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## Clinical Neuroscience Research

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## Table of Contents

1	<b>Application of Neuromuscular Electrical Stimulation Therapy in Stroke Rehabilitation</b> <i>Ling Ge</i>
7	<b>Research Progress on the Composition of Cerebral Arterial Thrombus in Acute Ischemic Stroke</b> <i>Xupeng Wu, Shaoshuai Wang, Changxin Li, Hong Liu</i>
20	<b>Effectiveness of a High-risk Fall Care Program based on the “Safety-support-collaboration” Model in a Neurology Department</b> <i>Shuhui Zhao, Manhui Hu</i>
26	<b>Novel Immunotherapy Strategies for Brain Tumors</b> <i>Mubashir Ahmad Khan, Reza Mirzaeiebrahimabadi, Muhammad Abubakar, Baqaur Rehman</i>
43	<b>The Effectiveness of Neurological Rehabilitation Therapy in Improving Motor Function and Daily Living Abilities in Stroke Patients with Hemiplegia</b> <i>Haiyu Jia</i>
48	<b>Discussion on the Splitting Treatment Technique in Gamma Knife Treatment Plans</b> <i>Gang Yin</i>
55	<b>Research Progress on the Correlation between Oral Diseases and Chronic Kidney Diseases</b> <i>Yuhan Shao</i>
60	<b>Comparative Study on the Treatment of Schizophrenia Patients with Paliperidone and Risperidone Orally Disintegrating Tablets</b> <i>Jingfang Liu</i>
66	<b>Observation on the Effects of Cognitive Behavioral Therapy on Neuropsychiatric Symptoms and Quality of Life in Patients with New-type Drug Abuse</b> <i>Luyu Wu, Pengfei Zhang</i>



# Application of Neuromuscular Electrical Stimulation Therapy in Stroke Rehabilitation

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**Abstract:** Stroke has a high incidence and disability rate, posing a heavy burden on patients, families, and society. Neuromuscular electrical stimulation (NMES) is a safe and effective rehabilitation treatment method that is increasingly being used in stroke rehabilitation therapy. This article reviews its current application status in treating various aspects such as limb swelling and spasms after stroke, explores its mechanism of action, clinical efficacy, and limitations, and provides a reference for clinical application.

**Keywords:** Neuromuscular electrical stimulation; Stroke; Rehabilitation therapy

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## 1. Introduction

In the current medical field, stroke is an extremely common and highly harmful sudden cerebrovascular disease that has received widespread attention. Its series of characteristics, such as high incidence, high mortality, and high disability rates, have made it one of the major public health issues in the 21st century, having a profound and heavy impact on society and many families <sup>[1]</sup>. In terms of the specific situation in China, the number of stroke patients is quite large. According to relevant statistical data, among people aged 40 and above in China as of 2019, the number of those who have had or are currently suffering from stroke reached approximately 17.04 million. This astonishing figure undoubtedly highlights the severe epidemic situation of stroke in China <sup>[2]</sup>. Moreover, it is worth noting that the prevalence of many risk factors that can induce stroke is also becoming more evident. Stroke can easily lead to nerve function damage, which can cause varying degrees of disability in patients, thereby severely affecting their daily self-care abilities. This phenomenon is well-known in the industry <sup>[3]</sup>. Although rehabilitation training is widely used in clinical practice, there are significant limitations in relying solely on it for treatment in terms of relieving muscle spasms and improving limb function. These limitations manifest as a lengthy treatment cycle and difficulty ensuring patient compliance, which greatly affects the rehabilitation effect <sup>[4]</sup>. Currently,

neuromuscular electrical stimulation therapy (NMES) is a physical therapy with a mechanism of action to enhance muscle contraction that exhibits high application potential in stroke rehabilitation therapy <sup>[5]</sup>. A thorough analysis of the specific application of this therapy in stroke rehabilitation treatment is of profound significance for optimizing patient prognosis and improving their quality of life.

## **2. Treatment of limb swelling after stroke**

Neuromuscular electrical stimulation (NMES) therapy plays a significant role in the rehabilitation of stroke patients. As a type of low-frequency electrical therapy, it utilizes the electrical excitability of nerve cells to stimulate the muscles of the limbs, thereby effectively promoting the recovery process <sup>[6]</sup>. Specifically, NMES is administered by precisely placing electrode pads at corresponding points on the body. The electrical current induces muscle contraction through two pathways: directly causing muscle contraction or indirectly stimulating nerves to achieve muscle contraction. This creates a muscle pump effect, which elevates venous blood pressure, promotes blood flow toward the heart, effectively reduces local blood stagnation in the limbs, and ultimately achieves the goal of reducing swelling <sup>[7]</sup>. For example, when using NMES combined with pneumatic therapy to treat hand swelling after a stroke, one electrode pad is placed on the palm, and the other is placed on the trapezius muscle for a 20-minute session. Within 1 to 2 weeks after such treatment, there is a significant reduction in hand swelling and a noticeable improvement in the range of motion of the metacarpophalangeal and interphalangeal joints, highlighting the remarkable effectiveness of this therapy in treating limb swelling after stroke <sup>[8]</sup>.

## **3. Treatment of spasticity after stroke**

After a stroke, damage to the upper motor neurons often leads to spasticity, resulting in abnormally increased muscle tension. This manifests as muscle stiffness and limited joint movement, which can significantly impact patients. If not managed properly, their gait and daily activities can be severely disrupted <sup>[9]</sup>. Among the various clinical treatments for spastic hemiplegia after stroke, neuromuscular electrical stimulation (NMES) plays a crucial role as a commonly used physical therapy in Western medicine. It utilizes pulsed currents to stimulate the nerves controlling the muscles, enhancing the electrical excitability of nerve cells and promoting muscle contraction <sup>[10]</sup>. According to Zhang Zhengyang's research, after 8 weeks of treatment, the BBS and FMA scores of both patient groups improved compared to before treatment, and the observation group showed more prominent results <sup>[11]</sup>. This fully demonstrates that the combined treatment of reducing yin and nourishing yang acupuncture with neuromuscular electrical stimulation can effectively improve balance and motor functions in patients with spastic hemiplegia after stroke.

## **4. Treatment of shoulder pain and shoulder joint subluxation after stroke**

Shoulder pain and shoulder joint subluxation are common occurrences after a stroke. Their mechanisms are associated with factors such as muscle weakness around the shoulder joint, joint capsule laxity, and pain. Between 32.0% and 81.0% of hemiplegic patients are prone to shoulder joint subluxation, often accompanied by limited range of motion and pain, which severely affects their quality of life <sup>[12]</sup>. Furthermore, the incidence of shoulder pain caused by soft tissue issues is as high as 74.8%. This type of shoulder pain not only impairs joint and limb function but also impacts sleep and psychological well-being <sup>[13]</sup>. Wang Yuanyuan et al. conducted a study using

rehabilitation therapy combined with NMES for treatment <sup>[14]</sup>. The results showed that the total effective rate of treatment and the FMA score in the observation group were higher than those in the control group, with a greater range of shoulder joint motion and a lower VAS score. This suggests that adding NMES to conventional rehabilitation therapy can significantly improve the treatment effectiveness for patients with shoulder joint subluxation after a stroke. Stimulating muscle contraction around the shoulder joint enhances muscle strength, improves joint stability, effectively reduces pain, and further improves the range of shoulder joint motion and upper limb motor function.

## **5. Treatment of swallowing disorders after stroke**

In the early stage of stroke, about 34.4% of patients will experience swallowing disorders, and within 30 days, aspiration pneumonia caused by swallowing disorders is often the main factor leading to patient death <sup>[15]</sup>. NMES stimulates the pharynx and muscle groups related to swallowing by using low-frequency pulsed currents, which is very beneficial for the repair and reconstruction of the swallowing reflex arc, thereby improving patients' quality of life and rehabilitation effects <sup>[16]</sup>. Liu Yiyi's observation group experiment involved placing the negative electrode of the device on the upper edge of the hyoid bone and the middle position of the line connecting the maxilla to the hyoid bone <sup>[17]</sup>. Each round of electrical stimulation lasted for 4 seconds, with an intensity of 5–25 mA and a frequency of 30–80 Hz. After each round, there was a 5-second rest. At the same time, patients were instructed to swallow quickly during the electrical pulses, for 15 minutes each time, twice a day, for 30 days. The results showed that the observation group had higher hyoid-larynx complex mobility indicators and lower swallowing function scores compared to the control group. This suggests that combined NMES rehabilitation therapy can promote the recovery of mobility and effectively improve swallowing function.

## **6. Treatment of aphasia after stroke**

Aphasia can be classified into various types such as motor, sensory, and conductive based on the location of brain damage, with motor aphasia being the most common <sup>[15]</sup>. Currently, clinical treatment for patients primarily with motor aphasia relies on basic medications and nursing care. Although this approach can restore language function and improve neurological function to some extent, it often fails to meet patients' expectations. Studies have shown that combining neuromuscular electrical stimulation with conventional basic medication and nursing care in the treatment of post-stroke aphasia patients yields significant results, improving both language function and quality of life <sup>[18]</sup>. Meanwhile, research has also found that using this method to treat patients with motor aphasia can enhance clinical efficacy, further optimize language and neurological functions, and improve quality of life, even leading to improvements in hemorheology <sup>[19]</sup>.

## **7. Treatment of limb dysfunction after stroke**

After a stroke occurs, the patient's central nervous system is damaged, which severely affects their ability to control their limbs, leading to decreased muscle strength and disuse atrophy, ultimately resulting in limb dysfunction <sup>[20]</sup>. A study targeted patients with these limb dysfunctions by first implementing rehabilitation training interventions, followed by further treatment combined with a neuromuscular electrical stimulation system <sup>[21]</sup>. The results showed that after the combined intervention, the patients' MAS scores were significantly lower than

those when only rehabilitation training was performed. This indicates that the combination of these two treatment methods can effectively reduce muscle spasms and significantly improve patients' muscle strength levels. This is due to the unique advantages of the neuromuscular electrical stimulation system, which can simulate the facilitation techniques used in exercise therapy, precisely control the affected limbs, and design targeted inhibitory measures based on actual reflex conditions. This effectively reduces the incidence of limb spasms and provides strong support for functional recovery in stroke patients <sup>[22]</sup>.

## 8. Treatment of urinary incontinence after stroke

Urinary incontinence is a common and troublesome issue for patients after a stroke, falling under the category of neurogenic urinary incontinence. Statistics show that approximately 40%–60% of stroke patients hospitalized will experience this condition <sup>[23]</sup>. Currently, treatment methods for urinary incontinence primarily include bladder management, dietary adjustments, and pelvic floor muscle training <sup>[24]</sup>. A study involving 74 patients with post-stroke urinary incontinence revealed that combining acupuncture and neuromuscular electrical stimulation of the bladder region resulted in better outcomes in the observation group compared to the control group, specifically in terms of slow muscle fibers and integrated fiber amplitude <sup>[25]</sup>. Additionally, the observation group had lower ICI-Q-SF scores and higher I-QOL scores. These findings suggest that the integration of acupuncture and neuromuscular electrical stimulation of the bladder region in the treatment of post-stroke urinary incontinence can significantly enhance the strength and endurance of pelvic floor muscles, improve coordination among muscle groups, effectively alleviate symptoms of urinary incontinence, and enhance patients' quality of life in daily activities.

## 9. Conclusion and prospects

NMES is a safe and effective rehabilitation treatment that exhibits broad application prospects in the field of stroke rehabilitation therapy. It can improve various complications, effectively promote the recovery of patients' neurological function, and thereby enhance their quality of life. However, NMES treatment is not flawless. There are still limitations in selecting treatment parameters, planning treatment regimens, and evaluating treatment effects, which require further exploration. It is foreseeable that with the continuous advancement of technology and the deepening of clinical research, NMES will play a more critical role in the process of stroke rehabilitation therapy.

## Disclosure statement

The author declares no conflict of interest.

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# Research Progress on the Composition of Cerebral Arterial Thrombus in Acute Ischemic Stroke

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**Abstract:** Acute cerebral infarction, with a high incidence, disability, and recurrence rate, has brought a huge social burden to China and other countries. Understanding the pathological characteristics of cerebral thrombus can help in the selection of individualized treatment plans, thereby improving the good prognosis rate and reducing the recurrence rate of cerebral infarction patients. This article reviews the composition and imaging characteristics of cerebral thrombus, the relationship between cerebral thrombus composition and cerebral vascular recanalization therapy, the correlation between cerebral thrombus composition and the etiology of cerebral infarction, and the dynamic evolution of cerebral thrombus, to provide a more theoretical basis for the treatment of acute ischemic stroke.

**Keywords:** Acute cerebral infarction; Thrombectomy; Cerebral artery thrombus; Pathology

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## 1. Introduction

The number of patients with stroke in China ranks first in the world, and it is the number one killer threatening the lives of Chinese people. Among them, ischemic stroke accounts for about 80% of the stroke incidence, and the incidence rate has been increasing in recent years <sup>[1]</sup>. Timely and effective recanalization therapy for acute ischemic stroke can significantly improve the symptoms and prognosis of patients <sup>[2]</sup>. Intravenous thrombolysis and cerebral arterial endovascular therapy stand out as the most effective recanalization treatments currently available. However, while intravenous thrombolysis shows an effective reperfusion rate of less than 50% and an improvement rate of only about 30%, cerebral arterial endovascular therapy boasts an effective recanalization rate of over 80% <sup>[3]</sup>. Despite this success, the proportion of patients with a favorable prognosis remains below 50% <sup>[4]</sup>. The effectiveness of recanalization therapy can be influenced by several factors, such as the patient's underlying disease and the duration of treatment. However, the histological characteristics of the thrombus undoubtedly play a crucial role, significantly impacting the effectiveness of both intravenous thrombolysis and intravascular

treatments<sup>[5]</sup>. This article reviews the relevant research on cerebral thrombus in patients with acute cerebral infarction in recent years, aiming to be helpful for the clinical diagnosis and treatment of ischemic stroke.

## **2. The composition and internal structure of cerebral thrombus**

Based on numerous clinical trials on the removal of thrombus during endovascular treatment of intracranial arterial occlusion, people have gained more and more understanding of the components and internal structure of cerebral thrombi.

### **2.1. Components of thrombus**

A typical cerebral thrombus is composed of red blood cells, fibrin, platelets, white blood cells, von Hemophilia factor (vWF), and neutrophil extracellular traps (NETs)<sup>[5-7]</sup>. In addition, some rare noncellular components can also be found in thrombus, such as vascular intimal tissue, pathogenic bacteria, or calcified components.

#### **2.1.1. Red blood cells, fibrin, platelets, and white blood cells**

Red blood cells, fibrin, and platelets are the three components with the highest relative content in thrombus, and they all have various forms in thrombus. Among them, red blood cells can be divided into double concave disc-shaped red blood cells, double concave intermediate red blood cells, polyhedral intermediate red blood cells, polyhedral red blood cells, smooth surface convex red blood cells, and spiny red blood cells. Fibrin can be divided into bundle-like fibrin, fibrous-like fibrin, sponge-like fibrin, and fragmented fibrin. Platelets can also be divided into ordinary platelets and activated spherical platelets<sup>[8]</sup>. In contrast, the proportion of white blood cells in thrombus is relatively small with a mostly diffuse manner distribution, often coexisting with fibrin. Its content is negatively correlated with the content of red blood cells, and there are significant changes in the content of different kinds of thrombus<sup>[8-9]</sup>. Currently, thrombus classification primarily relies on Hematoxylin and Eosin (H&E) and Martius Scarlet Blue (MSB) staining methods. These methods semi-quantitatively measure the proportion of the first three main components in the thrombus<sup>[10]</sup>. Thrombus can be divided into red thrombus rich in red blood cells, white thrombus rich in fibrin/platelets, and mixed thrombus<sup>[11]</sup>.

#### **2.1.2. Other components**

NETs and vWF: NETs are secreted by neutrophils and are mainly composed of collagen, histone, and DNA. They participate in the formation of thrombus by interacting with platelets, red blood cells, vWF, and so on, and antagonize thrombolytic drugs by stabilizing the thrombus and promoting coagulation<sup>[12-15]</sup>. Mature thrombus has a higher content of NETs compared to fresh thrombus<sup>[16]</sup>. vWF is a large polymeric plasma protein synthesized by megakaryocyte and endothelial cells, which plays an important role in platelet adhesion<sup>[17-18]</sup>. It is often co-located with platelets in thrombus, so platelet-rich thrombus is also found to be rich in vWF content. NETs and vWF are negatively correlated with red blood cell content<sup>[19-20]</sup>.

Vascular wall components, infectious embolus, calcified embolus: In rare cases, vascular intima, subintimal tissue, and other vascular wall components can be found in the removed thrombus, indicating that there may be more operations or relatively remote thrombus removal sites during the thrombus removal process<sup>[21-22]</sup>. Infection is an important factor of AIS, especially for infective endocarditis<sup>[23]</sup>. The complicated cerebral embolism in this patient is likely to be an infectious embolus. Pathogenic bacteria are also found in the thrombus of a few patients without signs of infection before surgery, which emphasizes the necessity of conducting microbial analysis of the

thrombus<sup>[24]</sup>. Sometimes, calcified components are found in blood clots, indicating a high possibility of arterial origin<sup>[25]</sup>. A relatively small proportion of cerebral embolism is found to be calcified embolus, and it should be noted that the effectiveness of thrombectomy treatment for this type of embolism is relatively poor<sup>[26]</sup>.

## **2.2. The internal structure of thrombus**

The heterogeneity of cerebral thrombosis is not only related to the content and morphology of different components within it but also to the spatial relative positions of various components in the thrombus. By histological and immunofluorescence, Pir et al. found that different thrombi are composed of different proportions of red blood cell-rich and platelet-rich regions<sup>[27]</sup>. The structure of the red blood cells-rich region is simple, consisting of dense red blood cells, thin fibrin grids, and a small number of white blood cells. The structure of platelet-rich regions is relatively complex, consisting of platelet polymers, thick and tightly arranged fibrin, and vWF merging together, containing a large number of white blood cells and NETs. These two regions are distributed in a layered or staggered manner, with white blood cells and NETs mainly distributed at the interface of the two regions and in regions rich in platelets. By electron microscopy, Meglio et al. found that the vast majority of thrombi have a distinct shell structure<sup>[6]</sup>. The outer shell is composed of high-density fibrin and platelets, while the inner core is composed of relatively loose red blood cells and sparse fibrin. The heterogeneity of thrombus is mainly because of the change of the inner core. They also verified that thrombus coat formation resistant to thrombolytic drugs is mediated by repeated in vitro experiments.

## **3. Cerebral thrombus composition and imaging examination**

Although the study and observation of thrombus removed by endovascular treatment are more direct, it may cause damage to the original structure of the thrombus and loss of some components during surgical procedures or pathological analysis, thereby affecting the evaluation of the original volume, and content of various components, and physical properties of the thrombus<sup>[28]</sup>. Hence, the ideal strategy is to determine or roughly understand the composition of cerebral thrombus or embolism in situ through auxiliary examinations before intervention, which can guide clinical physicians to develop more accurate treatment methods. At present, scholars have applied bioelectrical impedance technology and nanotechnology to study the histological characteristics of in situ thrombus<sup>[29–31]</sup>. In addition, an artificial neural network classifier developed based on the features of thromboradiomics can also perform better prediction before surgery<sup>[32]</sup>. However, for most centers, skull CT and MRI, as common imaging examinations, are still the simplest and easiest ways to observe the thrombus in situ in vessel occlusion under living conditions. They can have some understanding of the composition and morphology of the thrombus before treatment, which is helpful to provide some information for the development of treatment strategies.

### **3.1. CT and composition of cerebral thrombus**

#### **3.1.1. Thrombus density and components**

The high-density artery sign (HAS) displayed on conventional CT scans is significantly associated with a thrombus rich in red blood cells, as well as better recanalization and good thrombolysis response<sup>[33–37]</sup>. The occluded large intracranial arteries are associated with thrombus rich in fibrin/platelets and are less sensitive to intravenous thrombolysis and thrombectomy<sup>[10,36]</sup>. Intracranial arterial high density (HU value > 130) suggests that it may be a calcified embolus causing cerebral vascular occlusion<sup>[38]</sup>. Through proteomic analysis of thrombus, it is found that HAS-positive thrombus is rich in actin and other protein components related to the development of atherosclerosis,

which further indicates that the possibility of LAA origin is high, while HAS-negative thrombus contains a large number of complement proteins, fibrin stabilized coagulation factor XIII, and so on, which indicates that the possibility of thrombus being cardiogenic is high<sup>[39]</sup>.

### **3.1.2. Thrombus permeability and composition**

The permeability of a thrombus refers to the degree to which blood can pass through the thrombus structure and is quantitatively measured by both NCCT and single-phase CTA for thrombus attenuation<sup>[40]</sup>. Thrombosis with high permeability is rich in red blood cells, and high thrombus permeability is a good predictive factor for AIS recanalization treatment, which is associated with good functional prognosis and better clinical outcomes after intravenous thrombolysis with rt-PA<sup>[41]</sup>. However, Berdit et al. found a strong correlation between the higher permeability of thrombus, lower levels of red blood cells, and higher levels of fibrin/platelets<sup>[42]</sup>. Therefore, a large sample size of a prospective cohort study is still needed to explore the correlation between the permeability of thrombus and the pathology and clinical prognosis of thrombus.

## **3.2. MRI and composition of cerebral thrombus**

The low signal observed on the GRE sequence of MRI imaging that spreads outward around cerebral thrombosis is called a magnetic susceptibility vessel sign (SVS). This special imaging sign is common in thrombus rich in red blood cells, and the absence of SVS often indicates a thrombus rich in fibrin<sup>[43–44]</sup>. However, there is currently no clear conclusion regarding the correlation between SVS and stroke etiology and its prognostic value for recanalization therapy. In addition to this typical imaging sign, the application of high-resolution magnetic resonance vascular wall imaging can evaluate the anatomical characteristics and thrombus burden of occluded vessels before surgery, and also assist in identifying the cause of arterial occlusion, such as carotid artery dissection, which is beneficial for the selection of surgical instruments and thrombectomy plans<sup>[45]</sup>.

## **4. Composition of cerebral thrombus and cerebral vascular recanalization therapy**

### **4.1. Composition of cerebral thrombus and intravenous thrombolysis**

The composition of the thrombus has a certain impact on the thrombolytic effect of alteplase. A thrombus rich in red blood cells is more sensitive to thrombolysis than a thrombus rich in platelets<sup>[44]</sup>. The content and spatial arrangement of various components in different thrombi can also affect the effectiveness of intravenous thrombolysis. The area rich in red blood cells in the thrombus is easily dissolved by rt-PA due to the thin arrangement of fibrin, while the area rich in platelets has a dense arrangement of fibrin and contains a large amount of vWF and extracellular DNA that are resistant to thrombolytic drugs, making them less likely to be dissolved by rt-PA. There are significant differences in the proportion and arrangement of these two regions in different thrombi, which in turn leads to different thrombolytic reactivity<sup>[5]</sup>. Observation of thrombolytic-resistant clots by scanning electron microscopy reveals a dense shell structure consisting of fibrin, vWF, and aggregated platelets, which renders the thrombus difficult to dissolve<sup>[6]</sup>. Further studies using scanning electron microscopy and transmission electron microscopy have shown that thrombolytic-resistant thrombus contains a large number of compressed deformed red blood cells, and the surface fibrin is more densely arranged<sup>[46]</sup>. In addition, higher levels of NETs in thrombus are associated with resistance to thrombolytic drugs, possibly due to the formation of scaffold-like structures by NETs<sup>[15]</sup>. Special attention should be paid to the thrombolysis of patients with purulent embolism secondary to infective endocarditis because the direct infiltration of septic



substances on the vessel wall and the arteritis and infected aneurysms mediated by it will cause an increased risk of hemorrhagic transformation <sup>[47]</sup>.

In vitro thrombolysis with alteplase combined with deoxyribonuclease 1 (DNase1) was performed on the thrombus taken out by intravascular treatment, and obvious effects were observed <sup>[16]</sup>. As a protease that can lyse and regulate vWF activity, animal experiments showed that ADAMTS13 could be dissolved in the thrombus rich in vWF <sup>[20]</sup>. Therefore, composite thrombolytic drugs targeting fibrin and non-fibrin components in thrombus may significantly improve the effectiveness of thrombolysis in the future, but the combination of multiple drugs may bring greater risks so more research is needed to improve safety <sup>[48]</sup>.

## 4.2. Composition of cerebral thrombus and cerebral artery thrombectomy

The composition of the thrombus may have a significant impact on the difficulty and effectiveness of arterial thrombectomy. A systematic evaluation study in 2016 focused on multiple studies on the composition of cerebral thrombus after thrombectomy from 2005 to 2015 and found that the composition of thrombus was not related to the recanalization rate of cerebral artery thrombectomy <sup>[37]</sup>. Subsequent studies found a positive correlation between the content of red blood cells in the thrombus and the results of thrombectomy <sup>[33, 49]</sup>. Compared to thrombus rich in fibrin/platelets, thrombus rich in red blood cells have shorter thrombectomy times, less frequency of thrombectomy and secondary embolism, and better vascular recanalization effects and clinical outcomes <sup>[50–53]</sup>. Compared to previous semi-quantitative analyses of the proportion of various main components in thrombus, a recent study prepared thrombus into homogenates and quantitatively measured the specific content of red blood cells, platelets, and white blood cells. It was found that platelet content was positively correlated with the number of thrombectomy operations and thrombectomy time <sup>[54]</sup>.

The different compositions of thrombus can lead to differences in their physical properties, which in turn affects the effectiveness of thrombectomy <sup>[55]</sup>. In vitro experiments have found that an increase in the content of red blood cells in thrombus increased their viscosity and elasticity, and the friction coefficient of thrombus rich in fibrin/platelets was significantly higher than that of thrombus rich in red blood cells <sup>[56–57]</sup>. However, a recent in vitro study of a small sample of thrombus removed from patients with acute cerebral infarction found that the stiffness of the thrombus increased with the increase of fibrin/platelet content <sup>[58]</sup>. However, compared with fibrin-rich thrombus, red blood cell-rich thrombus is more deformable and less frictional, making this thrombus easier to dislodge <sup>[59]</sup>. The suction catheter can only be in contact with the proximal surface of the thrombus, while the grid of the stent retrieval can be embedded in the overall thrombus to generate greater grasping force and reduce the risk of thrombus escape, resulting in a thrombus rich in red blood cells. The one-pass probability is higher than that of aspiration thrombectomy <sup>[60–61]</sup>.

The content of other components in the thrombus also has a certain correlation with the results of arterial thrombectomy. Studies have confirmed that higher levels of white blood cells in thrombus are associated with lower recanalization rates and poorer clinical outcomes <sup>[9]</sup>. The content of NETs in the thrombus was found to increase the number of times of thrombus removal, prolong the time of thrombus removal, and was negatively correlated with the recanalization rate <sup>[15, 62]</sup>. The increase of vWF content in the thrombus was also found to be associated with poorer recanalization results <sup>[19]</sup>. In addition, the presence of blood vessel wall components in the thrombus is associated with a lower recanalization rate, and the time and frequency of thrombus removal for infected thrombus-containing bacteria are both longer but have no significant impact on clinical outcomes and prognosis <sup>[21, 24]</sup>. A recent study found a correlation between higher levels of S100b1 in thrombus and the

occurrence of cerebral hemorrhage after thrombectomy<sup>[63]</sup>.

## **5. Correlation between the composition of cerebral thrombus and etiology of cerebral infarction**

TOAST classification is currently the most commonly used method to classify the etiology of cerebral infarction. Its significance lies in that it can guide clinicians to carry out more appropriate secondary preventive treatment for patients and effectively reduce the recurrence rate. Therefore, many scholars try to explore the correlation between the composition of cerebral thrombus and the etiology of cerebral infarction, to better guide clinical treatment.

### **5.1. Red blood cells, fibrin/platelets, and etiological classification**

In 2006, Marder conducted the first histological study on thrombus in patients with acute cerebral infarction and found that there was no significant difference between the main components of cardiogenic thrombus and arterial thrombus<sup>[64]</sup>. However, this result may be affected by the low efficiency of the thrombectomy device used at the time and lack of credibility. A study from Japan in 2008 analyzed the source of cerebral thrombus through autopsy of patients with cerebral infarction and found that arterial thrombus was rich in platelets and platelets, and cardiogenic thrombus was rich in red blood cells<sup>[65]</sup>. This conclusion is also unreliable because the composition of this thrombus may be influenced by post-mortem hemodynamic changes. Subsequently, a series of studies both domestically and internationally have found that cardiogenic thrombosis contains higher levels of fibrin/platelets and lower levels of red blood cells, while arterial thrombosis contains higher levels of red blood cells<sup>[7, 42, 50, 53, 66–69]</sup>. At the same time, many studies have drawn different conclusions on the relationship between the main composition of thrombus and the classification of cerebral infarction etiology. These studies have found that cardiogenic thrombus is rich in red blood cells, while non-cardiogenic thrombus is rich in fibrin/platelets<sup>[33, 37, 43, 70–72]</sup>. A systematic review and meta-analysis only found that the content of fibrin was higher in cardiogenic and cryptogenic thrombus than in arterial thrombosis, while there was no significant difference in the content of red blood cells, platelets, and white blood cells in thrombus of different causes<sup>[73]</sup>. However, a systematic review and meta-analysis only found that the content of fibrin in cardiogenic and cryptogenic thrombus was higher than that in arterial thrombus, while the content of red blood cells, platelets, and white blood cells in thrombus of different etiologies was not significantly different<sup>[73]</sup>. However, some recent studies have found that there is no significant difference in the main components of cardiogenic thrombus and large artery atherosclerotic thrombus<sup>[74–75]</sup>. Therefore, there is no consistent conclusion on the relationship between the etiological types of cerebral infarction and the proportion of main components in cerebral thrombus.

It is worth noting that strokes of unknown etiology account for approximately 25% of ischemic strokes<sup>[76]</sup>. In most studies, it was found that the thrombus components had similar histological features and clinical prognosis to those of cardiogenic thrombus<sup>[7, 66, 68]</sup>. Recently, Kauw et al. used cardiac CTA to examine 370 patients with acute ischemic stroke and found that 6% of non-atrial fibrillation patients had left atrial appendage thrombus, and these patients would probably be classified as unknown etiology stroke in most medical centers<sup>[77]</sup>. Therefore, cerebral embolism of unknown etiology may partly come from left atrial appendage thrombus in non-atrial fibrillation patients.

### **5.2. Other components and etiological classification**

Maekawa et al. studied the recovered thrombus and found that there was no significant difference in the leukocyte

content in thrombus from different sources<sup>[50]</sup>. However, some studies have also found that higher levels of leukocytes are associated with cardiogenic thrombus<sup>[9, 78]</sup>. Therefore, there is no consistent conclusion about the correlation between the white blood cell content in thrombus and the etiology of cerebral infarction. Similarly, no correlation was found between the proportion of neutrophils in thrombus and TOAST classification in patients with acute cerebral infarction, and the relationship between the content of NETs and vWF in thrombus and TOAST classification was also uncertain<sup>[15, 20, 23]</sup>.

Considering that the inflammatory response plays an important role in the development of aortic atherosclerosis, through the study of inflammatory cells and inflammatory mediators in thrombus, it was found that the contents of CD3+T cells and IL-1 $\beta$  in aortic atherosclerotic thrombus were significantly higher for cardiogenic thrombus and thrombus of unknown etiology<sup>[79–80]</sup>. However, there are still few studies on the relationship between the content of inflammatory mediators in thrombus and the etiology, so more research is still needed to confirm.

## 6. The dynamic evolution of cerebral thrombus

This study emphasizes the importance of time in ultra-early cerebral infarction intravenous thrombolytic therapy, mainly on the basis that ischemic brain tissue will evolve into irreparable necrotic brain tissue over time<sup>[81–82]</sup>. However, after cerebral infarction, in addition to ischemic brain tissue, the thrombus itself also changes dynamically<sup>[83]</sup>. The stiffness and coefficient of friction of fresh thrombus are low; the thrombus has good permeability, is highly sensitive to thrombolytic drugs, and is easy to take out. As time goes by, there are more and more fibrin deposits and more extensive fibrin and red blood cells. Cross-linking promotes more maturity and stability of thrombus, and the content of NETs in mature thrombus is relatively higher, and the possibility of thrombus being lysed and removed gradually decreases<sup>[84–87]</sup>. For patients receiving intravenous thrombolysis, the earlier the application of rt-PA, the greater the possibility of benefit<sup>[88]</sup>. Similarly, there is a significant correlation between the time interval from onset to recanalization of cerebral artery thrombectomy patients and clinical results. With the extension of the time interval, the effectiveness of patients with cerebral artery thrombectomy in comparison with the drug control-only group gradually decreases, and the effective reperfusion rate decreases with the extension of the time from medical treatment to femoral artery puncture (DPT)<sup>[89–90]</sup>. Kim et al. used thin CT scans of middle cerebral artery thrombus in patients with thrombolysis and found that the degree of thrombus dissolution and density gradually decreased with the prolongation of OTT (onset to treatment)<sup>[91]</sup>. Studies of the high-density sign of early middle cerebral arteries decreased over time, suggesting that the relative proportion of red blood cells in the thrombus gradually decreased over time<sup>[92]</sup>. With the development of thrombus, the content of fibrin will also increase in the further deposition of the original thrombus<sup>[93]</sup>. Other studies found that the content of white blood cells, fibrin, citrulline histone, and vWF in patients whose time from onset to femoral artery puncture was within 4 to 8 hours was significantly higher than that in patients whose time from onset to femoral artery puncture was within 4 hours<sup>[94]</sup>. Recent studies both domestically and internationally have found that the content of fibrin, platelets, and white blood cells in an old thrombus is higher than that in a fresh thrombus<sup>[95–96]</sup>. The above studies all suggest the dynamic evolution of cerebral artery thrombus. The change of thrombus in the time dimension may have a certain impact on the correlation between the histological characteristics of cerebral thrombus and imaging findings and the correlation with the etiology of cerebral infarction, which needs further research to confirm.

## 7. Conclusion

In summary, through the study of thrombus in patients with acute cerebral infarction, it can be found that the histological characteristics of thrombus have a certain influence on the sensitivity of intravenous thrombolysis, the difficulty of arterial thrombus removal, and the imaging characteristics of thrombus. The composition of the drug is dynamically changing, which will help the development of new thrombolytic drugs and thrombectomy devices and the improvement of stroke treatment procedures. However, there is no consistent conclusion on the correlation between thrombus components and the etiology of cerebral infarction. New research methods on thrombus using proteomics or new biomarkers may be used to clarify different sources of thrombus for effective secondary prevention in patients. In addition, actively exploring new inspection methods that can analyze intracranial cerebral artery thrombus in patients before treatment will have great guiding significance for the selection of treatment strategies.

## Disclosure statement

The authors declare no conflict of interest.

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# Effectiveness of a High-risk Fall Care Program based on the “Safety-support-collaboration” Model in a Neurology Department

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**Abstract:** *Objective:* To analyze the effect of the high-risk fall care program based on the “safety-support-cooperation” model in neurological profound. *Methods:* 80 patients who were admitted to the Department of Neurology from December 2021 to December 2023 were randomly divided into an observation group and a control group, and were treated with conventional nursing care and conventional + “safety-supportive-cooperative” nursing care program for high-risk falls, respectively. The effects of the two groups were evaluated. *Results:* After the nursing care, the patients’ fall prevention self-management ability was stronger, and the scores of each dimension were higher,  $P < 0.05$ . After the nursing care, the fall risk of the observation group was relatively lower,  $P < 0.05$ , and the incidence rate of falls in the observation group was lower,  $P < 0.05$ . *Conclusion:* In the nursing care of neurological patients, based on the “safety-support-cooperation” model, it is possible to establish a high-risk fall nursing care program, which is based on “safety-support-cooperation.” *Conclusion:* The establishment of a high-risk fall care program based on the “safety-support-cooperation” model in the care of neurological patients can help improve patients’ self-management ability, reduce the incidence of falls, and improve patient safety.

**Keywords:** Safety-support-collaboration model; High-risk fall care; Neurology; Application

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## 1. Introduction

In neurology, if a patient unintentionally falls on a horizontal surface and unconsciously changes his or her position, it will elevate the degree of disability, increase the patient’s sense of pain, increase the patient’s psychological burden, and contribute to the increase in the patient’s hospitalization time. A large number of studies have shown that in neurology, falls are not impossible to prevent and control, the risk factors involved are relatively more preventable and controllable, and the establishment of a sound fall prevention strategy can help to reduce the incidence of falls. Therefore, attention should be paid to fall prevention care in neurology, combining clinical practice

experience, summarizing and analyzing fall-related risk factors, giving “safety-supportive-cooperative” mode, establishing a targeted and systematic fall care program, improving the frequency of communication between nursing staff and patients, enhancing the level of health education, strengthening patients’ physical and mental adaptability, and realizing a better understanding of fall prevention. Strengthening patients’ physical and mental adaptability can achieve effective control of falls and other adverse events <sup>[1]</sup>. The present study analyzes the effectiveness of this high-risk fall care program to help improve care strategies for neurological patients.

## **2. Information and methodology**

### **2.1. General information**

When selecting the research subjects for this study, the researchers started with the patients admitted to the Department of Neurology. Patients whose treatment time was between December 2021 and December 2023 were selected, counting 80 cases, and were randomly divided into the observation group and the control group. In the observation group, there were 27 males and 13 females, with a mean age of  $55.36 \pm 8.71$  years. In the control group, there were 28 men and 12 women, with a mean age of  $55.42 \pm 8.69$  years. Analyzing the data of the two groups shows no significant differences,  $P > 0.05$ .

Inclusion criteria: Patients who were conscious and admitted to the Department of Neurology were selected. Patients with limb muscle strength higher than grade 4 were selected.

Exclusion criteria: Exclude patients who have lost their ability to take care of themselves and are bedridden. Exclude patients with a history of mental illness or poor nutritional indicators.

### **2.2. Methodology**

#### **2.2.1. Control group control method**

Adoption of routine care model. The nursing staff will carry out routine publicity and education, distribute fall prevention health education manuals to patients, and improve the patient’s knowledge of fall prevention. Moreover, attention should be paid to the management of the patient’s inpatient environment, to remove the potential safety hazards in the patient’s surrounding environment.

#### **2.2.2. Control methods for the observation group**

Implement a fall prevention care program based on the “Safe-Supportive-Collaborative” model in addition to routine care measures.

First of all, the construction of a falls prevention nursing team should be focused on, which mainly involves nurse leaders and specialist nursing staff, instructing team members to search for relevant literature, summarize and analyze clinical nursing experience, and assess the risk factors of falls through discussion, to provide support for the construction of a targeted nursing program <sup>[2]</sup>. At the same time, training should be provided to team members to inform them of the knowledge related to “safety-support-cooperation” fall care, to enhance their professionalism, to cultivate their professionalism, to strengthen their safety awareness, and to provide support for fall prevention care.

Secondly, fall prevention care measures are implemented. First, carry out safety management. Nursing staff should pay attention to the setting of the fall list, placing the list in the fall-prone places such as the bedside and the bathroom, and doing a good job of setting high-risk anti-slip warning signs. During this process, nursing staff should actively carry out rounds of observation to assess the time of high risk of falling, such as 00:00–8:00, to confirm whether the patient is at risk of falling <sup>[3]</sup>. Secondly, a quality control team should be established to ensure

the effective implementation of fall prevention strategies. Thirdly, improve the level of cooperation between medical and nursing staff and patients, increase health promotion and education, and build diversified promotion pathways, such as new media and brochures, and so on, to explain the key points of fall prevention to patients and their families through videos or pictures, and so on, thus improving the ability of patients to save themselves from falls and reduce the level of patient injuries<sup>[4]</sup>.

Finally, the nursing staff needs to communicate with the patient's companion to improve the safety awareness of the companion, the patient's behavior, and other constraints to reduce the incidence of falls.

### 2.3. Observation of indicators

A self-developed fall prevention self-management behavior questionnaire was developed to assess patients' fall prevention and management skills.

Patients' risk of falling was analyzed by the Morese Falls Assessment Scale. If the patient obtained a score between 0–24, it was low risk. If the patient obtained a score between 25–44, it was a medium risk. If the patient obtained a score higher than 45, it was considered high risk.

Statistically analyzing the status of the patient's fall generation, if the patient did not produce significant injury, it was grade 0. If the patient had a mild injury, it was grade 1. If the patient had a moderate injury, it was grade 2. If the patient had a severe injury, it was grade 3.

### 2.4. Statistical treatment

SPSS 23.0 was used for data processing, and the count data were tested by  $\chi^2$  test. Measurement data row  $t$ -test. If  $P < 0.05$ , the difference between the data was significant.

## 3. Results

### 3.1. Falls prevention self-management skills

As shown in **Table 1**, after the care, the patients were more capable of self-management of fall prevention, with higher scores on all dimensions,  $P < 0.05$ .

**Table 1.** Falls prevention self-management skills before and after care in both groups (Mean  $\pm$  SD)

Groups	Number of samples	Pre-nursing	Aftercare	$t$	$P$
Environmental management					
Observation group	40	10.48 $\pm$ 2.36	17.63 $\pm$ 2.34	12.125	0.001
Control group	40	10.51 $\pm$ 2.35	14.23 $\pm$ 2.48	11.351	0.001
$t$	-	0.215	9.362	-	-
$P$	-	0.832	0.002	-	-
Drug management					
Observation group	40	12.26 $\pm$ 2.39	21.05 $\pm$ 3.21	11.214	0.001
Control group	40	12.28 $\pm$ 2.37	15.64 $\pm$ 3.25	10.223	0.001
$t$	-	0.083	9.597	-	-
$P$	-	0.934	0.001	-	-



**Table 1 (Continued)**

Groups	Number of samples	Pre-nursing	Aftercare	<i>t</i>	<i>P</i>
Daily behavior management					
Observation group	40	14.32 ± 2.38	26.48 ± 3.51	13.196	0.001
Control group	40	14.35 ± 2.35	20.34 ± 3.21	10.467	0.001
<i>t</i>	-	0.449	9.825	-	-
<i>P</i>	-	0.656	0.001	-	-
Falls self-help behavior management					
Observation group	40	20.35 ± 3.21	34.56 ± 3.69	12.234	0.001
Control group	40	20.41 ± 3.18	28.85 ± 3.37	9.857	0.001
<i>t</i>	-	0.171	8.862	-	-
<i>P</i>	-	0.865	0.004	-	-
Risky behavior management					
Observation group	40	21.01 ± 3.26	34.01 ± 3.64	13.201	0.001
Control group	40	21.04 ± 3.23	27.53 ± 3.41	10.634	0.001
<i>t</i>	-	0.164	9.214	-	-
<i>P</i>	-	0.869	0.003	-	-
Health belief management					
Observation group	40	12.31 ± 2.23	21.36 ± 2.34	9.857	0.001
Control group	40	12.34 ± 2.25	18.62 ± 2.51	8.253	0.010
<i>t</i>	-	0.753	8.125	-	-
<i>P</i>	-	0.367	0.011	-	-
Disease symptom management					
Observation group	40	14.52 ± 2.35	26.05 ± 3.21	14.567	0.001
Control group	40	14.55 ± 2.32	21.49 ± 2.66	9.967	0.001
<i>t</i>	-	0.623	7.234	-	-
<i>P</i>	-	0.578	0.020	-	-

### 3.2. Risk of falls

As shown in **Table 2**, the observation group had relatively lower nursing risks for aftercare,  $P < 0.05$ .

**Table 2.** Risk of falls before and after care in both groups [ $n$  (%)]

Groups	Number of samples	Pre-nursing			Aftercare		
		Low risk	Medium risk	High risk	Low risk	Medium risk	High risk
Observation group	40	12 (30.00)	18 (45.00)	10 (25.00)	25 (62.50)	13 (32.50)	2 (5.00)
Control group	40	13 (32.50)	16 (40.00)	11 (27.50)	20 (50.00)	11 (27.50)	9 (22.50)
$\chi^2$	-	0.112			10.256		
<i>P</i>	-	0.941			0.001		

### 3.3. Incidence of falls

As shown in **Table 3**, the incidence of falls was lower in the observation group,  $P < 0.05$ .

**Table 3.** Incidence of falls in the two groups [ $n$  (%)]

Groups	Number of samples	Level 0	Level 1	Level 2	Level 3	Total incidence
Observation group	40	1 (2.50)	1 (2.50)	2 (5.00)	0 (0.00)	4 (10.00)
Control group	40	3 (7.50)	4 (10.00)	3 (7.50)	2 (5.00)	12 (30.00)
$\chi^2$	-	-	-	-	-	13.234
$P$	-	-	-	-	-	0.001

## 4. Discussion

Neurology operation links are affected by the patient's nerve damage and other factors so their limb function may have certain problems, resulting in a relatively high probability of falling, elevating the patient's pain, which may lead to patient disability, increasing the patient's psychological burden, delaying the patient's recovery rate, and increasing the patient's hospitalization time. At the same time, when hospitals review the quality of care, the incidence of falls is one of the main criteria. If routine care is implemented, the degree of attention to fall prevention nursing intervention is not high, as the focus is on the monitoring and maintenance of the patient's vital signs, so the nursing effect is relatively poor, the fall prevention nursing measures formulated are not targeted enough and do not pay attention to the strengthening of the patient's awareness of preventing falls, which reduces the patient's ability in fall self-management<sup>[5]</sup>. Therefore, nursing staff should pay attention to fall prevention care, analyze the clinical nursing experience in neurology, identify the risk factors for falls, and adjust and optimize the fall prevention care plan by combining the relevant literature, to maintain the safety of patients.

The construction and implementation of a fall care program under the "safety-support-collaboration" model will strengthen the fall prevention awareness of patients and their families, establish a diversified education pathway, improve patients' self-management ability, supplement the training of nursing staff to improve their safety awareness and professionalism, and promote the quality of care, thus reducing patients' risk of falling<sup>[6]</sup>.

The results of this study show that after the nursing care, the observation group has stronger fall prevention self-management ability. The reason for this is that the implementation of fall prevention nursing measures focuses on strengthening the patients' awareness of fall prevention, and through multi-path educational modes, such as new media and publicity brochures, it improves the patients' knowledge of the hazards of falls and the key points of fall prevention, enhances the patients' self-management ability, and promotes the improvement of the patient's self-management level. Relevant studies have shown that, if patients are not provided with health education on fall prevention, their awareness of self-management is not strong, and they do not pay attention to falls, they may overestimate their mobility, or even carry out dangerous activities independently, which will increase the risk of falls<sup>[7]</sup>. The construction of a "safety-support-collaboration" nursing system will focus on the creation of a safe environment, provide patients with fall prevention nursing services, improve the quality of health education, raise the level of patients' awareness, and strengthen patients' self-protection ability, to achieve the prevention of falls<sup>[8]</sup>.

Through this study, it was found that after the nursing care, the observation group had a relatively low risk of falls and a low incidence of falls. The main reason for this is that the implementation of the observation group's nursing program pays attention to the prevention of falls, establishes a fall prevention nursing team, enhances the safety awareness and professionalism of the team members through training and other means,

provides high-quality nursing care for the patients, and creates a relatively safe environment to reduce the risk of falls. At the same time, the promotion work will be carried out through video and pictures, to improve the patient's self-care ability and self-management awareness, reduce the risk of patient falls, and reduce the degree of physical injury<sup>[9]</sup>. In addition, nursing staff will pay attention to the communication with the patient's companion, improve the companion's understanding of the hazards of falls, enhance the safety awareness of the companion, appropriately increase the companion time, and support the patient, so that the probability of the patient's fall decreases, and provide assistance for the patient's recovery<sup>[10]</sup>.

In conclusion, consideration should be given to the special characteristics of patients and attention should be paid to fall care in neurology nursing. A sound fall protection program should be established based on "safety-supportive-cooperative" to increase the knowledge of fall care publicity and enhance the patients' self-management ability, reducing the risk of falls and promoting the improvement of patient safety.

## Disclosure statement

The authors declare no conflict of interest.

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# Novel Immunotherapy Strategies for Brain Tumors

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**Abstract:** Glioblastoma is the most common and aggressive malignant brain tumor, responsible for a poor prognosis and treatment perspective. Despite advancements in investigating novel therapeutic approaches for brain tumors and glioblastoma, there is less progress in improving patients' survival outcomes. Several hurdles hinder effective treatment, including the immunosuppressive tumor microenvironment (TME), the blood-brain barrier, and extensive heterogeneity. Despite these challenges, immunotherapies are promising and effective therapeutic breakthroughs for the therapy of brain tumor types such as gliomas. Multiple new techniques are being explored including chimeric antigen receptor T-cell therapy, oncolytic virus, cytokine-based treatment, immune checkpoint inhibitors, and vaccine-based techniques. Finally, the present review paper aims to summarize the existing developments of microglia, neutrophils, monocyte-derived macrophages, border-associated macrophages, and potential novel therapeutic options and recent advances in immunotherapies for brain tumors.

**Keywords:** Brain tumor; Glioblastoma; Immunotherapy; CAR T-cell therapy

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## 1. Introduction

Brain tumors are abnormal growths of cells in or around the brain and can be malignant or benign. Brain tumors can start in the brain as primary or spread from another part of the body as metastatic. Treatment for brain tumors varies depending on the type of tumor, its grade, and the patient's overall health. Treatment options may include surgery, radiation therapy, chemotherapy, or a combination of these therapies. The most common type is gliomas, which arise from supportive cells in the brain. Other notable primary tumors include meningiomas, pituitary tumors, and metastatic brain tumors <sup>[1-2]</sup>.

Glioblastoma (GBM) starts from glial cells and is classified according to its histological characteristics. Together with microvascular proliferation and tumor necrosis, the characteristics that characterize this category also comprise hypercellularity, nuclear atypia, and deregulation of mitotic processes <sup>[3]</sup>. Therefore, they are categorized as primary when there has been no previous history or as secondary if they have advanced from low-

grade astrocytomas. Primary GBMs account for the bulk of instances, whereas secondary GBMs, which typically affect young people, only make up 5 to 10% of cases <sup>[4]</sup>. Immunotherapies have produced medicines that have significantly improved overall survival (OS) and changed clinical practice. Relative to those with brain metastases, people with original brain tumors have not benefited as much from OS. The histology of the initial tumor primarily determines the wide range of OS related to secondary brain cancers in adults <sup>[5]</sup>. Diagnose-specific prognostic instruments, such as the diagnosis-specific Graded Prognostic Assessment, are being developed since OS for individuals with brain metastases differs greatly. Patients with primary brain tumors have not shown a significant improvement in their overall survival during the previous ten years, compared to those with brain metastases <sup>[6]</sup>. Immunotherapies did have a major therapeutic advantage for patients with brain metastases, but they have not demonstrated a compelling clinical advantage for patients with original brain tumors <sup>[7]</sup>.

In primary brain malignancies and brain metastases, the number of lymphocytes that infiltrate the tumor varies. The infiltration of CD3+ lymphocytes is over 50% higher in brain metastases than in glioblastoma or low-grade glioma <sup>[8]</sup>. The oncometabolite 2-hydroxyglutarate, which is generated by mutant IDH and prevents T-cell activation, is one theory for the procedure. Microglial cells dominate the inflammatory milieu of gliomas, and a significant portion of monocyte-derived macrophages are present in tumors carrying the IDH mutation. Moreover, it is recognized that several epigenetic subgroups affect lymphocyte infiltration <sup>[9]</sup>.

Secondly, the failure of current immune therapies for glioma may be explained by the lack of checkpoints. A decreased PD-L1 activity is seen in the tumor microenvironment of lower-grade gliomas. A tiny fraction of those with IDH wildtype tumors have alternative checkpoints, such as lymphocyte-activation gene 3 (LAG-3), which are almost nonexistent in glioma patients in general. Soluble PD-L1 (sPD-L1) was found to be positively correlated with survival in peripheral blood, with glioma patients having a greater amount of sPD-L1 than those with brain metastases <sup>[10]</sup>. Individuals with glioblastoma showed a greater neutrophil-to-lymphocyte ratio (NLR), which is similar to the idea of an immunosuppressive surrounding. Thirdly, glioblastoma individuals often have a smaller tumor mutational burden (TMB) than melanoma or non-small cell lung cancer (NSCLC) individuals. Immune checkpoint inhibitor-treated individuals with melanoma and NSCLC show a link between anti-tumor reactions and TMB. Individuals with glioblastoma do not show this correlation <sup>[11]</sup>.

The investigation has concentrated on finding distinct driver mutations whereby particular inhibitors can be created. Therefore, the creation of such medications may lead to an improvement in OS. Therefore, the identification of novel targets for primary or secondary brain cancers is promised by the identification of molecular mechanisms in gliomagenesis <sup>[12]</sup>. To investigate the gene expression-based subgroups and their connection to the immune authorization, single-cell investigations have revealed four primary glioblastoma cellular phases that are impacted by distinct genetic processes and microenvironment pieces: (a) Neuron-progenitor-like cells were found to be enriched in cyclin-dependent kinase (CDK) expansions; (b) oligodendrocyte-progenitor-like cells were found to be enhanced in platelet-derived growth factor receptor alpha (PDGFRA) amplification; (c) astrocyte-like cells demonstrated a more regularity of EGFR enhancement; and (d) mesenchymal-like cells were identified as having NF1 mutations. Four pathway-based categories can be identified when all the molecular data is combined: (1) glycolytic/pluriprimetabolic; (2) neural; (3) mitochondrial; and (4) proliferative/progenitor <sup>[13–14]</sup>.

An additional use for molecular-specified network analysis is the assessment of glioblastoma temporal alterations. This assessment can assist in identifying resistance strategies and ascertain if a target maintains stability over time. This method reveals a great deal of variation over time among the various subgroups, particularly modifications to metabolism. Third, the immunological microenvironment can also be characterized through the



assessment of gene expression. The production of macrophage receptors with collagenous structure (MARCO), which promote mesenchymal transition, is linked to these TAM <sup>[15–16]</sup>.

Intratumoral CD8, stromal PD-L1 expression, and immune cell concentration were linked to reactions in patients with brain metastases, based on initial reactions to immunotherapies in individuals with melanoma and NSCLC <sup>[17]</sup>. The anatomical place of brain metastases influences the composition of myeloid cells, which varies from other metastatic locations. Previous treatments, including radiation treatment, can alter the microenvironment, resulting in an environment that is either immune-depleted or enriched. The genes linked to metabolic processes such as oxidative phosphorylation are responsible for driving this immunological makeup <sup>[18]</sup>.

In recent times, various novel therapeutic strategies have been investigated, such as vaccinations, chimeric antigen receptor T (CAR-T) cells, immunocytokines, antibody-drug conjugates, and novel immune checkpoint inhibitors. Because glioblastoma expresses EGFR differently, antibody conjugates that target EGFR domain II take advantage of this protein's amplification to provide chemotherapy selectively. The phase 3 trial in patients with freshly confirmed glioblastoma did not demonstrate a survival benefit, whereas the phase 2 research in recurrent glioblastoma seemed to provide the anticipated increased OS <sup>[19]</sup>.

There are many different types of central nervous system (CNS) tumors, however, they are frequently broadly classified as benign or malignant. The most prevalent ones in adults are brain metastases, gliomas, and meningiomas <sup>[20]</sup>. These investigations demonstrated that tissue-resident and monocyte-derived macrophages (MoMACS), which are thought to be primarily protumorigenic, predominate in aggressive brain malignancies. Studies used immune checkpoint inhibitor therapy because brain tumor cells were shown to contain PDL1 <sup>[21]</sup>. Therapy rejection is believed to be caused by factors in the tumor immune microenvironment, such as minimal cytotoxic T cell infiltration, minimal mutational stress absence of neoantigens, and local macrophage “corruption” leading to the establishment of an immune suppressive milieu. Chimeric antigen receptor (CAR)-T cells, dendritic cell (DC) immunization, oncolytic viral therapy, and cytokine antibody combinations to boost local infiltration and anti-tumor action are among the additional therapies that are presently being researched <sup>[22]</sup>.

The arachnoid cap cell layer of the meninges, specifically, is where meningiomas originate. Up until the onset of signs, they can grow to considerable sizes and typically expand gradually. While meningiomas are usually classified as benign (WHO Grade 1), 7% of cases appear as atypical (Grade 2) and 2% as malignant (Grade 3). After ten years, the total life rates for Grade 2 and 3 meningiomas are 50–79% and 14–34%, accordingly. 10% to 30% of individuals with systemic tumor burden develop brain metastases; they usually appear at stage IV of the illness <sup>[23]</sup>. Melanoma, lung cancer, and breast cancer are the three principal tumor types that metastasize to the brain most frequently. Brain metastases are being treated locally with surgery and stereotactic radiotherapy, as well as more recently developed systemic remedies including immune checkpoint inhibitors and targeted medicines. Although brain metastases are amenable to these therapies, they have the potential to advance, return, or multiply <sup>[24]</sup>.

## 2. Advancements in immunotherapy

The way that various cancer forms are treated has been transformed by immunotherapy. By “turning off” T cells, immunological checkpoints (IC) control the effectiveness of the immune reaction and prevent the death of healthy cells. Inhibitory checkpoint receptors on T cells are normally blocked by immune checkpoint inhibitors (ICI). There are now several clinical trials using CAR-T cells that have been designed to treat high-grade gliomas. Personalized T cells, or CAR-T cells, are derived from the patient's blood and genetically modified in a lab to

possess a particular T-cell receptor that identifies an accurate tumor antigen <sup>[25]</sup>. The CAR-T cells can attach the antigen following injection and eliminate the cancer cells. There was no cytokine release syndrome or off-tumor damage. In conclusion, larger-scale research has shown that all immunotherapeutic trials for glioblastoma have been unsatisfactory thus far <sup>[26]</sup>. There is some promise for the future with newer strategies such as CAR-macrophages or immune cytokines fused to IL12. All possible therapeutic options for treating brain tumors are summarized in **Figure 1**.



**Figure 1.** Illustrate the all key treatment options for brain tumors and glioblastoma with traditional and novel strategies.

## 2.1. Microglia

The brain parenchyma contains resident microglia that are embryonic and can regenerate themselves despite the need for replacement by macrophages produced from monocytes (MoMacs). It is unclear exactly what part CNS-resident microglia play in the glioma microenvironment, and it may play several different roles. The homeostatic markers SALL1, TMEM119, and P2RY12 are normally expressed in healthy brains and are occasionally decreased in brain tumors <sup>[27]</sup>. Apolipoprotein E and the NLRP1 inflammasome facilitated the production of IL-1b in glioma-associated microglia. Primarily found in IHD-WT GBM, microglia producing CX3CR1 and PDGFRA displayed an enhanced sensitivity to TGFb1, indicating the expanding, Ki67+ phenotype. Microglia also exhibited an inflammatory character with an elevation of CD14 and CD64 in human brain tumor tissues. In neocortical slice cultures, they also produce HMOX1 and develop IL10, which leads to CD8 T-cell depletion via the STAT3-BLIMP-1 axis. Reactivated effector T cells, on the other hand, were the outcome of HMOX1 microglia reduction. Inhibitory signals, such as the “do not eat me” signal CD47, which interacts with the receptor SIRPA, are expressed by brain tumor cells. It was recently demonstrated that by increasing macrophage phagocytosis, anti-

CD47 antibodies that interfere with SIRPA anti-phagocytosis reduce tumor development. Subsequent dissection showed that anti-CD47 therapy gave CX3CR1-expressing microglia the ability to inhibit tumor expansion, prolonging longevity in mice lacking CCR2-recruited macrophages <sup>[28–29]</sup>.

## 2.2. Border associated macrophages

Meningeal macrophages, perivascular macrophages (PVMs), and choroid plexus macrophages are the so-called border-associated macrophages (BAMs) that live at CNS interfaces. It is yet unknown what part they play in the microenvironment of aggressive brain tumors. Better research has been done on BAMs and their ontogeny in the mouse brain. Current studies on mouse brain macrophages using a single-cell atlas revealed six main BAM subgroups <sup>[30]</sup>. Fate tracing showed that subdural BAMs are of embryonic origin and that a small subset of choroid plexus epithelial macrophages represents an individual type of microglia. PVMs in the tumor microenvironment (TME) of other tumor types have been attributed to various roles. They are the infiltration of malignant cells, the promotion of tumor angiogenesis, and the initiation of metastatic spread <sup>[31]</sup>. There is a correlation between the density of tumor microvessels and PVM recurrence. PVMs accumulated in the perivascular space of recurrent GBM in human specimens of brain metastases and ICI-treated GBM, while PVMs invaded the tumor tissue in brain metastases <sup>[32]</sup>.

## 2.3. Monocyte-derived macrophages

There may be variations in the proportion of MoMacs to microglia between distinct kinds of brain tumors. Originating from the bone marrow, MoMacs invade aggressive brain tumors to take over as the predominant population. This is particularly true for IDH wildtype gliomas, while the IDH variant exhibits higher frequencies of microglia. From brain metastases from breast and lung cancer to melanoma, the number of MoMacs developed, while the opposite was true for microglia. Monocytes are the source of MoMacs, which are attracted by chemokine receptors that regulate brain metastasis movement, such as CX3CR1 or C3AR1 <sup>[33–34]</sup>. These MoMacs take on the characteristics of the tumor type and develop an immune-suppressive nature. An immune checkpoint receptor that may be investigated as a strategy in the future is LILRB2. CSF-1 receptor inhibitors were employed as an immunotherapy strategy and improved survival in GBM mice specimens <sup>[35]</sup>. Microglia may be impacted by these blockers as well. Using the GL261 glioma cell line, different preclinical research decreased CSF1R restriction exclusively on mature TAMs while increasing the proportion of monocytes, presumably because the monocyte-to-macrophage transformation is changed. This work also demonstrated the competition for space between microglia and MoMacs, as well as the adaptive processes that increase the amount of microglia in the malignancy to preserve TAM concentrations when monocyte inflow is impaired. The compensatory CSF2R-STAT5 pathway drove tumor recurrence and TAM activation after CSF1R suppression in a breast cancer brain metastases model <sup>[36]</sup>.

Tumor-associated microglia generated a proinflammatory phenotype in a preliminary system of lung-brain metastases, while MoMacs established patterns of alternative stimulation, such as antigen presentation and wound recovery, according to large quantities and single-cell RNA sequencing expression accounts. The division of MoMacs into two groups, referred to as M1 and M2, is inaccurate and unsupported by the available data, as there is a complex and flexible framework of overlapping macrophage subtypes <sup>[34]</sup>. Several indicators expressed on potential anti-inflammatory MoMacs have been investigated as potential therapeutic approaches in animal studies. For instance, in the GL261 model, MerTK inhibition reduced the number of TAMs and vascular development while increasing survival. S100A4 is an additional immunotherapy target on MoMacs, and TAMs depleted of



S100A4 exhibited enhanced phagocytic efficiency. S100A4, a little calcium-binding protein, has been shown in various tumor forms to prevent TAMs from going through apoptosis. MoMacs promote glioma cell phagocytosis and aggressive chemokine release, which in turn promotes T-cell accumulation. Effective T-cell lethality requires the expression of MHC class II antigen on MoMacs, and its absence results in CD8 T-cell malfunction through osteopontin <sup>[37]</sup>.

## **2.4. Neutrophils**

Neutrophils are the more common form of granulocytes found in circulation in the blood, and they originate from the bone marrow. Increased circulating neutrophil counts were found to be a negative prognostic factor in the context of brain tumors. A higher neutrophil-to-lymphocyte proportion in particular was associated with a more severe general survival rate. It is still unknown what role they play in the tumor microenvironment. According to certain research, active neutrophils in gliomas are myeloid-derived suppressor cells that produce nitric oxide and arginase, which aid in immune regulation <sup>[38]</sup>. Additionally, it was demonstrated that gliomas can control systemic myeloid differentiation in the bone marrow remotely, producing neutrophils that are predisposed to a morphology that supports malignancies <sup>[39]</sup>. There are currently few options for treating major brain tumors like GBM. Therapy procedures for patients with GBM take into account multimodal therapeutic techniques that work in concert to eradicate the tumor, although therapy is challenging, costly, and prone to therapeutic failure. However, it is important to consider the drawbacks of present therapies to create new ones or enhance established procedures <sup>[40]</sup>.

## **2.5. Surgical method**

The surgical approach, which depends on the maximum safe resection of the tumor, has become the cornerstone of GBM treatment because it allows for the histological diagnosis and inherited analysis of the tumor along with decreasing the size of the neoplastic mass and the symptoms brought on by parenchymal compression. Achieving a gross total excision as thoroughly and securely as feasible without jeopardizing the patient's functioning is the goal of surgery. Compared to partial resection or biopsy, complete resection has been linked to an increased likelihood of survival and no recurrence <sup>[41]</sup>. In this way, some instruments were created to optimize the surgical process and minimize any potential neurological impairments brought on by the technique. However, surgery alone cannot treat GBMs as nearly the condition will relapse. Additionally, there is a risk that the patient will experience a neurological lack as a consequence of the surgery, which could preclude the need for chemotherapy and radiation therapy, which makes the procedure exceedingly fragile, costly, and complex. It also requires a skilled neurosurgeon and advanced imaging machinery. As a result, it is critical to precisely balance the advantages and disadvantages of the surgical approach <sup>[42]</sup>.

## **2.6. Radiotherapy**

Presently, radiotherapy (RT) is a form of treatment centered on the application of radiation doses targeted at particular areas that have gained popularity in the 1970s and 1980s. Because phase III clinical research established the significance of adjuvant chemotherapy and radiation in the postoperative period of GBM during this year, this approach has been the accepted protocol for GBMs ever since <sup>[43]</sup>. Although RT is quite effective as a treatment option for tiny recurrent tumors, it has a significant restriction in that there is little evidence to support its use in recurrent gliomas. Radiation usage must also be prudent because the treatment plan necessitates knowledge about the patient's prior radiation exposure, the tumor's location, and the maximum dose that may be administered to a

certain tissue. Lastly, the therapy algorithm evaluates the patient's functional condition and the rate at which the disease is progressing. For this reason, chemoradiotherapy is not recommended for people over 70 who do not have an excellent operational condition as determined by the Intensive Care Unit scale's Functional Status Score<sup>[44]</sup>.

## 2.7. Chemotherapy

Temozolomide (TMZ) is the highest highly successful treatment for GBM available today. It is an alkylating drug that does not require the cell cycle. The capacity to traverse the blood-brain barrier and transferrable cytosolic transition to the cell nucleus account for this effectiveness. For newly confirmed GBM, the present standard procedure is for daily administration of 75 mg/m<sup>2</sup> of TMZ for the duration of the 6-week radiation treatment. Following that, 5 days are spent at 150–200 mg/m<sup>2</sup> for each 28-day cycle, totaling 6 cycles of the medication<sup>[45]</sup>. Additionally, non-methylation of the MGMT promoter results in roughly 55% of GBMs having intrinsic or acquired resistance to treatment. This decreases the pharmacological effectiveness of the alkylating drugs by removing the alkyl groups from the guanine's O6 position. By reducing TMZ cytotoxicity through the base excision repair route, chemotherapeutic resistance can also be attributed to another cause<sup>[46]</sup>.

## 2.8. Tumor microenvironment involvement

It is becoming increasingly evident how the tumor microenvironment affects how the defense system responds to cancer. It is common to refer to the central nervous system (CNS) as an immune-privileged region that responds to alloantigen assaults with diminished vigor. Two theories have historically been proposed to explain the characteristics of CNS immune access: (1) the blood-brain barrier (BBB); and (2) the lack of traditional lymphatic outflow of CNS antigens. The blood-brain barrier (BBB) is a partially permeable biological barrier made up of pericytes, astrocyte end-feet, and particular endothelial cells (which are not fenestrated but are securely linked by tight junctions). Its primary job is to closely control the flow of ions, chemicals, and cells such as immune cells between the brain and the blood<sup>[47]</sup>. One of the greatest obstacles to immunotherapy is the capacity to restrict the movement of potentially neurotoxic chemicals, mainly through ATP-binding cassette transporter-mediated efflux. The CNS offers an immune-privileged setting that promotes tumor development and growth, as evidenced by the requirement for both the generation of cancer-specific T cells and their direct interaction with malignant cells for effective anti-tumor reactions<sup>[48]</sup>.

## 2.9. Immunosuppressive mechanisms in GBM

Immunotherapy is a novel cancer medication, but it depends heavily on the presence of preexisting anti-tumor antibodies. It is well known that GBM causes systemic and local immunosuppression, which makes immune-modulating treatments more difficult to apply. By releasing a range of soluble substances that have diverse immunosuppressive impacts, GBM cells can elude immune surveillance. Prostaglandin E2, interleukin 10, and transforming growth factor  $\beta$  (TGF- $\beta$ ) are the most well-characterized GBM-derived immunomodulatory proteins<sup>[49]</sup>. In addition to not producing Th-1 or Th-2 cytokines in response to TCR stimulation, these transformed suppressor cells additionally exhibit TGF- $\beta$  and impede the growth of regular T cells in vitro. Furthermore, natural killer (NK) cells and CD8+ T lymphocytes have the activating receptor NKG2D downregulated by TGF- $\beta$ 1, which prevents them from being cytotoxic to GBM cells. However, TGF- $\beta$ 2 can downregulate HLA-DR antigen expression on tumor cells, which can help immunological evasion from T lymphocytes and avoid neoantigen delivery. When combined, these stimulations of T or NK cell activity impair the immune system's ability to

effectively eliminate tumor cells <sup>[50]</sup>. In GBM, IL-10 is also essential for regulating the proliferation of resident, invading, and tumor cells, mostly causing an immunosuppressive phenotype. Elevated levels of TGF- $\beta$ , CCL2, IL-4, and several anti-inflammatory cytokines were linked to higher production of IL-10. TAMs inhibit antigen-presenting protein development when IL-10 is present, which reduces CD4<sup>+</sup> T cell activation. In addition to TGF- $\beta$ , IL-10 can also induce the transformation of naive T cells expressing FOXP3 into Treg cells, which in turn results in immunosuppression mediated by Tregs. On the other hand, new research has demonstrated that a subgroup of HMOX1<sup>+</sup> myeloid cells that release IL-10 and are spatially localized in tumor areas that resemble mesenchymal tissue also causes T-cell exhaustion and hence serves the tumor microenvironment <sup>[51]</sup>.

Consequently, it has been demonstrated that PGE-2 plays a crucial role in mediating immunosuppressive action by promoting the growth of myeloid-derived suppressor cells (MDSCs). VEGF is one of the primary goals in the therapy of glioblastoma since it is the greatest significant modulator of angiogenesis in this disease. Lastly, hypoxia inhibits efficient anti-tumor immune reactions by regulating the expression patterns of immunomodulatory surface ligands such as programmed death-ligand 1 (PDL-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and others via the stimulation of hypoxia-inducible factor 1- $\alpha$  <sup>[52]</sup>. Through the production of several cell surface immunosuppressive factors, including the so-called immunological checkpoint molecules (ICs), GBM cells might weaken anti-tumor reactions. Membrane-bound PDL-1, which is coupled to programmed cell death-1 (PD-1) on the surface of activated T-cells, can cause T-cell exhaustion in GBM and immunosuppressive cells. To prevent T cell-mediated death, PDL-1 overexpression in the tumor microenvironment promotes obstruction, a mechanism known as a “molecular shield.” On the other hand, GBM cells that express the CD95 (Fas) ligand can also reduce the intensity of an immune response by causing invading lymphocytes to undergo CD95-dependent apoptosis. Last but not least, it has been demonstrated that lectin-like transcript-1 (LLT-1) and indoleamine 2,3-dioxygenase 1 (IDO) respectively restrict NK cell function and boost intratumoral Treg and myeloid-derived suppressor cells <sup>[53]</sup>.

## 2.10. Cytokine Therapy

The foundation of cytokine therapy for GBM is the application of pro-inflammatory cytokines to encourage the immune system's stimulation and the restoration of the tumor's immunosuppressive milieu. IL-12, TNF- $\alpha$ , and IFN- $\alpha$  have primarily been evaluated as potential glioblastoma treatments. IFN- $\alpha$  inhibits tumor angiogenesis and immune suppression-related gene expression, but it also increases T cell and macrophage performance and reduces their fatigue in this way. Conversely, TNF- $\alpha$  stimulates T cell activation by promoting dendritic cell maturation, while IL-12 is linked to higher CAR-T cell efficiency, improved CD4<sup>+</sup> T cell infiltration, and reduced T-regulatory cell abundance in the tumor microenvironment <sup>[54]</sup>.

However, at maximal tolerable doses, IFN- $\alpha$  treatment has limited efficacy and a considerable possibility for systemic toxicity. A user's injury is implied by the risk of collateral consequences. Research studies include headaches, chills, gastrointestinal complaints, hypotension, and a drop in both systolic and diastolic blood pressure. This indicates that, at least for the time being, the therapy is a restricted supply. Furthermore, administering TNF- $\alpha$  presents a challenge due to its documented ability to create toxicities in patients when administered intravenously. Interleukin-7 agonists were recently discovered to have the potential to reverse the lymphopenia brought on by the conventional treatment for GBM and to strengthen the immune system by increasing CD8 serial lymphocytes in murine models. However, further research is required to apply these findings to patients with primary glioma <sup>[55]</sup>.

## 2.11. Inhibitors used for immune checkpoint

Molecular receptors known as immune checkpoints serve as inhibitory mechanisms to limit exaggerated immune responses and stop the system from becoming uncontrollably active. T cells (CD4 and CD8), dendritic cells (DC), natural killer (NK) cells, and B cells all have these receptors. Certain processes seen in cancer cells enable them to lessen the immune system's efficacy while attacking mutant cells. One of these ways involves the production of chemicals that communicate directly with immune checkpoint receptors, reducing immunological activity by blocking vital defense system cells <sup>[56]</sup>. As a result, immune checkpoint inhibitors have become a viable treatment option to stop immune cells from being inhibited due to interactions between their receptors and chemicals made by glioblastoma cancer cells. In this context, research has determined the primary immune checkpoint receptors and their physiological significance in glioblastoma. The immune system cells that express PD-1, T-cell immunoglobulin and mucin domain 3 (TIM3), CTLA4, lymphocyte activation gene 3 (LAG3), T-cell immunoglobulin and ITIM domain (TIGIT), and CD96 are inhibitory receptors. Cancer cells produce the ligands that bind to these receptors <sup>[57]</sup>.

## 2.12. CAR T-cell therapy

Chimeric antigen receptors are artificial receptors that can reroute T lymphocyte immune reactions to a particular target antigen. As a result, T cells can produce both immediate and long-term impacts by inducing intricate antitumor reactions. The extracellular domain of CAR-Ts includes an internal T cell signaling domain, a flexible hinge, a transmembrane region, and a tumor binding site in the form of the single-chain variable fragment (scFv). Furthermore, CARs can be classified as first, second, or third generation based on the quantity of CD3 $\zeta$  stimulatory domains they contain. The majority of contemporary CARs feature two costimulatory domains connected to CD3 $\zeta$  to enhance their signaling activation capacity <sup>[58]</sup>. Since CAR-Ts have proven to be a successful therapy for hematological malignancies, the goal is to modify the approach for solid tumors like GBM so that, independent of the delivery of the peptide by histocompatibility complexes, the stimulation of T cells in the tumor microenvironment supports targeted immunological mechanisms of cell death to specific targets in the tumor, yielding the same level of success as the treatment in non-solid tumors <sup>[59]</sup>.

EGFRvIII is an oncogenic mutation type found in human malignancies that enables the immune system to recognize particular tumor antigens. EGFRvIII is comparatively prevalent, particularly in GBM, where the alteration is seen in about 30% of cases. Because EGFRvIII promotes tumor oncogenic signaling, its levels in GBM patients are thought to be a poor prognostic indicator. In this regard, 10 patients with recurrent EGFRvIII + GBM were assessed in the first clinical trial that looked into CAR-T therapy targeted at EGFRvIII <sup>[60]</sup>. The outcomes showed that infusion-based delivery of CAR-T cells is an appropriate technique to employ, as there was no indication of cytokine release syndrome or harm irrespective of the tumor microenvironment. No patient experienced GBM regression, and one patient maintained stable disease for longer than 18 months, even though the study's goal was not to assess the therapy's efficacy <sup>[61]</sup>. In addition, current research that examined EGFRvIII as a potential therapeutic target for GBM analyzed the apheresis and infusion products from the earlier investigation and found that PD1 is a predictor of peripheral graft and progression-free survival in transduction products of patients with EGFRvIII-targeted CAR-Ts. However, before the development of CAR-Ts, the aforementioned relationships did not exist. Consequently, it has been suggested that the PD1 marker may indicate a greater outcome to treatment for recurrent GBM and that the variations in therapeutic outcomes observed in the research are due to the infusion product's manufacture <sup>[62-63]</sup>.



About 80% of GBMs express HER2, another tumor-associated antigen. Nevertheless, the receptor is also present in healthy host cells, which means that when HER2 is employed as a specific target antigen, it may cause autoimmunity. The initial study using HER2 CAR T cells in cancer patients did not yield encouraging results. One patient's acute toxicity resulted in death as a result of the trial. Although it exists in normal tissues, IL-13R $\alpha$ 2 is not significantly expressed in normal brain tissue, and it is another tumor-associated antigen that is present in up to 50% of GBM. It's significant to note that three patients with recurrent GBM were enrolled in the first trial that assessed the safety and viability of using CAR-Ts that target IL-13R $\alpha$ 2 for therapy <sup>[64]</sup>. As a result, by inhibiting antigen release and lowering excess tumor toxic effects, it turned out to be a viable solution for problems with the present therapy. Furthermore, an additional preliminary study generated an IL-13R $\alpha$ 2 directed towards a humanized third-generation CAR, assessed its effectiveness against GBM in vitro, and documented that the receptor produced good findings that validate its application in clinical research <sup>[65]</sup>.

As a result, CAR-T therapy that targets particular antigens is extremely promising and may one day be used as a treatment option for solid tumors like GBM that have a bad prognosis. The scant data, however, nevertheless presents several obstacles for the therapeutic approach to overcome. The intricacy of the tumor microenvironment and immune cells' ability to enter the central nervous system are the primary barriers to a safe and successful CAR-T treatment. The primary cause of the first is the presence of both the endothelium and epithelial blood-brain barriers. The second happens as a result of GBM's complicated and dynamic tumor microenvironment, which can thwart CAR-T cells' ability to recognize a single, distinct target antigen <sup>[66]</sup>.

### 2.13. Oncolytic viruses

Oncolytic viruses (OVs) have been more widely used in the therapy of tumors, particularly GBM, in recent years. Because of its advantages, including its tumor restrictions and absence of distant metastases, OVs are especially well-suited for GBM therapy. This makes the employment of viruses at this location a viable method of immunotherapy. For its mitigating impacts, they are delivered intratumorally or intravenously. Viruses known as OVs are classified as mildly pathogenic viruses since they can only infect, multiply, and kill cancer cells while sparing healthy cells and causing tumor cells to undergo apoptosis <sup>[67]</sup>. Tumor-specific cell death and the stimulation of the host's systemic antitumor and/or antiviral immunity are the mechanisms by which this happens. By using pattern recognition receptors and pathogen-associated molecular trends, OVs thus trigger the innate immune system and trigger the attraction of immune cells such as Th1 cells, neutrophils, macrophages, natural killer cells, and their cytokines, which in turn stimulate cell lysis. Additionally, this process triggers an adaptive immune response to novel cancer antigens and may result in a long-term immunotherapy side effect. Moreover, OVs can be employed as non-replicating viral vectors to transfer therapeutic genes, acting as an effective means of delivering genes to cancer cells <sup>[68–69]</sup>.

### 2.14. Vaccine-based therapy

The idea of vaccination treatments is a noteworthy development in the recent discussion of immunotherapy's enormous potential for treating and stabilizing oncological disorders. In this regard, the idea of a different treatment for GBM that uses vaccination to provide patients with a better prognosis is a topic of considerable discussion and investigation. Numerous vaccines with diverse immunological foundations have been created and evaluated for the management of GBM. There are four standard methods on which to develop GBM vaccines: Using genetic data from the tumor itself, peptide and DNA vaccines are more targeted in their application. mRNA-based

vaccines using viral vectors and cellular vaccines based on dendritic cells manufactured additionally with tumor antigens <sup>[70-71]</sup>. Generally speaking, the idea underlying this wager is the immune response, taking into account the tumor's capacity to elude the specific immune reaction. Thus, the immune system itself more particularly, a reaction orchestrated by T cells competent of identifying tumor antigens and retaliating against them, is one of the strategies discovered to "fight" this illness. Thus, the first suggestion seeks to elicit an immune reaction using targeted tumor antigens (TSAs), utilizing as a starting point peptides derived from tumor features that elicit an anti-tumor immune response by imitating neoantigens in glioblastoma cells. A second strategy for developing anti-tumor vaccines is the use of personalized neoantigen vaccines, which have shown promise in improving mortality in patients recently diagnosed with GBM by changing the immunological milieu of the disease <sup>[72]</sup>.

There are, however, some areas of disagreement with this vaccine treatment due to tumor heterogeneity, which results in factors conveyed distinctly in each individual and would require high specificity when manufacturing the vaccine. Additionally, the vaccine is not very effective when used on a large scale, which makes it difficult to include patients. Antigenic escape in the face of cancers lacking this antigen is another drawback of this treatment. Furthermore, the collection of peptides for the vaccine base encounters an obstacle because the connection between a variable tumor profile and the potential formation of nonspecific epitopes, a tumor formed not from mutations but rather from heightened manifestations of variables found in normal tissues, raises the risk of reactions that extend outside the tumor affection, including inflammatory events and autoimmune reactions in other areas <sup>[73]</sup>.

DC vaccines are one of the most exciting fields of research right now, and they have been receiving attention as well. This is because of their function in immune modulation in the context of GBM. As a result, they play a crucial role in the development of developed immunity as well as the differentiation, antigen presentation, and lymphocytic reaction. In light of this, it can be observed in GBM images that DCs appear to exist in an impeded or immature state, resulting in decreased work. This could be linked to the severe tumor microenvironment. The immune microenvironment's inhibitory effect also contributes to DCs' low function, which is detrimental to bodily functions but can be corrected by DC vaccinations. This is because DC vaccines work by activating previously inhibited T cells in vitro, typically from the influenced individual themselves. This boosts the patient's adaptable reaction, increases the production of MHCs, cytokines, and chemokines, and encourages a rapid movement of immune cells to the immunosuppressive microenvironment present in GBM <sup>[74]</sup>. According to some research, DC vaccinations can currently enhance the prognosis for GBM, with younger patients showing better outcomes in some age-related parameters. Another study, a phase II clinical trial, revealed that some patients who received the vaccination following tumor removal had a median overall survival of 23.4 months. However, as a meta-analysis of randomized controlled studies on DC vaccine efficacy showed, there was no appreciable difference in overall patient survival when the vaccination was given to recently identified glioblastoma individuals. Therefore, more research and trials with more advanced phases are still needed in this field, and future research should better examine its capacity to inhibit glioma <sup>[75]</sup>.

Other vaccination concepts have been tried out, such as basing the vaccine on isocitrate dehydrogenase, an enzyme whose mutation only happens in tumor cells, providing an intriguing tumor-specific antigen. Furthermore, given their effectiveness in treating and preventing other diseases, vaccines that inactivate tumors are also attracting research attention. However, the efficacy of these treatments for treating neoplasms is still low, necessitating further study for their growth and utilization in GBM. The application of these alternative vaccination strategies requires more sophisticated study. Therefore, selecting the right immunological activation



while lowering vaccination toxicity is crucial for vaccine therapy. The immunological changes brought on by the tumor microenvironment, the patient's immune condition, and potential negative events that must be minimized must all be considered in the hunt for TSA and potential substitutes. Furthermore, a crucial factor is that, despite the fleeting pattern toward customized vaccinations, figuring out how to render this fresh reality possible prompts the requirement to look for a combination of antigens with a wider range. This requires considering the long-term immunological reaction, how the vaccine handle will affect the creature, and future projections, all of which make the development of studies with more reliable results imperative. Furthermore, when compared to the use of particular vaccinations alone, the potential for combining vaccines with other immunotherapies has demonstrated significant benefit and this strategy should be further researched and taken into account in patient care <sup>[76-77]</sup>.

### 3. Immunotherapy limitations and challenges

There are numerous treatments for immunotherapy accessible now to treat GBM. These comprise genetically engineered T cells, immune checkpoint inhibitors, oncolytic viruses, and vaccinations. Given the ability to alter or strengthen the immune system equipment to target and eliminate tumor cells, immunotherapy has shed light and produced a great deal of excitement for the cure of glioblastoma multiforme (GBM). In this regard, the numerous ongoing research and clinical trials may yield positive outcomes in growing the application of these treatments in the coming years. However, there are still several barriers that prevent immunotherapy from being effectively used to treat glioblastoma. These barriers can be connected to specific immunological and anatomical aspects, as well as administration routes and side effects <sup>[78]</sup>.

Immunotherapy for GBM is severely limited by the blood-brain barrier. The ineffective treatment activity of these specialized endothelial cells linked to astrocytes and pericytes is caused by their obstruction of medication transport. Furthermore, GBM can change the BBB, creating the brain tumor barrier, a structurally distinct barrier that further impairs the absorption of therapeutic drugs <sup>[79]</sup>. Furthermore, considering the quick development of resistant clones following the deliberate eradication of vulnerable ones, intratumoral heterogeneity is crucial to immunotherapy tolerance. The tumor's immunosuppressive milieu presents another difficulty for the immunotherapeutic strategy. The use of CAR-T cells is hampered by Treg cell overexpression because it inhibits effector T cells. The practical application of cytokine therapy is severely limited by its systemic usage, which displays serious side effects and inadequate absorption, despite its ability to modify the microenvironment of GBM and result in greater maturation of DC cells, T cell infiltration, and decreased exhaustion. In this sense, more research on the subject may offer more choices for overcoming these obstacles in the near future <sup>[80-81]</sup>.

### 4. Conclusion

A shortened survival time and a decreased standard of life are linked to malignant brain tumors. Myeloid cells have just been identified as the dominant component of the immune microenvironment of malignant cancers. It is getting more obvious that comprehending therapy failures and tumor progression depends on understanding the myeloid landscape in the TME. For GBM patients, the immunotherapy's promise as demonstrated by earlier and ongoing clinical trials offers hope. It is anticipated that a variety of therapies will be applied to minimize side effects and enhance healing. The hazards and expenditures associated with surgery, radiotherapy, and chemotherapy point to several problems that other methods do not have. Additionally, these methods are better suited for palliative care than for healing. Nevertheless, before they can be used, some issues related to their use

must be resolved. Immune checkpoint inhibitors have the potential to impede GBM's immunosuppressive tactics, although the human reaction to these drugs has never yet equaled the effectiveness seen in studies on animals. Since chimeric antigen receptor T cell therapy can reroute the immune reaction to particular objectives, it is also an exciting therapy option. Additionally, vaccine-based therapy is being explored for the immunotherapy of brain tumors. To sum up, there are benefits and drawbacks to the immunotherapy choices. Therefore, it is essential to make more progress in preventing adverse effects and the ineffectiveness of the promising new immunotherapies that have just been found to extend patient life and lessen suffering in the near future.

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## Disclosure statement

The authors declare that they have no conflict of interest.

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# The Effectiveness of Neurological Rehabilitation Therapy in Improving Motor Function and Daily Living Abilities in Stroke Patients with Hemiplegia

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**Abstract:** *Objective:* To explore the effects of neurological rehabilitation therapy on motor function and daily living abilities in stroke patients with hemiplegia. *Methods:* Fifty stroke patients with hemiplegia admitted to the hospital were randomly divided into an observation group and a control group, with 25 patients in each group. The control group received conventional rehabilitation therapy, while the observation group underwent additional neurological rehabilitation therapy. The therapeutic effects were compared between the two groups. *Results:* Post-treatment results showed that the observation group achieved significantly better recovery in motor function, balance ability, and daily living abilities compared to the control group, with a lower incidence of complications during the rehabilitation period. *Conclusion:* Adding neurological rehabilitation therapy during the rehabilitation period of stroke patients with hemiplegia can effectively enhance recovery outcomes.

**Keywords:** Stroke hemiplegia; Neurological rehabilitation therapy; Motor function; Daily living abilities; Therapeutic effectiveness

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## 1. Introduction

Stroke is a cerebrovascular disease that poses a severe threat to human health, characterized by high incidence, disability, and mortality rates<sup>[1,2]</sup>. With advancements in medical care, the survival rate of stroke patients has significantly improved, but sequelae such as hemiplegia remain a major challenge<sup>[3]</sup>. Hemiplegia, one of the most common complications of stroke, often leads to motor dysfunction and decreased self-care ability, imposing a heavy burden on families and society<sup>[4,5]</sup>. Therefore, timely and effective treatment for post-stroke hemiplegia is particularly important.

In recent years, neurological rehabilitation therapy, as a comprehensive treatment method, has gained increasing attention in the rehabilitation of stroke patients with hemiplegia<sup>[6]</sup>. Based on the theory of

neuroplasticity, neurological rehabilitation therapy employs various approaches, including physical therapy, occupational therapy, speech therapy, and psychological therapy, aiming to promote neural function recovery and reconstruction, thereby improving motor function and daily living abilities<sup>[7]</sup>.

However, systematic, comprehensive, and in-depth research on the efficacy of neurological rehabilitation therapy in improving motor function and daily living abilities in stroke patients with hemiplegia remains limited. This study aims to evaluate the effectiveness of neurological rehabilitation therapy in this context, providing a scientific basis for rehabilitation strategies in stroke patients with hemiplegia, improving their quality of life, and reducing the burden on families and society.

## **2. Materials and methods**

### **2.1. General information**

Fifty stroke patients with hemiplegia admitted to the department between January 2020 and June 2022 were selected as study subjects. The patients were randomly divided into an observation group and a control group, with 25 patients in each group. In the observation group, there were 15 male and 10 female patients, with an average age of  $(64.00 \pm 2.30)$  years. In the control group, there were 14 male and 11 female patients, with an average age of  $(64.50 \pm 2.40)$  years.

### **2.2. Methods**

During the rehabilitation period, both groups received tailored treatments for blood pressure regulation, lipid-lowering, neuroprotection, antiplatelet aggregation, and improvement of cerebral circulation. The control group underwent conventional rehabilitation training, which included early passive limb function exercises to promote blood circulation and reduce limb stiffness. Gradual progressions included limb function training, getting out-of-bed activities, and daily living skills training.

The observation group received additional neurological rehabilitation therapy based on the treatments provided to the control group. This therapy involved using a neuromuscular electrical stimulator. Patients were assisted to adopt a seated position, with electrode pads placed on areas such as the upper arm, deltoid, and wrist extensor muscles. The settings included a biphasic pulse waveform with a frequency of 20–30 Hz and a duty cycle of 1 second:5 seconds. Treatment parameters were adjusted in real time based on the patient's tolerance. Therapy was conducted once daily, five times per week, for a total duration of 12 weeks.

### **2.3. Observation criteria**

- (1) Evaluation of limb motor function and daily living ability: The Fugl-Meyer Assessment (FMA) scale was used to evaluate motor function, and the Modified Barthel Index (MBI) was employed to assess daily living ability. Both scales have a maximum score of 100, with higher scores indicating better recovery in these functions.
- (2) Complication rate comparison: The incidence of complications during the rehabilitation period was recorded and compared between the two groups.
- (3) Balance ability assessment: The Berg Balance Scale was used to evaluate balance ability between the two groups.

## 2.4. Statistical analysis

Data from the two groups were processed using SPSS 20.0 software. Measurement indicators were described as mean  $\pm$  standard deviation (SD), and *t*-tests were performed. Count indicators were expressed as frequency (*n*) and percentage (%), and chi-squared ( $\chi^2$ ) tests were used. A statistical significance level of  $P < 0.05$  was applied for all comparisons.

## 3. Results

### 3.1. Comparison of limb motor function and balance ability before and after neurological rehabilitation intervention

Before treatment, there was no significant difference in the indicators between the two groups ( $P > 0.05$ ). After treatment, the observation group demonstrated significantly better recovery of limb motor function and balance ability compared to the control group ( $P < 0.05$ ), as shown in **Table 1**.

**Table 1.** Comparison of limb motor function and balance ability between the two groups (mean  $\pm$  SD)

Group	<i>n</i>	Physical movement function (score)		Balance ability (score)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	25	55.3 $\pm$ 6.1	88.2 $\pm$ 9.5	21.5 $\pm$ 8.6	37.8 $\pm$ 8.7
Control group	25	55.5 $\pm$ 6.2	79.6 $\pm$ 8.3	16.6 $\pm$ 10.8	31.2 $\pm$ 9.0
<i>t</i> / $\chi^2$ value		0.1149	3.4086	1.718	2.500
<i>P</i> value		0.9089	0.0013	0.0923	0.0159

### 3.2. Comparison of daily living ability and incidence of complications before and after neurological rehabilitation intervention

Before treatment, there was no significant difference in the indicators between the two groups ( $P > 0.05$ ). After treatment, the observation group exhibited significantly better recovery in daily living ability compared to the control group ( $P < 0.05$ ). Additionally, the incidence of complications was significantly lower in the observation group after rehabilitation, as shown in **Table 2**.

**Table 2.** Comparison of daily living ability and incidence of complications between the two groups (mean  $\pm$  SD)

Group	<i>n</i>	Daily living ability (score)		Incidence of complications
		Before treatment	After treatment	
Observation group	25	55.4 $\pm$ 6.2	89.4 $\pm$ 9.7	1 (4.0%)
Control group	25	55.5 $\pm$ 6.3	79.2 $\pm$ 8.4	6 (24.0%)
<i>t</i> / $\chi^2$ value		0.0565	3.9745	4.1528
<i>P</i> value		0.9551	0.0002	0.0415

## 4. Discussion

Stroke is one of the most prevalent cerebrovascular diseases significantly impacting human health <sup>[1,2]</sup>. The condition causes substantial damage to neural functions in the brain, leading to varying degrees of hemiplegia,

speech disorders, and other sequelae <sup>[7]</sup>. Patients often face increased risks of complications due to prolonged immobility, which exacerbates their suffering and extends recovery periods <sup>[8]</sup>. Currently, conventional treatments for post-stroke hemiplegia primarily involve symptomatic medication and rehabilitation training to improve motor function, but the results are often suboptimal <sup>[8]</sup>. To enhance rehabilitation efficiency for such patients, this study implemented neurological rehabilitation interventions, which yielded notable recovery outcomes.

Neuromuscular electrical stimulation (NMES) is a critical component of neurological rehabilitation <sup>[9,10]</sup>. By delivering low-frequency pulsed currents during treatment, it effectively stimulates local muscles, enhancing their autonomous contraction capabilities. This process alleviates peripheral tissue edema, promotes blood circulation, increases the excitability of muscle tissue, and ultimately improves neural conduction and muscle function <sup>[11]</sup>. In this study, it was observed that compared to conventional rehabilitation training, neurological rehabilitation significantly enhanced patients' motor and balance abilities. Additionally, this method accelerated venous lymphatic return, improved lower limb blood circulation and joint function, and reduced the formation of deep vein thrombosis during immobilization <sup>[12]</sup>.

The findings of this study further corroborate these benefits, showing that patients' daily living abilities improved significantly after neurological rehabilitation intervention. More importantly, the incidence of complications decreased markedly following the intervention. These results highlight the therapeutic efficacy of neurological rehabilitation for post-stroke hemiplegia.

In summary, integrating neurological rehabilitation into the management of post-stroke hemiplegia plays a critical role in enhancing recovery efficiency, promoting the restoration of motor function, and improving daily living abilities. This approach offers new hope to stroke patients, potentially improving their quality of life and alleviating the burden on families and society.

However, this study has certain limitations, such as a small sample size and a short observation period. Further large-scale, multicenter studies are needed to validate the long-term efficacy and safety of neurological rehabilitation. Moreover, exploring the effects of combining neurological rehabilitation with other therapeutic methods could provide more personalized and comprehensive rehabilitation plans for stroke patients.

In conclusion, neurological rehabilitation shows promising application prospects in the recovery of post-stroke hemiplegia patients. Nevertheless, continued in-depth research and refinement are necessary to better address patients' rehabilitation needs.

## Disclosure statement

The author declares no conflict of interest.

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# Discussion on the Splitting Treatment Technique in Gamma Knife Treatment Plans

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**Abstract:** *Objective:* In clinical Gamma Knife treatment, when patients have multiple or large lesions, a single Gamma Knife plan may require extended treatment time, making it difficult for patients to complete the session. This study explores the proper application of the splitting treatment technique in Gamma Knife treatment plans to create segmented plans for patients. *Methods:* Utilizing the design and output functions of the radiotherapy planning system, this study examines the typical errors in clinical treatment plans designed for the Moonlight Gamma Knife. Different splitting approaches were analyzed by comparing beam-on time for each target and calculating beam-on time error rates. Based on this, the appropriate splitting treatment technique for Gamma Knife treatment plans was discussed. *Results:* Scenarios where dose curves of multiple lesions intersect were categorized into three types: complete intersection, partial intersection, and no intersection. Complete intersection cases were further divided into Type I and Type II complete intersections. For cases with completely intersecting dose curves, the Gamma Knife plans should be split using the upper-lower segmentation method. For cases with no intersection, plans can be split based on individual lesions. For partial intersection cases, either the upper-lower segmentation or lesion-based segmentation method may be used. However, careful handling of target weighting at the dose curve intersection is necessary to ensure dose accuracy. For large lesions, the upper-lower segmentation method is recommended. *Conclusion:* To meet clinical treatment requirements, the proper application of the splitting treatment technique in Gamma Knife treatment plans is essential. This ensures dose accuracy in radiotherapy, thereby guaranteeing treatment efficacy and patient safety.

**Keywords:** Gamma Knife; Splitting treatment plan; Beam-on time; Dose curve

**Online publication:** December 26, 2024

## 1. Introduction

Gamma Knife treatment, as a non-invasive radiosurgical technique, has achieved significant success in the field of neurosurgery since its inception. It uses precisely focused gamma rays to deliver high-dose radiation to lesions while minimizing damage to surrounding healthy tissues<sup>[1,2]</sup>.

When patients have multiple or large lesions, using a single treatment plan for one session results in

prolonged treatment time, making it difficult for patients to complete the session. Under the same prescribed dose, increasing the number of fractions reduces the single-session dose, which compromises the Gamma Knife's advantage of delivering a high single-session dose. The splitting treatment technique addresses this by ensuring efficacy while meeting the practical treatment needs of patients<sup>[3]</sup>.

Plan splitting is often complex, requiring careful balancing of treatment doses and radiation coverage among different lesions<sup>[4]</sup>. This study explores the appropriate application of the splitting treatment technique in Gamma Knife treatment plans to facilitate segmented treatment for patients.

## **2. Materials and methods**

### **2.1. Materials**

This study utilized the planning design and output functions of the Xi'an Integrated Luna-260<sup>TM</sup> Gamma Knife Radiotherapy Planning System 3.0 (RTPS) to explore the splitting treatment technique for Gamma Knife treatment plans.

### **2.2. Research methods**

Using the planning design and output functions of the radiotherapy planning system, typical clinical treatment plans prone to design errors in Luna-260<sup>TM</sup> Gamma Knife planning were identified. Plans were designed using different splitting methods, and the beam-on times for each target point were recorded. The beam-on time error rates were compared and analyzed to investigate the correct splitting technique for Gamma Knife treatment plans.

### **2.3. Principles of the splitting treatment technique**

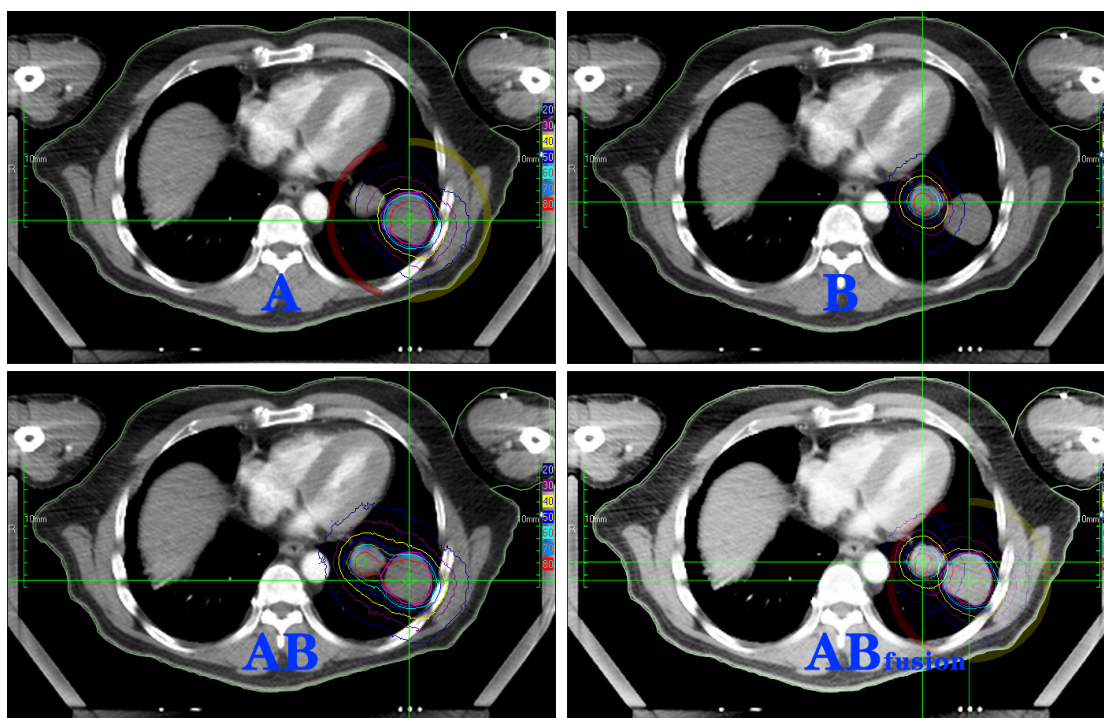
The splitting treatment technique for Gamma Knife treatment plans involves dividing a single treatment plan into two or more plans to meet the patient's treatment needs<sup>[5]</sup>.

## **3. Clinical application of the splitting treatment technique**

### **3.1. Typical clinical Gamma Knife treatment plan**

A male patient with liver cancer and pulmonary metastases underwent Gamma Knife treatment at the hospital in October 2024. Two adjacent metastatic lesions in the lungs required treatment, as illustrated in **Figure 1**.

The combined treatment plan (Plan AB) for lesions 1 and 2 provides the most accurate beam-on time for each target point, serving as a reference for evaluating other splitting plans, as shown in **Figure 1AB**.



**Figure 1.** Dose curve diagram for two adjacent lesions (complete intersection type II). **Figure 1AB** represents the dose curve diagram for the combined treatment of lesions 1 and 2. **Figure 1A** represents the dose curve diagram for Plan A, which treats lesion 2. **Figure 1B** represents the dose curve diagram for Plan B, which treats lesion 1.

### 3.2. Evaluation of lesion-based splitting plans

For lesion-based splitting, lesions 1 and 2 were treated separately, with Plan A designed for lesion 1 (**Figure 1A**) and Plan B designed for lesion 2 (**Figure 1B**).

For a single treatment session with a prescription dose of 5 Gy at the 50% isodose line, the beam-on times for target points in Plans A, B, and AB are compared in **Table 1**.

**Table 1.** Comparison of beam-on times (seconds) across splitting methods

Plan	Target	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
AB		105	175	175	140	332	273	332	227	329	175	262	175	122	87	280
A	Split by lesion	137	/	/	182	/	356	/	297	/	/	342	/	160	114	365
B		/	201	201	/	383	/	383	/	379	201	/	201	/	/	/
EF		105	175	175	140	332	273	339	231	336	178	266	178	122	87	280
E	Split by upper-lower	105	175	175	140	333	273	/	/	/	/	/	/	/	/	280
F		/	/	/	/	/	/	353	241	351	187	277	187	127	91	/

(Note: Data in **Table 1** were collected from the typical clinical treatment plans listed. The prescribed single-session dose was 5 Gy at the 50% isodose line. The table compares beam-on times (in seconds) across different splitting methods. Data marked as “/” indicate that the plan does not include the corresponding target point.)

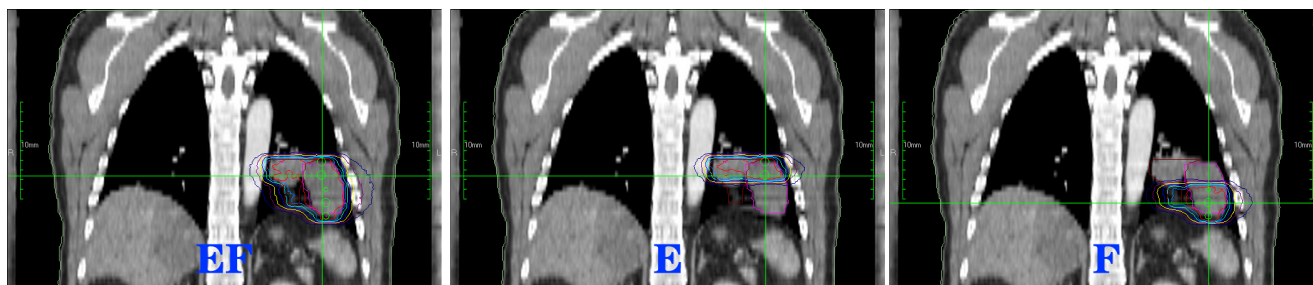
The error rates for beam-on times in Plan A compared to the original combined Plan AB for each corresponding target point are as follows: target point 1:  $(137-105)/105 = 30.48\%$ , target point 4: 30%, target point 6: 30.4%, target point 8: 30.84%, target point 11: 30.53%, target point 13: 31.15%, target point 14: 31.03%, and target point 15: 30.36%. The average beam-on time error rate for all target points in Plan A is 30.6%.

For Plan B, the error rates for each target point are: target point 2:  $(201-175)/175 = 14.86\%$ , target point 3: 14.86%, target point 5: 15.36%, target point 7: 15.36%, target point 9: 15.2%, target point 10: 14.86%, and target point 12: 14.86%. The average error rate for all target points in Plan B is 15.05%.

This indicates that splitting the plan in this manner introduces significant beam-on time errors, leading to inaccurate treatment doses.

**Figure 1AB<sub>fusion</sub>** shows the image resulting from merging **Figures 1A** and **1B**. The overlapping isodose lines for lesions 1 and 2 demonstrate that when lesion 1 is treated with Plan A and lesion 2 with Plan B, each lesion is influenced by the dose from the other's target points to varying degrees. This results in dose error rates that exceed beam-on time error rates, explaining the inaccuracy of this splitting method.

### 3.3. Evaluation of upper-lower splitting plans



**Figure 2.** Coronal dose curve diagram for correct splitting plans. **Figure 2EF** represents the combined dose curve diagram for lesions 1 and 2, corresponding to the same plan as **Figure 1AB**. **Figure 2E** represents the dose curve diagram for Plan E, which targets the upper half of EF. **Figure 2F** represents the dose curve diagram for Plan F, targeting the lower half of EF.

First, lesions 1 and 2 were treated as a whole to design Plan EF (**Figure 2EF**). Then, the lesions were split into upper and lower parts along the cranio-caudal axis, resulting in two separate plans: Plan E (**Figure 2E**) and Plan F (**Figure 2F**).

The coronal dose curve diagrams in **Figure 2** illustrate the differences before and after splitting.

For a single-session prescribed dose of 5 Gy at the 50% isodose line, the beam-on times for Plans E, F, and EF are shown in Table 1. All beam-on times in Plan E are identical to those in Plan EF, resulting in an average beam-on time error rate of 0. For Plan F, the error rates for each target point compared to Plan EF are: target point 7:  $(353-339)/339 = 4.13\%$ , target point 8: 4.33%, target point 9: 4.46%, target point 10: 4.46%, target point 11: 4.13%, target point 12: 5.06%, target point 13: 4.1%, and target point 14: 4.6%. The average beam-on time error rate for Plan F is 4.41%.

In summary, the lesion-based splitting method (Plan AB) resulted in an average beam-on time error rate of 23.34%. In contrast, the upper-lower splitting method (Plan EF) achieved a significantly lower average error rate of 2.35%. After splitting Plan EF into Plans E and F, Plan E showed no beam-on time errors, while Plan F retained minor errors due to the inherent uneven dose distribution in the original Plan EF. However, the splitting process improved dose uniformity between the upper and lower parts. Thus, Gamma Knife treatment plans for such cases

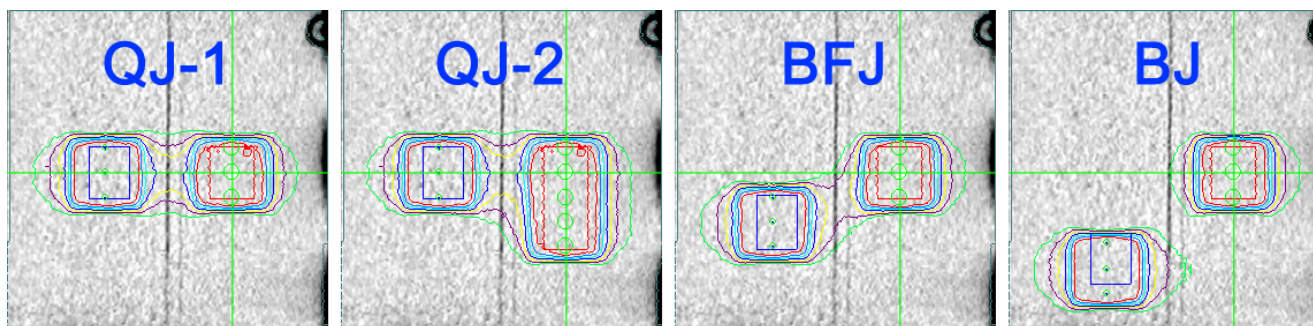


should adopt the upper-lower splitting design. The use of the correct splitting technique is critical, as it directly affects dose accuracy, treatment efficacy, and patient safety <sup>[6]</sup>.

## 4. Results

As a senior radiotherapy treatment planner (physicist), I have been designing Gamma Knife and accelerator treatment plans since 2006, having developed over 12,000 Gamma Knife treatment plans for more than 10,000 patients. This section provides a summary and experience-sharing regarding common errors in designing split treatment plans for Gamma Knife therapy. Feedback and corrections from experts and colleagues are welcome.

To correctly apply Gamma Knife treatment plan splitting techniques, it is first necessary to distinguish the intersection types of dose curves for multiple lesions. Based on the type of intersection, the appropriate splitting technique can be selected. Drawing on clinical experience in Gamma Knife treatment plan design, I categorize the possible intersection scenarios of dose curves for multiple lesions into three main types: complete intersection, partial intersection, and no intersection. The complete intersection type can further be divided into complete intersection Type I and complete intersection Type II, as illustrated in **Figure 3**.



**Figure 3.** Intersection types of dose curves for multiple lesions. **QJ-1** represents complete intersection Type I, **QJ-2** represents complete intersection Type II, **BFJ** represents partial intersection, and **BJ** represents no intersection.

In clinical treatment plan design:

- (1) For complete intersection types (as shown in **Figures 3 QJ-1** and **QJ-2**), the Gamma Knife plan should be split using the upper-lower splitting method.
- (2) For no intersection types, the lesion-based splitting method is appropriate. In cases where a patient has multiple lesions, even if they are in the same transverse plane, they can still be considered a no-intersection type if the distance between the lesions is sufficiently large and their minimum dose curves do not overlap.
- (3) For large lesions, the upper-lower splitting method should always be used.
- (4) For partial intersection types (as shown in **Figure 3 BFJ**), the dose curves for various lesion parts may both intersect and remain separate. This type can be addressed using either the upper-lower splitting method or the lesion-based splitting method.

When handling multi-lesion treatment plans, errors are more likely to occur for inexperienced physicians or treatment planners. The most common mistake lies in misjudging the intersection type of dose curves for multiple lesions. Partial intersection types are often incorrectly classified as no intersection types, leading to the erroneous

use of lesion-based splitting methods and resulting in dose deviations <sup>[7]</sup>.

## 5. Discussion

When there is uncertainty in determining the intersection type of dose curves for multiple lesions, the treatment plan should first be designed as a whole. The dose curve intersection type should then be assessed, and the correct Gamma Knife treatment plan splitting technique should be applied <sup>[8]</sup>. The intersecting dose curves of multiple lesions significantly influence one another because overlapping dose curves (as shown in **Figure 1 AB<sub>fusion</sub>**) increase the dose to adjacent lesions. This leads to dose deviations, which, in turn, affect the beam-on time for target points.

Advantages of Gamma Knife treatment plan splitting techniques:

- (1) Improved dose accuracy for lesions: Splitting treatment plans ensures that each lesion receives an appropriate radiation dose.
- (2) Enhanced flexibility for patient treatment: This technique allows for personalized treatment plans tailored to the patient's specific conditions, including lesion size, location, quantity, and overall health status.
- (3) Ensured treatment efficacy and safety: By precisely controlling the radiation dose and its range, damage to surrounding normal tissues is minimized, reducing the risk of treatment-related complications <sup>[9]</sup>.

Limitations of Gamma Knife treatment plan splitting techniques:

- (1) Treatment time: Splitting the treatment plan may increase the total treatment time and number of sessions. However, this resolves the issue of prolonged single-session treatments that patients may struggle to endure, meeting treatment demands while ensuring efficacy.
- (2) Technical expertise requirements: This technique demands high levels of experience and professional skills from radiation treatment planners (physicists), ensuring dose accuracy.
- (3) Cost: Implementing this technique may increase treatment costs, including equipment use, human resources, and subsequent monitoring <sup>[10]</sup>.

In clinical Gamma Knife treatments, when a patient has multiple or large lesions, a single Gamma Knife treatment plan often requires extended treatment time that patients may find difficult to endure. To meet patient needs, correctly applying Gamma Knife treatment plan splitting techniques enables phased treatment while ensuring the accuracy of the radiation dose. This approach ultimately ensures both the efficacy and safety of the patient's treatment.

## Disclosure statement

The author declares no conflict of interest.

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# Research Progress on the Correlation between Oral Diseases and Chronic Kidney Diseases

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**Abstract:** *Objective:* To review the research progress on the correlation between oral diseases and chronic kidney diseases. *Methods:* Recent Chinese literature on the treatment, analysis, and correlation studies of oral diseases and chronic kidney diseases was collected. A comprehensive review, analysis, induction, and organization of the literature were conducted. *Results:* A high correlation exists between oral diseases and chronic kidney diseases, which mutually reinforce each other. *Conclusion:* A deep-level association exists between oral diseases and chronic kidney diseases. Persistent inflammatory symptoms can promote the elevation of C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, thereby exacerbating the development of chronic kidney diseases. Therefore, clinicians should comprehend the mechanism of interaction between oral diseases and chronic kidney diseases to foster diverse clinical thinking, improve the treatment efficacy of chronic kidney diseases, and effectively shorten disease duration.

**Keywords:** Oral diseases; Periodontitis; Chronic kidney diseases; Correlation; Interleukin-6 (IL-6)

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## 1. Introduction

The correlation between oral diseases and chronic kidney disease (CKD) is a significant area of medical research with implications for improving patient outcomes. Poor oral health, particularly periodontal disease, is often directly linked to systemic inflammatory responses. This inflammation can potentially exacerbate the progression of CKD through various factors and pathways. Conversely, patients with CKD exhibit suppressed immune function, rendering them highly susceptible to oral infections, which can further deteriorate their overall health. By improving oral hygiene, the risk of bacteremia is significantly reduced, thereby slowing the progression of CKD. In conclusion, understanding the correlation between these two conditions and analyzing previous scholarly research on both diseases is crucial for developing more comprehensive treatment strategies for CKD and mitigating the risk of complications.

## 2. Nephropathy and chronic kidney disease

In the clinical field, nephropathy typically refers to diseases diagnosed as related to kidney organs, such as glomerulonephritis, pyelonephritis, lupus nephritis, and similar conditions. Generally, nephropathy is difficult to cure once it manifests, and if the disease duration exceeds three months, abnormalities in urine and related blood indicators, as well as abnormalities in renal pathology and imaging, or a glomerular filtration rate (GFR) less than 60%, may indicate CKD. Failure to receive timely and effective treatment for CKD can lead to further disease progression, potentially culminating in chronic renal failure, renal insufficiency, and ultimately, uremia. According to statistics from medical departments, the most common type of CKD currently is chronic renal insufficiency, characterized by elevated levels of urea nitrogen and creatinine, kidney volume atrophy, and potential anemia or elevated parathyroid hormone (PTH) levels <sup>[1]</sup>.

CKD is typically characterized by the “three highs” and “three lows.” The “three highs” refer to a high incidence rate, high fatality rate, and a high probability of concomitant cardiovascular diseases. The “three lows” indicate low awareness of kidney disease, low rates of prevention and treatment, and low awareness of concomitant cardiovascular diseases. Surveys show that the prevalence of CKD among the Chinese population aged 40 and above exceeds 10%, but the awareness rate remains below 5% <sup>[2]</sup>.

## 3. Correlation between oral diseases and chronic kidney diseases

### 3.1. Factors influencing chronic kidney diseases from oral diseases

Numerous scholars have conducted in-depth studies on the correlation between oral diseases and chronic kidney diseases based on clinical experience.

Some scholars have indicated that inflammation, a critical risk factor, can lead to the progression of CKD to end-stage renal disease (ESRD), subsequently triggering uremia. The inflammatory response generated by CKD and ESRD often serves as a key factor leading to cardiovascular disease (CVD). Additionally, patients with CKD frequently experience a significant burden of periodontal inflammation, typically characterized by persistent inflammatory symptoms. Levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ) may exhibit varying degrees of elevation <sup>[3]</sup>.

Some scholars have conducted a meta-analysis on the influencing factors of periodontal basic treatment for patients with chronic kidney diseases. During the research phase, scholars provided the same duration of nephrology treatment to two groups of patients (experimental group and control group), with the experimental group receiving additional periodontal basic treatment. Meta-analysis revealed that patients who underwent periodontal basic treatment exhibited decreased levels of CRP and IL-6, although the underlying mechanism remains unclear. The analysis suggests that lipopolysaccharides and other bacterial components within periodontal pathogens may activate inflammatory factors or induce acute reactions in hepatocytes. Periodontal basic treatment can effectively eliminate these pathogens, thereby reducing the extent of inflammation. Furthermore, scholars noted that CRP, IL-6, and TNF- $\alpha$  can enter the bloodstream through periodontal pocket ulcers and spread to distant organs <sup>[4]</sup>.

Scholars have pointed out that signaling pathways are key factors in the development of CKD influenced by periodontitis. During the research phase, scholars have suggested that latent membrane protein 1 encoded by the Epstein-Barr virus (EB virus) may generate a series of inflammatory factors, such as interleukin-8 (IL-8), through these signaling pathways. These factors are believed to be involved in the progression of chronic periodontitis (CP). While there is currently no research confirming that CP can directly cause CKD through signaling pathways,



studies have demonstrated that the activation of these pathways may be involved in the process linking CP to CKD. Typically, high expression of certain factors in these pathways may induce the expression of inflammatory markers such as CRP and IL-6, which can contribute to the progression of CKD <sup>[5]</sup>. Additionally, an increase in these factors can lead to elevated levels of TNF- $\alpha$  and interleukin-1 beta (IL-1 $\beta$ ) in the serum, resulting in damage to renal tubules, glomeruli, and interstitial tissue. Based on an experimental study involving 80 rats, it has been proven that CP can enhance the levels of TNF- $\alpha$  and IL-1 $\beta$  through activated signaling pathways, thus promoting the occurrence of CKD. However, scholars have also noted that the research conclusions are based on animal experiments, and further confirmation is needed in human studies <sup>[6]</sup>.

In 2020, some scholars conducted an analysis of the impact of periodontitis on renal interstitial fibrosis. They utilized a mouse model combining periodontitis and renal interstitial fibrosis for experimentation. Their findings suggested that periodontitis may be a potential risk factor for renal interstitial fibrosis. It promotes the expression of inflammatory factors such as matrix metalloproteinase-9 (MMP9), TNF- $\alpha$ , IL-1 $\beta$ , and interleukin-17A (IL-17A) in kidney tissues, while also facilitating the infiltration of neutrophils, thereby exacerbating the inflammatory response in kidney tissues. As the most common oral disease, periodontitis can lead to a systemic micro-inflammatory state. A series of toxic products, including lipopolysaccharides from periodontal pathogens, can induce host cells to secrete cytokines. These bacteria can aggravate the systemic inflammation level as the inflammation progresses. Through periodontal pathogen inoculation experiments in mouse mouths, it was found that pathogenic bacteria can significantly affect kidney function and histopathological changes in mice <sup>[7]</sup>. Within the category of periodontal pathogens, such as *Porphyromonas gingivalis* and *Prevotella intermedia*, they can trigger local inflammation by producing various toxic substances and enzymes. This local inflammation can transform into systemic inflammation via the bloodstream, intensifying chronic systemic inflammation, which is particularly detrimental to patients with CKD <sup>[8]</sup>.

In this process, serum CRP serves as an important inflammatory marker. The continuous action of periodontal pathogens increases the stimulation of CRP synthesis in the patient's liver, resulting in elevated CRP levels. The specific mechanism may involve the release of bacterial lipopolysaccharides and other inflammatory mediators like interleukin-6, which further activate the body's immune response <sup>[9]</sup>.

Compared to patients with other diseases, CKD patients are more prone to overreact to these microorganism-related inflammations. Their immune response is often disrupted due to decreased renal function. This enhanced inflammatory state not only exacerbates the destruction of periodontal tissues in CKD patients but may also accelerate the progression of CKD. By increasing the patient's systemic CRP level, it rapidly increases the risk of cardiovascular complications. Therefore, periodontal disease is not just a simple localized oral health issue for CKD patients; it is a critical factor affecting their overall health <sup>[10]</sup>.

Regarding the role of *Porphyromonas gingivalis* in the development of chronic kidney disease, research has shown that as the primary periodontal pathogen, its interaction with the immune system is the main cause of increased serum CRP levels <sup>[11]</sup>. When *Porphyromonas gingivalis* invades periodontal tissue, the body produces IgG antibodies targeting its antigens. The IgG antibody-antigen reaction activates the complement system, releasing various inflammatory mediators, including cytokines such as the common IL-6 and TNF- $\alpha$ . The release of these cytokines promotes the synthesis of CRP in the patient's liver, with IL-6 playing a dominant role. IL-6 directly stimulates CRP synthesis by binding to hepatocyte receptors. Additionally, *Porphyromonas gingivalis* and its metabolic products, such as lipopolysaccharide (LPS), can directly trigger the activation of monocytes and macrophages, further amplifying the inflammatory response in patients and exacerbating the increase in CRP

levels. This mechanism indicates that *Porphyromonas gingivalis* is not just a simple local oral infection. The systemic inflammatory response it triggers plays a crucial role in the elevation of CRP levels <sup>[12]</sup>.

### 3.2. Factors influencing chronic kidney disease on oral diseases

Scholars have specifically investigated the mutual promotion mechanism between periodontitis and CKD among elderly patients. The findings reveal that patients with CKD, due to the dysfunction of their immune system, are more susceptible to infection by periodontal pathogenic bacteria. Elderly patients with CKD often exhibit characteristics of decreased cellular and bodily immune function, such as reduced cell count, dysfunctional neutrophils, and suppressed neutrophil activity. These immune system abnormalities hinder the body's ability to effectively recognize and eliminate invading pathogenic microorganisms. Major periodontal pathogenic bacteria, including *Porphyromonas gingivalis*, can proliferate easily in a state of immunocompromise, subsequently triggering and exacerbating periodontitis <sup>[13]</sup>. Simultaneously, the accumulation of urea nitrogen and other metabolic waste products in the blood of CKD patients can also influence changes in the oral environment, such as reduced salivary flow and altered pH levels. These alterations provide favorable conditions for the growth of pathogenic microorganisms. Furthermore, the chronic inflammatory state induced by CKD, primarily manifested by elevated levels of inflammatory mediators, including IL-6 and TNF- $\alpha$ , can intensify the periodontal inflammatory response. Therefore, compared to individuals with a healthy constitution, patients with CKD are more susceptible to developing systemic inflammation from local periodontal infections. This further increases the burden on the body's immune system, leading to a vicious cycle of disease progression <sup>[14]</sup>.

Additionally, scholars have pointed out that patients with chronic kidney disease, affected by decreased renal function, can experience loss and retention of trace elements in their serum. This, in turn, affects bone structure and contributes to a higher incidence of oral diseases. Research indicates that the impact of chronic kidney disease on the body's bone structure originates from metabolic disorders of trace elements caused by decreased renal function. CKD patients often exhibit characteristics of hyperphosphatemia and hypocalcemia. These metabolic disorders stimulate increased secretion of PTH, leading to renal osteodystrophy, which manifests as osteomalacia, osteoporosis, and other conditions. These bone metabolism disorders directly affect the health and stability of the body's alveolar bone, making it more prone to resorption and loss, and increasing the risk of tooth loosening and falling out. Typically, patients with CKD experience dysfunction in vitamin D metabolism, resulting in a continuous decline in active vitamin D levels. This exacerbates calcium absorption disorders and osteoporosis <sup>[15]</sup>.

## 4. Conclusion

Based on a comprehensive analysis of numerous past scholarly research findings, a profound and mutually influential relationship exists between oral diseases and CKD. Oral diseases have the potential to elevate levels of CRP, IL-6, and TNF- $\alpha$ , thereby exacerbating the progression of CKD. Conversely, patients with chronic kidney diseases, due to the dysregulation of their immune systems, face a higher risk of developing oral diseases. Furthermore, in the context of impaired renal function, patients may experience changes in bone structure, leading to an increased risk of oral health issues such as tooth loss.

However, numerous aspects of the underlying mechanisms linking oral diseases to chronic kidney diseases remain to be further elucidated and confirmed. Most scholars have conducted their experiments using animal models. Therefore, it is imperative to continuously accumulate clinical experience and conduct further validations based on in-depth research to corroborate these findings.

## Disclosure statement

The author declares no conflict of interest.

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# Comparative Study on the Treatment of Schizophrenia Patients with Paliperidone and Risperidone Orally Disintegrating Tablets

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**Abstract:** *Objective:* To evaluate the therapeutic effects of paliperidone and risperidone orally disintegrating tablets on schizophrenia (SCH). *Methods:* A total of 66 hospitalized SCH patients admitted between April 2022 and October 2023 were selected. They were randomly divided into two groups using a random number table. The study group was treated with paliperidone, while the control group was treated with risperidone orally disintegrating tablets. Differences in efficacy, symptom scores, and adverse reaction rates were compared between the two groups. *Results:* The overall efficacy rate in the study group was similar to that of the control group ( $P > 0.05$ ). After three months of treatment, Positive and Negative Syndrome Scale scores in both groups were significantly lower than those before treatment, with the study group exhibiting lower symptom scores than the control group ( $P < 0.05$ ). The adverse reaction rate in the study group was lower than that in the control group ( $P < 0.05$ ). *Conclusion:* Paliperidone demonstrates therapeutic efficacy for SCH patients comparable to risperidone orally disintegrating tablets. However, paliperidone significantly improves disease symptoms and reduces medication-related side effects.

**Keywords:** Paliperidone; Risperidone orally disintegrating tablets; Schizophrenia; Symptom scores; Adverse reactions

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## 1. Introduction

Schizophrenia (SCH) is a chronic psychiatric disorder caused by the combined effects of psychological factors, genetic predisposition, and neurotransmitter dysfunction. Its symptoms include emotional apathy, slowed thinking, and self-directed speech, often accompanied by self-harming or violent behaviors<sup>[1]</sup>. The conventional treatment approach involves oral medications, primarily risperidone orally disintegrating tablets, which antagonize serotonin (5-HT) and dopamine (DA) receptors to alleviate symptoms. However, prolonged use of risperidone is associated with high drug resistance, frequent side effects, and suboptimal efficacy.

Paliperidone, an atypical second-generation therapeutic drug, exhibits strong antagonistic effects on dopamine



D2 receptors (D2R). It effectively alleviates both positive and negative symptoms without significantly inducing extrapyramidal reactions, offering a higher safety and benefit profile <sup>[2]</sup>. This study evaluated the therapeutic differences between paliperidone and risperidone orally disintegrating tablets in 66 hospitalized SCH patients.

## 2. Materials and methods

### 2.1. General information

A total of 66 hospitalized SCH patients treated between April 2022 and October 2023 were selected. The patients were randomly divided into two groups using a random number table. The study group included 33 patients (19 males and 14 females), aged 26–50 years, with a mean age of  $38.14 \pm 3.35$  years. The duration of illness ranged from 9 to 20 years, with a mean of  $15.19 \pm 3.18$  years. Body mass index (BMI) ranged from 18.5 to 28.1 kg/m<sup>2</sup>, with a mean of  $22.59 \pm 2.64$  kg/m<sup>2</sup>. The control group also included 33 patients (20 males and 13 females), aged 27–48 years, with a mean age of  $37.81 \pm 3.18$  years. The duration of illness ranged from 10 to 20 years, with a mean of  $15.91 \pm 3.25$  years. BMI ranged from 18.4 to 28.3 kg/m<sup>2</sup>, with a mean of  $22.68 \pm 2.77$  kg/m<sup>2</sup>. Comparisons of general characteristics between the two groups showed no statistically significant differences ( $P > 0.05$ ), indicating comparability.

Inclusion criteria: Patients presenting typical symptoms such as delusions or slow thinking; adult patients under 80 years of age; stable condition, capable of cooperating with medication; relatively complete clinical data; agreement to participate in the study.

Exclusion criteria: Patients who received related drug treatment within the past month; allergic to study drugs; suffering from malignant tumors or other severe diseases; severely manic and unable to cooperate; SCH caused by trauma or other factors; withdrawal during the study.

### 2.2. Methods

The study group was treated with paliperidone (produced by Livzon Pharmaceutical Group, National Drug Approval No. H20080217, specification: 4 mg). The initial dose during the first week was 4 mg per dose, administered three times daily. Based on the patient's condition, the dosage could be increased weekly, with an incremental dose of 4 mg per administration. The maximum oral dose per administration was 16 mg, administered three times daily, with a total daily dose of less than 48 mg. The treatment duration was three months.

The control group was treated with risperidone orally disintegrating tablets (produced by Qilu Pharmaceutical, National Drug Approval No. H20070271, specification: 0.5 mg). The initial dose was 1 mg per administration, taken once daily. After one week of treatment, the dosage could be increased to 3–4 mg per administration, taken once daily. The treatment duration was three months.

### 2.3. Observation indicators

- (1) Symptom scores: Assessed using the Positive and Negative Syndrome Scale (PANSS), which includes positive symptoms (7–49 points), general psychopathology symptoms (16–112 points), and negative symptoms (7–49 points). The total score ranges from 30 to 210 points, with higher scores indicating more severe symptoms.
- (2) Adverse reactions: Observed the incidence of side effects such as weight gain, insomnia, extrapyramidal reactions, nausea, and elevated prolactin levels.



## 2.4. Criteria for evaluating efficacy

- (1) Cured: Reduction in PANSS score > 80%.
- (2) Significant improvement: Reduction in PANSS score between 50–80%.
- (3) Initial improvement: Reduction in PANSS score between 25–49%.
- (4) No improvement: Reduction in PANSS score < 25%.

## 2.5. Statistical analysis

Data were processed using SPSS 28.0. Measurement data were expressed as (mean  $\pm$  standard deviation) and compared using *t*-tests. Count data were expressed as [*n* (%)] and compared using  $\chi^2$  tests. Statistical significance was set at  $P < 0.05$ .

## 3. Results

### 3.1. Comparison of efficacy between the two groups

**Table 1** shows that the total effective rate of treatment in the study group was comparable to that of the control group ( $P > 0.05$ ).

**Table 1.** Comparison of efficacy between the two groups [*n* (%)]

Group	<i>n</i>	Cured	Significant improvement	Initial improvement	No improvement	Total effective rate
Study group	33	15 (45.45)	10 (30.30)	6 (18.18)	2 (6.06)	31 (93.94)
Control group	33	12 (36.36)	11 (33.33)	5 (15.15)	5 (15.15)	28 (84.85)
$\chi^2$	-	-	-	-	-	1.438
<i>P</i>	-	-	-	-	-	0.230

### 3.2. Comparison of symptom scores between the two groups

After treatment, symptom scores in both groups were significantly lower than before treatment. The study group exhibited significantly lower symptom scores compared to the control group ( $P < 0.05$ ), as shown in **Table 2**.

**Table 2.** Comparison of symptom scores between the two groups (mean  $\pm$  SD, points)

		Study group ( <i>n</i> = 33)	Control group ( <i>n</i> = 33)	<i>t</i>	<i>P</i>
Positive symptoms	Before treatment	31.42 $\pm$ 3.59	31.40 $\pm$ 3.55	0.023	0.982
	After treatment	10.15 $\pm$ 1.98	14.09 $\pm$ 2.07	7.901	< 0.001
	<i>t</i>	29.803	24.198	-	-
	<i>P</i>	< 0.001	< 0.001	-	-
General psychopathology symptoms	Before treatment	40.19 $\pm$ 4.82	40.77 $\pm$ 4.91	0.484	0.630
	After treatment	20.53 $\pm$ 2.98	25.74 $\pm$ 3.46	6.554	< 0.001
	<i>t</i>	19.930	14.374	-	-
	<i>P</i>	< 0.001	< 0.001	-	-

**Table 2 (Continued)**

		Study group ( <i>n</i> = 33)	Control group ( <i>n</i> = 33)	<i>t</i>	<i>P</i>
Negative symptoms	Before treatment	23.77 ± 3.06	23.91 ± 3.15	0.183	0.855
	After treatment	9.88 ± 1.52	12.43 ± 1.60	6.638	< 0.001
	<i>t</i>	23.353	18.666	-	-
	<i>P</i>	< 0.001	< 0.001	-	-
Total score	Before treatment	95.38 ± 7.12	96.08 ± 7.25	0.396	0.694
	After treatment	40.56 ± 5.83	52.26 ± 6.11	7.959	< 0.001
	<i>t</i>	34.221	26.550	-	-
	<i>P</i>	< 0.001	< 0.001	-	-

### 3.3. Comparison of adverse reaction rates between the two groups

**Table 3** shows that the adverse reaction rate in the study group was significantly lower than in the control group (*P* < 0.05).

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

Group	<i>n</i>	Weight gain	Insomnia	Extrapyramidal reaction	Nausea	Elevated prolactin	Incidence
Study group	33	0	1 (3.03)	0	1 (3.03)	0	2 (6.06)
Control group	33	1 (3.03)	3 (9.09)	1 (3.03)	2 (6.06)	1 (3.03)	8 (24.24)
$\chi^2$	-	-	-	-	-	-	4.243
<i>P</i>	-	-	-	-	-	-	0.039

## 4. Discussion

The pathogenesis of SCH involves genetic, environmental, and biological factors, resulting from a combination of these influences. SCH is characterized by complex clinical manifestations and a prolonged disease course, which significantly affect patients' cognitive function, emotional perception, thought patterns, language expression, and behavioral habits [3]. SCH typically presents with positive symptoms such as disorganized speech, hallucinations, or delusions, which may lead to abnormal behaviors. Over time, these behaviors often give rise to negative symptoms like emotional apathy and lack of motivation. Additionally, many SCH patients experience cognitive symptoms such as memory impairment and difficulty concentrating, severely impacting their daily lives.

Treatment for SCH involves a comprehensive approach, including psychotherapy, social support, and pharmacotherapy. The primary goal is to alleviate symptoms, minimize the impact of the disease on quality of life, and reduce relapse rates. Currently, antipsychotic medications are the standard treatment, primarily working as D2R antagonists to improve both positive and negative symptoms and stabilize the condition [4].

Risperidone is a commonly used antipsychotic derived from benzisoxazole. It has a high affinity for 5-HT and DA receptors and binds to  $\alpha 1$ -adrenergic receptors, exerting its antipsychotic effects. Lacking cholinergic receptor activity, risperidone effectively alleviates positive symptoms due to its strong D2R antagonism. Its orally disintegrating tablet (ODT) formulation dissolves rapidly in saliva, requiring minimal water for swallowing,

offering significant convenience. With a high oral bioavailability, peak plasma concentration occurs 1–2 hours post-administration, and its half-life is approximately 24 hours, allowing stable therapeutic effects <sup>[5]</sup>. However, long-term use of risperidone ODT may cause adverse effects such as electrocardiogram abnormalities, nausea, vomiting, and insomnia, which can reduce medication adherence and efficacy.

Paliperidone, a novel medication for SCH, acts as a D2R antagonist and modulates DA and 5-HT balance, thus addressing cognitive and negative symptoms. With a dual antagonistic mechanism for DA and 5-HT receptors, it improves neurotransmitter secretion <sup>[6]</sup>. Specifically, D2R inhibition prevents stereotypical behaviors induced by substances like apomorphine, enhancing central nervous function. Similarly, 5-HT receptor inhibition counteracts abnormal behaviors induced by compounds like para-chloramphetamine and tryptamine, alleviating disease symptoms <sup>[7]</sup>. Paliperidone also disrupts DA metabolic pathways, exerting stronger effects on the striatum and reducing extrapyramidal reactions.

The results indicate that the total effective treatment rate in the study group was comparable to that in the control group ( $P > 0.05$ ). A detailed analysis suggests that both medications are multi-receptor agents. Risperidone ODT lacks anticholinergic activity, modulating DA and 5-HT receptor expression to achieve stable therapeutic effects <sup>[8]</sup>. Similarly, paliperidone acts on these receptors, sharing a similar mechanism of action with risperidone, which accounts for their comparable efficacy. However, paliperidone upregulates DA concentrations in the prefrontal cortex, enhancing cognitive function and achieving a slightly higher total effective rate than risperidone <sup>[9]</sup>.

Symptom scores in the study group were significantly lower than those in the control group after treatment ( $P < 0.05$ ). D2R, a neurotransmitter receptor, regulates emotional behavior and motor function. Its genetic polymorphisms are associated with SCH pathogenesis and clinical outcomes. Paliperidone's pronounced D2R antagonism modulates DA levels, improving emotional and motor control and alleviating related symptoms <sup>[10]</sup>. Furthermore, its D2R inhibitory effect is stronger than that of conventional drugs like risperidone, leading to significant improvements in both positive and negative symptoms.

The adverse reaction rate in the study group was lower than that in the control group ( $P < 0.05$ ). A specific analysis indicates that prolonged risperidone ODT use affects the extrapyramidal system, leading to extrapyramidal reactions. In contrast, paliperidone exhibits a higher affinity for 5-HT receptors, reducing interference with the extrapyramidal system and thereby minimizing adverse reactions <sup>[11]</sup>. Additionally, paliperidone has a shorter half-life, with faster distribution and metabolism, reducing the likelihood of drug accumulation and associated adverse effects. Consequently, it demonstrates fewer long-term adverse reactions.

However, SCH patients present with individual differences in constitution, disease progression, and drug tolerance. During pharmacotherapy, regular monitoring of coagulation function, liver and kidney function, and other indicators is necessary to assess improvement and adjust dosages appropriately, avoiding overmedication <sup>[12]</sup>. Additionally, patients should be observed for discomfort during treatment. In cases of adverse effects such as nausea or akathisia, the underlying cause should be identified, and discontinuation or targeted interventions should be considered to prevent severe reactions.

## 5. Conclusion

In conclusion, paliperidone demonstrates comparable efficacy to risperidone ODT in the treatment of SCH but offers superior symptom improvement and a lower risk of adverse effects, making it a more advantageous therapeutic option.

## Disclosure statement

The author declares no conflict of interest.

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# Observation on the Effects of Cognitive Behavioral Therapy on Neuropsychiatric Symptoms and Quality of Life in Patients with New-type Drug Abuse

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**Abstract:** The purpose of this study is to observe the effects of cognitive behavioral therapy (CBT) on neuropsychiatric symptoms and quality of life in patients with new-type drug abuse. *Methods:* Sixty patients with new-type drug abuse admitted to the hospital from April 2023 to March 2024 were randomly divided into a control group and an observation group. The control group received conventional treatment, while the observation group received additional cognitive behavioral therapy. The scores of the self-rating symptom scale (SCL-90), self-rated health measurement scale (SRHMS), short-form 36 health survey (SF-36), and patient satisfaction were compared between the two groups before and after treatment. *Results:* After treatment, compared with the control group, the observation group showed significant improvements in SCL-90 scores, SRHMS scores in all dimensions, and SF-36 scores ( $P < 0.001$ ). The satisfaction score of the observation group was also significantly higher than that of the control group ( $P < 0.05$ ). *Conclusion:* For patients with new-type drug abuse, cognitive behavioral therapy can significantly improve psychiatric symptoms, relieve anxiety and depression, reduce hallucinations and delusions, and enhance quality of life, leading to positive changes in physical, psychological, and social functions.

**Keywords:** Cognitive behavioral therapy; New-type drug abuse; Neuropsychiatric symptoms; Quality of life

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## 1. Introduction

The abuse of new types of drugs has become increasingly serious, posing significant harm to individuals, families, and society<sup>[1]</sup>. The misuse of these novel drugs not only leads to physical dependence but also triggers a series of neuropsychiatric symptoms, severely affecting the quality of life of patients. Traditional drug



rehabilitation treatments primarily focus on physiological detoxification, but their effectiveness in improving patients' psychological and social functioning is limited. Cognitive behavioral therapy (CBT), as an effective psychological treatment method, has been widely used in the treatment of various psychological disorders [2]. This study aims to explore the impact of CBT on neuropsychiatric symptoms and quality of life in patients abusing new types of drugs, providing a reference for clinical treatment.

## 2. Materials and methods

### 2.1. General information

Sixty patients abusing new types of drugs who were treated at the hospital from April 2023 to March 2024 were selected as the study subjects. The patients were divided into a control group and an observation group using the random number table method, with 30 patients in each group. The age range of the control group was 22–55 years, and the duration of drug abuse was 1–5 years. The age range of the observation group was 20–53 years, and the duration of drug abuse was 1–6 years. There were no statistically significant differences between the two groups in terms of gender, age, and duration of drug abuse (**Table 1**) ( $P > 0.05$ ), indicating comparability. Inclusion criteria were as follows: (1) met the diagnostic criteria for new drug abuse in the Chinese Classification of Mental Disorders, Third Edition (CCMD-3); (2) aged between 18 and 60 years; (3) volunteered to participate in the study and signed an informed consent form. Exclusion criteria were as follows: (1) patients with severe physical diseases who could not tolerate treatment; (2) patients with severe mental illnesses such as schizophrenia; (3) patients with cognitive impairments who could not cooperate with treatment.

**Table 1.** Comparison of general information between the two groups

Group	Number of cases (n)	Gender (n)		Average age (Mean $\pm$ SD, years)	Average duration of illness (Mean $\pm$ SD, years)
		Male	Female		
Control group	30	18	12	35.61 $\pm$ 8.36	2.82 $\pm$ 1.28
Observation group	30	16	14	34.83 $\pm$ 7.96	3.12 $\pm$ 1.40
$\chi^2/t$ value		0.272		0.370	0.866
$P$ value		0.602		0.713	0.390

### 2.2. Methods

#### 2.2.1. Control group

The control group received conventional treatment, which specifically included the following: (1) Pharmacotherapy: Medications were administered to manage withdrawal symptoms, alleviating physical discomforts such as nausea, vomiting, insomnia, and muscle pain caused by cessation of drug use. This helped patients to smoothly transition through the physiological detoxification phase. (2) Health Education: Through methods like conducting lectures and distributing educational materials, patients were comprehensively informed about the types of drugs, their harms, and addiction mechanisms, as well as the methods and importance of drug rehabilitation. This aimed to fully educate patients on the severe detrimental effects of drugs on their physical, mental, and social well-being, thereby strengthening their awareness and resolve to quit drugs. (3) Rehabilitation training: Physical training activities such as running and fitness exercises were conducted to

assist patients in restoring their physical functions. Additionally, vocational skill training was provided, tailored to patients' interests and strengths, including skills like handicrafts and computer operations. This prepared patients for employment after their reintegration into society.

### **2.2.2. Observation group**

In addition to conventional treatment, the observation group received cognitive behavioral therapy. The therapy was conducted by professionally trained psychotherapists, twice a week, for 60 minutes each session, over a total of 12 weeks. The specific components of the therapy included: (1) Cognitive intervention: Through the use of real-life case studies and group discussions, patients were guided to deeply analyze the reasons and processes behind drug abuse, as well as the severe physical and psychological harms caused by it. The aim was to help patients identify and correct misperceptions and attitudes towards drugs, such as the erroneous belief that drug use can alleviate stress or bring happiness. Patients were encouraged to reflect on their own behaviors and tap into their inner motivations for quitting drugs, thereby strengthening their confidence and determination to overcome addiction. (2) Behavioral intervention: Patients were taught practical skills and methods to resist drug temptations, such as avoiding places where they had previously used drugs and steering clear of high-risk situations like associating with drug-using peers. Additionally, they were instructed in relaxation techniques like deep breathing and progressive muscle relaxation to cope with tension and anxiety that may arise during the detoxification process. Through the establishment of behavioral contracts, patients were assisted in developing healthy lifestyle habits, such as maintaining regular sleep schedules, engaging in daily moderate exercise, and cultivating interests like painting and music. These activities served to enrich their spiritual lives and reduce their reliance on drugs. (3) Emotional management: Patients were helped to recognize and accurately express their emotions, gaining an understanding of the causes and manifestations of different feelings. Engaging and interactive methods like role-playing and scenario simulations were utilized to guide patients in learning effective ways to cope with negative emotions. One such technique was cognitive reframing, which involves changing perspectives and evaluations of events to adjust emotional responses. The goal was to enhance patients' ability to handle stress and setbacks, enabling them to face various challenges in life with a more positive and healthy mindset.

## **2.3. Observation indices**

### **2.3.1. Neuropsychiatric symptom score**

The symptom checklist-90 (SCL-90) was selected for analysis. This scale consists of 90 items, divided into 10 factors, namely somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and others. Each item is rated on a 1–5 scale, with higher scores indicating more severe symptoms. The maximum score is 100.

### **2.3.2. Health score**

The health score is analyzed using the self-rated health measurement scale (SRHMS). This scale consists of 48 items, covering three dimensions: physiological health, psychological health, and social health. The higher the patient's score, the better their health status, with a maximum score of 90.

### 2.3.3. Quality of life score

The quality of life score is assessed using the short form-36 health survey (SF-36). This scale includes eight dimensions: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The total score is 100, and the higher the patient's score, the higher their quality of life.

### 2.3.4. Satisfaction

The satisfaction is evaluated using a self-made satisfaction scale developed by the hospital. The scale consists of 10 items, each rated on a 1–10 scale, with a maximum score of 10. The higher the score, the higher the patient's satisfaction with the treatment.

## 2.4. Statistical methods

Data analysis was continued using SPSS 27.0. Measurement data were described using mean  $\pm$  standard deviation and analyzed with a *t*-test. Count data were described using frequency (%) and compared between groups using a chi-square test. A *P*-value less than 0.05 was considered statistically significant, indicating a meaningful difference.

## 3. Results

### 3.1. Comparison of neuropsychiatric symptom scores before and after treatment

Before treatment: The SCL-90 scale scores of the two groups were similar, and there was no statistically significant difference ( $P > 0.05$ ). This indicates that the groups were comparable before the treatment.

After Treatment: The control group showed some changes in scores. The observation group showed a significant increase in scores. There was a statistically significant difference between the two groups ( $P < 0.001$ ). (See **Table 2** for detailed data.)

**Table 2.** Comparison of SCL-90 scale scores before and after treatment

Group	Number of cases	SCL-90	
		Before treatment	After treatment
Control group	30	64.79 $\pm$ 2.38	74.85 $\pm$ 2.77
Observation group	30	65.28 $\pm$ 2.57	93.06 $\pm$ 2.46
<i>t</i> value		0.766	26.923
<i>P</i> value		0.447	<0.001

### 3.2. Comparison of health scores before and after treatment between the two groups

There were no significant differences in the scores of various dimensions of the SRHMS scale between the two groups before treatment ( $P > 0.05$ ). After treatment, the observation group had significantly higher scores in the dimensions of physical health, psychological health, and social health compared to the control group, with statistically significant differences ( $P < 0.001$ ). (See **Table 3** for detailed data.)

**Table 3.** Comparison of SRHMS scale scores before and after treatment between the two groups

Group	Number of cases (n)	Physical health		Psychological health		Social health	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	30	14.46 ± 1.46	18.91 ± 1.79	12.40 ± 1.50	17.69 ± 1.76	13.14 ± 1.25	18.60 ± 1.50
Observation group	30	14.69 ± 1.31	26.81 ± 1.32	12.24 ± 1.36	25.84 ± 1.47	13.31 ± 1.43	26.43 ± 1.20
<i>t</i> value		0.642	19.455	0.433	19.467	0.490	22.326
<i>P</i> value		0.523	<0.001	0.667	<0.001	0.626	<0.001

### 3.3. Comparison of quality of life scores before and after treatment between two patient groups

Before treatment, there was no significant difference in the SF-36 scale scores between the two groups ( $P > 0.05$ ). However, after treatment, the scores of the observation group were significantly higher than those of the control group, indicating a statistically significant difference ( $P < 0.001$ ). (See **Table 4** for detailed data.)

**Table 4.** Comparison of SF-36 scale scores before and after treatment between two patient groups

Group	Number of cases	SCL-90	
		Before treatment	After treatment
Control group	30	60.18 ± 2.41	75.34 ± 3.01
Observation group	30	60.22 ± 2.39	94.24 ± 2.78
<i>t</i> value		0.065	25.265
<i>P</i> value		0.949	<0.001

### 3.4. Comparison of patient satisfaction scores between two groups

The satisfaction scores of patients in the observation group were significantly higher than those in the control group, and the difference was statistically significant ( $P=0.029 < 0.05$ ). (See **Table 5** for detailed data.)

**Table 5.** Comparison of patient satisfaction scores between two groups

Group	Number of cases (n)	Satisfaction score
Control group	30	7.14 ± 1.17
Observation group	30	8.49 ± 1.34
<i>t</i> value		2.244
<i>P</i> value		0.029

## 4. Conclusion

The abuse of new drugs often leads to a series of complex and severe neuropsychiatric symptoms in patients, such as anxiety, depression, hallucinations, and delusions. These symptoms severely interfere with patients' normal thinking and emotional expression, greatly affecting their living conditions <sup>[3]</sup>. Cognitive behavioral

therapy, through systematic cognitive intervention, helps patients deeply analyze their own misconceptions about drugs and guides them to re-examine the significant harm caused by drugs to various aspects of their physical, mental, and emotional lives. This fundamentally changes patients' attitudes and cognitive models towards drugs <sup>[4]</sup>. Simultaneously, behavioral intervention and emotional management training teach patients how to effectively deal with drug temptation and negative emotions, enhancing their self-control and psychological adjustment abilities. Through this series of comprehensive treatment measures, patients' psychiatric symptoms have significantly improved, gradually restoring normal mental and psychological function.

Through a controlled study of 60 patients abusing new types of drugs, this study found that cognitive behavioral therapy has significant effects on improving patients' neuropsychiatric symptoms, enhancing their health status, and quality of life, and increasing patient satisfaction. Compared to conventional treatments, cognitive behavioral therapy can more effectively help patients cope with various issues caused by drug abuse, facilitating their recovery and reintegration into society. In terms of improving psychiatric symptoms, cognitive behavioral therapy utilizes unique cognitive interventions to assist patients in gaining deep insights into their own misconceptions about drugs. During the treatment process, patients, guided by psychotherapists, re-examine the dangers of drugs, correct misconceptions such as "drug use can relieve stress", and fundamentally change their attitudes towards drugs. In the behavioral intervention phase, patients learn skills to resist drug temptations, such as avoiding high-risk situations and refusing unhealthy social interactions, effectively reducing the risk of relapse <sup>[5]</sup>. Emotional management training enables patients to master methods of identifying and regulating emotions, enhancing their psychological resilience, thus significantly alleviating psychiatric symptoms such as anxiety and depression, and facing life with a more positive and stable mindset <sup>[6]</sup>. Regarding the improvement of quality of life, cognitive behavioral therapy helps patients establish regular daily routines, cultivate healthy interests such as exercise and reading, gradually restore their physical functions, and increase their vitality. On the psychological level, patients learn to actively cope with life's setbacks, continuously improving their self-identity and sense of happiness. Moreover, by improving interpersonal relationships, patients can better integrate into their families and society, rediscover their own values, achieving comprehensive improvement in their quality of life.

Cognitive behavioral therapy (CBT) is supported by a rigorous theoretical framework and rich practical experience. Professional psychotherapists, through systematic training, can tailor personalized treatment plans based on individual patient differences. During the treatment process, various flexible methods such as case analysis, group discussions, and role-playing are employed to fully engage patients' enthusiasm and initiative, thereby enhancing their participation and compliance <sup>[7-8]</sup>. Furthermore, treatment duration and frequency can be reasonably adjusted according to patients' actual circumstances, facilitating its implementation in diverse medical settings.

In summary, CBT has demonstrated remarkable effectiveness in the treatment of patients abusing novel drugs. This therapy significantly improves patients' psychiatric symptoms, effectively alleviates negative emotions such as anxiety and depression, and elevates patients' quality of life. However, due to the relatively small sample size and limited study duration of this research, there is a need to expand the sample size and conduct long-term follow-up studies in the future, to more comprehensively evaluate the efficacy and safety of CBT. Simultaneously, efforts should be intensified to train and promote CBT techniques, elevating the level of clinical treatment and bringing benefits to a broader population of patients abusing novel drugs.



## Disclosure statement

The authors declare no conflict of interest.

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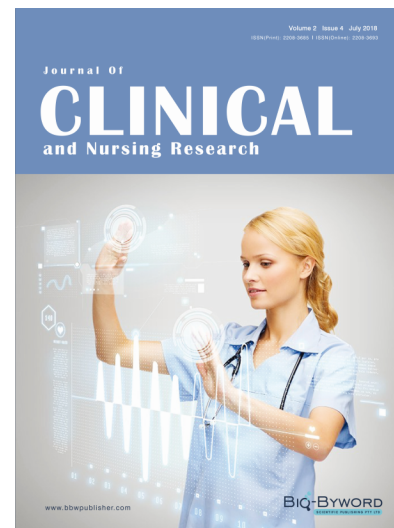
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