

# Asia Pacific Journal of Clinical Medical Research

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## Asia Pacific Journal of Clinical Medical Research

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# Stroke Risk Prediction and Assessment Based on Big Data Analysis

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**Abstract:** Stroke is a common cardiovascular and cerebrovascular disease with high morbidity, high mortality and high disability rate. In this paper, a stroke risk prediction and evaluation model based on support vector machine, random forest, BP neural network and genetic algorithm optimization neural network algorithm was established by using a raw dataset including 10 characteristic variables such as gender, age, hypertension, heart disease, and 1 stroke target variable. The experimental results show that the average blood glucose level, body mass index, hypertension and other variables have a great impact on the risk of stroke, and the neural network algorithm optimized by the genetic algorithm performs slightly better than the other three models.

**Keywords:** Stroke; BP Neural Network; Genetic Algorithm; Support Vector Machine; Random Forest; Risk Prediction Evaluation

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## 1.Introduction

Cerebral apoplexy, commonly known as stroke. The latest Global Burden of Disease study (GBD) shows that the overall lifetime risk of stroke in China is 39.9%, ranking first in the world, almost 2 out of every 5 people suffer from stroke, and about 1.94 million people die from stroke in China every year. According to the data of the Stroke Prevention and Control Engineering Committee of the National Health Commission, in 2020, the prevalence rate of stroke in residents over 40 years old in China was 2.61%, the incidence rate was 505.23/100,000, and the mortality rate was 343.4/100,000. According to the First finance and Economics, cerebrovascular epidemiology data show that globally, the lifetime risk of stroke in people over the age of 25 is 24.9%, and the figure in China is close to 40%, that is, 40% of people are likely to have a stroke from the age of 25.

According to the announcement issued by the National Health Commission, the regional differences of the fluid characteristics of stroke are as follows: developing countries are greater than developed countries; The differences in the population are as follows: morbidity and mortality increase with the increase of age, the prevalence of stroke in males is generally higher than that in females in all countries, and the incidence of stroke in different races in the same region is significantly different. The disease factors associated with stroke include high blood pressure, heart disease, diabetes, transient ischemic attack, etc., poor lifestyle including smoking, excessive alcohol consumption, etc.

The purpose of this paper is to study the factors that have a great impact on stroke disease, and to achieve early intervention of the disease and reduce the prevalence rate through scientific methods to assist diagnosis. Combining the medical field

and machine learning can expand the application range of algorithms, enrich the theoretical basis, and provide new ideas for solving medical problems.

## 2. Research status at home and abroad

In 2002, Lumley<sup>[7]</sup> and other researchers conducted a 6.3 year follow-up of 5,711 residents over 65 years old with no history of stroke, constructed a sex-specific prediction equation using the characteristic variables most associated with stroke, and conducted experiments on a Web-based interactive platform to develop a model for predicting stroke in elderly Americans. In 2015, Xu Xiao et al.<sup>[1]</sup> established a fuzzy comprehensive evaluation model for stroke by quantifying fuzzy data based on various signs and factors of stroke and using genetic algorithm. In 2015, Manuel D. G.<sup>[8]</sup> and other researchers conducted a cohort survey of 82,259 Ontario residents since 2001, recording 3,236 stroke events. They constructed an index to comprehensively assess the impact of health habits and stress on stroke risk, which individuals can use for stroke risk assessment. In 2017, Lai Xinxing<sup>[2]</sup> standardized clinical data based on 547 cases of clinical trials, screened out independent risk factors for early neurological deterioration, and analyzed the relationship between DWI-ASPECTS scores and early neurological deterioration and its predictive ability. The correlation between neuroimaging and early neurological deterioration was analyzed by brain topography. In 2019, Wu Juhua<sup>[3]</sup> et al. identified 12 risk factors and built a neural network model for stroke risk prediction, and found 6 most important factors, such as total cholesterol and low density lipoprotein, with a prediction accuracy of 97.10%. In 2020, Luo Yishu<sup>[4]</sup> et al. proposed a multi-feature combined diagnosis model based on LSTM for clinical auxiliary diagnosis of ischemic stroke. The overall performance of the model reached 84%, which could provide a reference for doctors in differential diagnosis. In 2021, Hou Yumei<sup>[5]</sup> et al. built a prediction model of stroke incidence through data mining and Logistic regression model, enabling patients to self-monitor the risk of stroke occurrence and improving the convenience of stroke prevention. In 2023, Yang Huijie<sup>[6]</sup> et al. recorded the basic information of the enrolled patients, collected fasting blood samples to measure CRP, Alb and other indicators, and calculated CAR. Cervical DSA imaging was used to measure carotid artery stenosis, and the degree of stenosis on the most severe side was used as the assessment basis to study the relationship between the ratio of serum C-reactive protein and albumin and carotid artery stenosis in patients with acute cerebral infarction.

## 3. Data analysis

### 3.1 Data collection

There are 11 variables in the dataset, totaling 40,911 rows of data. The specific fields and meanings are shown in Table 1.

Table 1 : Description of variables

variable	implication	value
sex	sex	0= male, 1= female
age	age	R
hypertension	hypertension	0= None, 1= Yes
heart_disease	Heart disease	0= None, 1= Yes
ever_married	Marital status	0= "No", 1= "Yes"
work_type	Type of work	0= "Child", 1= "government work", 2= "never work", 3= "private", 4= "self-employed"
Residence_type	Residential type	0= "Rural", 1= "urban"
avg_glucose_level	Residential type	R
bmi	Body mass index	R
smoking_status	Whether you smoke or not	0= "No", 1= "Yes"
stroke	Have you had a stroke	0= "No", 1= "Yes"

### 3.2 Data preprocessing

#### 3.2.1 Missing value

Using the `isnan()` command in matlab, find the missing value. Three empty values are detected in the "sex" column, which

account for a very small proportion of the total data, less than 0.01%. Therefore, the `disp(sum())` command is used to delete the value directly.

### 3.2.2 Outliers

First, descriptive statistics are performed on the data, and the total number, average value, standard deviation, minimum value, first quartile, second quartile, third quartile and maximum value of each variable are output. For the “age” variable, the minimum value is -9, which is obviously not common sense. So delete the rows where the “age” variable is less than or equal to 0. A total of 81 lines were deleted. It can be seen from the data that `avg_glucose_level` (blood sugar level) is high when it is 100-125 mg/dL, and `bmi` (body mass index) is overweight when it is 25-29.9. Descriptive statistics show that, The average value of `avg_glucose_level` is about 122.1, and the average value of `bmi` is about 30.4, which is not within the normal range. It is speculated that there are outliers. Draw a box plot to detect whether there are outliers. Draw box plots for the continuity variables “age”, “`avg_glucose_level`” and “`bmi`” respectively. There are 922 abnormal data in total, accounting for 2.25% of the original data set, which is relatively large. Consider using other methods to determine outliers.

Figure 1 : age box diagram

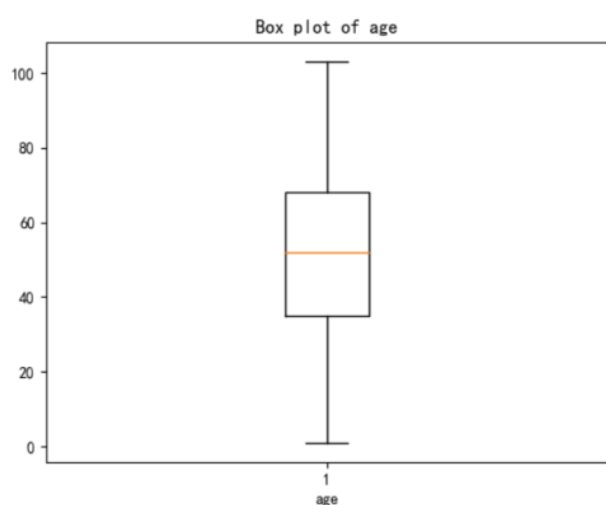


Figure 2 :bmi box plot

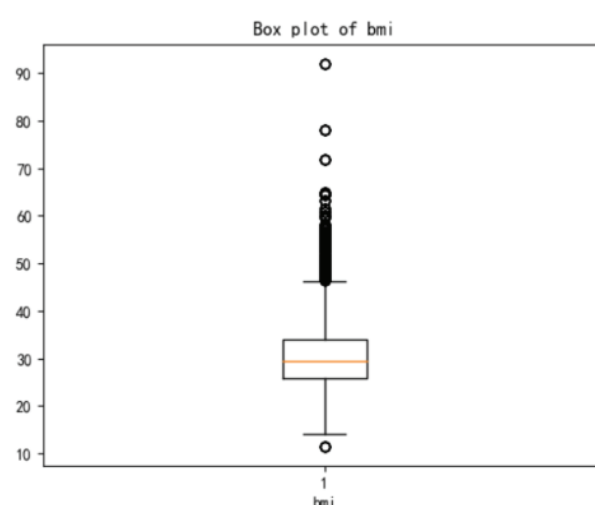
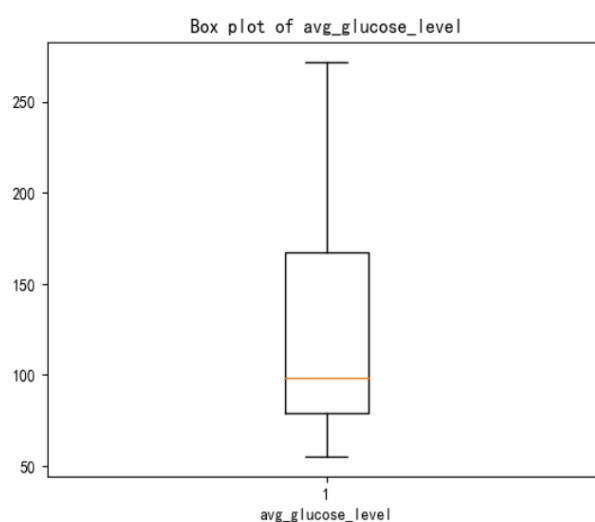


Figure 3:avg\_glucose\_level box diagram



Using the Laida criterion ( $3\sigma$  criterion) to find outliers, a total of 496 outliers were found.

For data points identified as outliers, further analysis of the source and possible causes. If the outliers are caused by actual physiological changes or disease conditions, retain these outliers and pay special attention to the impact of this part of the data in the analysis. In the case of outliers caused by measurement errors, the data combined with medical expertise should be cleaned to ensure that the handling of outliers is in line with the actual situation and will not cause loss or distortion of information. According to the relevant data of the National Population Health Sciences Data Center and the relevant data of

the interview of the experts of the Cardio-Cerebrovascular disease network, 391 outliers were deleted.

### 3.3 Data visualization

#### 3.3.1 For discrete variables

In order to clearly show the relationship between each discrete variable and stroke, this paper visually shows the distribution and trend of data through cross-contingency tables, which can better identify the correlation and mutual influence between different variables.

Table 2: Cross contingency table of partial discrete variables and stroke

variable	value	stroke		total
		0	1	
sex	0	7870(43.662%)	10155(56.338%)	18025
	1	12286(54.824%)	10124(45.176%)	22410
total		20156	20279	40435
hypertension	0	18026(56.682%)	13776(43.318%)	31802
	1	2130(24.673%)	6503(75.327%)	8633
total		20156	20279	40435
heart_disease	0	19079(54.156%)	16151(45.844%)	35230
	1	1077(20.692%)	4128(79.308%)	5205
total		20156	20279	40435

According to Table 2, the probability of stroke is much higher in people with hypertension and diabetes than in people without stroke. The probability of stroke is 33.464% higher in people with diabetes and 31.919% higher in people with hypertension. The correlation between hypertension and heart\_disease and stroke was high and hypertension and heart\_disease were judged. For the ever\_married variable, the probability of having a stroke without being married was lower than that of being married. For the work\_type variable, children and government workers have a very low probability of stroke, while the other types of work have high stress, which may increase the probability of stroke. For sex, Residence\_type and smoking\_status, the proportion of stroke and non-stroke is very balanced, and the impact of the four variables on stroke cannot be directly judged.

#### 3.3.2 For continuous variables

The density curves of three variables, age, avg\_glucose\_level and bmi, and stroke, can be drawn. It can be found that age and bmi are normally distributed, which accords with the real data.

As can be seen from Figure 4, when the value of age variable is greater than 70, the proportion of stroke patients is significantly higher than that of non-stroke patients.

Normal blood glucose usually refers to the fasting blood glucose concentration in milligrams per deciliter (mg/dL). The generally accepted normal range of blood sugar is postprandial blood sugar (after two hours) : less than 140 mg/dL. Figure 5 shows that when the value of avg\_glucose\_level variable is greater than 170, the proportion of stroke patients is significantly higher than that of non-stroke patients. This suggests that hyperglycemia can increase the incidence of stroke and is an independent risk factor for stroke.

The normal BMI for adults is between 18.5 and 23.9, and if a BMI below 18.5 is considered underweight, a BMI of 24 to 27 is overweight, and a BMI of 28 to 32 is obese. If your BMI is over 32, you are considered obese. Figure 6 shows that when the bmi variable is between 24 and 30, the proportion of people who have had a stroke is significantly higher than that of people who have not had a stroke. This suggests that the higher the obesity, the higher the incidence of stroke.

Figure 4: Curve of stroke value frequency and age density

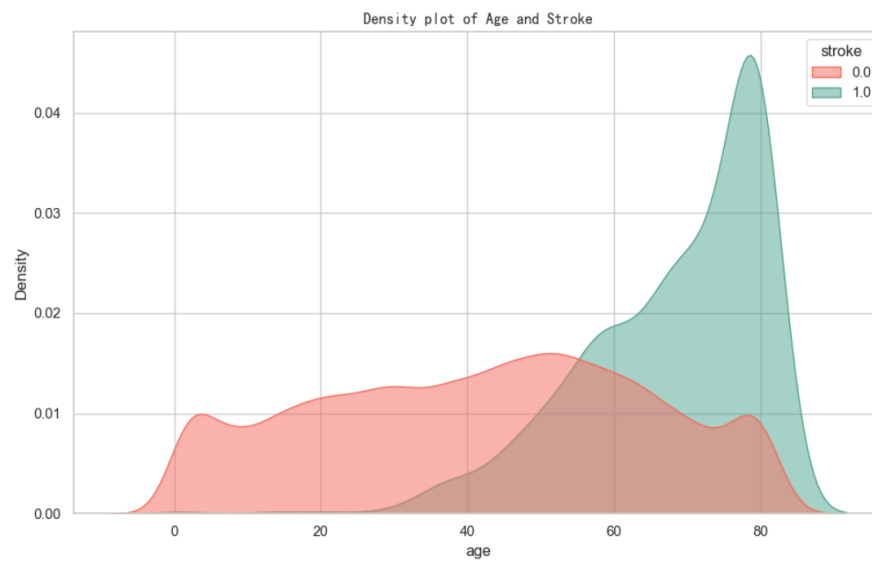


Figure 5: Graph of the value frequency of stroke and the density of avg\_glucose\_level

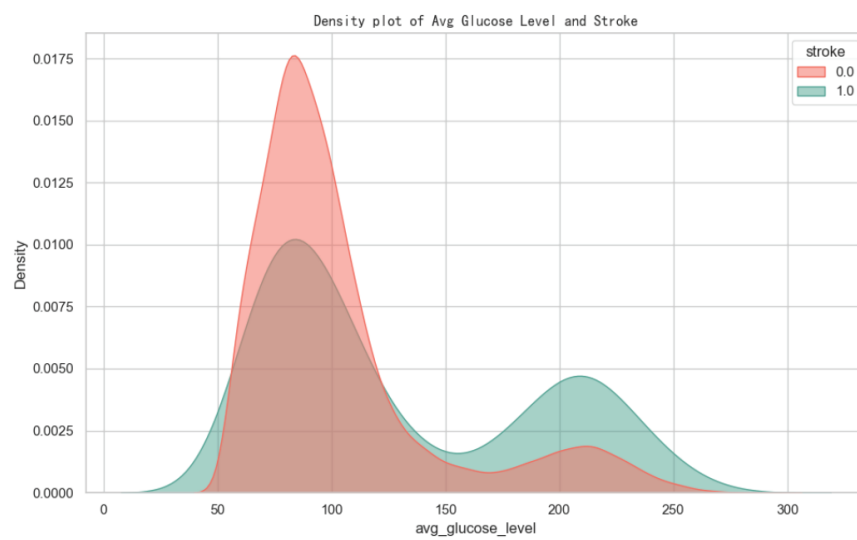
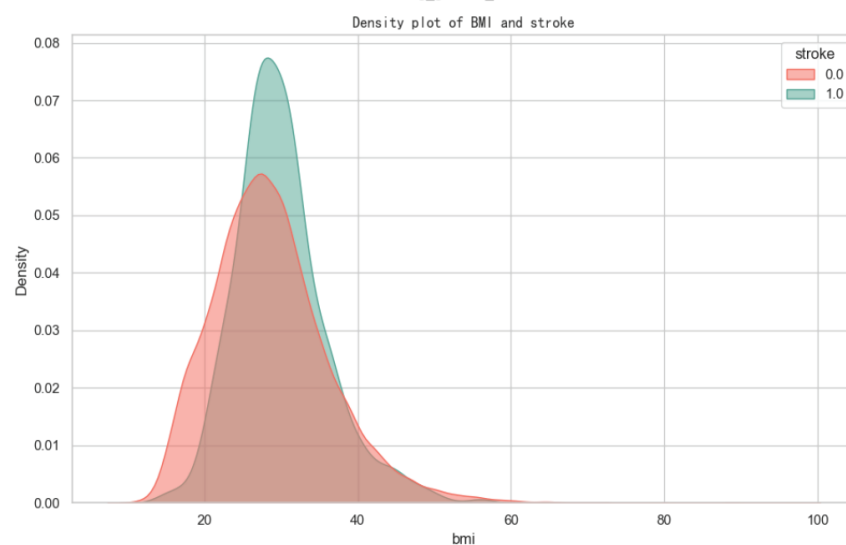


Figure 6: Curves of stroke value frequency and bmi density



### 3.4 Correlation analysis

#### 3.4.1 For discrete variables

The Pearson Chi-square test enables statistical significance levels and effect sizes, making it easier to comprehensively evaluate the relationship between variables. Pearson Chi-square test is suitable for data where the sample size is large enough and both categorical variables are discrete variables. Therefore, Pearson Chi-square test can be used for correlation analysis of discrete variables in this data.

The chi-square test results are as follows:

*Table 3: Results of chi-square test between stroke and some categorical variables*

variable	value	stroke		total	Inspection method	X <sup>2</sup>	P
		0	1				
sex	0	7870	10155	18025	pearson Chi-square test	497	0.000***
	1	12286	10124	22410			
total		20156	20279	40435			
variable	value	stroke		total	Inspection method	X <sup>2</sup>	P
		0	1				
hypertension	0	18026	13776	31802	pearson Chi-square test	2782	0.000***
	1	2130	6503	8633			
total		20156	20279	40435			
variable	value	stroke		total	Inspection method	X <sup>2</sup>	P
		0	1				
heart_disease	0	19079	16151	35230	pearson Chi-square test	2031	0.000***
	1	1077	4128	5205			
total		20156	20279	40435			
Note: ***, ** and * represent significance levels of 1%, 5% and 10% respectively							

From the above analysis results, it can be seen that the correlation between stroke and Residence\_type is not significant, and there is a highly significant correlation with other variables.

#### 3.4.2 For continuous variables

This paper aims to study the correlation between three continuous variables and the stroke variable. As mutual information does not rely on the distribution assumption of data and has good robustness to outliers and noise data, it is adopted for the correlation analysis.

*Table 4 Mutual Information Coefficient*

variable	Stroke
age	0.017
avg_glucose_level	0.667
bmi	0.228

From Table 4, it can be seen that all three variables have a positive relationship with the stroke variable. The variable of avg\_glucose\_level has the highest correlation with the stroke variable. The bmi variable also has an impact on stroke, while the age variable has the least impact.

Bivariate analysis can reveal the direction of the association (positive correlation, negative correlation, or no correlation) and

the degree of association (correlation coefficient) between two continuous variables. In this paper, plots were made for the pairwise relationships between the three variables of age, avg\_glucose\_level, bmi and stroke. As can be seen from Figures 7, 8 and 9, when the age is above 60 years old, regardless of the blood glucose level and the BMI index, the probability of stroke is very high. When the blood glucose level is higher than 200, regardless of the age and the BMI index, the probability of stroke is also relatively high.

Figure 7 Scatter Plot of Age and Blood Glucose Level

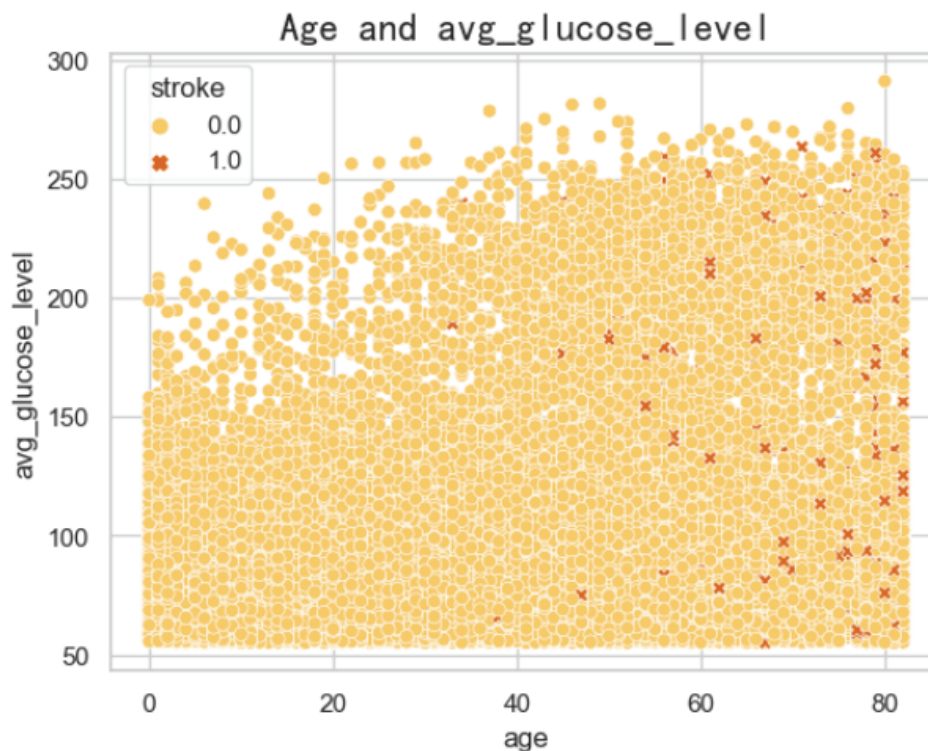


Figure 8 Scatter Plot of Age and BMI Index

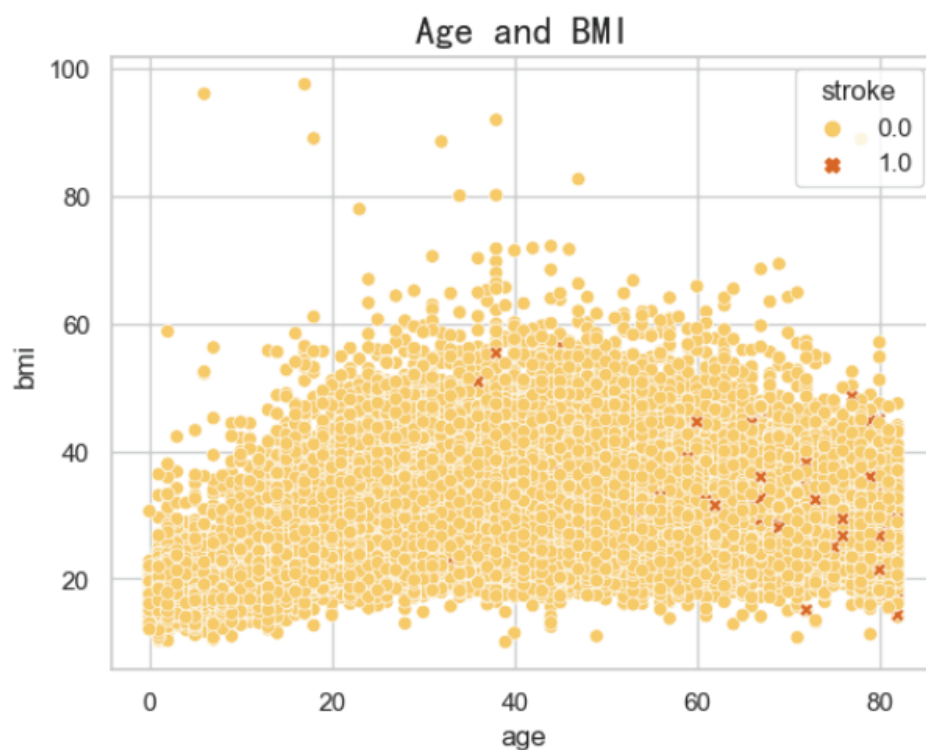
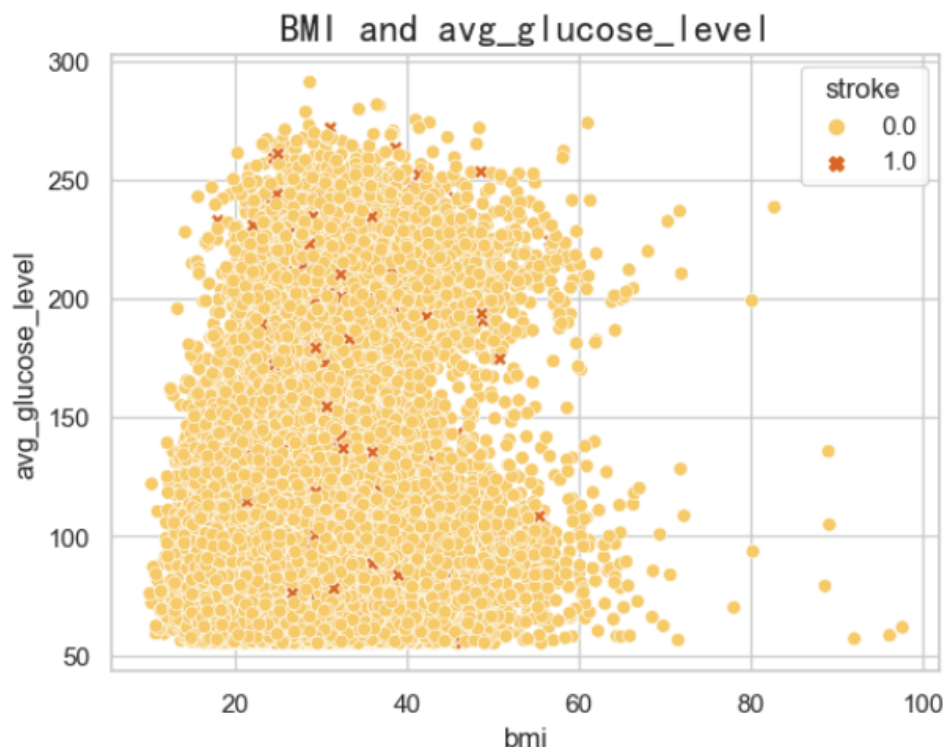




Figure 9 Scatter Plot of BMI Index and Blood Glucose Level



## 4. Stroke Risk Prediction

### 4.1 Support Vector Machine

The support vector machine is a binary classification model that can handle high-dimensional data and has a relatively high prediction accuracy. In stroke prediction, data of individuals with strokes and those without strokes can be used as samples, and classification can be carried out through the SVM algorithm to predict whether a person will have a stroke. According to the confusion matrix, the number of True Positives (TP) is 3223, the number of False Negatives (FN) is 796, the number of False Positives (FP) is 890, and the number of True Negatives (TN) is 3178.

Table 5 Evaluation Indicators of the Support Vector Machine

Support Vector Machine Indicators	Values
Accuracy	0.792
Precision	0.784
Recall	0.802

From the results in Table 5, it can be seen that although the accuracy and precision of the support vector machine are relatively low, and it fails to achieve an excellent classification effect.

### 4.2 Random Forest

Random forest is an ensemble learning algorithm. It is a classifier that contains numerous decision trees, and it can synthesize the prediction results of decision trees to improve the accuracy of the model. Random forest can effectively deal with overfitting and handle high-dimensional data. It has good robustness and interpretability and is suitable for classification and regression problems. According to the confusion matrix, the number of True Positives (TP) is 4018, the number of False Negatives (FN) is 1, the number of False Positives (FP) is 24, and the number of True Negatives (TN) is 4044.

Table 6 Evaluation Indicators of Random Forest

Random Forest Indicators	Values
Accuracy	0.994
Precision	0.997
Recall	1



From the results in Table 6, it can be seen that the accuracy and precision of the random forest are extremely high, exceeding 99%. The classification results obtained using the random forest are highly persuasive.

The random forest can output feature importance. Feature importance refers to the contribution degree of each feature to the prediction result of the model. Feature importance is calculated by measuring the degree of reduction in the Gini index brought by each feature when the model splits each node of the decision tree. The lower the Gini index, it indicates that the model has a higher degree of dependence on this feature, so the feature importance is also higher.

*Table 7 Ranking of Feature Importance*

Variable	Importance
age	0.277742
avg_glucose_level	0.222129
bmi	0.059261
work_type	0.053656
hypertension	0.037157
Residence_type	0.036793
smoking_status	0.034687
heart_disease	0.032677
ever_married	0.029671
sex	0.007046

As can be seen from Table 7, among the continuous variables, age, avg\_glucose\_level, and bmi contribute the most to stroke. Among the discrete variables, work\_type contributes the most to stroke, which is consistent with the results of the chi-square test. In contrast, sex has the least impact on stroke.

#### 4.3 BP Neural Network

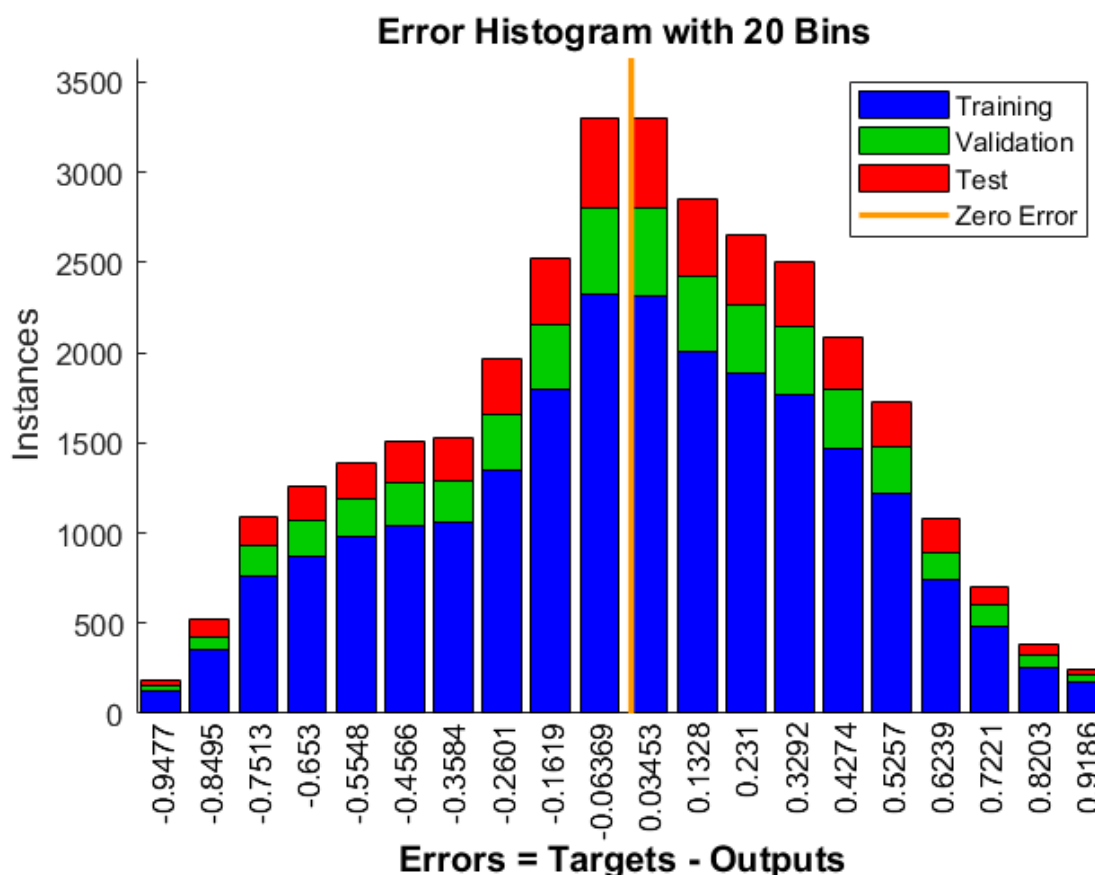
The main components of a BP neural network include the input layer, hidden layer, and output layer. The input layer is responsible for receiving the original data, the hidden layer is responsible for feature extraction and data transformation, and the output layer is responsible for generating the final prediction results. During the training process, the BP algorithm calculates the error between the prediction results and the actual targets, and then propagates the error backward from the output layer to the input layer, adjusting the network weights and biases layer by layer to minimize the error. By adjusting the training function and transfer function, it can accurately predict whether a person has a stroke. According to the confusion matrix, for the BP neural network as a whole, the number of True Positives (TP) is 12300, the number of False Negatives (FN) is 4087, the number of False Positives (FP) is 3457, and the number of True Negatives (TN) is 12953.

Before optimizing the neural network with the heuristic algorithm, both the accuracy and precision of the model are lower than 0.8, resulting in a poor prediction effect.

*Table 8 Evaluation Indicators of the Neural Network*

Neural Network Indicators	Values
Accuracy	0.760
Precision	0.520
Recall	0.789

Figure 15 Error Histogram



The closer the error is to 0, the better. As can be seen from Figure 15, a large portion of the data falls outside the range of -0.4 and 0.4. It can also be observed that the prediction effect of the neural network before optimization is poor.

#### 4.4 Neural Network Optimized by Genetic Algorithm

The genetic algorithm is an optimization method that simulates the biological evolution process. The solutions to the problem are represented as chromosomes, and an initial population of solutions is randomly generated. By evaluating the fitness of the chromosomes, the better chromosomes are selected for reproduction, and operations such as crossover and mutation are carried out to generate new chromosomes. Through iterative evolution, the chromosome with the highest fitness in the population is finally output as the optimal solution.

According to the confusion matrix, the number of True Positives (TP) is 198, the number of False Negatives (FN) is 0, the number of False Positives (FP) is 0, and the number of True Negatives (TN) is 7984.

Table 9 Evaluation Indicators of the Neural Network Optimized by the Genetic Algorithm

Indicators of the Neural Network Optimized by the Genetic Algorithm	Values
Accuracy	0.933
Precision	1.00
Recall	0.933

It can be seen from the results in Table 9 that the accuracy, precision and recall rate of the neural network optimized by the genetic algorithm are extremely high, exceeding 90%. The neural network optimized by the genetic algorithm has achieved excellent results in the classification task.

## 4.5 Comparison of Model Performance

Table 10 Comparison of Model Performance

	Precision	Advantages	Disadvantages
Support Vector Machine(SVM)	0.777	Insensitive to outliers.	The training speed is relatively slow.
Random Forest	0.998	It performs well in handling the interactions between features and high - dimensional datasets, and can obtain the importance of features.	It may overfit.
BP (Back Propagation) Neural Network	0.520	The hidden layer can learn new features that contribute to classification.	It requires a large amount of parameter adjustment and experimentation.
Neural Network Optimized by Genetic Algorithm	1.00	Global search finds better solutions for neural networks.	The computational cost is relatively high.

According to the data in Table 10, the precision rates of both the Support Vector Machine and the BP Neural Network fail to reach 0.8, indicating relatively low classification accuracy. The Random Forest and the Neural Network optimized by the Genetic Algorithm perform excellently, with their precision rates both exceeding 0.99, demonstrating outstanding performance in classification tasks. However, the Random Forest has the risk of overfitting, while the Neural Network optimized by the Genetic Algorithm can find better solutions through global search, providing potential advantages for improving classification accuracy. By comparing factors such as the performance, interpretability, and computational cost of different models, the Neural Network model optimized by the Genetic Algorithm is finally adopted, achieving the best classification effect and prediction ability.

## 5. Conclusions and Recommendations

### 5.1 Conclusions

1. There is an obvious correlation between age and stroke. Especially in the age group of 90 years old and above, the incidence rate of stroke increases significantly, accounting for about 90% of the population in this age group. This indicates that the risk of stroke increases significantly with the growth of age.
2. Blood glucose level is closely related to stroke. When the average blood glucose level is higher than 170, the proportion of stroke patients is significantly higher than that of the non-stroke population. High blood glucose level may be a manifestation of diabetes, and the risk of stroke among diabetic patients is much higher than that among people with normal blood glucose levels. When the blood glucose concentration exceeds 150, regardless of the BMI value, the risk of stroke increases significantly.
3. The BMI index is also associated with stroke. When the BMI index is greater than 21, the number of stroke patients gradually increases. Especially when the BMI exceeds 27, the proportion of stroke cases is higher than that of non-stroke cases.
4. The comprehensive results of the feature importance ranking of the random forest and the chi-square test show that age, hypertension, and heart disease have a very significant impact on stroke, and there is a close correlation between these factors and stroke.

### 5.2 Recommendations

1. Regularly monitor blood pressure, blood glucose, and BMI index, and keep them within the normal range. Control your diet, avoid high-sugar and high-fat foods, and maintain an appropriate weight. Eat more vegetables, fruits, whole grains, and low-fat dairy products, and reduce the intake of saturated fats and trans fats.
2. Actively prevent hypertension and heart disease by strengthening physical exercise, quitting smoking and limiting alcohol consumption, maintaining mental health, etc. Seek medical advice in a timely manner and receive guidance and treatment from professional doctors.
3. Maintain an appropriate weight. Use diet and exercise to maintain a normal weight and avoid obesity.

4. For patients with heart disease, follow the doctor's advice for drug treatment and lifestyle adjustments. Pay attention to heart symptoms such as chest pain, shortness of breath, dizziness, etc., and seek medical attention promptly.
5. Pay attention to the adjustment of lifestyle. Keep a regular work and rest schedule, avoid excessive fatigue and stress, and maintain a peaceful mindset.
6. Strengthen health education, improve the awareness of stroke risks, cultivate healthy living habits and behaviors, and enhance the awareness of self-care.

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## Conflict of Interests

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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# Early Weight-Bearing Following Ankle Fractures: Is the 1 Week Weight-Bearing Regimen Superior to the 4 Week Regimen?

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**Abstract: Background:** Early weight bearing can accelerate the recovery of ankle function, but the timing of weight bearing has not been clarified. In this study, the efficacy and safety of weight-bearing at 1 week and 4 weeks after ankle fracture were further investigated. **Methods:** Forty-six postoperative ankle fracture patients were enrolled and divided into 1-week group (23) and 4-week group (23) according to randomized numerical table method. All patients underwent routine rehabilitation. On this basis, weight-bearing was started at 1 week after surgery in the 1-week group and at 4 weeks after surgery in the 4-week group. Both groups underwent a 6-week trial intervention. Ankle pain and function were assessed by VAS, AOFAS, and OMAS scales at 2, 4, and 6 weeks after treatment. **Results:** There was no statistically significant difference in the general data of patients in the 2 groups before surgery ( $P > 0.05$ ). At 2 weeks postoperatively, the VAS of the 1-week group was higher than that of the 4-week group, and the scores of the Pain item in AOFAS and Swelling item in OMAS were lower than that of the 4-week group. At 4 weeks postoperatively, the VAS was higher in the 1-week group than in the 4-week group. At 6 weeks postoperatively, the VAS was lower in the 1-week group than in the 4-week group, and the scores of the Pain, Maximum walking distance, and Sagittal motion items in the AOFAS, and the scores of the Stiffness and Swelling items in the OMAS were higher than in the 4-week group. **Conclusions:** A rehabilitation strategy of early weight-bearing implemented 1 week after surgery in patients with ankle fractures can effectively reduce the degree of ankle stiffness and accelerate the recovery of ankle function in patients.

**Keywords:** Ankle Fracture; Early Weight Bearing; Postoperative Rehabilitation; Healing Effect

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Fracture of the ankle joint (FAJ) is a prevalent intra-articular fracture seen in clinical practice, representing approximately 3.92% of all systemic fractures.<sup>12</sup> Current research indicates that early mobilization plays a key role in the recovery process of ankle fractures.<sup>6, 13</sup> However, the initiation point for weight-bearing after ankle fracture during postoperative rehabilitation is still controversial. Several studies have suggested starting weight-bearing between 2 to 6 weeks postoperatively,<sup>2, 5, 14</sup> while some more radical approaches suggest initiating weight training as early as the day after surgery.<sup>13</sup>

The aim of this single-blind randomized controlled study was to compare short-term rehabilitation outcomes in ankle fracture patients at 1 week (study group) and 4 weeks of weight-bearing (control group) after surgery.

## 1. Material And Methods

## 1.1 Subject Recruitment

G\*Power 3.1.9.7 was employed to compute the statistic. Based on prior studies,<sup>16</sup> with a statistic of 0.8, alpha of 0.05, and effect size of 0.37, each group's minimum sample size was 21 (total 42). Accounting for a 10% dropout rate, the study's minimum sample size was 46. Before intervention, all subjects consented and signed the form, then randomized into 1-week and 4-week groups. The technical roadmap is in Figure 1. The same researcher did the cluster randomization.

In the 1-week group, patients started weightbearing one week after surgery, and in the 4-week group, four weeks after. Both had similar surgeries and post-op care. The same therapist did routine and early weight-bearing rehab.

Rehab for both groups had quadriceps isometric contraction training, ankle joint active-passive flexion from post-op day 2, and daily medium-frequency electrical stimulation on the operated leg. Weight-bearing was applying weight for movement, like walking with axillary cane or foot-supported walker under doctor's guidance with both feet on the ground.

## 1.2 Inclusion criteria and exclusion criteria

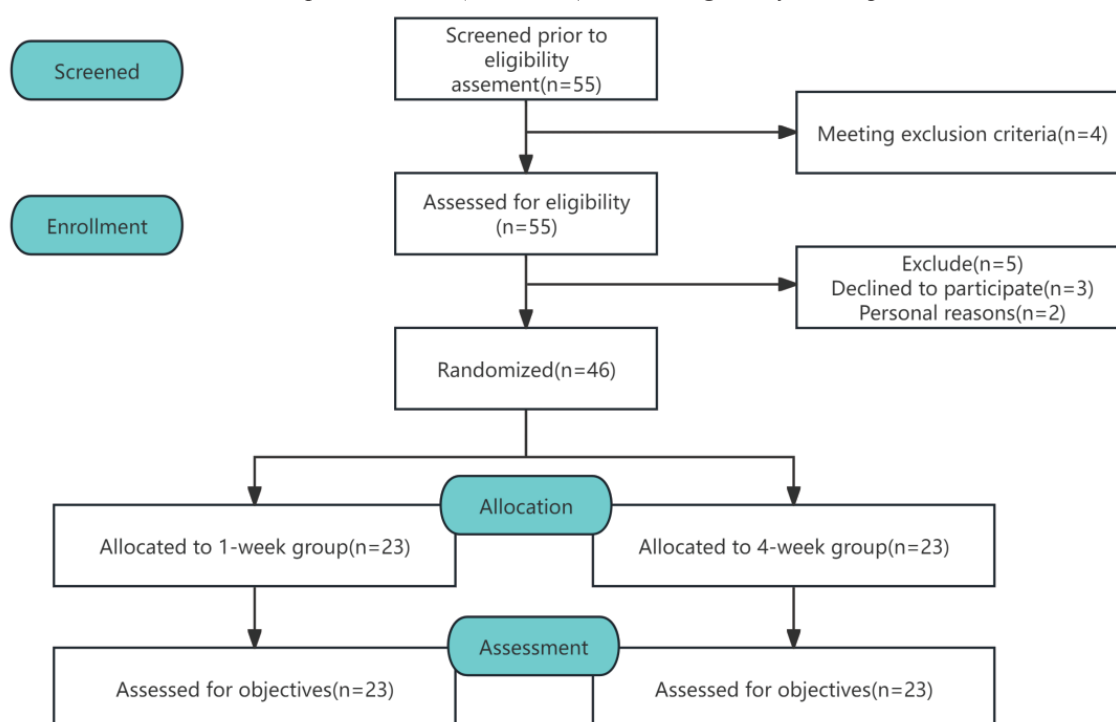
Inclusion criteria: (1) Closed ankle fractures. (2) Surgery was completed within 48 hours after fracture or after 1 week when the soft tissue swelling subsided. (3) The surgical approach was conventional incision and reduction with internal fixation. (4) All patients and their families gave informed consent to this study.

Exclusion criteria: (1) Open fracture or pathologic fracture. (2) Combined vascular ligament injury and neurological dysfunction. (3) Severe organ disease and diabetes mellitus and other underlying diseases affecting postoperative healing. (4) Mobility or cognitive disorders, poor compliance.

## 1.3 Clinical evaluation

Basic preoperative data were collected. The following relevant data were collected at 2, 4, and 6 weeks postoperatively in both groups: (1) Ankle Hindfoot Scale (AOFAS): a functional system score for the ankle and hindfoot that was developed and recommended by the American Association of Foot and Ankle Surgeons.<sup>10</sup> (2) Olerud Molander Ankle Rating Scale (OMAS): the OMAS is a scoring system for evaluating the outcome of patients with ankle fractures proposed, and it is very widely used in ankle fracture scoring.<sup>11</sup> (3) Visual analogue scale (VAS): The VAS score is a clinical evaluation method used to assess subjective pain in subjects.<sup>12</sup>

Figure 1. Flowchart of the trial from the baseline. All patients were assessed posttreatment (at 6 weeks) and at long-term follow-up



It should be noted that due to limited follow-up duration and imaging exams, some components of the AOFAS ankle-hindfoot system score and OMAS rating scale, such as abnormal gait, specific physical activities and ankle-hindfoot couldn't be

assessed. Moreover, due to site constraints, the walking distance item in the OMAS ankle scoring scale was changed from one block to 100 meters.<sup>13</sup>

## 1.4 Statistical analysis

The 2 groups (1-week vs 4-week) were compared at the 2, 4 and 6 weeks post-surgery for the outcomes (VAS,OMAS and AOFAS etc.) and analyze the relevant data together with the baseline information. The data obtained from the study were processed using SPSS27.0 software, and the normality test and the test of variance alignment were carried out first. If the data obeyed the normal distribution, the statistical description of the quantitative data was carried out by means of the mean and the standard deviation (), and the comparisons were made by using the repeated measures ANOVA if the variance was aligned, or the t'test if the variance was not aligned. If the data did not obey the normal distribution, the median or the quartile spacing was described. the qualitative data were described by the chi-square test (y), and the ranked data were tested by rank sum test.  $P < 0.05$  was considered to be a statistical difference. If the data did not obey normal distribution, the median or interquartile spacing was used to describe the data. the chi-square test (y) was used for qualitative data, and the rank-sum test was used for hierarchical data.  $P < 0.05$  was considered to be statistically different.

## 2.Results

### 2.1 Participants

A total of 55 individuals diagnosed with FAJ were enrolled in the study between July 2023 and November 2024, with 9 patients failing to complete the full assessment or treatment. The participant flow is shown in Figure 1. No wound infections or adverse postoperative complications were observed. Imaging assessments revealed indistinct fracture lines and no abnormal bone alignment, detachment, loosening, or fixation breakage in all patients. There were no statistically significant differences in preoperative characteristics like gender, age, and Lange-Hansen fracture typing between the two groups ( $P > 0.05$ ), as presented in Table 1.

Table 1. Baseline demographics and fracture pattern (n = 46)

Demographic factor	1-week group	4-week group	$\chi^2/t$	p
Gender				
Male	12	13	0.088	0.767
Female	11	10		
Age(years)	44.30±15.58	45.83±13.66	0.352	0.726
Lange-Hansen				
SA	5	5	1.037	0.904
SER	2	2		
PER	14	13		
PA	2	2		
PD	0	1		

### Outcomes of VAS after receiving the intervention in the 1-week and 4-week group

As shown in Table 2, there were significant main effect of groups for VAS scores in both groups, time, and significant interaction effect of time of and groups ( $p < 0.05$  of all). The results of the simple effect test showed that the between-group simple effect were significant at 2, 4, and 6 weeks postoperatively ( $p < 0.05$  of all), and significant simple effect for time of measurement in the weight bearing condition at 1 and 4 week postoperatively ( $p < 0.05$  for both). Multiple comparisons revealed that in the weight-bearing condition at 1 and 4 week postoperatively, VAS values measured at 2, 4, and 6 weeks postoperatively decreased sequentially, all at the level of significance ( $p < 0.001$  of all).



Table 2. Visual analogue scale ( $\bar{X} \pm s$ )

	Time			Time	Groups	Time and groups
Groups	2 weeks	4 weeks	6 weeks	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
1-week group	7.47±0.59	5.32±0.44	2.03±0.61	<0.001	0.004	<0.001
4-week group	6.53±0.46	4.97±0.46	2.60±0.53abc			

a represents a significant simple effect for time between the two groups ( $P < 0.05$ )

b represents a significant simple effect for groups between the two groups ( $P < 0.05$ )

c represents a significant interaction effect of time and groups between the two groups ( $P < 0.05$ )

## 2.2 Outcomes of AOFAS after receiving the intervention in the 1-week and 4-week group

The results are shown in Table 3:

The main effect of time and the interaction effect between measurement time and group for the Pain were significant ( $p < 0.001$  for both). The results of the simple effect test showed significant simple effect for groups when tested 2 and 6 weeks postoperatively, ( $p < 0.05$  for both), and significant simple effect for time of measurement in the weight-bearing condition at 1 and 4 weeks postoperatively ( $p < 0.001$  for both). Multiple comparisons revealed that in the weight-bearing condition at 1 week postoperatively, the Pain item scores progressively increased at 2, 4, and 6 weeks postoperatively, all at the level of significance ( $p < 0.001$ ). In the weight-bearing condition at 4 weeks postoperatively, the Pain item scores at 2 weeks postoperatively were lower than those measured at 4 and 6 weeks postoperatively and reached the level of significance ( $p < 0.001$ ).

The main effect of time for the Activity limitations, support requirement was significant ( $p < 0.001$ ). The simple effect test showed significant simple effect for time of measurement in the weight-bearing condition at 1 and 4 weeks postoperatively ( $p < 0.001$  for both).

The main effect of groups, time and the interaction effect of time and groups for the Maximum walking distance was significant ( $p < 0.05$  of all). The results simple effect test showed that the simple effect of groups was significant when tested at 6 weeks ( $p < 0.001$ ), and a significant simple effect for time of measurement in the weight bearing condition at 1 and 4 weeks postoperatively ( $p = 0.001$ ). Multiple comparisons revealed that the Maximum walking distance, blocs item scores progressively increased in the weight-bearing condition at 1 week postoperatively, and reached the significance level at 2, 4, and 6 weeks postoperatively ( $p = 0.029$ ). In the weight-bearing condition at 4 weeks postoperatively, the Maximum walking distance, blocs score at 2 weeks postoperatively was lower than that measured at 4 and 6 weeks postoperatively and reached the significance level ( $p < 0.001$ ).

The main effect of time for the Walking Surfaces in the AOFAS was significant ( $p < 0.001$ ). A simple effect test showed a significant simple effect for time of measurement in the weight-bearing condition at 1 and 4 weeks postoperatively ( $p < 0.001$  for both).

The main effect of group, time and the interaction effect of time and groups for Sagittal motion in the AOFAS were significant ( $p < 0.05$  of all). A simple effect test showed significant simple effect for time of measurement in the weight-bearing condition at 1 and 4 weeks postoperatively ( $p < 0.001$ ), and the simple effect of groups was significant when tested at 6 weeks postoperatively ( $p < 0.001$ ). Multiple comparisons revealed that in the weight-bearing condition at 1 week postoperatively, the Sagittal motion item scores at 2 weeks postoperatively differed from those at 4 and 6 weeks postoperatively and reached the level of significance ( $p < 0.001$ ). In the weight-bearing condition at 4 weeks postoperatively, the Sagittal motion score at 2 weeks postoperatively was lower than at 4 weeks postoperatively and reached the significance level ( $p = 0.004$ ).

The main effect of time for the Hindfoot motion scale test was significant ( $p < 0.001$ ). A simple effect test showed a significant simple effect for time of measurement in the weight-bearing condition at 1 and 4 weeks postoperatively ( $p < 0.05$  for both).

The main effect of time of Ankle-hindfoot stability was significant ( $p = 0.007$ ). A simple effect test showed a significant simple effect for time of measurement in the weight-bearing condition at 1 and 4 week postoperatively ( $p = 0.01$  for both).

All other results not mentioned were not statistically different ( $p > 0.05$ ), details of which can be seen in Table 3.



Table3. AOFAS Ankle-Hindfoot System Score( $\bar{X} \pm s$ )

Note	Groups	Time			Time	Groups	Time and groups
		2 weeks	4 weeks	6 weeks	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
Pain	1-week group	2.17±4.21	13.91±8.91	26.95±11.05	<0.001	0.307	<0.001
	4-week group	4.21±5.10	15.65±10.80	17.39±6.90ac			
Activity limitations, support requirement	1-week group	4.13±2.83	4.83±0.65	7.65±1.56	<0.001	0.193	0.107
	4-week group	4.52±2.99	4.83±1.00	6.09±2.30a			
Maximum walking distance	1-week group	0.69±0.97	3.08±1.67	4.30±1.02	<0.001	0.001	0.021
	4-week group	0.69±0.97	2.47±1.64	2.73±1.05abc			
Walking Surfaces	1-week group	1.04±1.46	2.60±1.94	4.13±1.01	<0.001	0.087	0.615
	4-week group	0.91±1.41	2.08±1.83	3.43±0.84a			
Sagittal motion (flexion plus extension)	1-week group	2.78±1.88	5.04±2.16	5.73±2.02	<0.001	0.069	0.014
	4-week group	2.43±1.99	4.34±2.05	3.17±1.52ac			
Hindfoot motion (inversion plus eversion)	1-week group	1.43±1.53	2.87±1.91	4.17±1.74	<0.001	1	0.424
	4-week group	1.82±1.49	3.00±1.80	3.65±1.79a			
Ankle-hindfoot stability (anteroposterior, varus-valgus)	1-week group	4.17±4.08	5.217±3.89	6.60±3.10	0.007	0.209	0.969
	4-week group	3.13±3.99	4.522±4.05	5.91±3.59a			

a represents a significant simple effect for time between the two groups( $P < 0.05$ )

b represents a significant simple effect for groups between the two groups( $P < 0.05$ )

c represents a significant interaction effect of time and groups between the two groups( $P < 0.05$ )

### 2.3 Outcomes of OMAS after receiving the intervention in the 1-week and 4-week group

The results are shown in Table 3:

The main effect of time for the Pain was significant ( $p < 0.001$ ). The results of the simple effect test showed significant simple effect for measurement time in the weight-bearing condition at 1 and 4 weeks postoperatively ( $p < 0.001$  for both).

The main effect of groups for the Stiffness was significant ( $p < 0.001$ ), and the interaction effect between time and group was significant ( $p = 0.002$ ). The results of the simple effect test showed that the simple effect of groups was significant when tested 6 weeks postoperatively( $p < 0.001$ ). Multiple comparisons revealed that in the 1-week postoperative weight-bearing condition, the 2-week postoperative Stiffness score was lower than the 6-week and reached the level of significance ( $p = 0.001$ ). In the weight-bearing condition at 4 weeks postoperatively, Stiffness scores at 2 and 4 weeks postoperatively were higher than those measured at 6 weeks postoperatively and reached the level of significance, respectively ( $p = 0.024$ ).

There were significant main effect of groups,time and interaction effect of time and groups for the Swelling ( $p < 0.05$  of all). A simple effect test showed significant simple effect for group when tested 2 and 6 weeks postoperatively( $p < 0.001$  for both),and significant simple effect for time of measurement in the weight-bearing condition at 1 and 4 weeks postoperatively( $p < 0.001$ ). Multiple comparisons revealed that in the 1-week postoperative weight-bearing condition, Swelling scores measured at 2, 4, and 6 weeks postoperatively increased sequentially, all at the significance level ( $p = 0.004$ ).

The main effect of time for the Supports was significant ( $p < 0.001$ ). A simple effect test showed significant simple effect for time in the weight-bearing condition at 1 and 4 week postoperatively ( $p < 0.05$  for both).

The main effect of time for the Activity was significant ( $p < 0.001$ ), and the interaction effect between time and group was significant ( $p = 0.01$ ). The results of the simple effect test showed a significant simple effect of measurement time in the weight-bearing condition at 1 and 4 weeks postoperatively ( $p < 0.001$ ). Multiple comparisons revealed that in the 1-week postoperative weight-bearing condition, Activity scores measured at 2, 4, and 6 weeks postoperatively increased sequentially, all at the significance level ( $p < 0.001$ ). In the weight-bearing condition at 4 weeks postoperatively, Activity scores at 2 weeks postoperatively were lower than those measured at 4 and 6 weeks postoperatively and reached the level of significance ( $p < 0.001$ ).

All other results not mentioned were not statistically different ( $p > 0.05$ ), details of which can be seen in Table 4.

Table 4. Olerud Molander Ankle Rating Scale ( )

		Time			Time	Groups	Time×Groups
Note	Groups	2 weeks	4 weeks	6 weeks	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
Pain	1-week group	3.04±2.49	13.26±7.32	22.82±4.72	<0.001	0.194	0.36
	4-week group	2.39±2.55	13.04±9.50	19.34±6.62a			
Stiffness	1-week group	4.78±5.10	7.8±4.22	9.13±2.88	0.294	<0.001	0.002
	4-week group	5.22±5.10	5.22±5.10	1.74±3.88bc			
Swelling	1-week group	1.52±3.51	5.65±3.78	9.13±1.93	<0.001	0.019	<0.001
	4-week group	7.17±4.21	7.39±3.95	6.08±3.67abc			
Supports	1-week group	1.30±2.24	5.21±3.19	7.39±2.55	<0.001	0.895	0.25
	4-week group	1.95±2.49	4.13±3.58	7.60±2.55a			
Activity	1-week group	3.04±4.70	12.17±4.47	18.04±2.915	<0.001	0.021	0.01
	4-week group	3.91±4.9	11.08±4.25	13.26±4.158abc			

a represents a significant simple effect for time between the two groups( $P < 0.05$ )

b represents a significant simple effect for groups between the two groups( $P < 0.05$ )

c represents a significant interaction effect of time and groups between the two groups( $P < 0.05$ )

### 3. Discussion

In our study, postoperative ankle fracture patients underwent varying weight-bearing timing in conjunction with conventional rehabilitation. It shows that the time main effect was significant for the majority of the indicators, which represents a positive effect of weight-bearing activity and rehabilitation on postoperative ankle fracture patients.

#### 3.1 Pain

Analysis of pain indicators in Table 2 shows that patients in the 1-week group were more prone to ankle pain 2 weeks postoperatively. This might be due to early weight-bearing and ambulation potentially worsening mechanical nerve damage from fractures, intraoperative trauma, and surgical incisions, releasing inflammatory mediators and pain-causing substances. This could increase pain receptor sensitivity, lower the pain threshold, and lead to more postoperative pain.<sup>18</sup> Additionally, early mobilization after surgery may cause anxiety and fear in patients, activating the anterior cingulate cortex in the brain and intensifying pain perception.<sup>17</sup>

Moreover, although pain in both groups gradually decreased with increasing postoperative time, there was no statistically

significant difference in pain levels at 4 weeks postoperatively. At 6 weeks, patients in the 4-week group had more pain than those in the 1-week group. Note that although the comparison of VAS scores between the two groups showed a significant difference at 6 weeks, the difference in their means was relatively small (2.03 vs. 2.60), and the pain scores in the AOFAS indicated that the pain levels of patients in both groups were in the mild to moderate range.

The lack of statistical difference in pain scores between the two groups in Table 4 could be due to the scoring criteria of the pain scale, which evaluates pain during walking on different surfaces. It's observed that most patients in the 1-week group, after 2 weeks postoperatively, were restricted to indoor ambulation, which might not completely match the scale's assessment parameters.

### 3.2 Swell

Data in Tables 3 and 4 show that patients in the 1-week group had a higher incidence of ankle joint swelling at 1 week than those in the 4-week group. This difference may result from early weight-bearing and poor venous return in the limb. The gravitational force on damaged blood vessels and soft tissues due to fracture and surgical trauma triggers the release of inflammatory mediators like  $\text{TNF-}\alpha$  and prostaglandin E2, increasing vascular permeability and causing blood, lymphatic fluid, and tissue fluid to accumulate in the interstitial space, worsening swelling. Also, early weight-bearing intensifies soft tissue stimulation at the injury site, leading to more tissue fluid exudation, potentially hindering blood supply and circulation, and increasing swelling and discomfort.<sup>4, 19</sup> Through continuous stimulation, joint function gradually improves and tissue fluid exudation decreases.

### 3.3 Joint stiffness

Analysis of the anterior-posterior activity data in Table 2 and joint stiffness metrics in Table 4 showed no statistically significant difference in ankle joint mobility between the 1-week and 4-week postoperative groups. The stiffness in the 1-week postoperative group improved as postoperative time increased, perhaps due to swelling improvement. In the 4-week group, patients had ankle joint stiffness with restricted dorsiflexion and extension 6 weeks after surgery. This stiffness might result from the accumulation of lymphocytes, mast cells, and macrophages in the joint capsule because of prolonged immobilization, along with increased expression of inflammatory factors like  $\text{TGF-}\beta 1$ , which stimulate fibroblasts and lead to joint capsule fibrosis.<sup>10</sup> Prolonged immobilization also causes contracture and stiffness in muscles like the calf triceps, fibularis longus, and tibialis anterior, as well as in the joint capsule and peripheral ligaments, further restricting ankle joint mobility.<sup>9</sup>

### 3.4 Walk

From the Maximum walking distance item in Table 3, the maximum walking distance of patients in the 1-week group gradually increased as time advances and was greater than that of the 4-week group at 6 weeks postoperatively. There are three possible reasons:

Firstly, according to Wolff's law,<sup>20</sup> bone grows faster under stress. As the 1-week group started weight-bearing earlier than the 4-week group, their bones might have healed better and could endure the stresses from walking for longer and at higher speeds.

Secondly, early weight-bearing activity prevents joint stiffness (as mentioned before) and slows muscle atrophy. Compared to the 4-week group, patients in the 1-week group may have stronger and more enduring peri-ankle muscles, enabling them to walk longer distances.

Finally, weight-bearing activity can stimulate the metabolism of articular cartilage and surrounding soft tissues, which may help restore joint function.<sup>11</sup> Patients in the 1-week group might have better functional ankle motion when they began weight-bearing activity earlier.

### 3.5 Work and daily activity

The study findings indicate that the work and daily activity scores in the 1-week group increased with postoperative time, but which in the 4-week group increased only at 4 weeks postoperatively and then stagnated. This phenomenon may be attributed to ankle joint stiffness from prolonged bracing. These factors can lead to various adaptive changes in muscles resulting in muscle mass loss or atrophy, ultimately leading to muscle dysfunction. Muscle and joint dysfunction can restrict activities

such as walking, running, and climbing stairs. Previous studies have shown a 30% loss of muscle mass over several weeks of disuse.<sup>3,8</sup> The long-lasting effect of joint stiffness and muscle mass loss due to prolonged bracing have been documented.<sup>15</sup> At 6 weeks postoperatively, both patient groups scored corresponds to 'same as before the injury' and 'decreased speed', indicating that the limitation in work and daily activities of postoperative ankle patients at 4 weeks is mainly lead to a drop in pre-injury work speed, not a change in work nature or difficulty.

### 3.6 Postoperative complication

None of the early weight-bearing patients exhibited abnormal foot alignment in postoperative imaging, so the foot alignment item of the AOFAS Ankle-Hindfoot Rating Scale was not included in analysis, which aligns with previous research results.<sup>1</sup>

## Conclusion

The ankle joint, due to its unique anatomical structure, is liable to injuries and fractures, and has a surgical rate of around one-fourth.<sup>7</sup> Such injuries often occur among the working population, and the long period of postoperative rehabilitation can greatly affect patients' financial earnings and social contributions. Conducting weight-bearing activities one week after surgery may speed up the recovery of ankle joint function and relieve stiffness. Adopting a more relaxed attitude towards early postoperative activity after ankle fracture surgery might benefit patients and society as a whole.

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no

## Conflict of Interests

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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# Effect of Mindfulness Behavioral Training Combined with Exercise Intervention on Postoperative Functional Recovery and Quality of Life in Elderly Patients with Lumbar Spine Fractures

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**Abstract: Objective:** To investigate the positive effect of mindfulness training and exercise therapy on functional recovery and quality of life in elderly patients with fractures of the lower back. **Methods:** Collection of medical records of patients with lumbar vertebral fractures in Suzhou Municipal Hospital (North District), 60 patients underwent percutaneous vertebroplasty (PVP/PKP), they were divided into control and experimental groups according to a random number table, 30 people per group; In addition to traditional care method, Also intervened with behavioural awareness training and exercise therapy, By comparing the Oswestry dysfunction index score (ODI), visual simulation score (VAS), ability of daily living score (ADL), quality of life score (SF-36), To evaluate the effectiveness of the intervention. **Results:** Before the intervention, the ODI, VAS, ADL, and SF-36 scores were basically the same, with no significant difference ( $P>0.05$ ). After treatment, the ODI and VAS scores of the experimental group and the control group were significantly lower, and the experimental group was significantly lower than the control group ( $P<0.05$ ); the ADL scores of the experimental group were significantly higher than those of the control group ( $P<0.05$ ); their SF-36 quality of life scores in all dimensions were significantly higher ( $P<0.05$ ). **Conclusion:** Through the rehabilitation treatment method combining mindfulness behavior training and exercise intervention, it can effectively promote the functional recovery of osteoporotic lumbar fractures in the elderly, thus reducing their pain and improving their quality of life.

**Keywords:** Mindfulness Training; Exercise Intervention; Osteoporosis; Fracture of Lumbar Vertebrae; Functional Recovery; Quality of Life

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## Introduction

At present, my country is gradually entering an aging society, and the incidence of osteoporosis (OP) increases with age. It has become one of the chronic diseases that seriously threaten the health of the middle-aged and elderly people<sup>[1]</sup>. With the increase of age, the degree of osteoporosis will continue to increase, which will lead to a continuous increase in the incidence of osteoporotic fractures<sup>[2]</sup>. Therefore, the elderly have become a high-risk group for fractures. The spine is the most common site of osteoporotic fractures (OPF), and osteoporotic vertebral compression fractures (OVCF) are the most



common type of OPF. Clinical diagnosis and treatment need to be based on imaging to determine the severity of the injury. If the injury is relatively mild, conservative treatment can be used, taking the form of bed rest or brace protection combined with drug treatment; for patients with a higher degree of injury, surgical treatment is required, and vertebroplasty (PVP/PKP) can be performed after the patient's condition stabilizes<sup>[3]</sup>. Surgical treatment is only the first step in solving the problem, helping patients relieve pain and repair the structure, while rehabilitation treatment is required for functional recovery. Many patients lack understanding of postoperative rehabilitation, which leads to poor postoperative functional recovery and reduced self-care ability, which in turn affects the quality of life of themselves and their families. Therefore, how to help patients with lumbar fractures reduce postoperative pain and improve their quality of life has become a hot topic in postoperative rehabilitation. Early exercise training is particularly important for osteoporotic patients after fracture surgery, which can reduce bone loss and promote early recovery from trauma<sup>[4]</sup>. Studies have found that mindfulness training can also relieve stress to a limited extent for pain relief, and has an effectiveness comparable to that of first-line drugs<sup>[5]</sup>, which helps patients complete postoperative rehabilitation training more actively<sup>[6]</sup>. For patients, this can help patients reduce the pressure of postoperative rehabilitation, help patients adjust their mentality, and ensure better completion of rehabilitation training. Based on this, this study combined mindfulness behavioral training with exercise therapy intervention to explore its effects on functional recovery and quality of life in elderly patients after lumbar fracture surgery.

## 1. Materials and methods

### 1.1 Clinical data

This study selected 60 patients who visited the Department of Orthopedics of Suzhou Municipal Hospital (North District) from July 2022 to March 2023 and were diagnosed with lumbar fractures through physical examination and imaging. Inclusion criteria included: (1) met the diagnostic criteria for osteoporosis in the "Guidelines for the Diagnosis and Treatment of Osteoporosis"; (2) all patients met the indications for surgical treatment; (3) currently had single-segment vertebral lesions; (4) were over 60 years old; (5) had complete clinical data and signed informed consent. Exclusion criteria included: (1) had serious underlying diseases, organ dysfunction or malignant tumors; (2) had multi-segment vertebral fractures; (3) had incomplete posterior vertebral wall damage and kyphosis; (4) had spinal cord injury or lower limb neurological symptoms; (5) had vertebral re-fracture or bone cement leakage during surgery; (6) had cognitive, mental or language communication disorders. The patients were divided into a control group and an experimental group according to the random number table method, with 30 cases in each group. The baseline data of the two groups of patients are shown in Table 1. There was no statistical difference in the age of the two groups of experimental subjects ( $P>0.05$ ), and the surgical method was not an influencing factor. This study complies with ethical principles and has been approved by the Ethics Committee (KL901173).

Table 1 Comparison of general information of the two groups of patients ( $\bar{x} \pm s$ )

Group	n	Gender		Age (years)	Surgical method	
		Male	Female		PVP	PKP
Experimental Group	30	18 (60%)	12 (40%)	67.50±4.38	17 (56.7%)	13 (43.3%)
Control group	30	17 (56.7%)	13 (43.3%)	67.70±3.35	14 (46.7%)	16 (53.3%)
$\chi^2/t$		0.069		-0.199	0.601	
$P$		0.793		0.843	0.438	

### 1.2 Methods

#### 1.2.1 Control group

In this trial, patients with lumbar fractures in the control group were given routine care (including anti-osteoporosis treatment for 2 months), health education was provided to patients before and after surgery, and patients were informed of the precautions after lumbar fracture surgery after discharge, and were asked to come back for follow-up examinations on schedule.

### 1.2.2 Experimental group

The experimental group received two months of mindfulness behavioral training and exercise intervention on the basis of routine care.

Mindfulness behavioral training program: Before the patient left the hospital, the purpose, main content, key points and precautions of mindfulness training were explained to the patient so that the patient could smoothly carry out the next training.

(1) Breathing training (weeks 1-2): When you are calm, lie on your back or sit, suppress your thoughts, stay relaxed, pay attention to the feeling of breathing, feel the fluctuations in your abdomen, and take deep breaths; (2) Relaxation training (weeks 3-4): Based on breathing training, the patient sits, closes his eyes and takes deep breaths, gradually relaxing the muscles from the head to the abdomen and then to the legs. Each session lasts for 10 minutes; (3) Five senses training (weeks 5-6): Use the five senses to perceive the world, cultivate the ability to capture information through the five senses of vision, touch, taste, hearing, and smell, do not judge everything around you, only focus on the five senses, and keep the mind in the present state; (4) Life training (weeks 7-8): The patient tries to bring mindfulness into various activities in daily life, constantly practice in daily life, internalize it, and gradually form his own pattern.

Exercise intervention plan: Preoperative and postoperative exercise prescriptions were given to the 10 patients in the experimental group, and the patients were given movement guidance. Since all the patients in this trial were elderly patients with lumbar fractures and had varying degrees of osteoporosis, relatively simple and easy-to-complete movements were selected in the formulation of the exercise prescription to avoid psychological burden on the patients, which made it difficult for them to persist. (1) Lower limb muscle strength training: ① Straight leg raising training: The patient lies on his back and lifts one leg off the bed to form a 30-degree angle with the bed surface. Each movement should last for 10 seconds, with both legs alternating, 15 times/set, 3-5 sets/day; ② Side leg raising training: The patient lies on his side, with his upper body parallel to the bedside, and straightens the upper leg and lifts it upward to form a 30-50 degree angle with the bed surface. Each movement lasts for 10 seconds, with both legs alternating, 15 times/set, 3-5 sets/day; (2) Back muscle training: The patient lies on his back, flexes his hips and knees, so that the headrest, elbows and feet follow the bed, the buttocks are tightened and raised, the trunk is in a straight line, and the waist, back, thighs and calves are all off the bed surface. The patient should rise and fall slowly each time, lift to the highest point as much as possible, and hold for 20-30 seconds. After each movement, rest for 3-5 seconds, 5-10 times/set, 2-3 sets/day. If the patient can complete the exercise smoothly, the elbow support can be removed, leaving only the headrest and heels on the bed. Other training requirements are the same as above. (3) Balance training: ① Standing with two feet apart: The patient stands upright with his feet apart, one hand supporting the wall or the handrail, and the other hand naturally lowered. Slowly move the right foot in front of the left foot so that both legs are on the same horizontal line, and continue for 15-20 seconds; alternate between the left and right sides, 10 times/group, 2-3 groups/day; ② Standing on one foot: The patient stands in place, with his feet as wide as his shoulders, one hand supporting the wall or the handrail, and the other hand naturally lowered. Slowly lift one side of the calf and hold for 10 -20 seconds, alternate between the left and right sides, 10 times/group, 2-3 groups/day; ③ Walking on tiptoes: The patient stands with his feet as wide as his shoulders, his hands naturally hanging on both sides of the body, lifts his heels and uses the forefoot for support and walks forward 5 meters at a normal walking speed, then turns around and returns to the starting point at the same speed. One round trip is one group, 3-5 groups/day.

The lower limb strength training in the above exercise prescription can be performed before surgery. Instruct patients to proceed step by step during the training, ensure safety, and avoid holding their breath. If dizziness, nausea, chest tightness, shortness of breath, etc. occur during the training, stop the exercise immediately.

### 1.3 Evaluation indicators

(1) Oswestry Disability Index (ODI) score<sup>[7]</sup>: Oswestry Disability Index (ODI) score is the most widely used functional scoring table for lumbar spine diseases and can be used for comparison before and after treatment. ODI score consists of 10 questions, each with 5 points, and the total score ranges from 0-50 points. The higher the patient's score, the more severe the functional disability; (2) Visual Analogue Scale (VAS) score<sup>[8]</sup>: Visual Analogue Scale (VAS) refers to the patient's subjective feeling based on the pain score from 0 to 10 points. The higher the score, the more severe the pain: 0-2 points indicate mild



pain; 2-4 points indicate mild pain; 4-6 points indicate moderate pain; 6-8 points indicate severe pain; 8-10 points indicate severe pain. If the VAS score decreases after the intervention, it means that the intervention is effective; otherwise, it means that it is ineffective; (3) Activities of Daily Living (ADL) score<sup>[9]</sup>: Daily living ability (ADL) refers to the necessary activities that humans perform every day to meet their daily needs. Currently, ADL is scored clinically using the Barthel Index Scale, which includes 10 aspects, 10 points for each aspect, and a total score of 100 points. 100 points indicates normal; 61-99 points indicate mild dependence; 41-60 points indicate moderate dependence; and less than 40 points indicate severe dependence. The Barthel index has the advantages of simplicity, accuracy, and high sensitivity, and has been widely used in clinical practice. (4) Quality of life score: The SF-36 summary scale is used<sup>[10]</sup>. This scale is a universal scale for measuring the health and quality of life of people of different ages and diseases. It includes four dimensions: postoperative physical function, social role, emotional state, and vitality<sup>[11]</sup> (Table 2). Each dimension has 10 small items, each item has 10 points, and the total score is 100. The higher the score, the higher the quality of life. Because this scale is sensitive to changes, many studies have used this scale to evaluate the effect of treatment.

Table 2 Specific content of each score

Indicators	Specific details
ODI	Intensity of pain, self-care, lifting, walking, sitting, standing, sleeping, sex life, social life, travel
ADL	Eating, bathing, washing face independently, dressing, controlling bowel movements, using the toilet, transferring from bed to chair, walking, and climbing stairs
SF-36	Physical functions, social roles, emotional states, vitality

## 1.4 Statistical methods

SPSS 26.0 software was used to analyze the data. All experimental data that conformed to normal distribution were expressed as mean±standard deviation ( $\bar{x} \pm s$ ). Independent sample t test and chi-square test were used for comparison between the two groups, and paired t test was used for comparison within the group.  $P < 0.05$  indicated that the difference was statistically significant.

## 2 Results

### 2.1 Comparison of ODI and VAS scores before and after intervention between the experimental group and the control group (Table 3)

Before the intervention, there was no significant difference in ODI and VAS scores between the two groups ( $P > 0.05$ ); after two months of mindfulness behavioral training and exercise therapy intervention, the ODI and VAS scores of both groups decreased compared with before the intervention, and the ODI and VAS scores of the experimental group were lower than those of the control group, and the difference was statistically significant ( $P < 0.05$ ).

### 2.2 Comparison of ADL scores before and after intervention between the experimental group and the control group (Table 4)

Before the intervention, there was no significant difference in the ADL scores of the two groups ( $P > 0.05$ ); after two months of mindfulness behavioral training and exercise therapy intervention, the ADL scores of both groups were significantly improved, and the scores of patients in the experimental group were higher than those in the control group, and the difference was statistically significant ( $P < 0.05$ ).

### 2.3 Comparison of SF-36 scores in each dimension between the experimental group and the control group before and after intervention (Table 5)

Before the intervention, there was no significant difference in the scores of each dimension of SF-36 between the two groups ( $P > 0.05$ ); after two months of mindfulness behavioral training and exercise therapy intervention, the scores of each dimension of SF-36 between the two groups were significantly improved, and the scores of patients in the experimental group were higher than those in the control group, and the difference was statistically significant ( $P < 0.05$ ).

Table 3 Comparison of ODI scores and VAS scores before and after intervention between the experimental group and the control group ( $\bar{x} \pm s$ , points)

Group	n	ODI		VAS	
		Before	After	Before	After
Experimental Group	30	41.60±5.95	31.80±6.25*	7.00±1.05	2.60±1.70*
Control group	30	41.05±5.87	35.60±5.41*	7.10±0.88	4.20±1.79*
<i>t</i>		0.360	2.518	0.400	3.550
<i>P</i>		0.720	0.015	0.691	0.001

Compared with the same group before intervention, \*P<0.05

Table 4 Comparison of ADL scores between the experimental group and the control group before and after intervention ( $\bar{x} \pm s$ , points)

Group	n	ADL	
		Before	After
Experimental Group	30	35.09±7.82	70.00±6.67*
Control group	30	35.30±7.89	65.50±5.80*
<i>t</i>		0.104	2.788
<i>P</i>		0.918	0.007

Compared with the same group before intervention, \*P<0.05

Table 5 Comparison of SF-36 scores in each dimension between the experimental group and the control group before and after intervention( $\bar{x} \pm s$ , points)

Group	n	Physical Function		Social Role		Emotional state		Vitality	
		Before	After	Before	After	Before	After	Before	After
Experimental Group	30	64.12±9.34	90.34±9.77*	65.79±10.67	89.41±9.68*	60.78±11.23	88.97±10.67*	60.94±10.26	86.11±10.37*
Control group	30	63.92±8.32	82.65±9.45*	66.78±10.23	83.47±10.37*	60.12±10.78	80.79±11.03*	60.31±9.88	78.32±11.23*
<i>t</i>		0.088	3.009	0.367	2.293	0.232	2.920	0.242	2.791
<i>P</i>		0.931	0.003	0.715	0.025	0.817	0.005	0.809	0.007

Compared with the same group before intervention, \*P<0.05

### 3. Discussion

As the aging process of society continues to intensify, the incidence of osteoporosis (OP) will increase with age. Osteoporotic fractures are caused by osteoporosis and are more common in the upper limbs, spine, and hips. In addition, fractures will aggravate osteoporosis again, leading to an increased risk of secondary fractures<sup>[12]</sup>. After percutaneous vertebroplasty, not only drugs are needed for anti-osteoporosis treatment, but functional rehabilitation training is also necessary to consolidate the effect of surgical treatment.

The results of this study showed that after 2 months of intervention, the ODI score and VAS score of the experimental group were lower than those of the control group, indicating that mindfulness behavioral training combined with exercise intervention can improve lumbar dysfunction and relieve pain after osteoporotic lumbar fracture surgery; at the same time, the results of the study showed that after the intervention, the ADL score and the scores of each dimension of SF-36 in the

experimental group were significantly higher than those in the control group, suggesting that the intervention of mindfulness behavioral training combined with exercise therapy can help patients restore normal activity functions, enable them to return to a normal social environment, and thus improve their quality of life.

Patients with lumbar fractures usually have lumbar pain and limited mobility. Elderly patients with lumbar fractures usually undergo surgical treatment, which can repair the fracture site, improve the spinal sequence to restore it to normal, improve the stability of the spine, reduce the pressure on the peripheral nerves, thereby reducing the patient's pain symptoms and further promoting the repair of nerve function<sup>[13]</sup>. Before surgery, most patients are anxious about the surgical trauma and results. After surgery, patients are anxious about persistent pain, lesion characterization, wound healing, functional recovery, quality of life and other issues. In this trial, after 2 months of mindfulness behavioral training, the experimental group not only had a decrease in VAS scores, but also had a significant increase in the scores of the two dimensions of physical function and emotional state in the SF-36 score compared with the control group. This shows that mindfulness training can relieve pain and effectively help patients improve negative emotions and reduce fear of the disease. Chen et al. helped patients maintain a good mentality through psychological intervention, and participated more actively in early rehabilitation training, promoting patients' functional recovery and accelerating their return to society<sup>[14]</sup>.

Studies have shown that mindfulness training can adjust the body's basal metabolism, regulate the autonomic nervous system, and thus improve sensory sensitivity<sup>[15]</sup>. In addition, some experiments have shown that mindfulness practice can improve the body's immunity. After conducting mindfulness training on patients with hemiplegia after stroke, it was found that mindfulness training can effectively help patients improve their acceptance of the disease, reduce their cognitive stress, and reduce their painful experience<sup>[16]</sup>. In this experiment, mindfulness training can enable patients to have a clearer understanding of their fractures and the negative effects they bring, and to focus on the current feelings in continuous practice, using this self-awareness method to deal with the anxiety and fear generated in their hearts. Lumbar dysfunction is a common symptom of osteoporotic lumbar fractures. ODI score is a common indicator of lumbar dysfunction. In this experiment, we conducted 2-month lumbar and lower limb muscle strength training on postoperative patients. The results showed that the patients who underwent lumbar muscle training after fracture surgery had lower ODI scores and VAS scores than the control group, and the recovery of lumbar function and pain relief were more obvious than those in the control group ( $P < 0.05$ ). In addition, the results showed that in terms of ADL, the experimental group performed better than the control group in walking and going up and down stairs, indicating that muscle strength training helps improve patients' joint function and daily living ability. Chiang CH et al.<sup>[17]</sup> found that the ODI scores of patients who underwent lumbar muscle training were significantly higher than those of other patients after 6 months. This suggests that lumbar muscle training after vertebroplasty can help improve lumbar function in patients with osteoporotic lumbar fractures, which is consistent with the findings of Chen BL et al.<sup>[18]</sup>. In addition, a study by Zhu et al.<sup>[19]</sup> pointed out that if effective early functional exercise is not performed after vertebroplasty for osteoporotic lumbar fractures, disuse atrophy of the lower back muscles will occur. Functional back muscle training can promote the growth of skeletal muscle volume and increase blood supply, relieve local muscle tissue and nerve root edema, thereby improving neuromuscular control, reducing muscle atrophy due to disuse, making the waist muscles stronger, forming a strong peripheral support, maintaining the mechanical stability of the spine, reducing the load on the lumbar spine, and promoting the recovery of damaged tissues<sup>[20]</sup>.

Balance ability is an important indicator for measuring the degree of recovery of motor function and is of great significance for elderly patients with lumbar fractures. A large number of literatures show that even if exercise intervention does not significantly increase bone mass, it can improve the balance of the elderly, thereby reducing the risk of falls and fractures. Decreased balance ability and decreased lower limb muscle strength are important causes of falls<sup>[21]</sup>. Balance disorders in the elderly are closely related to the decline of vision, vestibular function and proprioception. When designing the exercise program, this trial specifically strengthened the balance ability and lower limb muscle strength training of elderly patients. Lower limb muscle strength loss caused by bed rest after osteoporotic lumbar fracture surgery is more likely to cause patients to fall when walking after surgery. Therefore, it is not only necessary to conduct lower limb muscle strength training for patients after surgery, but also to guide patients to perform muscle strength training while they are bedridden before surgery

to help them maintain muscle strength. Studies have shown that personalized progressive exercise prescriptions can help patients strengthen their lower limb muscle strength and improve their lower limb stability, which can better prevent falls in the elderly<sup>[22]</sup>, promote patients to better participate in family and social activities, and improve their quality of life.

In summary, the rehabilitation treatment method combining mindfulness behavioral training and exercise therapy can effectively promote the functional recovery of osteoporotic lumbar fractures in the elderly, thereby alleviating the pain of patients and improving their quality of life.

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no

## Conflict of Interests

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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# Application Value of Electromyography Combined with Heart Rate Variability in the Diagnosis of Diabetic Peripheral Neuropathy

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**Abstract: Purpose:** To explore the clinical value of Electromyography (EMG) and Heart Rate Variability (HRV) in the diagnosis of early DPN and provide the basis for early diagnosis, treatment, and prevention of DPN. **Methods:** 105 patients with type 2 diabetes mellitus (T2DM) in the Changji People's Hospital were treated from January 2023 to December 2023. They were stratified into DPN-symptomatic (DPN group, n=55) and DPN-asymptomatic (NDPN group, n=50) cohorts based on the presence or absence of clinically confirmed diabetic peripheral neuropathy. The clinical biochemical indicators, nerve electromyography, and HRV parameters were obtained from electronic medical records, and differences in detection results were compared between the two groups. Logistic regression was applied to analyze the influencing factors of DPN in diabetes patients. The receiver operating characteristic (ROC) curve was applied to analyze the diagnostic value of EMG combined with other parameters for DPN. **Results:** From the results of the general information, diabetes duration, glycosylated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and FBG in the DPN group were significantly differences compared with the NDPN group ( $p<0.05$ ). There were no statistically significant differences in gender, age years, uric acid, and other general data ( $p>0.05$ ). Compared with the NDPN group, the motor nerve conduction velocity (MNCV), sensory nerve conduction velocity (SNCV) of the ulnar nerve, median nerve, and tibial nerve in the DPN group were statistically significant ( $p>0.05$ ). The DPN group had higher average F wave latency and H wave latency in the tested nerve, with statistical significance ( $p<0.05$ ). HRV parameters decreased significantly (SDNN, rMSSD, PNN50, and SDANN, all  $p<0.05$ ). ROC analysis showed that the area under the ROC curve (AUC) of the combined diagnosis of DPN by duration of diabetes, HbA1c, EMG, and HRV was 0.897, the accuracy was 82.86%, the sensitivity was 78.00%, and the specificity was 87.27%. The AUC of the combined diagnosis of the four parameters for DPN was significantly higher than that of each alone ( $p<0.05$ ). **Conclusion:** The combination of EMG and HRV has a high value in the assessment of DPN and can be used for early assessment of the extent of the lesion.

**Keywords:** Diabetes Peripheral Neuropathy; Electromyography; Heart Rate Variability; Diagnosis

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## 1.Introduction

With the development of the world economy and the gradual improvement of people's living standards and quality, diabetes has become a worldwide epidemic<sup>[1]</sup>. Diabetic peripheral neuropathy (DPN), one of the most prevalent chronic complications



of diabetes, imposes a substantial economic burden on healthcare systems due to its progressive nature and associated treatment costs<sup>[2,3]</sup>. The onset of diabetes peripheral neuropathy is insidious. When patients have obvious symptoms, they are often in the late stage of the disease, which often leads to irreversible nerve injury<sup>[4]</sup>. In the later stage, there will be serious consequences such as limb sensation and movement disorders, foot ulcers, and even death<sup>[5,6]</sup>. It not only resulted in a significant decline in the quality of life of patients but also placed a substantial financial burden on healthcare systems and society in general<sup>[7]</sup>. Therefore, for patients with diabetes peripheral neuropathy, early diagnosis and prevention are considered to be far more effective than treatment.

Electromyography is a simple and effective auxiliary method for diagnosing diabetic peripheral neuropathy, and can accurately reflect the degree of peripheral nerve damage in patients<sup>[8]</sup>. It evaluates the occurrence and development of DPN by detecting the velocity and amplitude of peripheral nerve conduction. Heart rate variability (HRV) is an important indicator for assessing diabetic peripheral neuropathy (DPN), especially valuable in early diagnosis and disease assessment. By monitoring HRV, the impaired autonomic function of diabetic patients can be detected at an early stage, so that timely interventions can be taken to reduce the occurrence of complications<sup>[9][10]</sup>. This study aims to investigate a novel diagnostic protocol integrating EMG and HRV analyses for enhancing the precision of DPN identification, with the ultimate goal of informing evidence-based therapeutic decision-making in diabetes care.

## 2. Materials and methods

### 2.1 Subjects

This study included 105 inpatients with type 2 diabetes mellitus (T2DM) who were enrolled between January 2023 and December 2023 at the Changji People's Hospital. They were divided into a DPN group (27 men, 28 women) and an NDPN group (28 men, 22 women) according to the presence or absence of peripheral neuropathy. The diagnosis criteria for T2DM were based on the 2023 Standards for the Medical Management of Diabetes by American Diabetes Association (ADA)<sup>[11]</sup>. The diagnostic criteria for DPN followed the 2025 Standards of care in Diabetes published by the ADA<sup>[12]</sup>. The inclusion criteria were as follows: (1) Compliance with type 2 diabetes; (2) Patients with neuropathy meeting the diagnostic criteria for DPN; (3) Age 18-80 years old; (4) Patients' medical records were complete. The Exclusion criteria were as follows: (1) Complicated with acute complications of diabetes mellitus; (2) Combined cardiovascular, pulmonary, hepatic, renal, hematopoietic system and other serious diseases not caused by diabetes; (3) Serious primary diseases and mental illnesses. (4) Peripheral neuropathy caused by other reasons. (5) Pregnant or lactating women. (6) Patients with incomplete clinical data.

### 2.2 Clinical data collection

The clinical data and medical histories of T2DM patients were obtained from electronic medical records. Baseline data on age, sex, and diabetes duration were collected. The following laboratory parameters were assessed: fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total bilirubin (TBIL), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), serum creatinine (Cr) and urinary microalbumin (mAlb) levels.

### 2.3 Nerve conduction studies (NCS)

All patients were examined using an electromyographic evoked potential meter (Viking Quest 4, America). Latency, amplitude, motor conduction velocity, and sensory conduction velocity of the bilateral median, ulnar, and tibial nerves were measured and recorded. In addition, the F-wave latency of all tested nerves and H-reflex of the tibial nerve were detected. These neurophysiological examinations were performed in a quiet environment and the temperature in the electrophysiology laboratory was maintained at 22-28°C during tests. The abnormal judgment of NCS according to the NCS reference value of the Chinese population, and the abnormal H-reflex and F wave refer to the standard formulated<sup>[13,14]</sup>.

### 2.4 Heart Rate Variability (HRV)

The time-domain parameters were measured and recorded using a 24-h Holter monitor (Zhongqi Biomedical Electronics Co., Ltd., Wuhan, China), which included the standard deviation of all normal to normal R-R intervals (SDNN, ms), standard deviation of 5-minute average NN intervals (SDANN, ms), square root of the mean of the squares of successive NN interval differences (rMSSD, ms) and the percentage of intervals >50 ms different from preceding interval (PNN50, %). HRV was

considered abnormal if at least two of the following six abnormal parameters were met: SDNN < 50 ms, SDANN < 40 ms, PNN50 < 0.75%, rMSSD < 15 ms<sup>[15,16]</sup>.

## 2.5 Statistical analysis

Data were collected using SPSSAU (Beijing QingSi Technology Co., Ltd) and Z stats software (Hangzhou Mr. Zheng Statistical Technology Co., Ltd). The continuous variables were expressed as mean  $\pm$  standard deviation, these not satisfying normal distribution were shown as M (25th-75th percentiles), and categorical variables were expressed as percentages (%). T-tests or Mann–Whitney U tests were carried out to compare the differences in these variables and the chi-square test for categorical variables between two groups. The significance level of tests in this study was considered as  $p < 0.05$ .

## 3. Results

### 3.1 Comparison of clinical characteristics between two groups

A total of 105 patients (mean age =  $57.19 \pm 10.43$  years) were enrolled in this work, which consists of 47 (44.77%) males and 58 (55.24%) females. The baseline clinical characteristics (gender, age, and clinical biochemical indicators) of patients are given in Table 1. When comparing the general clinical data between the DPN group and the NDPN group, the results revealed that there were significant differences in age, duration of diabetes, HbA1c, FBG, TC, and LDL-C ( $p < 0.05$ ). There was no significant difference in Sex, TBIL, HDL-C, UA, Cr and mAlb. HbA1c, FBG, TC, and LDL-C were significantly increased compared with the NDPN group.

Table 1. Comparison of the biochemical indicators between the NDPN and DPN groups.

Group	DPN (n=55)	NDPN (n=50)	t/ $\chi^2$ /z	p
Sex (Male/Female)	25/30	22/28	0.022	0.881
Age (years)	$60.05 \pm 11.13$	$57.00 \pm 6.32$	1.750	0.084
Diabetes duration (years)	$9.05 \pm 5.42$	$4.60 \pm 4.56$	4.533	0.000 *
HbA1C (%)	$10.29 \pm 1.96$	$8.39 \pm 1.94$	4.971	0.000 *
TBIL	$11.61 \pm 3.29$	$11.15 \pm 4.98$	0.553	0.581
FBG (mmol/L)	$9.59 \pm 3.71$	$7.87 \pm 3.16$	2.554	0.012 *
TC (mmol/L)	$4.62 \pm 0.82$	$4.11 \pm 0.93$	3.018	0.003 *
HDL-C (mmol/L)	$1.10 \pm 0.32$	$1.12 \pm 0.39$	-0.326	0.745
LDL-C (mmol/L)	$2.71 \pm 0.76$	$2.30 \pm 0.77$	2.699	0.008 *
Cr ( $\mu$ mol/L)	$58.48 \pm 19.40$	$57.24 \pm 10.13$	0.416	0.679
UA ( $\mu$ mol/L)	235.00 (195.50, 306.00)	258.00 (211.25, 287.50)	-0.65	0.513
mAlb (mg/L)	8.50 (3.00, 21.05)	8.40 (3.87, 14.82)	-0.57	0.568

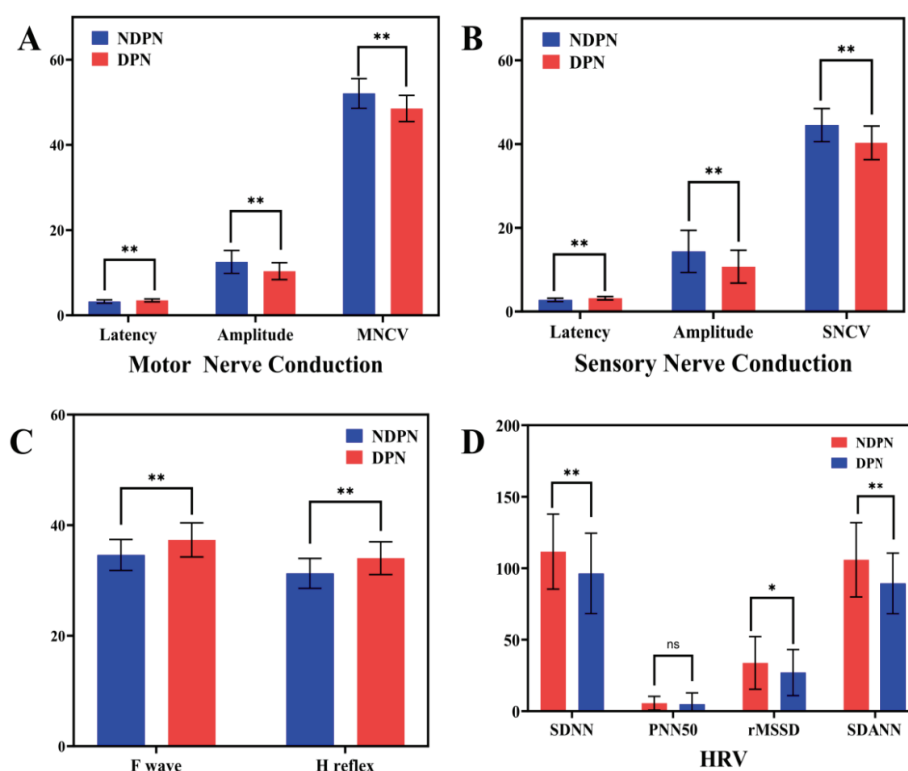
### 3.2 Neurophysiological examination results of patients

In this study, the latencies, amplitudes, motor and sensory conduction fiber velocity of the nerve were measured, and the difference in each parameter of the ulnar nerve, median nerve, and tibial nerve (Figure 1). For the comparison of motor nerve conduction detection parameters, as shown in Table S1, for the ulnar nerve and median nerve, the latency in the DPN group was significantly longer than that in the NDPN group and reached statistical significance. For the tibial nerve, latency was longer in the DPN group but did not reach statistical significance ( $4.02 \pm 0.59$  vs.  $3.85 \pm 0.62$ ,  $p = 0.095$ ). Regarding the amplitude results, we found that amplitude significantly lowered in all tested nerves compared to the control group ( $p < 0.05$ ). As



shown in Table S2, for the comparison of sensory nerve conduction detection parameters, we found that the latency of each nerve ( $p < 0.05$ ) was significantly longer and the amplitude of the ulnar and median nerve was lower ( $13.65 \pm 5.80$  vs.  $16.33 \pm 6.08$ ,  $16.30 \pm 8.43$  vs.  $24.38 \pm 10.17$ ,  $p < 0.05$ ) in DPN group than in NDPN group. Yet no statistical significance in the latency of the ulnar nerve and the amplitude of the tibial nerve. Table S3 shows that the motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) were significantly reduced in the DPN group, compared with the NDPN group ( $p < 0.05$ ).

Figure 1. Comparison of indicators of electromyography and HRV between the two groups. ( $p < 0.05^*$ ,  $p < 0.001^{**}$ )



### 3.3 Comparison of F wave and H-reflex detection parameters between the two groups

As shown in Table S4, the average latency of the F wave of the tibial nerve, median nerve, and ulnar nerve in the DPN group was significantly longer than that in the NDPN group, and the difference was statistically significant ( $p < 0.05$ ). The H-reflex minimum latency of the tibial nerve in the DPN group was significantly longer than that in the NDPN group ( $p < 0.05$ ).

### 3.4 Comparison of the parameters of HRV detection between the two groups.

Statistically significant differences were found in SDNN, rMSSD, PNN50, and SDANN between DPN and NDPN groups ( $p < 0.05$ ), as shown in Table 2.

Table 2. Time domain indicators of HRV comparisons between the two groups.

Group	DPN	NDPN	t / z	p
SDNN (ms)	$96.35 \pm 28.14$	$111.64 \pm 26.23$	-2.872	0.005*
PNN50 (%)	1.00 (0.00, 5.50)	5.00 (2.00, 8.00)	-2.380	0.017*
rMSSD (ms)	23.00 (16.50, 34.50)	31.50 (20.25, 39.00)	-2.320	0.020*
SDANN (ms)	$89.38 \pm 21.23$	$105.86 \pm 25.97$	-3.573	0.001*

### 3.5 The risk factors of DPN were analyzed by binary logistic regression

As shown in Table 3, using DPN as the dependent variable, variables with statistical significance in univariate analysis and those that were professionally considered to have an impact on outcome were included in a binary logistic regression model,

which showed that duration of diabetes, HbA1c, LDL-C, and SDANN were independent factors influencing the occurrence of outcome ( $p < 0.05$ ).

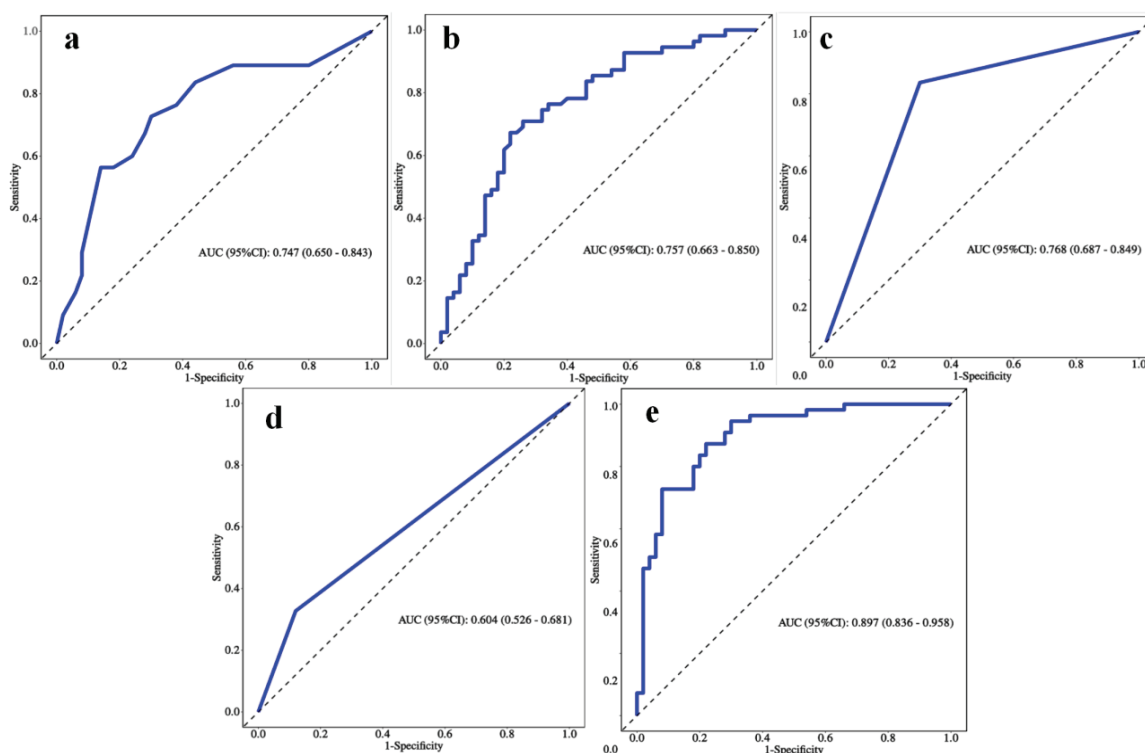
Table 3. Risk factors of DPN.

Variables	Single-factor logistic regression					Multinomial logistic regression				
	$\beta$	S.E	Z	P	OR (95%CI)	$\beta$	S.E	Z	P	OR (95%CI)
Duration of diabetes	0.181	0.047	3.866	<.001 *	1.199 (1.093 ~ 1.314)	0.221	0.058	3.830	<.001 *	1.247 (1.114 ~ 1.396)
HbA1c	0.483	0.116	4.178	<.001 *	1.621 (1.292 ~ 2.033)	0.516	0.138	3.735	<.001 *	1.675 (1.278 ~ 2.195)
LDL-C	0.693	0.271	2.560	0.010 *	1.999 (1.176 ~ 3.397)	0.951	0.379	2.514	0.012 *	2.589 (1.233 ~ 5.438)
SDANN	-0.029	0.009	-3.253	0.001 *	0.971 (0.954 ~ 0.988)	-0.023	0.012	-1.971	0.049 *	0.977 (0.955 ~ 0.999)
PNN50	-0.016	0.030	-0.520	0.603	0.984 (0.928 ~ 1.044)	0.026	0.046	0.557	0.577	1.026 (0.937 ~ 1.124)

### 3.6 The diagnostic efficacy of these duration of diabetes, HbA1c, EMG, HRV and their combination for DPN

ROC curve results showed that the AUC of the duration of diabetes, HbA1c, EMG, and HRV in diagnosing DPN were 0.747, 0.757, 0.768 and 0.604 respectively, and the AUC of the combination of the four was 0.897, significantly higher than that of each single index ( $p < 0.05$ ), as shown in Figure 2 and Table S5.

Figure 2. The ROC curve (a) Duration of diabetes, (b) HbA1c, (c) EMG and (d) HRV and (e) their combined diagnosis of DPN.



## 4. Discussion

DPN is one of the main and common microvascular complications of diabetes mellitus, which can cause considerable morbidity in many patients<sup>[17,18]</sup>. The typical clinical manifestations are symmetrical numbness and motor and sensory disorders in the distal extremities<sup>[19, 20]</sup>. DPN is also an insidious disease and only a small number of patients have symptoms and signs in the early stage<sup>[21]</sup>. If the treatment is not timely, it may lead to gradual aggravation of nerve damage and serious

sequelae, such as diabetic foot, which may lead to non-traumatic amputation of patients<sup>[22]</sup>. Therefore, for diabetes patients, DPN is a risk factor for disability and death and it is very important to early screen and diagnose peripheral neuropathy of people with diabetes in the early stage and take effective target measures to prevent the conditions, progression, and complications.

Regarding the clinical biochemical indicators, our data suggested that the HbA1c, TC, LDL-C, and Cr levels were higher in DPN group than in NDPN group. HbA1c level can reflect the blood glucose levels in patients with diabetes mellitus (for 8-12 weeks)<sup>[23]</sup>. It was also an independent risk factor for DPN in the multivariate analysis of this population<sup>[24]</sup>. Meanwhile, the results of the present study demonstrated that with the extension of the duration of diabetes and unqualified glycemic control, the prevalence of DPN increases significantly, which is consistent with the results of Hu et al<sup>[6]</sup>. Abnormal blood lipid metabolism is also a risk factor for DPN<sup>[25]</sup>. Based on our study, the results suggested that patients with DPN have higher peripheral blood TG, TC content, and lower HDL-C levels.

Electromyography has a high detection rate for minor neurologic lesions and can assist in the clinical screening and diagnosis of DPN. The results of the electromyography examination, showed that there were significant differences in the sensory latency, amplitude, MNCV and SNCV of all the examined nerves between the two groups ( $p < 0.05$ ), and the sensory amplitude of the DPN group was significantly lower than that the NDPN group, which suggests that diabetic patients with neurological symptoms had peripheral nerve sensory and motor dysfunction, and the electromyography results were consistent with clinical symptoms. Diabetes mellitus patients' bodies are in a state of hyperglycemia, neurons can not synthesize nutrients, resulting in axonal damage, inducing nutritional disorders of nerve endings, leading to damage to distal nerves, and with the prolongation of the disease, the more serious the impact of the nerve fibers by the metabolism of glucose, which contributes to the body's lack of compensatory function, aggravating nerve damage<sup>[26]</sup>. Significant oxidative stress exists in patients with diabetes mellitus complicated by peripheral neuropathy, which contributes to the decline in neuron number and slowing of nerve conduction velocity due to oxidative stress in cells, and the oxidative stress worsens with the increase in diabetes duration, further decreasing the nerve conduction velocity<sup>[27]</sup>. As a result, there is a significant difference between motor and sensory nerve conduction in electromyography. The single NCS detection often reduces the detection rate. The NCS detection is combined with F wave and H-reflex detection to make up for the shortcomings of traditional techniques avoid missed diagnosis and misdiagnosis and improve the diagnostic value of DPN. For all tested nerves, the average latency of the F wave in DPN group was significantly longer than that in the NDPN group. Meanwhile, the H-reflex of the tibial nerve was explored and the H-wave minimum latency of tibial nerve in DPN group was significantly longer than that in NDPN group ( $p < 0.05$ ), indicating that the detection of H-reflex was helpful for early diagnosis of DPN. DPN patients are prone to prolonged terminal motor latencies and slowed nerve conduction velocities, while F-wave latencies can reflect proximal neuropathy<sup>[28]</sup>. The H-reflex detects motor neuron excitability, and any lesion in the nerve reflex arcs can cause abnormalities of the H-reflex, which can be revealed even in diabetic patients with minor nerve injuries, which further demonstrates the value of neurography in the assessment of DPN<sup>[29][30]</sup>.

Heart rate variability is an important indicator for assessing DPN, especially valuable in early diagnosis and disease assessment. By monitoring HRV, the impaired autonomic function of diabetic patients can be detected at an early stage, so that timely interventions can be taken to reduce the occurrence of complications. Decreased HRV in DPN patients suggests that the cardiac autonomic nervous system was impaired and that the vagus nerve was more likely to be impaired before the sympathetic nerve or that the vagus nerve was more severely impaired than the sympathetic nerve<sup>[31][32]</sup>. It has been reported in the literature that the correlation between patients with type 2 diabetes mellitus with peripheral neuropathy and their cardiac autonomic function analyzed by HRV shows that the duration of diabetes is closely related to the decline in HRV, and the most significant decline in HRV is in the first 5-10 years of the disease, so it is important to strengthen the strict control of blood glucose and early intervention therapy to slow down the development of the time of diabetic complications<sup>[33]</sup>. Tarvainen et al. reported that cardiac autonomic regulation is reduced in hyperglycemia without significant changes in sympathetic-vagal balance, that hyperglycemia is associated with a decrease in mean and heart rate, and that sustained high levels of blood glucose are an underlying factor contributing to the development of DPN in diabetic patients<sup>[34]</sup>. In this study,

the results showed that heart rate variability indices (SDNN, rMSSD, SDANN) were significantly lower in the DPN group than in the NDPN group ( $p < 0.05$ ), which further confirms the diagnostic value of heart rate variability in diabetic peripheral neuropathy. We also analyzed the independent risk factors for DPN using binary logistic regression analysis, which showed that duration of diabetes, HbA1c, LDL-C, and SDANN were independent risk factors for DPN ( $p < 0.05$ ). The diagnostic efficacy of diabetes duration, HbA1c, EMG, and HRV for DPN was analyzed using ROC curves, and the results showed that the AUC of combining the four indicators was 0.90, the sensitivity was 87%, the specificity was 85%, which was significantly higher than that of each of the individual indicators ( $p < 0.05$ ). These results suggest that EMG combined with heart rate variability is valuable for early diagnosis and assessment of diabetic peripheral neuropathy.

## 5. Conclusion

In conclusion, our findings show that the pathological and physiological changes of the peripheral nerves in T2DM patients have already appeared in the early stage without symptoms of neurological damage, not only in the distal nerve, but also in the proximal nerve, and the proximal end is damaged earlier and more significantly than the distal end. Electromyography and heart rate variability tests are valuable in the early diagnosis and assessment of diabetic peripheral neuropathy. Electromyography is mainly used to assess nerve damage by detecting nerve conduction velocity and wave amplitude, while HRV reflects the degree of the lesion by evaluating cardiac autonomic function. The combination of the two can provide a more comprehensive assessment of the severity of diabetic peripheral neuropathy, and provide a more accurate basis for clinical prevention, early treatment and prognostic assessment.

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## Conflict of Interests

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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# Study on the Mechanism of Salvia Miltiorrhiza in the Treatment of Prostatic Hyperplasia Based on Online Pharmacology

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**Abstract: Objective:** This study aims to investigate the potential molecular mechanism of Salvia miltiorrhiza in treating benign prostatic hyperplasia (BPH) based on network pharmacology. **Methods:** Active components of Salvia miltiorrhiza were screened via the TCMSD database, and their potential targets were predicted using Swiss Target Prediction. BPH-related targets were obtained from Gene Cards and OMIM databases. Common targets between the herb and BPH were used to construct a protein-protein interaction (PPI) network via STRING and visualized using Cytoscape. Core targets were identified, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted ( $P \leq 0.01$ ). **Results:** A total of 57 active components and 818 targets of Salvia miltiorrhiza were identified. Intersection analysis yielded 458 potential targets associated with BPH. PPI network analysis revealed core targets including SRC, PIK3R1, and PIK3CA. GO enrichment analysis indicated that the targets were primarily associated with biological processes (BP) such as calcium ion homeostasis, cellular components (CC) including focal adhesions, and molecular functions (MF) such as tyrosine kinase activity. KEGG pathway analysis indicated that Salvia miltiorrhiza may exert therapeutic effects through pathways including MAPK, PI3K-Akt, and calcium signaling ( $P \leq 0.01$ ). **Conclusion:** Salvia miltiorrhiza may regulate BPH through a multi-component, multi-target, and multi-pathway network, providing a theoretical basis for its clinical application.

**Keywords:** Salvia Miltiorrhiza; Benign Prostatic Hyperplasia; Network Pharmacology; Active Components; Signaling Pathway; Molecular Mechanism

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## Preface

Benign prostatic hyperplasia (BPH) is a common urological disease in middle-aged and elderly men, characterized by abnormal proliferation of prostate stromal and glandular cells, leading to urethral obstruction. Clinically, it is manifested as frequent urination, urgency, and difficulty in urination, seriously affecting the quality of life of patients<sup>[1, 2]</sup>. According to statistics, the incidence of BPH in men over 60 years old exceeds 50% globally, and it reaches 83% in those over 80 years old<sup>[3]</sup>. Although modern medical treatment mainly relies on  $\alpha$ -receptor blockers (such as tamsulosin),



5 $\alpha$ -reductase inhibitors (such as finasteride), and surgery, these methods have side effects such as drug tolerance and sexual dysfunction<sup>[4,5]</sup>. Therefore, exploring safer and more effective treatment strategies has become a current research hotspot.

Traditional Chinese medicine (TCM) shows unique advantages in the treatment of BPH. Its multi-target and low-toxicity characteristics make it a potential treatment option. Among them, *Salvia miltiorrhiza* Bge., as a representative of blood-activating and stasis-resolving herbs, has been widely used in clinical practice and has significant effects in improving the urination function and microcirculation of the prostate in BPH patients<sup>[6,7]</sup>. The active components of *Salvia miltiorrhiza* include tanshinones (such as tanshinone IIA and cryptotanshinone), salvianolic acids (such as salvianolic acid B), and volatile oils, etc.<sup>[8]</sup>. Modern pharmacological studies have shown that *Salvia miltiorrhiza* has significant therapeutic effects on BPH model animals through mechanisms such as anti-inflammation, antioxidation, inhibition of cell proliferation, and regulation of apoptosis<sup>[8,9]</sup>. However, its mechanism of action is not yet fully understood, especially the synergistic mechanism of the “component - target - pathway” network, which still requires in-depth research.

Network pharmacology, as an emerging method integrating systems biology and pharmacology, can systematically analyze the multi-target action mechanism of traditional Chinese medicine formulas through the construction of “drug - component - target - disease” networks<sup>[10]</sup>. This study takes *Salvia miltiorrhiza* as the object and, relying on databases such as TCMSP and Swiss Target Prediction, constructs a “component - target - pathway” network to reveal the potential molecular mechanism of *Salvia miltiorrhiza* in the treatment of BPH, providing a theoretical basis for its clinical precise medication and new drug development.

## 1. Materials and Methods

### 1.1 Screening of *Salvia miltiorrhiza* components entering the blood

The active components of *Salvia miltiorrhiza* were retrieved from the Traditional Chinese System Pharmacology Database and Analysis Platform (TCMSP, <https://tcmbspw.com/tcmbsp.php>). According to the TCMSP target screening guidelines and compound ADME (absorption, distribution, metabolism, excretion) parameters, the conditions of oral bioavailability (OB)  $\geq 30\%$  and drug-likeness (DL)  $\geq 0.18$  were set to screen and establish a database of core components of *Salvia miltiorrhiza*<sup>[11]</sup>.

### 1.2 Prediction of *Salvia miltiorrhiza* active component targets

The collected chemical components were imported into the Swiss Target Prediction database (<http://swisstargetprediction.ch/>), and the targets with a result Probability greater than 0 were selected to establish a compound target database and imported into Cytoscape 3.7.2 for visualization.

### 1.3 Collection of potential targets for the treatment of BPH by *Salvia miltiorrhiza* 1.3 Gene search and target identification

The human gene database GeneCards (<https://www.genecards.org/>) and OMIM database (Online Mendelian Inheritance in Man, <http://www.omim.org>) were used to search for genes related to benign prostatic hyperplasia (BPH) with the keyword “benign prostatic hyperplasia”. Duplicates were removed, and the intersection with the targets of the core components of *Salvia miltiorrhiza* was taken to obtain the potential targets of *Salvia miltiorrhiza* in the treatment of BPH.

### 1.4 Construction of protein-protein interaction network

The targets collected in 1.3 were imported into the STRING platform (<https://string-db.org/>) for protein-protein interaction (PPI) analysis. The species was set as human, and the minimum interaction threshold was set to 0.9 for screening. Disconnected nodes were hidden to construct the PPI network relationship. The results were downloaded in\*.tsv format and imported into Cytoscape 3.7.2 for visualization. The Network analyzer plugin was used to analyze the network characteristics of the targets.

### 1.5 Gene ontology and signaling pathway analysis

The potential targets of *Salvia miltiorrhiza* in the treatment of BPH were analyzed for gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment using Xiantao Academic Platform. The data obtained from the enrichment analysis tool were sorted according to -logP value. The top 10 entries of GO biological processes (BP), cellular components (Cc), and molecular functions (MF) were selected, and the top 10 entries of KEGG pathway enrichment analysis results were selected. Enrichment plots were drawn for each.

## 2.Results

### 2.1 Prediction results of core components and targets of *Salvia miltiorrhiza*

A total of 57 active components of traditional Chinese medicine were retrieved and screened from TCMSP to establish a database, as shown in Table 1. A total of 4,354 predicted targets were obtained through Swiss Target Prediction, and 3,536 duplicates were removed, resulting in a final prediction of 818 targets. The network of traditional Chinese medicine components and targets was constructed using Cytoscape 3.7.2, as shown in Figure 1. The network contained 873 nodes and 3,051 edges. In the figure, edges represent interaction relationships, blue square nodes represent component targets, and pink circular nodes represent active components. Using the keyword “benign prostatic hyperplasia”, disease targets were searched through the GeneCards database and OMIM database, resulting in 4,281 and 217 targets related to BPH, respectively. After removing duplicates, a total of 4,354 related targets were obtained. The intersection with the targets of the core components of *Salvia miltiorrhiza* was taken to obtain 458 potential targets of *Salvia miltiorrhiza* in the treatment of BPH (Figure 2).

Table 1 Summary of Active Components of *Salvia miltiorrhiza*

No.	MOL ID	Active ingredient	OB(%)	DL
01	MOL001659	Poriferasterol	43.83	0.76
02	MOL001601	1,2,5,6-tetrahydrotanshinone	38.75	0.36
03	MOL001771	poriferast-5-en-3beta-ol	36.91	0.75
04	MOL001972	isoimperatorin	45.46	0.23
05	MOL002222	sugiol	36.11	0.28
06	MOL002651	Dehydrotanshinone II A	43.76	0.40
07	MOL002776	Baicalin	40.12	0.75
08	MOL000569	digallate	61.85	0.26
09	MOL000006	luteolin	36.16	0.25
10	MOL006824	$\alpha$ -amyrin	39.51	0.76
11	MOL007036	5,6-dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	33.77	0.29
12	MOL007041	2-isopropyl-8-methylphenanthrene-3,4-dione	40.86	0.23
13	MOL007048	(E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid	48.24	0.31
14	MOL007049	4-methylenemiltirone	34.35	0.23
15	MOL007050	2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	62.78	0.40
16	MOL007051	6-o-syringyl-8-o-acetyl shanzhiside methyl ester	46.96	0.71
17	MOL007058	formyltanshinone	73.44	0.42
18	MOL007061	Methylenetanshinquinone	37.07	0.36
19	MOL007063	przewalskin a	37.11	0.65
20	MOL007064	przewalskin b	110.32	0.44
21	MOL007069	Przewaquinone c	55.74	0.40
22	MOL007077	sclareol	43.67	0.21
23	MOL007079	tanshinaldehyde	52.47	0.45
24	MOL007081	Danshenol B	57.95	0.56
25	MOL007082	Danshenol A	56.97	0.52

No.	MOL ID	Active ingredient	OB(%)	DL
26	MOL007085	Salvilenone	30.38	0.38
27	MOL007088	cryptotanshinone	52.34	0.40
28	MOL007093	dan-shexinkum d	38.88	0.55
29	MOL007094	danshenspiroketallactone	50.43	0.31
30	MOL007098	deoxyneocryptotanshinone	49.4	0.29
31	MOL007100	dihydrotanshinlactone	38.68	0.32
32	MOL007101	dihydrotanshinoneI	45.04	0.36
33	MOL007105	epidanshenspiroketallactone	68.27	0.31
34	MOL007107	C09092	36.07	0.25
35	MOL007108	isocryptotanshi-none	54.98	0.39
36	MOL007111	Isotanshinone II	49.92	0.40
37	MOL007115	manool	45.04	0.20
38	MOL007119	miltionone I	49.68	0.32
39	MOL007120	miltionone II	71.03	0.44
40	MOL007121	miltipolone	36.56	0.37
41	MOL007122	Miltirone	38.76	0.25
42	MOL007123	miltirone II	44.95	0.24
43	MOL007124	neocryptotanshinone ii	39.46	0.23
44	MOL007125	neocryptotanshinone	52.49	0.32
45	MOL007127	1-methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione	34.72	0.37
46	MOL007130	prolithospermic acid	64.37	0.31
47	MOL007132	(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	109.38	0.35
48	MOL007140	(Z)-3-[2-[(E)-2-(3,4-dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid	88.54	0.26
49	MOL007141	salvianolic acid g	45.56	0.61
50	MOL007142	salvianolic acid j	43.38	0.72
51	MOL007143	salvilenone I	32.43	0.23
52	MOL007145	salviolone	31.72	0.24
53	MOL007149	NSC 122421	34.49	0.28
54	MOL007154	tanshinone iia	49.89	0.40
55	MOL007155	(6S)-6-(hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	65.26	0.45
56	MOL007156	tanshinone VI	45.64	0.30

Fig.1 Relationship between the components and targets of drug

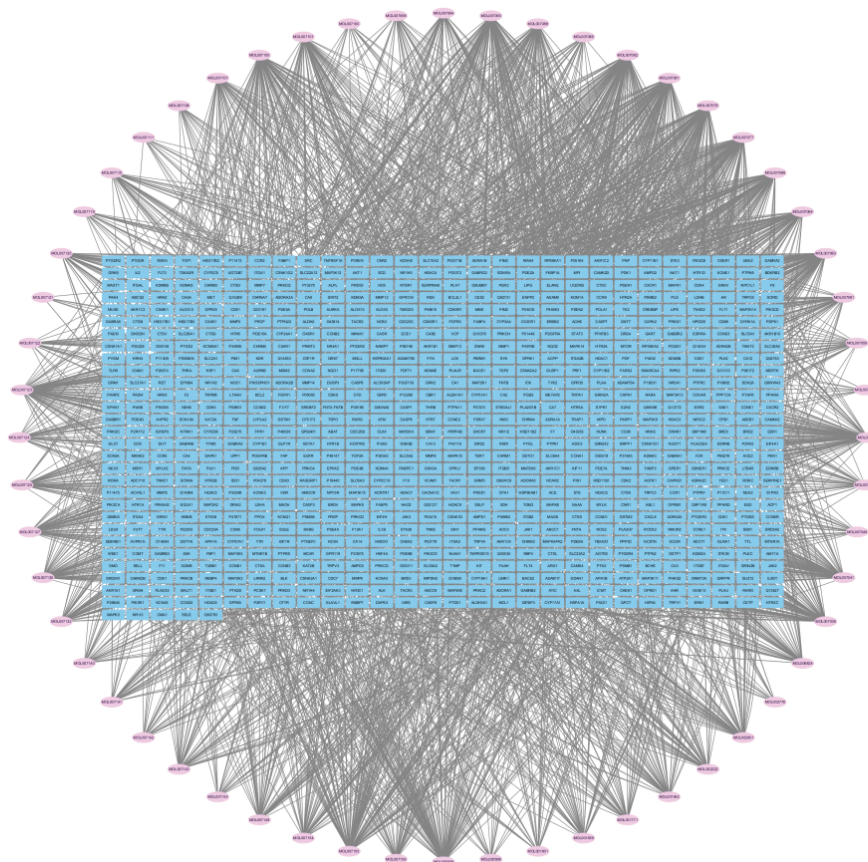


Fig.2 VENN chart of drug-disease targets

Prostatic hyperplasia

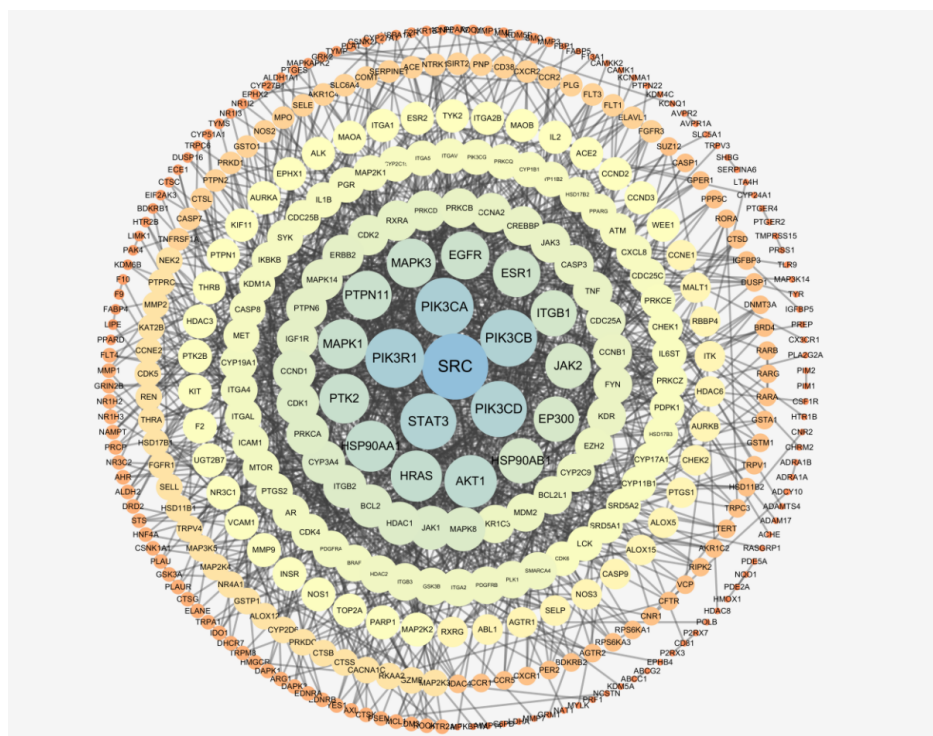
Salvia



## 2.2 PPI Network Results

The PPI relationships obtained from the STRING 11.0 platform were imported into Cytoscape 3.7.2 software for visualization analysis, generating the PPI network as shown in Figure 3. This network consists of 372 nodes and 1,415 edges, where edges represent PPI relationships, circular nodes represent target proteins, and node colors indicate the degree values. It can be seen that targets such as SRC, PIK3R1, and PIK3CA play a core role in the network, with degree values of 55,44,and 43 respectively,and they are worthy of further study.

Fig.3 Target protein-protein interaction network



Note: Color range , the degree value decreases from left to right

### 2.3 GO and KEGG Enrichment Results

GO analysis includes three branches, namely molecular function (MF), cellular component (CC), and biological process (BP). The processes with  $P \leq 0.01$  were screened, and the top ten enriched processes were listed (Figure 4). Among them, at the BP level, the predicted targets were mainly related to cellular calcium ion homeostasis, calcium ion homeostasis, and regulation of cytosolic calcium ion concentration; at the CC level, tyrosine kinase activity, threonine kinase activity, and focal adhesion had a relatively large proportion; at the MF level, they were closely related to protein binding, identical protein binding, and protein tyrosine kinase activity. Through KEGG enrichment analysis, 183 signaling pathways with  $P \leq 0.01$  were obtained for the potential pathways involved in the treatment of benign prostatic hyperplasia by the core components of *Salvia miltiorrhiza*. Figure 5 lists the top 10 enriched pathways. Among them, MAPK signaling pathway, PI3K-Akt signaling pathway, and Calcium signaling pathway are closely related to benign prostatic hyperplasia. KEGG enrichment analysis indicates that the core components of *Salvia miltiorrhiza* may act on these pathways, thereby playing a role in the treatment of benign prostatic hyperplasia.

Fig.4 Results of GO enrichment analysis

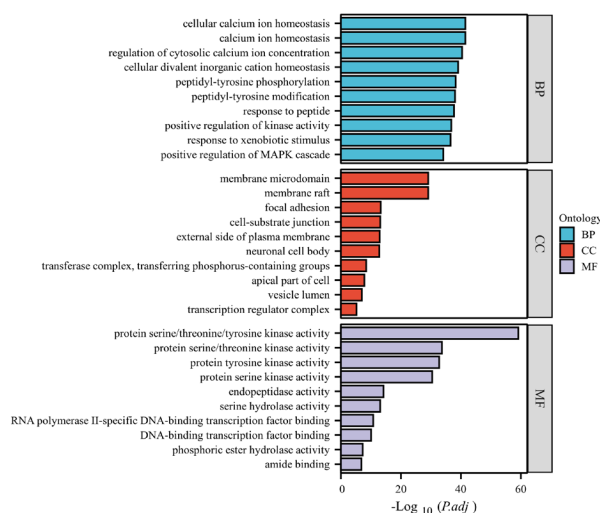
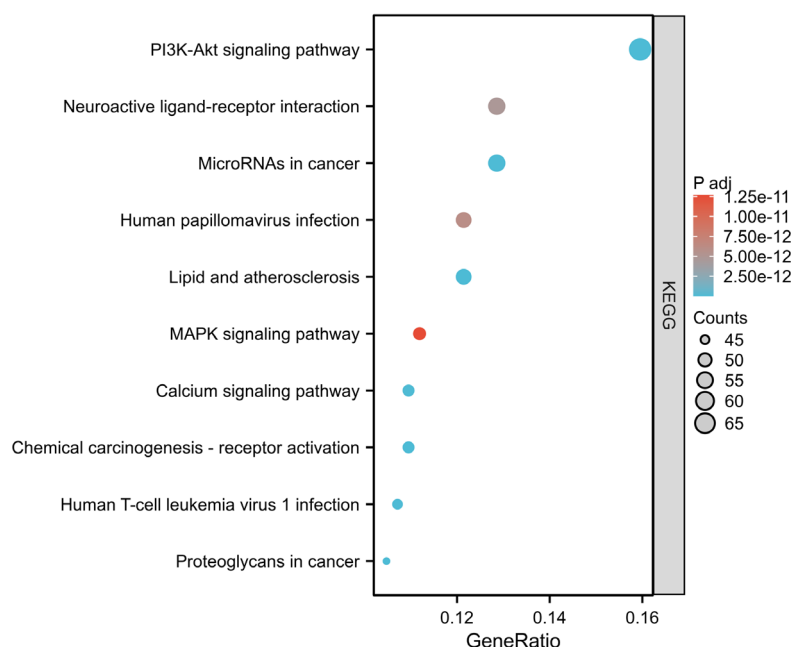




Fig.5 Results of KEGG enrichment analysis



### 3. Discussion

In this study, 57 active ingredients of *Salvia miltiorrhiza* were screened by network pharmacology method, and their target sites were predicted. It was found that *Salvia miltiorrhiza* exerted therapeutic effects on BPH through the synergistic mechanism of multiple components, multiple targets and multiple pathways. The specific results are as follows:

#### 3.1 Core target analysis

PPI network analysis shows that SRC (degree 55), PIK3R1 (44), and PIK3CA (43) are the core targets of Danshen in treating BPH. Among these, SRC, as a non-receptor tyrosine kinase, is highly expressed in prostate stromal cells. Its phosphorylation can activate the MAPK pathway, promoting <sup>[12]</sup> deposition in the extracellular matrix. PIK3CA (PI3K catalytic subunit) forms an heterodimer with PIK3R1 (regulatory subunit), which regulates the survival and proliferation of prostate cells through the PI3K/Akt pathway<sup>[13]</sup>. Clinical samples show that p-Akt (Ser473) expression in BPH tissue is significantly higher than in normal tissue ( $P < 0.01$ )<sup>[14]</sup>, consistent with the enrichment results of this study's targets.

#### 3.2 Signal pathway analysis

KEGG enrichment analysis shows that *Salvia miltiorrhiza* primarily exerts its effects through the MAPK, PI3K-Akt, and calcium signaling pathways. The MAPK pathway plays a crucial role in regulating cell proliferation and apoptosis; its inhibitor U0126 can significantly reduce prostate volume ( $p < 0.05$ )<sup>[14]</sup>. Key nodes in the calcium signaling pathway (hsa04020), such as CACNA1C and CALM1, are involved in the contraction of prostatic smooth muscle, and *Salvia miltiorrhiza* alleviates urethral obstruction by modulating calcium homeostasis<sup>[15]</sup>. Notably, GO enrichment analysis indicates that the “focal adhesion” (CC layer) pathway is closely associated with interstitial fibrosis in the prostate. *Salvia miltiorrhiza* IIA can inhibit the expression of fibrosis markers ( $\alpha$ -SMA, Collagen I) induced by TGF- $\beta$ 1, which aligns well with the CC enrichment results from this study<sup>[16]</sup>.

#### 3.3 Synergistic action of multiple targets

The synergistic effects of multiple components in *Salvia miltiorrhiza* are key mechanisms for its treatment of BPH. For example, shenqu can act on multiple targets simultaneously (such as SRC and EGFR), reflecting the characteristic of “synergistic action” in traditional Chinese medicine. Additionally, the anti-inflammatory effects of *Salvia miltiorrhiza* enhance its therapeutic efficacy by modulating the inflammatory-proliferative axis (such as PTGS2 and ESR1).

In summary, this study systematically analyzed the potential molecular mechanisms of *Salvia miltiorrhiza* in treating BPH using network pharmacology methods, revealing its multi-pathway, multi-target, and multi-channel synergistic action pattern. This research provides a theoretical framework for the combined traditional Chinese and Western medicine treatment of BPH.

and offers candidate targets for the development of new drugs targeting BPH. Future studies can further explore the specific mechanisms of action of the core components of *Salvia miltiorrhiza* through molecular docking and experimental validation, providing a more comprehensive evidence chain for the development of novel BPH treatment strategies derived from *Salvia miltiorrhiza*.

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no

## Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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# Neuropharmacology of Neurotransmitter Systems: Current Drugs and Their Effects on Neural and Neuroendocrine Pathways

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**Abstract:** The intricate interplay between neurotransmitter systems, neural circuits, and neuroendocrine pathways underpins brain function and dysfunction in neurological and psychiatric disorders. This review synthesizes contemporary advances in neuropharmacology, focusing on dopaminergic, serotonergic, glutamatergic, and GABAergic systems, and their roles in regulating motor control, cognition, emotion, and stress responses. Dopaminergic pathways, including the nigrostriatal, mesolimbic, and mesocortical circuits, are explored in the context of Parkinson's disease, schizophrenia, and addiction, with emphasis on pharmacological agents such as L-DOPA, antipsychotics, and amphetamines. Serotonergic modulation through SSRIs and psychedelics is examined for its impact on mood and neuroplasticity, while glutamatergic and GABAergic systems are discussed in relation to synaptic plasticity, excitotoxicity, and therapeutic innovations like ketamine and benzodiazepines. The neuroendocrine system, particularly the hypothalamic-pituitary-adrenal (HPA) axis, is highlighted for its role in stress-related disorders and interactions with neurotransmitter networks. Despite progress, significant challenges persist, including translational gaps between preclinical models and human trials, species-specific receptor disparities, and ethical dilemmas surrounding cognitive enhancers and genetic manipulation. Emerging frontiers such as nanotechnology-enabled drug delivery, optogenetics, and gut-brain axis modulation are reviewed as transformative approaches to overcome these barriers. Personalized medicine, integrating neuroimaging biomarkers and pharmacogenomics, promises to tailor therapies to individual neural and genetic profiles, while biased agonists and closed-loop systems exemplify the shift toward circuit-specific interventions. Ethical considerations, including equitable access to advanced therapies and responsible innovation, are underscored as critical to ensuring societal benefit. By harmonizing molecular precision with systems neuroscience, this review advocates for interdisciplinary strategies to advance neuropharmacology, ultimately aiming to restore dynamic neural and neuroendocrine homeostasis in health and disease.

**Keywords:** Neurotransmitter Systems; Pharmacological Interventions; Systems Neuroscience; Neuroendocrine Interactions; Translational Challenges; Personalized Medicine; Emerging Technologies

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## 1.Introduction

The brain's ability to regulate complex behaviors, emotions, and physiological functions hinges on the precise coordination of neurotransmitter systems, which act as chemical messengers to modulate neural circuits. Neurotransmitters such as dopamine,

serotonin, glutamate, and GABA orchestrate everything from motor control and sleep-wake cycles to emotional regulation and cognitive processing. For instance, dopamine pathways in the nigrostriatal system govern voluntary movement, while serotonin in the raphe nuclei influences mood and sleep architecture. Disruptions in these systems—whether due to genetic, environmental, or pathological factors—can lead to profound dysfunction, manifesting as Parkinson's disease (dopamine depletion), depression (serotonin imbalance), or epilepsy (glutamate-GABA dysregulation). These systems also interface with neuroendocrine pathways, such as the hypothalamic-pituitary-adrenal (HPA) axis, linking neural activity to hormonal responses critical for stress adaptation and metabolic homeostasis.

Pharmacology bridges the gap between neurotransmitter dysfunction and therapeutic intervention by designing drugs that selectively target receptors, transporters, or enzymes within these systems. For example, selective serotonin reuptake inhibitors (SSRIs) alleviate depression by enhancing synaptic serotonin levels, while antipsychotics block dopamine D2 receptors to mitigate psychosis in schizophrenia. Advances in neuropharmacology have expanded beyond symptom management to address the root causes of disorders, such as NMDA receptor modulators for treatment-resistant depression or monoclonal antibodies targeting amyloid- $\beta$  in Alzheimer's disease. Furthermore, drugs like levodopa, which crosses the blood-brain barrier to replenish dopamine in Parkinson's disease, exemplify how pharmacokinetic principles can restore neural circuit integrity. This synergy between molecular targeting and systems neuroscience has revolutionized treatment paradigms, enabling precision therapies that recalibrate dysfunctional networks rather than merely masking symptoms.

This review synthesizes contemporary research on how pharmacological agents interact with neurotransmitter and neuroendocrine systems to restore neural homeostasis. We first examine major neurotransmitter pathways—dopaminergic, serotonergic, glutamatergic, and GABAergic—detailing the mechanisms of current drugs (e.g., L-DOPA, ketamine, benzodiazepines) and their impact on circuit-level dynamics, as revealed by neuroimaging and electrophysiology. Next, we explore neuroendocrine targets, including HPA axis modulators and their role in stress-related disorders. Throughout, we highlight translational challenges, such as reconciling preclinical animal models with human neurobiology, and emerging strategies like pharmacogenomics and optopharmacology. By integrating molecular mechanisms with systems-level outcomes, this review underscores the transformative potential of interdisciplinary approaches in neuropharmacology, paving the way for therapies that harmonize neural circuit function with whole-body physiology.

## 2. Main

### 2.1 Dopaminergic System: Pathways, Pharmacology, and Neuroendocrine Interactions

The dopaminergic system, comprising the mesocortical, mesolimbic, and nigrostriatal pathways, serves as a critical modulator of motor function, reward processing, and executive cognition<sup>[1]</sup>. The nigrostriatal pathway, originating in the substantia nigra pars compacta (SNc) and projecting to the dorsal striatum, is essential for voluntary movement coordination. Degeneration of SNc dopamine neurons in Parkinson's disease (PD) disrupts striatal-thalamocortical signaling, leading to bradykinesia and rigidity<sup>[2]</sup>. In contrast, the mesolimbic pathway, which connects the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and amygdala, drives reward-seeking behaviors and emotional responses. Overactivation of this pathway, as seen in schizophrenia, contributes to psychosis and hallucinations<sup>[3]</sup>. The mesocortical pathway, linking the VTA to the prefrontal cortex (PFC), regulates working memory and decision-making, with hypoactivity implicated in cognitive deficits of schizophrenia and attention-deficit/hyperactivity disorder (ADHD)<sup>[4]</sup>.

Pharmacological interventions targeting dopaminergic receptors aim to restore circuit balance. L-DOPA, a dopamine precursor, remains the gold standard for PD treatment. By bypassing degenerated SNc neurons and replenishing striatal dopamine, L-DOPA restores thalamocortical relay efficiency, alleviating motor symptoms<sup>[5]</sup>. However, chronic use induces dyskinesias due to pulsatile dopamine receptor stimulation and maladaptive plasticity in striatal medium spiny neurons<sup>[6]</sup>. Amphetamines, which block dopamine reuptake and enhance presynaptic release, are employed in ADHD to bolster mesocortical dopamine levels, improving attention and executive function via enhanced DLPFC engagement<sup>[7]</sup>. Conversely, antipsychotics (e.g., haloperidol, risperidone) antagonize D2 receptors in the mesolimbic pathway, attenuating psychosis in schizophrenia. However, excessive D2 blockade in the nigrostriatal pathway can induce extrapyramidal side effects (e.g., tardive dyskinesia), while underactivity in the mesocortical pathway exacerbates cognitive deficits<sup>[8]</sup>.

Systems neuroscience has illuminated how dopaminergic drugs reshape functional connectivity. Resting-state fMRI studies demonstrate that L-DOPA normalizes striatal-thalamocortical circuit activity in PD patients, enhancing synchronization between the putamen and supplementary motor area (SMA) <sup>[9]</sup>. Similarly, antipsychotics reduce hyperconnectivity between the NAc and limbic regions (e.g., amygdala) in schizophrenia, though excessive suppression may impair salience detection <sup>[10]</sup>. PET imaging further reveals that optimal D2 receptor occupancy (65–78%) is critical for balancing therapeutic efficacy and side effects <sup>[11]</sup>.

Dopaminergic signaling also intersects with neuroendocrine regulation. The tuberoinfundibular pathway, projecting from the hypothalamus to the pituitary gland, tonically inhibits prolactin secretion via D2 receptor activation. Antipsychotic-induced D2 blockade disrupts this inhibition, causing hyperprolactinemia—a side effect linked to infertility, osteoporosis, and galactorrhea <sup>[12]</sup>. Newer agents with partial D2 agonism (e.g., aripiprazole) mitigate this risk by stabilizing, rather than abolishing, dopamine signaling <sup>[13]</sup>.

## 2.2 Serotonergic System: Modulation of Mood, Cognition, and Neuroendocrine Function

The serotonergic system, originating primarily in the dorsal raphe nucleus, projects widely to cortical, limbic, and hypothalamic regions, regulating mood, cognition, sleep, and stress responses <sup>[14]</sup>. Serotonin (5-HT) exerts its effects through 14 receptor subtypes, with 5-HT<sub>1A</sub> autoreceptors modulating raphe neuron firing and 5-HT<sub>2A</sub> receptors influencing cortical plasticity <sup>[15]</sup>. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, block the serotonin transporter (SERT), increasing extracellular 5-HT levels and promoting neuroplasticity in the hippocampus and prefrontal cortex (PFC) <sup>[16]</sup>. Psychedelics like psilocybin, a 5-HT<sub>2A</sub> agonist, induce rapid synaptic rewiring and disrupt default mode network (DMN) connectivity, correlating with antidepressant and anxiolytic effects <sup>[17]</sup>. Conversely, chronic stress depletes 5-HT, exacerbating depressive symptoms and impairing hippocampal neurogenesis <sup>[18]</sup>.

Systems neuroscience reveals that SSRIs enhance functional connectivity between the PFC and amygdala, normalizing hyperactive limbic responses in depression <sup>[19]</sup>. Psilocybin's acute disruption of the DMN, observed via fMRI, is followed by long-term increases in global brain network integration, suggesting a reset of maladaptive neural patterns <sup>[20]</sup>. Serotonin also modulates the hypothalamic-pituitary-adrenal (HPA) axis, with 5-HT<sub>1A</sub> receptor activation dampening cortisol release during stress <sup>[21]</sup>. SSRI-induced HPA axis normalization may underlie delayed therapeutic onset, as cortisol levels decline over weeks <sup>[22]</sup>.

## 2.3 Glutamatergic System: Excitatory Signaling, Synaptic Plasticity, and Therapeutic Innovation

The glutamatergic system, the brain's primary excitatory network, mediates synaptic plasticity, learning, and memory through ionotropic (NMDA, AMPA, kainate) and metabotropic (mGluR) receptors <sup>[23]</sup>. NMDA receptors (NMDARs) are critical for long-term potentiation (LTP) in the hippocampus and PFC, while excessive glutamate release contributes to excitotoxicity in epilepsy and neurodegenerative diseases <sup>[24]</sup>. Ketamine, an NMDAR antagonist, rapidly alleviates treatment-resistant depression by enhancing AMPA receptor trafficking and promoting synaptogenesis in the PFC <sup>[25]</sup>. Topiramate, an AMPA/kainate receptor modulator, reduces cortical hyperexcitability in migraine and epilepsy by dampening glutamate release <sup>[26]</sup>.

Neuroimaging studies demonstrate that ketamine increases resting-state connectivity between the PFC and limbic regions, counteracting depression-related hypoconnectivity <sup>[27]</sup>. Conversely, NMDAR hypofunction in schizophrenia, modeled by phencyclidine (PCP), disrupts gamma oscillations and frontotemporal coherence, as seen in EEG/MEG studies <sup>[28]</sup>. The glutamatergic system also interfaces with neuroendocrine pathways: hypothalamic NMDARs regulate corticotropin-releasing factor (CRF) release, linking stress to HPA axis hyperactivity <sup>[29]</sup>. Recent advances include the FDA-approved NMDA-targeting drug esketamine for depression and mGluR5 antagonists in fragile X syndrome trials <sup>[30]</sup>.

## 2.4 GABAergic System: Inhibitory Control, Circuit Dysregulation, and Pharmacological Modulation

The GABAergic system, the brain's primary inhibitory network, maintains excitatory-inhibitory (E/I) balance through GABA-A (ionotropic) and GABA-B (metabotropic) receptors <sup>[31]</sup>. GABA-A receptors, which bind benzodiazepines (e.g., diazepam), mediate fast synaptic inhibition in cortical interneurons and thalamic reticular nuclei, modulating anxiety, sleep, and seizure thresholds <sup>[32]</sup>. GABA-B agonists like baclofen reduce spasticity in multiple sclerosis by enhancing spinal cord inhibition and are explored for addiction treatment via suppression of mesolimbic dopamine release <sup>[33]</sup>. Dysregulated GABA

signaling underlies epilepsy (E/I imbalance), anxiety (amygdala hyperactivity), and insomnia (thalamocortical dysrhythmia) <sup>[34]</sup>. fMRI studies reveal that benzodiazepines reduce amygdala-PFC functional connectivity in generalized anxiety disorder, restoring top-down emotional regulation <sup>[35]</sup>. In epilepsy, PET imaging shows reduced GABA-A receptor density in the thalamus, which anticonvulsants like vigabatrin (GABA transaminase inhibitor) partially restore <sup>[36]</sup>. GABAergic drugs also influence neuroendocrine function: hypothalamic GABA inhibits CRH neurons, and benzodiazepines suppress HPA axis hyperactivity during acute stress <sup>[37]</sup>. Novel agents, such as zuranolone (a GABA-A receptor-positive allosteric modulator), show promise in postpartum depression by enhancing tonic inhibition in limbic circuits <sup>[38]</sup>.

## 2.5 Neuroendocrine System: Bridging Neural Circuits and Hormonal Regulation in Health and Disease

The neuroendocrine system integrates neural activity with endocrine signaling to regulate physiological homeostasis, stress responses, and behavior. Central to this system is the hypothalamic-pituitary-adrenal (HPA) axis, a hierarchical network where hypothalamic corticotropin-releasing factor (CRF) stimulates pituitary adrenocorticotropic hormone (ACTH) release, driving adrenal cortisol secretion <sup>[39]</sup>. Cortisol, a glucocorticoid, exerts negative feedback on the HPA axis via hippocampal glucocorticoid receptors (GRs), modulating immune function, metabolism, and emotional memory <sup>[40]</sup>. Dysregulation of this axis—marked by hypercortisolism in depression or hypocortisolism in post-traumatic stress disorder (PTSD)—impairs neural circuits governing fear (amygdala), executive control (prefrontal cortex; PFC), and memory (hippocampus) <sup>[41]</sup>. Chronic stress exacerbates HPA axis hyperactivity, leading to hippocampal atrophy and prefrontal cortical dysfunction, which are hallmarks of mood and anxiety disorders.

Pharmacological interventions targeting the HPA axis aim to restore hormonal equilibrium. CRF receptor antagonists (e.g., verucerfont) block CRF1 receptors to dampen HPA axis hyperactivity in anxiety and depression. However, clinical trials have shown mixed efficacy, partly due to challenges in blood-brain barrier penetration and receptor subtype selectivity <sup>[42]</sup>. Glucocorticoid receptor modulators, such as mifepristone (a GR antagonist), ameliorate psychotic depression by normalizing cortisol signaling and reducing dopaminergic hyperactivity in the striatum <sup>[43]</sup>. Conversely, synthetic glucocorticoids like dexamethasone suppress inflammation but risk hippocampal atrophy and cognitive deficits with prolonged use <sup>[44]</sup>. Emerging therapies, including vasopressin V1B receptor antagonists (e.g., relcovaptan), target upstream regulators of ACTH release, showing promise in Cushing's syndrome and stress-related disorders <sup>[45]</sup>.

Systems neuroscience has elucidated how neuroendocrine drugs reshape brain connectivity and plasticity. Resting-state fMRI studies demonstrate that CRF antagonists reduce functional hyperconnectivity between the amygdala and PFC in anxiety disorders, restoring top-down emotional regulation <sup>[46]</sup>. Chronic stress-induced hippocampal GR downregulation correlates with volumetric shrinkage in depression, a phenomenon reversible with SSRIs through enhanced neurogenesis <sup>[47]</sup>. PET imaging reveals that mifepristone normalizes striatal dopamine release in psychotic patients, linking HPA axis dysfunction to dopaminergic hyperactivity <sup>[43]</sup>. These findings underscore the bidirectional relationship between neuroendocrine signaling and neural circuit dynamics.

The HPA axis also interacts with neurotransmitter systems to modulate stress responses. Serotonin (via 5-HT1A receptors) inhibits CRF neuron activity in the hypothalamus, explaining the delayed therapeutic onset of SSRIs in stress-related disorders <sup>[48]</sup>. GABAergic interneurons in the hypothalamus suppress CRF release, a mechanism exploited by benzodiazepines to alleviate acute stress responses <sup>[49]</sup>. Conversely, hypercortisolism increases ventral striatal dopamine release, contributing to anhedonia and reward circuit dysfunction in depression <sup>[50]</sup>. These interactions highlight the neuroendocrine system's role as a mediator between neural circuits and systemic physiology, offering therapeutic avenues for disorders at the intersection of neurology and endocrinology.

## 2.6 Emerging Frontiers in Neuropharmacology: Nanotechnology, Optogenetics, and the Gut-Brain Axis

The field of neuropharmacology is undergoing a transformative shift with the advent of cutting-edge technologies that enable precise targeting of neural circuits, enhance drug delivery, and exploit interactions between the gut and brain. These innovations promise to overcome longstanding challenges in treating neurological and psychiatric disorders.

Nanotechnology has revolutionized drug delivery by enabling precise transport of therapeutic agents across the blood-brain barrier (BBB), a major obstacle in treating central nervous system (CNS) disorders. Lipid-based nanoparticles, for example,

enhance the bioavailability of drugs like temozolomide for glioblastoma by encapsulating the drug in liposomes that evade immune detection and accumulate in tumor tissue <sup>[51]</sup>. Similarly, curcumin nanoparticles functionalized with amyloid- $\beta$ -targeting ligands show promise in Alzheimer's disease by promoting plaque clearance and reducing neuroinflammation <sup>[52]</sup>. Nanoparticles can also be engineered for sustained release, minimizing off-target effects and reducing dosing frequency. For instance, dopamine-loaded nanoparticles are being explored to provide continuous striatal dopamine delivery in Parkinson's disease, potentially mitigating the motor fluctuations caused by oral L-DOPA <sup>[53]</sup>.

Optogenetics and chemogenetics allow unprecedented spatiotemporal control over neural activity, enabling researchers to dissect the roles of specific circuits in behavior and disease. Optogenetics uses light-sensitive proteins (e.g., channelrhodopsin) to activate or inhibit neurons with millisecond precision. For example, optogenetic stimulation of dopamine neurons in the ventral tegmental area (VTA) has been shown to reverse depressive-like behaviors in rodent models <sup>[54]</sup>. Chemogenetics, through tools like DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), enables remote control of neural activity using inert ligands. DREADDs targeting serotonin neurons in the dorsal raphe nucleus have elucidated their role in anxiety and fear extinction <sup>[55]</sup>. These technologies are not only research tools but also hold therapeutic potential. For instance, optogenetic restoration of gamma oscillations in the prefrontal cortex has improved cognitive deficits in schizophrenia models <sup>[56]</sup>.

The gut-brain axis, a bidirectional communication network linking the enteric nervous system to the CNS, has emerged as a novel therapeutic frontier. The gut microbiome influences neurotransmitter synthesis, neuroinflammation, and blood-brain barrier integrity. Probiotics like *Lactobacillus rhamnosus* increase hippocampal brain-derived neurotrophic factor (BDNF) and reduce anxiety-like behaviors in mice by modulating vagus nerve signaling <sup>[57]</sup>. Pharmacobiotics—microbiota-derived metabolites such as short-chain fatty acids (SCFAs) and tryptophan derivatives—directly interact with host physiology. For example, SCFAs like butyrate enhance microglial maturation and suppress neuroinflammation in Alzheimer's models <sup>[58]</sup>, while tryptophan metabolites activate aryl hydrocarbon receptors to regulate serotonin synthesis in the gut, impacting mood and cognition <sup>[59]</sup>. Clinical trials are exploring fecal microbiota transplantation (FMT) and dietary interventions to treat conditions ranging from depression to Parkinson's disease, underscoring the gut's role as a “second brain” in neuropsychopharmacology.

## 2.7 Challenges, Ethical Considerations, and Future Directions in Neuropsychopharmacology

Neuropsychopharmacology faces significant translational and ethical hurdles despite its remarkable advancements. A persistent issue is the translational gap between preclinical models and human outcomes: approximately 90% of findings from animal studies fail to replicate in clinical trials, partly due to species-specific differences in receptor expression and neural circuitry. For example, rodent models of depression often rely on serotonin receptor (5-HT<sub>2A</sub>) mechanisms that diverge from human pathophysiology <sup>[60]</sup>. Similarly, the therapeutic promise of drugs like ketamine—a rapid-acting antidepressant—is tempered by dissociative side effects and abuse potential, while chronic L-DOPA use in Parkinson's disease induces dyskinesias through maladaptive striatal plasticity <sup>[61]</sup>. These limitations underscore the need for more human-relevant models, such as induced pluripotent stem cell (iPSC)-derived neurons or 3D brain organoids, to bridge the translational divide.

Ethical dilemmas further complicate progress. Cognitive enhancers like modafinil, prescribed off-label to healthy individuals for improved focus, blur the line between therapy and enhancement, raising concerns about equity and societal pressure to pursue “cosmetic neurology” <sup>[62]</sup>. Meanwhile, CRISPR-edited animal models, though revolutionary for studying genetic contributions to disorders like autism, provoke debates about the ethical limits of genetic manipulation in neuroscience <sup>[63]</sup>. Addressing these challenges demands rigorous validation of preclinical models, transparent regulatory frameworks, and inclusive public dialogue on the societal implications of emerging neurotechnologies.

The future of neuropsychopharmacology lies in personalized medicine and circuit-specific interventions tailored to individual genetic, neural, and lifestyle profiles. Integration of neuroimaging biomarkers—such as default mode network (DMN) connectivity patterns in depression—with pharmacogenomics (e.g., COMT Val158Met polymorphism predicting SSRI response) could minimize trial-and-error prescribing and optimize therapeutic outcomes <sup>[64]</sup>. Biased agonists, which target specific receptor conformations, offer enhanced precision; for instance, kappa opioid receptor antagonists show promise in alleviating anhedonia without the addictive risks of mu opioid drugs <sup>[65]</sup>.



Closed-loop systems exemplify the synergy between pharmacology and neuromodulation. In epilepsy, responsive neurostimulation devices paired with GABAergic drugs dynamically suppress seizures by detecting aberrant neural activity and delivering targeted electrical or pharmacological interventions <sup>[66]</sup>. Advances in AI-driven drug discovery are accelerating the identification of novel targets, such as allosteric modulators for metabotropic glutamate receptors (mGluRs), while brain organoids derived from patient iPSCs provide platforms for testing personalized therapies in autism and schizophrenia <sup>[67]</sup>.

Equally critical is addressing ethical and accessibility challenges. Ensuring equitable access to breakthrough therapies—such as CRISPR-based gene editing or nanoparticle drug delivery—requires global collaboration to prevent disparities in health-care. Regulatory frameworks must evolve to balance innovation with safety, particularly for technologies like optogenetics, which could revolutionize addiction treatment but carry risks of misuse.

## Conclusion: Integrating Molecular Mechanisms and Systems-Level Insights

The interplay between neurotransmitter systems, neuroendocrine pathways, and neural circuits underscores the complexity of brain function and its vulnerability to dysfunction. Pharmacological interventions, from SSRIs to ketamine, have revolutionized treatment for neurological and psychiatric disorders, yet their success hinges on understanding both molecular targets (e.g., receptors, transporters) and systems-level outcomes (e.g., network connectivity, hormonal feedback). Emerging tools—nanoparticles, optogenetics, and gut-brain axis modulators—offer unprecedented precision, while ethical and translational challenges demand innovative solutions. As the field advances, a holistic approach that bridges genes, circuits, and behavior will be essential to developing therapies that are not only effective but also equitable and sustainable. By embracing interdisciplinary collaboration and patient-centered innovation, neuropharmacology can illuminate the path toward healing the brain's intricate tapestry of connections.

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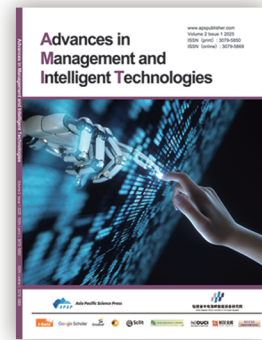


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