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Clinical characteristics and short-term outcomes of migraine with patent foramen ovale: a comparative study

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Abstract

Objective To analyze the clinical features and prognosis of migraine with PFO and explore their short-term prognostic factors.

Methods This study enrolled patients with migraine (MH) and patients with migraine with patent foramen ovale (MH-PFO) who were treated at two hospitals affiliated with Zunyi Medical University (December 2021–October 2022). The general information of the two groups of patients was compared, and the clinical characteristics of the patients with MH-PFO were analyzed. All participants underwent standardized follow-ups at 1 and 3 months posttreatment; the patients were assessed using the Headache Impact Test-6 (HIT-6), the Zung Self-Rating Anxiety Scale (SAS), and the Zung Self-Rating Depression Scale (SDS). Prognostic analysis included multivariate logistic regression.

Results 239 patients with migraine completed the follow-up (MH group: 67; MH-PFO group: 172). Compared with the MH group, the MH-PFO group presented significantly earlier symptom onset ($P < 0.001$), a greater incidence of migraine aura (36.6% vs. 3.0%), a greater family history of migraine (28.5% vs. 9.0%), and elevated HIT-6/SAS/SDS scores and D-dimer levels (all $P < 0.05$). The medication response was poorer in the MH-PFO group ($P < 0.05$). Compared with medication, surgical intervention in the MH-PFO group reduced the severity of headache and anxiety/depression (all $P < 0.05$). Migraine with aura (1 month: OR = 0.159; 3 months: OR = 0.218), intrinsic right-to-left shunt (1 month: OR = 0.228; 3 months: OR = 0.060), and higher baseline HIT-6 scores (1 month: OR = 0.904; 3 months: OR = 0.879) were consistent predictors of reduced headache severity at the 1- and 3-month follow-ups postsurgery (all $P < 0.05$). A composite model integrating these factors demonstrated robust predictive accuracy for headache improvement after surgical treatment (AUC 0.84–0.89, $P < 0.05$; $0.7 < AUC < 0.9$, all $P < 0.05$).

Conclusion Compared to patients with MH, patients with MH-PFO have earlier symptom onset, higher rates of migraine aura, increased headache severity, more severe anxiety/depression, elevated D-dimer levels, and a greater incidence of family history of migraine. These patients respond more poorly to medication than patients with MH do. PFO closure has superior short-term efficacy in patients with migraine aura, intrinsic shunt, and high baseline HIT-6 scores (HIT-6 ≥ 59.5), highlighting the need for tailored therapeutic strategies.

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Keywords Patent foramen ovale, Migraine, Clinical characteristics, Treatment, Prognosis, PFO closure, Right-to-left shunt

Introduction

Migraine, a primary neurovascular headache disorder, ranks first among disabling neurological disorders and accounts for 20.1% of the total neurological disease-related disability burden [1]. Multiple theories have been proposed regarding its pathogenesis, which involves complex interactions between genetic and environmental factors [2, 3]. Patent foramen ovale (PFO), a common congenital cardiac anomaly, is typically asymptomatic. Since Del's 1998 discovery establishing PFO as an independent migraine risk factor [4], accumulating evidence has demonstrated its bidirectional association: migraine patients have a higher PFO incidence, and vice versa [5–7]. Thus, PFO is recognized as a potential migraine etiology.

The pathophysiology of PFO-associated migraine remains unclear, with proposed mechanisms including paradoxical embolism, vasoactive substance bypass, and cerebral autoregulation dysfunction [8]. These mechanisms partially overlap with those of pure migraine, but differences in mechanisms may result in distinct clinical features between patients with migraine with and without PFO. However, comparative studies remain limited, and the clinical differences between these two groups remain unclear.

PFO comorbidity complicates migraine management and drug development, with current therapies showing limited efficacy. The efficacy of PFO closure, a potentially important treatment for patients with migraine with PFO, remains controversial. While early trials reported reduced headache frequency/duration [9, 10], two landmark studies in recent years have demonstrated no superiority over medical therapy in unselected populations [11, 12]. Current guidelines lack consensus on surgical indications because there is insufficient evidence for identifying optimal surgical candidates [13].

We hypothesize that the distinct clinical profiles of patients with MH-PFO influence surgical outcomes. This study compares MH and MH-PFO cohorts to identify actionable predictors for optimizing treatment strategies through clinical feature-based surgical response prediction.

Study subjects and methods

Study subjects

Patients with migraine who visited the Department of Cardiology or Neurology of the Second Affiliated Hospital of Zunyi Medical University and the Third Affiliated Hospital of Zunyi Medical University from December 2021 to October 2022 were included. All the subjects underwent detailed collection of headache-related medical history, laboratory biochemical index testing, and contrast-enhanced transcranial Doppler (c-TCD) examination. The study design (Fig. 1) was approved by the ethics committee of The Third Affiliated Hospital of Zunyi Medical University. All patients provided written informed consent prior to participation. All methods were conducted in accordance with the approved guidelines.

The inclusion criteria were as follows: ① all patients with migraine who met the classification and diagnostic criteria for migraine listed in the third edition of the International Classification of Headache Disorders (ICHD-3) in 2018 [14] and who were aged 18–65 years; ② migraine with PFO group (MH-PFO): patients who met the criteria in ① and had positive findings upon contrast-transcranial Doppler (c-TCD) combined with transoesophageal echocardiography (TEE), contrast transthoracic echocardiography (c-TTE), transthoracic echocardiography (TTE), or PFO CT examination, with two or more examinations indicating the presence of PFO; ③ Pure migraine group (MH): patients who met the criteria in ① and had negative c-TCD examination findings.

The exclusion criteria were as follows: ① presence of positive neurological signs; ② presence of somatization disorders and comorbid psychiatric disorders; ③ history of other chronic diseases, such as severe heart, liver, kidney, lung, and blood system diseases; ④ history of head trauma; ⑤ presence of organic lesions (such as infarction, hemorrhage, mass, and aneurysm) detected on head CT images; ⑥ presence of keratitis or acute or chronic suppurative otitis media; ⑦ current intake of oral contraceptives, current pregnancy, or history of irritable bowel syndrome; ⑧ recent major life events.

The following general information was collected: ① basic information including sex, age, age of onset, menopausal status in females, hypertension status, diabetes status, smoking history, alcohol consumption history, family history of migraine, unilateral or bilateral headache, headache severity, headache attack frequency (days/month), average duration of headache (minutes), headache burden (headache attack frequency × average duration of headache) [15], and presence of migraine

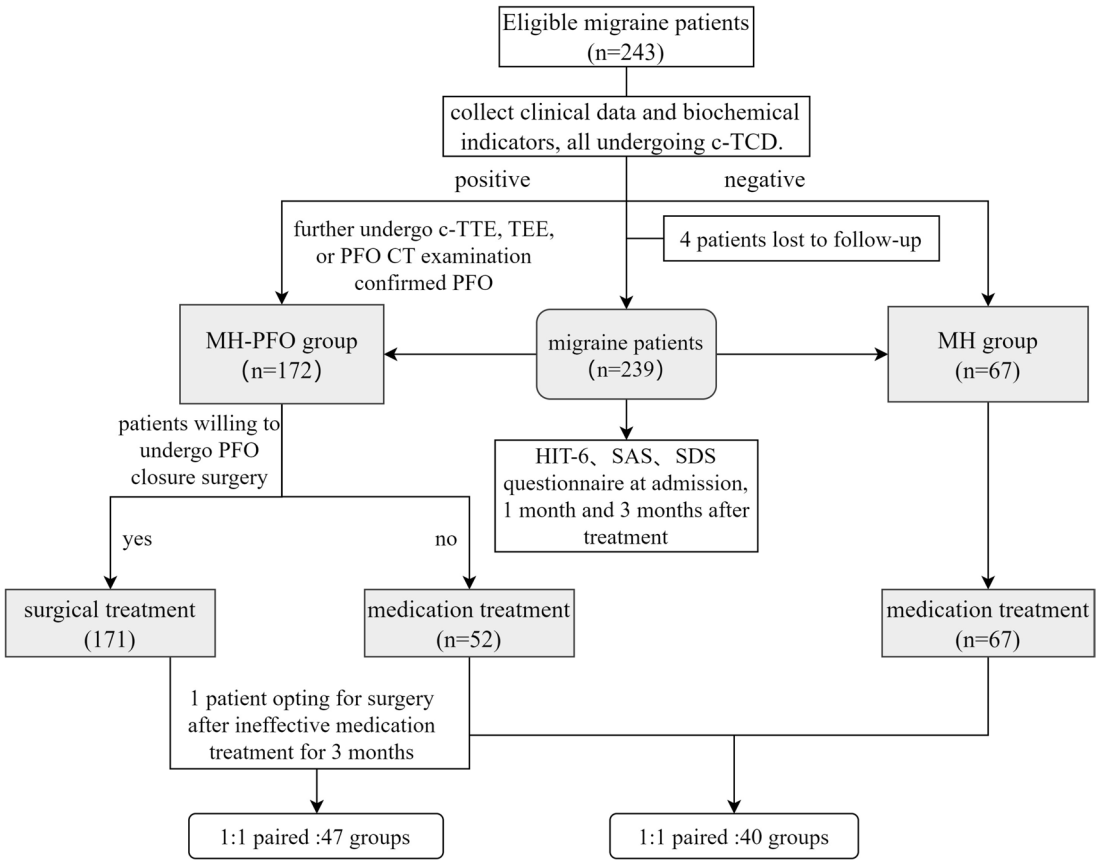

Fig. 1 Schematic of the study protocol. c-TCD, contrast-transcranial Doppler; CT, computed tomography

aura; ② biochemical indicators including coagulation function, D-dimer levels, blood lipids levels, and complete blood count; ③ imaging data: c-TCD results (classification, grade); ④ scoring data: Headache Impact Test-6 (HIT-6) score, Self-Rating Anxiety Scale (SAS) score, and Self-Rating Depression Scale (SDS) score.

Research methods

Rationality of the sample size

A sample size estimation using G*Power based on pilot data showing a 20% treatment effect ($d=0.5$, $\alpha=0.05$, $\beta=0.2$) yielded a minimum requirement of 160 participants. The final cohort included 239 patients, ensuring adequate statistical power.

Scale data collection

Two investigators who underwent standardized training collected data from the scales used in this study.

Scale scoring criteria

① HIT-6 scoring criteria: the impact of headaches on patients' quality of life was evaluated using the HIT-6 scale. Scores ≤ 49 indicate no impact, scores of 50–55 indicate some impact, scores of 56–59 indicate significant impact, and scores ≥ 60 indicate severe impact; ② SAS scoring criteria: patient anxiety was assessed using the SAS. The frequency of symptoms defined by the items was multiplied by 1.25 to obtain the standard score (rounded to the nearest integer). Scores < 50 indicate no anxiety, scores of 50–59 indicate mild anxiety, scores of 60–69 indicate moderate anxiety, and scores > 69 indicate severe anxiety; ③ SDS scoring criteria: patient depression was assessed using the SDS scale. The rough score was multiplied by 1.25 to obtain the standard score (rounded to the nearest integer). Scores < 53 indicate no depression, scores of 53–62 indicate mild depression, scores of 63–72 indicate moderate depression, and scores > 72 indicate severe depression; ④ Visual Analogue Scale for Pain (VAS) scoring criteria: Headache severity was evaluated using the VAS scale [16]. Scores of 1–3 indicate mild headache, scores of 4–6 indicate moderate headache, and scores of 7–10 indicate severe headache.

PFO grading and classification

① Criteria for grading the PFO shunt volume:

During c-TCD examination, a unilateral cerebral artery is monitored. The test is considered positive if high-intensity signals indicative of microemboli appear on the TCD spectrum within 25 s and negative if no microembolic signals are detected. The shunt volume is graded based on the number of microembolic signals:

- Grade 0 (negative): no microembolic signals.
- Grade I (minor shunt): 1–10 microembolic signals unilaterally.
- Grade II (moderate shunt): 10–25 microembolic signals unilaterally.
- Grade III (large shunt): > 25 microembolic signals unilaterally (non-shower type).
- Grade IV (large shunt): shower-like microembolic signals, where individual microbubbles cannot be distinguished (shower type).

② Criteria for PFO classification:

Patients underwent contrast-enhanced transcranial Doppler (c-TCD) examination. A unilateral cerebral artery was monitored, and the appearance of high-intensity microembolic signals (MES) on the TCD spectrum within 25 s was defined as a positive result. Positive cases were further classified into subtypes based on the physiological state during which MES were detected.

- Intrinsic type: Microembolic signals are detected at rest during c-TCD examination.
- Latent type: No microembolic signals are detected at rest, but they become detectable following a Valsalva maneuver.

Treatment methods

① medication treatment: patients with MH (migraine without PFO) and patients with MH-PFO who refused surgical treatment received acute medication treatment for 10–15 days and standardized preventive medication treatment for at least 3 months according to the 2016 Chinese Migraine Prevention and Treatment Guidelines [17]; ② surgical treatment: patients with confirmed MH-PFO underwent closure treatment with their consent. After surgical contraindications were excluded, puncture was performed under general anesthesia, followed by routine right heart catheterization and closure treatment. After surgery, routine electrocardiography and echocardiography were performed. Low-molecular-weight heparin (100 U/kg, once every 12 h) was used for anticoagulation for 2 days, followed by regular clopidogrel (75 mg) combined with aspirin (100 mg) once daily for 3 months. Each surgery was performed by at least two qualified surgeons.

Follow-up

All patients with migraine were followed up at 1 and 3 months after treatment (± 5 days) through outpatient visits or phone calls. The follow-up items included the HIT-6, SAS, and SDS scores at 1 and 3 months after treatment. The surgical treatment patients also underwent TTE and re-examination of their c-TCD results at follow-up, with any surgical complications recorded.

Efficacy evaluation

According to relevant literature [18], a decrease of ≥ 6 points in the HIT-6 score after treatment compared with baseline at admission is considered a good prognosis, whereas a decrease of < 6 points is considered a poor prognosis.

Statistical methods

All the data were analyzed by SPSS 20.0. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous data are presented as the mean ± standard deviation ($\bar{x} \pm s$), whereas nonnormally distributed data are presented as the median and interquartile range [M (P25, P75)]. Group comparisons were performed using t tests (between-group comparisons of score changes were performed with a single-sample t test applied to the differences) or nonparametric tests. Categorical data are presented as percentages (%), and group comparisons were performed using Chi-square tests or Fisher's exact tests. Binary logistic regression analysis was used for the multivariate analysis. ROC curves were plotted using MedCalc to analyze the predictive value of various indicators and models for prognosis. All the graphs and charts were created using GraphPad Prism 8, and a significance level of $P < 0.05$ was used.

Results

General information

243 cases were evaluated, with 4 patients lost to follow-up, resulting in the inclusion of 239 patients. All 239 patients with migraine completed a 3-month follow-up, including 67 patients in the MH group (18 males and 49 females, with an average age of 51.10 ± 11.13 years) and 172 patients in the MH-PFO group (46 males and 126 females, with an average age of 40.77 ± 13.18 years). Among the patients with MH-PFO, 52 chose medication treatment, and 121 chose surgical treatment (with 1 patient opting for surgery after ineffective medication treatment for 3 months). None of the surgical patients had postoperative complications or residual shunts during the follow-up period.

No demographic or laboratory differences were observed between the MH and MH-PFO groups regarding sex distribution, lifestyle factors, comorbidities, or routine blood parameters (all $P > 0.05$). Both cohorts were predominately female and displayed similar unilateral headache patterns. However, compared with patients with MH, patients with MH-PFO presented distinct clinical characteristics, including earlier symptom onset, a higher prevalence of nonmenopausal status (61.1% vs. 28.6%), a greater incidence of family migraine history (28.5% vs. 9.0%), increased aura presentation (36.6% vs. 3.0%), and more severe headache intensity (42.4% vs. 20.9%). The MH-PFO group also presented greater headache burden, elevated D-dimer levels [0.24 (0.18–0.31) vs. 0.16 (0.12–0.23) μg/mL], and significantly higher admission scores across all assessment scales (HIT-6, SAS, and SDS; all $P < 0.05$). The baseline HIT-6 scores revealed that among patients with simple migraine, the majority (49.3%) experienced headaches that moderately impacted their daily lives, whereas a greater proportion of patients in the PFO-comorbid group (42.4%) suffered from headaches that severely affected their quality of life (Table 1, Fig. 2).

Table 1 Demographic and clinical characteristics of the MH and MH-PFO groups

Project	MH ($n = 67$)	MH-PFO ($n = 172$)	$T/Z/\chi^2$	P
Age at onset (years)	45.54 ± 12.96	34.78 ± 13.56	5.574	< 0.001
Female (%)	49(73.1)	126(73.3)	0.035	0.985
Female premenopausal (%)	14(28.6)	77(61.1)	14.966	< 0.001
Cigarette smoking (%)	11(16.4)	20(11.6)	0.980	0.322
Alcohol consumption (%)	3(4.5)	2(1.2)	NA	0.136
Hypertension (%)	12(17.9)	18(10.5)	2.435	0.119
Diabetes mellitus (%)	2(3.0)	1(0.6)	NA	0.191
Family history of migraine (%)	6(9.0)	49(28.5)	10.384	0.001
Migraine severity			10.532	0.005
Mild	4(6.0)	12(7.0)		
Moderate	49(73.1)[a]	87(50.6)[b]		
Severe	14(20.9)[a]	73(42.4)[b]		
Migraine with aura (%)	2(3.0)	63(36.6)	27.563	< 0.001
Unilateral migraine (%)	42(62.7)	117(68.0)	0.617	0.432
Headache burden (hours/month)	18.00(10.00–32.00)	28.00(12.00–50.00)	− 2.357	0.018
Baseline HIT-6 (points)	54.00(50.00–57.00)	59.00(54.50–62.00)	− 5.811	< 0.001
No effect	8(11.9)	13(7.6)		
Mild impact	33(49.3)[a]	29(16.9)[b]		
Moderate impact	19(28.4)	57(33.1)		
Severe impact	7(10.4)[a]	73(42.4)[b]		
Baseline SAS score (points)	42.00(40.00–45.00)	45.00(41.00–47.00)	− 3.007	0.003
No anxiety	60(89.6)	137(79.7)		
Mild anxiety	6(9.0)	26(15.1)		
Moderate anxiety	1(1.5)	6(3.5)		
Severe anxiety	0(0)	3(1.7)		
Baseline SDS score (points)	48.00(45.00–52.00)	51.00(47.00–55.00)	− 2.019	0.044
No depression	50(74.6)[a]	102(59.3)[b]		
Mild depression	11(16.4)[a]	57(33.1)[b]		
Moderate depression	5(7.5)	10(5.8)		
Major depression	1(1.5)	3(1.7)		

Different superscript letters indicate significant differences between the two column groupings ($P < 0.05$)

P values after Bonferroni correction

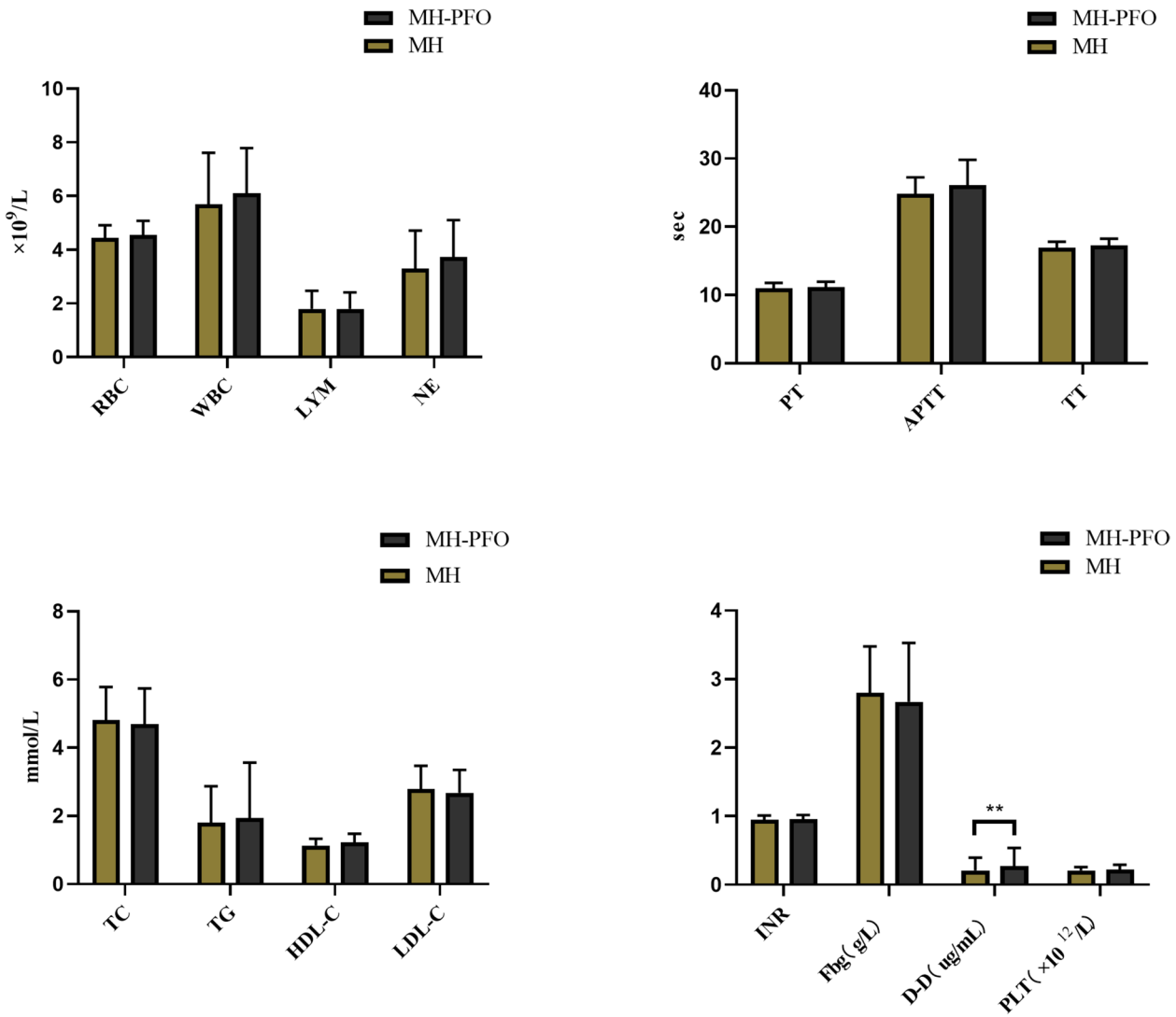

Fig. 2 Comparison of biochemical profiles between the MH and MH-PFO groups. $^{**}P < 0.01$ vs. the MH-PFO group; RBC, red blood cells; WBC, white blood cells; LYM, lymphocytes; NE, neutrophil; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; INR, international normalized ratio; Fbg, fibrinogen; D-D, D-dimer; PLT, platelet

Prognostic analysis

Prognostic analysis of medication treatment in the patients with MH-PFO

(1) Comparison between the good prognosis group and the poor prognosis group after medication treatment.

119 patients with migraine received medication treatment (MH = 67, MH-PFO = 52). After the medication treatment, there were statistically significant differences between the good prognosis group and the poor prognosis group in terms of age, the presence of PFO, baseline HIT-6 score, PT, and TG at 1 month (all $P < 0.05$). Three months after medication treatment, there were persistent disparities in the baseline HIT-6 and SDS scores between the prognostic groups (both $P < 0.05$) (Supplementary Table 1).

(2) Multivariate logistic regression analysis of factors affecting headache prognosis at 1 and 3 months after medication treatment.

Six variables (age, concurrent PFO, baseline HIT-6 score, baseline SDS score, PT, and TG) with $P < 0.05$ from Supplementary Table 1 were selected as independent variables for the multivariate logistic

regression analysis. Concurrent PFO (OR = 5.487, 95% CI 1.343–24.411, $P = 0.018$) and baseline HIT-6 scores (OR = 0.830, 95% CI 0.723–0.953, $P = 0.008$) were factors affecting the prognosis at 1 month after medication treatment. Concurrent PFO (OR = 5.274, 95% CI 1.302–21.356, $P = 0.020$), baseline HIT-6 score (OR = 0.862, 95% CI 0.763–0.973, $P = 0.016$), and baseline SDS score (OR = 0.903, 95% CI 0.834–0.978, $P = 0.012$) were factors affecting the prognosis at 3 months after medication treatment (Table 2).

(3) The prognoses in the 1:1 paired MH group and the MH-PFO group after medication treatment were analyzed.

According to the conclusions in Table 2, 40 matched pairs of patients with MH and patients with MH-PFO receiving pharmacological treatment were established through 1:1 matching on the basis of baseline HIT-6 (± 2 points) and SDS (± 4 points) scores. A comparative analysis of the general data between the two groups revealed differences in age, age at onset, presence of migraine aura, and D-dimer status (Supplementary Table 2). As shown in Table 2, these factors did not affect the efficacy of the medication treatment in the patients, and the two groups were comparable. A comparative analysis of the reduction in scores after medication treatment in the two groups revealed that the prognosis of headaches in the MH-PFO group was worse than that in the MH group after both 1 and 3 months of medication treatment (17.5% vs. 47.5% and 20.0% vs. 45.0%, respectively; all $P < 0.05$). Neither group showed significant improvement in anxiety or depression scores after treatment (Table 3, Fig. 3A–C).

Table 2 Multifactor logistic analysis of factors affecting medication treatment efficacy

Independent variables	B	*P*	OR	95% CI
1 month after treatment				
Concurrent PFO	1.702	0.018	5.487	1.343–24.411
Baseline HIT-6	−0.186	0.008	0.830	0.723–0.953
3 months after treatment				
Concurrent PFO	1.663	0.020	5.274	1.302–21.356
Baseline HIT-6	−0.149	0.016	0.862	0.763–0.973
Baseline SDS score	−0.102	0.012	0.903	0.834–0.978

Prognostic analysis of surgical treatment in the patients with MH-PFO

(1) Comparison between the good prognosis group and the poor prognosis group after surgical treatment in the patients with MH-PFO.

171 patients with MH-PFO underwent surgical treatment. At 1 month postsurgery, significant differences in family history of migraine, shunt magnitude, c-TCD grade/type, migraine severity, presence of aura, admission HIT-6 scores, and LYM scores were detected between the good and poor headache prognosis groups (all $P < 0.05$). At the 3-month follow-up, statistically significant differences persisted in hypertension, family history of migraine, shunt magnitude, c-TCD grade/type, presence of aura, headache burden, admission HIT-6 scores, and LYM scores (all $P < 0.05$) (Supplementary Table 3).

Table 3 Analysis of prognosis differences between the MH and MH-PFO groups after medication treatment

Project	MH (*n* = 40)	MH-PFO (n = 40)	Z/χ^2	*P*
Good prognosis after 1 month of treatment (%)	19(47.5)	7(17.5)	8.205	0.004
Change in score after 1 month of treatment (points)				
HIT-6	−5.00(−8.00 to −2.00)	−3.00(−4.00 to −1.00)	−3.027	0.002
SAS	−1.00(−5.00 to 0.00)	0.00(−3.75 to 0.00)	−1.315	0.188
SDS	−3.00(−5.00 to −0.25)	−1.00(−3.75 to 0.00)	−1.812	0.070
Good prognosis after 3 months of treatment (%)	18(45.0)	8(20.0)	5.698	0.017
Change in score after 3 months of treatment (points)				
HIT-6	−4.50(−8.00 to −2.00)	−2.00(−5.00 to 0.00)	−2.889	0.004
SAS	−2.00(−5.00 to 0.00)	−1.00(−4.00 to 0.00)	−1.008	0.313
SDS	−2.00(−5.00 to 0.00)	−1.00(−3.75 to 1.00)	−1.425	0.154

Patients in the medication-treated MH and MF-PFO groups were 1:1 matched according to baseline HIT-6 (± 2 points) and SDS (± 4 points) scores

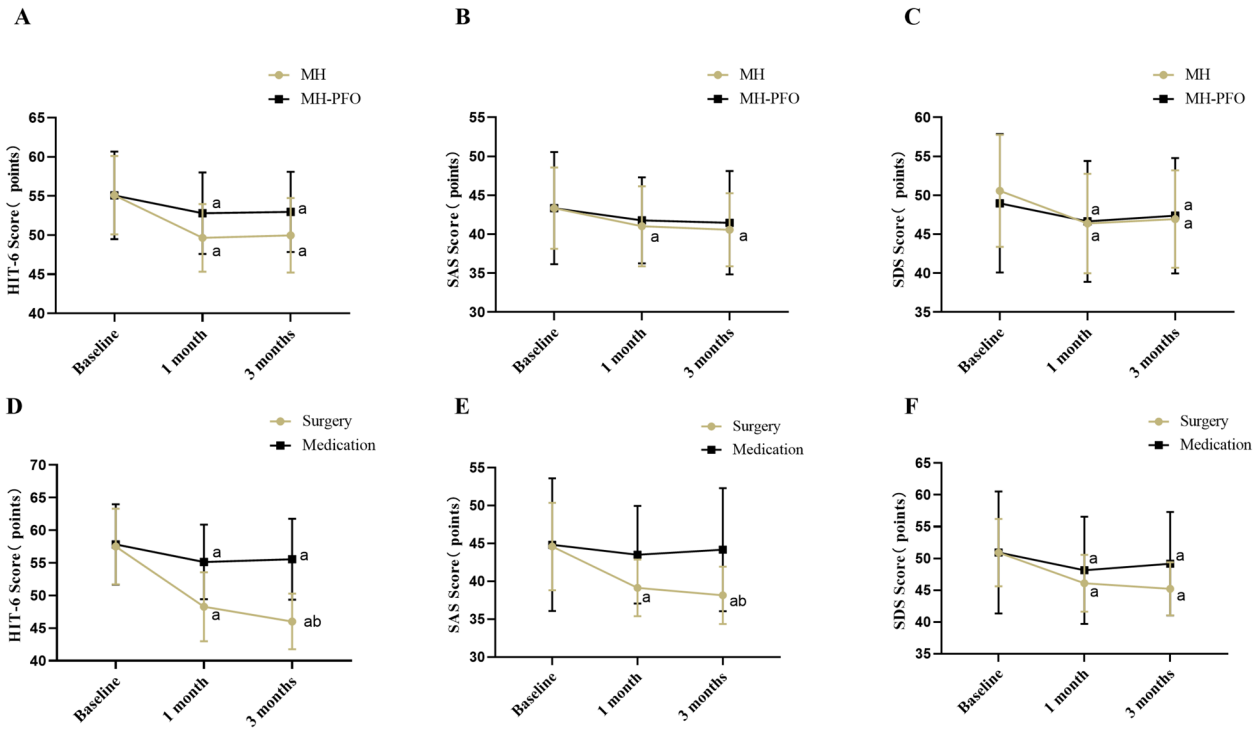

Fig. 3 Trends of changes in various scores after treatment. **C** Patients in the medication-treated MH and MH-PFO groups were 1:1 matched according to baseline HIT-6 (±2 points) and SDS (±4 points) scores. **D**–**F**: Patients with MH-PFO in the surgical treatment group and medication treatment group were 1:1 matched by the presence of migraine aura, baseline HIT-6 score (±2 points), c-TCD classification, and baseline SDS score (±4 points). **A** Changes in HIT-6 scores between the MH group and the MH-PFO group after medication treatment. **B** Changes in SAS scores between the MH group and the MH-PFO group after medication treatment. **C** Changes in SDS scores between the MH group and the MH-PFO group after medication treatment. **D** Changes in HIT-6 scores between the surgical treatment group and the medication treatment group in MH-PFO patients. **E** Changes in SAS scores between the surgical treatment group and the medication treatment group in patients with MH-PFO. **F** Changes in SDS scores between the surgical treatment group and the medication treatment group in patients with MH-PFO. a, Each time period after treatment compared to the time of admission, $P<0.05$; b, 3 months after treatment compared to 1 month after treatment, $P<0.05$

(2) Multivariate logistic regression analysis of factors influencing postoperative headache prognosis in patients with MH-PFO

10 factors with $P<0.05$ from Supplementary Table 3 were selected as independent variables, with prognosis (0 = good, 1 = poor) as the dependent variable. A multivariate logistic regression analysis with the "Forwards: Conditional" method (entry criteria: $P<0.05$; removal criteria: $P>0.10$) revealed that migraine with aura (OR = 0.159, 95% CI: 0.052–0.488, $P=0.001$), intrinsic-type c-TCD classification (OR = 0.228, 95% CI: 0.088–0.591, $P=0.002$), and admission HIT-6 score (OR = 0.904, 95% CI: 0.827–0.989, $P=0.028$) were identified as independent predictors of headache prognosis at 1 month post-surgery. Similarly, migraine with aura (OR = 0.218, 95% CI 0.053–0.892, $P=0.034$), intrinsic-type PFO on c-TCD (OR = 0.060, 95% CI 0.012–0.287, $P<0.001$), and admission HIT-6 score (OR = 0.879, 95% CI 0.791–0.978, $P=0.018$) remained significant predictors at the 3-month follow-up (Table 4).

Table 4 Multifactor logistic regression analysis of factors affecting headache prognosis after surgery

Independent variables	*B*	*P*	OR	95% CI
1 month after treatment				
Migraine with aura	−1.837	0.001	0.159	0.052–0.488
Intrinsic type	−1.480	0.002	0.228	0.088–0.591
Baseline HIT-6	−0.101	0.028	0.904	0.827–0.989
3 months after treatment				
Migraine with aura	−1.524	0.034	0.218	0.053–0.892
Intrinsic type	−2.815	< 0.001	0.060	0.012–0.287
Baseline HIT-6	−0.129	0.018	0.879	0.791–0.978

(3) Prognostic analysis of the patients with MH-PFO undergoing surgical treatment and medication treatment in a 1:1 matched group.

Using the prognostic factors from Table 4 (surgical outcomes) and 2 (pharmacological outcomes), namely migraine with aura, baseline HIT-6 scores

(± 2 points), c-TCD classification (matched type), and baseline SDS scores (± 4 points), 47 matched pairs of surgically and pharmacologically treated patients with MH-PFO were analyzed through 1:1 matching. A comparative analysis of the demographic data revealed no statistically significant differences between the groups (all $P > 0.05$), confirming comparability (Supplementary Table 4). At the 1-month follow-up, the surgical treatment group demonstrated a superior headache prognosis (70.2% vs. 14.9%, $P < 0.001$) and greater improvements in anxiety/depression scores (all $P < 0.05$) than did the medication group. These advantages persisted at the 3-month follow-up, with the surgical treatment group showing improved headache prognosis rates (83.0% vs. 17.0%, $P < 0.001$) and significantly better anxiety/depression score improvements (all $P < 0.001$) (Table 5, Fig. 3D–F).

(4) Predictive efficacy of various indicators and combined indicator models for postoperative headache prognosis in patients with MH-PFO.

The predictive values of various indicators and the combined indicator models in Table 4 for predicting postoperative headache prognosis in patients with MH-PFO after 1 month of surgical treatment were compared. The AUC values for c-TCD classification, migraine with aura, admission HIT-6 score, and their combination in predicting 1-month postoperative headache prognosis in patients with MH-PFO ranged between 0.7 and 0.9. The combined model (AUC = 0.841) outperformed individual predictors (HIT-6 score (AUC = 0.727), migraine with aura (AUC = 0.716), and c-TCD classification (AUC = 0.701)). A statistically significant difference ($P < 0.05$) was observed between the combined AUC and individual AUC values. The combination

Table 5 Prognosis analysis between the surgical treatment group and medication treatment group

Project	Surgical treatment ($n = 47$)	Medication treatment ($n = 47$)	*Z*	*P*
Good prognosis after 1 month of treatment (%)	33(70.2)	7(14.9)	29.419	< 0.001
Change in score after 1 month of treatment (points)				
HIT-6	− 9.00(− 14.00 to − 4.00)	− 3.00(− 4.00 to − 1.00)	− 4.940	< 0.001
SAS	− 5.00(− 10.00 to − 2.00)	0.00(− 3.00 to 0.00)	− 4.184	< 0.001
SDS	− 5.00(− 8.00 to − 1.00)	− 1.00(− 4.00 to 0.00)	− 2.469	0.014
Good prognosis after 3 months of treatment (%)	39(83.0)	8(17.0)	40.894	< 0.001
Change in score after 3 months of treatment (points)				
HIT− 6	− 11.00(− 16.00 to − 6.00)	− 2.00(− 4.00 to 0.00)	− 6.509	< 0.001
SAS	− 5.00(− 11.00 to − 2.00)	0.00(− 4.00 to 1.00)	− 4.414	< 0.001
SDS	− 6.00(− 9.00 to − 2.00)	− 1.00(− 4.00 to 1.00)	− 3.577	< 0.001

The surgical treatment and medication treatment patients with MH-PFO groups were 1:1 matched by aura, baseline HIT-6 scores (± 2 points), c-TCD classification, and baseline SDS scores (± 4 points)

Table 6 Analysis of the predictive efficacy of various indicators and combined indicator models for postoperative headache prognosis after surgery

Project	AUC	95% CI	*P*	Cutoff value	Sensitivity (%)	Specificity (%)
1 month after treatment						
c-TCD type	0.701	0.611–0.781	< 0.001	-	65.90	74.40
Migraine with aura	0.716	0.627–0.795	< 0.001	-	56.10	87.20
Baseline HIT-6	0.727	0.639–0.804	< 0.001	≥ 59.50	57.30	84.60
Tripartite joint	0.841	0.763–0.901	< 0.001	-	76.90	84.10
3 months after treatment						
c-TCD type	0.783	0.699–0.853	< 0.001	-	64.60	92.00
Migraine with aura	0.690	0.600–0.771	0.004	-	50.00	88.00
Baseline HIT-6	0.785	0.701–0.854	< 0.001	≥ 58.50	65.60	80.00
Tripartite joint	0.891	0.821–0.940	< 0.001	-	76.00	88.50

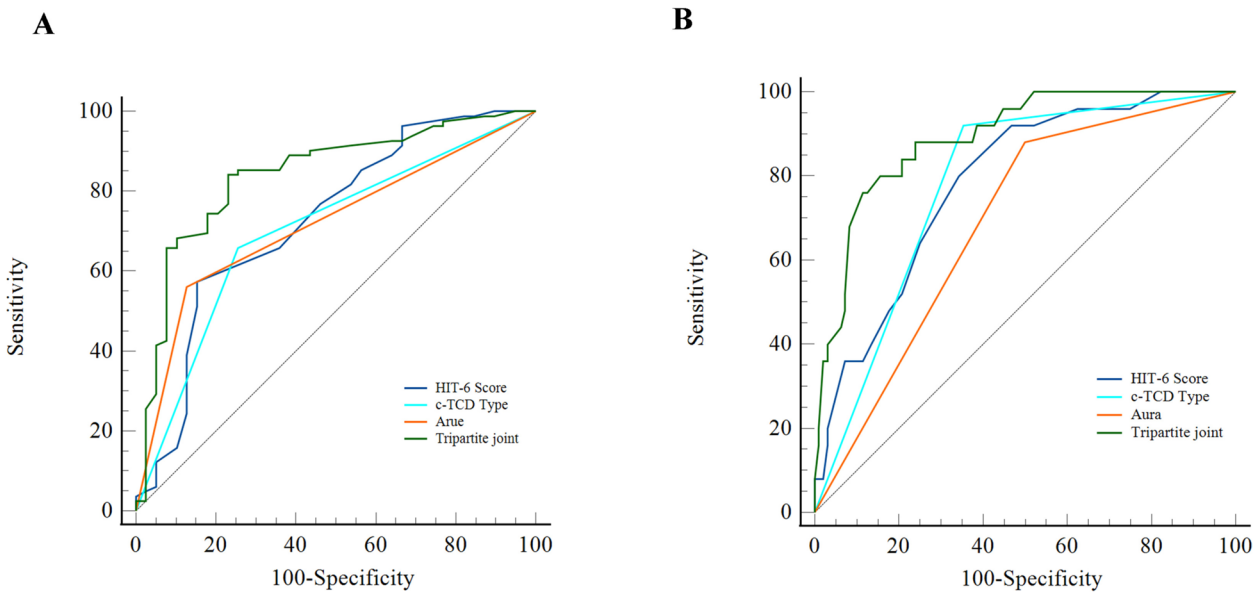

Fig. 4 ROC curves of various indicators and combined indicator models for predicting postoperative headache prognosis in patients with MH-PFO. **A** ROC curve for predicting headache prognosis 1 month after surgical treatment using individual indicators and combined indicator models. **B** ROC curve for predicting headache prognosis 3 months after surgical treatment using individual indicators and combined indicator models

of the c-TCD classification, migraine with aura, and admission HIT-6 score (≥59.5 points) demonstrated robust predictive accuracy, with a sensitivity of 76.9% and a specificity of 84.1% (Table 6, Fig. 4A).

The predictive values of various indicators and combined indicator models for postoperative headache prognosis in patients with MH-PFO 3 months after surgical treatment were compared. The combined model (AUC = 0.891) surpassed individual predictors (HIT-6 score (AUC = 0.785), c-TCD classification (AUC = 0.783), and migraine with aura (AUC = 0.690)). A statistically significant difference ($P < 0.05$) was observed between the combined AUC and individual AUC values. The combination of the c-TCD classification, migraine with aura, and admission HIT-6 score (≥58.5 points) demonstrated effective predictive accuracy for 3-month postoperative prognosis in patients with MH-PFO, with a sensitivity of 76.0% and a specificity of 88.5% (Table 6, Fig. 4B).

Discussion

This prospective cohort study systematically reveals the unique clinical features, treatment responses, and prognostic predictors of patients with MH-PFO, offering novel insights for individualized therapeutic strategies. The key findings and mechanisms are summarized as follows:

1. Clinical differences between patients with MH-PFO and patients with MH

Patients with MH-PFO share similarities with those with MH, including onset predominantly in young to middle-aged females and unilateral moderate-to-severe headaches [14]. However, patients with MH-PFO presented with earlier onset, were more likely to be premenopausal females, and had more frequent migraine aura, greater headache burden/severity, elevated anxiety/depression scores, higher D-dimer levels, and a greater family history of migraine.

The earlier onset in patients with MH-PFO may be related to their greater proportion of premenopausal females (61.1%). Estrogen likely amplifies the pathological effects of RLS on migraine by modulating vasomotor reactivity (e.g., decreased estrogen enhances vasoconstriction, increases right heart pressure, and aggravates RLS, further impairing vascular tone) [19, 20], although direct evidence remains lacking.

Animal models have demonstrated that RLS permits venous microemboli to bypass pulmonary filtration, directly entering the cerebral circulation and triggering cortical spreading depression (CSD) and neuroinflammation—mechanisms underlying aura susceptibility [21]. Microemboli-induced cerebral ischemia activates the trigeminovascular system, releasing calcitonin gene-related peptide (CGRP) and substance *P*, which provoke dural mast cell degranulation, neurogenic inflammation, and trigeminal nocicep-

tor activation [22]. In addition, vasoactive substances (e.g., CGRP, substance *P*, and 5-HT) bypass pulmonary metabolism via RLS, crossing the blood–brain barrier to stimulate trigeminal pathways [23]. These mechanisms collectively explain the increased headache severity in patients with MH-PFO, which is consistent with our observations. Recent evidence has revealed elevated serum CGRP levels in patients with MH-PFO, which are correlated with RLS severity and were shown to decrease post-PFO closure, further supporting this hypothesis [24, 25]. Studies have shown that CGRP can trigger migraine aura [26], which is consistent with the observation in this study that many patients with MH-PFO have migraine aura.

Elevated anxiety/depression in patients with MH-PFO may stem from RLS-mediated 5-HT dysregulation and severe headache burden. PFO-RLS allows gut-derived 5-HT to bypass pulmonary monoamine oxidase degradation, thus directly activating the limbic system (e.g., the amygdala and anterior cingulate) to exacerbate mood disorders [27]. Concurrently, headache upregulates prefrontal-limbic functional connectivity, forming a vicious "pain–emotion" cycle [28].

Elevated D-dimer levels may reflect subclinical coagulation activation, which is potentially linked to RLS-mediated hypoxia, although direct evidence is lacking. In patients with migraine with PFO-RLS, venous blood from the right heart system that bypasses pulmonary oxygenation directly enters the left heart and mixes with arterial blood, causing PFO-RLS-mediated chronic hypoxia [29]. This aligns with reports of hypercoagulability in patients with migraine at high altitudes [30]. The increased family history prevalence of migraine in patients with MH-PFO suggests the possible existence of genetic susceptibility.

2. Treatment response disparities
   Patients with MH-PFO showed poorer responses to medication than did the patients with MH, but specific subgroups exhibited simultaneous headache and mood improvement post-PFO closure. This discrepancy may be attributed to the following:
   Mechanistic specificity: conventional drugs (e.g., β-blockers and CGRP monoclonal antibodies) target peripheral nociception or vasodilation, whereas MH-PFO involves RLS-related microembolism and central sensitization [31]. PFO closure eliminates RLS-driven pathological cascades.
   Secondary mood improvement: post-closure headache relief indirectly alleviates the emotional burden.
3. Predictive model and clinical implications
   On the basis of preoperatively available indicators (intrinsic RLS, presence of aura, HIT-6 score ≥ 59.5), the combined prediction model constructed in this study performed well (AUC = 0.84–0.89), with both sensitivity (76.0–76.9%) and specificity (84.1–88.5%) values superior to those of single parameters (AUC = 0.69–0.79). This aligns with Ashina's "biomarker-guided precision therapy" framework [32], supporting cost-effective patient stratification in clinical practice.
4. Limitations and future directions
   Consistent with prior studies [33, 34], although specific patients with MH-PFO benefitted from PFO closure in this cohort, establishing definitive indications and evaluating long-term outcomes necessitate additional research. Furthermore, this study was primarily limited by the following: (1) short-term follow-up: the 3-month observation period precludes the assessment of long-term outcomes, particularly regarding potential recurrence or delayed complications of PFO closure. (2) Selection bias: the single-center design and nonrandomized surgical cohort (enriched with severe cases) may limit generalizability. Future multicentre trials with broader inclusion criteria are warranted. (3) Unmeasured confounders: despite 1:1 propensity score matching, residual confounding by lifestyle factors (e.g., diet, exercise patterns) and medication adherence could influence outcomes. For example, poor adherence to postoperative antiplatelet therapy might attenuate surgical benefits, although this was not systematically tracked. (4) Biomarker limitations: The lack of serial measurements of pathophysiological markers (e.g., CGRP and 5-HT) hinders the mechanistic exploration of treatment responses. (5) Heterogeneity in pharmacotherapy: there were variations in medication types and dosing regimens across patients. Although this reflects real-world practice, it may introduce noise in assessing pharmacological efficacy.

Furthermore, although PFO closure demonstrated superior short-term efficacy in reducing headache severity and comorbid anxiety/depression in this study, these findings should be interpreted as preliminary. The nonrandomized inclusion of surgical candidates, particularly those with severe symptoms, may have introduced selection bias. Definitive conclusions regarding surgical superiority require validation through large-scale randomized controlled trials (RCTs) with extended follow-up periods.

Conclusion

These preliminary findings suggest that patients with MH-PFO have earlier symptom onset, higher rates of aura, greater headache severity, more severe anxiety/depression, elevated D-dimer levels, and a greater family history of migraine. Moreover, these patients respond more poorly to medication than do patients with MH, and PFO closure may offer short-term advantages in patients with MH-PFO with migraine aura, intrinsic shunt, and high baseline HIT-6 scores (≥ 59.5). These findings require validation through randomized controlled trials to establish causal efficacy and refine patient selection criteria.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02645-w.

Supplementary materials 1.

Supplementary materials 2.

Supplementary materials 3.

Supplementary materials 4.

Author contributions

YL and JZ provided project conceptualization, design, and guidance for this research project. YS and TX provided technical guidance on inspection methods for this study. YS and YX were responsible for collecting research materials. FF and YS were responsible for data analysis and interpretation. YS drafted and wrote the manuscript text, and NH made revisions and final drafts. All the authors reviewed the manuscript.

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Data availability

Data are provided within the supplementary information files.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki of 1975 as revised in 2000. This study was approved by the Institutional Review Board of The Third Affiliated Hospital of Zunyi Medical University (Approval No: LL-202404190010). All patients or their legal guardians in this study authorized the release of their medical records and information.

Consent for publication

Informed consent was obtained from all individual participants included in the study who were alive at follow-up.

Competing interests

The authors declare that they have no competing interests.

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