its early stages, its promising future in clinical applications is of far-reaching significance. The monitoring of brain development of preterm infants by CUS is effective and accurate, providing more accurate brain development monitoring and more effective treatment programs for preterm infants.

Keywords: CUS; Preterm infants; Brain development; Neurodevelopment; Research progress

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1. Introduction

With the rapid development of perinatal medicine, the birth rate of preterm infants continues to rise worldwide^[1]. However, preterm infants often face severe challenges of neurodevelopmental disorders due to their immature physiological development. Especially, as the core of the human body function, the development of the brain directly affects children's future cognitive, motor, and other neurological functions. Therefore, close monitoring of their brain development has become essential^[2]. Early assessment of brain development in preterm infants is of great significance for the prevention and improvement of neurodevelopmental problems. Cranial Ultrasonography (CUS) plays an important role in the neonatal intensive care unit (NICU) because of its convenience, non-

radiation, cost-effectiveness, and real-time dynamic monitoring^[3]. CUS can capture the brain structure and hemodynamic changes of preterm infants in real time, providing clinicians with intuitive and powerful evaluation tools, which are helpful in formulating accurate treatment plans.

This review aims to comprehensively analyze the application status of craniocerebral ultrasound in monitoring brain development in preterm infants and explore the research progress of craniocerebral ultrasound in evaluating brain structure, monitoring cerebral blood flow, and predicting neurodevelopmental prognosis. Through in-depth analysis of the existing literature, this article aims to reveal how craniocerebral ultrasound can help clinicians better understand the complex process of brain development and its potential risks in preterm infants, and to look forward to the future development direction. With the continuous progress of new ultrasound technology, cranial ultrasound is expected to play a broader and deeper role in the monitoring of brain development in preterm infants.

2. Brain development before birth

The development and maturation of the brain is an intricate and long journey from the fetal period, the neonatal period, and the adult period^[4]. The development of the nervous system begins in the ectoderm, where the neural tube grows and differentiates to give rise to the brain and spinal cord. At about the third week of embryonic development, the neural plate begins to form and is completely transformed into the neural tube during the following week, and its apical part continues to evolve into the brain. By the end of the fourth week of embryonic development, the tip of the neural tube develops into the forebrain, midbrain, and hindbrain. The forebrain develops most rapidly, and its front part gradually develops into two cerebral hemispheres, while the posterior part of the forebrain develops into the thalamus and hypothalamus. The development of the midbrain is relatively slow. The hindbrain and the endbrain evolved into the pons and cerebellum, respectively, and the medulla oblongata. In the middle of pregnancy, as nerve cells proliferate, differentiate, and migrate to various regions of the brain, the cerebral cortex begins to form, and gradually forms sulci and gyri. The hindbrain and the endbrain gradually form the pons, cerebellum, and medulla oblongata, while the cerebellum develops on the dorsal side of the brainstem and covers it. The inner lumen of the neural tube forms the main structure of the ventricle, and the shape of the ventricle is closely related to the development of the brain. The two lateral ventricles, the third ventricle, and the fourth ventricle, which evolved from the anterior cerebral bubble cavity, constitute the ventricular system. The lateral ventricle is connected to the third ventricle through the interventricular foramen, while the mesencephalic aqueduct connects the third and fourth ventricles.

In the development of the central nervous system, myelination begins in the fetal period. It is a process in which axons are encapsulated by lipid substances, which is closely related to the conduction of nerve impulses and cognitive function. White matter is mainly composed of axons, which are lighter in color and are responsible for the transmission of signals between the two cerebral hemispheres. Gray matter, which is darker in color and composed of neuronal bodies, dendrites, and glial cells, is mainly responsible for the processing of brain information, such as perception, movement, and cognition, which plays a key role.

3. Neurodevelopmental abnormalities in preterm infants and their influencing factors

Preterm infants are those born before 37 weeks of gestation. According to the World Health Organization definition, preterm infants are divided into several categories: extremely preterm (<28 weeks of gestation), very

preterm (28–32 weeks of gestation), and moderate-to-late preterm (32–37 weeks of gestation). Preterm infants face many risks of poor health and neurodevelopmental outcomes due to their low gestational age. Neurodevelopmental immaturity in preterm infants is associated with poor vascular autoregulation, incomplete myelination of white matter, and incomplete proliferation and differentiation of cortical cells ^[5]. According to the principle of the “two-hit” hypothesis, G et al. demonstrated that the factors of abnormal brain development in preterm infants may be caused by a combination of developmental disruption and external injuries (including hypoxia, mechanical ventilation time, low glucose, etc.) ^[6]. If the whole process of neurodevelopment is disturbed at any stage, the neonatal neurodevelopment will be affected.

A common form of hypoxic brain injury in preterm infants is germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH). Stem cells in the germinal matrix differentiate into neurons and then migrate to functional areas of the cerebral cortex, which typically dissipate by 35 weeks of gestation. The vascular network of the germinal matrix is the most blood-rich region of the developing brain. Especially in preterm infants with a gestational age of less than 32 weeks, their vascular system is not mature, and their ability to autonomously regulate blood flow is weak. Especially, fetal distress in utero or asphyxia during delivery, electrolyte imbalance, respiratory failure, and other conditions may lead to neonatal cerebral ischemia and hypoxia, and vascular rupture and hemorrhage ^[7–8]. In turn, it can cause complications such as post-hemorrhagic hydrocephalus and leukomalacia.

Another serious brain injury in preterm infants is white matter injury (WMI) ^[9]. White matter is mainly located in the arterial watershed region. During the third trimester of pregnancy, with the active development of paraventricular vessels and the maturation of oligodendrocytes, the white matter is particularly vulnerable to injury. Oligodendrocytes are responsible for forming the myelin sheath, a structure that is very sensitive to ischemia ^[10]. In addition, the role of gut microbes in the neurodevelopment of preterm infants has gradually become prominent, forming a microbiota-gut-brain axis, which affects the occurrence of WMI in preterm infants through metabolites produced by gut microbes, and also regulates cytokines and mediates oxidative stress ^[11]. The lack of microbiota and its metabolites may aggravate WMI in preterm infants. Preterm infants with white matter damage may present with a variety of neurodevelopmental abnormalities, including cognitive impairment, learning and memory impairment, impaired motor coordination, language impairment, audio-visual impairment, hyperactivity, emotional problems such as anxiety and depression, and even serious complications such as cerebral palsy ^[12, 14].

4. Application of cranial ultrasound in the assessment of brain development in preterm infants

4.1. Evaluation of brain development by two-dimensional ultrasound

Two-dimensional ultrasound is usually performed through the unclosed fontanelle of children, and a small convex or linear probe is selected for sector scanning. The fontanelle includes the anterior fontanel (commonly used), the lateral fontanel, and the mastoid fontanel, which are all transparent windows of cranial ultrasound examination. Craniocerebral ultrasound is a detailed assessment of brain development in children through specific ultrasound sections. Two-dimensional cranial ultrasound can be used to evaluate the development and maturation of the brain, which can be monitored as follows: identification of brain structures; Evaluation of the ventricular system; observation of sulci and gyri ^[14–15].

4.1.1. Identification of brain structures

The degree of brain development was evaluated by measuring the diameters of the main brain structures (transverse diameter of the brain, frontal lobe thickness, insula, length of corpus callosum, ventricular system, basal ganglia, brain stem, cerebellum, etc.). The diameter of brain structures in preterm infants is smaller than that in term infants, and the overall brain volume is smaller.

Sun et al. showed in their study on the correlation between neonatal cranial ultrasound indicators and neurodevelopment that there were differences in the length of the corpus callosum, the length of the cerebellar vermis, and the area and perimeter of the insula in neonates with neurodevelopmental abnormalities, and the brain diameter of neonates with neurodevelopmental abnormalities was smaller than that of neonates with normal development ^[16]. Liu et al. showed that the growth rate of the corpus callosum in some very low birth weight preterm infants with severe intellectual or motor development abnormalities was lower than that in the normal group at 3–6 weeks after birth, which was similar to the conclusion of Anderson et al. ^[17–18]. Many years ago, the decrease in the growth rate of the corpus callosum before 6 weeks after birth can serve as a warning factor for abnormal brain neurodevelopment in preterm infants. In a prospective study of very low birth weight preterm infants, Huang et al. evaluated the linear growth of the corpus callosum and the cerebellar vermis by cranial ultrasound ^[19]. After a corrected gestational age of 30.5 weeks, the growth rate of the corpus callosum was 1.72 mm/week, and the growth rate of the length of the cerebellar vermis was 0.78 mm/week. This may be helpful for early identification of preterm infants at risk of neurodysplasia and timely intervention. Zhou et al. conducted a study on the correlation between brain ultrasound manifestations and gestational age and birth weight in preterm infants at different gestational ages ^[20]. Gestational age was negatively correlated with the average gray value of white matter in the basal ganglia, frontal lobe, parietal lobe, and occipital lobe, while birth weight was also negatively correlated with the average gray value of the above brain tissue. The results indicate that the average gray value of brain tissue can be used to evaluate the development of the neonatal brain and provide important reference information for clinical practice.

4.1.2. Evaluation of the ventricular system

By observing the size and shape of the lateral ventricle, septum pellucidum, the third ventricle, and the fourth ventricle, the authors evaluated whether there was ventricular expansion or hydrocephalus, so as to explore its effect on the brain nerve development of premature infants. Ventriculomegaly (VM) refers to an increase in the volume of the ventricles caused by the accumulation of cerebrospinal fluid. Ventriculomegaly is the most common cause. Obvious ventriculomegaly is often accompanied by other structural abnormalities or chromosomal abnormalities, which are closely related to children's intellectual and motor development ^[21]. The ventricular system of premature infants is not fully developed and does not retract. Ultrasound examination can observe that the shape of the ventricle is extended, S-shaped, or wider than that of the full-term infants, which may be related to the maturity of brain tissue and the characteristics of cerebrospinal fluid circulation.

4.1.3. Observation of sulci and gyri

The greater the gestational age at birth, the more gyri, the deeper the sulci, the more tortuosity, and the smaller the cerebral space. Two-dimensional ultrasound of the brain of premature infants can show that the brain parenchyma is fine, the cerebral sulci and gyrus are less, the cerebral sulci are shallow, and even the cerebral sulci structure is not formed, and the differentiation of the insula is not complete.

4.2. Assessment of brain development by 3D ultrasound

Three-dimensional ultrasound technology began to be used in pediatric brain examination in the 1980s, which can provide morphological imaging and quantitative volume analysis after multi-directional scanning of the brain. Compared with two-dimensional ultrasound, the images are richer and more three-dimensional, and the brain structure is more intuitive, and the judgment of brain volume is more accurate. Maria et al. measured the whole brain volume, thalamus, frontal cortex, and cerebellum volume of premature infants and newborns at different gestational ages at one month after birth using three-dimensional ultrasound, and compared the results with the neurodevelopment results of children at two years old ^[22]. The study found that the brain volume of children with neurodysplasia was significantly reduced, and had high accuracy. Isabel et al. used cranial ultrasound (US) to continuously measure the brain volume of preterm infants until corrected term, and established cross-sectional and longitudinal reference values of cerebellar size in preterm infants, suggesting that extrauterine life may affect the growth of the cerebellum, resulting in impaired cerebellar development ^[23]. Three-dimensional cranial ultrasound technology can also provide a comprehensive assessment of brain development in preterm infants, combined with other new ultrasound technologies. With the further development and application of technology, three-dimensional ultrasound is expected to provide a more accurate and comprehensive assessment method for the brain development of preterm infants.

4.3. Evaluation of brain development by ultrasound cerebral blood flow parameters

Transcranial Doppler ultrasound (TCD) is one of the non-invasive techniques for monitoring cerebral blood flow, which plays an important role in evaluating the brain development of premature infants. This technique accurately measures the blood flow velocity, resistance index, and other blood flow parameters of the main cerebral arteries (such as the middle cerebral artery (MCA) and anterior cerebral artery (ACA)). To explore the relationship between cerebral blood flow and brain development. Arditi et al. found that in extremely preterm infants, higher right MCA systolic velocity was associated with worse neonatal perception, and higher left MCA systolic velocity was associated with higher Mental Development Index (MDI) scores at 24 months, findings that suggest the impact of left-right cerebral blood flow differences on neurodevelopment ^[24]. CAI et al. investigated the association between hemodynamic parameters of the middle cerebral artery (MCA) and neurodevelopment in preterm infants ^[25]. The peak systolic velocity (PSV) and end diastolic velocity (EDV) of the neurodysplasia group were significantly lower than those of the good prognosis group, while the pulsatility index (PI), resistance index (RI), and the ratio of peak systolic velocity to end diastolic velocity (S/D) were significantly higher than those of the good prognosis group. The results of these studies suggest that clinicians, Early evaluation of cerebral blood flow in preterm infants is of great clinical significance for predicting later brain nerve development. In addition, in a recent study, Kenichi et al. studied the relationship between intracranial venous (ICV) pulsation and intraventricular hemorrhage (IVH), and found that severe IVH had persistent and significant intracranial venous pulsation, and pulsation index (ICVPI = minimum/maximum ICV velocity) may help to predict severe IVH ^[26]. This is of great significance for reducing the adverse brain consequences of preterm infants.

4.4. New ultrasound technologies

4.4.1. Elastography

Ultrasound elastography, including strain elastography (SE), transient elastography (TE), and shear wave elastography (SWE), uses ultrasound to apply pressure to tissues and calculate tissue deformation to evaluate

tissue stiffness and infer tissue physical properties and composition through non-invasive mechanical action. Elastography can be used to quantitatively or semi-quantitatively evaluate the changes in brain tissue stiffness, which provides a new perspective for the diagnosis of brain development and lesions. Neuronal differentiation, glial cell proliferation, gyri formation, and myelination may affect brain stiffness. Therefore, the changes in stiffness between preterm and term infants can reflect the differences in developmental stages ^[27]. Albayrek and Kasap compared the brain stiffness of term and preterm infants using SWE and observed that the stiffness of various regions of the brain of term infants was higher than that of preterm infants, similar to Kim et al.'s study ^[28–29]. Wang et al. showed in their study that the mean elastic modulus values of periventricular white matter, thalamus, and choroid plexus in preterm infants were lower than those in term infants, and the BMI of preterm and term infants was positively correlated with the mean elastic modulus values of bilateral periventricular white matter, thalamus, and choroid plexus ^[30]. Therefore, ultrasound elastography is expected to become a new method for predicting delayed brain development or poor prognosis in preterm infants.

4.4.2. Superb microvascular imaging

Superb microvascular imaging (SMI) is an advanced non-invasive ultrasound Doppler technology, which can clearly display the low-velocity microvascular network in the brain, including the striatum and the extrastriate vessels ^[31]. With fetal development, the distribution, density, and flow velocity of the above vessels also change. SMI can monitor these changes in real time and provide quantitative indicators for brain maturity. Superb microvascular imaging technology is eager to provide a non-invasive and highly sensitive tool for the detection of brain maturity in neonates or premature infants, and has broad clinical application prospects. With the update and iteration of ultrasound instruments, it may become a major auxiliary tool for neonatal brain functional imaging in the future.

4.4.3. Contrast-enhanced ultrasound technology

Contrast-enhanced ultrasound (CEUS), also known as contrast-enhanced ultrasound (CEUS), improves the visualization of blood vessels by injecting a microbubble contrast agent into the body, allowing more accurate qualitative and quantitative assessment of brain perfusion ^[29]. In the field of neonatal brain imaging, CEUS technology can provide a more accurate delineation of brain microblood flow than traditional ultrasound technology. In 2013, Kastler's group showed that contrast-enhanced ultrasound through the anterior fontanel (TCEUS) was more accurate than magnetic resonance imaging (MRI) in the diagnosis of neonatal brain lesions ^[32]. As an emerging diagnostic technology, CEUS is being more and more widely used in the diagnosis of central nervous system diseases in children. Ceus not only enriches the diagnostic methods of traditional ultrasound, computed tomography (CT), or MRI, but also is more suitable for children due to its high safety ^[33]. With its unique imaging ability, CEUS technology has shown great potential and application prospects in the diagnosis of neonatal brain diseases, and provides a powerful diagnostic tool for pediatricians.

5. Challenges and future directions of cranial ultrasound in brain development

Since the 1970s, computer technology has helped medical diagnosis, especially medical image analysis. In 2006, deep learning, especially convolutional neural network (CNN), made a major breakthrough in image recognition. At present, deep learning is mainly used to analyze MRI to monitor the brain development of premature infants

^[34–35]. However, due to the limitations of ultrasound images, such as dynamic scanning and low resolution, the related research of deep learning is in its infancy ^[36]. However, ultrasound images are non-invasive and real-time monitoring, which has the potential to monitor the brain development of preterm infants. CNN has been used in MRI analysis, but its application in ultrasound images is still in its infancy. Researchers hope to overcome the technical difficulties, improve the processing accuracy and reliability, and promote the use of computer language to make a major breakthrough in the assessment of brain development in preterm infants.

Future research will focus on the development and optimization of deep learning algorithms, aiming to improve the quality of ultrasound images and enhance the recognition of brain development features in preterm infants. Using advanced image processing technology to reduce noise and enhance key brain structures, and exploring the fusion of MRI and USI data to accurately assess brain maturity and developmental changes. Multi-modality imaging fusion will facilitate the discovery of comprehensive biomarkers and the early identification of developmental deviations. The self-adaptability and learning ability of deep learning algorithms will optimize ultrasound image analysis and improve the accuracy of brain structure segmentation. With the continuous progress of ultrasound and computer technology, personalized precision medical programs will provide stronger support for the monitoring of brain development in preterm infants.

6. Conclusions

This article reviews the application status, current problems, and future development of CUS in monitoring brain development in preterm infants, and highlights the absolute advantages of ultrasound in the NICU. By elaborating the evaluation methods of brain structure, ventricular system, and cerebral sulci and gyrus, it is proved that craniocerebral ultrasound provides strong support for the early identification of neurodevelopmental abnormalities in preterm infants. In addition, with the introduction of ultrasound cerebral blood flow parameters and new technologies such as elastography, superb microvascular imaging, and contrast-enhanced ultrasound technology, the application of cranial ultrasound in the evaluation of brain development in preterm infants is more promising. In the future, with the continuous progress of technology, craniocerebral ultrasound is expected to play a more accurate and comprehensive role in the monitoring of brain development in preterm infants, provide more detailed and reliable diagnostic information for clinical practice, help optimize treatment plans, and improve the prognosis of cerebral neurodevelopment in preterm infants.

Disclosure statement

The authors declare no conflict of interest.

References

- [1] Kline JE, Illapani VSP, He L, et al., 2024, Early Cortical Maturation Predicts Neurodevelopment in very Preterm Infants. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, 105(5): 460–465.
- [2] Van der Windt L, Simons NE, De Ruigh AA, et al., 2024, Long-term Child Follow-up after Randomised Controlled Trials Evaluating Prevention of Preterm Birth Interventions: A Systematic Review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 2024(303): 35–41.
- [3] Alfaiji J, 2023, Use of Cranial Ultrasound Prior to the Start of Therapeutic Hypothermia for Newborn

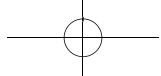
Encephalopathy. *Cureus*, 15(4): e37681.

- [4] Iwata R, 2022, Temporal Differences of Neurodevelopment Processes between Species. *Neuroscience Research*, 2022(177): 8–15.
- [5] Liu L, Chen Y, Huang BL, et al., 2024, Application of Magnetic Resonance Diffusion Tension Imaging in the Prognosis Evaluation of White Matter Injury and Neurodevelopment in Premature infants. *Shandong Medicine*, 64(4): 7–12.
- [6] Aylward GP, 2024, Alterations in Preterm Brain Development: Relation to Developmental Assessment and Prediction. *American Journal of Perinatology*, 41(7): 826–830.
- [7] Razif NAM, D’Arcy A, Waicus S, et al., 2024, Neonatal Encephalopathy Multiorgan Scoring Systems: Systematic Review. *Frontiers in Pediatrics*, 2024(12): 1427516.
- [8] Pineles BL, Mendez-Figueroa H, Chauhan SP, 2022, Diagnosis of Fetal Growth Restriction in a Cohort of Small-for-gestational-age Neonates at Term: Neonatal and Maternal Outcomes. *American Journal of Obstetrics & Gynecology MFM*, 4(5): 100672.
- [9] Kaul YF, Karimi AG, Johansson M, et al., 2024, MRI Findings, Looking Behaviour and Affect Recognition in very Preterm Children: A Pilot Study. *Physiology & Behavior*, 2024(280): 114553.
- [10] Qiu JY, Wang Q, Chen ZJ, et al., 2023, Research Progress of Cranial Ultrasound in Evaluating Brain Development in Premature Infants. *Journal of Gannan Medical College*, 43(1): 72–76.
- [11] Wang Y, Zhu J, Zou N, et al., 2023, Pathogenesis from the Microbial-gut-brain Axis in White Matter Injury in Preterm Infants: A Review. *Frontiers in Integrative Neuroscience*, 2023(17): 1051689.
- [12] Ping P, Yuan TM, 2021, Neuroprotection in Preterm Infants with Brain Injury: A Review. *Chinese Journal of Neonatology*, 36(1): 65–68.
- [13] Yuan TM, Yu HM, 2014, Rerecognition of Brain Injury in Preterm Infants. *Chinese Journal of Perinatal Medicine*, 17(5): 289–292.
- [14] Zhou CL, Tang ZZ, 2006, Neonatal Cranial Ultrasound Diagnosis 2nd Edition. Peking University Medical Press, Beijing.
- [15] Guideline Developed in Conjunction with the American College of Radiology (ACR), the Society for Pediatric Radiology (SPR), the Society of Radiologists in Ultrasound (SRU), 2014, AIUM Practice Guideline for the Performance of Neurosonography in Neonates and Infants. *Journal of Ultrasound in Medicine*, 33(6): 1103–1110.
- [16] Sun HT, Cao S, Shen Y, et al., 2019, Correlational Analysis of Neonatal Brain Ultrasound Indicators and Neonatal Behavioral Neurological Score. *Modern Practical Medicine*, 31(3): 299–301 + 429.
- [17] Liu RK, Sun J, Hu LY, et al., 2015, Correlation between Growth Rate of Corpus Callosum and Neuromotor Development in Preterm Infants. *Chinese Journal of Contemporary Pediatrics*, 17(8): 841–846.
- [18] Anderson NG, Laurent I, Woodward LJ, et al., 2006, Detection of Impaired Growth of the Corpus Callosum in Premature Infants. *Pediatrics*, 118(3): 951–960.
- [19] Huang HC, Chou HC, Tsao PN, et al., 2020, Linear Growth of Corpus Callosum and Cerebellar Vermis in very-low-birth-weight Preterm Infants. *Journal of the Formosan Medical Association*, 119(8): 1292–1298.
- [20] Zhou J, Zeng YR, Sun WQ, et al., 2019, Correlation between Neonatal Brain Development and Maternal Gestational Age and Birth Weight by Cranial Ultrasound. *Medical Review*, 25(16): 3317–3320.
- [21] Marinelli T, Yi JX, O’Shea TM, et al., 2024, Cerebral Palsy and Motor Impairment After Extreme Prematurity: Prediction of Diagnoses at Ages 2 and 10 Years. *The Journal of Pediatrics*, 2024(271): 114037.
- [22] Aisa MC, Barbati A, Cappuccini B, et al., 2021, 3-D Echo Brain Volumes to Predict Neurodevelopmental Outcome

- in Infants: A Prospective Observational Follow-up Study. *Ultrasound in Medicine & Biology*, 47(8): 2220–2232.
- [23] Benavente-Fernandez I, Rodriguez-Zafra E, Leon-Martinez J, et al., 2018, Normal Cerebellar Growth by Using Three-dimensional US in the Preterm Infant from Birth to Term-corrected Age. *Radiology*, 288(1): 254–261.
 - [24] Arditi H, Feldman R, Hammerman C, et al., 2007, Cerebral Blood Flow Velocity Asymmetry, Neurobehavioral Maturation, and the Cognitive Development of Premature Infants Across the First Two Years. *Journal of Developmental & Behavioral Pediatrics*, 28(5): 362–368.
 - [25] Cai R, 2024, Clinical Study of Color Doppler Ultrasound in Evaluating the Prognosis of Neurodevelopment in Preterm Infants, thesis, Soochow University.
 - [26] Tanaka K, Matsumoto S, Minamitani Y, et al., 2024, Changes in Internal Cerebral Vein Pulsation and Intraventricular Hemorrhage in Extremely Preterm Infants. *American Journal of Perinatology*, 41(S1): 37–45.
 - [27] Decampo D, Hwang M, 2018, Characterizing the Neonatal Brain with Ultrasound Elastography. *Pediatric Neurology*, 2018(86): 19–26.
 - [28] Albayrak E, Kasap T, 2018, Evaluation of Neonatal Brain Parenchyma Using 2-Dimensional Shear Wave Elastography. *Journal of Ultrasound in Medicine*, 37(4): 959–967.
 - [29] Bailey C, Huisman TAGM, De Jong RM, et al., 2017, Contrast-Enhanced Ultrasound and Elastography Imaging of the Neonatal Brain: A Review. *Journal of Neuroimaging*, 27(5): 437–441.
 - [30] Wang J, Zhang Z, Xu X, et al., 2021, Real-time Shear Wave Elastography Evaluation of the Correlation between Brain Tissue Stiffness and Body Mass Index in Premature Neonates. *Translational Pediatrics*, 10(12): 3230–3236.
 - [31] Goeral K, Hojreh A, Kasprian G, et al., 2019, Microvessel Ultrasound of Neonatal Brain Parenchyma: Feasibility, Reproducibility, and Normal Imaging Features by Superb Microvascular Imaging (SMI). *European Radiology*, 29(4): 2127–2136.
 - [32] Kastler A, Manzoni P, Chapuy S, et al., 2014, Transfontanellar Contrast Enhanced Ultrasound in Infants: Initial Experience. *Journal of Neuroradiology*, 41(4): 251–258.
 - [33] Plut D, Prutki M, Slak P, 2023, The Use of Contrast-Enhanced Ultrasound (CEUS) in the Evaluation of the Neonatal Brain. *Children*, 10(8): 1303.
 - [34] Tang J, Yang P, Xie B, et al., 2023, A Deep Learning-Based Brain Age Prediction Model for Preterm Infants via Neonatal MRI. *IEEE Access*, 2023(11): 68994–69004.
 - [35] Saha S, Pagnozzi A, Bourgeat P, et al., 2020, Predicting Motor Outcome in Preterm Infants from very Early Brain Diffusion MRI using a Deep Learning Convolutional Neural Network (CNN) Model. *NeuroImage*, 2020(215): 116807.
 - [36] Qi FY, Qiu M, Wei GH, 2023, A Review of Ultrasound Image Diagnosis of Thyroid Diseases Based on Deep Learning. *Journal of Biomedical Engineering*, 40(5): 1027.

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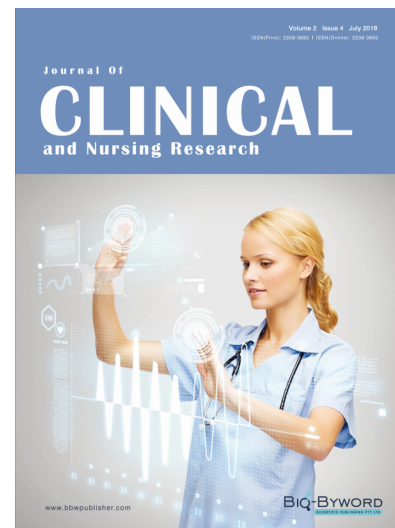
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