

abnormalities, and other damages. It can be classified into viral hepatitis, autoimmune liver disease, drug-induced liver disease, alcoholic liver disease, non-alcoholic fatty liver disease, and various clinical disease stages that result from their occurrence and progression, such as cirrhosis and liver failure <sup>[1]</sup>. Hepatitis is prevalent worldwide, and China is a major country for hepatitis cases. In 1944, Linsey reported that pancreatitis is a complication of hepatitis. Acute pancreatitis (AP) is an inflammatory response caused by the activation of pancreatic enzymes in acinar cells due to various stimuli, leading to the release of inflammatory factors and a local-to-systemic inflammatory reaction. The liver is often the most vulnerable and the first organ to be damaged in acute pancreatitis. Between 15% and 60% of patients with acute pancreatitis will develop liver injury. The global incidence of acute pancreatitis is 30–40 cases per 100,000 people per year, with a mortality rate of 1%–5% <sup>[2]</sup>. Among the fatal cases, 83% are attributed to liver failure <sup>[3]</sup>. From 1961 to 2016, the annual incidence rate of acute pancreatitis in countries such as the U.S. and Europe has increased by 2.77% to 3.67% <sup>[4]</sup>. Hepatitis and pancreatitis are both major causes of hospitalization for liver and gastrointestinal-related diseases, with considerable morbidity and mortality, contributing significantly to the medical and economic burden on society. Studies have shown that hepatitis viral infections are an independent predictor of poor outcomes in hospitalized AP patients, including higher mortality rates, longer hospital stays, and life-threatening complications <sup>[5]</sup>. Other studies have found that NAFLD can worsen the severity of AP, with the severity of AP increasing as NAFLD worsens <sup>[6]</sup>. When hepatitis is complicated by acute pancreatitis, AP can cause chronic liver disease to progress to ACLF <sup>[7]</sup>. During diagnosis and treatment, the clinical manifestations of hepatitis itself often make it difficult to detect the symptoms and signs of acute pancreatitis, which can affect the prognosis of patients with hepatitis complicated by acute pancreatitis. Most previous studies on hepatitis complicated by pancreatitis are case reports <sup>[8-10]</sup>, and relevant research is limited. This study analyzes and compares the etiology, clinical types, symptoms, signs, imaging findings, treatment, and prognosis of patients with hepatitis complicated by acute pancreatitis and acute pancreatitis alone, exploring its pathogenesis and summarizing the factors affecting prognosis, providing a basis for clinical diagnosis, treatment, and monitoring of the disease.

## **2. Materials and methods**

### **2.1. Study subjects**

Clinical data were collected from patients diagnosed with acute pancreatitis at Chengdu Public Health Clinical Medical Center from January 2017 to December 2023. Patients were included according to the diagnostic criteria for various types of hepatitis combined with acute pancreatitis and those diagnosed with acute pancreatitis alone. Cirrhosis and liver failure were diagnosed according to the 2023 “Chinese Clinical Diagnosis and Treatment Consensus on Liver Cirrhosis” and the 2018 revised “Guidelines for the Diagnosis and Treatment of Liver Failure” <sup>[11,12]</sup>. Drug-induced hepatitis was diagnosed based on the 2023 “Chinese Guidelines for the Diagnosis and Treatment of Drug-Induced Liver Injury” <sup>[13]</sup>. Non-alcoholic fatty liver disease (NAFLD) was diagnosed based on the 2018 “Guidelines for the Prevention and Treatment of Non-Alcoholic Fatty Liver Disease (2018 Update)” <sup>[14]</sup>.

### **2.2. Diagnosis and inclusion criteria**

(1) Acute pancreatitis clinical diagnostic criteria <sup>[15]</sup>: Acute pancreatitis is diagnosed when two of the

following three criteria are met: (a) persistent and typical upper abdominal pain radiating to the back; (b) serum amylase and/or lipase levels exceeding three times the normal upper limit; (c) characteristic imaging findings of AP.

- (2) Inclusion criteria for hepatitis combined with acute pancreatitis patients: (a) Discharged diagnosis of any type of hepatitis; (b) Discharged diagnosis of acute pancreatitis; (c) No clear common causes of pancreatitis at admission; (d) Complete clinical and laboratory data.
- (3) Inclusion criteria for acute pancreatitis patients: (a) Discharged diagnosis of acute pancreatitis; (b) No associated hepatitis, cirrhosis, liver failure, etc.; (c) Presence of clinical manifestations or test results related to pancreatitis at admission; (d) Complete clinical and laboratory data.

### 2.3. Data collection

- (1) General information: Age, gender, type and severity of hepatitis (presence of cirrhosis or liver failure), vital signs, and length of hospital stay.
- (2) Laboratory test indicators: Blood amylase, blood lipase, triglycerides (TG), total bilirubin (TBil), white blood cell (WBC) count, neutrophil percentage (NEUT%), C-reactive protein (CRP) levels, PTA%, ALT, AST, hemoglobin (HB), red blood cell (RBC) count, platelet (PLT) count, and viral load and genotype for viral hepatitis.
- (3) Imaging results: Ultrasound, CT, MRI findings.
- (4) Treatment: Medications and prognosis.

### 2.4. Statistical analysis

The normality of continuous variables was first tested using the Kolmogorov-Smirnov test. For normally distributed continuous variables, data were expressed as mean  $\pm$  standard deviation (SD) and compared using the independent two-sample *t*-test. For non-normally distributed variables, data were expressed as median (interquartile range) M (P25–P75) and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as counts and percentages [*n* (%)], and compared using the chi-squared ( $\chi^2$ ) test. Variables with statistically significant differences in univariate analysis were included in a multivariate binary logistic regression model. All statistical analyses were performed using SPSS 26.0, and a *P*-value  $< 0.05$  was considered statistically significant.

## 3. Results

### 3.1. Etiology and clinical type distribution characteristics

Among the 53 patients with hepatitis complicated by acute pancreatitis, 29 (54.7%) had viral hepatitis (see **Table 1** for the distribution and outcomes of various types of hepatitis). Among the 56 patients with acute pancreatitis, the causes were gallstones in 19 cases (33.9%), alcohol consumption in 4 cases (7.1%), hyperlipidemia in 15 cases (26.8%), and other or unknown causes in 18 cases. **Table 2** shows the distribution and outcomes of various clinical types.



**Table 1.** Etiology and prognosis of hepatitis complicated with pancreatitis

Etiology		Number of cases	Prognosis	
			Improved	Discharged or death
Viral hepatitis	HAV	2	1	1
	HBV	23	16	7
	HCV	3	3	0
	HBV + HCV	1	1	0
Fatty liver		13	10	3
Drug-induced hepatitis		4	4	0
Unknown cause		7	6	1

**Table 2.** Clinical types and outcomes of hepatitis complicated with pancreatitis

Etiology		Number of cases	Prognosis	
			Improved	Discharged or death
Acute hepatitis		7	7	0
Chronic hepatitis	Moderate hepatitis	4	4	0
	Severe hepatitis	13	12	1
Cirrhosis		3	3	0
Liver failure	Acute	2	1	1
	Subacute	4	2	2
	Chronic acute	13	6	7
	Chronic	8	7	1

## 3.2. Comparison of clinical characteristics between the two groups

### 3.2.1. General information

A total of 109 patients were included in this study. Among them, 53 had hepatitis complicated by acute pancreatitis, with an average age of  $47.62 \pm 14.058$  years. There were 37 males (69.8%) and 16 females (30.2%), with a male-to-female ratio of 2.31:1. The remaining 56 patients had acute pancreatitis, with an average age of  $52.57 \pm 15.682$  years. There were 35 males (60.3%) and 21 females (36.2%). There was no significant difference in age and gender between the two groups. The mean hospitalization time in the hepatitis and pancreatitis group was significantly longer than that in the pancreatitis-only group ( $P < 0.05$ ).

### 3.2.2. Clinical manifestations

Among the 53 patients with hepatitis complicated by acute pancreatitis, 48 experienced abdominal pain, 16 had abdominal bloating or discomfort, 14 had nausea and/or vomiting, and 5 had a fever (1 with a peak of  $38.9^{\circ}\text{C}$ , 1 with  $38.7^{\circ}\text{C}$ , the others had a low-grade fever). Three patients had diarrhea, 22 had fatigue, poor appetite, and aversion to oily foods, and 2 had acid reflux or heartburn. Two patients had no abdominal pain, diarrhea, nausea, vomiting, or fever, and were diagnosed only by routine imaging and blood tests for lipase and amylase

levels. Among the physical signs, 7 patients had muscle rigidity, 35 had abdominal tenderness, and 9 had rebound tenderness. 18 patients had no obvious abdominal signs, and 2 had neither symptoms nor signs of acute pancreatitis.

Among the 56 patients with acute pancreatitis, only 2 had no abdominal pain. 22 patients experienced abdominal bloating or discomfort, 24 had nausea and/or vomiting, 6 had fever (1 with a peak of 39.0°C, others had low-grade fever), 1 had chills, 3 had diarrhea, 3 had belching, 3 had poor appetite or anorexia, and 1 had acid reflux or heartburn. Physical signs included muscle rigidity in 8 patients, abdominal tenderness in 54 patients, and rebound tenderness in 3 patients. Only 2 patients had no significant abdominal signs, and 1 patient had neither symptoms nor signs of acute pancreatitis.

### 3.2.3. Laboratory examination characteristics and comparison

Laboratory test results were compared between the hepatitis complicated with pancreatitis group and the pancreatitis-only group. The hepatitis and pancreatitis group had significantly lower blood amylase, lipase, PTA%, and PLT levels compared to the pancreatitis-only group ( $P$  values all  $< 0.05$ ). The TBil level in the hepatitis and pancreatitis group was significantly higher than in the pancreatitis-only group ( $P$  values all  $< 0.05$ ). There were no significant differences between the two groups in WBC ( $\times 10^9/L$ ), NEUT (%), ALT, AST, hs-CRP, and triglyceride levels (Table 3).

Among the patients with viral hepatitis complicated by pancreatitis, 23 had hepatitis B and completed HBV DNA testing. Among them, 6 had HBV DNA levels  $\geq 1.0E+06$  IU/mL, 5 had levels  $\geq 1.0E+03$  IU/mL and  $\leq 1.0E+06$  IU/mL, and 12 had levels  $< 1.0E+03$  IU/mL. Four patients had hepatitis C and completed HCV RNA testing and genotyping. Among them, HCV RNA levels were concentrated in the range of  $\geq 1.0E+03$  IU/mL and  $\leq 1.0E+06$  IU/mL, with genotypes of 1b in 1 patient, 3b in 2 patients, and 6a in 1 patient.

**Table 3.** Comparison of laboratory indicators between two groups (mean  $\pm$  SD)

Indicator	Hepatitis complicated with pancreatitis ( $n = 53$ )	Acute pancreatitis ( $n = 56$ )	Statistic	$P$ -value
Age	47.62 $\pm$ 14.058	52.57 $\pm$ 15.682	1.731	$> 0.05$
Hospitalization time (days)	15.36 $\pm$ 7.73	10.38 $\pm$ 5.75	-3.233	$< 0.05$
Blood amylase (U/L)	321.5 (105.0–776.5)	582.5 (281.25–1,583.50)	2.404	0.016
Blood lipase (U/L)	243.0 (105.5–665.0)	720.5 (246.25–1,499.98)	3.275	0.001
TBil ( $\mu$ mol/L)	94.8 (59.85–203.00)	21.5 (12.2–33.3)	-6.167	$< 0.001$
PTA (%)	55.625 (36.025–86.225)	93.75 (77.775–109.400)	5.833	$< 0.001$
PLT ( $\times 10^9/L$ )	152.5 (104.5–203.0)	191.5 (153.75–249.25)	2.658	0.008
ALT (U/L)	90.5 (37.8–266.5)	61 (37.25–234.00)	-1.248	0.212
AST (U/L)	111.5 (40.5–293.0)	71 (30.5–188.5)	-1.767	0.077
WBC ( $\times 10^9/L$ )	9.51 $\pm$ 4.83	10.28 $\pm$ 4.19	0.867	$> 0.05$

### 3.2.4. Imaging features and comparison

In the hepatitis complicated with pancreatitis group, 22 patients underwent ultrasound examination. Four cases showed pancreatic enlargement and reduced echogenicity in the pancreatic parenchyma, suggesting pancreatitis, with a positive rate of 18.2% (4/22). Two cases showed pancreatic fullness, which was considered

in conjunction with the clinical condition but was not definitively diagnosed as pancreatitis. The remaining 16 cases had no abnormal pancreatic echogenicity or poor imaging due to gas interference.

In the pancreatitis-only group, 30 patients underwent ultrasound examination. Six cases reported pancreatic enlargement, thickening of the surrounding fascia, and other signs suggestive of pancreatitis, with a positive rate of 20% (6/30).

In the hepatitis complicated with pancreatitis group, 30 patients underwent upper abdominal CT scans. Twenty-three cases showed pancreatic enlargement or fullness, with peripancreatic edema and exudation, suggesting pancreatitis. One case reported extensive necrotizing pancreatitis and one case showed pancreatic tail enlargement with reduced echogenicity but without a clear diagnosis of pancreatitis. Five cases showed no obvious pancreatic morphological abnormalities, with a positive rate of 80% (24/30). In the pancreatitis-only group, 39 patients underwent upper abdominal CT scans, and 31 cases showed pancreatic enlargement and swelling with peripancreatic exudative changes. Two cases were considered necrotizing pancreatitis, with a positive rate of 84.6% (33/39).

In the hepatitis complicated with pancreatitis group, 8 patients underwent MRI. Seven cases showed peripancreatic exudative changes consistent with pancreatitis, with a positive rate of 87.5% (7/8). In the pancreatitis-only group, 11 patients underwent MRI, and pancreatitis was clearly reported in 10 cases, with a positive rate of 90.91% (10/11). Both groups had 3 patients who refused further imaging examinations after elevated lipase or amylase levels were detected. There were no significant differences in the positive rates of ultrasound, CT, or MRI between the two groups.

### **3.3. Univariate analysis of prognosis in hepatitis complicated with acute pancreatitis patients**

Univariate analysis showed that TBil, PTA%, liver failure, NEUT%, HB, REC, PCT, and diuretic use were associated with prognosis in patients with hepatitis complicated by acute pancreatitis.

### **3.4. Multivariate analysis of prognosis in hepatitis complicated with acute pancreatitis patients**

Liver failure was correlated with TBil and PTA% levels, HB, and REC levels. Factors with smaller *P*-values were included in the multivariate analysis. Multivariate binary logistic regression analysis showed that liver failure, NEUT%, and REC were independent risk factors affecting the prognosis of patients with hepatitis complicated by acute pancreatitis (*P* values all < 0.05).

## **4. Discussion**

From the general data, there were no significant differences in age between the hepatitis complicated with pancreatitis group and the pancreatitis-only group. The majority of patients were male, with a male gender tendency observed in the hepatitis complicated with pancreatitis group, though the exact cause remains unclear<sup>[16]</sup>. Regarding etiology, various types of hepatitis, including viral hepatitis, drug-induced hepatitis, and non-alcoholic fatty liver disease, can be complicated by pancreatitis, with more than half of the patients having viral hepatitis. Previous studies<sup>[17-19]</sup> have shown that acute pancreatitis is associated with hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections. Since 1999, multiple studies have reported cases of acute

pancreatitis associated with the hepatitis E virus (HEV) <sup>[20-23]</sup>, and there have been reports of autoimmune pancreatitis associated with autoimmune hepatitis <sup>[24,25]</sup>, though most of these are case reports. This study did not find a clear link to these rarer cases. Among the 56 pancreatitis patients, the most common cause was cholelithiasis, followed by hyperlipidemia, consistent with studies by Zhu *et al.* and Yin *et al.* <sup>[26,27]</sup>. Recent research by Wu *et al.* <sup>[28]</sup> shows that hyperlipidemia has become the most common cause of pancreatitis in the Yangzhou region of China, with its incidence rising globally. In this study, 32.1% of the pancreatitis cases had an unknown cause, and some of these patients did not undergo lipid testing, so hyperlipidemia may well be the most common cause. Acute pancreatitis can occur at any stage of hepatitis, with the highest incidence of liver failure and severe hepatitis. It is therefore understandable that the hospitalization time for patients with hepatitis complicated by pancreatitis was significantly longer than for the pancreatitis-only group.

In this study, most patients with hepatitis complicated by acute pancreatitis experienced upper abdominal dull or distending pain, with only 6 cases presenting with more severe pain radiating to the lower back. These patients often had fatigue, poor appetite, and aversion to greasy food, along with fewer cases of nausea and vomiting. In contrast, acute pancreatitis patients often had more severe abdominal pain, radiating to the back or waist, and some had colicky pain, with more noticeable nausea and vomiting. During physical examination, a higher proportion of pancreatitis patients showed significant signs, with only 2 cases lacking notable tenderness. Clinical symptoms and signs of hepatitis complicated by acute pancreatitis were atypical, with abdominal pain not clearly defined and often accompanied by digestive symptoms like fatigue, poor appetite, and aversion to greasy foods. This made it prone to misdiagnosis or missed diagnosis. In terms of imaging, although the positive diagnostic rates for ultrasound, CT, and MRI in the pancreatitis group were slightly higher than in the hepatitis complicated by the pancreatitis group, no significant difference was found. Both groups had slightly higher MRI-positive rates compared to abdominal CT, but the differences were not significant. Both abdominal CT and MRI had significantly higher positive rates than abdominal ultrasound. For diagnosing hepatitis complicated by acute pancreatitis, when clinical symptoms are atypical and indicators like lipase or amylase are insufficient for a clear diagnosis, abdominal CT or MRI should be performed promptly. If the patient cannot cooperate or refuses further examination, ultrasound should be the first choice.

From the laboratory tests, the levels of blood amylase, lipase, PTA%, and PLT in the hepatitis complicated with pancreatitis group were significantly lower than in the pancreatitis-only group (*P* values all < 0.05), while the TBil level in the hepatitis complicated with pancreatitis group was significantly higher than in the pancreatitis-only group (*P* values all < 0.05). In hepatitis complicated by pancreatitis, the higher TBil level was likely influenced by the underlying liver damage, with worse coagulation function and platelet levels. Hepatitis-related liver damage might also affect pancreatic secretion and metabolic function, which could influence blood amylase and lipase levels. Alternatively, the difference in the timing of clinical diagnosis between the two groups, influenced by atypical symptoms and signs, could explain the differences in lab results. The WBC ( $\times 10^9/L$ ) and NEUT (%) levels in the hepatitis complicated with pancreatitis group were lower than in the pancreatitis-only group, while ALT and AST levels were higher, but without significant statistical differences. Hepatitis patients might have lower baseline WBC values, so the actual increase after developing pancreatitis may be less noticeable, with the lack of significant differences possibly due to a small sample size.

Among patients with viral hepatitis complicated by pancreatitis, 22 cases of hepatitis B virus (HBV) were tested for HBV DNA. Five cases had levels  $\geq 1.0E+06$  IU/mL, five cases had levels  $\geq 1.0E+03$  IU/mL and  $\leq 1.0E+06$  IU/mL, and 12 cases had levels <  $1.0E+03$  IU/mL. Four cases of hepatitis C virus (HCV) were tested

for HCV RNA and genotyping. The HCV RNA levels were concentrated between  $\geq 1.0\text{E}+03$  IU/mL and  $\leq 1.0\text{E}+06$  IU/mL, with genotypes 1b, 3b, and 6a identified, but there was no notable concentration of any specific genotype. A study<sup>[29]</sup> confirmed that HBV viral load is positively correlated with the incidence of pancreatitis, but this study did not find a clear trend in the HBV viral load distribution, likely because most of the patients had clinical types of liver failure or cirrhosis, and some had previously undergone antiviral treatment.

To date, no research has fully elucidated the exact pathogenesis of hepatitis-associated pancreatitis. As early as 1995, Cavallari *et al.* reported a case of a hepatitis B virus (HBV) patient with fatal acute necrotizing pancreatitis, showing strong signs of viral replication<sup>[30]</sup>. The autopsy revealed the presence of HBsAg and HBV DNA in the cytoplasm of pancreatic acinar cells, suggesting that pancreatitis may be directly caused by HBV infection. The potential role of impaired immunity might allow hepatitis viruses to affect the pancreas, reaching it via the bloodstream or bile. Current research suggests possible mechanisms, including direct cellular damage caused by extrahepatic viral replication or immune processes induced by overwhelming host immune responses during liver inflammation, both of which are potential sources of hepatitis-related pancreatitis. Hepatitis viruses are distributed in immune cells across various organs, including the liver, with lymphoid tissues being a potential target for HEV replication. Jung and colleagues recorded signs of cytotoxic and inflammatory cell infiltration in the pancreas of pigs infected with porcine HEV-3 and found that pancreatic cell damage was associated with necrotic apoptosis<sup>[16]</sup>. Necrotic apoptosis, also known as programmed cell necrosis, can be triggered by various stimuli, with the most studied being TNF signaling<sup>[31]</sup>. When TNF- $\alpha$  binds to TNF receptor 1 (TNFR1), the intracellular death domain of TNFR1 binds to the TNFR1-associated death domain protein. This recruits Fas-associated protein with a death domain and caspase 8 to form a death-inducing signaling complex, leading to apoptosis<sup>[32]</sup>. In this process, inhibiting caspase activity alternately activates RIP3, which then phosphorylates and oligomerizes MLKL downstream, causing necrotic apoptosis<sup>[33]</sup>. Further research is needed to uncover the mechanism by which HEV inhibits caspase activity. IFN  $\alpha$  may participate in the development of pancreatitis through various mechanisms. Hypertriglyceridemia, a well-known cause of acute pancreatitis, is a result of interferon treatment. On another pathway, interferon  $\alpha$  can stimulate immune responses leading to pancreas-specific autoimmune diseases. Furthermore, RBV-induced anemia and chronic hemolysis may lead to gallstones, one of the most common causes of acute pancreatitis<sup>[34]</sup>. Steroid and diuretic treatments for hepatitis can increase pancreatic enzyme secretion, thickening pancreatic fluid, causing pancreatic duct blockage, and triggering acute pancreatitis. Previous studies<sup>[35,36]</sup> suggest that pancreatic blood circulation disorders may be the main cause of acute pancreatitis, and the degree of microcirculation disorder in the pancreas is strictly correlated with the severity of acute pancreatitis. Improving pancreatic blood flow circulation can protect the pancreas<sup>[37]</sup>. In cases of liver damage, especially in severe hepatitis, cirrhosis, and liver failure, pancreatic injury may be caused by coagulation dysfunction, infection, or ischemic-hypoxic states.

Univariate analysis showed that lower TBil, PTA%, liver failure, NEUT%, lower HB, REC, PCT, and diuretic use were all risk factors for poor prognosis in hepatitis complicated by acute pancreatitis. Multivariate binary logistic regression analysis revealed that liver failure, NEUT%, and REC were independent risk factors affecting prognosis in patients with hepatitis complicated by acute pancreatitis (*P* values all < 0.05).

## 5. Conclusion

In conclusion, this study demonstrates that hepatitis complicated by acute pancreatitis presents unique clinical



features, including atypical symptoms and altered laboratory values such as lower amylase, lipase, PTA%, and PLT, alongside higher TBil levels. Imaging with CT or MRI proves valuable for diagnosis, especially in cases with nonspecific symptoms, though ultrasound remains a useful initial tool. Key independent prognostic factors—liver failure, NEUT%, and REC—indicate poorer outcomes, suggesting that patients with underlying liver disease require close monitoring. These findings highlight the complex interplay between hepatic and pancreatic conditions and the need for tailored diagnostic and therapeutic approaches to improve outcomes in affected patients.

## Disclosure statement

The authors declare no conflict of interest.

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# Analysis of Tacrolimus Combined with Glucocorticoids for Refractory Nephrotic Syndrome

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**Abstract:** *Objective:* To analyze changes in liver and kidney function and lipid metabolism in patients with refractory nephrotic syndrome (RNS) after receiving different treatments. *Methods:* A total of 64 patients treated in the Wuwei Hospital of Traditional Chinese Medicine from January 2018 to January 2021 were included in this study. All subjects were diagnosed with RNS and randomly assigned to groups: a control group (32 cases) and an observation group (32 cases). The control group received cyclophosphamide + glucocorticoids, while the observation group received tacrolimus + glucocorticoids, both for six months. The various indicators of the two groups were compared. *Results:* After six months of treatment, the overall clinical efficacy rate of the observation group was significantly higher than that of the control group. Six months post-treatment, levels of serum ALT, AST, BUN, SCr, 24 h UTP, TG, and TC were reduced in both groups compared to baseline levels, with reductions more pronounced in the observation group. Serum ALB levels increased in both groups, with a more significant increase in the observation group. Statistical analysis showed these differences were significant ( $P < 0.05$ ). There were no significant changes in FBG levels in either group ( $P > 0.05$ ). *Conclusion:* For RNS patients, treatment with tacrolimus combined with glucocorticoids significantly reduces liver function damage, improves kidney function and lipid metabolism, and enhances clinical efficacy.

**Keywords:** Nephrotic syndrome; Refractory; Tacrolimus; Glucocorticoids; Kidney function

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## 1. Introduction

Refractory nephrotic syndrome (RNS) is a clinical progression stage resulting from the sustained development of various primary renal diseases, making it a common type of urinary system-related disease<sup>[1]</sup>. Patients with RNS often exhibit clinical manifestations such as massive proteinuria and hyperlipidemia, making treatment challenging and prone to relapse, thus requiring timely and effective therapeutic intervention<sup>[2]</sup>. Glucocorticoid therapy is a primary treatment for RNS, suppressing immune and inflammatory responses, often combined

with cyclophosphamide. However, some patients experience suboptimal treatment results or glucocorticoid resistance, which may lead to progression to end-stage renal disease, impacting prognosis <sup>[3]</sup>. Tacrolimus, a novel phosphatase inhibitor with potent immunosuppressive effects, has been gradually introduced into clinical practice to enhance treatment efficacy. Based on this, this study aims to analyze changes in liver and kidney function and lipid metabolism in RNS patients after different treatments.

## **2. Materials and methods**

### **2.1. General information**

This study was approved by the hospital's medical ethics committee, and informed consent was signed by the patients' families. Sample selection period: from January 2018 to January 2021, with a total of 64 cases, all of which were patients with refractory nephrotic syndrome (RNS). They were randomly divided into a control group ( $n = 32$ ) and an observation group ( $n = 32$ ) based on a random number table method. The age range in the control group was 20–60 years, with an average age of  $40.04 \pm 3.12$  years; the duration of illness ranged from 1 to 6 years, with an average of  $3.41 \pm 0.30$  years; the body mass index (BMI) ranged from 18 to 24 kg/m<sup>2</sup>, with an average of  $21.48 \pm 1.03$  kg/m<sup>2</sup>; the gender ratio was 18 males and 14 females. The observation group had an age range of 21–60 years, with an average age of  $40.08 \pm 3.14$  years; the duration of illness ranged from 1 to 7 years, with an average of  $3.43 \pm 0.32$  years; BMI ranged from 18 to 24 kg/m<sup>2</sup>, with an average of  $21.46 \pm 1.02$  kg/m<sup>2</sup>; and a gender ratio of 16 males and 16 females. A comparison of these demographic data showed no statistically significant differences ( $P > 0.05$ ), allowing for normal inter-group comparisons in the study.

### **2.2. Inclusion and exclusion criteria**

Inclusion criteria: (1) Patients clinically diagnosed with RNS who met the relevant content of the “Expert Consensus on Immunosuppressive Therapy for Adult Nephrotic Syndrome in China” <sup>[4]</sup>; (2) Those with stable conditions and vital signs; (3) Those who had not received immunosuppressive therapy prior to enrollment.

Exclusion criteria: (1) Patients with mental disorders affecting normal communication; (2) Patients with allergic reactions to the study drugs; (3) Patients with immune-related diseases.

### **2.3. Methods**

Control group: Intravenous infusion of 800 mg/m<sup>2</sup> of cyclophosphamide for injection mixed with 250 mL of sodium chloride injection, once a month; oral prednisone acetate tablets at a dose of 0.5–1.0 mg/kg/day, once daily.

Observation group: Tacrolimus capsules at a dose of 0.05–0.1 mg/kg/day, administered twice daily; oral prednisone acetate tablets were administered as in the control group. Both groups received treatment for six months.

### **2.4. Observation indicators**

- (1) Clinical efficacy: The overall clinical efficacy rate in both groups after six months of treatment was evaluated according to the standards in the “Expert Consensus on Immunosuppressive Therapy for Adult Nephrotic Syndrome in China” <sup>[4]</sup>, including significant effect, effective, and ineffective. These criteria are described as follows: disappearance of relevant clinical symptoms and return of laboratory



indicators to normal; significant improvement in relevant clinical symptoms and laboratory indicators; and no change in relevant clinical symptoms and laboratory indicators after treatment.

- (2) Liver function indicators: Fasting venous blood was collected before and six months after treatment in both groups, with a collection volume of 6 mL. Blood samples were centrifuged at 4°C for 10 minutes (3,500 rpm) to extract serum. Of this, 2 mL of serum was used to measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin (ALB) levels by double-antibody sandwich enzyme-linked immunosorbent assay at the above time points.
- (3) Kidney function indicators: The remaining 2 mL of serum was used to measure serum urea nitrogen (BUN) and serum creatinine (SCr) levels in both groups before and six months after treatment using an enzyme-coupled rate method. Additionally, 24-hour urine samples were collected from patients before and six months after treatment, and a PF-100 automatic biochemical analyzer (Shenzhen Pukang Electronics Co., Ltd.) was used to detect 24-hour urine protein quantification (24-hour UTP).
- (4) Glucose and lipid metabolism: The remaining 2 mL of serum was analyzed with an automatic biochemical analyzer to measure serum triglyceride (TG) and cholesterol (TC) levels in both groups before and six months after treatment. Fasting fingertip blood (about 2 mL) was collected at the above time points, and a glucometer (model: HGM-121) produced by Suzhou Erda Medical Equipment Co., Ltd. was used to measure fasting blood glucose (FBG) levels in both groups.

## 2.5. Statistical analysis

SPSS 26.0 was used for data analysis in this study, with  $P < 0.05$  as the threshold for statistically significant differences. Measurement data and count data are presented as (mean  $\pm$  standard deviation) and [ $n$  (%)], respectively, and  $t$ -tests and  $\chi^2$  tests were used for analysis.

## 3. Results

### 3.1. Comparison of clinical efficacy between the two groups after six months of treatment

**Table 1** compares the total clinical efficacy rate of the control and observation groups after six months of treatment, showing that the observation group had a significantly higher efficacy rate ( $P < 0.05$ ), indicating a statistically significant difference as calculated by statistical software.

**Table 1.** Comparison of clinical efficacy after six months of treatment in the two groups [ $n$  (%)]

Group	$n$	Significant effect	Effective	Ineffective	Total effectiveness
Control	32	9 (28.13)	15 (46.88)	8 (25.00)	24 (75.00)
Observation	32	13 (40.63)	17 (53.13)	2 (6.25)	30 (93.75)
$\chi^2$					4.267
$P$					0.039

### 3.2. Comparison of liver function indicators before and after six months of treatment in the two groups

**Table 2** compares liver function indicators in the control and observation groups before and six months after treatment. Results show that after six months of treatment, serum ALT and AST levels in both groups decreased

compared to pre-treatment levels, with the observation group showing lower levels than the control group. Serum ALB levels increased, with the observation group showing higher levels than the control group. The differences were statistically significant ( $P < 0.05$ ).

**Table 2.** Comparison of liver function indicators before and after six months of treatment in the two groups (mean  $\pm$  SD)

Group	n	ALT (U/L)		AST (U/L)		ALB (ng/mL)	
		Before	After	Before	After	Before	After
Control	32	56.25 $\pm$ 9.40	46.81 $\pm$ 7.53*	78.88 $\pm$ 9.86	52.17 $\pm$ 7.39*	29.10 $\pm$ 3.15	34.47 $\pm$ 2.81*
Observation	32	55.96 $\pm$ 9.05	43.30 $\pm$ 4.07*	77.92 $\pm$ 9.81	44.48 $\pm$ 5.17*	30.16 $\pm$ 3.08	38.61 $\pm$ 2.26*
<i>t</i>		0.126	2.320	0.390	4.823	1.361	6.494
<i>P</i>		0.900	0.024	0.698	< 0.001	0.178	< 0.001

\*Note:  $P < 0.05$  compared to pre-treatment

### 3.3. Comparison of kidney function indicators before and after six months of treatment in the two groups

**Table 3** compares kidney function indicators in the control and observation groups before and after six months of treatment. Results indicate that serum BUN, SCr, and 24-hour UTP levels decreased in both groups after six months of treatment compared to pre-treatment levels, with the observation group showing lower levels than the control group. These differences were statistically significant ( $P < 0.05$ ).

**Table 3.** Comparison of kidney function indicators before and after six months of treatment in the two groups (mean  $\pm$  SD)

Group	n	BUN (mmol/L)		SCr ( $\mu$ mol/L)		24-hour UTP (g)	
		Before	After	Before	After	Before	After
Control	32	10.13 $\pm$ 1.01	8.38 $\pm$ 1.11*	106.18 $\pm$ 10.04	90.68 $\pm$ 9.31*	4.08 $\pm$ 1.04	1.66 $\pm$ 0.32*
Observation	32	10.06 $\pm$ 1.05	6.07 $\pm$ 1.02*	105.94 $\pm$ 10.06	81.11 $\pm$ 8.18*	4.15 $\pm$ 1.01	0.79 $\pm$ 0.07*
<i>t</i>		0.272	8.668	0.096	4.368	0.273	15.024
<i>P</i>		0.787	< 0.001	0.924	< 0.001	0.786	< 0.001

\*Note:  $P < 0.05$  compared to pre-treatment

### 3.4. Comparison of glucose and lipid metabolism indicators before and after six months of treatment in the two groups

**Table 4** compares glucose and lipid metabolism indicators in the control and observation groups before and after six months of treatment. Results show that serum TG and TC levels decreased in both groups after six months of treatment compared to pre-treatment levels, with the observation group showing lower levels than the control group, indicating a statistically significant difference ( $P < 0.05$ ). FBG levels showed no significant difference before and after treatment in both groups ( $P > 0.05$ ).

**Table 4.** Comparison of glucose and lipid metabolism indicators before and after six months of treatment in the two groups (mean  $\pm$  SD, mmol/L)

Group	n	TG		TC		FBG	
		Before	After	Before	After	Before	After
Control	32	5.73 $\pm$ 1.07	4.02 $\pm$ 1.31*	7.28 $\pm$ 1.17	5.31 $\pm$ 1.04*	5.08 $\pm$ 1.11	4.96 $\pm$ 1.02*
Observation	32	5.61 $\pm$ 1.09	2.57 $\pm$ 0.76*	7.21 $\pm$ 1.15	3.42 $\pm$ 1.02*	5.01 $\pm$ 1.15	4.89 $\pm$ 1.06*
<i>t</i>		0.444	5.416	0.241	7.339	0.248	0.269
<i>P</i>		0.658	< 0.001	0.810	< 0.001	0.805	0.789

\*Note:  $P < 0.05$  compared to pre-treatment

## 4. Discussion

The incidence of refractory nephrotic syndrome in clinical practice continues to show a significant upward trend. The kidneys, being vital organs, are at risk of severe complications if patients do not receive timely and effective treatment, potentially endangering their lives. Currently, cytotoxic drugs combined with glucocorticoids are commonly used in clinical treatment, which can alleviate patients' symptoms to some extent; however, the associated toxic side effects limit their clinical efficacy<sup>[5,6]</sup>.

Tacrolimus is a neurocalcin inhibitor with strong immunosuppressive properties and relatively mild drug toxicity. In previous studies, it was mainly used for liver disease treatment. Nowadays, tacrolimus has been found to not only provide immunosuppression but also effectively inhibit platelet aggregation and reduce inflammatory responses, making it widely used in the treatment of refractory nephrotic syndrome<sup>[7]</sup>. The results of this study indicate that, after six months of treatment, the total clinical efficacy rate in the observation group was significantly higher than in the control group. Additionally, the observation group showed lower serum ALT and AST levels and higher serum ALB levels compared to the control group after six months of treatment. This suggests that tacrolimus combined with glucocorticoids can reduce liver function damage in patients with refractory nephrotic syndrome and improve clinical efficacy, consistent with findings by Ding in clinical practice<sup>[8]</sup>.

Analyzing these findings, the following explanation emerges: in patients with refractory nephrotic syndrome, the disease severity often leads to substantial proteinuria, causing a decrease in plasma colloid osmotic pressure and significant protein loss from the liver, which in turn impairs liver function and leads to abnormal serum ALT, AST, and ALB levels. When tacrolimus enters the body, it can effectively inhibit T lymphocyte proliferation, offering strong immunosuppressive effects, while being metabolized by the liver's cytochrome enzyme P-450-3A4 isoenzyme, thereby reducing liver damage. Furthermore, tacrolimus does not exhibit bone marrow suppression, allowing it to bind with endogenous cell receptors in the cytoplasm and form complexes that, in conjunction with glucocorticoids, enhance therapeutic efficacy<sup>[9,10]</sup>.

The study results also show that serum BUN, SCr, 24 h UTP, TG, and TC levels in the observation group were lower than in the control group after six months of treatment, with no significant difference in FBG levels. This suggests that tacrolimus combined with glucocorticoids can effectively improve kidney function and lipid metabolism in patients with refractory nephrotic syndrome without affecting blood glucose levels, which is consistent with the findings of Deng *et al.*<sup>[11]</sup>. Analyzing this, the following explanation is derived: serum BUN,

SCr, and 24 h UTP are commonly used clinical markers of kidney function damage, while serum TG and TC are primary indicators of blood lipid metabolism, all of which can be used to assess the severity of refractory nephrotic syndrome. Treatment with tacrolimus and glucocorticoids can directly act on relevant effector cells and induce the liver enzyme system to effectively inhibit transcription factor dephosphorylation, thereby improving kidney function and regulating blood lipid metabolism<sup>[12]</sup>.

## 5. Conclusion

In summary, tacrolimus combined with glucocorticoids in patients with refractory nephrotic syndrome can significantly reduce liver function damage, improve kidney function and blood lipid metabolism, and enhance clinical treatment efficacy.

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## Disclosure statement

The author declares no conflict of interest.

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# Application Value of Targeted Nursing Intervention for Pediatric Nutritional Iron-Deficiency Anemia

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**Abstract:** *Objective:* To evaluate the nursing effects of targeted care for children with nutritional iron-deficiency anemia (IDA). *Methods:* A total of 88 children with IDA admitted to the hospital from November 2021 to November 2023 were selected (each child included one accompanying family member). Using a random number table, the participants were divided into two groups: the observation group, which received targeted nursing care, and the reference group, which received standard nursing care. The anemia correction rate, nutritional indicators, and family knowledge level were compared. *Results:* The anemia correction rate in the observation group was higher than in the reference group, with post-nursing nutritional indicators superior to those in the reference group. Additionally, family members in the observation group had a higher level of knowledge ( $P < 0.05$ ). *Conclusion:* Targeted nursing can effectively correct anemia symptoms in children with IDA, improve nutritional indicators, and increase family members' knowledge, demonstrating high nursing effectiveness.

**Keywords:** Pediatric nutritional iron-deficiency anemia; Targeted nursing; Anemia correction rate; Nutritional indicators; Knowledge level

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## 1. Introduction

Iron deficiency anemia (IDA) is a common form of anemia in children, with causes linked to organ dysfunction, environmental changes, malnutrition, and immune system diseases. IDA persistently reduces the immune function of affected children, impacting their physical and mental health. Iron supplements and other pharmacological treatments are effective therapies for children with IDA, as they can improve nutritional status and correct anemic symptoms. However, due to the young age of these patients, their compliance with medication is often low<sup>[1]</sup>. Additionally, IDA prognosis is influenced by multiple factors, including dietary structure and sleep quality. Therefore, children with this condition require targeted nursing to adjust individual dietary and lifestyle habits,

enhance medication adherence, and control the progression of anemia<sup>[2]</sup>. Based on this, the present study selected 88 children with IDA and 88 family members to analyze the effects of targeted nursing interventions.

## 2. Materials and methods

### 2.1. General information

A total of 88 children with IDA who were treated at the hospital from November 2021 to November 2023 were included, along with 88 accompanying family members. The participants were divided into groups using a random number table. In the observation group, there were 44 children, including 27 boys and 17 girls, aged 1 to 6 years, with an average age of  $3.18 \pm 0.42$  years. Among the 44 family members, there were 11 males and 33 females, aged 26 to 56 years, with an average age of  $34.65 \pm 3.17$  years. In the reference group, there were 44 children, including 26 boys and 18 girls, aged 1 to 5 years, with an average age of  $3.02 \pm 0.39$  years. The 44 family members included 13 males and 31 females, aged 24 to 55 years, with an average age of  $34.71 \pm 3.29$  years. There was no significant difference between the groups in terms of demographic data ( $P > 0.05$ ).

Inclusion criteria: Comprehensive diagnosis of IDA based on blood tests, clinical symptoms, and signs; age  $< 7$  years; normal mental state of the child; informed consent obtained.

Exclusion criteria: Severe liver disease, cognitive impairment, malignant tumors, or missing clinical data.

### 2.2. Methods

The reference group received standard nursing care: regular monitoring of vital signs, guidance on healthy eating, and appropriate supplementation with trace elements to improve nutritional status.

The observation group received targeted nursing care:

- (1) Psychological care: Assess the child's age. For children under 3 years old, whose language and cognitive abilities are limited, toys, games, and cartoons were used to bridge communication gaps, with nicknames like "baby" or "sweetie" to create a friendly atmosphere, helping to ease the child's unfamiliarity and encourage cooperation with care procedures. For children 3 years or older, who can express themselves and have a stronger sense of independence, comic-style educational materials or videos were provided, combining images and sound to enhance understanding of nursing concepts. Family members' cultural level, occupation, and personality were assessed to understand their psychological state and IDA awareness, allowing for tailored psychological support. In cases of panic or worry, successful cases were introduced with explanations of IDA's preventability and treatability, highlighting treatment and nursing processes to increase self-care awareness. For those experiencing anxiety or restlessness, family members were encouraged to read parenting books and IDA information booklets, helping them better understand disease care and management. Support groups or educational lectures were organized to alleviate feelings of helplessness and isolation, promoting communication among caregivers and continuous learning about IDA.
- (2) Dietary care: For mild anemia (hemoglobin level of 90–110 g/L), caregivers were advised to encourage iron-rich foods such as lean meat, animal liver, green leafy vegetables, fish, soy products, egg yolks, and blood-based products, along with vitamin C supplementation. For moderate to severe anemia (hemoglobin 60–90 g/L or  $< 60$  g/L), iron supplements were also provided in addition to dietary changes. Children with poor digestion were advised to eat small, frequent meals with thorough

chewing; for those with reduced appetite, frequent changes in food flavor were recommended to enhance the appeal of meals.

- (3) Lifestyle care: For children with stable conditions, light exercise was recommended, such as sun exposure and light jogging, with a daily exercise time of around 20 minutes, avoiding intense activity. Sufficient sleep was also encouraged, with bedtime set before 9 p.m. and sleep duration of approximately 10 hours to improve overall well-being.
- (4) Medication care: Iron supplements may cause gastrointestinal irritation, resulting in nausea, vomiting, and diarrhea. Therefore, low doses were administered, timed between meals, and combined with vitamin C. Caregivers and children were informed that iron intake may lead to darkened teeth and black stools to prevent unnecessary concern. For injections, the appropriate dose was calculated and administered in divided doses via intramuscular injection to enhance absorption.

### 2.3. Observation indicators

- (1) Anemia correction rate: (a) Significant correction as normal nutritional indicators and resolution of anemia symptoms after 1 week of intervention; (b) Basic correction as improved nutritional indicators and relief of anemia symptoms after 1 week of intervention; (c) No correction as abnormal nutritional indicators and no change in anemia symptoms after 1 week of intervention.
- (2) Nutritional indicators: Fasting venous blood samples were collected from the children. Hemoglobin levels were measured with an automated blood cell analyzer, ferritin with a chemiluminescence immunoassay analyzer, and serum iron with a spectrophotometric test kit.
- (3) Family knowledge level: A custom knowledge assessment scale was used, covering disease knowledge, dietary knowledge, exercise knowledge, medication knowledge, and precautions. Each category was scored out of 100 points, with higher scores indicating better knowledge mastery.

### 2.4. Statistical analysis

Data analysis was conducted using SPSS 28.0 software. Measurement data were expressed as mean  $\pm$  standard deviation (SD) and compared with *t*-tests. Count data were expressed as [*n* (%)] and compared with  $\chi^2$  tests. Results were considered statistically significant at  $P < 0.05$ .

## 3. Results

### 3.1. Comparison of anemia correction rates between the two groups

**Table 1** shows that the anemia correction rate in the observation group was higher than in the reference group ( $P < 0.05$ ).

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

Group	<i>n</i>	Significant correction	Basic correction	No correction	Correction rate
Observation	44	24	18	2	42 (95.45)
Reference	44	19	16	9	35 (79.55)
$\chi^2$					5.091
<i>P</i>					0.024

### 3.2. Comparison of nutritional indicators between the two groups

Before nursing, there was no difference in nutritional indicators between the two groups ( $P > 0.05$ ). After nursing, the nutritional indicators in the observation group were higher than those in the reference group ( $P < 0.05$ ), as shown in **Table 2**.

**Table 2.** Comparison of nutritional indicators between the two groups before and after nursing (mean  $\pm$  SD)

Group	n	Hemoglobin (g/L)		Ferritin ( $\mu$ g/L)		Serum iron ( $\mu$ mol/L)	
		Before	After	Before	After	Before	After
Observation	44	91.65 $\pm$ 6.78	112.05 $\pm$ 7.98	13.61 $\pm$ 2.15	27.68 $\pm$ 3.11	13.35 $\pm$ 2.11	20.73 $\pm$ 3.11
Reference	44	91.69 $\pm$ 6.27	103.67 $\pm$ 7.41	13.57 $\pm$ 2.19	17.83 $\pm$ 3.06	13.29 $\pm$ 2.14	15.96 $\pm$ 3.04
<i>t</i>	-	0.029	5.104	0.086	14.975	0.132	7.275
<i>P</i>	-	0.977	0.000	0.931	0.000	0.895	0.000

### 3.3. Comparison of knowledge mastery scores between family members of both groups

**Table 3** shows that the knowledge mastery scores of family members in the observation group were higher than those in the reference group ( $P < 0.05$ ).

**Table 3.** Comparison of knowledge mastery scores between the two groups (mean  $\pm$  SD)

Group	n	Disease knowledge	Dietary knowledge	Exercise knowledge	Medication knowledge	Precautions
Observation	44	88.98 $\pm$ 4.13	90.57 $\pm$ 3.53	88.94 $\pm$ 3.51	92.12 $\pm$ 3.41	92.48 $\pm$ 3.27
Reference	44	84.02 $\pm$ 4.10	85.16 $\pm$ 3.42	84.02 $\pm$ 3.46	87.19 $\pm$ 3.20	89.15 $\pm$ 3.22
<i>t</i>	-	5.654	7.301	6.622	6.993	4.813
<i>P</i>	-	0.000	0.000	0.000	0.000	0.000

## 4. Discussion

The pathogenesis of IDA involves an iron deficiency, leading to decreased hemoglobin levels and subsequent microcytic anemia, which is prevalent in pediatric populations <sup>[3]</sup>. Symptoms of this condition include indigestion, pale skin and mucous membranes, reduced immunity, and are often accompanied by malnutrition, which further affects the child's physical and intellectual development. Children with this condition require dietary adjustments or iron supplements to adequately replenish iron levels and improve anemia. To enhance medication adherence and ensure effective treatment, targeted nursing care is often combined with other interventions <sup>[4]</sup>.

Targeted nursing care, rooted in a human-centered approach, is a new nursing method that considers the physiological and psychological state of the child holistically. This approach allows for detailed nursing services that enhance the rationality and comprehensiveness of nursing interventions. The goals are more refined, enabling dynamic assessment of the child's nursing needs and adjustments to nursing measures to comprehensively improve the quality of care <sup>[5]</sup>.

In this study, the anemia correction rate in the observation group was higher than in the control group, and post-nursing nutritional indicators were superior in the observation group ( $P < 0.05$ ). Analysis suggests

that targeted nursing can comprehensively assess the severity of anemia in children, provide tailored dietary guidance, and gradually normalize the child's eating habits, encouraging adherence to an iron-rich diet. Additionally, enhanced medication nursing improves caregivers' understanding of medication, ensuring adherence to prescribed regimens, reducing instances of unauthorized dosage changes or premature discontinuation, significantly improving anemia treatment outcomes and effectively enhancing the child's nutritional indicators<sup>[6,7]</sup>. The knowledge level among caregivers in the observation group was also higher than that of the control group ( $P < 0.05$ ). This may be attributed to targeted nursing's emphasis on psychological support, where education is tailored to the child's age with personalized communication and psychological counseling provided to caregivers. This approach enables caregivers to effectively support treatment and nursing procedures, gradually strengthening their self-care capabilities<sup>[8]</sup>. Furthermore, life care helps caregivers adjust the child's lifestyle habits, improving their overall health. Through these humanized and individualized nursing practices, caregivers recognize the professionalism and rigor of the nursing plan and gain comprehensive knowledge of the relevant topics<sup>[9,10]</sup>.

## 5. Conclusion

In summary, targeted nursing care can improve the severity of IDA in pediatric patients, adjust their nutritional status, and significantly increase caregivers' knowledge of the condition, offering substantial nursing advantages.

## Disclosure statement

The author declares no conflict of interest.

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# Exploring the Interplay Between Cancer, Health, and Inflammation

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**Abstract:** Cancer is a complex disease influenced by various factors, including DNA damage, growth signals, and inflammation. Although inflammation has commonly not been considered carcinogenic, increasing evidence indicates its substantial involvement in the onset and progression of cancer, especially in the presence of chronic microbial infections. This review thoroughly analyzes the complex relationship between cancer, health, and inflammation by introducing pathological and physiological features of inflammation. The study explores the various factors that might enhance inflammation, including infections and para-inflammation caused by tissue stress. It will also explore the changing comprehension of microorganisms about health and illness, clarifying their possible influence on the development of several malignancies, including colon, pancreatic, gastric, and prostate cancers. In addition, the study emphasizes the development of new therapy approaches that specifically target chronic inflammations and their associated cancers. This review seeks to enhance the comprehension of the intricate correlation between cancer, inflammation, and human health by combining existing research.

**Keywords:** Cancer; Tissue stress; Inflammation; Human health; Therapeutic interventions

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## 1. Introduction

Cancer is a significant global health issue, resulting in a considerable number of diseases and fatalities. During the year 2012, there were an estimated 14 million incidences of cancer that were newly diagnosed and eight million deaths directly linked to the disease. Estimations suggest that the incidence of cancer will increase, reaching around 22 million new cases annually by 2030<sup>[1]</sup>. Additionally, it is estimated that there will be around 13 million deaths annually due to cancer. The rise in cancer prevalence is partially attributed to the expansion of the population and the process of aging. Nevertheless, it is expected that alterations in cultural, economic, and lifestyle aspects associated with human growth will also impact and increase the cancer profile in the future<sup>[2,3]</sup>. Various research has demonstrated a robust correlation between socioeconomic advancement, inflammation,

and cancer. The existing body of literature offers valuable insights that may be used to shape strategies and establish goals to effectively address the burden of cancer. Additionally, it emphasizes the variations in cancer susceptibility and impact among varying degrees of human development. This review seeks to evaluate the worldwide occurrence of cancer concisely, its correlation with inflammation, and the general state of human health, explicitly emphasizing the variations in cancer prevalence among various levels of human development <sup>[4]</sup>. This review focuses on the relationship between inflammation and cancer in various types and risk factors that affect cancer, as well as the treatments with corresponding outcomes that include disabilities and life expectancy cases.

Knowledge of the underlying health elements affecting cancer is essential since the elements of health can significantly affect the possibilities of cancer in terms of early detection and survival rates <sup>[5]</sup>. The causes of cancer include nursing factors like the type of diet, exercise regimes, and tobacco use, as well as environmental conditions and heredity <sup>[6]</sup>. Lack of a healthy diet and physically inactive lifestyle are some of the significant factors that lead to obesity. This fact has been widely accepted as a precursor to several diseases and cancers. Furthermore, smoking is associated with instances of lung cancer as well as various other kinds of cancer. If these risk factors are further defined, they can reduce total body cancer <sup>[7]</sup>. Additionally, knowing of risks originating from genetics can help integrate the methods of individualized medicine in preventive and therapeutic practices, thus improving the efficacy of prevention measures and drugs. Understanding the factors affecting health requires further identification and scrutiny to make possible changes regarding the approaches of public health interventions that would allow for the unique needs and concerns of various populations to be addressed. This results in better diagnosis and effective management of cancer and lowered incidence of the disease <sup>[8]</sup>.

Inflammation has also been directly linked to the risk of new cancer events and enhanced mortality rates, according to multiple studies <sup>[9]</sup>. That is why the exact pathogenic mechanism of many long-term illnesses, like stress or cancer, is called chronic low-grade inflammation. Chronic psychological stress leads to sustained elevation of circulating cytokines in the blood, which is responsible for mild peripheral and central inflammation <sup>[10,11]</sup>. NF- $\kappa$ B, STAT3, and mTOR pathways regulate the synthesis of cytokines, which provoke inflammation and further modulate their activity <sup>[12]</sup>. The studies regarding the fact that the NF- $\kappa$ B/STAT3 oncofetal gene for FAT10 upregulation is unfavorable to the p53 tumor suppressor gene that is overexpressed with a significantly higher rate of enhancement <sup>[13]</sup>. One of the other molecular changes identified as having a direct link with high chances of an individual developing tumors is the alteration or complete knockout of p53 protein that results from *TP53* gene mutations. Also, Romeo et al., in their recent study in 2009, confirmed that the end-of-life experiences of patients can be measured by the quality-of-life index and ACE. This study also revealed the same as the study conducted by Noman on how Mutant p53 proteins facilitate the survival of cancer cells through increased ROS production, synthesis of pro-inflammatory cytokines, activation of mTOR, suppression of autophagy, and suppression of UCP2. They also noted that the p53 distribution usually occurs in a dispersed manner, and as for the currently described standard p53 scattering pattern, certain conditions were meant to decrease the action of mutated TP53 in supporting the survival of the cancerous cells <sup>[12]</sup>. Moreover, the compounds also stimulated the said pro-inflammatory and cancer-promoting cytokines and had a positive reinforcement toward tumor promotion <sup>[12]</sup>.

Stress, hypoxic cancers, metabolism, anti-cancer therapy, cancer-inducing inflammation, angiogenesis, cytokine- production, and so on can be the possibility of the cause <sup>[14]</sup>. They affect tumor development

depending on cell proliferation and increase the invasiveness of the cancer cells through the epithelial-mesenchymal transition. Furthermore, VEGF and its receptors show an increase in tumor angiogenesis. The following research works provided preeminence of the points above, all of which aid the integration of technology in the learning and teaching process <sup>[15,16]</sup>.

Additionally, one should note that when cancer cells produce more pro-inflammatory cytokines, it may result in multiple drug resistance; this is likely attributed to an autocrine feedback mechanism <sup>[14]</sup>. This is because chronic stress or cancer will place the body on a pro-inflammatory status, which then triggers other stress responses. This condition can change the cancer biology and be associated with neuroinflammation. Neuroinflammation refers to a condition that involves monocyte activation, microglia activation, and disruption of the blood-brain barrier (BBB) <sup>[17,18]</sup>. This then caused an aggregation of macrophages in the lymph nodes and splenic spaces by stress releasing them in the brain by continued release of catecholamine <sup>[19]</sup>. It is these cells that later become hyperinflammatory, and they facilitate the migration of cells into the brain <sup>[17-19]</sup>. In this context, sustained inflammation increases the up-regulation of high cell adhesion molecules on the cerebral endothelium to facilitate the attachment of monocytes and their diapedesis through the endothelium. Lastly, this results in the metamorphosis of the monocytes into cells with strong microglia features. For this reason, we can find out that the monocyte infiltration caused by chronic stress and CCR2-dependent is not related to the damage to the BBB <sup>[20]</sup>. MIF has been reported to be up-regulated under conditions of chronic stress, to directly facilitate the recruitment of monocytes by engaging the CCL2/CCR2 signaling pathway, and is also mandatory for maintaining chronic neuroinflammation <sup>[21-23]</sup>. The interactions between inflammation, human stages of development, and cancer are unpredictable yet diverse. It is, therefore, important for public health stakeholders to better understand these interactions to develop and implement better strategies and interventions that can help reduce the occurrence of cancer and improve treatment outcomes.

## 1.1. Cancer and health

Malignant diseases of the cancer category are common and manifested by the proliferation and ongoing proliferation of abnormal cells. If this proliferation is to go unchecked, it can lead to death. Cancer can often develop in any of the body's organs or tissues. Over a hundred types of cancer are termed after the body part where and/or from where they arise. Lung cancer arises from cells found in the lungs, whereas brain cancer arises from cells found in the brain <sup>[24]</sup>. The main categories of cancer include as follows.

Carcinomas are malignant neoplasms arising from the epidermis or the epithelial tissues surrounding internal organs. Examples include breast, lung, and colorectal cancer. Sarcomas are cancerous tumors that originate from connective tissues.

Leukemias are cancerous growths that develop in the hematopoietic tissue, particularly the bone marrow. This leads to the overproduction and release of abnormal blood cells into the circulatory system. Lymphomas and myelomas are tumors that originate from the defense system. Neoplasms are CNS cancers that originate in the tissues of the brain and spinal cord <sup>[25]</sup>.

## 1.2. Cancer epidemiology

Cancer is a prominent cause of morbidity and mortality on a global scale. The WHO documented roughly 14 million cases of cancer and around 8 million deaths caused by cancer in 2012. The expected burden is set to rise, as forecasts indicate a yearly increase of 22 million new cases and 13 million fatalities by 2030. The

increase in this phenomenon can be attributed to various variables, such as the expansion of the population and the aging of individuals, along with changes in lifestyle and the environment linked to socioeconomic progress. Cancer incidence remains an area that shows relative distribution differences by geographical areas, age, gender, and social status. The universal types are common in developed nations, such as breast and prostate cancer, based on advanced diagnostic methods and increased life expectancy. On the other hand, economically developed countries are less likely to be affected by these infections causing cancer, such as cervical cancer from viruses and liver cancer from viruses <sup>[26]</sup>.

Some of the leading well-identified causes of cancer that affect humanity globally include tobacco smoking, misuse of alcohol, poor diet, tendency to perform little or no exercise, and exposure to viruses. Suppose there is any single social vice that remains the most significant cause of cancer deaths. Smoking, which accounts for about 22 percent of all cancer-related deaths. In addition, Human exposure to hazardous substances at the workplace, such as carcinogens, radiation, and environmental toxins, increases the likelihood of cancer significantly. The best approach to address this health threat is a holistic approach that includes prevention, timely diagnosis, treatment, and support for the patient. Preventable risk factors, which require strategies that can be changed, controlling over-vaccination, screening, and promoting access to medical care services, are vital for reducing the likelihood of cancer and improving results <sup>[27]</sup>.

## **2. Inflammation and its physiological role in the body**

Inflammation, defined by the literal meaning of the word being an abbreviation for “inflammatory,” a term meaning “to flame,” is a critical function in the body that serves the purpose of protecting cell membranes from damage or infection by pathogens <sup>[28,29]</sup>. Inflammation is a vital human body condition, though it continues as a chronic disease. Inflammation is related to diseases with lengthy intervals, such as neurological disorders, cancer, and cardiovascular illnesses. Inflammation is an elaborate process of coordinated and dynamic events involving a cascade of clear and well-orchestrated events, such as responses within cells and blood vessels and the release of specific mediators <sup>[30,31]</sup>. The mechanisms involve the migration of leukocytes, plasma, and substances towards the site of inflammation. Immune cells secrete various chemicals and signaling molecules, such as histamine, cytokines, and free radicals. Each of these chemicals promotes inflammation <sup>[29]</sup>. Inflammatory responses consist of two distinct stages: major and minor. There are different mechanisms at play in each phase.

### **2.1. Acute inflammation**

Inflammatory responses can occur at the vascular and cellular levels during the acute inflammatory phase. When the tissue is injured or invaded by microorganisms, vascular events commence — the vessels dilate and become hyperpermeable. This enables inflammatory mediators to move in and results in the formation of interstitial edema. The ability of cells to pass through the circulatory system and invade other tissues is essential for inflammatory reactions <sup>[32]</sup>. Some chemical messengers involved in the trigger of leukocyte migration include microbial endotoxins, the C5a complement component, interleukins, and the secretions from basophil. It is recognized that these cells are the first responders at sites of severe inflammation. The invasion of the immune system is a complex phenomenon characterized by leukocyte interactions with the lining of blood vessels, which is found in postcapillary veins <sup>[33]</sup>. This process involves several cellular activities, such as the



capture, rolling, and firm adhering of leukocytes to the endothelium lining of tiny blood arteries. Some CAMs are explained as follows: intercellular adhesion molecular-1 (ICAM-1), intercellular adhesion molecular-2 (ICAM-2), integrin, and selectin, which are involved in these actions. The selectins can be classified into three families: P-selectin and E-selectin, which are on endothelial cells, and L-selectin, which is on leukocytes. It is also necessary to mention the interaction between the white blood cells and the endothelium due to the high affinity between the human protein-integrating protein CD11/CD18, present in the white blood cells, and the CAMs, located in endothelial cells <sup>[34]</sup>. Once adherence is established, white blood cells send out pseudopods through the intercellular spaces of the endothelial row and penetrate the sub-endothelial basement lamina. It can be called white blood cell invasion and transendothelial migration <sup>[35]</sup>.

## 2.2. Chronic inflammation

Mononuclear cells, particularly monocytes and lymphocytes, fibroblast proliferation, collagen fiber synthesis, connective tissue growth, and the eventual creation of granulomas are hallmarks of chronic inflammation <sup>[36]</sup>. In chronic inflammation, inflammatory cells enter the damaged area and produce ROS, RNS, proteases, and so on. These species are responsible for tissue destruction. Diseases of the inflammatory bowel, rheumatoid arthritis, and cancer are among the chronic inflammatory illnesses linked to mutations in the *p53* gene <sup>[36]</sup>.

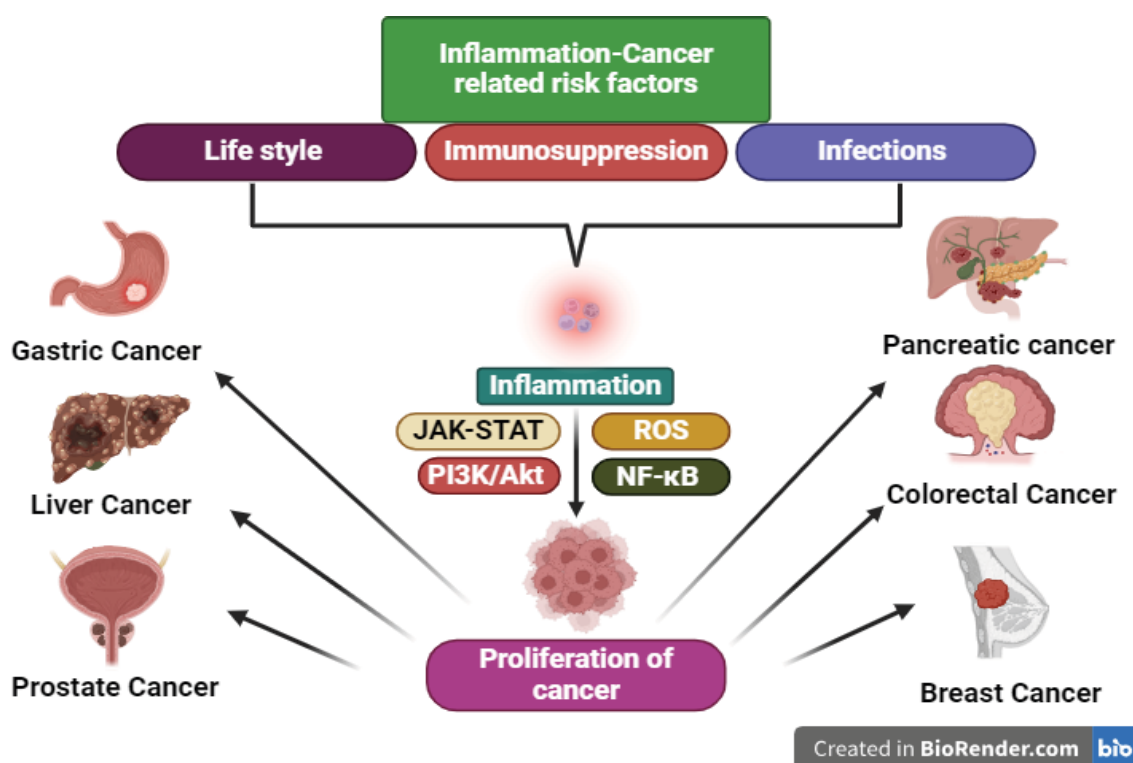
## 2.3. Key inflammatory mediators

Many different chemical mediators released by damaged tissues, inflammatory cells, and the bloodstream actively regulate the inflammatory response. Thromboxanes, leukotrienes, and prostaglandins are eicosanoids; peptides like bradykinin histamine and serotonin are all part of this class of chemical mediators. Although additional cell types can secrete cytokines, the primary sources of cytokine release include vascular cells, fibroblasts, and endothelial cells, among others <sup>[37]</sup>.

## 2.4. Mechanisms of inflammation

Complex molecular and cellular mechanisms contribute to inflammation and the immunological system's reaction to pathogens or damaged tissues <sup>[38]</sup>. At the outset, chemical signals released by damaged or sick tissues attract several immune cells to the site of inflammation, including lymphocytes, macrophages, and neutrophils <sup>[39]</sup>. These cytokines, chemokines, and prostaglandins are just a few of the pro-inflammatory substances released by these cells. By increasing vascular permeability and inducing vasodilation, these substances bring additional immune cells to the affected area. The primary signaling pathways for inflammation are NF- $\kappa$ B, STAT3, and MAPKs <sup>[40]</sup>. Essential proteins for the immune response, such as inflammatory cytokines, are controlled by these pathways <sup>[41]</sup>. Also, warning signs activate multi-protein complexes called inflammasomes, and they play an essential role in producing cytokines like interleukin-1 $\beta$  (IL-1 $\beta$ ) that enhance inflammation. Imbalance in these pathways can result in long-term inflammation and have a role in developing several types of cancers, such as gastric, liver, colorectal, prostate, and breast cancer (**Figure 1**) <sup>[42]</sup>.





**Figure 1.** Role of inflammation in the development of several types of cancers such as gastric cancer, liver cancer, colorectal cancer, prostate cancer, and breast cancer

### 3. Link between inflammation and cancers

In 1863, Rudolf Virchow made the initial connection between inflammation and cancer. He noticed the presence of leukocytes in cancerous tissues, indicating that cancer may potentially arise in areas of long-lasting inflammation. In the last 150 years, the understanding of this correlation has dramatically progressed. At first, it was believed that substances that cause irritation and tissue damage, leading to inflammation, could promote cell growth and contribute to cancer formation <sup>[43]</sup>. Nevertheless, it is currently acknowledged that other variables beyond cell proliferation influence the distinctive aberrant growth of cancer <sup>[44]</sup>. These factors include growth hormones, DNA damage chemicals, an active stroma, and an inflammatory environment <sup>[45]</sup>. In contrast, inflammation in typical circumstances typically subsides on its own because of the creation of anti-inflammatory cytokines. Unregulated chronic inflammation can disturb regular cellular processes, resulting in the development of different types of cancer (**Table 1**). Additional evidence substantiating this connection is derived from research indicating that most cancerous tissues display an inflammatory element in their surrounding environment. This condition is characterized by changes in the structure of tissues, the development of new blood vessels (angiogenesis), the invasion of white blood cells (leukocytes), a significant presence of tumor-associated macrophages (TAMs), and elevated levels of signaling chemicals called cytokines and chemokines <sup>[45]</sup>.

**Table 1.** Interconnections between inflammation and different types of cancers

No	Type of cancer	The primary cause of inflammation	Inflammatory pathway	Reference
1	Gastric cancer	<i>Helicobacter pylori</i>	Activation of MEK/ERK, NF- $\kappa$ B, and $\beta$ -catenin pathways	[78,79]
2	Liver cancer	Hepatitis B (HBV) and C (HCV)	Mediated by CD8 <sup>+</sup> T cells, NK cells, and macrophages producing ROS and nitrogen compounds	[54,80]
3	Pancreatic cancer	Smoking, genetic predisposition, and infections	Activation of NF- $\kappa$ B pathway	[57,81]
4	Colorectal cancer	Inflammatory bowel disease (IBD) leads to chronic intestinal inflammation	Immune cells produce cytokines, ROS, and RNS, causing DNA damage	[69,82]
5	Breast cancer	Abundance of Methyl bacterium and disruptions in estrogen metabolizing bacteria	Chronic inflammations cause disruptions in a cellular pathway	[69,83]

### 3.1. Gastric cancer

*Helicobacter pylori* produces one instance of cancer associated with inflammation <sup>[46]</sup>. By creating virulence factors, particularly cytotoxin-associated gene (Cag) A, *H. pylori* causes inflammatory reactions in the host <sup>[47]</sup>. Host inflammatory protein pathways, such as MEK/ERK, NF- $\kappa$ B, and  $\beta$ -catenin, are activated by this factor. About 70% of stomach adenocarcinomas, chronic gastritis, and mucosa-associated lymphoid tissue (MALT) lymphomas are caused by *H. pylori*, the first bacteria to be classified as a carcinogen by the WHO <sup>[48]</sup>. Research conducted on animal models has shown that mice infected exclusively with *H. pylori* display more widespread tumor profiles in comparison to germ-free and antibiotic-treated controls <sup>[48]</sup>. This indicates that *H. pylori* alone may not be enough to cause cancer and is likely to interact with other factors. Gastric cancer growth has been associated with Epstein-Barr Virus (EBV) infection, which is marked by aberrant gene methylation, specifically affecting *RUNX1*, *RBM5*, and *PSME1* <sup>[48]</sup>. Environmental variables, such as smoking, along with the host's genetic susceptibility (particularly, differences in genes encoding IL-1B, IL-10, and TNF) and interactions between specific bacterial virulence factors (cagPAI, T4SS, CagA), have an impact on the outcome of infection <sup>[49]</sup>. Despite a decline in the occurrence of stomach cancer in recent years as a result of enhanced knowledge about its causes and better treatment decision-making, it continues to be the second most common cause of cancer-related fatalities globally <sup>[50]</sup>.

### 3.2. Liver cancer

Primary liver cancer, known as hepatocellular carcinoma (HCC), was the third leading cause of cancer-related deaths worldwide <sup>[51]</sup>. Liver inflammation and damage are associated with about 90% of HCC cases. There is a substantial correlation between chronic inflammation in the liver and the development of hepatic fibrosis, cirrhosis, and, finally, HCC <sup>[52]</sup>. Influenza with Hepatitis B and C together causes increased inflammation of the liver and factors the incidence of hepatocellular carcinoma (HCC) by more than twenty. He et al. found that HBV and HCV preferentially target CD8<sup>+</sup> T cells and natural killer (NK) cells to cause inflammation and liver injury. Some of the resulting inflammatory mediators include macrophages and neutrophils, reactive oxygen species (ROS), and nitrogen compounds. These factors increase the DNA damage connected with HCC and other forms of cancer <sup>[53,54]</sup>. *Helicobacter hepaticus* and other microorganisms involved in the digestive system are also proven to be related to liver cancer <sup>[55]</sup>. This is supported by the appearance of tumors and activation of

the NF- $\kappa$ B signaling pathway after introducing *H. hepaticus* in the gastrointestinal tract <sup>[56]</sup>.

### 3.3. Pancreatic cancer

This aggravates inflammation of the pancreatic tissue and subsequently leads to an increased risk of pancreatic cancer as well as an increased number of pancreatic stellate cells <sup>[57]</sup>. Various causes are involved in developing long-term pancreatitis; some of them are effects of the environment, including smoking, heredity, the existence of metabolic disorders, and infections <sup>[58]</sup>. Research of the past done on experimental human and animal models suggests that certain types of bacteria may be behind the inflammation usually detected in pancreatic cancer patients <sup>[59]</sup>. The studies have revealed a strong relationship between the existence of periodontal infections and an individual more vulnerable to pancreatic cancer <sup>[60]</sup>. The 5-year survival rate of pancreatic cancer is among the lowest being at 3%–7%, and this is an inferior figure <sup>[61]</sup>. Bacterial identification may lead to the development of the specific medication against these periodontal germs, as well as the identification of the biomarkers useful for distinguishing high-risk individuals — such a discovery could contribute to total cancer inception prevention <sup>[62]</sup>.

### 3.4. Colorectal cancer

CRC is the third most diagnosed cancer worldwide and is found to be more common in IBD patients, a chronic inflammatory condition that is on the rise. Among them, there are indicator features of inflammation in the intestines associated with IBD: the infiltration of immune cells — macrophages, neutrophils, and others <sup>[63]</sup>. Patients with IBD often have inflammation and ulcerations, and the cells produce cytokines, as this production enhances free radicals, proteolytic enzymes, and inflammatory reactions <sup>[61,64]</sup>.

RNS and ROS are excessive in inflammatory bowel diseases, which have been suggested to promote tumor growth in the intestinal tract <sup>[65]</sup>. DNA damage due to ROS/RNS accumulation and external mutagen activation leads to cancer cell migration and spreading to adjacent tissues <sup>[66]</sup>. Furthermore, comparing the molecular signals produced in inflammatory bowel disease shows remarkable similarities with those produced in colorectal cancer. It is a critical factor that promotes tumor development in colorectal cancer. Cytokines are defined as the collection of molecules, whereas the one referred to as interleukin <sup>[67]</sup>. Diversity, an imbalance in the gut microbial community, relates to inflammation in inflammatory bowel disease (IBD) and colorectal cancer (CRC) risk. Genome sequencing studies have demonstrated an association between a particular bacterial species to be involved in the development of colon cancer. This bacterial species has higher quantities in the tissues of patients with this disease <sup>[68]</sup>. Its exact role is not clearly understood, but it significantly affects disease progression <sup>[69]</sup>.

### 3.5. Breast and prostate cancer

The leading cause of cancer-related mortality in women is breast cancer, whereas in men, it is prostate cancer <sup>[70]</sup>. Inflammation and bacteria have been implicated in the development of various illnesses in previous research <sup>[71]</sup>. Cancer patients show a dramatic decrease in the presence of Methyl bacteria in breast tissue, which is linked to tumors that have a higher likelihood of spreading. Disruptions in bacteria that participate in estrogen metabolism can lead to an elevation of estrogen levels in the bloodstream, thereby raising the probability of developing breast cancer <sup>[72,73]</sup>. As could be expected, there invariably exists inflammatory cells in the rectal vicinity together with prostate cancer in men <sup>[74]</sup>. Anaerobic bacteria may make themselves noticeable if the tumor

grows and reduces oxygen levels in the body. Although it has been challenging to prove that bacteria have a role in prostate cancer, there is a link between inflammatory changes and prostate infection <sup>[75]</sup>. This link has the potential to lower the prostate's protective barrier, which in turn can aid in the progression of cancer. The risk of developing a prostate infection is associated with shifts in the urinary tract's microbial composition <sup>[76,77]</sup>.

#### **4. Therapeutic interventions for cancers**

Cancer treatment involves a comprehensive strategy that includes different approaches to therapy and nutritional recommendations. Chemotherapy involves using platinum-based compounds and other drugs, causing tumor cells to undergo programmed cell death and toxicity. However, the effectiveness of chemotherapy can be affected by the microorganisms in the gut <sup>[84,85]</sup>. This would imply that probiotics can improve treatment regimens while reducing the side effects of chemotherapy. Another strength of cancer care that has made rapid progress in cancer treatment is immunotherapy, a remarkably immune checkpoint inhibitor. The relevance of bacterial composition to patient clinical outcomes stems from the evidence that the gut microbiome can alter the pharmacologic actions of drugs.

People should consume more fruits, vegetables, and fiber-rich food to manage and prevent cancer. Lignans and isothiocyanates, other micronutrients found in the diet, have anti-cancer properties. This demonstrates that some foods have potential in the treatment of cancer. In summary, there is an opportunity for better cancer treatment outcomes and better overall health of patients by combining two medical approaches, immunotherapy, and chemotherapy, and making dietary adjustments <sup>[83]</sup>.

#### **5. Conclusion**

In conclusion, this review has provided in-depth knowledge of the link between cancer, health, and inflammation, focusing on various mechanisms underlying cancer progression. This study has emphasized the importance of examining chronic microbial infections and inflammation in therapeutic approaches since they play a part in the initiation and progression of cancer. This study is critical because it focuses on the many factors contributing to cancer development through inflammation and demonstrates the role of bacteria in promoting tumor growth. Investigating these relationships in the future will empower the creation of novel treatment paradigms that focus on the cancer cells and target the cause of inflammation. This will help the research community develop better ways of managing cancer in the future. This may result in better patient outcomes and a more evolved approach to cancer.

#### **Disclosure statement**

The authors declare no conflict of interest.

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# Research Progress and Mechanisms of Acupuncture Combined with Transcutaneous Vagal Nerve Stimulation in the Treatment of Cognitive Impairment after Stroke

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**Abstract:** Cognitive impairment is a common complication after stroke, which not only affects the rehabilitation process of patients but also increases the family and socio-economic burden. Finding an effective treatment for cognitive impairment after stroke is urgent. Acupuncture can effectively activate blood circulation, dredge collaterals, tonify qi and blood, and regulate yin and yang. It is an effective method for the treatment of cognitive impairment after stroke. Recent studies have shown that acupuncture combined with various modern rehabilitation techniques, such as transcutaneous vagus nerve stimulation, has better clinical effects than either acupuncture or rehabilitation therapy alone. This article reviews the clinical research and basic mechanisms in this field by searching Chinese and English literature from the past 20 years, aiming to provide research ideas for future studies on the combined treatment of post-stroke cognitive impairment and related mechanisms.

**Keywords:** Percutaneous vagal nerve stimulation; Cognitive impairment after stroke; Stroke; Acupuncture

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## 1. Introduction

Post-stroke cognitive impairment (PSCI) is a clinical phenomenon secondary to stroke, characterized by cognitive decline lasting less than six months. This condition encompasses cognitive impairment caused by various types of stroke, including multiple infarctions, key brain area infarctions, subcortical infarctions, and cerebral hemorrhage <sup>[1]</sup>.

In recent years, population aging has become increasingly prominent in China, with stroke emerging as the leading cause of mortality among Chinese residents <sup>[2]</sup>. As the incidence of stroke continues to rise annually,



its high disability, mortality, and recurrence rates have resulted in a growing number of patients experiencing cognitive impairment after stroke. Reports indicate that up to 69.8% of stroke patients in Asian countries experience cognitive decline within three months<sup>[3]</sup>, and stroke increases the risk of dementia by 4 to 12 times<sup>[4]</sup>. Severe cases can significantly impact patients' quality of life and social activities, imposing a substantial burden on families and society. Therefore, early intervention and treatment of PSCI are crucial for preventing and managing cognitive impairment after stroke.

Currently, the main treatment methods for PSCI patients include drug therapy, management of mental and behavioral symptoms, and rehabilitation treatments combining traditional Chinese and Western medicine<sup>[5,6]</sup>. Studies suggest that rehabilitation techniques, such as percutaneous vagal nerve stimulation, also have certain clinical effects<sup>[7]</sup>.

With advancements in medicine, exploring ways to combine traditional Chinese and Western rehabilitation therapies holds significance for improving the efficacy of PSCI treatment. Percutaneous vagal nerve stimulation is a rehabilitation technique that regulates the vagus nerve network. The various branches of the vagus nerve govern functional structures involved in memory processing, and studies have shown that vagus nerve stimulation (VNS) can promote cognitive recovery<sup>[8,9]</sup>.

Acupuncture combined with percutaneous vagal nerve stimulation can effectively improve cognitive impairment after stroke and delay its progression. Therefore, the primary aim of this study is to summarize clinical research on acupuncture combined with percutaneous vagal nerve stimulation in treating PSCI. This aims to provide new and more effective treatment methods and ideas for PSCI and offer clinical evidence for the application of acupuncture combined with percutaneous vagal nerve stimulation in PSCI management.

## **2. PSCI overview**

### **2.1. Clinical manifestations**

Stroke imposes a significant burden in China. In 2020, the prevalence and incidence of stroke in China were 2.6% and 50.52 million, respectively<sup>[10]</sup>. Approximately one in three stroke patients develop post-stroke cognitive impairment (PSCI)<sup>[11]</sup>. PSCI is characterized by cognitive impairment that occurs within six months after a stroke and persists for more than three months. The occurrence of a stroke is a prerequisite for the diagnosis of PSCI, with ischemic stroke being the most common type, although hemorrhagic stroke is also included. The primary clinical manifestation is mild cognitive impairment, with daily life and work abilities being normal or only slightly affected.

### **2.2. Epidemiological data of PSCI**

Epidemiological data on PSCI have been widely reported, but significant variability exists among studies. Differences arise due to the selection of study populations, research timelines, sampling periods, research contexts, cognitive tests used, and cutoff values<sup>[12]</sup>. Recent studies have reported that many stroke patients develop cognitive impairment following stroke events<sup>[13,14]</sup>. The incidence of PSCI ranges from 11% to 42%, while the proportion of PSCI without dementia varies from 14% to 29%<sup>[15]</sup>. To date, no large-scale study on the incidence of PSCI has been conducted in China. The prevalence of related conditions has increased significantly, with the growing incidence of PSCI posing substantial challenges to patients' quality of life, mental health, family caregiving, and economic resources.

### 2.3. The pathogenesis of PSCI

The pathogenesis of PSCI is not fully understood in modern medicine. It is highly complex and influenced by multiple factors, with considerable variability among studies. The pathogenesis encompasses neuroanatomical and pathological changes, cerebral microvascular lesions, neurodegenerative diseases, genetic factors, and molecular mechanisms<sup>[7]</sup>. Molecular mechanisms involve nerve cell apoptosis, oxidative stress-induced nerve cell damage, neuroinflammatory injury, white matter damage, neural pathway disruptions, blood-brain barrier dysfunction, synaptic plasticity impairment, amyloid- $\beta$  protein deposition in the brain, cholinergic system dysfunction, excitatory amino acid cytotoxicity, and oxygen free radical damage mechanisms<sup>[7]</sup>.

### 3. Acupuncture treatment of PSCI

Acupuncture treatment for PSCI does not have a direct counterpart in terms of disease nomenclature. However, based on its clinical manifestations, PSCI corresponds to traditional Chinese medicine (TCM) diseases such as “dementia,” “forgetfulness,” and related conditions. Ye Tianshi stated in *Clinical Guide Medical Records* from the Qing Dynasty: “At the beginning of apoplexy, diuresis is obvious in the elderly,” suggesting that cognitive impairment may manifest in the early stages of stroke<sup>[16,17]</sup>. Therefore, PSCI is secondary to stroke, with its pathological basis rooted in the brain. TCM considers the disease’s origin in the kidney, while it is also closely related to the heart, liver, spleen, and other organs. The etiology and pathogenesis are complex. Physicians across generations have believed that the disease is centered in the brain, with turbid phlegm and blood stasis as primary pathological factors. Its therapeutic mechanisms may involve promoting neuron regeneration and repair, regulating the balance of qi and blood, and harmonizing the functions of the internal organs.

Currently, PSCI is treated through drug therapy, management of mental and behavioral symptoms, and TCM and Western rehabilitation techniques. Acupuncture has gained increasing attention due to its multi-target, multi-mechanism, safe, and effective characteristics, including scalp acupuncture, ear acupuncture, buccal acupuncture, and body acupuncture.

#### 3.1. Scalp acupuncture selection

The pathology of cognitive impairment after stroke is located in the brain. Shao Tongzhen stated in *The Doctor is Easy to Manage the Brain*: “The brain is the master of the body, also known as the residence of the soul. The body can perceive movement, remember ancient and modern times, and process all things due to the brain’s power.” The brain, considered the sea of marrow, governs emotion and perception. Regulating brain meridians is thus a critical aspect of achieving therapeutic effects.

Zhang and Li<sup>[18]</sup> used Baihui as the central point and alternately needled three groups of Bagua points in eight directions around Baihui. After analyzing scale data and homocysteine levels post-treatment, it was concluded that this therapy improves various aspects of patients’ cognitive abilities. Cai *et al.*<sup>[19]</sup> utilized scalp acupuncture combined with back Shu points, targeting Sishen Cong, Baihui, Shenting, Shenshu, Ganshu, Pishu, Feishu, and Xinshu (bilateral points). Statistically significant improvements in MoCA, MBI, and SF-36 scores indicated that scalp acupuncture combined with back Shu acupuncture is effective for mild to moderate cognitive impairment after stroke.

Zhang<sup>[20]</sup> applied the Tongdu Tiaoshen acupuncture method, combined with cognitive training, on points such as Baihui, Shenting, Yintang, Shuigou, Chengzhu, and Lianquan. Analysis of MoCA scores post-treatment

demonstrated improvements in cognitive function and daily living abilities in PSCIND patients. Zhou *et al.* [21] employed scalp acupuncture (parietal line, frontal line, frontal line 1, and frontal line 2) combined with donepezil hydrochloride. Serum levels of A $\beta$ , Smur100 $\beta$ , and BDNF, along with MoCA and MMSE scale scores, were analyzed. Results showed that scalp acupuncture inhibits the expression of A $\beta$  and Smur100 $\beta$ , increases serum BDNF protein, and improves cognitive dysfunction.

Zhai *et al.* [22], through a review of domestic core periodical literature from the past 10 years, concluded that head, neck, and face points, particularly Baihui, Sishen Cong, Shenting, and Fengchi, are primary for treating post-stroke cognitive impairment. For example, Baihui, located at the intersection of the hand and foot Yang meridians with the Governor meridian, is believed to regulate qi and blood flow to the brain, thereby nourishing the marrow and improving cognitive function. Clinical studies suggest that acupuncture at Baihui enhances memory in stroke patients by strengthening brain network connections between the hippocampus, frontal lobe, and parietal lobe [23].

### 3.2. Body needle selection

Body acupuncture is a traditional method for treating stroke sequelae and has a long history. The *An and B Classic of Acupuncture and Moxibustion* states: “Loss of wisdom is the domain of Neiguan.” Acupoint selection varies among practitioners based on individual patient differences and clinical presentation. Acupuncture enhances cerebral blood flow (CBF) and metabolism, thereby improving cognitive function [24].

Wang *et al.* [25] identified Baihui, Shenting, Sishen Cong, Sanyinjiao, Zusanli, and Neiguan as the most frequently used points for treating PSCI in clinical trials published in Chinese and English journals over the past 15 years. Wang [26] divided patients into three groups: basic treatment, routine acupuncture, and abdominal acupuncture (targeting Zhongwan, Xiawan, Qihai, Guanyuan, and Daheng). Scores for MoCA, LOTCA, and improved Barthel were significantly better in the treatment group compared to controls. Gao *et al.* [27] utilized data mining to analyze effective acupoints for PSCI, identifying points such as Neiguan, Sanyinjiao, Zusanli, Taixi, Shenmen, Taichong, Fenglong, and Xuehai.

## 4. Study on the mechanism of percutaneous vagal stimulation in the treatment of PSCI

“The ear is the gathering place of the clan pulse” and “the ear is connected to the brain” indicate that the “ear” is closely linked to the meridians and the brain. The twelve meridians extend throughout the body, reaching the brain, which is considered the Abode of the Spirit. This suggests that stimulation of the ear can regulate mental functions. Modern anatomical studies have also revealed that the ear connects to the brain through the vagus nerve, glossopharyngeal nerve, facial nerve, and ototemporal nerve.

The vagus nerve, the longest and most widely distributed cranial nerve, extends from the brain to the ear, neck, chest, and abdominal organs. It comprises general visceral motor and sensory fibers, general somatosensory fibers, and special visceral motor fibers. A percutaneous vagal nerve stimulator is a physiotherapeutic tool developed in recent years for treating certain intractable conditions. Since the vagus nerve in the neck, chest, and abdomen is located deep within the body and difficult to access directly, the exposed auricular region, which contains vagus nerve afferent fibers, offers a direct pathway to the central nervous system.

#### 4.1. Regulation of cerebral blood flow

Numerous studies have demonstrated that transcutaneous vagus nerve stimulation (tVNS) can regulate and increase cerebral blood flow <sup>[28-30]</sup>. This effect may result from the stimulation of the vagus nerve, which dilates cerebral blood vessels through a neural reflex mechanism, thereby improving the blood supply to brain tissue <sup>[31,32]</sup>. Enhanced cerebral blood flow supports improved neuronal metabolism and function, reducing damage to neurons caused by ischemia and hypoxia. This mechanism provides a therapeutic effect on PSCI <sup>[33]</sup>.

#### 4.2. Regulation of the neurotransmitter system

Transcutaneous vagus nerve stimulation can also modulate the brain's neurotransmitter system, increasing the release of key neurotransmitters such as acetylcholine and dopamine <sup>[34]</sup>. Acetylcholine plays a crucial role in cognitive processes like learning and memory <sup>[35]</sup>. Dopamine, involved in the regulation of the reward system and motivational behavior, also affects cognitive function <sup>[36]</sup>. By promoting the release of these neurotransmitters, tVNS enhances neuronal signal transmission and synaptic plasticity, thereby improving cognitive function.

#### 4.3. Inhibition of neuroinflammatory response

Transcutaneous vagus nerve stimulation can inhibit neuroinflammatory responses and reduce the levels of inflammatory factors <sup>[37]</sup>. This effect may be due to the tVNS stimulation of the vagus nerve, which activates the cholinergic anti-inflammatory pathway through a neural reflex mechanism, thereby suppressing the release of inflammatory factors <sup>[38]</sup>. Reducing inflammatory responses not only mitigates neuronal injury and death but also enhances the neurotransmitter system and neural plasticity, contributing to the therapeutic effects of tVNS on PSCI <sup>[39]</sup>.

Wang *et al.* <sup>[40]</sup> employed tVNS to stimulate the ear cavity and auricular concha, targeting ear acupoints associated with the vagus nerve (e.g., liver, spleen, kidney, pancreas, heart, lung, trachea, Sanjiao, endocrine). Data showed that serum levels of TNF- $\alpha$ , IL-6, and IL-1 $\beta$  were significantly lower in the tVNS group on days 1 and 3 post-operation compared to sham stimulation and control groups. Theoretically, percutaneous vagus nerve stimulation activates efferent vagus nerve impulses in the concha region, thereby initiating the cholinergic anti-inflammatory pathway and suppressing the inflammatory response <sup>[41]</sup>.

Inflammatory responses in the nervous system are major contributors to PSCI. Following ischemic damage, activated stromal cells and inflammatory mediators lead to immune cell infiltration, blood-brain barrier dysfunction, cellular edema, neuronal destruction, and apoptosis <sup>[42]</sup>. Studies suggest that serum markers and elevated levels of inflammatory factors like C-reactive protein, IL-6, and IL-12 in cerebrospinal fluid are associated with PSCI pathogenesis <sup>[43,44]</sup>.

Qi *et al.* <sup>[45]</sup> conducted a study on 98 patients undergoing knee or hip arthroplasty. In this study, the stimulation group received electrical vagus nerve stimulation after anesthesia induction, while the control group did not. Cognitive impairment incidence was observed on day 7, before discharge, and two months post-operation. Results indicated that the tVNS significantly reduced cognitive impairment on day 7 and before discharge but had no significant effect two months post-operation. Furthermore, the stimulation group exhibited lower white blood cell counts on the first post-operative day, suggesting that the mechanism of tVNS in reducing cognitive impairment may involve suppression of the postoperative inflammatory response.

In a water maze experiment on epileptic rats, VNS intervention significantly improved spatial learning



and memory <sup>[46]</sup>. VNS reduced IBA-1 protein expression in the hippocampus, a marker of microglia activation. Microglia-mediated central inflammatory responses are critical contributors to hippocampal neuron damage and cognitive impairment in epilepsy <sup>[47,48]</sup>. Decreased levels of TNF- $\alpha$ , IL-6, and IL-1 $\beta$  further suggested that VNS may reduce hippocampal inflammation by inhibiting microglia activation and promoting anti-inflammatory effects. Therefore, percutaneous vagus nerve stimulation can potentially treat cognitive impairment by alleviating inflammation.

#### **4.4. Promotion of neuroplasticity**

Transcutaneous vagus nerve stimulation promotes neuroplasticity by enhancing neuronal regeneration and synaptic formation. This effect may occur because tVNS stimulation of the vagus nerve regulates the expression of neurotrophic and growth factors in the brain <sup>[49]</sup>. Increased neuroplasticity facilitates cognitive function recovery, making it a beneficial therapeutic approach for PSCI <sup>[50,51]</sup>.

### **5. Acupuncture combined with transcutaneous vagus nerve stimulation in the treatment of PSCI**

Acupuncture and tVNS operate through distinct mechanisms. Acupuncture primarily regulates meridian qi, blood flow, and visceral function, while tVNS modulates cerebral nerve activity and immune system functions. When used together, these approaches can exert synergistic effects, enhancing therapeutic efficacy.

Both acupuncture and tVNS are relatively safe treatments with minimal side effects. Acupuncture may occasionally cause localized pain, minor bleeding, or bruising, whereas tVNS may lead to skin allergies, irritation, or discomfort. Combining these treatments could potentially mitigate the occurrence of such adverse effects by balancing their individual risks.

Overall, the combination of acupuncture and tVNS represents a promising integrative approach for the treatment of cognitive impairment following stroke, leveraging their complementary mechanisms to achieve better clinical outcomes.

### **6. Summary**

Acupuncture has increasingly been shown to be a promising intervention for the treatment of PSCI, demonstrating positive effects on patients' cognitive function <sup>[52]</sup>. Data mining has revealed that the top five acupoints for PSCI treatment are Baihui, Shenting, Sishencong, Fengchi, and Neiguan, with the primary meridians involved being the Governor Vessel, Gallbladder Meridian, Spleen Meridian, and Stomach Meridian <sup>[53]</sup>.

The disease primarily affects the brain and is associated with kidney essence deficiency, brain loss, phlegm, and blood stasis that obstruct the orifices, leading to cognitive dysfunction. Acupuncture targeting key points such as Baihui, Shenting, and Sishencong can clear the orifices, stimulate the brain, and improve cognitive impairment. Acupoints like Neiguan and Shenmen on the upper limbs and Zusanli, Sanyinjiao, and Taichong on the lower limbs can address limb dysfunction by dispelling wind, nourishing blood, invigorating circulation, and unblocking the meridians and collaterals <sup>[54]</sup>.

The Governor Vessel, which connects to the brain, is central to these treatments as it regulates the marrow sea, clears brain pathways, and aligns with the brain's association with the kidneys <sup>[55]</sup>. Research has shown that



acupuncture significantly improves cognition, memory, orientation, and daily living activities <sup>[56,57]</sup>. According to TCM, acupuncture balances qi and blood, reduces stroke sequelae, and effectively treats cognitive impairment <sup>[58]</sup>.

The pathogenesis of PSCI is not fully understood but may involve inflammatory responses. Stroke-induced activation of macrophages and the release of inflammatory mediators can breach the blood-brain barrier, leading to nerve damage and cognitive decline <sup>[59]</sup>. While VNS typically requires implanting electrodes around the cervical vagus nerve, it reduces systemic inflammation and neuroinflammation, thereby improving cognitive function. However, its invasive nature makes it less acceptable to patients. In contrast, tVNS is non-invasive, portable, and well-tolerated, making it a more practical option <sup>[60]</sup>.

The effects of VNS on cognitive impairment after stroke depend on the recovery stage. In the chronic phase, VNS promotes brain function recovery and neuroplasticity, whereas in the acute phase, it provides neuroprotection, facilitates neuroregeneration and angiogenesis, and enhances neuroplasticity <sup>[61-63]</sup>.

Acupuncture combined with tVNS offers significant improvements in PSCI symptoms by leveraging their complementary mechanisms <sup>[64]</sup>. However, limitations in current research, including study quality, sample size, and potential language bias, highlight the need for large-scale, multicenter, high-quality randomized controlled trials. These trials will better establish the safety, long-term efficacy, and scientific foundation for integrating acupuncture and tVNS into post-stroke rehabilitation. Such efforts could pave the way for innovative therapeutic strategies to slow cognitive impairment progression.

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# Therapeutic Efficacy of Reduced Glutathione in Emergency Treatment of Organophosphorus Pesticide Poisoning and Its Impact on ALT, AST, CRP, and IL-6 Levels

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**Abstract:** *Objective:* To analyze the efficacy of reduced glutathione (GSH) in the emergency treatment of patients with organophosphorus pesticide poisoning (AOPP). *Methods:* A total of 100 AOPP patients admitted to the emergency department between January 2022 and January 2024 were selected and randomly divided into two groups. The observation group ( $n = 50$ ) received GSH combined with conventional treatment, while the reference group ( $n = 50$ ) received conventional treatment alone. The overall treatment efficacy, serum indicators, and adverse reaction rates were compared. *Results:* The observation group exhibited a higher overall treatment efficacy compared to the reference group ( $P < 0.05$ ). Post-treatment, serum indicator levels in the observation group were lower than those in the reference group, and the adverse reaction rate was also lower in the observation group ( $P < 0.05$ ). *Conclusion:* GSH can improve the overall treatment efficacy in AOPP patients, protect liver function, reduce inflammatory responses in the body, and minimize post-treatment adverse effects, thus accelerating recovery and demonstrating significant therapeutic advantages.

**Keywords:** Reduced glutathione; Organophosphorus pesticide poisoning; Emergency treatment; Therapeutic efficacy

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## 1. Introduction

Organophosphorus pesticide poisoning (AOPP) refers to the inhalation or contact with pesticides containing high levels of phosphorus-containing organic compounds. Symptoms include mental disorders, excessive sweating, and respiratory paralysis. AOPP is predominantly acute, with a rapidly progressive course and a high risk of mortality, necessitating prompt emergency treatment<sup>[1]</sup>. Common emergency treatments include administering pralidoxime and atropine, along with early gastric lavage, to slow disease progression, eliminate toxins, and reduce disease severity. However, these treatments do not adequately protect liver function or

reverse liver damage and inflammatory processes, resulting in a suboptimal prognosis.

Therefore, this study utilized reduced glutathione (GSH) as a treatment, which can counteract free radical generation, protect liver and kidney function, detoxify effectively, and enhance clinical outcomes. Given the high feasibility of this therapy, 100 AOPP patients were included to evaluate the efficacy of GSH.

## 2. Materials and methods

### 2.1. General information

A total of 100 patients with acute organophosphorus pesticide poisoning (AOPP) treated in the emergency department between January 2022 and January 2024 were selected and randomly divided into two groups. The observation group included 50 patients (26 males and 24 females) aged 25–75 years, with a mean age of  $54.18 \pm 3.95$  years. The time from poisoning to admission ranged from 1 to 4 hours, with a mean time of  $1.58 \pm 0.61$  hours. The reference group also included 50 patients (28 males and 22 females) aged 23–74 years, with a mean age of  $54.92 \pm 4.14$  years. The time from poisoning to admission ranged from 1 to 3 hours, with a mean time of  $1.53 \pm 0.58$  hours. No significant differences were observed in baseline characteristics between the two groups ( $P > 0.05$ ).

Inclusion criteria: Patients met the diagnostic criteria for AOPP as outlined in the “Guidelines for the Diagnosis and Differential Diagnosis of Acute Organophosphorus Pesticide Poisoning”<sup>[2]</sup>; exhibited typical symptoms such as abdominal pain, generalized muscle spasms, and nausea; were diagnosed with AOPP based on cholinesterase activity and toxicological tests; had complete baseline data; and provided informed consent to participate.

Exclusion criteria: Patients with infectious diseases such as AIDS or syphilis; allergic to emergency medications; had coagulation disorders; were diagnosed with severe comorbidities such as malignant tumors; or withdrew during the study.

### 2.2. Methods

Reference group: Patients received standard treatment:

- (1) Gastric lavage: A gastric tube was inserted, and 10–20 liters of clean water were infused to wash the stomach until the gastric effluent was clear.
- (2) Atropine treatment: Patients were administered atropine sulfate injection (Jilin Jibang Pharmaceutical Co., Ltd., National Drug Approval Number H20053923, 1 mL: 5 mg). The initial dose was 5 mg via intravenous injection, followed by additional injections of 1–5 mg every 10 minutes until signs of atropinization appeared.
- (3) Pralidoxime therapy: Patients received pralidoxime iodine (Tianjin Pharmaceutical Group Xinzheng Co., Ltd., National Drug Approval Number H20066022, 20 mL: 0.5 g). The initial dose was 1.0 g via intravenous injection, followed by a supplementary dose of 0.5 g every 12 hours.

Observation group: Patients received standard treatment combined with GSH therapy. Reduced glutathione (GSH) for injection (Chongqing Yaoyou Pharmaceutical Co., Ltd., National Drug Approval Number H20051600, 2.0 g) was administered at a dose of 2.0 g mixed in 100 mL of normal saline via intravenous infusion once daily.

The treatment duration for both groups was 7 days.

## 2.3. Observation indicators

- (1) Serological markers: Venous blood samples (5 mL) were collected before treatment and on the 7th day of treatment. Samples were centrifuged for 10 minutes at 3000 rpm. Serum alanine transaminase (ALT) and aspartate transaminase (AST) levels were measured using an automatic biochemical analyzer. C-reactive protein (CRP) was determined using an immunoturbidimetric method, and interleukin-6 (IL-6) levels were measured using an enzyme-linked immunosorbent assay (ELISA).
- (2) Adverse reaction rate: The incidence of intermediate syndrome, respiratory depression, and pulmonary edema was recorded.

## 2.4. Efficacy evaluation criteria

- (1) Markedly effective: Poisoning symptoms completely resolved after 7 days of treatment, and ALT and AST levels returned to normal.
- (2) Effective: Poisoning symptoms alleviated after 7 days of treatment, with ALT and AST levels reduced by  $> 50\%$ .
- (3) Ineffective: No improvement in poisoning symptoms after 7 days of treatment, with ALT and AST levels reduced by  $\leq 50\%$  or increased.

## 2.5. Statistical analysis

Data were processed using SPSS 28.0 software. Measurement data were expressed as mean  $\pm$  standard deviation (SD) and analyzed using  $t$ -tests. Count data were expressed as frequencies and percentages [ $n$  (%)] and analyzed using  $\chi^2$  tests. A  $P$ -value  $< 0.05$  was considered statistically significant.

# 3. Results

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

**Table 1** shows that the overall treatment efficacy in the observation group was significantly higher than in the reference group ( $P < 0.05$ ).

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

Group	Cases	Markedly effective	Effective	Ineffective	Overall effective rate
Observation	50	29	18	3	47 (94%)
Reference	50	25	15	10	40 (80%)
$\chi^2$	-	-	-	-	4.332
$P$	-	-	-	-	0.037

## 3.2. Comparison of serological indicators between the two groups

Before treatment, there were no significant differences in serological indicators between the two groups ( $P > 0.05$ ). After 7 days of treatment, the levels of serological indicators in the observation group were significantly lower than those in the reference group ( $P < 0.05$ ), as shown in **Table 2**.

**Table 2.** Comparison of serological indicators between the two groups before and after treatment (mean  $\pm$  SD)

Group	Cases	ALT (U/L)		AST (U/L)		CRP (ng/mL)		IL-6 (pg/mL)	
		Before	After	Before	After	Before	After	Before	After
Observation	50	79.84 $\pm$ 6.91	49.18 $\pm$ 4.32	76.95 $\pm$ 6.86	48.95 $\pm$ 4.11	16.35 $\pm$ 2.98	3.77 $\pm$ 0.52	117.35 $\pm$ 19.42	62.48 $\pm$ 5.11
Reference	50	79.92 $\pm$ 7.12	61.77 $\pm$ 4.83	77.15 $\pm$ 6.91	59.84 $\pm$ 4.18	16.42 $\pm$ 2.93	6.48 $\pm$ 1.47	116.84 $\pm$ 20.37	67.94 $\pm$ 5.83
<i>t</i>	-	0.057	13.738	0.145	13.136	0.118	12.290	0.128	4.980
<i>P</i>	-	0.955	0.000	0.885	0.000	0.906	0.000	0.898	0.000

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

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

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

Group	Cases	Intermediate syndrome	Respiratory depression	Pulmonary edema	Incidence rate
Observation	50	1	1	0	2 (4%)
Reference	50	3	4	1	8 (16%)
$\chi^2$	-	-	-	-	4.000
<i>P</i>	-	-	-	-	0.046

## 4. Discussion

AOPP is a common condition in emergency medicine. It occurs when organophosphate pesticides enter the body via oral ingestion, respiratory tract, or skin, binding tightly with cholinesterase to produce phosphorylated cholinesterase. This process reduces the bioactivity of acetylcholinesterase, inhibits its breakdown capability, increases acetylcholine levels at neuromuscular and synaptic junctions, and enhances cholinergic excitation, leading to pronounced neurological symptoms<sup>[3]</sup>. Early symptoms of AOPP include miosis and confusion, while disease progression can result in respiratory failure and sudden death. Current emergency treatments, such as gastric lavage, help flush out pesticide residues from the stomach, preventing systemic absorption and reducing the toxic effects on various organs<sup>[4]</sup>. Atropine administration can act on muscarinic receptors to dilate blood vessels, relieve smooth muscle spasms, improve blood circulation, and shorten recovery time. Pralidoxime iodine can bind rapidly to organophosphate compounds in pesticides, preventing excessive inhibition of cholinesterase and restoring enzyme activity, thereby alleviating respiratory muscle paralysis and promoting toxin elimination. These measures stabilize the condition and alleviate symptoms but have limitations in protecting liver and kidney function.

GSH is present in the cytoplasm and participates in redox processes, maintaining cellular health. Under normal conditions, the body can continuously synthesize GSH, which has strong antioxidant properties<sup>[5]</sup>. However, during AOPP, endogenous GSH is insufficient to meet detoxification demands, necessitating exogenous supplementation. GSH promotes the inactivation of reactive oxygen species (ROS) by binding with free radicals, reducing oxidative stress, and mitigating organ damage caused by pesticide components.

Exogenous GSH improves metabolic function, increases GSH levels, and enhances enzyme activation. It binds to ROS and aldehydes in the liver, preventing excessive lipid peroxidation, modulating oxidative stress markers, and protecting liver cells from damage by improving their membrane stability and repairing injured hepatocytes <sup>[6]</sup>.

As a naturally synthesized peptide, GSH contains abundant sulfhydryl groups and is widely distributed in body tissues to maintain cellular activity. It acts as a cofactor for enzymes involved in glycolysis and oxidative metabolism, binding with free radicals to generate harmless compounds, repair tissue damage, and enhance detoxification efficacy <sup>[7]</sup>. The results showed an overall treatment efficacy of 94.0% in the observation group compared to 80.0% in the reference group ( $P < 0.05$ ), consistent with findings by Xie <sup>[4]</sup>, indicating the reliability of this study.

AOPP causes pesticides to target liver tissue, resulting in significant hepatocyte damage, increased membrane permeability, and the release of ALT and AST into the plasma. Myocardial injury caused by poisoning can also elevate serum ALT levels <sup>[8]</sup>. CRP, an acute-phase protein, increases in response to inflammation triggered by poisoning, while IL-6 is a sensitive early marker of infection, both of which rise significantly during systemic inflammation <sup>[9]</sup>. GSH exerts potent free radical scavenging and detoxifying effects, forming low-toxicity compounds with a high metabolic rate that facilitates pesticide elimination. This reduces oxidative stress, cell membrane damage, and ALT/AST levels <sup>[10]</sup>. GSH also possesses strong anti-inflammatory properties, suppressing inflammatory mediators and alleviating systemic inflammation, thereby reducing CRP and IL-6 levels. In this study, the observation group showed significantly lower levels of all serological markers after 7 days of treatment compared to the reference group ( $P < 0.05$ ), demonstrating the ability of GSH to improve liver function and mitigate inflammatory responses.

GSH exhibits stable pharmacokinetics, high bioavailability, sustained therapeutic effects, and minimal cumulative toxicity with prolonged use, resulting in fewer adverse reactions. The observation group had a lower adverse reaction rate than the reference group ( $P < 0.05$ ), supporting these findings.

## 5. Conclusion

In summary, GSH provides effective treatment for AOPP by reducing ALT and CRP levels, minimizing adverse effects, and improving overall therapeutic outcomes, thereby supporting better clinical recovery.

## Disclosure statement

The author declares no conflict of interest.

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# Clinical Observation of Carteolol Hydrochloride Eye Drops Combined with Travoprost Eye Drops in the Treatment of Open-Angle Glaucoma

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**Abstract:** *Objective:* To analyze the therapeutic effects of carteolol hydrochloride (CAR) eye drops combined with travoprost (TRA) eye drops in the treatment of open-angle glaucoma (OAG). *Methods:* A total of 72 OAG patients (87 eyes) hospitalized between October 2020 and October 2023 were randomly divided into two groups. The combination group received CAR and TRA eye drops, while the control group received CAR eye drops alone. Treatment outcomes were compared in terms of total efficacy rate, visual acuity, intraocular pressure, visual function indicators, hemodynamic parameters, and ocular surface damage indicators. *Results:* The combination group showed a higher total efficacy rate compared to the control group. After 3 months of treatment, the combination group had better visual acuity, lower intraocular pressure, higher mean sensitivity, lower mean defect, lower resistance index, and higher end-diastolic velocity and peak systolic velocity compared to the control group ( $P < 0.05$ ). Additionally, the combination group exhibited higher corneal fluorescein staining scores, shorter tear breakup time, and lower Schirmer tear test values compared to the control group ( $P < 0.05$ ). *Conclusion:* The combination of CAR and TRA eye drops improves visual acuity, effectively reduces intraocular pressure, enhances visual function, regulates ocular hemodynamics, and mitigates ocular surface damage in OAG patients, demonstrating superior therapeutic efficacy.

**Keywords:** Carteolol hydrochloride eye drops; Travoprost eye drops; Open-angle glaucoma; Visual acuity; Intraocular pressure

**Online publication:** November 28, 2024

## 1. Introduction

The primary cause of glaucoma is elevated intraocular pressure (IOP), which leads to optic nerve damage and subsequent manifestations such as intraocular ischemia, vision loss, and blurred vision<sup>[1]</sup>. Open-angle glaucoma (OAG) is a common subtype of glaucoma characterized by symptoms of glaucoma despite an open anterior chamber angle. OAG develops gradually, with complex etiological factors such as hemodynamic abnormalities,

genetic predisposition, and improper eye use. These factors disrupt the integrity of the retinal nerve fiber layer, cause significant optic disc cupping, and may even lead to blindness in severe cases.

Carteolol hydrochloride (CAR) eye drops are commonly used in the treatment of OAG. They block  $\beta_2$ -adrenergic receptors located in the epithelial cells of the ciliary muscle region, thereby regulating aqueous humor secretion and controlling IOP. CAR eye drops have strong affinity and exhibit sympathomimetic effects, offering high safety during use <sup>[2]</sup>. However, the efficacy of CAR eye drops as a monotherapy is limited and cannot fully restore ocular physiological function.

Travoprost (TRA) eye drops, derived from prostaglandin analogs, activate prostaglandin F2 $\alpha$  receptors (FP receptors) to inhibit the uveoscleral pathway and promote aqueous humor outflow. This increases the space between ciliary muscles, achieving IOP reduction. This study included 72 OAG patients (87 eyes) to evaluate the therapeutic effects of CAR combined with TRA eye drops.

## **2. Materials and methods**

### **2.1. General information**

A total of 72 patients with open-angle glaucoma (OAG), accounting for 87 eyes, were treated between October 2020 and October 2023 and were randomly divided into two groups using a random number table.

Combination group: 36 patients (42 eyes), including 21 males (25 eyes) and 15 females (17 eyes). Six cases involved both eyes and 30 cases involved one eye. Patient ages ranged from 27 to 55 years, with a mean age of  $38.65 \pm 4.19$  years. The duration of illness ranged from 2 to 17 months, with a mean duration of  $9.85 \pm 1.75$  months.

Control group: 36 patients (45 eyes), including 22 males (27 eyes) and 14 females (18 eyes). Nine cases involved both eyes and 27 cases involved one eye. Patient ages ranged from 25 to 58 years, with a mean age of  $38.70 \pm 4.23$  years. The duration of illness ranged from 1 to 18 months, with a mean duration of  $10.13 \pm 1.82$  months.

No statistically significant differences were found between the two groups regarding baseline data ( $P > 0.05$ ).

Inclusion criteria: Open anterior chamber angle, intraocular pressure  $> 20$  mmHg, with symptoms such as optic disc cupping and retinal fiber layer damage; suitability for eye drop treatment; complete clinical data; normal mental status; informed consent and agreement to participate.

Exclusion criteria: Presence of other ophthalmic diseases; liver or kidney dysfunction; immunological diseases or malignancies; psychiatric disorders; withdrawal from the study.

### **2.2. Methods**

- (1) Control group: Treated with CAR eye drops (manufactured by China Otsuka Pharmaceutical Co., Ltd., approval number H10970025, 5 mL: 0.1 g). One drop was applied twice daily for 3 months.
- (2) Combination group: In addition to CAR eye drops, patients were given TRA eye drops (manufactured by ALCON Cusi, S.A., import license number H20181024, 2.5 mL: 0.1 mg). One drop was applied once daily at bedtime for 3 months.

### **2.3. Observation indicators**

- (1) Visual acuity and intraocular pressure: Visual acuity was assessed using a standard international vision chart, while intraocular pressure was measured using a non-contact tonometer. Patients were instructed

to focus on the red indicator inside the instrument, with adjustments made to ensure proper focus and automatic measurement of intraocular pressure values.

- (2) Visual function indicators: A fully automated perimeter was used in a darkroom to assess the visual field, calculating mean sensitivity (MS) and mean defect (MD).
- (3) Hemodynamic indicators: Central retinal artery resistance index (RI), end-diastolic velocity (EDV), and peak systolic velocity (PSV) were assessed using color Doppler ultrasonography.
- (4) Ocular surface damage indicators:
  - (a) Corneal fluorescein staining (FLs): Fluorescein dye was applied to the corneal area to assess epithelial cell damage. A 4-grade scoring system (0–3) was used, where 0 indicated no staining and 3 indicated ulceration.
  - (b) Tear breakup time (BUT): Fluorescein sodium solution was instilled into the conjunctival sac. Patients blinked four times and then gazed straight ahead. The time from the last blink to the appearance of a black spot on the cornea was recorded as BUT. A value  $\geq 10$  seconds indicated tear film stability.
  - (c) Schirmer tear test (STT): Standard filter paper strips were folded and placed in the outer third of the conjunctival sac, with the patient's eyes closed for 5 minutes. The strip was removed, and wetting  $> 10$  mm was considered positive.

The above indicators were assessed before and after 3 months of treatment.

## 2.4. Evaluation criteria for efficacy

- (1) Significant effect: Intraocular pressure reduction of 5.1–10.0 mmHg.
- (2) Initial effect: Intraocular pressure reduction of 1.0–5.0 mmHg.
- (3) No effect: Intraocular pressure reduction  $< 1.0$  mmHg, or an increase in intraocular pressure.

## 2.5. Statistical analysis

Data were analyzed using SPSS 28.0 software. Continuous data were expressed as mean  $\pm$  standard deviation (SD) and analyzed using *t*-tests. Categorical data were expressed as [*n* (%)] and analyzed using chi-squared tests. Statistical significance was set at  $P < 0.05$ .

## 3. Results

### 3.1. Comparison of overall effectiveness rates between groups

**Table 1** shows that the overall effectiveness rate was significantly higher in the combination group compared to the control group ( $P < 0.05$ ).

**Table 1.** Comparison of overall effectiveness rate between groups [*n* (%)]

Group	Eyes	Significant effect	Initial effect	No effect	Total effective rate
Combination	42	21 (50.00)	18 (42.86)	3 (7.14)	39 (92.86)
Control	45	20 (44.44)	15 (33.33)	10 (22.22)	35 (77.78)
$\chi^2$	-	-	-	-	3.887
<i>P</i>	-	-	-	-	0.049

### 3.2. Comparison of visual acuity and intraocular pressure between groups

Before treatment, visual acuity and intraocular pressure levels were comparable between the two groups ( $P > 0.05$ ). After 3 months of treatment, the combination group showed significantly better visual acuity and lower intraocular pressure compared to the control group ( $P < 0.05$ ), as shown in **Table 2**.

**Table 2.** Comparison of visual acuity and intraocular pressure between groups before and after treatment (mean  $\pm$  SD)

Group	Eyes	Visual acuity		Intraocular pressure (mmHg)	
		Before	After	Before	After
Combination	42	2.45 $\pm$ 0.39	4.52 $\pm$ 0.40	23.89 $\pm$ 3.16	18.27 $\pm$ 2.05
Control	45	2.46 $\pm$ 0.31	4.08 $\pm$ 0.37	23.92 $\pm$ 3.18	20.97 $\pm$ 2.11
<i>t</i>	-	0.133	5.330	0.044	6.047
<i>P</i>	-	0.895	0.000	0.965	0.000

### 3.3. Comparison of visual function indicators between groups

Before treatment, the visual function indicators were comparable between the two groups ( $P > 0.05$ ). After 3 months of treatment, the combination group had significantly better visual function indicators than the control group ( $P < 0.05$ ), as shown in **Table 3**.

**Table 3.** Comparison of visual function indicators between groups before and after treatment (mean  $\pm$  SD, dB)

Group	Eyes	MS		MD	
		Before	After	Before	After
Combination	42	13.65 $\pm$ 2.18	18.69 $\pm$ 2.24	13.71 $\pm$ 2.05	9.42 $\pm$ 1.56
Control	45	13.69 $\pm$ 2.27	16.02 $\pm$ 2.17	13.74 $\pm$ 2.09	11.56 $\pm$ 1.67
<i>t</i>	-	0.084	5.646	0.068	6.165
<i>P</i>	-	0.933	0.000	0.946	0.000

### 3.4. Comparison of hemodynamic indicators between groups

Before treatment, the hemodynamic indicators were similar between the two groups ( $P > 0.05$ ). After 3 months of treatment, the combination group showed significantly better hemodynamic indicators than the control group ( $P < 0.05$ ), as shown in **Table 4**.

**Table 4.** Comparison of hemodynamic indicators between groups before and after treatment (mean  $\pm$  SD)

Group	Eyes	RI		EDV (cm/s)		PSV (cm/s)	
		Before	After	Before	After	Before	After
Combination	42	0.77 $\pm$ 0.18	0.61 $\pm$ 0.15	7.88 $\pm$ 1.29	10.58 $\pm$ 1.43	2.72 $\pm$ 0.53	3.77 $\pm$ 0.61
Control	45	0.79 $\pm$ 0.21	0.71 $\pm$ 0.19	7.84 $\pm$ 1.32	9.17 $\pm$ 1.39	2.74 $\pm$ 0.50	3.11 $\pm$ 0.59
<i>t</i>	-	0.475	2.712	0.143	4.663	0.181	5.129
<i>P</i>	-	0.636	0.008	0.887	0.000	0.857	0.000



### 3.5. Comparison of ocular surface damage indicators between groups

Before treatment, the ocular surface damage indicators were comparable between the two groups ( $P > 0.05$ ). After 3 months of treatment, the combination group showed significantly better results than the control group ( $P < 0.05$ ), as shown in **Table 5**.

**Table 5.** Comparison of ocular surface damage indicators between groups before and after treatment (mean  $\pm$  SD)

Group	Eyes	FLs (point)		BUT (s)		STT (mm)	
		Before	After	Before	After	Before	After
Combination	42	2.12 $\pm$ 0.57	2.81 $\pm$ 0.39	6.78 $\pm$ 1.19	5.81 $\pm$ 0.73	7.44 $\pm$ 1.17	6.81 $\pm$ 0.82
Control	45	2.14 $\pm$ 0.53	2.55 $\pm$ 0.31	6.80 $\pm$ 1.21	6.19 $\pm$ 0.78	7.49 $\pm$ 1.24	7.18 $\pm$ 0.76
<i>t</i>	-	0.170	3.454	0.078	2.342	0.193	2.184
<i>P</i>	-	0.866	0.001	0.938	0.022	0.847	0.032

## 4. Discussion

The pathological manifestations of open-angle glaucoma (OAG) include elevated intraocular pressure (IOP) and optic nerve damage. The underlying mechanisms are as follows:

- (1) Mechanical theory: Elevated IOP disrupts axonal transport, leading to rapid apoptosis of retinal ganglion cells, optic nerve atrophy, and visual field defects.
- (2) Vascular theory: Damage to ocular vasculature causes impaired blood supply, resulting in optic nerve degeneration and altered ocular blood flow parameters, leading to severe ischemia of the optic nerve<sup>[3]</sup>.

Based on these mechanisms, IOP-lowering treatments are essential to slow the progression of visual function damage and alleviate symptoms in OAG patients.

CAR eye drops are one of the treatment options for OAG. They reduce aqueous humor production, effectively controlling IOP<sup>[4]</sup>. As a non-selective  $\beta_2$  receptor blocker, CAR eye drops exhibit a high affinity for  $\beta$  receptors, similar to adrenaline agonists, and avoid side effects like reduced heart rate, ensuring high safety during treatment. TRA eye drops activate FP receptors, enhancing receptor activity to relax ciliary muscles and facilitate aqueous humor outflow<sup>[5]</sup>. This helps address aqueous humor drainage obstruction, reducing its accumulation and pressure on the ocular wall, thus preventing optic nerve atrophy and preserving visual fields and acuity.

The results indicate that the total effectiveness rate in the combination group (92.86%) was significantly higher than in the control group (77.78%) ( $P < 0.05$ ). This aligns with findings by Lian *et al.*<sup>[6]</sup>, supporting the reliability and validity of the present study. After 3 months of treatment, the combination group demonstrated better visual acuity, lower IOP, higher MS, and lower MD levels compared to the control group ( $P < 0.05$ ).

The superior outcomes of the combination therapy can be attributed to the pharmacokinetics of TRA eye drops. Administered topically, TRA components are widely distributed within corneal stromal tissue, increasing drug concentration in the affected areas and enhancing bioavailability<sup>[7]</sup>. Corneal epithelial esterases continuously hydrolyze the drug, producing a significant amount of free prostaglandin acid, which dilates outflow pathways in the sclera and cornea, degrades extracellular matrix, and relaxes ciliary muscles. This increases aqueous humor outflow and reduces IOP<sup>[8]</sup>. Combined with CAR eye drops, this treatment protects optic nerve function, restores visual acuity, and effectively lowers IOP, yielding superior therapeutic outcomes.

The combination group demonstrated lower RI levels and higher EDV and PSV levels compared to the control group ( $P < 0.05$ ). TRA eye drops strongly activate prostaglandin receptors, dilating ocular capillaries and restoring blood flow. Additionally, the drug enhances vascular endothelial growth factor activity, accelerating neovascularization<sup>[9]</sup>. When combined with CAR eye drops, the treatment enhances localized effects, synergistically improving anterior chamber lymphatic circulation and ocular hemodynamics.

The combination group exhibited higher FLs scores, shorter BUT, and lower STT values compared to the control group ( $P < 0.05$ ). The combination therapy improved tear film stability and increased tear secretion, moisturizing the ocular surface and alleviating irritation to prevent ocular surface damage. Furthermore, the treatment expanded small ocular blood vessels, regulated microcirculation, and improved ocular tissue metabolism, thus protecting the ocular surface<sup>[10]</sup>.

## 5. Conclusion

In conclusion, the combination of CAR and TRA eye drops significantly improves visual acuity and IOP in OAG patients. It comprehensively enhances visual function and hemodynamic indicators while preventing ocular surface damage. This treatment demonstrates notable clinical efficacy and offers significant advantages in therapeutic application.

## Disclosure statement

The author declares no conflict of interest.

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# Application of Multidisciplinary Collaborative Interventions in the Early Rehabilitation of Patients with Hemorrhagic Stroke and Kinesiophobia

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**Abstract:** *Objective:* This study aims to explore the role of multidisciplinary collaborative interventions in the early rehabilitation of patients with hemorrhagic stroke and kinesiophobia. *Methods:* Using a convenience sampling method, 100 patients with hemorrhagic stroke and kinesiophobia admitted to the Department of Neurology at Nantong First People's Hospital between January 2022 and December 2023 were selected as subjects. Fifty patients admitted between January 2022 and January 2023 were assigned to the control group, while 50 patients admitted between February 2023 and December 2023 were assigned to the experimental group. The control group received conventional care, while the experimental group received multidisciplinary collaborative interventions provided by a team consisting of neurologists, rehabilitation therapists, psychological counselors, and nurses. The study evaluated the differences in emotional state (using the Hospital Anxiety and Depression Scale, HAD), kinesiophobia level (using the Tampa Scale for Kinesiophobia, TSK), functional recovery (using the modified Rankin Scale, mRS), and daily living abilities (using the Barthel Index, BI) before and after intervention. *Results:* After the intervention, the HAD scores in the experimental group were significantly lower than those in the control group ( $P < 0.05$ ). The TSK scores in the experimental group were also significantly lower than in the control group ( $P < 0.05$ ), while mRS and BI scores showed significant improvement compared to the control group ( $P < 0.05$ ). *Conclusion:* Multidisciplinary collaborative interventions have significant effects in reducing kinesiophobia, promoting functional recovery, and improving the quality of life in patients with hemorrhagic stroke.

**Keywords:** Hemorrhagic stroke; Kinesiophobia; Multidisciplinary collaborative interventions; Early rehabilitation

**Online publication:** November 28, 2024

# 1. Introduction

Hemorrhagic stroke refers to non-traumatic bleeding caused by ruptured cerebral blood vessels, including intracerebral hemorrhage and subarachnoid hemorrhage, accounting for 20%–40% of all strokes <sup>[1]</sup>. In China, the proportion of hemorrhagic strokes reaches as high as 47.6% <sup>[2]</sup>. Stroke often leaves varying degrees of neurological deficits, and early rehabilitation has been evidence-based as the most effective method to reduce disability rates, making it the preferred rehabilitation approach for stroke patients <sup>[3]</sup>. Due to pain, fear of rebleeding, anxiety, and other reasons, stroke patients often avoid turning over, coughing, early mobilization, rehabilitation therapy, and exercise <sup>[4]</sup>, which subsequently affects their recovery.

Kinesiophobia refers to a specific psychological phenomenon characterized by marked resistance and fear of movement due to fear of activity <sup>[5]</sup>. This concept was first applied to pain patients <sup>[6]</sup>, and it has been shown that kinesiophobia is a more critical factor than pain in determining physical activity levels <sup>[7]</sup>. Research on kinesiophobia has been more extensive in postoperative patients, and in recent years, it has also been studied in other diseases. However, there is limited research on hemorrhagic stroke. Building on research from other disciplines, this study implemented multidisciplinary interventions for patients with hemorrhagic stroke and kinesiophobia, achieving favorable results.

# 2. Materials and methods

## 2.1. General information

Using a convenience sampling method, 100 patients with hemorrhagic stroke and kinesiophobia who met the inclusion criteria and were admitted to the Department of Neurology at Nantong First People's Hospital between January 2022 and December 2023 were selected as study subjects. General information is shown in **Table 1**.

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

Group	<i>n</i>	Gender		Age				Education level			Occupation		
		M	F	< 45	45–65	66–85	> 85	< PS	SS	> U	Unempl	Retd	Employ
Control	45	30	15	5	12	18	10	8	25	12	7	23	15
Experimental	45	28	17	6	14	14	11	6	22	17	6	25	14
$\chi^2 / Z$	-	0.312		0.275				1.003			0.835		
<i>P</i>	-	0.652		0.863				0.825			0.785		

Abbreviations: M, male; F, female; PS, primary school; SS, secondary school; U, university; Unempl, unemployed; Retd, retired; Employ, employed.

Inclusion criteria: (1) Confirmed diagnosis of intracerebral hemorrhage or subarachnoid hemorrhage; (2) Presence of neurological deficits; (3) TSK-11 score indicating kinesiophobia <sup>[8]</sup>; (4) Informed consent provided and voluntary participation in the study.

Exclusion criteria: (1) Patients with impaired consciousness unable to cooperate; (2) Patients with severe organic diseases.

Informed consent forms were signed by all participants who met the inclusion and exclusion criteria.



## 2.2. Study methods

### 2.2.1. Formation of a multidisciplinary collaborative team

The multidisciplinary intervention team for kinesiophobia was led by the department chief and head nurse and included: one chief neurologist, one attending physician, one resident physician, one rehabilitation therapist (mid-level or above), one psychological counselor (mid-level or above), and 2–3 nurses (senior nurses with over five years of experience in neurology).

### 2.2.2. Development of the preliminary intervention plan

#### 2.2.2.1. Literature review

Keywords such as “hemorrhagic stroke,” “stroke rehabilitation,” “TSK-11 scale,” “kinesiophobia,” “Hemorrhagic Stroke,” “Kinesiophobia,” and “Stroke Rehabilitation” were searched in major domestic and international databases. Filters included studies published in the past five years, in Chinese or English, and categorized as journal articles, theses, conference papers, guidelines, or consensus documents. Relevant information was extracted based on the objectives, methods, results, and conclusions of the literature to provide a theoretical basis for this study’s plan design.

#### 2.2.2.2. Joint plan development

- (1) Neurologists: Develop treatment and pain/sedation (if necessary) protocols.
- (2) Neurologists and rehabilitation therapists: Jointly develop early rehabilitation plans.
- (3) Psychological counselors: Conduct psychological evaluations and interventions.
- (4) Rehabilitation therapists and nurses: Guide and assess rehabilitation exercises.
- (5) Nurses: Provide health education, collect and analyze data, and support intervention implementation.
- (6) Head nurse: Coordinate the implementation of the plan and oversee progress.

A detailed diagram of the intervention process is shown in **Table 2** below.

**Table 2.** Intervention responsibilities and measures

Interveners	Intervention measures	Timing and frequency
Nurses	Use the TSK-11 scale to evaluate kinesiophobia, provide routine health education on diet and sleep, show educational videos, and guide family members in supporting and encouraging the patient. Collect all assessment scores and scales, collaborating with doctors, counselors, and therapists.	Post-48 hours after hemorrhage onset, once neurological deficits stabilize
Psychological counselors	Assess the patient’s psychological state and understanding of early rehabilitation. Identify the causes of kinesiophobia, provide positive psychological support, and intervene in negative mindsets.	Within 24 hours of admission, 3 times per week
Ward doctors	Manage pain based on the underlying causes of headaches, such as elevated intracranial pressure or blood-induced meningeal irritation. Administer appropriate analgesics and, if necessary, combine sedatives and analgesics per physician orders.	From admission, throughout hospitalization
Rehabilitation therapists	Implement early bedside rehabilitation, including aerobic breathing exercises, proper limb positioning, bed mobility, sitting/standing balance training, gait training, and sit-to-stand transitions.	Gradual increase from small sessions, up to twice daily, 30 minutes per session

### 2.2.3. Training and evaluation

The intervention plan underwent team-wide training, conducted 1–2 times weekly for 45 minutes per session. A

post-training evaluation was conducted, requiring a passing score of 80 or higher. After two weeks of training, all team members passed the assessment and were familiarized with the intervention plan.

## **2.2.4. Implementation of the plan**

### **2.2.4.1. Control group intervention methods**

The control group received routine neurological care for hemorrhagic stroke, including bed rest, functional limb positioning, distribution of stroke rehabilitation manuals, and explanations of early rehabilitation significance and methods using visual aids (posters, videos). Patients and families were guided in performing active and passive limb exercises daily, 20–30 minutes per session, progressing gradually until discharge.

### **2.2.4.2. Experimental group intervention methods**

- (1) Post-48 hours of admission: Once neurological deficits stabilized, bedside rehabilitation began. Responsibility nurses scored patients on the TSK-11 scale. A score  $>26$  indicated kinesiophobia<sup>[9]</sup>, and the results were shared with the multidisciplinary team.
- (2) Psychological support: Counselors assessed patients' psychological states and knowledge of early rehabilitation, identified causes of kinesiophobia, and provided psychological support to address negative mindsets.
- (3) Pain management: For severe headaches, appropriate analgesics were administered per the underlying cause, such as diuretics for intracranial pressure reduction or sedative-analgesic combinations per physician orders<sup>[10]</sup>.
- (4) Rehabilitation training: Therapists guided progressive bedside rehabilitation exercises, starting with low-intensity activities and gradually increasing to twice daily, 30 minutes per session, as tolerated<sup>[11,12]</sup>.
- (5) Routine education: Nurses provided daily health education, played videos in wards, guided families on supportive care, and collected evaluation scores while collaborating with other team members.

## **2.3. Evaluation tools**

- (1) Hospital Anxiety and Depression Scale (HAD): A 14-item scale with two dimensions (anxiety and depression). Each item is scored from 0–3, with a total score of 42. Higher scores indicate greater severity.
- (2) Tampa Scale for Kinesiophobia (TSK): The TSK-11 scale is a simplified 11-item version of the original TSK, scored from 11 to 44. Higher scores indicate greater kinesiophobia<sup>[13]</sup>.
- (3) Modified Rankin Scale (mRS): A clinical tool to assess disability and quality of life in stroke patients. Scores  $\leq 2$  indicate functional independence, while scores  $\geq 3$  indicate some level of disability.
- (4) Barthel Index (BI): Measures daily living abilities with 10 items scored from 0–10, for a total score of 100. Higher scores reflect greater independence.

## **2.4. Data collection methods**

Before the study, multidisciplinary team members were trained on scoring scales and assessment methods. Responsibility nurses completed HAD, TSK-11, mRS, and BI assessments within 48 hours of admission and on the day before discharge. Assessments were conducted face-to-face, with patients completing the scales independently or assisted by nurses for illiterate or physically impaired individuals. The response rate was 100%.

## 2.5. Statistical methods

SPSS 22.0 software was used for analysis. Statistical methods included chi-squared tests, *t*-tests, and normality tests. The significance level was set at  $\alpha = 0.05$ .

## 3. Results

There were no statistically significant differences between the two groups in gender, age, occupation, or education level ( $P > 0.05$ ), as shown in **Table 1**. Scores for HAD, TSK-11, mRS, and BI before and after the intervention are presented in **Table 2**.

**Table 2.** Comparison of HAD, TSK-11, mRS, and BI scores between the two groups before and after the intervention

Group	n	HAD score		TSK-11 score		mRS score		BI score	
		Before	After	Before	After	Before	After	Before	After
Control	45	36.02 ± 2.17	23.11 ± 1.87	38.05 ± 3.08	30.02 ± 4.23	3.02 ± 0.24	2.58 ± 0.12	50.29 ± 2.21	70.23 ± 3.01
Experimental	45	36.11 ± 2.15	15.32 ± 1.05	37.23 ± 4.02	23.12 ± 5.02	3.09 ± 0.32	2.01 ± 0.04	50.11 ± 2.24	80.11 ± 3.35
<i>t</i>	-	2.353	1.023	-1.315	-5.672	0.382	1.041	4.367	5.765
<i>P</i>	-	0.065	< 0.001	0.176	< 0.001	0.625	< 0.001	0.189	< 0.001

## 4. Discussion

### 4.1. The significance of multidisciplinary team collaboration in early rehabilitation of hemorrhagic stroke patients with kinesiophobia

Patients with kinesiophobia following hemorrhagic stroke often exhibit avoidance behaviors towards rehabilitation exercises and daily activities due to pain and fear of recurrent bleeding, which hinders early rehabilitation. A multidisciplinary team, comprising doctors, nurses, and rehabilitation therapists, provides patients with positive emotional support, personalized rehabilitation plans, and detailed health guidance. This collaborative approach encourages active participation in early rehabilitation, thereby reducing the degree of disability and improving patients' self-care abilities.

### 4.2. Analysis of the multidisciplinary team intervention content

#### 4.2.1. Multidisciplinary team collaboration improves emotional well-being of hemorrhagic stroke patients

It is widely acknowledged that there is a critical period after stroke during which rehabilitation can promote favorable neuroplasticity and suppress maladaptive neuroplasticity in the infarct area. However, this rehabilitation effect diminishes significantly over time<sup>[14]</sup>. Stroke patients often experience negative emotions such as anxiety and depression due to pain and hemiplegia. Studies have shown that post-stroke anxiety occurs in up to 50.1% of patients, while depression affects as many as 56.6%. These negative emotions reduce treatment adherence and cooperation, thereby hindering recovery progress<sup>[15]</sup>. Early intervention by psychologists and attending doctors can promptly identify and address these negative emotions, alleviating tension and fear, reducing kinesiophobia, and enhancing motivation for rehabilitation exercises.

#### **4.2.2. Multidisciplinary team collaboration monitors kinesiophobia throughout the rehabilitation process**

Multidisciplinary team collaboration enhances the continuity and comprehensiveness of healthcare services<sup>[16]</sup>. From the moment patients are admitted, psychologists and rehabilitation therapists are involved in the entire rehabilitation process. This ensures that patients receive timely support and solutions to any issues that arise, maximizing their active participation<sup>[17]</sup>. This integrated approach significantly boosts patients' confidence and determination to engage in rehabilitation.

#### **4.2.3. Multidisciplinary collaboration as a key measure to improve self-care abilities**

A multidisciplinary team provides thorough evaluations of patients' conditions, promptly intervenes in negative emotions, and offers guidance and support. Rehabilitation therapists develop individualized rehabilitation plans and implement exercises tailored to patients' needs. By maintaining patient dignity and encouraging them to utilize their residual abilities, the team helps improve patients' self-care capacities.

### **5. Conclusion**

Multidisciplinary team collaboration effectively reduces kinesiophobia in hemorrhagic stroke patients, fosters early and active participation in rehabilitation exercises, shortens hospital stays, decreases disability, and enhances self-care abilities. This approach offers comprehensive and professional care for patients with hemorrhagic stroke and kinesiophobia. However, due to the lack of long-term follow-up results and the study's single-center design, future studies should include multi-center research and extended follow-up periods to evaluate long-term outcomes.

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### **Disclosure statement**

The authors declare no conflict of interest.

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# Analysis of the Current Filing Status of Traditional Chinese Medicine Preparations Using Traditional Technology in Medical Institutions of Shaanxi Province

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**Abstract:** *Objective:* To summarize and analyze the application of traditional technology in preparing traditional Chinese medicine (TCM) preparations in medical institutions in Shaanxi Province after implementing the “Implementation Rules for the Record Management of Traditional Chinese Medicine Preparations in Medical Institutions in Shaanxi Province (Trial)” (“Implementation Rules”), and to provide a reference for the filing of TCM preparations. *Methods:* The TCM preparations recorded by medical institutions in Shaanxi Province since March 2019 were statistically summarized. The filing status was comprehensively and systematically analyzed based on the number of institutions and preparations, the ratio of commissioned to self-production, dosage form distribution, and the level of medical institutions. *Results:* Since implementing the Implementation Rules, a total of 479 TCM preparations have been filed in the province. Among these, 262 were commissioned for production, and 217 were self-produced, covering 17 dosage forms such as granules, pills, capsules, mixtures, and powders. A total of 86 medical institutions have filed preparations, most of which are located in Xi'an, Xianyang, and Weinan, with these three cities accounting for the largest number of filings. *Conclusion:* The policy on the TCM preparation filing system has been widely recognized and deeply implemented in Shaanxi Province. Third-level medical institutions are the primary contributors to preparation filings. Regional differences exist in the development of preparation filing, indicating significant potential for further growth in the province's filing efforts.

**Keywords:** Shaanxi Province; Medical institutions; Traditional Chinese medicine preparations; Current filing situation

**Online publication:** November 27, 2024

# 1. Introduction

Pharmaceutical preparations in medical institutions refer to self-used, fixed-prescription formulations that are not commercially available and must be prepared by medical institutions based on their clinical needs, with the approval of relevant national administrative departments <sup>[1]</sup>. These preparations are divided into two categories: chemical preparations and traditional Chinese medicine preparations <sup>[2]</sup>. Among these, traditional Chinese medicine preparations in medical institutions represent a unique form of traditional Chinese medicine preparation in China. They are produced using safe and effective fixed prescriptions based on traditional Chinese medicine theory and extensive clinical application experience <sup>[3]</sup>.

The development of traditional Chinese medicine is an indispensable part of China's medical and healthcare system. To better inherit and promote traditional Chinese medicine, ensure its sustainable development, and safeguard the physical and mental health of the Chinese people, the Standing Committee of the National People's Congress promulgated the "Law of the People's Republic of China on Traditional Chinese Medicine" on December 25, 2016 <sup>[4]</sup>. Article 31 of this law states: "The state encourages medical institutions to prepare and use traditional Chinese medicine preparations based on their clinical needs, supports the preparation of traditional Chinese medicine preparations using traditional techniques, and promotes the development of new traditional Chinese medicine drugs based on these preparations." Article 32 specifies: "Traditional Chinese medicine preparations made by medical institutions must obtain preparation approval numbers as prescribed by law. However, preparations using only traditional techniques may be produced after filing with the drug supervision and administration department of the provincial, autonomous region, or municipal government where the medical institution is located, without the need to obtain an approval number."

On February 12, 2018, the former General Administration of the Food and Drug Administration issued the "Announcement on the Implementation of Filing Management for the Preparation of Traditional Chinese Medicine Preparations by Medical Institutions Using Traditional Techniques" (No. 19, 2018) <sup>[5]</sup> (hereinafter referred to as the "Filing Announcement"). This announcement clearly defined the scope of "traditional techniques for preparing traditional Chinese medicine preparations," outlined the materials required for filing, and introduced "three exemptions and one strengthening" (exemption from clinical trials, exemption from efficacy and toxicity studies, and strengthening source and process control). It also distinguished traditional Chinese medicine preparation filings from registration materials, relaxed the qualifications for medical institutions to file traditional Chinese medicine preparations, and permitted commissioned production <sup>[6]</sup>.

On March 19, 2019, the Shaanxi Provincial Drug Administration and the Shaanxi Provincial Administration of Traditional Chinese Medicine jointly issued the "Implementation Rules for the Filing Management of the Preparation of Traditional Chinese Medicine Preparations by Applying Traditional Techniques in Shaanxi Provincial Medical Institutions (Trial)" <sup>[7]</sup>. This document outlined the procedures and requirements for filing traditional Chinese medicine preparations in Shaanxi medical institutions, along with the scope of their use, marking the beginning of filing practices for traditional Chinese medicine preparations in Shaanxi Province.

By analyzing filing data for traditional Chinese medicine preparations across different provinces, Sichuan Province has completed 3,168 filings, Jilin Province 1,008, Henan Province 726, Guangdong Province 402, Beijing 239, Jiangsu Province 198, Tianjin 182, and Shandong Province 138. As a major province for traditional Chinese medicine, it is worth investigating the filing situation in Shaanxi Province. This article examines the number of filings, varieties, commissioned production versus self-production, dosage forms, and other factors for medical institutions in Shaanxi Province. The goal is to provide references for improving the filing process

for traditional Chinese medicine preparations in Shaanxi Province and potentially across the country.

## 2. Methodology

- (1) Access the website of the Shaanxi Provincial Drug Administration (<https://mpa.shaanxi.gov.cn/>), navigate to the “Regulatory Information” section, and enter the “Query of Pharmaceutical Preparations Information in Medical Institutions” page. Select “Filing of Traditional Chinese Medicine Preparations” as the licensing matter and “Establishment” as the licensing type.
- (2) Access the website of the National Health Commission of the People’s Republic of China (<http://www.nhc.gov.cn/>), navigate to the “Services” → “List Query” → “Hospital Practice Registration” module in sequence.
- (3) Input the relevant information into an Excel spreadsheet to create a database titled “Filing Varieties of Traditional Chinese Medicine Preparations Prepared by Applying Traditional Techniques in Shaanxi Provincial Medical Institutions.”

## 3. Results

### 3.1. Cumulative number of filed traditional Chinese medicine preparations and filing medical institutions

As of June 27, 2024, a total of 479 traditional Chinese medicine preparations have been filed on the Shaanxi Provincial Drug Administration website. Among these, 5 were filed in 2019, 73 in 2020, 138 in 2021, 95 in 2022, 59 in 2023, and 109 between January and June 2024. The earliest filed preparation was Chuanzhi Xinnaotong Capsules, approved on July 15, 2019, and produced by the Shaanxi College of Traditional Chinese Medicine Pharmaceutical Factory, commissioned by Zhouzhi United Hospital. This marked the beginning of traditional Chinese medicine preparation filings in Shaanxi Province. These figures indicate that, following the implementation of the “Implementation Rules,” medical institutions in Shaanxi Province actively prepared and interpreted the relevant documents to proceed with filings.

A total of 131 medical institutions have applied for the filing of traditional Chinese medicine preparations. By year, there were 3 institutions in 2019, 16 in 2020, 33 in 2021, 29 in 2022, 19 in 2023, and 31 from January to June 2024. See **Table 1**.

**Table 1.** Number of filed traditional Chinese medicine preparations and cumulative number of filing medical institutions in Shaanxi Province from March 19, 2019, to June 27, 2024

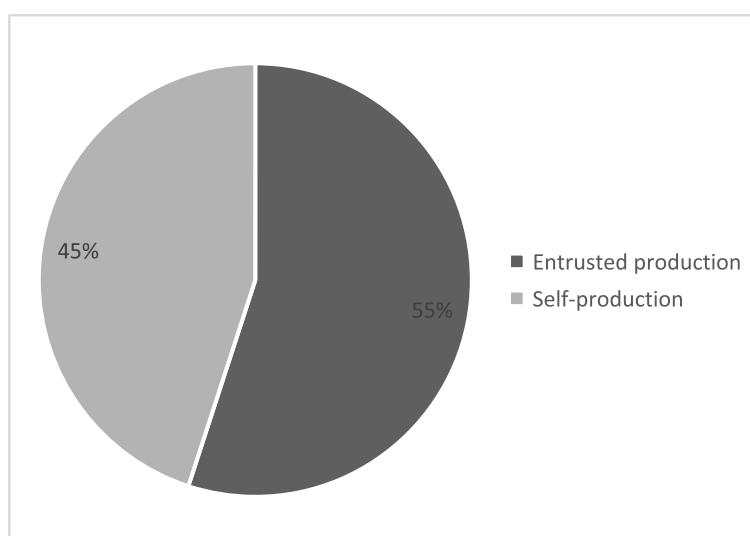
City	Number of filed preparations (pcs)							Cumulative number of filing medical institutions (pcs)						
	2019	2020	2021	2022	2023	2024	Total	2019	2020	2021	2022	2023	2024	Total
Ankang	0	0	7	0	0	0	7	0	0	1	0	0	0	1
Baoji	0	17	0	5	0	0	22	0	2	0	2	0	0	4
Hanzhong	0	3	2	15	2	1	23	0	2	1	4	2	1	10
Shangluo	0	0	3	3	0	2	8	0	0	1	1	0	1	3
Tongchuan	0	0	5	1	5	0	11	0	0	2	1	1	0	4

**Table 1 (Continued)**

City	Number of filed preparations (pcs)							Cumulative number of filing medical institutions (pcs)						
	2019	2020	2021	2022	2023	2024	Total	2019	2020	2021	2022	2023	2024	Total
Weinan	0	9	12	10	6	13	50	0	2	2	3	2	5	14
Xi'an	5	31	60	37	29	74	236	3	6	17	13	9	18	66
Xianyang	0	7	23	16	12	16	74	0	3	7	4	4	5	23
Yanan	0	0	25	8	0	0	33	0	0	1	1	0	0	2
Yulin	0	6	1	0	5	3	15	0	1	1	0	1	1	4
Total	5	73	138	95	59	109	479	3	16	33	29	19	31	131

### 3.2. Production status of filed traditional Chinese medicine preparations

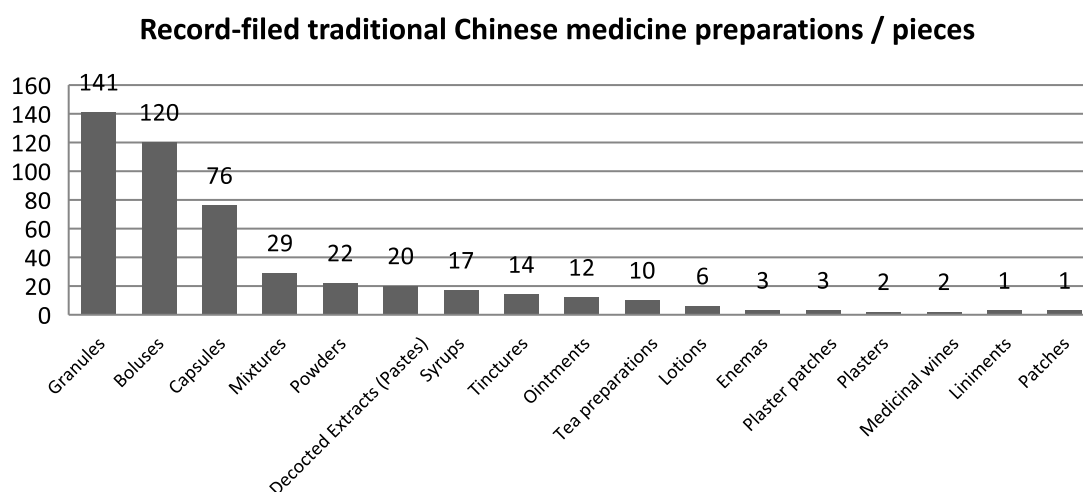
Of the filed traditional Chinese medicine preparations, 262 varieties (54.70%) were produced through commissioned production, while 217 varieties (45.30%) were self-produced. See **Figure 1**.



**Figure 1.** Entrusted production and self-production of traditional Chinese medicine preparations in Shaanxi Province

### 3.3. Dosage forms of filed traditional Chinese medicine preparations

The filed traditional Chinese medicine preparations encompass 17 dosage forms, including granules, pills, capsules, mixtures, and powders, covering most forms of traditional Chinese medicine preparations. Granules accounted for 29.44%, pills 25.05%, capsules 15.87%, and mixtures 6.05%. See **Figure 2**.

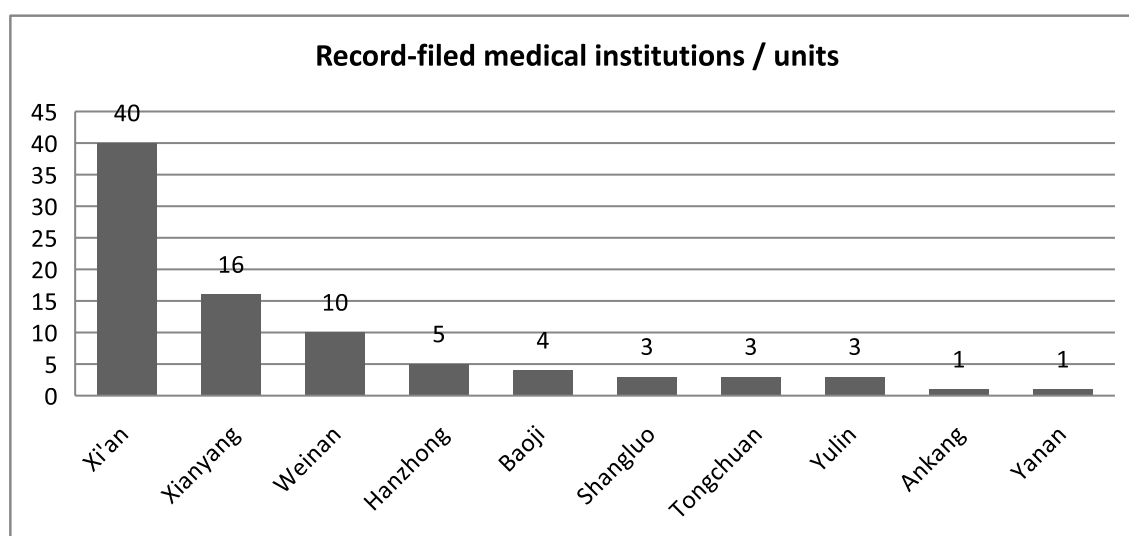


**Figure 2.** Distribution of dosage forms of filed traditional Chinese medicine preparations in Shaanxi Province (March 19, 2019–June 27, 2024)

### 3.4. Status of filing medical institutions

Geographically, significant disparities exist in the development of traditional Chinese medicine among cities and prefectures in Shaanxi Province. These differences are reflected in the number of filings and the number of filing institutions. From March 19, 2019, to June 27, 2024, of the 479 filed preparations, 236 (49.27%) were in Xi'an, 74 (15.45%) in Xianyang, and 50 (10.44%) in Weinan. Together, these cities accounted for 75.16% of all filings. See **Table 1**.

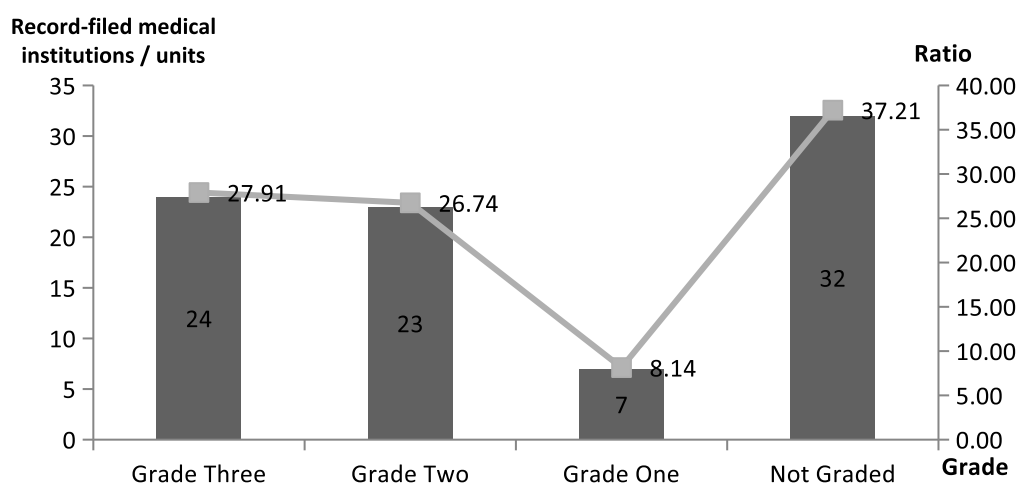
A total of 86 medical institutions in Shaanxi Province have filed traditional Chinese medicine preparations. The top three cities were Xi'an with 40 institutions (46.51%), Xianyang with 16 institutions (18.60%), and Weinan with 10 institutions (11.63%). See **Figure 3**. These figures highlight that Xi'an, Xianyang, and Weinan have made significant progress in filing traditional Chinese medicine preparations.



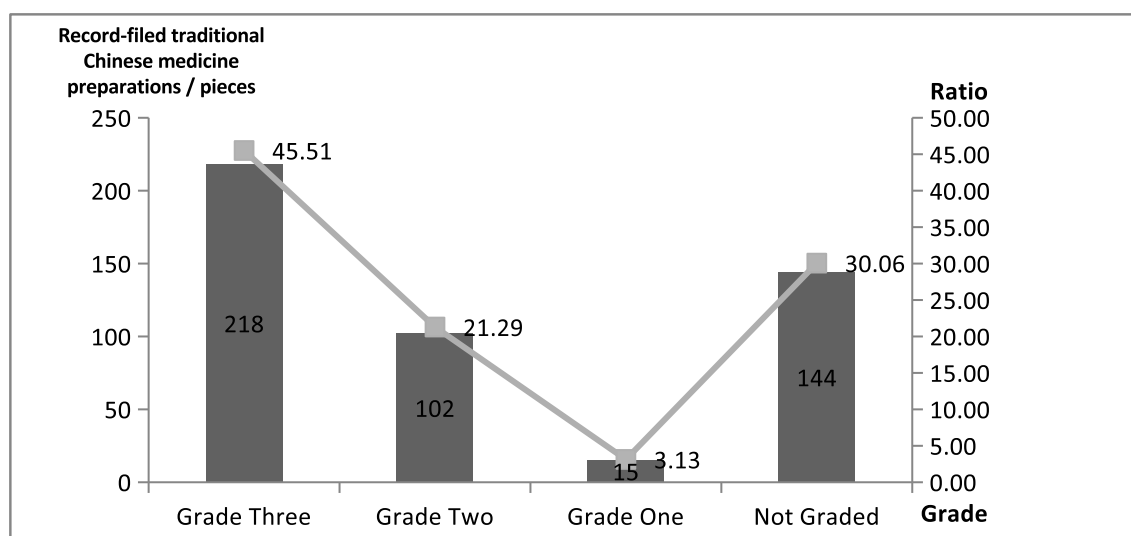
**Figure 3.** Geographic distribution of medical institutions filing traditional Chinese medicine preparations in Shaanxi Province



Among the 86 filing institutions, there were 24 tertiary medical institutions, primarily in Xi'an and Xianyang. Additionally, 23 were secondary medical institutions, 7 were primary medical institutions, and 32 were ungraded institutions. Tertiary institutions accounted for 218 filings (45.51%), secondary institutions 102 (21.29%), primary institutions 15 (3.13%), and ungraded institutions 144 (30.06%). See **Figures 4 and 5**.



**Figure 4.** Distribution of filing institutions by grade in Shaanxi Province (March 19, 2019–June 27, 2024)



**Figure 5.** Number of traditional Chinese medicine preparations filed by medical institution levels in Shaanxi Province

## 4. Discussion

Traditional Chinese medicine preparations in medical institutions are an integral part of traditional Chinese medicine. For a long time, they have played a vital role in safeguarding the physical and mental health of people in China and globally. When used rationally under the guidance of traditional Chinese medicine's foundational theories, these preparations contribute significantly to various aspects, such as establishing distinctive clinical specialties, preserving and inheriting traditional prescriptions, and transforming scientific and technological

advancements in traditional Chinese medicine.

In clinical practice, these preparations meet the needs of traditional Chinese medicine and fill gaps in the availability of marketed Chinese patent medicines. Their advantages have been particularly evident in the prevention and control of major public health events, such as novel coronavirus infections. Furthermore, traditional Chinese medicine preparations provide abundant resources and clinical experience, serving as a foundation for the research and development of new traditional Chinese medicine drugs. Based on the statistical analysis of the filing status of traditional Chinese medicine preparations in Shaanxi Province, the following conclusions and considerations are drawn:

#### **4.1. The policy of filing traditional Chinese medicine hospital preparations has gained widespread recognition in Shaanxi Province**

Since the implementation of the policy on filing traditional Chinese medicine preparations in medical institutions in Shaanxi Province on March 19, 2019, a total of 479 preparations have been filed, averaging approximately 80 filings annually. These filings involve 86 medical institutions across the province, including tertiary, secondary, primary, and ungraded institutions, as well as public and private hospitals and clinics.

Among these, ungraded medical institutions represent 37.21% of the total filing institutions, constituting the largest proportion. They are followed by tertiary (27.91%), secondary (26.74%), and primary medical institutions (8.14%). This distribution demonstrates the widespread acceptance and implementation of the traditional Chinese medicine preparation filing system in Shaanxi Province.

#### **4.2. Tertiary medical institutions are the main contributors to traditional Chinese medicine preparation filings**

Tertiary medical institutions account for 27.91% of the total filing institutions, yet the preparations filed by these institutions represent 45.51% of the total filings. This indicates that tertiary institutions play a leading role in the filing of traditional Chinese medicine preparations.

#### **4.3. Most filings of traditional Chinese medicine preparations are through commissioned production**

In Shaanxi Province, 54.70% of filed traditional Chinese medicine preparations are produced through commissioned production, representing a majority. Many of the filing institutions are relatively small, such as outpatient departments and clinics, which lack the facilities and resources required for preparation and quality inspection.

Due to these limitations, these institutions rely on commissioning qualified medical institutions or pharmaceutical manufacturers to produce and prepare traditional Chinese medicine preparations. Previous research has highlighted that up to 80% of medical institutions in Shaanxi Province face challenges related to suboptimal production environments and inadequate inspection facilities for pharmaceutical preparations. Additionally, personnel dedicated to preparation account for only 10% of pharmacy staff, and there is a notable shortage of qualified professionals. A lack of modern quality management practices further exacerbates the risk of quality issues in preparations <sup>[8]</sup>.

The “Law of the People’s Republic of China on Traditional Chinese Medicine and the Filing Announcement” stipulates that medical institutions must obtain a “Pharmaceutical Preparation License for Medical Institutions” to prepare traditional Chinese medicine preparations. Institutions without this license or lacking specific preparation

dosage forms authorized by the license may commission qualified units to handle production <sup>[4,5]</sup>.

The commissioned production model effectively supports the preparation and supply of traditional Chinese medicine preparations in medical institutions. Compared to the traditional “small workshop” production model, commissioned production ensures higher standards of quality control and safety evaluation <sup>[9]</sup>.

#### **4.4. Regional differences in the development level of traditional Chinese medicine preparation filings in Shaanxi Province**

The proportion of traditional Chinese medicine preparations filed in Xi’an, Xianyang, and Weinan cities accounts for 75.16% of the total filings in Shaanxi Province, with 76.74% of filing institutions located in these cities. This indicates significant regional disparities in the development level of traditional Chinese medicine preparation filings across the province. Uneven geographical distribution and varying quality levels of pharmaceutical preparations in medical institutions can be mitigated by establishing regional medical preparation centers, which would enhance the effective utilization of existing resources <sup>[9]</sup>. Current regional medical preparation centers in Shaanxi Province include Xi’an Chinese Medicine Encephalopathy Hospital <sup>[10]</sup>, Shaanxi Panlong Pharmaceutical Co., Ltd., and Yangling Biomedical Science and Technology Co., Ltd. <sup>[11]</sup>.

#### **4.5. Significant potential for increased filings of traditional Chinese medicine preparations in Shaanxi Province**

According to the 2022 Statistical Bulletin of the Development of Health Services in Shaanxi Province <sup>[12]</sup>, the province has 34,779 medical and health institutions, including 1,280 hospitals, 32,978 primary-level institutions, and 407 public health institutions. Leveraging the entire province’s medical resources could yield numerous proven, safe, and effective empirical prescriptions, ancient classical formulas, and modified prescriptions with extensive clinical use.

From 2019 to 2024, only 86 medical institutions applied for traditional Chinese medicine preparation filings, representing just 0.25% of all institutions. In 2019, the number of applications was only five, likely due to the system’s early-stage implementation. From 2020 onward, the number of filings exceeded 50 annually. Among the institutions submitting applications, the top three—Shaanxi Provincial Hospital of Traditional Chinese Medicine (62 filings), Yan’an Hospital of Traditional Chinese Medicine (33 filings), and the Second Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine (26 filings)—account for 25.3% of the total filings. These figures highlight the untapped potential for further filings in the province.

#### **4.6. Active policy support for traditional Chinese medicine preparation filings in Shaanxi Province**

The Filing Announcement issued by the former General Administration of the Food and Drug Administration states:

“Traditional Chinese medicine preparations prepared by medical institutions using traditional techniques include:

- (1) Solid (pills, powders, pellets, lozenges, etc.), semi-solid (ointments, plasters, etc.), and liquid (decoctions, etc.) traditional dosage forms made from Chinese herbal pieces by pulverization or only by water or oil extraction;
- (2) Granules made from Chinese herbal pieces by water extraction and capsules made from pulverized

Chinese herbal pieces;

(3) Medicated wines and tinctures made from Chinese herbal pieces by traditional extraction methods”<sup>[4]</sup>.

Subsequently, with the introduction of the “Implementation Rules (Trial),” the scope of these definitions was retained. As the filing of traditional Chinese medicine preparations progressed in Shaanxi Province, and in response to local circumstances, the “Implementation Rules (Trial)” were abolished. The “Notice of Shaanxi Provincial Drug Administration on Soliciting Public Opinions on the ‘Implementation Rules for the Filing Management of Traditional Chinese Medicine Preparations Prepared by Applying Traditional Techniques in Shaanxi Provincial Medical Institutions (Draft for Soliciting Opinions on Revision)’” (Shaanxi Drug Administration Letter [2024] No. 78)<sup>[13]</sup> was then issued.

Article 3 of the Draft for Soliciting Opinions on Revision introduced a revised definition of traditional Chinese medicine preparations. It retained the definitions outlined in (1) and (3) of the original Filing Announcement while updating (2) to include:

“Granules and capsules made from some or all of the Chinese herbal pieces by water extraction or direct pulverization.”

This enriched the connotation of traditional Chinese medicine preparations, fostering their inheritance, innovation, and development. Examples include Qutan Huoxue Tongbi Capsules, Weifukang Capsules, and Qibi Xingshen Granules.

Additionally, Shaanxi Province has implemented relevant policies regarding medical insurance payment and the dispensing of pharmaceutical preparations in medical institutions. Examples include:

- (1) The notice of Shaanxi Provincial Medical Insurance Bureau on including some therapeutic pharmaceutical preparations in medical institutions in the scope of medical insurance payment<sup>[14]</sup>.
- (2) The announcement on implementing emergency review and approval and emergency dispensing and use of pharmaceutical preparations in medical institutions for epidemic prevention and control.
- (3) The notice of the Office of Shaanxi Provincial Drug Administration on standardizing the management of dispensing and use of traditional Chinese medicine preparations in medical institutions.
- (4) The notice on further optimizing and guaranteeing the supply as well as dispensing and use of traditional Chinese medicine preparations for epidemic prevention.

These measures have facilitated the inclusion of certain therapeutic traditional Chinese medicine preparations in the Shaanxi Provincial Medical Insurance Fund’s payment scope. They have also actively promoted the dispensing and use of these preparations in medical institutions across the province, including within medical consortia.

Other provinces have introduced similar policies. For instance, Jiangxi Province allows varieties with a “Registration Approval Document for Pharmaceutical Preparations in Medical Institutions,” a “Re-registration Approval Document for Pharmaceutical Preparations in Medical Institutions,” or a “Filing Receipt for Traditional Chinese Medicine Preparations Prepared by Applying Traditional Techniques in Medical Institutions” from the Provincial Drug Administration to be dispensed in medical institutions with collaborative relationships within the province for two years. These varieties must have been used clinically for over two years with proven efficacy, safety, and stability and no serious adverse reactions<sup>[15]</sup>.

Jilin Province, similarly, has announced the first batch of 195 traditional Chinese medicine dispensing varieties. It requires that the listed preparations must have been used clinically for over three years, demonstrating efficacy, safety, and stability without serious adverse reactions. These preparations can be used

across public medical institutions within the province with collaborative relationships<sup>[16]</sup>.

These policies have reduced patients' economic burdens, encouraged medical institutions to file traditional Chinese medicine preparations, and supported the long-term development of such preparations in medical institutions<sup>[17]</sup>.

## 5. Conclusion

In conclusion, the work of filing traditional Chinese medicine preparations in medical institutions in Shaanxi Province has achieved significant results over six years. However, it is equally important to recognize the common challenges associated with the filing process in Shaanxi Province and across the country. These challenges include deficiencies in personnel, equipment, production environments, funding, and quality management within the traditional Chinese medicine preparation rooms of medical institutions. Additionally, there is a lack of intellectual property protection for traditional Chinese medicine preparations and insufficient awareness of new drug transformations<sup>[18-20]</sup>.

It is recommended that relevant governmental functional departments adopt a long-term perspective and increase investment to foster a favorable environment for the filing and management of traditional Chinese medicine preparations in medical institutions. Such efforts would contribute to the sustainable and high-quality development of outstanding traditional Chinese medicine preparations not only in Shaanxi Province but also nationwide.

## Disclosure statement

The authors declare no conflict of interest.

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# Effect of a Chest Compression Device for Scar Prevention Combined with Nurse-Patient WeChat Group on Scar Formation after Keloid Excision

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**Abstract:** *Objective:* To investigate the effect of a chest compression device for scar prevention combined with a nurse-patient WeChat group on scar formation after keloid excision. *Methods:* Forty patients with chest wall keloids who underwent keloid excision surgery at the Department of Plastic and Reconstructive Surgery, First Medical Center of PLA General Hospital from June 2022 to June 2024 were selected. They were randomly divided into two groups: the observation group (20 cases) and the control group (20 cases). Both groups underwent routine keloid excision, followed by compression therapy for 6 months. The observation group used a chest compression device, while the control group used a compression garment. Scar width, hypertrophy, and Vancouver Scar Scale (VSS) scores were compared between the two groups. *Results:* There were no significant differences between the two groups in terms of gender, age, disease course, lesion area, and lesion site ( $P > 0.05$ ). The overall effective rate in the observation group was 95.00%, significantly higher than the 65.00% in the control group, with a statistically significant difference ( $P < 0.05$ ). After a 6-month follow-up, all VSS indicators (except for pliability) in the observation group (using the chest compression device) were significantly lower than those in the control group ( $P < 0.05$ ). *Conclusion:* Compared to the traditional compression garment, the chest compression device for scar prevention is more effective in preventing scar hypertrophy after chest wall keloid excision and improving the appearance of scars. It is worth promoting for clinical application.

**Keywords:** Scar prevention; Compression device; Scar hypertrophy

**Online publication:** November 27, 2024

## 1. Introduction

Keloids are benign skin tumors, typically formed due to excessive proliferation and deposition of the extracellular matrix during the skin healing process<sup>[1,2]</sup>. This condition not only affects the patient's appearance

but can also cause functional impairments, significantly reducing their quality of life. Data shows that about 50% of keloids occur on the anterior chest wall, which is associated with the high skin tension in this area <sup>[3]</sup>. Currently, various treatments for keloids are available, including surgical excision, drug injections, silicone gel sheets, radiation therapy, and pressure therapy. While surgical excision is a commonly used primary treatment method, the risk of postoperative recurrence remains concerning, with recurrence rates ranging from 45% to 100% <sup>[4,5]</sup>. In the prevention and treatment of keloids, elastic compression has been widely adopted as a simple, safe, and cost-effective physical therapy. Its mechanism involves applying continuous pressure on the scar surface to reduce local blood flow, inhibiting fibroblast proliferation and collagen synthesis, thus effectively suppressing scar hypertrophy and promoting scar maturation <sup>[6]</sup>. In recent years, the chest compression device for scar prevention has gradually been applied in clinical practice as a new pressure therapy tool. This device can be customized according to individual differences and scar locations, providing continuous, uniform, and controllable pressure, effectively reducing scar hypertrophy and improving scar appearance. This study aims to explore the impact of a chest compression device for scar prevention on scar formation after keloid excision, offering more treatment options for clinical practice.

## **2. Materials and methods**

### **2.1. General information**

Forty patients with chest wall keloids, comprising a total of 36 lesions, who underwent keloid excision surgery at the Department of Plastic and Reconstructive Surgery of the First Medical Center of the PLA General Hospital between June 2022 and June 2024 were selected.

Inclusion criteria:

- (1) Patients with chest wall keloids treated at the Department of Plastic and Reconstructive Surgery
- (2) Age between 20 and 60 years
- (3) Clear consciousness, able to cooperate with treatment
- (4) Local patients who can return to the hospital for follow-up visits conveniently

Exclusion criteria:

- (1) Patients with severe heart, brain, liver, or kidney diseases
- (2) Patients with diabetes
- (3) Patients with cognitive impairment who cannot cooperate with treatment

### **2.2. Methods**

#### **2.2.1. Surgical method**

In this study, both groups of patients underwent standard keloid excision surgery. All surgeries were performed by the same experienced team of plastic surgeons to ensure consistency and professionalism in the surgical procedures. During surgery, the scar tissue was thoroughly excised while minimizing skin tension to reduce the risk of postoperative scar formation. Advanced cosmetic suturing techniques were used to achieve better aesthetic results during the recovery process.

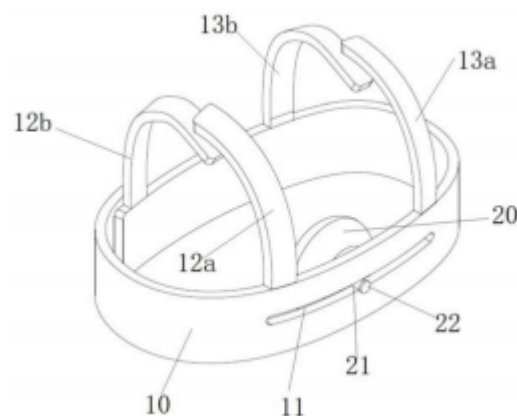
#### **2.2.2. Postoperative management**

After surgery, all patients received routine anti-infection treatment and regular wound care to reduce the risk

of postoperative infection and promote wound healing. Pressure therapy began after suture removal, which occurred 3 to 7 days postoperatively, to further prevent scar formation.

**Control group:** Traditional compression therapy and routine care were used. Photos of scar changes were taken monthly or bi-monthly to present to physicians during face-to-face consultations for timely adjustment of care plans.

**Observation group:** The scar-prevention chest compression device was used, which included a chest band and an airbag. The chest band was used to secure the patient's chest, while the airbag, shaped like a disk, was placed on the surgical incision. The rear of the airbag was connected to an air valve, which extended through a long slot on the front of the chest band to the exterior. This device simplified the structure, minimizing the compression area on the patient and focusing pressure on the surgical incision (see **Figure 1**).



**Figure 1.** Scar-prevention chest compression device

On top of routine care, a nurse-patient WeChat group was established. This care group aimed to better manage patients, provide personalized care services and promote patient recovery. Regular health education content related to the condition, including prevention and rehabilitation knowledge, was shared in the group through text, images, and videos to help patients better understand and accept the information. Patients were encouraged to ask questions, which were answered by medical staff or experienced patients. This helped reduce patients' concerns and anxiety, improving their confidence and cooperation with the treatment.

Both groups continued compression therapy for 6 months to assess the impact of different treatment methods on scar healing outcomes.

## **2.3. Observation indicators**

### **2.3.1. Efficacy rate**

Based on the degree of scar hypertrophy and patients' subjective symptoms, treatment outcomes were classified into the following categories:

- (1) Good outcome: Complete disappearance of itching and pain symptoms, flat scars, and no recurrence of the scar within 6 months.
- (2) Significant effect: Most itching and pain symptoms disappeared, with mild local scar hypertrophy. Scars were controlled, and scar thickness was reduced by 70%–80% as measured by scar 3D morphology

software <sup>[7]</sup>.

- (3) Ineffective: No reduction in itching and pain symptoms, significant hypertrophy observed, and no notable change in scar thickness compared to before.

$$\text{Efficacy rate} = (\text{Number of good outcomes} + \text{Number of significant effects}) / \text{Total number} \times 100\%.$$

### 2.3.2. Vancouver Scar Scale

The Vancouver Scar Scale (VSS) is an assessment tool used to quantify scar characteristics, with scores ranging from 0 to 15. A higher score indicates a more severe degree of scar hypertrophy. The scale includes four main components:

**Table 1.** Vancouver Scar Scale (VSS)

Evaluation criteria	Score range
Skin color	0 points: Color similar to surrounding normal skin, nearly normal
	1 point: Lighter color
	2 points: Mixed colors
	3 points: Darker color
Vascularity	0 points: Normal skin color, similar to other body parts
	1 point: Pinkish color
	2 points: Reddish color
	3 points: Purplish color
Thickness	0 points: Normal thickness
	1 point: Thickness between 0–1 mm
	2 points: Thickness between 1–2 mm
	3 points: Thickness between 2–4 mm
	4 points: Thickness over 4 mm
Pliability	0 points: Normal pliability
	1 point: Supple (deforms with minimal resistance)
	2 points: Yielding (deforms under pressure)
	3 points: Firm (resists deformation, moves in a block-like manner under pressure)
	4 points: Banding (feels like a cord, contracts when the scar stretches)
	5 points: Contracture (scar permanently shortened, leading to disability and distortion)

### 2.4. Statistical analysis

SPSS 23.0 statistical software was used for data analysis. Measurement data conforming to a normal distribution were expressed as mean  $\pm$  standard deviation (SD), and comparisons between the two groups were performed using *t*-tests. Count data were expressed as percentages (%), and comparisons between groups were performed using the  $\chi^2$  test. A *P*-value of  $< 0.05$  was considered statistically significant.



### 3. Results

#### 3.1. Comparison of baseline data between the two groups

There were no statistically significant differences between the two groups in terms of gender, age, disease duration, lesion area, or lesion site ( $P > 0.05$ ), making them comparable. See **Table 2**.

**Table 2.** Comparison of baseline data between the two groups

Group	<i>n</i>	Gender		Age (mean $\pm$ SD, years)	Average disease duration (mean $\pm$ SD, months)	Lesion area (mean $\pm$ SD, cm <sup>2</sup> )
		Male	Female			
Control	20	7	13	38.95 $\pm$ 6.52	7.20 $\pm$ 2.31	8.60 $\pm$ 4.01
Observation	20	10	10	35.85 $\pm$ 10.78	6.87 $\pm$ 2.87	9.10 $\pm$ 3.94
$\chi^2 / t$		0.921		0.113	0.401	0.398
<i>P</i>		0.337		0.273	0.691	0.693

#### 3.2. Postoperative treatment effects after 6 months in both groups

The total efficacy rate in the observation group was 95.00%, which was significantly higher than the control group's 65.00%, showing a statistically significant difference ( $P = 0.048$ ). See **Table 3**.

**Table 3.** Postoperative treatment effects after 6 months [*n* (%)]

Group	<i>n</i>	Good outcome	Significant effect	Ineffective	Total efficacy rate
Control	20	8 (40.00%)	5 (25.00%)	7 (35.00%)	13 (65.00%)
Observation	20	16 (80.00%)	3 (15.00%)	1 (5.00%)	19 (95.00%)
$\chi^2$		3.906			
<i>P</i>		0.048			

#### 3.3. Comparison of VSS scores after 6 months post-surgery

The observation group had significantly lower VSS scores in terms of skin pigmentation, vascularity, thickness, and total score compared to the control group (all  $P < 0.05$ ). However, the difference in pliability was not statistically significant ( $P > 0.05$ ). See **Table 4**.

**Table 4.** Comparison of VSS scores after 6 months post-surgery (mean  $\pm$  SD, points)

Group	Vancouver Scar Scale (VSS)				
	Pigmentation	Vascularity	Thickness	Pliability	Total score
Control	1.84 $\pm$ 0.94	1.47 $\pm$ 0.81	2.43 $\pm$ 1.10	1.57 $\pm$ 0.91	7.31 $\pm$ 2.35
Observation	1.13 $\pm$ 0.67	0.81 $\pm$ 0.58	1.51 $\pm$ 0.81	1.23 $\pm$ 0.74	4.68 $\pm$ 1.81
<i>t</i>	2.751	2.963	3.012	1.296	3.965
<i>P</i>	0.009	0.005	0.005	0.203	< 0.001

## 4. Discussion

Keloids are a pathological condition that forms due to excessive tissue repair following skin damage. The histopathological basis primarily manifests as an overaccumulation of the extracellular matrix, mainly collagen, and abnormal proliferation of fibroblasts. The anterior chest area is a common site for keloid formation, usually developing from minor skin injuries caused by various factors and progressing with noticeable symptoms such as itching, pain, or a feeling of tightness<sup>[9]</sup>. Although the exact pathogenesis of keloids is still unclear, many researchers believe that individual differences and the high tension in the chest skin are significant contributing factors<sup>[10]</sup>. Despite early postoperative radiotherapy, recurrence may still occur due to the interplay of multiple factors. The specific mechanisms of recurrence are not yet fully understood in both domestic and international research. Studies have shown that the persistent high tension in the chest area, frequent daily activities, and injuries crossing the midline make keloids more prone to proliferation, leading to a higher recurrence rate<sup>[11,12]</sup>. Some scholars suggest that tension promotes fibroblast proliferation and reduces apoptosis, inducing the synthesis of large amounts of extracellular matrix, which in turn leads to collagen fiber rearrangement and vascular proliferation. These changes collectively promote the formation and proliferation of pathological scars<sup>[13]</sup>. Therefore, reducing skin tension in the chest can help inhibit the proliferation and recurrence of keloids to some extent<sup>[14]</sup>. In clinical practice, the use of chest compression devices for preventive measures has been shown to effectively achieve elastic compression. Compared to traditional compression garments, this device allows for more precise control of pressure distribution, especially in specific areas like the scapula and chest, providing better pressure regulation.

This study suggests that in the observation group, the total efficacy rate reached 95.00%, significantly higher than the control group's 65.00%, with a statistically significant difference ( $P < 0.05$ ). After six months of follow-up, the scar scores in the observation group (using the chest compression device for keloid prevention) were lower than those in the control group across all parameters of the VSS, except for pliability, with statistically significant differences ( $P < 0.05$ ). These results indicate that the chest compression device has a significant clinical effect in preventing keloid proliferation.

## 5. Conclusion

In summary, the use of a chest compression device for preventive intervention can effectively control local pressure distribution, and inhibit excessive fibroblast proliferation and collagen deposition, thus reducing the risk of scar proliferation and recurrence. Compared to traditional compression garments, this device offers more precise pressure regulation, higher patient comfort, and better adherence, making it a promising option for clinical application.

## Disclosure statement

The authors declare no conflict of interest.

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# Analysis of the Impact of Nutritional Intervention Combined with Predictive Nursing on the Nutritional Status, Quality of Life, and Adverse Reactions in Patients Undergoing Chemotherapy for Lung Cancer

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**Abstract:** *Objective:* To evaluate the intervention effect of nutritional intervention combined with predictive nursing on patients undergoing chemotherapy for lung cancer. **Methods:** A total of 88 lung cancer chemotherapy patients admitted between January 2023 and June 2024 were selected and randomly divided into groups using a random number table. The experimental group (44 cases) received nutritional intervention combined with predictive nursing, while the control group (44 cases) received predictive nursing alone. Nutritional status scores, nutritional indicators, quality of life scores, and adverse reaction rates were compared between the two groups. *Results:* After the intervention, the nutritional status scores of the experimental group were lower than those of the control group, while the levels of nutritional indicators in the experimental group were better than those in the control group. The quality of life scores in the experimental group were lower than in the control group, and the adverse reaction rates were also lower in the experimental group ( $P < 0.05$ ). *Conclusion:* Nutritional intervention combined with predictive nursing can improve the nutritional status of lung cancer chemotherapy patients, regulate multiple nutritional indicators, enhance quality of life, and reduce chemotherapy-related adverse reactions.

**Keywords:** Nutritional intervention; Predictive nursing; Lung cancer chemotherapy; Nutritional status; Quality of life

**Online publication:** November 28, 2024

## 1. Introduction

Lung cancer is a high-risk malignant tumor that requires comprehensive treatments such as surgical resection and chemotherapy to prolong patients' survival and improve their quality of life. As a common treatment for lung cancer, chemotherapy can kill cancer cells, reduce tumor size, and mitigate disease severity<sup>[1]</sup>. However,

chemotherapy drugs also damage healthy cells, leading to adverse reactions such as nausea, vomiting, or loss of appetite, which can trigger malnutrition and reduce patients' adherence to chemotherapy. Therefore, nursing interventions should be implemented during lung cancer chemotherapy with the goal of improving patients' tolerance to chemotherapy and ensuring its safety. Predictive nursing comprehensively assesses the risk factors associated with chemotherapy to enhance its effectiveness through efficient and proactive care measures. However, it pays insufficient attention to the patient's nutritional status, thus requiring the integration of nutritional intervention. This intervention can dynamically evaluate the patients' nutritional condition and implement a comprehensive and detailed nutritional intervention plan to prevent malnutrition and improve physiological function<sup>[2]</sup>. Based on this, the study selected 88 lung cancer chemotherapy patients to explore the effects of nutritional intervention combined with predictive nursing.

## **2. Materials and methods**

### **2.1. General information**

Eighty-eight patients undergoing chemotherapy for lung cancer who were admitted between January 2023 and June 2024 were selected and randomly divided into groups using a random number table. The experimental group consisted of 44 patients: 26 male and 18 female, aged 42 to 72 years, with an average age of  $(55.29 \pm 4.72)$  years. The control group also consisted of 44 patients: 27 male and 17 female, aged 41 to 71 years, with an average age of  $(54.37 \pm 4.67)$  years. There was no statistically significant difference in the general information between the two groups ( $P > 0.05$ ).

Inclusion criteria: Patients met the relevant standards of the "Guidelines for the Diagnosis and Treatment of Primary Lung Cancer (2022)." They were aged 18 to 70 years, eligible for chemotherapy, with an expected chemotherapy cycle of no fewer than 3 sessions and a survival period longer than 6 months. Patients had normal language and comprehension abilities, could cooperate with regular follow-ups, and were informed of and consented to participate in the study.

Exclusion criteria: Patients with language or mental disorders, systemic infections, multiple tumors, heart, liver, or kidney dysfunction, or severe malnutrition were excluded, as were those who withdrew from the study midway.

### **2.2. Methods**

The control group received predictive nursing care:

- (1) Gastrointestinal care: Patients were instructed to take antiemetics before each chemotherapy session and maintain a varied, high-nutrition diet.
- (2) Skin care: Before and after chemotherapy, blood vessels were repeatedly flushed with saline. After chemotherapy, the puncture site was compressed for 10 minutes to prevent phlebitis. For long-term chemotherapy, a central venous catheter was left in place, and the puncture site was heated periodically to dilate blood vessels and prevent tissue hypoxia.
- (3) Hair loss care: Preventive measures against hair loss include shoulder and neck massages, sun exposure, and the application of hair care oils.
- (4) Cognitive care: Caregivers assessed the patient's thought patterns and corrected misconceptions through verbal guidance, examples of successful cases, educational talks, and health lectures. Patients were encouraged to read psychology books, listen to music, and watch television to alleviate negative emotions.



- (5) Behavioral intervention: Patients were guided to lie still for 10 minutes daily, combined with deep breathing exercises for full-body relaxation. If their physical condition allowed, muscle contraction and relaxation exercises were performed as tolerated. Patients were encouraged to get out of bed daily, walk with support, climb stairs, and perform self-care activities like dressing and washing to gradually restore their independence.

The experimental group received nutritional intervention combined with predictive nursing, with the same predictive nursing plan as the control group. The nutritional intervention plan included:

- (1) Nutritional assessment: Within 24 hours of admission, caregivers provided patients with the Nutrition Risk Screening 2002 (NRS 2002), Patient-Generated Subjective Global Assessment (PG-SGA), and Quality of Life Questionnaire (EORTC QOL-C30) to evaluate their nutritional risk and quality of life. Physical measurements were taken to assess nutritional status. Patients were given a detailed explanation of the purpose and benefits of nutritional intervention combined with predictive nursing and were guided to join a WeChat group and follow the department's public account. After gathering the patients' basic information, they received a lung cancer nutrition management manual, with detailed explanations of nutritional therapy for lung cancer. Based on the assessment results, patients received targeted care, such as nutritional consultations, oral nutritional supplements, or parenteral nutrition. Their daily meal intake, preferences, and frequency were recorded, and family members were trained in techniques like food exchange and dietary structure adjustment.
- (2) Nutritional plan: Patients' daily energy target was 25–30 kcal/kg, with a protein requirement of 1.2–2 g/kg per day. Care was differentiated based on the NRS 2002 score. For scores below 3, continuous monitoring of nutritional status and dietary guidance were provided. For scores of 3 or higher, the “Five-Step Nutritional Therapy Principle” was followed: nutritional education was provided, and interventions such as oral nutrition, full enteral nutrition, enteral and parenteral nutrition, or total parenteral nutrition were chosen. Oral and enteral nutrition were prioritized. Dietary plans were adjusted to ensure that whole grains and tubers made up more than one-third of the staple diet, with daily vegetable intake between 300–500g, fruit intake between 200–300g, and a focus on high-quality proteins like meat, eggs, and dairy.
- (3) Follow-up care: Patients participated in weekly group discussions in the WeChat group every Friday at 6 p.m., where they shared their nutritional status and raised concerns. The group administrator summarized common issues and provided answers through educational materials and videos. A weekly WeChat video follow-up service, shorter than 10 minutes, was conducted to fully understand the patient's nutritional status outside the hospital and improve individual care plans.

Both groups were treated for 3 months.

### **2.3. Observational indicators**

- (1) Nutritional status: The PG-SGA was used for assessment, which includes a self-evaluation form and a medical staff evaluation form, with the total score being the sum of the two. Scores between 0 and 1 indicated no malnutrition, 2 to 3 suggested suspected malnutrition, 4 to 9 indicated moderate malnutrition, and scores of 9 or higher indicated severe malnutrition.
- (2) Nutritional indicators: Before the intervention and after 3 months of continuous intervention, venous blood was drawn, centrifuged, and analyzed using an automatic biochemical analyzer to measure serum

albumin (ALB), hemoglobin (Hb), and total lymphocyte count (TLC).

- (3) Quality of life: The EORTC QOL-C30 was used for evaluation, consisting of 30 items, including 5 functional domains, 1 overall quality of life domain, and 9 symptom domains. Items 1–28 were scored from 1 to 4, while items 29–30 were scored from 1 to 7, with total scores ranging from 30 to 126. Quality of life was calculated using negative scoring.
- (4) Adverse reactions: Rates of adverse reactions, such as loss of appetite, diarrhea, nausea, vomiting, constipation, phlebitis, and hair loss, were observed.

## 2.4 Statistical analysis

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

## 3. Results

### 3.1. Comparison of nutritional status scores between the two groups

**Table 1** shows that before the intervention, there was no significant difference in the nutritional status scores between the two groups ( $P > 0.05$ ). After 3 months of intervention, the nutritional status scores of the experimental group were significantly lower than those of the control group ( $P < 0.05$ ).

**Table 1.** Comparison of nutritional status scores between the two groups (mean  $\pm$  SD, points)

Group	<i>n</i>	Before intervention	After intervention
Experimental	44	3.15 $\pm$ 0.43	1.53 $\pm$ 0.37
Control	44	3.17 $\pm$ 0.45	1.89 $\pm$ 0.41
<i>t</i>		0.213	4.324
<i>P</i>		0.832	0.000

### 3.2. Comparison of nutritional indicators between the two groups

**Table 2** shows that before the intervention, there was no significant difference in nutritional indicators between the two groups ( $P > 0.05$ ). After 3 months of intervention, the nutritional indicator levels in the experimental group were significantly better than those in the control group ( $P < 0.05$ ).

**Table 2.** Comparison of nutritional indicators between the two groups before and after intervention (mean  $\pm$  SD)

Group	<i>n</i>	ALB (g/L)		Hb (g/L)		TLC	
		Before	After	Before	After	Before	After
Experimental	44	46.35 $\pm$ 4.91	55.70 $\pm$ 4.45	106.95 $\pm$ 15.98	113.06 $\pm$ 7.53	1.38 $\pm$ 0.43	1.66 $\pm$ 0.31
Control	44	46.31 $\pm$ 4.82	51.08 $\pm$ 4.42	106.72 $\pm$ 15.34	108.92 $\pm$ 7.47	1.40 $\pm$ 0.46	1.50 $\pm$ 0.34
<i>t</i>		0.039	4.886	0.069	2.589	0.211	2.307
<i>P</i>		0.969	0.000	0.945	0.011	0.834	0.023

Abbreviations: ALB, albumin; Hb, hemoglobin; TLC, total lymphocyte count.

### 3.3. Comparison of quality of life scores between the two groups

**Table 3** shows that before the intervention, there was no significant difference in quality of life scores between the two groups ( $P > 0.05$ ). After 3 months of intervention, the quality of life scores in the experimental group were significantly lower than those in the control group ( $P < 0.05$ ).

**Table 3.** Comparison of quality of life scores between the two groups (mean  $\pm$  SD, points)

Group	<i>n</i>	Before intervention	After intervention
Experimental	44	49.85 $\pm$ 4.33	25.15 $\pm$ 2.38
Control	44	49.72 $\pm$ 4.27	30.19 $\pm$ 2.47
<i>t</i>		0.142	9.747
<i>P</i>		0.888	0.000

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

**Table 4** shows that the adverse reaction rate in the experimental group was significantly lower than in the control group ( $P < 0.05$ ).

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

Group	<i>n</i>	Loss of appetite	Diarrhea	Nausea & vomiting	Constipation	Phlebitis	Hair loss	Incidence rate
Experimental	44	1	0	1	0	0	0	2 (4.55)
Control	44	2	1	2	1	1	1	8 (18.18)
$\chi^2$								4.062
<i>P</i>								0.044

## 4. Discussion

The development of lung cancer is typically slow, with no typical symptoms in the early stages, and it is often diagnosed in the middle or late stages, requiring early symptomatic treatment to achieve a better prognosis <sup>[3]</sup>. Currently, chemotherapy is a common treatment for lung cancer patients, effectively eliminating cancer cells and slowing disease progression, thus prolonging survival. However, chemotherapy drugs are highly irritating and can easily cause side effects such as nausea, vomiting, and loss of appetite, leading to malnutrition. Prolonged malnutrition can reduce the effectiveness of chemotherapy, lower the patient's quality of life, increase the treatment burden, and elevate the mortality rate <sup>[4]</sup>. Therefore, comprehensive nutritional and predictive nursing care during chemotherapy is essential to improve patient acceptance of treatment and ensure overall efficacy.

Predictive nursing is a relatively new nursing method that comprehensively evaluates the patient's disease condition and physical state, integrates various nursing measures, and provides anticipatory and comprehensive care services. This type of nursing can predict chemotherapy side effects and carry out targeted preventive care, thereby reducing discomfort during chemotherapy <sup>[5]</sup>. However, its scope of care is limited and may not provide scientific guidance on the patient's dietary structure. Therefore, it can be combined with nutritional intervention. Comprehensive nutritional intervention can effectively monitor the patient's nutritional status, analyze daily

nutritional requirements, and provide professional nutritional guidance <sup>[6]</sup>. The combined use of these nursing measures can comprehensively regulate the patient's nutritional status, resulting in superior care outcomes.

In this study, the experimental group showed lower post-intervention nutritional status scores, better nutritional indicators, lower quality of life scores, and fewer adverse reactions compared to the control group ( $P < 0.05$ ). These results are consistent with the findings of An and Ren <sup>[7]</sup>. The reason is that the nutritional intervention follows a process of screening, plan formulation, implementation, and monitoring, allowing for a comprehensive assessment of the patient's nutritional needs. Individualized nutritional intervention ensures timely and efficient nutritional support <sup>[8,9]</sup>. This care can extend to post-discharge care, continuously monitoring the patient's nutritional status, and compensating for the limitations of predictive nursing, thus enhancing the quality of care by utilizing the strengths of both nursing approaches.

## 5. Conclusion

In summary, nutritional intervention combined with predictive nursing can improve the nutritional status of lung cancer patients undergoing chemotherapy, enhance their quality of life, and prevent post-chemotherapy side effects, offering significant nursing advantages.

## Disclosure statement

The author declares no conflict of interest.

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# Study on the Anti-Radiation Function of Selenium-Enriched *Agaricus blazei* Murill Polysaccharides and Tea Polyphenol Compound Solution

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**Abstract:** Mice were administered a selenium-rich *Agaricus blazei* Murill (Se-AbM) polysaccharides and tea polyphenol compound solution for prevention and treatment. Following exposure to 2 Gy of infrared radiation, peripheral blood counts of white blood cells, red blood cells, and platelets were assessed, along with serum levels of apoptosis-related factors Fas and Fas ligand, inflammatory factors interferon-gamma and tumor necrosis factor-alpha, immune-related factors interleukin-3 and interleukin-6, and indicators of oxidative stress, including malondialdehyde, superoxide dismutase, and glutathione. The results showed significant differences in these indicators between the Se-AbM-treated group and the model group, suggesting that Se-AbM may inhibit apoptosis, enhance the clearance of free radicals in the body, improve antioxidant capacity, and provide a significant protective effect against radiation-induced immune damage.

**Keywords:** Selenium-rich *Agaricus blazei* Murill tea polyphenols; Anti-radiation; Free radicals

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## 1. Introduction

Selenium-enriched *Agaricus blazei* Murill (Se-AbM) is produced by artificially enriching the *Agaricus blazei* Murill variety with selenium and using polysaccharide extraction technology to obtain selenium-enriched *Agaricus blazei* Murill polysaccharides (Se-AbMP). Tea polyphenols (TP) are extracted from green tea through extraction technology. The Se-AbMP + TP compound solution is formulated with these two components in a specific ratio. Numerous studies have investigated the anti-radiation effects of AbMP<sup>[1,2]</sup>, and research has also explored the anti-radiation effects of TP<sup>[3,4]</sup>. However, no studies have reported on the combined anti-radiation effects of Se-AbMP and TP as a composite material. This study aims to examine the effects of the combined solution on blood components and histopathological changes in bone marrow following radiation damage and to preliminarily explore its mechanism of action, providing theoretical and experimental support for the health benefits of the combined solution.

## 2. Materials and methods

### 2.1. Materials

#### 2.1.1. Drug

The test compound, selenium-rich *Agaricus blazei* Murill polysaccharides and tea polyphenols (Se-AbMP + TP) compound solution, was provided by Guoling Elderly Care Service (Dalian) Co., Ltd.

#### 2.1.2. Experimental animals

Six-week-old male ICR mice of clean grade, weighing 21–22 g, were purchased from Liaoning Changsheng Biotechnology Co., Ltd. The mice were housed in a controlled environment with regulated temperature, humidity, and a standard light/dark cycle. Sterilized bedding was provided, and the mice had free access to food and water. Housing conditions were maintained at a temperature of 19–22°C and a relative humidity of 40%–50%.

#### 2.1.3. Reagents and instruments

The following were used:

(1) Enzyme-linked immunosorbent assay (ELISA) kits for mouse tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-3, interleukin (IL)-6, apoptosis-related factor Fas (CD95), apoptosis-related factor ligand (FasL), and  $\gamma$ -interferon (IFN- $\gamma$ ), provided by Jiangsu Enzyme Immune Industrial Co., Ltd.

Kits for detecting reduced glutathione (GSH), malondialdehyde (MDA), and superoxide dismutase (SOD), provided by Jiangsu Adison Biotechnology Co., Ltd.

(2) Multiskan<sup>TM</sup> FC microplate photometer, manufactured by Thermo Scientific.

### 2.2. Methodologies

#### 2.2.1. Grouping and drug administration

Twenty-four male ICR mice were randomly divided into three groups (eight mice per group) following a 7-day acclimatization period:

(1) Blank group: Sham-irradiated mice administered physiological saline.

(2) Model group: Irradiated mice administered physiological saline.

(3) Se-AbMP + TP administration group: Irradiated mice treated with Se-AbMP + TP (0.2 mL/10 g, twice daily).

An animal model of radiation injury was established using whole-body irradiation with <sup>60</sup>Co  $\gamma$ -rays at a total dose of 2.0 Gy, except for the blank group, which underwent sham irradiation with lead brick shielding. Se-AbMP + TP administration was initiated 7 days prior to irradiation and continued for 7 days post-irradiation. The blank and model groups received equivalent volumes of physiological saline during this period.

### 2.3. Observational indicators

#### 2.3.1. Peripheral blood cell count

On the 8th day after irradiation, 100  $\mu$ L of blood was collected from the canthus vein of mice in each group. Counts of white blood cells (WBCs), red blood cells (RBCs), and platelets (PLTs) were measured using a blood cell counting chamber under a light microscope to assess the condition of the model and the effects of SSC on peripheral blood cell counts.

### 2.3.1. Serum indicators

On the 8th day after irradiation, blood was collected from the abdominal aorta to prepare serum. ELISA kits were used to measure the levels of:

- (1) Apoptosis-related factors: Fas and FasL.
- (2) Inflammation-related factors: IFN- $\gamma$  and TNF- $\alpha$ .
- (3) Immune-related factors: IL-3 and IL-6.

Biochemical kits were used to detect the serum levels of oxidative stress markers: GSH, MDA, and SOD.

### 2.3.3. Bone marrow pathological changes

The femurs of mice were fixed in 4% paraformaldehyde, and bone marrow tissue was stained with hematoxylin and eosin (H.E). Pathological changes in the bone marrow were observed under a light microscope.

## 3. Results

### 3.1. The effect of Se-AbMP + TP on blood components in mice with radiation injury

As shown in **Table 1**, compared with the blank group, the numbers of RBCs, WBCs, and PLTs in the peripheral blood of the model group significantly decreased ( $P < 0.05$ ). In contrast, the Se-AbMP + TP-treated group exhibited significantly increased numbers of RBCs, WBCs, and PLTs in the peripheral blood compared with the model group ( $P < 0.05$ ). These results demonstrate that Se-AbMP + TP can reverse changes in blood cell composition in mice with radiation injury.

**Table 1.** Effects of selenium-enriched *Agaricus blazei* Murill polysaccharides and tea polyphenol compound solution on blood components in irradiated mice ( $n = 8$ )

Group	WBC ( $10^9/L$ )	RBC ( $10^{12}/L$ )	PLT ( $10^9/L$ )
Blank group	$9.58 \pm 1.11^{**}$	$10.65 \pm 1.25^{**}$	$1,033.0 \pm 75.6^{**}$
Model group	$7.94 \pm 0.97$	$8.67 \pm 0.95$	$890.6 \pm 57.3$
Se-AbMP + TP group	$9.23 \pm 0.56^*$	$10.12 \pm 0.95^*$	$984.3 \pm 84.3^*$

Note: Compared with the model group,  $^{**}P < 0.01$ ;  $^*P < 0.05$ .

### 3.2. Effects of Se-AbMP + TP on the levels of IFN- $\gamma$ , TNF- $\alpha$ , FAS, FASL, IL-3, and IL-6 in mice with radiation injury

As shown in Table 2, compared with the blank group, the levels of inflammatory factors IFN- $\gamma$  and TNF- $\alpha$  significantly increased in the model group ( $P < 0.05$ ). However, these levels significantly decreased in the Se-AbMP + TP group compared with the model group ( $P < 0.05$ ), indicating that Se-AbMP + TP can reduce the elevated inflammatory factor levels caused by radiation injury.

Additionally, the levels of apoptosis-related factors Fas and FasL were significantly higher in the model group compared with the blank group ( $P < 0.05$ ), but the Se-AbMP + TP group showed significantly reduced levels compared with the model group ( $P < 0.05$ ).

Furthermore, the serum IL-3 content significantly decreased ( $P < 0.05$ ) and IL-6 content significantly increased ( $P < 0.05$ ) in the model group compared with the blank group. Se-AbMP + TP treatment reversed these changes by significantly increasing IL-3 levels and decreasing IL-6 levels ( $P < 0.05$ ).

**Table 2.** Effects of selenium-enriched *Agaricus blazei* Murill polysaccharides and tea polyphenol compound solution on serum factors in irradiated mice ( $n = 8$ )

Group	IFN- $\gamma$ (pg/mL)	TNF- $\alpha$ (pg/mL)	Fas (pg/mL)	FasL (pg/mL)	IL-3 (pg/mL)	IL-6 (pg/mL)
Blank group	4.45 $\pm$ 0.96*	5.11 $\pm$ 0.74*	9.03 $\pm$ 1.47*	4.55 $\pm$ 1.01*	7.60 $\pm$ 1.35*	5.43 $\pm$ 0.78**
Model group	6.19 $\pm$ 1.40	6.48 $\pm$ 1.04	11.29 $\pm$ 1.28	6.29 $\pm$ 1.60	5.96 $\pm$ 0.84	6.98 $\pm$ 1.03
Se-AbMP + TP group	4.50 $\pm$ 1.56*	5.20 $\pm$ 1.03*	9.14 $\pm$ 1.66*	4.60 $\pm$ 1.01*	7.97 $\pm$ 1.20*	5.66 $\pm$ 0.55*

Note: Compared with the model group, \*\* $P < 0.01$ ; \* $P < 0.05$ .

### 3.3. Effects of Se-AbMP + TP on MDA, SOD, and GSH in mice with radiation injury

As shown in **Table 3**, the serum MDA content significantly increased in the model group compared with the blank group ( $P < 0.05$ ), while the SOD and GSH contents significantly decreased ( $P < 0.05$ ). Treatment with Se-AbMP + TP significantly decreased MDA levels and increased SOD and GSH levels compared with the model group ( $P < 0.05$ ). These results indicate that Se-AbMP + TP can reverse oxidative stress indicators in mice with radiation injury.

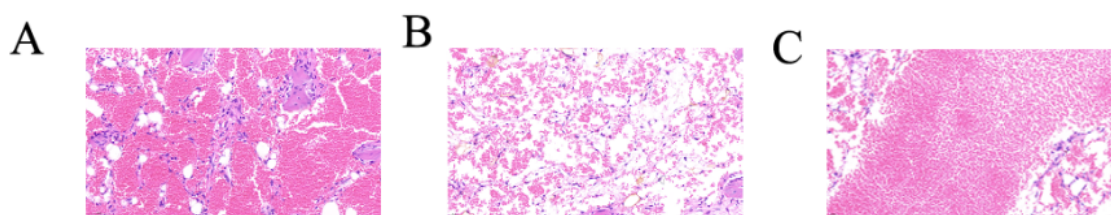
**Table 3.** Effects of selenium-enriched *Agaricus blazei* Murill polysaccharides and tea polyphenol compound solution on oxidative stress markers in irradiated mice ( $n = 8$ )

Group	MDA (mmol/mL)	SOD (U/L)	GSH (mmol/L)
Blank group	4.87 $\pm$ 1.15**	22.2 $\pm$ 2.4**	2.24 $\pm$ 0.64*
Model group	7.14 $\pm$ 1.72	17.8 $\pm$ 2.5	1.51 $\pm$ 0.38
Se-AbMP + TP group	5.21 $\pm$ 1.06*	21.2 $\pm$ 1.7*	2.22 $\pm$ 0.62*

Note: Compared with the model group, \*\* $P < 0.01$ ; \* $P < 0.05$ .

### 3.4. The effect of Se-AbMP + TP on pathological changes in bone marrow in mice with radiation injury

As shown in **Figure 1**, compared with the blank group, the model group exhibited a significant reduction in the number of bone marrow nucleated cells. In contrast, the Se-AbMP + TP-treated group showed a significant increase in the number of bone marrow nucleated cells compared with the model group. These results suggest that Se-AbMP + TP promotes the recovery of bone marrow nucleated cells in mice with radiation injury.



**Figure 1.** Pathological effects of selenium-enriched *Agaricus blazei* Murill polysaccharides and tea polyphenol compound solution on bone marrow in irradiated mice. (A) Bone marrow pathology of the blank group; (B) Bone marrow pathology of the model group; (C) Bone marrow pathology of the Se-AbMP + TP group

## 4. Discussion

Studies on the radiation resistance properties of various plants have been extensively conducted <sup>[5]</sup>. This study explored the combined radiation resistance effects of Se-AbMP and tea polyphenols.

Selenium possesses antioxidative, free radical-scavenging, and antimutagenic properties, providing comprehensive protection against various forms of radiation-induced damage.

As the primary active component of *Agaricus blazei* Murill, its polysaccharide exhibits remarkable antioxidant capacity. It enhances immune function, promotes cellular regeneration and repair, and mitigates the adverse effects of radiation on organs and tissues.

Se-AbMP combines the advantages of selenium and *Agaricus blazei* polysaccharides, resulting in enhanced anti-radiation effects.

Green tea polyphenols, a type of polyphenolic compound found in tea, exhibit strong antioxidant properties. These polyphenols exert their anti-radiation effects by competing with radiation products (including free radicals) and acting at multiple stages before, during, and after radiation-induced damage. Furthermore, green tea polyphenols regulate immune cell function, thereby reducing radiation-induced damage to the body.

## 5. Conclusion

In conclusion, the combination of tea polyphenols and Se-AbMP demonstrates significant anti-radiation effects and holds considerable value for health development in addressing radiation damage.

## Disclosure statement

The authors declare no conflict of interest.

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# Construction and Application Study of Postoperative Nursing Intervention Program for Osteoporotic Vertebral Compression Fractures

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**Abstract:** *Objective:* To explore the construction and application effect of a postoperative nursing intervention program for osteoporotic vertebral compression fractures. *Methods:* A total of 68 cases of osteoporotic vertebral compression fractures treated with vertebroplasty in our hospital from March 2023 to April 2024 were selected and randomly divided into the control group and the constructed program group, with 34 cases in each group. The control group received routine postoperative nursing after vertebroplasty, while the constructed program group was provided with a targeted postoperative nursing intervention program based on the control group, which was implemented postoperatively. The postoperative outcomes and thoracolumbar dysfunction of the two groups were compared. *Results:* The total postoperative efficacy rate in the constructed program group (97.06%, 33/34) was significantly higher than that in the control group (76.47%, 26/34) ( $P < 0.05$ ). The thoracolumbar dysfunction score in the constructed program group ( $15.02 \pm 1.36$ ) was significantly lower than that in the control group ( $22.56 \pm 2.41$ ) ( $P < 0.05$ ). *Conclusion:* Constructing a targeted nursing intervention program based on the postoperative nursing requirements for osteoporotic vertebral compression fractures and individual patient characteristics can effectively improve thoracolumbar dysfunction and enhance the postoperative surgical outcome. The clinical application of this program is reliable.

**Keywords:** Osteoporosis; Vertebral compression fracture; Postoperative nursing; Intervention program; Application effect

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## 1. Introduction

In recent years, the incidence of osteoporotic fractures has shown an increasing trend year by year, mainly due to the aggravation of population aging, which has led to a yearly rise in the incidence of fracture types such as osteoporotic vertebral compression fractures. This necessitates active improvement of prevention and control measures<sup>[1]</sup>. At present, the field of orthopedics has developed relatively comprehensive treatment methods for osteoporotic vertebral compression fractures, primarily using surgical methods such as vertebroplasty

to reconstruct the vertebral anatomical structure and restore vertebral function. However, the postoperative recovery period for patients is relatively long, requiring standardized treatment and intervention to improve postoperative vertebral function, alleviate osteoporosis, and reduce the risk of postoperative refracture<sup>[2]</sup>. Postoperative nursing care requirements for such fractures are high, and there are significant individual differences among patients, so routine nursing measures cannot meet all patient needs. It is therefore necessary to actively optimize postoperative nursing plans and construct individualized and comprehensive postoperative nursing programs for patients<sup>[3]</sup>. In light of this, our hospital developed a targeted postoperative nursing intervention program for patients based on the characteristics of osteoporotic vertebral compression fractures and the postoperative nursing requirements for vertebroplasty. We selected 68 cases of osteoporotic vertebral compression fractures treated with vertebroplasty in our hospital from March 2023 to April 2024 to compare and analyze the application value of this postoperative nursing intervention program.

## **2. Materials and methods**

### **2.1. General information**

A total of 68 cases of osteoporotic vertebral compression fractures treated with vertebroplasty in our hospital from March 2023 to April 2024 were selected and randomly divided into the control group and the constructed program group, with 34 cases in each. In the constructed program group, there were 19 males and 15 females, aged 63 to 75 years, with an average age of  $65.38 \pm 3.86$  years; the duration of osteoporosis ranged from 1 to 6 years, with an average of  $4.56 \pm 0.83$  years. In the control group, there were 20 males and 14 females, aged 62 to 75 years, with an average age of  $65.41 \pm 3.91$  years; the duration of osteoporosis ranged from 1 to 6 years, with an average of  $4.59 \pm 0.85$  years. The general information of the two groups is comparable ( $P > 0.05$ ). This study was approved by the hospital ethics committee.

### **2.2. Inclusion and exclusion criteria**

Inclusion criteria: (1) Patients diagnosed with osteoporotic vertebral compression fractures via MRI or CT; (2) met the indications for vertebroplasty; (3) first-time vertebral fracture cases; (4) complete patient data and stable physical signs; (5) all patients signed informed consent forms. Exclusion criteria: (1) Combined with vertebral burst fractures, spinal cord injury, or spinal stenosis; (2) combined with acute infectious diseases; (3) combined with spinal tumors; (4) secondary osteoporosis; (5) combined with rheumatic diseases; (6) long-term use of steroid medications.

### **2.3. Methods**

The control group received routine postoperative nursing after vertebroplasty, observing incision recovery, guiding standard osteoporosis medication treatment, closely monitoring the condition, providing dietary guidance, explaining postoperative rehabilitation points and main measures, and discussing precautions before discharge. The constructed program group received a targeted postoperative nursing intervention program in addition to the measures given to the control group, as follows:

- (1) Early postoperative targeted intervention: Postoperatively, the pain status was closely monitored, and the patient's limb position was adjusted to alleviate pain. Within 24 hours post-surgery, local ice application was applied to the wound area, placing a towel on the lateral lumbar side and a soft ice pack

for local cooling. Intermittent ice treatment was administered 24 to 72 hours post-surgery to reduce wound swelling and oozing, relieving early postoperative pain. The peripheral temperature of the patient's limbs was monitored, with warm infusion fluids to facilitate body temperature recovery. A soft pillow was placed on the patient's chest, helping them adjust to a prone position so the spine remained level, which promoted recovery.

- (2) Postoperative cognitive intervention: A structured discussion with the patient and family members explained osteoporosis mechanisms and principles, highlighting the close relationship between osteoporosis and vertebral fractures. Patients and family members were guided to recognize the importance of osteoporosis treatment, actively preventing re-fracture, and improving postoperative quality of life. Additionally, the recovery points and rehabilitation process, in line with the patient's surgical and pharmacological treatment plan, were clarified to encourage cooperation with nursing and treatment to reduce poor prognosis risks and alleviate postoperative discomfort. Using video, models, and illustrative tools, the postoperative recovery process and treatment requirements were demonstrated, encouraging patients to ask questions and patiently addressing any misunderstandings.
- (3) Psychological nursing: Active communication with patients was maintained to monitor emotional states, promptly identifying abnormalities. Patients were encouraged to express concerns, with patients listening to their needs, analyzing psychological issues, and providing targeted psychological counseling to alleviate negative emotional responses. Techniques like deep breathing and meditation were suggested to help relax. Light music or the patient's favorite entertainment could be played in their room or at home to foster a positive environment, distracting from postoperative anxiety or depression.
- (4) Individualized rehabilitation guidance: A rehabilitation management team consisting of nursing staff, attending physicians, physical therapists, and rehabilitation physicians was formed to develop a rehabilitation plan. In the early stages, patients were guided to perform appropriate limb movements in bed to improve flexibility and prevent muscle atrophy. Recovery progress was closely monitored, with guidance on aerobic exercises and strength training such as ankle pumps and limb muscle contraction exercises. Patients were encouraged to get out of bed as soon as possible to prevent deep vein thrombosis, with functional training targeting any mobility issues. For lower limb resistance training, knee extensions, and leg lifts were suggested; after fracture healing, balance training with support braces and back muscle strengthening exercises were incorporated. Patients were instructed on the requirements of each rehabilitation stage and encouraged to continue at-home exercises, focusing on strengthening back and abdominal muscles and enhancing overall balance.
- (5) Lifestyle guidance: Patients were guided to adopt a healthy lifestyle with moderate exercise and adequate sleep to aid recovery and improve osteoporosis. Based on individual recovery conditions, patients were encouraged to choose preferred forms of exercise, engaging in frequent short-duration sessions daily to improve muscle strength and bone density. Dietary adjustments were recommended, emphasizing a balanced diet with increased intake of high-calcium and high-protein foods. Protein sources such as beef, pork, fish, shrimp, and eggs were recommended, along with high-calcium foods like milk, shrimp shells, and sesame seeds. Fresh vegetables and fruits were suggested to increase vitamins and trace elements. Regular check-ups were encouraged to monitor nutritional indicators, with supplements like calcium and iron added under medical guidance to improve bone density and calcium

status.

- (6) Postoperative continuity of care: Before discharge, an individual health file was created for each patient, including personal and clinical treatment information. Communication methods after discharge were specified, including home and personal contact numbers. Patients were invited to join a WeChat group for ongoing communication. Postoperative symptoms and care points were explained, correcting any misunderstandings, and patients were guided to choose firm mattresses or hard beds for spinal support, improving recovery. Follow-ups via WeChat or phone were conducted to monitor recovery, reminding patients of regular check-ups and assisting with adjustments in rehabilitation to improve spinal function.

## 2.4. Observation indicators

- (1) Efficacy evaluation: Three months post-surgery, patient clinical efficacy was evaluated according to the “Expert Consensus on Diagnosis and Treatment of Osteoporotic Vertebral Compression Fractures (2021 Edition)” [4].
  - (a) Significant efficacy: Fracture healed, lumbar and back pain, and mobility restrictions fully resolved, daily activity restored, and bone density increased by about 50% compared to pre-surgery;
  - (b) Effective: Fracture healed, bone density increased by 25%–49% compared to pre-surgery, significant or partial improvement in lumbar and back symptoms, and daily activity markedly improved;
  - (c) Ineffective: Poor fracture healing, bone density improvement of less than 25% compared to pre-surgery, no significant improvement in lumbar and back symptoms, and no improvement in daily activities;
  - (d) Total effective rate = (Significant efficacy + Effective cases) / total cases × 100%.
- (2) Thoracolumbar dysfunction evaluation: The Oswestry Disability Index (ODI) was used to assess vertebral function (0–45 points), with higher scores indicating more severe dysfunction. Preoperative and 3-month postoperative scores were compared between the two groups.

## 2.5. Statistical analysis

SPSS 20.0 statistical software was used for data analysis, with mean ± standard deviation (SD) for measurement data, analyzed with the *t*-test; count data were represented as [*n* (%)] and analyzed with the  $\chi^2$  test. A *P*-value of < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Comparison of efficacy

The total effective rate in the constructed program group (97.06%, 33/34) was significantly higher than that in the control group (76.47%, 26/34) (*P* < 0.05). See **Table 1**.

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

Group	<i>n</i>	Markedly effective	Effective	Ineffective	Total effective rate
Constructed program group	34	19 (55.88)	14 (41.18)	1 (2.94)	33 (97.06)
Control group	34	11 (32.35)	15 (44.12)	8 (23.53)	26 (76.47)
$\chi^2$					5.022
<i>P</i>					0.015

### 3.2. Comparison of thoracolumbar dysfunction scores

Postoperative thoracolumbar dysfunction scores in both groups were significantly lower than preoperative scores ( $P < 0.05$ ). The postoperative thoracolumbar dysfunction score in the constructed program group ( $15.02 \pm 1.36$ ) was significantly lower than that in the control group ( $22.56 \pm 2.41$ ) ( $P < 0.05$ ). See **Table 2**.

**Table 2.** Comparison of thoracolumbar dysfunction scores (mean  $\pm$  SD)

Group	ODI score	
	Pre-operation	Post-operation
Constructed program group	$32.25 \pm 4.13$	$15.02 \pm 1.36^*$
Control group	$32.21 \pm 4.09$	$22.56 \pm 2.41^*$
<i>t</i>	0.078	5.408
<i>P</i>	0.879	0.014

\*Note: Compared with preoperative scores in the same group,  $P < 0.05$ .

## 4. Discussion

Osteoporosis is a common disease among the elderly and is a significant risk factor for fractures and disability in this population. With the influence of an aging population, the number of osteoporosis patients in China is rapidly increasing. These patients often experience bone loss and reduced vertebral support, making them more susceptible to vertebral compression fractures from external forces, which severely affects their motor function and quality of life [5]. Surgery is the main treatment method for such vertebral compression fractures, but postoperative rehabilitation demands are high. Long-term, effective nursing support is essential to improve prognosis and enhance the patient's quality of life [6,7].

Currently, clinical nursing research on osteoporotic vertebral compression fractures is increasing, with many studies indicating that conventional nursing models lack personalization and fail to meet the diverse needs of patients. Therefore, there is a need to actively explore highly individualized and targeted nursing plans to assist with postoperative recovery [8,9]. In light of this, the postoperative recovery requirements of such patients were analyzed, and years of experience in postoperative rehabilitation for vertebral compression fractures were summarized to create a patient-centered, personalized, and comprehensive nursing plan. A scientific postoperative nursing intervention plan was constructed accordingly.

This study followed the implementation of this targeted postoperative nursing intervention and found that the total effective rate in the constructed program group (97.06%) was significantly higher than that in



the control group (76.47%). This indicates that constructing and applying a targeted postoperative nursing intervention plan for these patients can effectively improve postoperative lumbar function and osteoporosis symptoms, helping to enhance overall recovery. Furthermore, the study also found that the thoracolumbar dysfunction score in the constructed program group was significantly lower than that of the control group. This suggests that the targeted nursing intervention plan can significantly improve recovery outcomes, promote the correction of thoracolumbar dysfunction, and improve prognosis, making it a reliable approach for clinical application.

## 5. Conclusion

In conclusion, constructing a targeted nursing intervention plan based on the postoperative nursing requirements for osteoporotic vertebral compression fractures and patient-specific characteristics can effectively improve thoracolumbar function and enhance surgical outcomes, making it a reliable option for clinical application.

## Disclosure statement

The authors declare no conflict of interest.

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# Evidence-based Nursing and Improving Patient Satisfaction: A Systematic Evaluation

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**Abstract:** *Objective:* This study aims to explore the effect of evidence-based nursing (EBN) on improving patient satisfaction by systematically evaluating the impact of EBN implementation through the analysis of 40 hospital-related literature articles. *Methods:* A review of 40 studies published from January 2022 to December 2023 related to EBN and patient satisfaction was conducted. The selection was based on specific inclusion and exclusion criteria, focusing on studies that involved EBN interventions. Data were extracted and statistically analyzed using patient satisfaction scores and nursing quality assessments to compare satisfaction before and after EBN implementation. *Results:* Literature analysis showed that patient satisfaction significantly improved after the implementation of EBN, with average satisfaction scores increasing from 82.5% before intervention to 91.3% after intervention ( $P < 0.05$ ). The application of EBN enhanced patients' care experience, reduced nursing errors, and significantly improved the efficiency and professional competence of healthcare staff. *Conclusion:* This study confirms that EBN has a significant effect on improving patient satisfaction, particularly in personalized care and evidence-based decision-making. Future efforts should promote EBN and standardize nursing processes to continuously improve care quality and patient satisfaction.

**Keywords:** Evidence-based nursing; Patient satisfaction; Nursing quality; Evidence-based decision-making; Literature analysis

**Online publication:** November 27, 2024

## 1. Introduction

With the continuous improvement of medical standards, patients' demands for healthcare service quality are increasing, making patient satisfaction one of the key indicators of healthcare quality<sup>[1-3]</sup>. Evidence-based nursing (EBN) is a scientific, evidence-based nursing method that has been widely applied in clinical practice in recent years. By integrating the best research evidence, the clinical experience of nurses, and patients' actual needs, EBN not only enhances care quality but also significantly improves patients' nursing experience<sup>[4-6]</sup>. However, systematic evaluations and research on the specific impact of EBN on patient satisfaction are still

lacking. To fill this gap, this study reviews and analyzes 40 hospital-related literature on EBN to explore its role in enhancing patient satisfaction <sup>[7-9]</sup>. Through literature analysis and statistical data, the study aims to clarify the clinical effectiveness of EBN, providing a reference for nursing practice and future research. The ultimate goal is to evaluate the effectiveness of EBN and provide scientific evidence for optimizing nursing management systems.

## **2. Materials and methods**

### **2.1. General data**

This study adopted a retrospective analysis method, selecting 40 studies from January 2022 to December 2023 on EBN implementation in hospitals. The studies were divided into an observation group and a control group. The observation group included 20 studies that implemented EBN, while the control group consisted of 20 studies that did not or only partially implemented EBN. The inclusion criteria were: studies explicitly focused on EBN and patient satisfaction analysis, complete patient satisfaction scores or related indicators, and studies published within the research period. Exclusion criteria were: incomplete data, lack of effective analysis, duplicate publications, or studies not involving patient satisfaction. All studies focused on adult patients, excluding pregnant women, psychiatric patients, and terminally ill patients.

### **2.2. Methods**

The control group did not implement systematic EBN and only used routine care processes, including basic monitoring, medication management, and daily care. The observation group, on the other hand, implemented EBN interventions, which included:

- (1) Nurses received EBN training, using the latest evidence-based medical research, combined with clinical experience and individual patient needs, to develop personalized care plans.
- (2) Regularly assessing patients' physiological and psychological conditions during care and dynamically adjusting care plans.
- (3) Strengthening communication with patients and families, providing health education, explaining care processes, and reducing anxiety.
- (4) Regularly updating the knowledge and skills of nursing staff, ensuring the quality of care. Patient satisfaction was assessed at least twice a week, and nursing error rates, length of hospital stay, and other indicators were recorded.

### **2.3. Observational indicators**

This study mainly observed the following indicators.

- (1) Patient satisfaction: Assessed through questionnaires filled out at discharge, with a score range of 0–100, focusing on patients' satisfaction with care quality, communication, and nursing staff attitudes.
- (2) Nursing quality: Evaluated by recording nursing error rates and complaint rates, including medication errors and operational mistakes. The length of hospital stay and complication rates were also recorded as secondary indicators to complement the evaluation of care effectiveness.

## 2.4. Statistical analysis

All data were analyzed using SPSS 25.0 software. Patient satisfaction scores and nursing error rates were expressed as mean  $\pm$  standard deviation (SD), and *t*-tests were used for comparison between groups. Qualitative data such as complaint rates and complication rates were expressed as percentages, and chi-squared tests were used for comparison. Statistical significance was set at  $P < 0.05$ .

## 3. Results

### 3.1. Patient satisfaction evaluation

Analysis of patient satisfaction scores from the 40 studies showed that the overall satisfaction of patients in the observation group was significantly higher than in the control group. The observation group had a satisfaction score of  $91.3 \pm 3.5$ , while the control group scored  $82.5 \pm 4.2$  ( $P < 0.01$ ), as shown in **Table 1**.

**Table 1.** Comparison of patient satisfaction scores between the observation group and control group

Group	<i>n</i>	Average satisfaction score (points)	Score $\geq 90$ points (%)	Score 80–89 points (%)	Score $< 80$ points (%)
Observation group	20	$91.3 \pm 3.5$	78%	19%	3%
Control group	20	$82.5 \pm 4.2$	45%	40%	15%
<i>t</i> value		8.42	5.28	2.94	3.77
<i>P</i> value		$< 0.01$	$< 0.01$	$< 0.05$	$< 0.01$

### 3.2. Nursing quality evaluation

In terms of nursing quality, the observation group had significantly lower error rates, complaint rates, and average hospital stays compared to the control group. The complication rate was also significantly lower in the observation group ( $P < 0.05$ ), as shown in **Table 2**.

**Table 2.** Comparison of nursing quality and incidence of complications between observation group and control group

Group	<i>n</i>	Nursing error rate (%)	Nursing complaint rate (%)	Length of hospital stay (days)	Complication rate (%)
Observation group	20	3.2%	2.5%	$9.4 \pm 2.1$	6.5%
Control group	20	8.6%	6.4%	$12.7 \pm 3.5$	12.3%
$\chi^2$ value		6.14	4.32	5.87	4.21
<i>P</i> value		$< 0.01$	$< 0.05$	$< 0.01$	$< 0.05$

## 4. Discussion

This study compared EBN with conventional nursing and found that EBN significantly improved patient satisfaction and nursing quality<sup>[10-12]</sup>. The observation group had notably lower nursing error rates, complaint rates, and hospital stays, indicating that EBN not only enhances the professional competence of nursing staff but also effectively reduces nursing errors, improving the overall patient experience. Additionally, the lower complication rate in the observation group further confirms the clinical effectiveness of EBN<sup>[13-15]</sup>. This result aligns with existing studies, suggesting that the promotion of EBN in clinical practice can effectively improve



care quality and patient satisfaction.

## 5. Conclusion

EBN significantly improves patient satisfaction, reduces nursing errors, and shortens hospital stays. It is recommended that EBN be widely implemented in clinical settings to continuously optimize nursing quality.

## Disclosure statement

The author declares no conflict of interest.

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# Development and Validation of a Frailty Risk Prediction Model for Community-Dwelling Elderly in Shanghai

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**Abstract:** *Background:* China is rapidly aging, increasing the burden on families, society, and public health services. The health of elderly individuals tends to deteriorate with age, and chronic conditions like frailty become more prevalent, driving up the use of healthcare services. Early screening and intervention for frailty are crucial in managing this demographic shift. While tools like the Fried Frailty Phenotype and Frailty Index assess frailty in communities, they are resource-intensive and only indicate frailty status without predicting risk or providing management recommendations. This study aims to develop a risk prediction model for frailty using real-world data, which can support the early detection of high-risk individuals in community settings. *Objectives:* To analyze the prevalence of frailty and its influencing factors in community-dwelling elderly, to construct a frailty risk prediction model and develop a nomogram, and to validate the model and assess its clinical utility. *Methods:* A cross-sectional survey of 420 elderly individuals in a Shanghai community health center was conducted (August 2022–March 2023). Data from various assessment tools were used to build a frailty prediction model through logistic regression, with validation conducted on 180 additional participants. The model's predictive performance was evaluated using the ROC, AUC, calibration curves, and decision curve analysis (DCA). *Results:* The frailty prevalence was 7.4%. Independent risk factors included social support, malnutrition, fatigue, sarcopenia, reduced grip strength, and sleep duration. The prediction model achieved an AUC of 0.968 in the training set and 0.939 in the validation set, indicating high discrimination and calibration. DCA confirmed the model's clinical utility. *Conclusion:* This study highlights a frailty prevalence rate of 7.4% among elderly individuals in Shanghai, with key risk factors identified. The validated frailty risk prediction model provides accurate and clinically effective frailty risk assessment, supporting targeted early interventions to prevent frailty in community settings.

**Keywords:** Frailty risk prediction; Community-dwelling elderly; Early intervention in aging

**Online publication:** November 27, 2024

## 1. Introduction

The United Nations Economic and Social Council defined the threshold for population aging in its 1957 report,

“Population Aging and Its Socio-Economic Implications,” noting that a country or region is considered to have entered an aging society when the proportion of the population aged 65 and over exceeds 7%. By 2000, China’s population aged 65 and reached 88 million, accounting for 7% of the total population, indicating that China had entered an aging society <sup>[1]</sup>. A country or region with 14% of its population aged 65 and over is considered an aged society, and a proportion of 20% defines a super-aged society. According to a 2022 announcement from China’s National Bureau of Statistics, individuals aged 60 and over accounted for 19.8% of the total population, while those aged 65 and over accounted for 14.9%. China is expected to enter a super-aged society by 2031 <sup>[2]</sup>. As China moves toward a deeply aged society, promoting healthy aging has become a key objective <sup>[3]</sup>.

The prevalence and incidence of frailty vary significantly across countries and regions. Surveys from the Survey of Health, Ageing, and Retirement in Europe (SHARE) found that Italy and Spain have a higher prevalence of frailty, while high-income countries generally show a lower prevalence <sup>[4]</sup>. Although the definition of frailty is not yet unified, most studies use the Frailty Phenotype assessment by Fried or the Frailty Index developed by Rockwood <sup>[5]</sup>. Frailty prevalence also differs based on assessment methods, with lower prevalence reported when using tools that measure only physical frailty, such as the Fried Frailty Phenotype (14.6%) <sup>[6]</sup>. Assessment tools focused on physical frailty provide a narrower, more specific definition of frailty and offer better comparability across studies.

Frailty prevalence also varies by setting. A meta-analysis of 56,407 elderly individuals highlighted differences in frailty prevalence across medical environments (community, outpatient, nursing home, hospitalization), finding the highest prevalence in hospitalized elderly people (39.3%) and the lowest in nursing homes (20%) <sup>[7]</sup>. This may relate to cultural and lifestyle differences across regions.

Frailty is a dynamic process influenced by multiple factors. Sociodemographic factors (age, gender, education level, income, living arrangements), physiological factors (weight, self-rated health, cognitive function, multimorbidity, polypharmacy), and behavioral factors (mobility limitations, smoking, drinking) are widely recognized as influencing frailty <sup>[8,9]</sup>. Although consensus exists on factors affecting frailty in community-dwelling elderly populations, differences in study design, region, population characteristics, and local medical levels continue to yield varied results, warranting further research.

Risk prediction models, also known as clinical prediction models, use statistical or machine learning methods to quantify health risks by analyzing patient characteristics, such as age, gender, medical history, and lifestyle <sup>[10]</sup>. These models include diagnostic models, which assess the likelihood of disease based on current symptoms and signs, and predictive models, which estimate future health outcomes <sup>[11]</sup>.

The present study aims to examine the prevalence and risk factors of frailty in elderly individuals in Chinese communities and to construct a frailty risk prediction model using logistic regression analysis. Internal validation will be conducted to ensure model accuracy and reliability in clinical practice, thereby supporting elderly healthcare strategies, optimizing prevention and intervention measures, and ultimately enhancing the quality of life for the elderly.

## 2. Methods

### 2.1. Study design

This study selected community-dwelling elderly individuals aged 60 and above from a central urban district in Shanghai as research subjects, conducting the research from July 2022 to March 2023.

Inclusion criteria: (1) Community elderly population aged 60 and above; (2) Clear consciousness, normal understanding, and expression ability; (3) Informed consent and willingness to participate in the study.

Exclusion criteria: (1) Refusal to sign informed consent; (2) Severe hearing or vision impairment, impeding normal communication; (3) Patients with poorly controlled schizophrenia; (4) Patients with severe physical diseases, such as advanced cancer or severe heart failure, preventing frailty assessment. A total of 420 samples were collected for the modeling set.

## **2.2. Data collection**

### **2.2.1. General information questionnaire**

A self-designed General Information Survey Questionnaire was used, including variables such as gender, age, education level, self-assessed health status, marital status, children, type and manner of residence, average monthly household income, number of chronic diseases, walking speed, grip strength, and lifestyle factors such as alcohol consumption, smoking, exercise habits, social support networks, and social activities.

### **2.2.2. Frailty assessment**

The Fried Frailty Phenotype, a widely used clinical frailty assessment tool focused on biological indicators of multi-system decline, was employed. This study used a modified version of the Fried Frailty Phenotype for frailty assessment.

### **2.2.3. Nutrition status assessment**

The Mini Nutritional Assessment (MNA) <sup>[12,13]</sup>, developed by Vellas *et al.* in 1990, evaluates nutritional status comprehensively, without invasive examination. Although the simplified MNA-SF <sup>[14]</sup> exists, this study employed the full MNA due to its higher sensitivity and comprehensiveness.

### **2.2.4. Cognitive status assessment**

The Mini-Mental State Examination (MMSE) <sup>[15]</sup> is widely used clinically to assess cognitive function, covering 11 items across five cognitive domains.

### **2.2.5. Depression status assessment**

The Geriatric Depression Scale (GDS-5) <sup>[16]</sup>, comprising five items and with a total score of 5 points, served as a screening tool for depressive symptoms. A score above 2 indicates depression, with higher scores suggesting increased severity.

### **2.2.6. Daily living ability assessment**

The Assessment of Activities of Daily Living (ADL) <sup>[17]</sup> includes two scales: the Basic Activities of Daily Living (BADL) scale and the Instrumental Activities of Daily Living (IADL) scale.

### **2.2.7. Sarcopenia screening**

The Strength, Assistance with Walking, Rising from a Chair, Climbing Stairs, and Falls (SARC-F) Scale <sup>[18]</sup> screens for sarcopenia risk with five items, each scored from 0 (none) to 2 (a lot or unable). A score of  $\geq 4$  suggests a need for further evaluation.



### 2.2.8. Social support assessment

The Social Support Rating Scale (SSRS) [8] measures social support across three dimensions: subjective support, objective support, and utilization of support, totaling ten items.

## 2.3. Statistical methods

Data normality was first assessed using the Shapiro-Wilk test. Normally distributed data were expressed as mean  $\pm$  standard deviation (SD) and analyzed using the two-sample *t*-test, while non-normally distributed data were described using the median and interquartile range, analyzed with the Wilcoxon rank-sum test. Categorical data were presented with frequencies and percentages, compared across groups using the chi-squared or Fisher's exact test. Variables with significant differences ( $P < 0.05$ ) in univariate analysis were selected. Stepwise forward logistic regression was used to address multicollinearity and identify predictive factors from the significant univariate variables. A multivariable logistic regression equation was developed, with results expressed as odds ratios (OR) and 95% confidence intervals (CI). A nomogram was constructed for visual analysis.

The model's discrimination was assessed using the area under the receiver operating characteristic curve (AUC), and a calibration curve evaluated the goodness of fit. Clinical benefit was evaluated with a decision curve. All analyses used two-tailed tests with  $P < 0.05$  as statistically significant.

For the validation set, the model's diagnostic ability was analyzed with the AUC, and calibration was assessed with a calibration curve. Clinical benefit was evaluated with a decision curve analysis (DCA).

Data analysis and visualization were performed using R software (R Version 4.3.1), including the "glmnet," "rms," "gplots," "Matrix," "pROC," and "ResourceSelection" packages, with *P*-values interpreted using two-tailed tests and  $P < 0.05$  as the significance threshold.

## 3. Results

A total of 420 community-dwelling elderly individuals participated in the modeling set for this study, divided into a frail group and a non-frail group, as shown in **Table 1**.

**Table 1.** Prevalence of frailty in community-dwelling elderly individuals in the modeling set ( $n = 420$ )

Frailty scale	Grouping	Categorization	Number	Proportion (%)
Frailty phenotype	Non-frail group	Health status	203	48.3
		Pre-frailty	186	44.3
	Frail group	Frailty	31	7.4

### 3.1. Univariate analysis

#### 3.1.1. Sociodemographic data

A Wilcoxon test was conducted to analyze sociodemographic data between the frail and non-frail groups, with detailed results shown in **Table 2**.

**Table 2.** Univariate analysis of socio-demographic data

Item		Non-frailty ( <i>n</i> = 389)	Frailty ( <i>n</i> = 31)	<i>Z</i> / $\chi^2$	<i>P</i>
Gender	Male	150 (38.6%)	14 (45.2%)	0.526	0.567
	Female	239 (61.4%)	17 (54.8%)		
Age		72 (68, 76)	77 (75, 83)	-4.434	< 0.001
Education	Elementary school or below	31 (8.0%)	2 (6.5%)	2.649	0.449
	Junior high school	109 (28.0%)	6 (19.3%)		
	High school / Vocational high school	130 (33.4%)	15 (48.4%)		
	College degree or above	119 (30.6%)	8 (25.8%)		
Marital status	Married	313 (80.5%)	26 (83.9%)	0.214	0.643
	Unmarried / Widowed / Divorced	76 (19.5%)	5 (16.1%)		
Income situation (Chinese Yuan)	< 2,000	13 (3.0%)	1 (3.2%)	2.135	0.477
	2,000–4,999	117 (30.1%)	12 (38.7%)		
	5,000–9,999	237 (60.9%)	18 (58.1%)		
	≥ 10,000	22 (6.0%)	0 (0.0%)		
Social Support Rating Scale		14 (12, 16)	15 (13, 18)	-2.083	0.037

### 3.1.2. Physical health-related data

The univariate analysis results of physical health conditions between frail and non-frail groups are presented in **Table 3**.

**Table 3.** Univariate analysis of physical health-related data

Item		Non-frailty ( <i>n</i> = 389)	Frailty ( <i>n</i> = 31)	<i>Z</i> / $\chi^2$	<i>P</i>
Meditation time	< 2 h	75 (19.3%)	5 (16.1%)	0.286	0.867
	2–4 h	135 (34.7%)	12 (38.7%)		
	> 4 h	179 (46.0%)	14 (45.2%)		
Sleep time		6.9 (5.8, 8.1)	5.3 (5.1, 6.5)	-5.336	< 0.001
Body mass index	Underweight	16 (4.1%)	3 (9.7%)	6.032	0.088
	Healthy weight	192 (49.4%)	20 (64.5%)		
	Overweight	142 (36.5%)	7 (22.6%)		
	Obesity	39 (10.0%)	1 (3.2%)		
Walking pace	Slow pace	110 (28.3%)	22 (71.0%)	24.280	< 0.001
	Normal pace	279 (71.7%)	9 (29.0%)		
Grip strength	Decreased grip strength	99 (25.4%)	26 (83.9%)	46.878	< 0.001
	Normal grip strength	290 (74.6%)	5 (16.1%)		
MNA	Risk of malnutrition	15 (3.9%)	9 (29.0%)	33.778	< 0.001
	Good nutrition	374 (96.1%)	22 (71.0%)		

**Table 3 (Continued)**

Item		Non-frailty ( <i>n</i> = 389)	Frailty ( <i>n</i> = 31)	<i>Z</i> / $\chi^2$	<i>P</i>
ADL	Normal	357 (91.8%)	22 (71.0%)	12.168	0.002
	Decreased functionality	24 (6.2%)	6 (19.4%)		
	Dysfunction	8 (2.0%)	3 (9.6%)		

### 3.1.3. Chronic disease and complication data

Results of univariate analysis for chronic diseases and complications are detailed in **Table 4**.

**Table 4.** Univariate analysis of chronic diseases and complications [*n* (%)]

Item		Non-frailty ( <i>n</i> = 389)	Frailty ( <i>n</i> = 31)	$\chi^2$	<i>P</i>
> 5 chronic diseases	Yes	82 (21.1%)	11 (35.5%)	3.455	0.063
	No	307 (78.9%)	20 (64.5%)		
Fatigue	Yes	132 (33.9%)	23 (74.2%)	19.987	< 0.001
	No	257 (66.1%)	8 (25.8%)		
Five Times Sit to Stand Test	Risk-free	177 (45.5%)	7 (22.6%)	6.128	0.014
	Fall risks	212 (54.5%)	24 (77.4%)		
Reduced food intake	Yes	52 (13.4%)	9 (29.0%)	5.675	0.030
	no	337 (86.6%)	22 (71.0%)		
Vision problems	Yes	76 (19.5%)	14 (45.2%)	11.197	0.001
	No	313 (80.5%)	17 (54.8%)		
Hearing issues	Yes	46 (11.8%)	11 (35.5%)	13.701	0.001
	No	343 (88.2%)	20 (64.5%)		
SARC-F	No sarcopenia	367 (94.3%)	19 (61.3%)	42.164	< 0.001
	Sarcopenia	22 (5.7%)	12 (38.7%)		

### 3.1.4. Cognitive function

Univariate analysis indicates statistically significant differences in cognitive function between frail and non-frail groups (*P* = 0.014), as shown in **Table 5**.

**Table 5.** Univariate analysis of cognitive function

Item		Non-frailty ( <i>n</i> = 389)	Frailty ( <i>n</i> = 31)	$\chi^2$	<i>P</i>
GDS-5	Normal	349 (89.7%)	27 (87.1%)	0.210	0.552
	Depression	40 (10.3%)	4 (12.9%)		
MMSE	Normal cognition	247 (63.5%)	13 (41.9%)	9.945	0.014
	Mild cognitive impairment	104 (26.7%)	13 (41.9%)		
	Moderate cognitive impairment	25 (6.4%)	1 (3.2%)		
	Severe cognitive impairment	13 (3.3%)	4 (12.9%)		

### 3.2. Multivariate logistic regression analysis

Binary logistic regression analysis was employed to further assess the factors influencing the degree of frailty. The dependent variable was the occurrence of frailty, and the independent variables were the 17 factors selected from the univariate analysis ( $P < 0.05$ ). A forward stepwise logistic regression method based on the partial maximum likelihood estimation was used for the multivariate logistic regression analysis. The assignment table of independent variables is shown in **Table 6**.

**Table 6.** Assignment table of independent variables

Item	Assignment
Age	Continuous variable
SSRS	Continuous variable
Sleep duration	Continuous variable
Hemoglobin	Continuous variable
Blood urea nitrogen (BUN)	Continuous variable
Blood glucose	Continuous variable
Fatigue	1 = Yes, 2 = No
Fall risk	0 = No risk of falling, 1 = Risk of falling
Reduced food intake	1 = No reduction in eating, 2 = Reduction in eating
Vision problems	1 = No, 2 = Yes
Hearing issues	1 = No, 2 = Yes
Decreased walking pace	0 = No, 1 = Yes
Decreased grip strength	0 = No, 1 = Yes
SARC-F	0 = Negative screening, 1 = Positive screening
MNA	0 = Good nutritional status, 1 = Risk of malnutrition
MMSE	1 = Normal cognitive function, 2 = Mild cognitive impairment, 3 = Moderate cognitive impairment, 4 = Severe cognitive impairment
ADL	0 = Completely normal, 1 = Decreased functionality, 2 = Significant dysfunction

The multivariate analysis results (**Table 7**) indicate that positive sarcopenia screening (OR = 20.625, 95% CI: 4.822–88.216), risk of malnutrition (OR = 16.899, 95% CI: 3.008–94.927), decreased grip strength (OR = 29.837, 95% CI: 7.010–126.996), and presence of fatigue (OR = 16.326, 95% CI: 4.18–63.768) are risk factors for the occurrence of frailty, while extended sleep duration is a protective factor against frailty. Notably, increased social support appears to be a risk factor for the development of frailty.

**Table 7.** Multivariate logistic regression analysis

Variable	$\beta$	Standard error	Distinctiveness	OR	95% Confidence interval	
					Lower limit	Upper limit
SSRS	0.336	0.100	0.001	1.399	1.15	1.702
Sleep time	-1.230	0.320	< 0.001	0.292	0.156	0.547
Fatigue	2.793	0.695	< 0.001	16.326	4.18	63.768
Grip strength	3.396	0.739	< 0.001	29.837	7.010	126.996
MNA	2.827	0.881	0.001	16.899	3.008	94.927
SARC-F	3.026	0.741	< 0.001	20.625	4.822	88.216
Constant	-7.016	2.573	0.006			

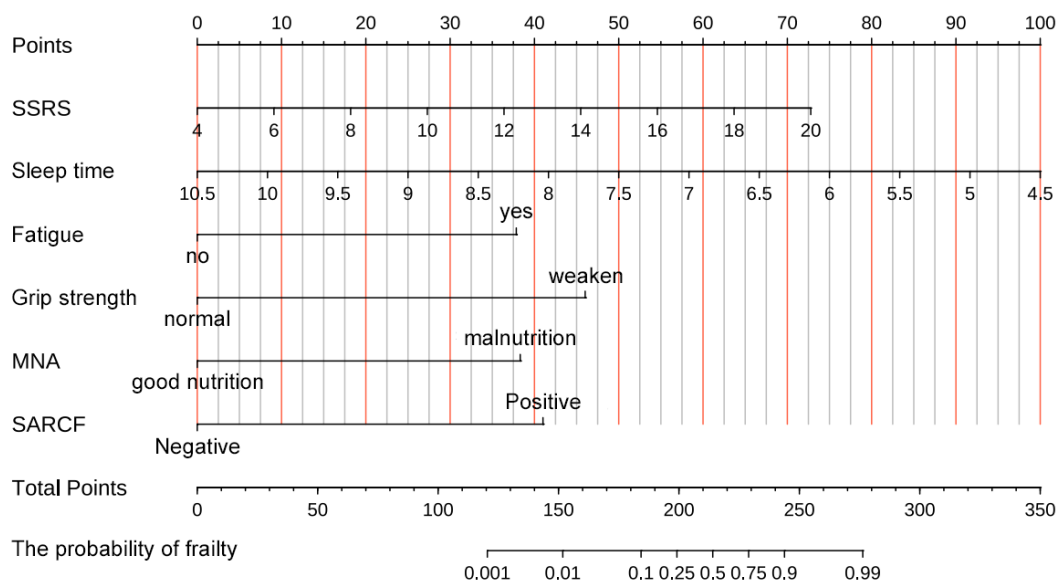
The logistic regression identified six independent frailty-related factors: SSRS score, sleep duration, fatigue, grip strength, MNA, and SARC-F. Based on these factors, the frailty risk prediction model equation is:

$$\text{Logit} = 0.336 \times \text{SSRS} - 1.230 \times \text{Sleep duration} + 2.793 \times \text{Fatigue} + 3.396 \times \text{Grip strength} + 2.827 \times \text{MNA} + 3.026 \times \text{SARC-F}$$

### 3.3. Frailty risk prediction nomogram

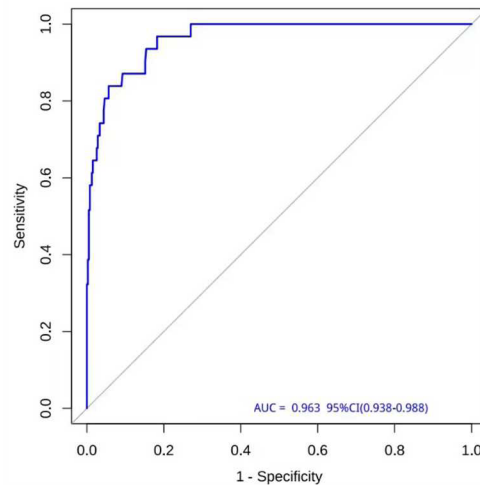
#### 3.3.1. Construction of a frailty risk prediction nomogram

Based on the community elderly frailty risk prediction model as described, a nomogram was developed. This nomogram assigns scores to six independent variables: SSRS, sleep duration, fatigue, grip strength, MNA, and SARC-F, according to the magnitude of their regression coefficients in the model, reflecting the importance of each variable in predicting frailty occurrence, as shown in **Figure 1**.

**Figure 1.** Nomogram for community elderly frailty risk prediction model

### 3.3.2. ROC curve of the community elderly frailty risk prediction model in the modeling set

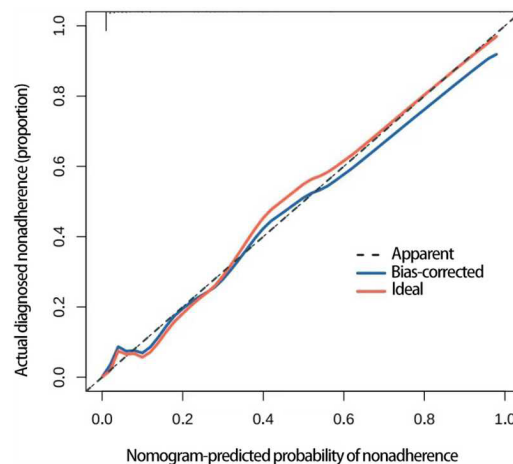
The nomogram model's performance was evaluated using modeling set data, with the ROC curve plotted and the AUC calculated. The model's AUC in the training set was 0.968 (95% CI: 0.938–0.988), with a sensitivity of 0.968, specificity of 0.817, Youden's index of 0.785, and an accuracy of 0.829 in identifying frailty, as shown in **Figure 2**.



**Figure 2.** ROC curve of the community-based frailty risk prediction model for the elderly

### 3.3.3. Calibration curve of the community elderly frailty risk prediction model in the modeling set

The predicted probabilities of frailty are closely aligned with actual occurrences, indicating high accuracy, as shown in **Figure 3**.

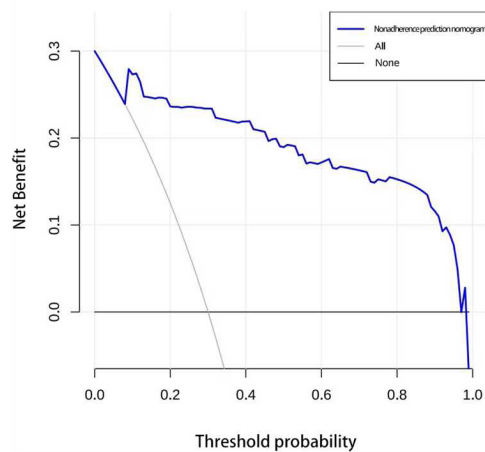


**Figure 3.** Calibration curve of the community-based frailty risk prediction model for the elderly

### 3.3.4. Decision Curve Analysis for predicting frailty risk in the modeling set

Decision Curve Analysis (DCA) visually assesses clinical applicability by showing changes in net clinical benefit across various thresholds. The DCA curve for the modeling set is positioned above both extremes, indicating good clinical utility with considerable net benefit. This is demonstrated in **Figure 4**. Internal validation resulted in a Brier Score of 0.056, showing the model's high predictive accuracy.





**Figure 4.** DCA for a community-based frailty risk prediction model for the elderly

### 3.4. Comparison of sociodemographic data between the modeling set and validation set

The study presents a univariate analysis of sociodemographic data between the modeling cohort ( $n = 420$ ) and the validation cohort ( $n = 180$ ), as detailed in **Table 8**.

**Table 8.** Univariate analysis of sociodemographic data of community elderly people in the modeling set and the validation set [ $n$  (%)]

Item		Modeling set ( $n = 420$ )	Validation set ( $n = 180$ )	$\chi^2$	$P$
Gender	Male	164 (39%)	61 (33.9%)	1.431	0.232
	Female	256 (61%)	119 (66.1%)		
Education	Elementary school and below	26 (6.2%)	9 (5.0%)	0.435	0.933
	Junior high school	116 (27.6%)	48 (26.7%)		
	High school / vocational high school	147 (35.0%)	65 (36.1%)		
	College degree or above	131 (31.2%)	58 (32.2%)		
Marital status	Married	339 (80.7%)	142 (78.9%)	0.264	0.607
	Unmarried / widowed / divorced	81 (19.3%)	38 (21.1%)		
Income	< 2,000	3 (0.7%)	2 (1.1%)	5.469	0.242
	2,000–4,999	129 (30.7%)	47 (26.1%)		
	5,000–9,999	255 (60.7%)	116 (64.4%)		
	$\geq 10,000$	22 (5.2%)	14 (7.8%)		
$\geq 5$ chronic disease	Yes	93 (22.1%)	42 (23.3%)	0.102	0.749
	No	327 (77.9%)	138 (76.7%)		
BMI	Underweight	19 (4.5%)	9 (5.0%)	4.573	0.206
	Normal weight	213 (50.7%)	99 (55.0%)		
	Overweight	148 (35.2%)	64 (35.6%)		
	Obesity	40 (83.3%)	8 (4.4%)		

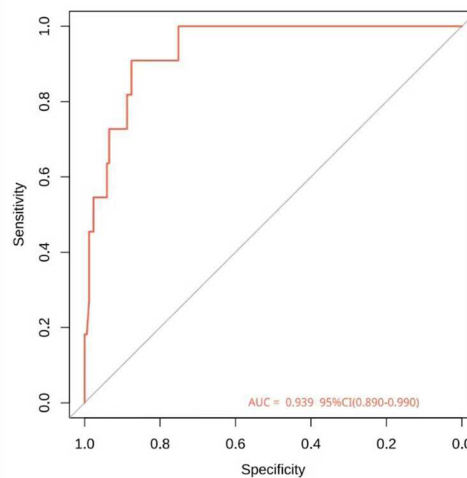
**Table 8 (Continued)**

	Item	Modeling set ( <i>n</i> = 420)	Validation set ( <i>n</i> = 180)	$\chi^2$	<i>P</i>
Walking pace	Slow pace	130 (31.1%)	53 (29.4%)	0.162	0.687
	Normal pace	288 (68.9%)	127 (70.6%)		
Grip strength	Decreased grip strength	125 (29.8%)	54 (30.0%)	0.003	0.953
	Normal grip strength	295 (70.2%)	126 (70.0%)		
Meditation time	< 2 h	80 (19.0%)	38 (21.1%)	4.309	0.230
	2–4 h	131 (31.2%)	65 (36.1%)		
	> 4 h	193 (46.0%)	67 (37.2%)		
Age	60–69 year	131 (31.2%)	65 (36.1%)	1.632	0.442
	70–79 year	222 (52.9%)	91 (50.6%)		
	≥ 80 year	67 (16.0%)	24 (13.3%)		
Sleep time	< 7h	231 (55.0%)	111 (61.7%)	2.285	0.131
	≥ 7h	189 (45.0%)	69 (38.3%)		

### 3.5. Internal validation of the frailty risk prediction model

#### 3.5.1. Discriminative performance of the model in the validation set

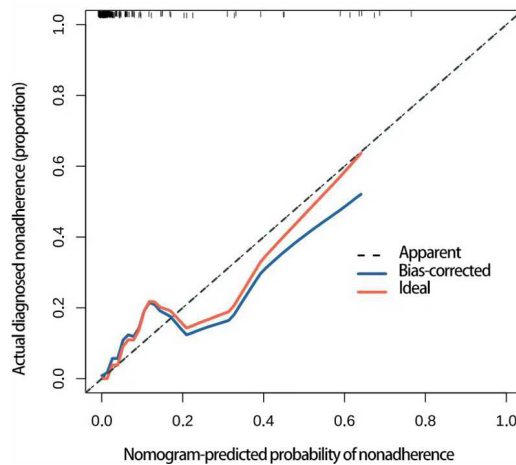
Using validation set data (*n* = 180), the model achieved an AUC of 0.939 (95% CI: 0.890–0.990) with a sensitivity of 0.909, specificity of 0.876, Youden’s index of 0.785, and an accuracy of 0.878. These metrics indicate good generalizability and predictive performance. See **Figure 5** for details.



**Figure 5.** ROC curve of frailty risk prediction model for the elderly in the community validation set

#### 3.5.2. Calibration of the model on the validation set

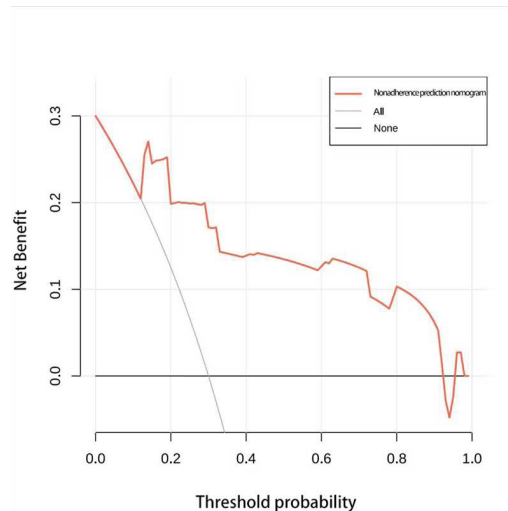
The calibration curve aligns closely with the ideal line, indicating acceptable calibration (Hosmer-Lemeshow test,  $\chi^2 = 2.321$ , *P* = 0.970), as shown in **Figure 6**.



**Figure 6.** Calibration curve of frailty risk prediction model for the elderly in the community validation set

### 3.5.3. Clinical effectiveness evaluation of the model in the validation set

DCA curves for the validation set are positioned above the extreme thresholds of “no clinical intervention for any patients” and “clinical intervention for all patients,” suggesting high clinical utility and net benefit, as detailed in **Figure 7**. The Brier Score of 0.034 in internal validation indicates the model’s strong predictive accuracy.



**Figure 7.** ROC curve for the frailty risk prediction model in the community elderly validation set

## 4. Discussion

Currently, China is gradually entering a stage of deep population aging, with the issue of aging becoming increasingly severe. As the proportion of the elderly population continues to rise, effectively improving the quality of health and elderly care services has become an urgent societal issue to address.

The ultimate goal of this research is to provide scientific evidence for improving and refining health and elderly care services through early prediction of frailty risks, thereby laying the foundation for preventing

adverse clinical events in the elderly. The first part of the study has completed the construction of the frailty risk prediction model, and further data collection is needed to complete model validation.

## **4.1. The clinical significance of building a frailty risk prediction model**

### **4.1.1. The importance of constructing a frailty risk prediction model**

Appropriate interventions may improve frailty status; however, interventions implemented in community-dwelling older adults have generally shown limited effectiveness. Many older adults are reluctant to be labeled as “frail,” and even if they have been identified as such, they still strive to appear healthy<sup>[19]</sup>. Some intervention studies targeting frailty have demonstrated that timely intervention and management can reduce the risk of frailty. This suggests that taking preventive measures in the early stages before frailty develops is crucial<sup>[20]</sup>. Therefore, one of the key strategies to address frailty is to identify high-risk but non-frail older adults and implement preventive interventions for them<sup>[21]</sup>.

## **4.2. Analysis of the incidence of frailty in community-dwelling elderly**

This study assessed the prevalence of frailty in the study population using the Fried Frailty Phenotype, with the frailty prevalence in the modeled community-dwelling elderly population being 7.4%. As seen in Table 1.1, a considerable proportion of the population is in the pre-frail stage. Although these individuals have not yet entered the frailty state, they are already exhibiting some early symptoms of frailty, indicating a decline in their health status that warrants close attention.

A comparison of frailty prevalence among elderly individuals across different economic regions in China and studies using various assessment tools shows that a 2019 systematic review by Han *et al.*, involving community-dwelling elderly from five regions—Beijing, Hong Kong, Jinan, Langfang, and Taiwan—reported an average frailty prevalence of 10% in China’s community elderly population<sup>[22]</sup>. In 2023, Zhou *et al.* expanded the regions included in their study to 23 provinces, and a meta-analysis indicated that the overall frailty prevalence among Chinese community residents was 10.1%<sup>[23]</sup>. The frailty incidence in this study is lower than in the above studies; however, another cross-sectional study conducted in Shanghai reported a frailty prevalence of 8.0% among community-dwelling elderly<sup>[24]</sup>.

Currently, there is no gold standard for measuring frailty, and most studies use the Fried Frailty Phenotype and Frailty Index (FI) to assess frailty<sup>[25]</sup>. Different frailty assessment tools may also lead to variations in frailty incidence. The frailty prevalence derived from the Fried Frailty Phenotype tends to be lower compared to other multidimensional frailty assessment tools<sup>[26]</sup>. A meta-analysis of the multidimensional frailty screening tool Tilburg Frailty Indicator (TFI) showed that the frailty incidence assessed using TFI was 41%<sup>[27]</sup>.

## **4.3. Selection of modeling elements for community frailty risk prediction model**

### **4.3.1. Sleep duration**

#### **4.3.1.1. Shortened sleep duration as an important risk factor for frailty**

Previous studies have shown that short sleep duration and poor sleep quality are significant risk factors for developing frailty. Frailty, characterized as a state of age-related decline in physiological reserve and increased vulnerability, often progresses alongside deteriorating sleep quality, potentially leading to various adverse health outcomes<sup>[28]</sup>. Sleep problems are a multidimensional concept, including aspects such as poor sleep quality, daytime sleepiness, short sleep duration, and insomnia symptoms<sup>[29]</sup>. The Pittsburgh Sleep Quality Index (PSQI)

is commonly used to quantify sleep quality in older adults. A cross-sectional study involving 392 older adults over the age of 65 found that participants reporting poor subjective sleep quality were more likely to exhibit symptoms of frailty<sup>[30]</sup>, emphasizing the direct link between sleep quality and frailty.

This study utilized validated sleep monitoring tools to examine the impact of sleep duration on frailty. The analysis indicated that extended sleep duration (OR = 0.292) was associated with a reduced risk of frailty, highlighting the importance of adequate sleep in preventing frailty and suggesting that optimizing sleep patterns may be an effective approach to reducing frailty risk.

#### **4.3.2. Malnutrition**

##### **4.3.2.1. Malnutrition as a risk factor for frailty in the elderly community**

Malnutrition includes both overnutrition and undernutrition, but in the elderly population, it predominantly refers to undernutrition. Approximately one-quarter of individuals over 65 are at risk of malnutrition<sup>[31]</sup>. Malnutrition can be classified into three categories based on its causes: malnutrition due to inflammatory diseases, malnutrition due to non-inflammatory diseases, and malnutrition due to non-disease factors<sup>[32]</sup>.

This study used the MNA to assess the nutritional status of elderly community residents. Results showed that 396 (94.3%) of the elderly were classified as having good nutritional status, while 24 (5.7%) were at risk of malnutrition. Although most elderly individuals in the community have good nutritional status, a small portion face undernutrition, which requires further attention and intervention.

Univariate analysis revealed a higher proportion of frailty among older adults at risk of malnutrition. Specifically, 9 (29.03%) of those at risk exhibited frailty, compared to only 22 (5.67%) of those with good nutritional status. This statistically significant difference ( $P < 0.001$ ) demonstrates a clear association between nutritional status and frailty, with findings consistent with previous research.

#### **4.3.3. Fatigue**

##### **4.3.3.1. The close relationship between fatigue and frailty in chronic diseases among the elderly**

Frailty, a state of gradual physical function decline, is characterized by core features such as fatigue, reduced grip strength, unintentional weight loss, and decreased physical activity<sup>[10]</sup>. Fatigue, described as extreme tiredness or drowsiness from insufficient sleep, prolonged labor, or stress, may signal age-related depletion of physiological reserves, posing risks for adverse health outcomes<sup>[33]</sup>. Although not yet considered a specific disease of old age, fatigue's strong association with chronic diseases in the elderly has garnered increased attention.

##### **4.3.3.2. Fatigue as an independent risk factor for frailty**

This study further confirmed that increased fatigue is an independent risk factor for frailty onset, with a weight of 16%, aligning with findings from most prior studies. A longitudinal aging study in Finland, spanning nine years, demonstrated that fatigue could be observed as an early marker of frailty, up to nine years before frailty manifests<sup>[34]</sup>. This finding underscores the critical role of fatigue in frailty onset and progression.

#### **4.3.4. Sarcopenia and grip strength**

##### **4.3.4.1. Sarcopenia and decreased grip strength as risk factors for frailty in community-dwelling older adults**

Grip strength, a key indicator of muscle strength, reflects changes in overall muscle strength. A cross-sectional

study found that decreased grip strength is a significant predictor of sarcopenia in older adults, with lower grip strength correlating with higher sarcopenia incidence <sup>[35]</sup>. Another study linked reduced grip strength with physical activity, balance ability, and cognitive function, making it an important indicator for assessing the health of this population <sup>[36]</sup>. These findings suggest that declining grip strength may serve as an early warning sign of muscle weakness and muscle mass reduction in older adults, which is crucial for the timely detection and management of sarcopenia.

This study found that decreased grip strength and positive screening for sarcopenia were independent risk factors for frailty in community-dwelling older adults. Data from **Tables 3** and **4** show that 29.8% of older adults had decreased grip strength, indicating that reduced grip strength is relatively common in this group. Additionally, the proportion of positive sarcopenia screenings was 8.1%, which, though relatively low, still requires attention.

### **4.3.5. Social support**

#### **4.3.5.1. Social support is closely related to the health of the elderly**

Social support is a complex, multidimensional concept that includes various forms of support individuals gain through relationships with others, encompassing emotional support, informational support, practical assistance, and social belonging. These elements, forming the Social Support Scale, highlight the importance of subjective support <sup>[37]</sup>. Research indicates that increased social support significantly reduces mortality rates among the elderly <sup>[38]</sup>, demonstrating its critical role in maintaining their health.

#### **4.3.5.2. Frail elderly in the community require more social support**

This study found a negative correlation between the level of social support and frailty occurrence, differing from prior research conclusions. Frail older adults reported higher levels of social support in the questionnaire, possibly reflecting the increased support needs among frail individuals, who may require assistance from family, the community, and social institutions to cope with frailty. By contrast, those with active social lives might report a smaller discrepancy between subjective expectations and reality, resulting in lower questionnaire scores. For example, an elderly person with an SSRS score of 20 might need more social support than one with a score of 10. The SSRS score could represent the gap between actual support received and the objective circumstances of frail individuals.

In conclusion, social support plays a vital role in preventing and managing frailty from a multidimensional perspective, encompassing family care, community programs such as elder education, and multidisciplinary medical teams involving general practitioners, nurses, and rehabilitation therapists to provide comprehensive, multi-level support <sup>[39]</sup>.

## **4.4. The application and discussion of line graphs in medical research**

### **4.4.1. Definition and uses of a nomogram**

Based on the previously constructed frailty risk prediction model for community-dwelling elderly individuals, a nomogram was developed. This nomogram assigns scores to six variables—SSRS, sleep duration, fatigue, grip strength, MNA, and SARC-F—to visually reflect the significance of each variable in determining frailty risk. In practical clinical use, healthcare professionals can determine the score for each variable based on the patient's actual condition, sum these scores, and then calculate the total. This total score corresponds to a probability



value for frailty, thus providing an estimate of the patient's frailty risk.

#### **4.4.2. Analysis of the variables in the nomogram for this study**

The nomogram results in this study highlight six major variables: SSRS, sleep duration, fatigue, grip strength, MNA, and SARC-F. Each variable is assigned a score based on its levels, and these scores collectively determine the total score, which corresponds to a specific probability of frailty.

By summing the scores from various health variables in the nomogram, a total score is obtained, which summarizes an individual's health status across multiple dimensions. This total score is directly proportional to frailty risk; the higher the total score, the greater the frailty risk. In the lower score range (below 100 points), the probability of frailty remains relatively low, while in the higher score range (above 150 points), the probability of frailty increases significantly.

#### **4.4.3. Visual presentation of multivariable analysis using the nomogram**

The study further validated the constructed frailty risk prediction model by collecting health check-up data from elderly individuals in the same community over different time periods. During validation, the model's discrimination, calibration, and effectiveness in clinical settings were comprehensively analyzed. Results showed that the frailty risk prediction model performed well across key metrics, exhibiting high discrimination, good calibration, and strong clinical applicability. These validation results affirm the model's reliability and practical value, establishing a foundation for its potential widespread application.

Applying this model in community healthcare practice enables early identification of elderly individuals at risk of frailty, providing a scientific basis for enhancing elderly health care. Early intervention can help lower the probability of frailty in elderly individuals, prevent adverse clinical events, improve quality of life, and reduce the healthcare burden on families and society.

#### **4.5. Evaluation of internal consistency and clinical performance of a frailty risk prediction model for community-dwelling elderly**

The model constructed in this study, after internal validation correction, achieved a C-statistic of 0.939 (95% CI: 0.890–0.990) in the validation set, a Brier score of 0.034, and the calibration curve demonstrates that the model's predicted frailty occurrence aligns with actual frailty incidence. With a specificity of 0.876, a Youden's index of 0.785, and an accuracy of 0.878, the model exhibits strong clinical effectiveness as reflected in the DCA curve, which remains above the two extreme threshold curves.

Overall, the frailty risk prediction model for the community-dwelling elderly developed in this study shows strong internal consistency and clinical performance. It can effectively differentiate between high- and low-risk elderly individuals for frailty and offers valuable decision-support information for clinicians.

### **5. Conclusion**

- (1) Frailty in community elderly is affected by six factors: The prevalence of frailty among elderly individuals aged 60 and above in Shanghai communities is 7.4%. Independent risk factors for frailty include short sleep duration, malnutrition, fatigue, sarcopenia, and decreased grip strength, while extended sleep duration serves as a protective factor. Frail elderly individuals especially require

adequate social support.

- (2) The frailty risk prediction model constructed in this study shows good discrimination, calibration, and clinical utility for preliminary frailty risk assessment: The risk prediction model developed for frailty is defined as  $\text{Logit} = 0.336 \times \text{SSRS} - 1.230 \times \text{Sleep Time} + 2.793 \times \text{Fatigue} + 3.396 \times \text{Grip Strength} + 2.827 \times \text{MNA} + 3.026 \times \text{SARC-F}$ . This model has been validated for discriminative ability, calibration, and clinical utility, providing a personalized frailty risk assessment in community settings. Early targeted interventions based on this model hold significant value in preventing frailty.

## 6. Limitations

The study scope is limited to Shanghai, China, with samples drawn from a single community, thus requiring further research with larger samples and multicenter studies to assess the model's applicability in other regions or countries. Since model data is sourced exclusively from community residents' health check-ups, it is currently suitable only for preliminary frailty assessment of community residents in Shanghai.

## Disclosure statement

The authors declare no conflict of interest.

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# Clinical Implications of Eosinopenia in Adult Brucellosis Patients

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**Abstract:** *Objective:* To analyze the differences between eosinopenia and non-eosinopenia brucellosis patients in depth. *Methods:* Medical records of brucellosis patients admitted to the Affiliated Infectious Diseases Hospital of Soochow University between January 1, 2013, and December 31, 2023, were reviewed retrospectively. Patients were categorized into an eosinopenia group and a non-eosinopenia group based on pre-treatment eosinophil levels. A nonparametric test was performed to estimate the differences between the two groups. *Results:* Among the 125 patients, 66 (52.80%) experienced eosinopenia. Patients with eosinopenia were older ( $52.09 \pm 15.63$  years vs.  $46.08 \pm 16.39$  years,  $P = 0.024$ ), had a higher proportion of hypertension (21.21% vs. 6.78%,  $P = 0.024$ ), and exhibited a greater likelihood of complications (75.76% vs. 35.59%,  $P = 0.000$ ), particularly hematological (68.18% vs. 23.73%,  $P = 0.000$ ) and relapse (19.70% vs. 6.78%,  $P = 0.040$ ). The eosinopenia group also showed higher levels of ALT (29.00 vs. 20.00,  $P = 0.003$ ), AST (29.00 vs. 22.00,  $P = 0.037$ ), and LOS (17.50 vs. 12.00,  $P = 0.000$ ). Among certain inflammatory indicators related to brucellosis, the eosinopenia group demonstrated lower levels, such as MPV (9.75 vs. 10.70,  $P = 0.000$ ), MLR (0.28 vs. 0.36,  $P = 0.002$ ), and SIRI (0.67 vs. 1.03,  $P = 0.004$ ). *Conclusion:* Brucellosis patients with eosinopenia differed in clinical manifestations and prognosis. Monitoring eosinophils may provide better prognostic assessment and suggest potential new treatment options.

**Keywords:** Brucellosis; Eosinopenia; Complication; Prognosis

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## 1. Introduction

Brucellosis, one of the most neglected zoonotic diseases globally, poses a major threat to human health and increases social burden. In recent years, the epidemiology of human brucellosis has changed significantly, with its geographical spread continuously expanding, especially in Asia <sup>[1]</sup>. In China, brucellosis cases have rapidly



increased since the mid-1990s, making it one of the infectious diseases with the highest reported morbidity rates. The morbidity rate rose from 0.07 per 100,000 in 1995 to 4.95 per 100,000 in 2021, with the number of deaths ranking among the top 10 legally reported infectious diseases of categories A and B <sup>[2]</sup>. This infectious disease urgently requires increased attention and comprehensive research.

Brucellosis often has a long and recurrent course, affecting multiple systems and organs. Hematologic abnormalities are frequently observed and are associated with infection, hypersplenism, phagocytosis, myelosuppression, diffuse anticoagulation, and autoimmune hemolysis <sup>[3]</sup>. However, current research primarily focuses on diseases such as cytopenia, hemophagocytic lymphohistiocytosis, and myelofibrosis <sup>[3-6]</sup>, with limited studies on eosinophils. A recent study on brucellosis <sup>[7]</sup> suggests that eosinopenia is a significant laboratory finding, indicating that the role of eosinophils may have been underestimated.

The correlation between eosinopenia and the severity of infectious diseases has recently been observed in influenza, COVID-19, and varicella [8–10]. This study aimed to analyze the clinical characteristics of brucellosis patients with eosinopenia to identify possible mechanisms and therapeutic targets.

## **2. Materials and methods**

### **2.1. Ethics statement**

This study adheres to medical ethics standards and was reviewed and approved by the Ethical Review Committee of the Affiliated Infectious Diseases Hospital of Soochow University (No: K2024-007-01). All treatments and procedures were performed with informed consent obtained from patients' family members.

### **2.2. Patient recruitment**

Brucellosis patients admitted to the Affiliated Infectious Diseases Hospital of Soochow University between January 1, 2013, and December 31, 2023, were considered eligible for enrollment. The inclusion criteria were as follows: (1) aged  $\geq 18$  years; (2) confirmed to have brucellosis by blood culture (blood samples cultured for more than seven days) or a positive serological test (Standard Tube Agglutination Test  $\geq 1:100$ ); (3) received standardized treatment; and (4) had complete clinical data. The exclusion criteria were as follows: (1) patients previously diagnosed with brucellosis; (2) patients for whom relapse could not be distinguished from reinfection; (3) patients with a history of infections, trauma, or surgery in the past month; (4) patients who were pregnant or lactating; and (5) patients with acute or chronic hepatitis, nephritis, tumors, blood system diseases, immune system diseases, or other severe organ diseases.

### **2.3. Data collection**

Collected data included demographic characteristics, clinical data, therapeutic schedule, and outcomes.

- (1) Demographic characteristics: Information on age, gender, epidemiological history, past medical history, personal history, symptoms, and complications was collected. All complications were determined based on the patient's symptoms and established laboratory tests and imaging examinations. Hematological abnormalities were defined as follows: blood hemoglobin  $< 120$  g/L for males and  $< 110$  g/L for females, leukocyte count  $< 4 \times 10^9$ /L, platelet count  $< 150 \times 10^9$ /L, and leukocyte count  $> 10 \times 10^9$ /L, corresponding to anemia, leukopenia, thrombocytopenia, and leukocytosis, respectively. Osteoarticular, respiratory, and genitourinary involvements were identified through imaging examinations, while



gastrointestinal involvement was indicated by elevated alanine aminotransferase or aspartate aminotransferase levels and related clinical symptoms.

- (2) Clinical data: Blood test results and inflammatory indicators were recorded. All blood samples were collected on the day of admission or the following morning after fasting. Blood test parameters included serum leukocyte count (WBC,  $10^9/L$ ), serum hemoglobin (HGB, g/L), serum platelet count (PLT,  $10^9/L$ ), serum neutrophil count (NE,  $10^9/L$ ), serum lymphocyte count (LY,  $10^9/L$ ), serum monocyte count (MON,  $10^9/L$ ), serum eosinophil count (EOS,  $10^9/L$ ), mean platelet volume (MPV, fL), red cell distribution width (RDW, %), alanine aminotransferase level (ALT, U/L), aspartate aminotransferase level (AST, U/L), gamma-glutamyl transferase level (GGT, U/L), alkaline phosphatase level (ALP, U/L), albumin (ALB, g/L), total bilirubin (TBIL,  $\mu\text{mol/L}$ ), serum creatinine (Cr,  $\mu\text{mol/L}$ ), glucose (GLU, mmol/L), serum C-reactive protein level (CRP), serum procalcitonin level (PCT), and microbiological results. Inflammation indices were calculated as follows: neutrophil-lymphocyte ratio (NLR) =  $NE \div LY$ ; platelet-lymphocyte ratio (PLR) =  $PLT \div LY$ ; monocyte-lymphocyte ratio (MLR) =  $MON \div LY$ ; systemic immune-inflammation index (SII) =  $PLT \times NE \div LY$ ; systemic inflammation response index (SIRI) =  $NE \times MON \div LY$ ; CALLY index =  $ALB \times LY \div (CRP \times 10)$ .
- (3) Therapeutic schedule: Information on treatment duration, therapeutic drugs, and length of stay (LOS) was recorded. Most patients received a 6-week course of treatment, which was extended based on symptoms if necessary. Patients with osteoarticular involvement received a 12-week course of treatment. Main therapeutic drugs included doxycycline (DOX), rifampicin (RIF), sulfamethoxazole/trimethoprim (SMZ/TMP), and ceftriaxone (CRO).
- (4) Outcomes: Outcomes were recorded as sequelae and relapse. Sequelae were considered present if the patient continued to experience discomfort related to brucellosis after *Brucella* had been eliminated from the body. If a patient exhibited symptoms associated with brucellosis during post-treatment follow-up, blood culture and serological tests were refined to confirm relapse.

## 2.4. Grouping criterion

Due to the absence of patients with elevated eosinophils, patients were categorized into eosinopenia and non-eosinopenia groups based on whether their pre-treatment eosinophil count was less than  $0.05 \times 10^9/L$ .

## 2.5. Statistical analysis

Data were analyzed using SPSS (IBM SPSS Statistics 23.0). Measurement data conforming to a normal distribution were expressed as mean  $\pm$  standard deviation (SD), with a *t*-test used for comparison between groups. Measurement data with a non-normal distribution were expressed as median (IQR), with comparisons between groups performed by the Mann-Whitney U test. Categorical data were expressed as percentages (%), with comparisons between groups performed by chi-squared test or Fisher exact test.  $P < 0.05$  was considered to indicate statistical significance.

# 3. Results

## 3.1. General characteristics

A total of 125 brucellosis patients were enrolled in the study, with 86 (68.80%) male and 39 (31.20%) female.

The average age was  $49.26 \pm 16.21$  years. Among them, 66 patients (52.80%) experienced eosinopenia. Patients with eosinopenia tended to be older ( $52.09 \pm 15.63$  years vs.  $46.08 \pm 16.39$  years,  $P = 0.024$ ) and exhibited a higher proportion of hypertension (21.21% vs 6.78%,  $P = 0.024$ ). No significant differences were noted between the eosinopenia and non-eosinopenia groups regarding diagnostic time, epidemiological history, personal history, or symptoms (**Table 1**).

**Table 1.** Comparison of epidemiological and clinical features between the eosinopenia group (Group 1) and the non-eosinopenia group (Group 2).

Variables	Total (n = 125)	Group 1 (n = 66)	Group 2 (n = 59)	P value
Male	86 (68.80%)	48 (72.73%)	38 (64.41%)	0.339
Age (years)	$49.26 \pm 16.21$	$52.09 \pm 15.63$	$46.08 \pm 16.39$	0.024
With epidemiology history	25 (20.00%)	11 (16.67%)	14 (23.73%)	0.375
Time consumed in diagnosis (months)	1.00 (0.50, 3.00)	1.00 (0.50, 2.00)	2.00 (0.75, 3.00)	0.058
Past history				
Hypertension	18 (14.40%)	14 (21.21%)	4 (6.78%)	0.024
Diabetes	10 (8.00%)	8 (12.12%)	2 (3.39%)	0.101
Personal history				
Smoking	19 (15.20%)	12 (18.18%)	7 (11.86%)	0.455
Drinking	5 (4.00%)	3 (4.55%)	2 (3.39%)	0.674
Symptoms				
Fever	115 (92.00%)	61 (92.42%)	54 (91.53%)	1.000
Weakness	115 (92.00%)	59 (89.39%)	56 (94.92%)	0.332
Arthralgia	101 (80.80%)	51 (77.27%)	50 (84.75%)	0.365
Sweating	75 (60.00%)	44 (66.67%)	31 (52.54%)	0.143
Muscle ache	55 (44.00%)	29 (43.94%)	26 (44.07%)	1.000
Lack of appetite	46 (36.80%)	28 (42.42%)	18 (30.51%)	0.196
Lymphadenopathy	15 (12.00%)	8 (12.12%)	7 (11.86%)	0.795
Cough	4 (3.20%)	2 (3.03%)	2 (3.39%)	1.000

### 3.2. Complications between eosinopenia and non-eosinopenia groups

The eosinopenia group showed a significantly higher probability of complications (75.76% vs. 35.59%,  $P = 0.000$ ). Hematological complications were more prevalent in the eosinopenia group (68.18% vs. 23.73%,  $P = 0.000$ ), with significantly higher rates of anemia (39.39% vs. 13.56%,  $P = 0.001$ ) and leukopenia (37.88% vs. 8.47%,  $P = 0.001$ ). There was no difference between groups for thrombocytopenia or leukocytosis. No differences were found for osteoarticular, respiratory, gastrointestinal, or genitourinary complications, though some complications occurred exclusively in the eosinopenia group (**Table 2**).

**Table 2.** Comparison of complications between the eosinopenia group (Group 1) and non-eosinopenia group (Group 2) [*n* (%)]

Variables	Total ( <i>n</i> = 125)	Group 1 ( <i>n</i> = 66)	Group 2 ( <i>n</i> = 59)	<i>P</i> value
With complications	71 (56.80%)	50 (75.76%)	21 (35.59%)	0.000
Hematological involvement	59 (47.20%)	45 (68.18%)	14 (23.73%)	0.000
Anemia	34 (27.20%)	26 (39.39%)	8 (13.56%)	0.001
Leukopenia	30 (24.00%)	25 (37.88%)	5 (8.47%)	0.000
Thrombocytopenia	9 (7.20%)	9 (13.64%)	0 (0.00%)	/
Leukocytosis	6 (4.80%)	3 (4.55%)	3 (5.08%)	1.000
Osteoarticular involvement	15 (12.00%)	10 (15.15%)	5 (8.47%)	0.283
Spondylodiscitis	11 (8.80%)	6 (9.09%)	5 (8.47%)	1.000
Sacroiliitis	2 (1.60%)	2 (3.03%)	0 (0.00%)	/
Osphyarthrosis	1 (0.8%)	1 (1.52%)	0 (0.00%)	/
Gonarthrits	1 (0.8%)	1 (1.52%)	0 (0.00%)	/
Gastrointestinal involvement	13 (10.40%)	9 (13.64%)	4 (6.78%)	0.251
Transaminase elevation	12 (9.60%)	8 (12.12%)	4 (6.78%)	0.373
Hepatosplenomegaly	1 (0.8%)	1 (1.52%)	0 (0.00%)	/
Respiratory involvement	3 (2.40%)	3 (4.55%)	0 (0.00%)	/
Hydrothorax	2 (1.60%)	2 (3.03%)	0 (0.00%)	/
Pneumonia	1 (0.8%)	1 (1.52%)	0 (0.00%)	/
Genitourinary involvement	1 (0.8%)	1 (1.52%)	0 (0.00%)	/
Epididymo-orchitis	1 (0.8%)	1 (1.52%)	0 (0.00%)	/
Two systems involvement	16 (12.80%)	14 (21.21%)	2 (3.39%)	0.003
More than two systems involvement	2 (1.60%)	2 (3.03%)	0 (0.00%)	/

### 3.3. Laboratory findings between eosinopenia and non-eosinopenia groups pre-treatment

Laboratory data taken before treatment initiation revealed that the eosinopenia group had lower WBC (4.44 [3.68, 6.43] vs. 5.70 [4.81, 6.70],  $P = 0.007$ ), HGB (125.00 [108.50, 133.00] vs. 134.00 [127.00, 141.00],  $P = 0.000$ ), PLT (169.00 [129.00, 228.75] vs. 220.00 [197.00, 274.00],  $P = 0.001$ ), and MON (0.37 [0.29, 0.48] vs. 0.52 [0.40, 0.81],  $P = 0.000$ ), but higher ALT (29.00 [16.00, 41.50] vs. 20.00 [11.00, 28.00],  $P = 0.003$ ) and AST (29.00 [19.00, 39.00] vs. 22.00 [15.00, 33.00],  $P = 0.037$ ) levels than the non-eosinopenia group. There were no significant differences in other indicators (**Table 3**).

**Table 3.** Comparison of laboratory findings between eosinopenia group (Group 1) and non-eosinopenia group (Group 2) pre-treatment

Variables	Total (n = 125)	Group 1 (n = 66)	Group 2 (n = 59)	P value
WBC ( $\times 10^9/L$ )	5.60 (4.09, 6.64)	4.44 (3.68, 6.43)	5.70 (4.81, 6.70)	0.007
HGB (g/L)	131.00 (116.00, 137.50)	125.00 (108.50, 133.00)	134.00 (127.00, 141.00)	0.000
PLT ( $\times 10^9/L$ )	208.00 (156.50, 265.50)	169.00 (129.00, 228.75)	220.00 (197.00, 274.00)	0.001
NE ( $\times 10^9/L$ )	3.06 (2.11, 4.32)	2.70 (1.78, 4.48)	3.09 (2.43, 4.30)	0.062
LY ( $\times 10^9/L$ )	1.51 (1.06, 1.83)	1.47 (1.05, 1.81)	1.61 (1.07, 1.90)	0.207
MON ( $\times 10^9/L$ )	0.43 (0.33, 0.66)	0.37 (0.29, 0.48)	0.52 (0.40, 0.81)	0.000
ALT (U/L)	21.00 (13.00, 37.50)	29.00 (16.00, 41.50)	20.00 (11.00, 28.00)	0.003
AST (U/L)	28.00 (18.00, 35.00)	29.00 (19.00, 39.00)	22.00 (15.00, 33.00)	0.037
GGT (U/L)	47.00 (33.00, 107.00)	47.00 (30.50, 94.00)	45.00 (36.00, 107.00)	0.089
ALP (U/L)	90.00 (78.00, 114.00)	90.00 (72.50, 110.50)	100.00 (79.00, 151.00)	0.145
Tbil ( $\mu\text{mol/L}$ )	11.50 (7.65, 14.90)	12.10 (7.65, 16.20)	11.50 (6.80, 12.20)	0.238
GLU (mmol/L)	5.42 (4.96, 6.37)	5.44 (5.11, 6.56)	5.30 (4.96, 5.82)	0.094
Creatinine ( $\mu\text{mol/L}$ )	56.35 (50.10, 69.48)	56.70 (49.25, 69.35)	55.80 (52.00, 72.00)	0.855
h-CRP (mg/L)	21.10 (10.40, 44.00)	20.80 (8.05, 33.95)	22.70 (11.15, 45.85)	0.376
PCT (ng/mL)	0.02 (0.00, 0.25)	0.00 (0.00, 0.45)	0.02 (0.00, 0.05)	0.221

### 3.4. Microbiological results, treatment, and outcomes

All patients in the study were referred after testing positive for blood cultures or having a serum agglutination test (SAT)  $\geq 1:100$  at an external facility. The eosinopenia group had a higher proportion of diagnoses based on blood culture (89.39% vs 72.88%,  $P = 0.021$ ). The duration of treatment did not differ significantly between groups; however, the length of stay was longer for patients with eosinopenia (17.50 [14.75, 23.00] vs. 12.00 [9.00, 14.00],  $P = 0.000$ ). The eosinopenia group also showed a higher likelihood of relapse (19.70% vs. 6.78%,  $P = 0.040$ ), though no differences were found for cases of multiple relapses or sequelae between the two groups (Table 4).

**Table 4.** Summary of microbiological, treatment, and outcome data between the eosinopenia group (Group 1) and non-eosinopenia group (Group 2)

Variables	Total (n = 125)	Group 1 (n = 66)	Group 2 (n = 59)	P value
Microbiological results				0.021
Blood culture	102 (81.60%)	59 (89.39%)	43 (72.88%)	
STA $\geq 1:100$	23 (18.40%)	7 (10.61%)	16 (27.12%)	
Treatment				
Treatment duration (weeks)	6.00 (6.00, 8.00)	6.00 (6.00, 8.00)	6.00 (6.00, 6.00)	0.558
LOS (days)	14.00 (12.00, 21.00)	17.50 (14.75, 23.00)	12.00 (9.00, 14.00)	0.000

**Table 4 (Continued)**

Variables	Total (n = 125)	Group 1 (n = 66)	Group 2 (n = 59)	P value
Antibiotic combinations				
DOX+RIF	89 (71.20%)	44 (66.67%)	45 (76.27%)	0.323
DOX+ SMZ/TMP	20 (16.00%)	11 (16.67%)	9 (15.25%)	1.000
DOX+RIF +CRO	15 (12.00%)	10 (15.15%)	5 (8.47%)	0.283
Others	1 (0.80%)	1 (1.52%)	0 (0.00%)	/
Outcome				
With relapse	17 (13.60%)	13 (19.70%)	4 (6.78%)	0.040
With twice relapse	6 (4.80%)	5 (7.58%)	1 (1.69%)	0.212
With more than twice relapse	1 (0.80%)	1 (1.51%)	0 (0.00%)	/
With sequelae	9 (7.20%)	7 (10.61%)	2 (3.39%)	0.170

### 3.5. Inflammatory markers between eosinopenia and non-eosinopenia groups pre-treatment

Analysis of inflammatory markers suggested potential differences associated with brucellosis. The eosinopenia group displayed lower levels in certain markers, including MPV (9.75 [9.20, 10.73] vs. 10.70 [10.00, 12.60],  $P = 0.000$ ), MLR (0.28 [0.19, 0.34] vs. 0.36 [0.23, 0.50],  $P = 0.002$ ), and SIRI (0.67 [0.37, 1.69] vs. 1.03 [0.64, 1.87],  $P = 0.004$ ). No differences were observed for RDW, NLR, PLR, SII, or the CALLY index (**Table 5**).

**Table 5.** Comparison of inflammatory markers between eosinopenia group (Group 1) and non-eosinopenia group (Group 2) pre-treatment

Variables	Total (n = 125)	Group 1 (n = 66)	Group 2 (n = 59)	P value
MPV (fL)	10.10 (9.40, 11.50)	9.75 (9.2, 10.73)	10.70 (10.00, 12.60)	0.000
RDW (%)	11.90 (10.90, 15.10)	13.45 (10.65, 15.40)	11.10 (11.10, 14.00)	0.144
NLR	2.05 (1.19, 3.53)	1.92 (0.96, 4.35)	2.06 (1.24, 3.34)	0.469
PLR	81.60 (68.61, 121.90)	84.85 (66.68, 121.59)	81.60 (68.79, 128.97)	0.663
MLR	0.29 (0.21, 0.44)	0.28 (0.19, 0.34)	0.36 (0.23, 0.50)	0.002
SII	424.08 (243.94, 781.71)	383.85 (178.90, 727.84)	444.46 (283.73)	0.055
SIRI	0.89 (0.49, 1.80)	0.67 (0.37, 1.69)	1.03 (0.64, 1.87)	0.004
CALLY index	0.20 (0.10, 0.38)	0.20 (0.12, 0.32)	0.26 (0.07, 0.53)	0.768

## 4. Discussion

Brucellosis is a zoonotic infectious disease caused by *Brucella* bacteria, which profoundly and multifacetedly impacts individuals and society. Asia bears the highest burden of human brucellosis among continents, creating a serious public health problem. Traditional agricultural practices, lifestyles, and the consumption of fresh dairy products, such as raw milk, contribute to this high prevalence<sup>[1]</sup>, particularly notable in China and deserving increased attention<sup>[2]</sup>.

The review of relevant literature <sup>[7,11,12]</sup> indicates that brucellosis complicated by eosinopenia is not uncommon, yet remains insufficiently studied. Eosinopenia frequently occurs in brucellosis, especially during the early acute phase, and is thought to aid in diagnosis. This study confirms these findings and further identifies distinct clinical characteristics and potential mechanisms in patients with eosinopenia.

Brucellosis is easily misdiagnosed, often progressing to a chronic phase due to its atypical clinical symptoms. Early diagnosis is both highly needed and challenging to achieve. Hematological complications, such as anemia, leukopenia, and thrombocytopenia, are frequently observed in brucellosis <sup>[4]</sup> and other infectious diseases <sup>[13]</sup>, thus limiting their diagnostic utility. When combining previous studies with findings from this research, eosinopenia emerges as an effective and convenient diagnostic aid.

This study further found that eosinopenia patients were older and had significantly higher risks of relapse and complications. Prior research on brucellosis <sup>[14-17]</sup> associates advanced age with increased risks of relapse and complications, potentially suggesting a poorer prognosis. This correlation adds reliability to the results of this study. While it remains unclear whether the age-related decline in the number and function of T cells, B cells, and NK cells—attributable to weakened immune function <sup>[18,19]</sup>—increases the likelihood of bone marrow suppression and eosinopenia during infections, eosinopenia may be considered a risk factor for poor prognosis.

A comparison with historical data reveals a higher proportion of hypertension in the eosinopenia group, attributed to the group's greater mean age rather than a direct association with brucellosis. Nonetheless, a potential connection between hypertension and brucellosis warrants blood pressure monitoring during treatment and further investigation into underlying mechanisms.

Eosinopenia was closely associated with complications, particularly hematological ones, in this study. The relevant literature does not address correlation studies between these two variables. However, based on available data, it can be hypothesized that eosinopenia results from infection, with the degree of decline potentially linked to the quantity and virulence of *Brucella abortus*, thereby influencing disease prognosis. This finding establishes a significant relationship between eosinopenia and complications.

A slight increase in transaminase elevation among the eosinopenia group was observed, though without statistical significance. However, significant elevations in ALT and AST levels suggest potential liver damage in this group. Another study <sup>[20]</sup> indicates that eosinophils accumulate in injured liver tissue during immune-mediated damage, secreting IL-4 locally to stimulate hepatocyte proliferation and support liver regeneration. It is possible that a low eosinophil count may adversely impact liver cell regeneration, though this study primarily involves liver tissue rather than blood, highlighting the need for expanded studies to clarify the mechanism.

While no differences in clinical symptoms, treatment duration, or antibiotic combinations were observed, the eosinopenia group experienced longer lengths of stay (LOS). Communication with attending physicians suggests that the older age and higher complication probability in the eosinopenia group necessitated cautious evaluation of treatment efficacy and side effects. Consequently, multiple evaluations and treatment adjustments, if necessary, extended the treatment duration.

Although CRP and PCT levels showed no differences between groups, an unexpected finding emerged regarding other inflammatory markers. Literature comparisons <sup>[21-27]</sup> identify potential diagnostic markers, with significant differences observed in MPV, MLR, and SIRI between groups. MPV, commonly used to gauge platelet function, typically decreases in severe brucellosis <sup>[21-23]</sup>, aligning with this study's findings. Some research <sup>[23,24]</sup> indicates that high MLR levels are predictive of an elevated risk for osteoarticular and genitourinary involvement, although one study <sup>[21]</sup> contests this, suggesting controversy. In this study, MON



levels were significantly lower in the eosinopenia group, with no LY differences, possibly explaining the low MLR. Limited research on SIRS and brucellosis exists; one study <sup>[27]</sup> suggests SIRS lacks diagnostic value, indicating a need for further studies.

This study found that the eosinopenia group exhibited both low SIRS and low MLR in association with a poorer prognosis. It can be speculated that the eosinopenia group may exhibit lower inflammation levels, which contrasts with theories positing that severe inflammation correlates with disease severity. Given that indexes were measured approximately one-month post-infection, it can be inferred that inflammation initially peaks following *Brucella* infection and subsequently declines without influencing disease progression, likely due to brucellosis-related immune evasion.

This study serves as an initial exploration of the clinical manifestations of brucellosis in eosinopenia patients. While it does not elucidate underlying mechanisms, it lays a foundation for future research and provides substantive support for the diagnosis and treatment of brucellosis.

## 5. Conclusion

Eosinopenia is a common manifestation of brucellosis. Brucellosis patients with eosinopenia exhibited differences in clinical indicators and prognosis, though not in clinical symptoms. This suggests that eosinophils may serve as a risk factor for assessing prognosis. Monitoring eosinophils could improve prognosis assessment and present potential new treatment options.

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## Disclosure statement

The authors declare no conflict of interest.

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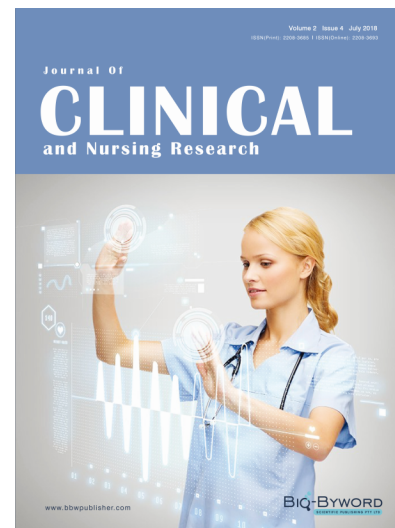
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