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Association between patent foramen ovale and migraine without aura: a community-based cross-sectional study in China

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ABSTRACT

Objectives To assess the influence of patent foramen ovale (PFO) on the prevalence of migraine without aura based on propensity score-matched samples in Southwest China.

Design Propensity-matched cross-sectional study.

Participants Residents over 20 years of age were recruited from 15 communities of Western China from July 2020 to October 2020. A total of 3741 residents having accepted to undergo contrast-transthoracic echocardiography and a standard structured questionnaire was assessed for the relationship between PFO and migraine without aura.

Primary and secondary outcome measures The primary outcome measures were the prevalence of migraine without aura across different degrees of right–left shunts.

Results A total of 3741 participants were included. Among them, 881 participants were diagnosed with PFO. The prevalence of migraine without aura in the PFO group was 12.83%, significantly higher than the other group (7.83%, p<0.0001). Analyses of the matched samples showed that the presence of a PFO increased the morbidity risk of migraine without aura (p < 0.001; OR=1.71, 95% CI 1.19 to 2.47).

Conclusion This community-based cross-sectional study pointed to a strong association between PFO and migraine without aura, especially when the shunt is large.

Trial registration number ChiCTR1900024623.

Strengths and limitations of this study

- This was the first community-based study to assess whether patent foramen ovale can increase the risk of migraine without aura.
- Another major strength of this study was the continuous follow-up of participants through high-quality registries.
- To reduce bias, we used multiple statistical models in a propensity score-matching process.
- The data are cross-sectional, not longitudinal.

INTRODUCTION

Migraine is a major disabling disease affecting individuals under 50 years of age,[1] which incurs a hefty burden on both individual and social well-being. The prevalence of migraine is high, ranging from 9.3%[2] to 14.4%.[3] Accurate recognition and appropriate treatment are necessary to reduce the burden of migraine and improve patient satisfaction.[4] Unfortunately, many patients with migraine have been historically underdiagnosed and undertreated.[5] Pharmacological treatment remains the first choice for patients with migraine. However, long-term pharmacological treatments may have low compliance rates, low effectiveness or undesirable side effects, and new drugs such as calcitonin gene-related peptide monoclonal antibodies are too expensive.[6 7] Although numerous drugs have been available, few patients are able to insist on receiving a standardised preventive treatment protocol.[8] Opioids are still abused among individuals with migraines across all ages and clinical settings, especially in underdeveloped regions,[9 10] resulting in a high risk of medication overuse headache,[11] disease chronification,[12 13] addiction and drug abuse. Therefore, internists and researchers are still looking for new treatments for patients with refractory or highly unsatisfactory medical therapy. In the context of long-term assessments, many studies have suggested that a patent foramen ovale (PFO) may be the potential aetiology or risk factor underpinning migraine.[14 15]

PFO, described as a 'back door to the brain',[16] is the most common congenital intracardiac right-to-left shunt in adults and has been implicated in the pathogenesis of many neurological conditions. Microembolism, vasoactive biochemical or diluted blood, bypassing the pulmonary circulation from the systemic venous circulation directly to the brain, giving rise to cortical spreading

depression, may result in migraine attacks.[17] Guidelines[17] have recommended the primary screening of patients\ with migraine with aura (MA) for PFO, but the relationship between PFO and migraine without aura (MO) remains controversial.[18 19] In the past decade, related studies have mostly consisted of case–control studies based in hospitals, which may have incurred a certain degree of admission bias.[8] Their results may eliminate some uncertainties and be more convincing if the sources of study participants are expanded across the community.

Here, we used contrast-transthoracic echocardiography (cTTE) and a standard structured questionnaire to assess the ratio and severity of PFO and migraine in the communities of Western China and control the baseline characteristics by propensity score to probe the relationship between PFO and MO. In addition, this study sought to determine the feasibility of deploying these technologies in community-oriented primary care settings and for the continuous tracking of cerebrovascular events.

DATA AND METHODS

Study design

This study was a community-based cross-sectional study and registered at the Chinese Clinical Trial Register. Written informed consent was obtained from all participants or their legal guardians. Text message recruitment letters and banner advertisements in local communities were used to recruit interested participants from 15 communities around the city of Chengdu, Sichuan, China, from July 2020 to October 2020.

Patient and public involvement

No patient was involved.

Participants

In this study, we recruited urban residents over 20 years of age who had lived in communities for more than 6 months. Patients were divided into two groups according to the outcome of cTTE: with and without PFO. Enrolled participants were excluded from the study if they met the following exclusion criteria: (a) a history of significant head trauma or MA, (b) with other cardiac abnormalities (except for PFO), (c) in the acute stage of vascular embolism or hypercoagulable state, (d) inadequate cubital venous access, (e) unable to perform the Valsalva manoeuvre (VM) due to severe heart or lung disease.

Variables

Detailed demographic information was obtained from the enrolled participants via face-to-face interviews based on a standard structured questionnaire. All baseline data were collected by trained workers, undergoing strict quality control assessments. The following information was assessed: age, gender, educational level, body mass index (BMI), smoking, alcohol drinking, regular tea, regular coffee, clinical history of headache, family history of migraine and mental health status.

Physical examinations and diagnoses were performed by the neurological internists. Each participant was asked if they had a history of migraine and answered a three-item identification questionnaire assessing the presence of migraine[20] for current symptoms. A positive primary screening result was defined as a positive answer to either question; thereafter, patients underwent an additional systematic and detailed examination questionnaire, the International Classification of Headache Disorders III,[21] assessing onset age, frequency, duration of headache, pain type, sensitivity to light and sound, visual disturbances, nausea, focal neurological symptoms and medications. An aura was defined as fully reversible visual, sensory, speech or other central nervous system symptoms which developed gradually, followed by migraine attacks or associated migraine symptoms.

Educational levels were divided into primary (less than 6 years of education), middle (6–9 years), high (9–12 years) and advanced (more than 12 years). BMI was divided into underweight (<18.5 kg/m^2), normal (≥18.5 kg/m^2), overweight (≥24 kg/m^2) and obesity (≥28 kg/m^2) according to the categorisation of BMI groups for Chinese adults released by the Ministry of Health of the People's Republic of China.[22] Smoking was defined as having at least one cigarette per day for more than 1 year. Alcohol consumption was defined as having at least one drink a week for more than half a year. Regular tea was defined as having tea at least three times a week for more than half a year, similar to regular coffee. Mental health symptoms were evaluated using the Pittsburgh Sleep Quality Index,[23] the 9-item Patient Health Questionnaire[24] and the 7-item Generalised Anxiety Disorder Scale.[25]

PFO screening test

Next, cTTE data were acquired using a Philips IE 33 with 1–5 MHz or 3–8 MHz multiplane transducers to assess for the presence of PFO. This was performed by two experienced sonographers who also jointly reviewed all videotapes and were unaware of the participants' clinical data.

A microbubble bolus from an agitated solution of 8 mL saline, 1 mL blood and 1 mL air was injected into the antecubital veins to increase sensitivity.[26] Prior to the examination, the sonographers informed the participants about VM. Participants were assessed for PFO at rest and during provocative manoeuvres (VM and coughing). Positive for the presence of a PFO was considered to be present if microbubbles were present in the left atrium or ventricle within three cardiac cycles from maximum right atrial opacification.[26] The degree of right-left shunt (RLS) was quantified based on the maximum value of detected microbubbles per frame in the left atrium at rest or during provocative manoeuvres: grade I (1–10), grade II (11–30) and grade III (>30 or the left atrium is filled with microbubbles).[26]

Statistical analysis

Continuous variables were described as mean and SD (mean±SD) and compared using a t test. Categorical variables were described as frequencies and percentages and compared using a X^2 test. All analyses were carried out using SAS (V.9.4) and R (V.4.1.0). A value of p<0·05 was considered statistically significant.

Chained equations (fully conditional specification) were used for the multiple imputation of absent data, and the imputation number was increased to 25. We used Rubin's rules to merge the outcomes of multiple data sets. Baseline characteristics of patients with and without PFO were matched using the propensity score method of 1:2 nearest neighbour matching with a calliper of 0.02 times the pooled estimate of the SD of the propensity score. In order to ensure the stability of the multiple imputation of absent data, two binary logistic regression models were set up to estimate the individual propensities for PFO, one model only adjusting for age and gender (no missing values), and another model adjusting for all variables (age, gender, educational level, BMI, smoking, alcohol drinking, regular tea, regular coffee, family history of migraine and mental health status). Covariate balance was assessed by the standardised mean difference and considered good when the absolute standardised mean difference was under 0.1. Next, we calculated ORs and 95% CIs to probe the risk of migraine among patients with PFO. We then conducted additional sensitivity analyses to prove the stability of our model, including 1:1 nearest neighbour matching (with a calliper of 0.02 times the pooled estimate), 1:3 nearest neighbour matching (with a calliper of 0.02 times the pooled estimate), variable ratio matching (without calliper), full matching (without calliper) and inverse probability of treatment weighting (with stabilised IPTW weights).

We further analysed how PFO differentially influenced the development of MO disease across different RLS grades by generalised overlap weighting.[27] Similarly, the estimation of generalised propensity scores was used by a multinomial logistic model. In one, we controlled for the effects of age and gender; in another, we adjusted all aforementioned variables. Subsequently, each grade of the RLS will have a propensity score. In the case of the four groups, since any two groups can be compared, each covariate has multiple standardised differences. For simplicity, we used the maximum value of the absolute value of multiple standardised differences for each covariate. Because generalised overlap weighting smoothly down weighted the units with propensity scores close to 0 or 1, we considered it a continuous version of direct trimming. Finally, we estimated the SE and CI based on the robust variance estimator.

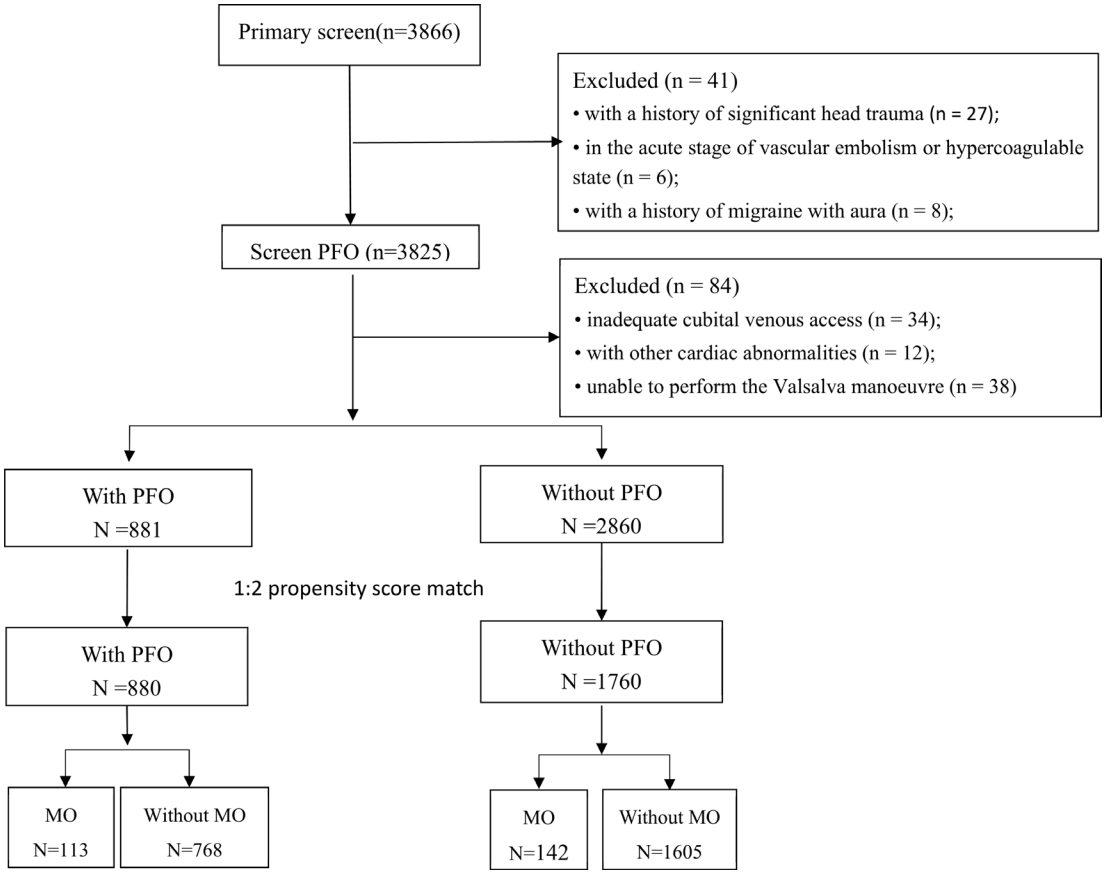

Figure 1 The flow of participants in this study. MO, migraine without aura; PFO, patent foramen ovale.

RESULTS

Demographics and operative details

Figure 1 represents the flow of the participants in this study. A total of 3741 participants fulfilled all inclusion/exclusion criteria and agreed to participate in the study.

The mean age (SD) of these participants was 50.90 (7.37) years, and the ratio of women was 74.5% (2786/3741). Among them, 881 (23.5%) participants were diagnosed as PFO-positive (666 women, mean age (SD): 50.27 (7.53) years) and 2860 as PFO-negative (2120 women, mean age (SD): 51.09 (7.31) years). Following a more detailed division, 2.25% (84 of 3741) had an RLS of grade I, 5.21% (195 of 3741) had an RLS of grade II and 16.09% (602 of 3741) had an RLS of grade III.

The positive rate of MO in the PFO group was 12.83%, which was significantly higher than that in the group without PFO (7.83%, p<0.0001). Additional baseline features are reported in table 1 and the number of participants with missing data for each variable are reported in online supplemental table A.

Propensity score matching for groups with and without PFO

Following 1:2 matching, the standardised mean differences of all variables were less than 0.1 without exception, meaning that the balance was better (details are shown in online supplemental table B). Propensity score-matched populations were generated to adjust for baseline differences and are reported in table 2 with outcomes.

Participants diagnosed with PFO showed a marked increase in the MO ratio compared with the other participants (12.79% vs 8.12%, p=0.0004, table 2). Following full adjustment, logistic regression analyses showed that PFO increased the risk of migraine (OR=1.71, 95% CI 1.19 to 2.47). The association remains significant in the adjustment model only by age and sex (OR=1.66, 95% CI 1.18 to 2.32). Multiple additional sensitivity analyses in the two adjustment models yielded similar results (details are shown in figure 2).

The relationship between RLS severity and MO

The details of the generalised overlap weighting are presented in online supplemental tables C and D. Controlling for the effects of age and gender, individuals who had a PFO with large shunts were 1.69 times more likely to report experiencing MO (OR=1.69, p<0.0001, 95% Cl 1.25 to 2.29). This significant effect was partially strengthened after controlling for all variables. In the fully adjusted model, individuals who had a PFO with

Table 1 Demographic characteristics after multiple imputation

Variable	Without PFO (n=2860)	With PFO (n=881)	SMD	P
Propensity score	0.2337 (0.0361)	0.2413 (0.0383)	0.1993	0.0060
Mean (SD) age, years	51.09 (7.31)	50.27 (7.53)	0.1106	0.0038
Gender, n (%)			0.0339	0.3816
Female	2120 (74.13)	666 (75.60)		
Male	740 (25.87)	215 (24.40)		
BMI, n (%)				0.7874
Underweight	76 (2.65)	21 (2.33)	0.0204	
Normal	1451 (50.72)	464 (52.62)		
Overweight	1051 (36.76)	312 (35.38)	0.0287	
Obesity	282 (9.88)	85 (9.67)	0.0076	
Educational level, n (%)				0.1878
Primary	940 (32.86)	254 (28.84)		
Middle	1349 (47.18)	439 (49.84)	0.0533	
High	416 (14.56)	140 (15.88)	0.0368	
Advanced	154 (5.40)	48 (5.44)	0.0073	
Smoking, n (%)	476 (16.64)	143 (16.20)	0.0126	0.7564
Alcohol, n (%)	430 (15.03)	134 (15.23)	0.0077	0.8492
Tea, n (%)	801 (28.01)	232 (26.29)	0.0387	0.3286
Coffee, n (%)	36 (1.25)	15 (1.68)	0.0352	0.3917
Sleep quality, mean (SD)	3.82 (2.48)	3.71 (2.46)	0.0451	0.2691
Anxiety, mean (SD)	1.01 (2.28)	1.10 (2.42)	0.0355	0.3734
Depression, mean (SD)	1.03 (2.10)	1.10 (2.14)	0.0320	0.4232
Family migraine, n (%)	355 (12.41)	141 (16.05)	0.1042	0.1001

BMI, body mass index; PFO, patent foramen ovale; SMD, standardised mean difference.

Table 2 Demographic characteristics (matched)

	Matched			
Variable	Without PFO (n=1747)	With PFO (n=880)	SMD	P
Propensity score	0.2404 (0.0370)	0.2411 (0.0379)	0.0004	0.6645
Mean (SD) age, years	50.37 (7.53)	50.28 (7.51)	0.0090	0.7850
Gender, n (%)			0.0128	0.7710
Female	1323 (75.75)	665 (75.59)		
Male	424 (24.25)	215 (24.41)		
BMI, n (%)				0.9760
Underweight	39 (2.21)	20 (2.33)	0.0108	
Normal	923 (52.81)	463 (52.59)		
Overweight	618 (35.37)	312 (35.41)	0.0107	
Obesity	168 (9.61)	85 (9.67)	0.0146	
Educational level, n (%)				0.9880
Primary	503 (28.77)	254 (28.86)		
Middle	874 (50.04)	439 (49.84)	0.0152	
High	277 (15.88)	140 (15.87)	0.0118	
Advanced	93 (5.31)	48 (5.44)	0.0128	
Smoking, n (%)	283 (16.19)	143 (16.22)	0.0113	0.8218
Alcohol, n (%)	263 (15.08)	134 (15.24)	0.0126	0.7824
Tea, n (%)	453 (25.90)	231 (26.28)	0.0147	0.7437
Coffee, n (%)	27 (1.55)	14 (1.63)	0.0090	0.8082
Sleep quality, mean (SD)	3.70 (2.41)	3.71 (2.46)	0.0137	0.8725
Anxiety, mean (SD)	1.06 (2.39)	1.09 (2.41)	0.0108	0.7587
Depression, mean (SD)	1.07 (2.20)	1.10 (2.13)	0.0096	0.8023
Family migraine, n (%)	266 (15.21)	141 (15.98)	0.0111	0.6238
MO, n (%)	142 (8.12)	113 (12.79)		0.0004

BMI, body mass index; MO, migraine without aura; PFO, patent foramen ovale; SMD, standardised mean difference.

large shunts were 1.65 times more likely to report experiencing MO (OR=1.65, p<0.0001, 95% CI 1.23 to 2.22). However, a PFO with moderate or small shunts was not.

DISCUSSION

This is the first community-based study in China to probe whether PFO can increase the risk of MO. In addition, all subjects were obtained from a prospective population cohort study in Southwest China and could undergo continuous follow-ups. This was a useful addition to existing epidemiological data and clinical research on PFO and MO in Southwest China. It showed that the MO ratio was higher in participants with PFO than in controls, especially in groups with large shunts.

An autopsy study of Hagen in 965 normal hearts revealed that PFO had a prevalence of 25.4% during the fourth through eighth decades.[28] In order to eliminate any possible interference of an extracardiac shunt, we used cTTE to evaluate the existence of PFO in this study. Our prevalence of PFO in the general population was 23.4%, which is similar to its universal prevalence. Our findings also estimated the ratio of MO in Han Chinese from the Sichuan Province to be similar to that in the Southeast Coast[29] or the Chinese mainland.[2]

The pathogenesis of migraine is complex. Current evidence demonstrates that various factors may increase the prevalence of migraine, including age, female sex, smoking, alcohol consumption, obesity, low educational status and family history.[30–32] Based on these known findings, we included all above variables in the propensity score model to balance the baseline characteristics as much as possible. By using various sensitivity analyses, we ensured the robustness of the results.

Our results are consistent with and extend the results of a large-scale case–control study by Wang *et al*, who found that the prevalence of RLS in MO was significantly higher than that in the healthy group (39.9% vs 29.4%, p<0.001).[14] Other studies have found that the prevalence of MO is similar in both populations with and without PFO.[18 19] However, as the author mentioned in the article, they ignored cohort studies, which are the best method for determining the incidence and natural history of a condition.[19]

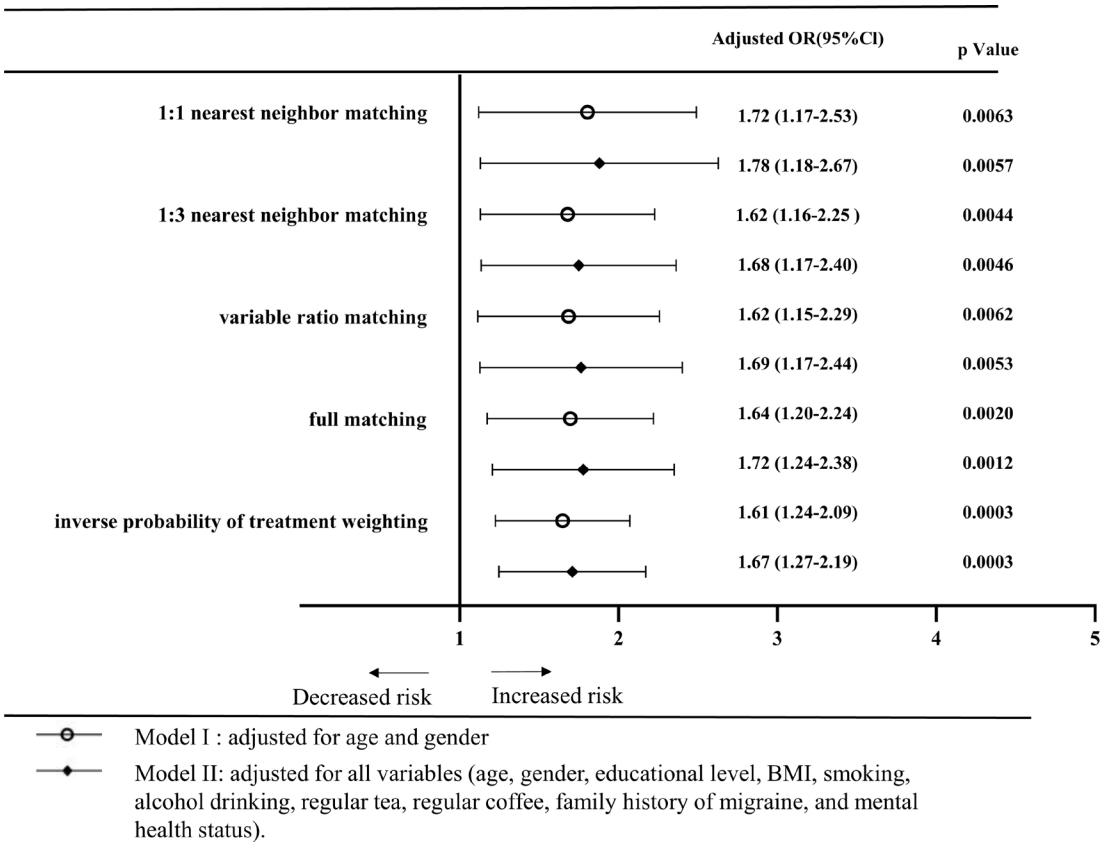

Figure 2 Multiple additional sensitivity analyses in two adjustment models for groups with and without PFO. BMI, body mass index; PFO, patent foramen ovale.

Our outcomes suggest that routine screening for PFO in migraine patients who are not responsive to treatments or find their medical therapy dissatisfactory may be necessary. With the help of various portable medical devices, it is possible to carry out migraine and PFO screening in the community, even in underdeveloped regions such as Southwest China. Given the finding that only 25% of patients who consulted a healthcare professional received an accurate migraine diagnosis,[5] it may be more meaningful to disseminate and implement migraine guidelines to community-oriented primary care than neurologists, which can markedly improve access to high-quality management for patients with migraine, reducing the consumption of health resources and socioeconomic burden.

There are some limitations to this study: first, a recall bias could not be excluded. Second, PFO increases the risk of cryptogenic stroke, and some residents failed to participate in this study due to death or physical disability from stroke. Thus, the prevalence of migraine in the PFO group may be underestimated.

CONCLUSION

In summary, in this study, based on the community population hitherto in China, we confirmed that PFO can increase the risk of MO, especially in groups with large shunts. Future work will continue to track respective cerebrovascular events and seek to understand if better management of PFO conditions improves migraine and whether primary screening for PFO should be carried out on a routine basis in patients with migraine who are not responsive to treatments or find their medical therapy dissatisfactory.

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Contributors LC is responsible for the overall content as a guarantor. LC and YT conceived and designed the work. YT conducted the study, carried out the statistical analysis and drafted the manuscript. AP and BP were involved in data collection and interpretation. LC involved in critical revision of the article and final approval of the version to be published. SH, XZ, YZ, WL and TS contributed to the acquisition of data. All authors have agreed to be accountable for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (2018-491). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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