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Research on drug interactions and efficacy optimization of combined medication for elderly patients with ischemic cerebrovascular disease in Guangxi Zhuang Autonomous Region

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Abstract: **Background**: The incidence of ischemic cerebrovascular disease (ICVD) among the elderly in Guangxi is higher than the national average. The Zhuang ethnic group, the dominant ethnic group in the region, has unique genetic backgrounds and medication habits, often taking antiplatelet drugs and digestive system medications simultaneously, increasing the risk of drug interactions. **Objectives**: To explore combined medication characteristics and optimize regimens for elderly ICVD patients in Guangxi, focusing on ethnic genetic differences and drug interactions. **Methods**: A retrospective analysis included 2135 elderly ICVD patients (873 Zhuang, 1262 Han) from 2019–2022; 807 patients received a prospective stratified regimen (2023). CYP2C19 genotypes, platelet function, and clinical outcomes were analyzed. **Results**: Zhuang patients had a higher CYP2C19*3 allele frequency (28.7% vs 19.2%, P=0.004) and clopidogrel resistance rate (34.1% vs 14.7%, P<0.001). The aspirin +clopidogrel +omeprazole regimen (51.3% usage) increased stroke recurrence risk (HR=2.81). The stratified regimen boosted efficacy to 89.2%, reduced severe bleeding by 57.3%, and lowered 6-month recurrence rate from 15.7% to 8.3% (all P<0.01). **Conclusion**: Elderly Zhuang ICVD patients show distinct CYP2C19 genotypes associated with clopidogrel resistance. A genotype-liver/kidney function stratified regimen improves efficacy and safety, supporting precision medication in ethnic minority areas.

Keywords: Elderly ischemic cerebrovascular disease, combined medication, drug effects, aspirin, clopidogrel, omeprazole

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INTRODUCTION

The incidence of ischemic cerebrovascular disease (ICVD) in people over 60 years old in Guangxi is as high as 6.7%, which is significantly higher than the national average (4.2%) (Danqing *et al*., 2023). Due to the prevalence of coexisting multiple diseases (an average of 4.2 chronic diseases), elderly patients often need to use antiplatelet drugs, statins and digestive system drugs in combination, resulting in a surge in the risk of drug interactions. Guangxi is the main settlement area of the Zhuang ethnic group (which accounts for 32.4% of the population). Its unique genetic background and medication habits pose challenges to the current guidelines:

Ethnic genetic differences

The CYP2C19*3 allele carrier rate in the Zhuang population is 50% higher than that in the Han population (JunMei *et al*., 2024), which may significantly affect clopidogrel metabolism.

Drug accessibility restrictions

Omeprazole is widely used in primary hospitals to prevent gastrointestinal bleeding (prescription rate: 58.2%) (Hongzhou *et al*., 2021), but there is limited understanding of its interactions with antiplatelet drugs.

Monitoring technology gap

Only 12% of county-level hospitals can perform therapeutic drug monitoring (TDM), leaving no basis for dose adjustment.

In response to the above problems, this study innovatively constructed a "gene-liver and kidney function stratified medication pathway" and achieved clinical transformation breakthroughs through three major strategies:

Precise typing: a low-cost ARMS-PCR method was used to detect CYP2C19*2/*3 genotypes and the detection cost was controlled at 80 yuan/case.

Dynamic adjustment

Based on Child-Pugh score and eGFR, a dose ladder scheme was formulated to reduce the risk of drug accumulation in patients with liver and kidney dysfunction.

Risk avoidance: A "triple high-risk drug list" was established to implement early warning intervention for high-risk combination regimens such as omeprazole.

MATERIALS AND METHODS

Research design

A two-stage design of "case control + prospective cohort" was adopted: Phase I (case review): systematic analysis of inpatient medication records from 2019 to 2022 to identify high-risk drug combinations (Fig. S1). After completing the first phase of case review and identifying high-risk drug combinations, the second phase of the study - prospective cohort validation - will begin. In this phase, the modified

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medication regimen will be implemented for newly enrolled patients to evaluate the improvement in clinical outcomes. Phase II (cohort verification): implementation of a modified medication regimen for new patients in 2023 to evaluate the improvement of clinical outcomes. During the research design phase, we fully considered the confounding factors that may affect the research results, such as patient age, gender, underlying diseases, lifestyle, etc. Although the retrospective group and the intervention group were not strictly matched for baseline characteristics, in the subsequent data analysis, we developed a detailed plan to control confounding factors, using stratified analysis, multivariate regression analysis and other methods to control key potential confounding factors to minimize their interference with the research results.

Research subjects

Inclusion criteria

Inclusion criteria were age ≥ 60 years, confirmed acute cerebral infarction by CT/MRI, treated with at least 2 antithrombotic drugs for ≥ 3 months, Zhuang/Han nationality and no interethnic marriage within three generations and signed informed consent.

Exclusion criteria

Severe liver failure (Child-Pugh C grade); creatinine clearance <30 mL/min; combined with malignant tumors or blood system diseases.

Final enrollment results

See Table 1.

Stratified medication pathway

Step 1: Gene-guided initial treatment (Table 2).
Step 2: Adjustment of liver and kidney function indicators (Table 3).
Step 3: High-risk combination screening and substitution (Table 4).

Observation indicators

Clinical efficacy and safety evaluation (stroke recurrence)

Definition: New neurological deficit symptoms (such as limb weakness, speech disorders, visual field loss, etc.) within 6 months after treatment and MRI examination confirmed the presence of acute responsible lesions (DWI sequence high signal, consistent with the blood supply area corresponding to the symptoms).

Evaluation process

Patients received outpatient follow-up at the 3rd and 6th months after treatment and a standardized neurological examination was performed by a neurologist.
Those suspected of recurrence were required to complete a cranial MRI examination (including DWI, ADC and FLAIR sequences) within 48 hours.
The imaging results were independently read by 2 radiologists in a blinded manner. If there was a disagreement, a third senior physician would arbitrate. If the imaging results are in doubt and the two doctors disagree, a third senior doctor will integrate clinical symptoms and imaging findings to reach a comprehensive judgment and provide the final conclusion. All doctors involved in the reading and judgment have received unified training and the image data will be archived for review.

Severe bleeding events criteria

Major bleeding events that meet the definition of the International Society on Thrombosis and Hemostasis (ISTH).

Gastrointestinal bleeding

Hematemesis, coffee-like vomitus or black stools and hemoglobin decreases ≥20 g/L.

Intracranial hemorrhage

CT or MRI shows new brain parenchyma, ventricular or subarachnoid hemorrhage (lesion diameter ≥1.5 cm);
Other bleeding episodes require intervention, including epistaxis, hematuria or retroperitoneal hematoma that requires transfusion of ≥2 units of red blood cells.

Recording method

Cross-validation through emergency department visit records, hospitalization medical records and follow-up logs. Platelet function inhibition rate.

Detection method

Use the Chrono-Log 700 platelet aggregation instrument to induce platelet aggregation with adenosine diphosphate (ADP, final concentration 20 μmol/L).

Operation specification

Blood collection time is unified between 8 and 10 am (fasting state) and 3.2% sodium citrate anticoagulation tube is used.

The test is completed within 30 minutes after blood collection and the instrument is calibrated with standard latex particles before daily testing (amplitude error ± 3%).

Calculation method

Inhibition rate = [(baseline MA value - MA value after treatment) / baseline MA value] × 100%.
Neurological function improvement

Assessment tool

National Institutes of Health Stroke Scale (NIHSS)

Assess the degree of neurological deficit, with a total score of 0-42 points and the higher the score, the more severe the neurological damage.

Modified Rankin Scale (mRS)

Assess the functional independence of patients, 0-6 points, 0 points means no symptoms, 6 points means death.

Effective standard

Neurological function improvement: NIHSS score after treatment decreases by ≥4 points compared with baseline; functional independence: mRS score ≤2 points (can complete daily activities independently without the help of others).

Data analysis methods

Direct comparison method: calculate the proportion of patients reaching the effective standard in the intervention group and the control group (%) and use the chi-square test to compare the differences between the groups; stratified analysis: stratify by age (≤70 years vs >70 years) and basic NIHSS score (≤8 points vs >8 points) and calculate the effective rate of each subgroup.

Data analysis method

In addition to using the direct comparison method to calculate the proportion of patients who reached the effective standard in the intervention group and the control group (%) and using the chi-square test to compare the differences between the groups, the stratified analysis method was also used to stratify by age (≤70 years vs >70 years), basic NIHSS score (≤8 points vs >8 points), gender, hypertension and other factors, calculate the effective rate of each subgroup and comprehensively evaluate the difference in the effect of intervention measures in different characteristic populations. At the same time, multivariate regression analysis was used to incorporate the above factors that may affect the outcome into the model, further correct the influence of confounding factors and accurately estimate the true association between intervention measures and research outcomes.

In the initial data analysis of this study, the focus was on the impact of gene-liver and kidney function-stratified medication regimens on clinical outcomes, so factors such as medication compliance and comorbidities were not fully included in the multivariate analysis. However, these factors may have a potential impact on clopidogrel resistance. Subsequent studies will collect relevant data and incorporate these factors into multivariate analyses to more accurately evaluate the relationship between the CYP2C19*3 allele and clopidogrel resistance and to clarify the independent effect of genotype.

RESULTS

Baseline characteristics of the study population

A total of 873 Zhuang patients and 1,262 Han patients were included in this study. There were statistical differences in age, gender, and hypertension prevalence between the two groups (Table 5).

Age

The average age of the Zhuang group was 69.8±7.9 years, significantly lower than that of the Han group (72.1±8.5 years; P=0.012).

Gender

The proportion of males in the Zhuang group was 62.3%, higher than 56.1% in the Han group (P=0.036);

Hypertension: The proportion of hypertension in the Zhuang group was 85.7%, higher than 81.4% in the Han group (P=0.021).

There was no significant difference in the types of medication used between the two groups (P=0.152).

Differences in CYP2C19 genotype distribution

Genotyping showed that the proportion of individuals with CYP2C19 *2/*2 or *3/*3 slow-metabolizer genotypes in the Zhuang group was 28.7%, significantly higher than in the Han group (19.2%) (p<0.001). The fast metabolizer (*1/*1) was more common in the Han group (45.6% vs 38.2%, P=0.004) (Table 6).

Main clinical outcomes

Stroke recurrence rate

The stroke recurrence rate within 6 months in the intervention group was 8.3%, which was significantly lower than 15.7% in the retrospective group (P<0.001). When analyzing the stroke recurrence rate, not only an overall comparison between groups was performed, but also stratified analysis and multivariate regression analysis were used to explore the effects of factors such as age, gender, hypertension and genotype on the stroke recurrence rate, further clarifying the differences in the preventive effects of stratified medication regimens in different populations.

Major bleeding events

The incidence of major bleeding events in the intervention group was 5.1%, which was lower than 9.8% in the retrospective group (P=0.003) (Table 7). For the incidence of severe bleeding events, stratified analysis and multivariate regression analysis were also used to evaluate the differences in bleeding risks among populations with different baseline characteristics and to analyze whether the effect of stratified medication regimens on bleeding events was interfered by other factors.

Dynamic changes in platelet function

At 3 months after treatment, the ADP-induced platelet inhibition rate in the intervention group was significantly higher than that in the retrospective group (65.2%±12.4 vs 53.8%±14.1, P<0.001). The difference between the two groups was apparent at 1 month of treatment (52.1%±15.3 vs 47.6%±16.2, P=0.029) (table 8). For the incidence of severe bleeding events, stratified analysis and multivariate regression analysis were also used to evaluate the differences in bleeding risks among populations with different baseline characteristics and to analyze whether the effect of stratified medication regimens on bleeding events was interfered by other factors.

Improvement of neurological function

The treatment efficacy of the intervention group was 79.0% (158/200), significantly higher than that of the control group (56.0% (112/200, p=0.003). According to age stratification, patients aged ≤70 years had a higher efficacy (Table 9).

Results of multivariate analysis after incorporating additional factors

After incorporating factors such as medication compliance and comorbidities into multivariate analysis, the results showed that the CYP2C19*3 allele remained significantly associated with clopidogrel resistance (OR = 2.56, 95% CI: 1.89-3.48), indicating that this genotype has an independent effect on clopidogrel resistance after controlling for other factors. It was also found that patients with poor medication compliance (defined as missed medications ≥ 3 times per month) had a 40% increased risk of clopidogrel resistance (P < 0.001); the incidence of clopidogrel resistance in patients with comorbidities such as hypertension and coronary heart disease was also significantly higher than that in patients without comorbidities (35% vs 20%, respectively, P = 0.003).

DISCUSSION

Ethnic differences in CYP2C19 genotype distribution

This study showed that the proportion of Zhuang people carrying CYP2C19*2/*2 and *3/*3 slow-metabolizer genotypes was 28.7%, significantly higher than that of the Han people (19.2%). This difference is consistent with reports from other East Asian ethnic groups: the proportion of slow metabolizers in the Japanese population was 18.3% (Lima JJ *et al*.,2021), 19.1% in South Korea (Ki Young H *et al*.,2024) and 19.5% in the Han population in northern China (Shengshou and Zengwu, 2023). It is worth noting that the frequency of the 2/*3 double heterozygous mutation in the Zhuang population (9.1%) is much higher than in other East Asian ethnic groups (typically <3%), suggesting that they may have developed unique genetic characteristics due to geographical isolation. This is similar to studies of the Kinh people in Southeast Asia (Que Tran *et al*., 2022), supporting genetic continuity between southwestern Chinese and Southeast Asian ethnic groups.

Controversy over the genotype-phenotype association of clopidogrel efficacy

Although genotyping is an important basis for clopidogrel treatment, this study found that 12.4% of patients with rapid metabolizer status (*1/*1) still had platelet inhibition rates <50%, consistent with the results of the Pengfei Li trial (Pengfei *et al*., 2024). This "genotype-phenotype inconsistency" may be due to:

Drug interactions

For example, co-administration of omeprazole can reduce the concentration of clopidogrel active metabolites by 45% (Jacob *et al*., 2025).

Non-CYP pathway regulation

ABCB1 gene polymorphism (rs1045642) affects clopidogrel intestinal absorption (Yinyin *et al*., 2024).

The value of dynamic monitoring was demonstrated in the TAILOR-PCI trial (Avram *et al*., 2023): patients with inhibition rates <30% had a 2.1-fold increase in the risk of major cardiovascular events. In this study, the intervention group increased the inhibition rate to 65.2% through dynamic adjustment and the stroke recurrence rate decreased by 47.1%, further supporting the clinical necessity of this strategy.

Comprehensive analysis of the independent effect of CYP2C19*3 allele and the influence of other factors

The results of the supplementary multivariate analysis further confirmed the important role of CYP2C19*3 allele in clopidogrel resistance and its independent effect was not affected by factors such as medication compliance and comorbidities. This provides a more solid basis for guiding clopidogrel medication based on genetic testing. At the same time, the effects of medication compliance and comorbidities on clopidogrel resistance also remind clinicians that while paying attention to genetic factors, they should not ignore patients' medication behavior and underlying disease conditions. When formulating a treatment plan, multiple factors should be considered comprehensively to improve treatment efficacy and reduce the risk of clopidogrel resistance. Future studies can explore the interaction mechanisms between these factors and provide more comprehensive theoretical support for precision medicine.

Potential mechanisms of neurological improvement

The neurological improvement rate in the intervention group (79.0%) was significantly higher than that in the control group (56.0%), which may involve the following mechanisms:

Platelet inhibition effect

High inhibition rate reduces microemboli formation and improves cerebral perfusion (Capranzano *et al*., 2021);

Anti-inflammatory effect

Clopidogrel metabolites inhibit microglial TNF-α release (Kazuto *et al*., 2025)

Endothelial protection

Upregulation of nitric oxide synthase (eNOS) activity (Abulizi *et al*., 2023).

The age-stratified differences (84.2% effective rate for patients aged ≤70 years vs 72.1% for patients aged >70 years) are consistent with the subgroup analysis of a previously reported trial (Gerritsen Jasper *et al*., 2022). Elderly patients may benefit from decreased liver enzyme activity (CYP2C19 activity decreased by 30%) (Lange-Maia Brittney *et al*., 2021).

Table 1: Comparison of basic information of the retrospective group and the intervention group of elderly patients with ischemic cerebrovascular disease in Beihai Hospital of Traditional Chinese Medicine, Guangxi Zhuang Autonomous Region from 2019 to 2023.

Group	N	Average age (years)	Male proportion	Average type of medication
Review Group (2019-2022)	1328	72.1±8.3	57.3%	4.6±1.2
Intervention Group (2023)	807	71.6±7.9	59.2%	3.8±1.1*
*P<0.01vs Review Group				

Table 2: Initial antiplatelet therapy regimen and dosage adjustment for patients based on CYP2C19 genotype.

CYP2C19Genome	Antiplatelet regimen	Dosage adjustment based on
*1/*1	Clopidogrel 75mgqd+aspirin 100mg qd	Standard metabolic capacity
*1/*2	Clopidogrel 150mg First dose→75mg qd	Intermediate metabolism requires loading dose
*3/*3	Ticagrelor 90mg bid	Switching to drugs that are not metabolized by CYP2C19 for slow metabolizers

Table 3: Adjustment of aspirin and statin therapy according to liver and kidney function indicators.

Liver and kidney function indicators	Aspirin Adjustment Program	Statins of choice
Child-Pugh A and eGFR≥60	100mg qd	Atorvastatin 20mg qd
Child-Pugh B or eGFR 30-59	75mg qd	Rosuvastatin 10mg qd
Child-Pugh C or eGFR<30	50mg qd (Not recommended for patients at high risk of bleeding)	Pravastatin 40mg qd

The above adjustment plan is based on the "Guidelines for Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack in China".

Table 4: High-risk drug combinations, clinical risks, alternatives and intervention time limits for combined medication in elderly patients with ischemic cerebrovascular disease in Guangxi.

High-risk portfolio	Clinical risks	Recommended alternatives	Intervention time limit
Clopidogrel +Omeprazole	Platelet inhibition rate↓28%	Switch to hemitoprazole 40mg qd	Within 24 hours
Warfarin + Danshen injection	INR value fluctuation > 2 times	Stop using Danshen or switch to Ginkgo biloba extract	Deactivate immediately
Amiodarone + simvastatin	Rhabdomyolysis risk ↑4.2 times	Switch to pravastatin 40 mg qd	Within 72 hours
Metformin + iohexol	The risk of acute kidney injury increased by 3.1 times	Stop metformin 48 hours before examination	Elective treatment
Digoxin + furosemide	Digoxin poisoning risk ↑2.8 times	Monitor serum potassium + digoxin concentrations	Weekly monitoring

Table 5: Comparison of baseline characteristics between Zhuang and Han patients with elderly ischemic cerebrovascular disease in Guangxi Zhuang Autonomous Region.

Feature	Zhuang ethnic group (n=873)	Han group (n=1262)	*P*-value
Age (years, mean ± SD)	69.8±7.9	72.1±8.5	0.012
Male proportion (%)	62.3	56.1	0.036
Combined hypertension (%)	85.7	81.4	0.021
Average type of medication used	4.7±1.3	4.5±1.1	0.152

In view of these differences in baseline characteristics, in subsequent analyses, stratified analysis and multivariate regression analysis were used to evaluate the differences in study outcomes in different subgroups and the effects of these factors on the outcomes were corrected to ensure the reliability of the study results.

Table 6: Comparison of CYP2C19 genotype distribution between Zhuang and Han patients with elderly ischemic cerebrovascular disease in Guangxi Zhuang Autonomous Region.

Genotype	Zhuang ethnic group (n=873)	Han group (n=1262)	*P*-value
*1/*1(Fast metabolism)	38.2%	45.6%	0.004
*1/*2, *1/*3	33.1%	35.2%	0.321
*2/*2, *3/*3	28.7%	19.2%	<0.001

Table 7: Comparison of clinical outcomes between the intervention group and the retrospective group after implementation of the stratified medication regimen.

Index	Intervention group (n=807)	Review group (n=1328)	*P*-value
Recurrent stroke rate (%)	8.3	15.7	<0.001
Serious bleeding events (%)	5.1	9.8	0.003

Table 8: Changes in platelet inhibition rate at different time points during treatment in the intervention group and the review group (mean ± SD, %).

Time	Intervention group (n=807)	Review group (n=1328)	*P*-value
Baseline	32.5±10.2	33.1±9.8	0.214
1 month	52.1±15.3	47.6±16.2	0.029
3 month	65.2±12.4	53.8±14.1	<0.001

Table 9: Analysis of neurological function improvement in the intervention group and the control group by age.

Subgroup	Intervention group effective rate (%)	Control group effective rate (%)	*P*-value
overall	79.0	56.0	0.003
≤70 years	84.2	61.5	0.001
>70 years	72.1	49.3	0.012

This study focused on the effects of stratified medication regimens on elderly patients with ischemic cerebrovascular disease. After the implementation of the regimen, the intervention group showed good improvement in neurological function and changes in some clinical indicators were also observed. Results such as stroke recurrence in this study may be interfered by a variety of confounding variables. To address this problem, we conducted a comprehensive multivariate regression analysis to control key confounding factors such as age and underlying disease status. After analysis, the adjusted results further confirmed that the stratified medication regimen we proposed is of practical significance in reducing the risk of stroke recurrence. However, this study still has certain limitations, such as some potential confounding factors (such as patient lifestyle, socioeconomic status, etc.) may not be fully covered in the regression model and follow-up studies need to be further improved. However, there are many aspects that need to be explored in depth during the research process.

The external validity of a study is an important indicator for measuring the universality of the research results. It reflects whether the research findings can be extended to a wider population and clinical scenarios. This study was designed to exclude patients with severe liver failure (Child-Pugh C grade), creatinine clearance < 30 mL/min (end-stage renal insufficiency) and patients with malignant tumors or hematological diseases. Although this exclusion strategy is of great significance in ensuring the internal validity of the study and reducing the interference of confounding factors, it inevitably affects the external validity. For patients with severe liver failure and end-stage renal insufficiency, their metabolic function is severely impaired and the absorption, distribution, metabolism and excretion of drugs in the body are significantly different from those of general patients. Such patients often require more complex treatment adjustments, but this study did not include them, making the research results unable to be directly applied to this special population. For patients with malignant tumors or hematological diseases, the disease itself and related treatments (such as radiotherapy, chemotherapy, immunotherapy, etc.) may interfere with the efficacy and safety of antithrombotic drugs, which is different from the core scenario of combined medication for elderly ischemic cerebrovascular disease focused on in this study. Therefore, the applicability of the conclusions of this study in these patient groups is limited. Despite these limitations, this study still achieved valuable results in terms of drug interactions and efficacy optimization of combined medication for the included elderly patients with ischemic cerebrovascular disease, providing an important reference for subsequent studies. Future studies can further expand the sample range, include these special patient

groups and conduct targeted studies to improve the external validity of the research results and provide more comprehensive guidance for a wider range of clinical practices.

Research limitations and academic significance

The limitations of this study include: no detection of CYP2C19*17 functional enhancement alleles; short follow-up time (6 months), while the DAPT study (Ravindra Reddy G *et al*., 2024) showed that the long-term efficacy of clopidogrel may decline.

Nevertheless, this study revealed, for the first time, the unique drug-metabolism characteristics of ethnic minorities in southwest China, providing ethnicity-specific evidence for precision medicine in East Asia.

CONCLUSION

This study revealed, for the first time, the unique drug-metabolism characteristics of ethnic minorities in southwest China and found that the proportion of CYP2C19 slow metabolizers in the Zhuang population was significantly higher than in the Han population. The high frequency of *2/3 double heterozygous mutations (9.1%) may aggravate clopidogrel hyporesponsiveness; 12.4% of fast metabolizers in the study had insufficient platelet inhibition, indicating that genotyping needs to be combined with functional testing to optimize treatment; clopidogrel may improve neurological function by inhibiting platelet activation, anti-inflammatory and endothelial protection pathways; this study fills the gap in drug genomic data for ethnic groups in southwest China and provides a basis for the formulation of regional guidelines, but the study has limitations such as not testing the CYP2C1917 function-enhancing allele and a short follow-up time, which can be further improved in future studies.

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Authors' contributions

Zhiling Cai: Idea and communication; Jiaguan Chen: Wrote the full text; Weili Li: Responsible for collecting materials; Nengzhen Pan: Processed the article data; Zhanxi Liu: Translated the full text.

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Data availability statement

The datasets generated during and/or analysed during the current research are available from the corresponding author on request.

Ethical approval

This study followed the Declaration of Helsinki guidelines and was approved by the Ethics Committee of the Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine (KY2024-057). All participants provided informed consent. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest

The authors declare no conflict of interest.

Supplementary data

https://www.pjps.pk/uploads/2026/06/SUP1781183377.pdf

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