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Risk factors for the development of cryptogenic stroke and the predictive value of right-to-left shunt in patent foramen ovale

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Abstract. – OBJECTIVE: The purpose of this study was to evaluate the relationship between the right-to-left shunt of the patent foramen ovale and the risk score for paradoxical embolism in cryptogenic stroke, as well as the risk factors for the development of cryptogenic stroke.

PATIENTS AND METHODS: A retrospective analysis was performed on 257 patients with cryptogenic stroke who were diagnosed and treated in our hospital from February 2020 to January 2022 as a study group, and 98 patients who were diagnosed and treated at the Department of Neurology in our hospital at the same time and excluded from stroke, were selected as the control group. Transcranial Doppler ultrasound acoustic contrast testing was used to grade right-to-left shunts of patent foramen ovale. Clinical information of individuals who had cryptogenic strokes was examined. The correlation between the right-to-left shunt of patent foramen ovale and the risk score for both cryptogenic stroke and paradoxical embolism was analyzed. The factors affecting the occurrence of cryptogenic stroke were investigated. The correlation between right-to-left shunt and paradoxical embolism risk score was explored. Receiver operator characteristic curve (ROC) analysis was used to evaluate each factor's clinical usefulness in predicting the occurrence of cryptogenic stroke.

RESULTS: No difference was observed in the history of hypertension, low-density lipoprotein, C-reactive protein and fibrinogen between the control group and the study group ($p<0.05$). In the study group with patent foramen ovale, the proportion of patients with grades I and II of the right-to-left shunt of patent foramen ovale was significantly lower than that in the control group, while the percentage of patients with grades III and IV was obviously greater than that in the control group ($p<0.05$). Right-to-left shunt grade, C-reactive protein, and fibrinogen were independent risk factors for cryptogenic stroke by logistic multivariate regression analysis ($p<0.05$). With an increase in the right-to-left shunt of the patent foramen ovale, patients' risk scores for paradoxical embolism increased considerably ($p<0.05$). In patients with cryptogenic stroke, the right-to-left shunt grade of the patent foramen ovale was positively connected with the paradoxical embolism risk score ($r=0.331$, $p<0.001$). ROC analysis results showed that the areas under the curves (AUC) of right-to-left shunt grading, C-reactive protein, and fibrinogen were 0.651, 0.871, and 0.779, respectively. The combination of the three indexes had an AUC of 0.908, a sensitivity of 87.90%, a specificity of 82.70%, and a Youden index of 0.706, indicating a high predictive value of the combination.

CONCLUSIONS: The right-to-left shunt of patent foramen ovale was an independent risk factor for cryptogenic stroke, which was positively correlated with the paradoxical embolic risk score. Its combination with clinical serologic indexes had a high clinical value for predicting cryptogenic stroke.

Key Words:
Patent foramen ovale, Right-to-left shunt, Cryptogenic stroke, Paradoxical embolic risk score.

Introduction

Stroke ranks as the second leading cause of mortality worldwide and is a major factor in the development of chronic disability. The incidence of stroke has significantly increased due to global population growth and the increase in the number of people over 65, especially in low- and middle-income developing countries[1]. To prolong interventional treatment and improve neurological function, neuroprotective therapeutic agents still need to be developed despite significant progress in postoperative recovery with continuous improvements in treatment.

The cause of cryptogenic strokes is unknown, accounting for about one-third of cases[2]. 27.3%

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of adults who have a patent foramen ovale are found[3] to have several pathological problems, the most significant of which is ischemic stroke. Compared to patients with strokes of known cause, patients with cryptogenic stroke have a greater incidence of patent foramen ovale[4]. In patients with cryptogenic stroke and patent foramen ovale, a patient-specific "patent foramen ovale-attributable fraction" may be determined using the paradoxical embolic risk score[5]. However, the relationship between the right-to-left shunt of the patent foramen ovale and the paradoxical embolic risk score in cryptogenic stroke is unclear.

Using transcranial Doppler ultrasound sonography, patients who had experienced a cryptogenic stroke were examined and categorized in order to explore the risk factors that influenced the development of cryptogenic stroke. Furthermore, we examined the relationship between the risk score for paradoxical embolism in cryptogenic stroke and the right-to-left shunt of the patent foramen ovale. In order to help with the clinical prevention and treatment of cryptogenic stroke, we aim to offer some references.

Patients and Methods

Study Population

A retrospective analysis was performed for 257 patients with cryptogenic stroke who were diagnosed and treated in our hospital from February 2020 to January 2022 as a study group. Among them, there were 147 cases of males and 110 cases of females, with a mean age of (53.79±8.46) years. According to the right-to-left shunt of the foramen ovale, patients were classified as grade I (68 cases), grade II (50 cases), grade III (78 cases), and grade IV (61 cases). The flowchart of patient selection is shown in Figure 1.

Inclusion criteria: (I) All study subjects met the diagnostic criteria regarding stroke[6], had an imaging diagnosis (rather than only a diagnosis of luminal infarct foci) and had a low-molecular-weight heparin diagnosis for an unexplained stroke. (II) The patient had complete clinicopathological data and had basic listening, reading and writing skills. (III) Informed consent was provided by patients and their families to participate in this study. Exclusion criteria: (I) Patients with ischemic stroke or lacunar cerebral infarction caused by cerebral small vessel disease with a clear etiology. (II) Patients who have experienced severe hepatic or renal dysfunction and cardiac dysfunction in the past. (III) Patients with concomitant infectious diseases or coagulation disorders. (IV) Patients with a previous history of transient ischemic attack, migraine, and syncope. (V) Patients with combined atrial septal defect and ventricular septal defect.

In addition, 98 patients who were diagnosed and treated in the Department of Neurology of our hospital at the same time and excluded from stroke, were selected as the control group. Among them, 53 cases were males, and 45 cases were females, with a mean age of (52.63±9.42) years. The study was approved by the the Ethics Committee of the Guang'an People's Hospital (approval number: 2020013) on January 13, 2020, and all methods were carried out in accordance with the Helsinki Declaration.

Diagnosis of Right-to-Left Shunt in the Foramen Ovale

A transcranial Doppler ultrasonography (EXP-9D; Nanjing Aostai Biotechnology, Jiangsu, China) was used to diagnose the right-to-left shunt in the foramen ovale[7]. The patient was positioned in the left lateral position with their head tilted to the right, and the venous access was on the left. A 1.6 MHz pulsed probe was used to detect the middle cerebral artery in the right temporal window, with a monitoring depth of 40-60 mm. Blood flow decreased but did not return to baseline when the ipsilateral common carotid artery was compressed, indicating that the detected vessel was the right middle cerebral artery. The parameters were adjusted to configure the contrast agent and the projectile injection. The bolus monitoring software was opened by the contrast surgeon after the injection, and within 25 seconds, the microbubbles (high signal) passing *via* the M-mode of the c-transcranial Doppler ultrasound sonogram were observed and recorded. Concurrently, the sonographer observed the right atrium for the passage of microbubbles into the left atrium and left ventricle during three cardiac cycles subsequent to the contrast injection. After a 5-minute break, the embolic monitoring software was turned back on to inject 10 ml of contrast agent, and the patient was told to perform the normal Valsalva maneuver after 5 seconds. The aforementioned test was repeated by the imaging doctor and sonographer, who alternated between doing the Valsalva maneuver for the aforesaid operation once every five minutes.

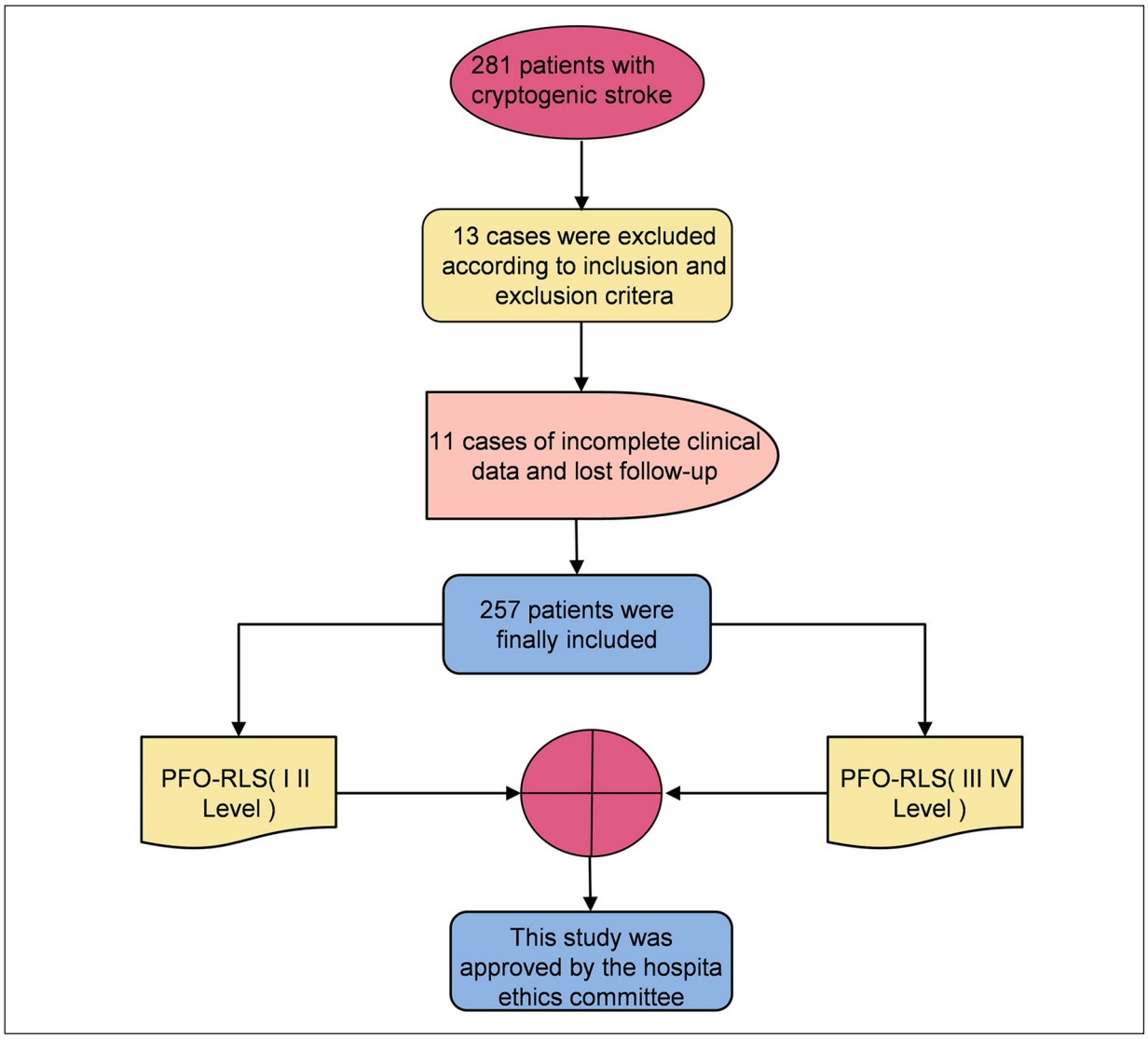

Figure 1. Flowchart of patient selection. PFO-RLS: patent foramen ovale right-to-left shunt.

Grading of the right-to-left shunt of the foramen ovale based on the count of emboli within 20 seconds: 1-10 emboli for grade I, 11-25 emboli for grade II, >25 emboli for grade III, and rain curtain-like emboli for grade IV.

Observation Indicators

Clinical data, including age, gender, smoking history, alcohol history, stroke history, deep vein thrombosis, right-to-left shunt grading, lipids, C-reactive protein, and fibrinogen, were collected.

The paradoxical embolism risk score was analyzed according to the study by Kent et al[8]: Five items, including the history of hypertension, history of diabetes, history of stroke or transient ischemic attack, smoking room, cortical infarction, and age, were used for the analysis, with a total of 10 points. A lower score indicated a more severe disease.

Statistical Analysis

Count data, such as gender, history of alcohol consumption, smoking history, past history, deep vein thrombosis, and right-to-left shunt were expressed as [cases (%)] and compared by χ^2 test. The measurement data, such as age, blood lipids, C-reactive protein, and fibrinogen, were tested

for normality and were found to all conform to the normal distribution, which was expressed in the form of mean ± standard deviation (SD). To determine the variables impacting the occurrence of cryptogenic stroke, multivariate logistic regression was used for the analysis. Pearson correlation test was used to analyze the correlation between the right-to-left shunt of patent foramen ovale and cryptogenic stroke and paradoxical embolism risk scores. Receiver operator characteristic curve (ROC) curves were used to analyze the clinical value of each factor in predicting the occurrence of cryptogenic stroke, as well as the clinical value of right-to-left shunt grading, C-reactive protein, fibrinogen and combined prediction of cryptogenic stroke. SPSS 24.0 (IBM Corp., Armonk, NY, USA) software was used for statistical data analysis in this study, and differences were considered statistically significant when $p<0.05$.

Results

Clinical Characteristics

No difference was observed in age, sex, history of smoking, history of alcohol consumption, history of diabetes, deep vein thrombosis, total cholesterol, triglycerides, and high-density lipoprotein between the control group and the study group ($p>0.05$). However, there were significant differences in the history of hypertension, low-density lipoprotein, C-reactive protein, and fibrinogen between the control group and the study group ($p<0.05$, Table I).

Relationship Between Right-to-Left Shunt of Patent Foramen Ovale and Cryptogenic Stroke

In the study group with patent foramen ovale, the proportion of patients with grades I and II of the right-to-left shunt of patent foramen ovale was significantly lower than that in the control group, while the percentage of patients with grades III and IV was obviously greater than that in the control group ($p<0.05$, Figure 2 and Table II).

Multivariate Analysis of Influences on the Occurrence of Cryptogenic Stroke

Right-to-left shunt grading, C-reactive protein, and fibrinogen were independent risk factors for cryptogenic stroke according to multivariate logistic regression analysis ($p<0.05$, Table III).

Relationship Between Right-to-Left Shunt and Paradoxical Embolic Risk Score in Patent Foramen Ovale

With an increase in the right-to-left shunt of the patent foramen ovale, patients' risk scores for paradoxical embolism increased considerably ($p<0.05$, Table IV).

Table I. Clinical characteristic of patients with cryptogenic stroke.

	Control group (n = 98)	Research group (n = 257)	χ^2/t	p
Age (years)	52.63 ± 9.42	53.79 ± 8.46	1.119	0.264
Gender (%)			0.280	0.597
Male	53 (54.08)	147 (57.20)		
Female	45 (45.92)	110 (42.80)		
Smoking (%)			0.414	0.520
Yes	36 (36.73)	104 (40.47)		
No	62 (63.27)	153 (59.53)		
Alcohol intake (%)			0.596	0.440
Yes	17 (17.35)	54 (21.01)		
No	81 (82.65)	203 (78.99)		
Hypertension (%)	22 (22.45)	99 (38.52)	8.157	0.004
Diabetes mellitus (%)	9 (9.18)	31 (12.06)	0.588	0.443
Deep vein thrombosis (%)			0.298	0.585
Yes	2 (2.04)	8 (3.11)		
No	96 (97.96)	249 (96.89)		
Lipid (mmol/L)				
Total cholesterol	4.36 ± 1.25	4.59 ± 1.74	1.196	0.233
Triglycerides	1.74 ± 0.61	1.85 ± 1.18	0.879	0.380
Low-density lipoprotein	2.48 ± 0.76	2.75 ± 1.03	2.361	0.019
High-density lipoprotein	1.14 ± 0.41	1.06 ± 0.53	1.348	0.179
C-reactive protein (mg/L)	1.83 ± 1.35	5.42 ± 2.13	15.530	< 0.001
Fibrinogen (g/L)	2.61 ± 0.74	3.38 ± 0.71	9.028	< 0.001

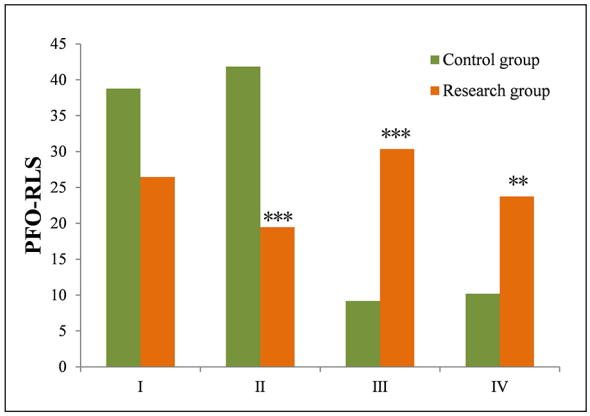

Figure 2. Relationship between right-to-left shunt of unclosed foramen ovale and cryptogenic stroke. PFO-RLS: patent foramen ovale right-to-left shunt. $^{**}p < 0.01$, $^{***}p < 0.001$ *vs*. Control group.

Correlation of Right-to-Left Shunt Classification with Paradoxical Embolic Risk Score

Pearson's correlation analysis revealed that the right-to-left shunt grade of the patent foramen ovale was positively connected with the paradoxical embolism risk score in patients with cryptogenic stroke (r=0.331, $p<0.001$, Figure 3).

Clinical Value of ROC Curve Analysis of Each Factor in Predicting the Occurrence of Cryptogenic Stroke

The results of ROC analysis showed that the AUC of right-to-left shunt grading, C-reactive protein, and fibrinogen to predict the occurrence of cryptogenic stroke were 0.651, 0.871, and 0.779, respectively. The AUC of the combination of three indexes was 0.908, with a sensitivity of 87.90%, a specificity of 82.70%, and a Youden index of 0.706, suggesting a high predictive value of the combination of the three (Table V, Figure 4).

Discussion

The current study discovered that right-to-left shunt grading, C-reactive protein, and fibrinogen were all independent risk factors for cryptogenic

Table II. Relationship between right-to-left shunt of unclosed foramen ovale and cryptogenic stroke.

Group	N	I	II	III	IV
Control group	98	38 (38.78)	41 (41.84)	9 (9.18)	10 (10.20)
Research group	257	68 (26.45)	50 (19.46)	78 (30.35)	61 (23.74)
χ^2		5.139	18.643	17.180	8.119
p		0.023	< 0.001	< 0.001	0.004

Table III. Multivariate analysis of influences on the occurrence of cryptogenic stroke.

Indicators	B	SE	Wald	*p*	OR	95% CI	
						Upper	Lower
Hypertension	0.357	0.227	3.512	0.483	1.952	1.225	4.173
Right-to-left shunt	0.625	0.425	10.335	< 0.001	2.818	1.225	7.260
Low-density lipoprotein	0.267	0.317	2.208	0.158	1.020	0.828	2.627
C-reactive protein	0.618	0.367	6.517	0.003	2.532	1.346	3.810
Fibrinogen	0.846	0.505	8.557	0.001	3.186	1.684	5.846

Table IV. Relationship between right-to-left shunt and paradoxical embolic risk score in patent foramen ovale.

Group	N	Paradoxical embolism risk score
Right-to-left shunt class I	68	4.12 ± 1.20
Right-to-left shunt class II	50	4.71 ± 1.32
Right-to-left shunt class III	78	5.26 ± 1.58
Right-to-left shunt class IV	61	5.47 ± 1.79
F		10.89
p		0.001

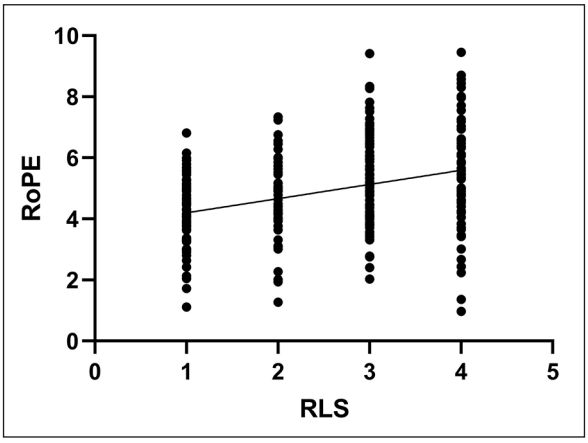

Figure 3. Correlation between right-to-left shunt and paradoxical embolism risk score in cryptogenic stroke with patent oval foramen.

stroke. Blood normally flows in a gradient from left to right because the left atrial pressure is typically higher than the right atrial pressure. However, by increasing pulmonary artery pressure, any disease that raises right atrial pressure can also induce right-to-left flow reversal[9]. According to this study, patients' paradoxical embolic risk scores rose dramatically as the right-to-left shunt of their patent foramen ovale widened. Furthermore, a high association was observed between the patients' right-to-left shunt and the paradoxical embolic risk score; that is, the greater the score, the greater the belief that the cryptogenic stroke was caused by a patent foramen ovale. Additionally, the ROC curve analysis demonstrated that the three variables – fibrinogen, C-reactive protein, and right-to-left shunt grading – had a better predictive value for the occurrence of cryptogenic stroke when combined than when evaluated separately. C-reactive protein, fibrinogen, and right-to-left shunt grading are crucial in determining the patient's status and estimating the likelihood of illness progression.

Related Research Progress and the Main Contribution of This Study

There are multiple potential causes of ischemic stroke, most of which are readily discernible by routine diagnostic evaluations[10,11]. However, in about 25% of cases, the etiology of stroke remains unknown. Unfortunately, the effectiveness of secondary preventive measures usually depends on the accurate and timely diagnosis of the underlying cause[12,13]. A study[14] has shown that ischemic stroke has a significant tendency to occur at a younger age. Hypertension, hyperlipidemia, diabetes, coronary heart disease, smoking, and alcohol abuse are common traditional risk factors. As studies on cryptogenic stroke have advanced, a novel and extensively applied method known as the TOAST system has emerged[15-17]. The TOAST system is widely used in both clinical practice and scientific research because of its ease of use. The congenital heart defect called patent foramen ovale is caused by the foramen ovale's inadequate closure[18,19]. Adults who still have a patent foramen ovale may be at risk for conditions including migraine and cryptogenic stroke[20]. A patent foramen ovale was discovered in over half of the individuals with cryptogenic stroke under 60, which was twice as common as in the general population[21]. It is unknown, therefore, if patent foramen ovale poses a separate risk for the occurrence of cryptogenic stroke.

Zhu et al[22] investigated the impact of morphologic features of the patent foramen ovale on the right-to-left shunt in patients with both patent foramen ovale and cryptogenic stroke, using transcatheter echocardiography and saline contrast transthoracic echocardiography. They discovered that the height of the patent foramen ovale and septal mobility were independent predictors of the effect of the right-to-left shunt. According to a report[23], venous emboli are a significant risk factor for cerebral infarction in patients with patent foramen ovale and are also a major contributor to blood abnormalities such as fibrinogen and C-reactive protein. Both C-reactive protein and fibrinogen are inflammatory markers. C-reactive protein is thought[24] to alter the conduction properties of atrial myocytes through atrial remodeling processes, which leave patients with a prothrombotic state. Furthermore, it has been suggested that C-reac-

Table V. Clinical value of ROC curve analysis of each factor in predicting the occurrence of cryptogenic stroke.

Variables	AUC	95% CI	*p*	Sensitivity	Specificity	Youden index
Right-to-left shunt	0.651	0.592-0.710	0.008	54.10%	80.60%	0.347
C-reactive protein	0.871	0.833-0.908	< 0.001	80.40%	81.00%	0.614
Fibrinogen	0.779	0.726-0.832	0.001	82.10%	59.20%	0.413
Combination	0.908	0.870-0.947	< 0.001	87.90%	82.70%	0.706

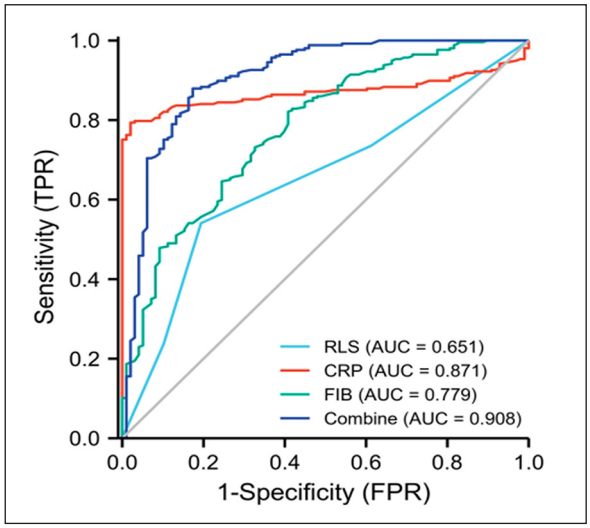

Figure 4. Clinical value of ROC curve analysis of each factor in predicting the occurrence of cryptogenic stroke.

tive protein may play a major role in atrial heart disease in cases of cryptogenic stroke. A study[25] has found that the increase in C-reactive protein, as a sensitive indicator of inflammation, is directly related to the occurrence of atherosclerosis and the risk of plaque rupture, which can identify the risk of disease in the population at an early stage and be used to evaluate the prognosis of the disease. Hemostasis or fibrinolysis, which normally maintains vascular integrity, can be disrupted, leading to the basic pathological endpoint of bleeding or thrombosis with vascular blockage[26]. *Via* a range of cellular receptors and mechanisms, fibrin can attach to leukocytes and change several aspects of inflammatory cell function[27], which can also have an impact on the body's hemodynamics and blood coagulation status, leading to venous thrombosis and affecting the onset and course of stroke[28,29]. Consequently, treating patients appropriately in light of the aforementioned contributing variables will aid in preventing or reducing the onset and progression of the illness.

Severe right-to-left shunts and large foramen ovale openings have been identified[30,31] as major causes of reverse embolism in stroke patients. Typically, the most recent thrombus is the source of arterial embolic thrombi in the larger circulation[32]. The patient's venous thrombus obstructs the main circulation arteries and causes a paradoxical embolism as it moves from the right heart to the left heart through a patent foramen ovale with a right-to-left shunt[33]. One clinical tool for detecting patients with strokes associated with patent foramen ovale is the paradoxical embolism score[34]. A high score for paradoxical embolism could indicate a higher risk of cryptogenic stroke and patent foramen ovale[35]. According to this study, patients' paradoxical embolic risk scores rose dramatically as the right-to-left shunt of their patent foramen ovale widened. Furthermore, a high association was observed between the patients' right-to-left shunt and the paradoxical embolic risk score; that is, the greater the score, the greater the belief that the cryptogenic stroke was caused by a patent foramen ovale. Additionally, the ROC curve analysis demonstrated that the three variables – fibrinogen, C-reactive protein, and right-to-left shunt grading – had a better predictive value for the occurrence of cryptogenic stroke when combined than when evaluated separately. C-reactive protein, fibrinogen, and right-to-left shunt grading are crucial in determining the patient's status and estimating the likelihood of illness progression. Thus, it provided evidence in favor of using the paradoxical embolic risk score for individuals who had experienced a cryptogenic stroke. Transcranial Doppler ultrasonography was also advised for individuals who scored highly on cryptogenic stroke in order to help identify the origin of the condition and enable quick symptomatic therapy.

Limitation and Future Scope

However, due to the small sample size, the findings of this study were not representative of all patients. As a retrospective analysis, the results might be biased to some extent. There is still a need to expand the sample size and use prospective studies for further analysis.

Conclusions

Right-to-left shunt grade, C-reactive protein, and fibrinogen were independent risk factors for cryptogenic stroke. The right-to-left shunt grade was significantly positively correlated with the paradoxical embolic risk score of cryptogenic stroke, and the combined detection with clinical serological indicators had high clinical value in predicting cryptogenic stroke. This study played an important role in guiding the treatment of patients with clinically related diseases, improving the prognosis of patients with cryptogenic stroke, and improving the quality of life of patients by understanding the correlation between patent foramen ovale right-to-left shunt and the paradoxical embolism risk score.

Conflict of Interest
The authors declare that they have no conflict of interests.

Ethics Approval
This study was approved by the Ethics Committee of the Guang'an People's Hospital (approval number: 2020013) on January 13, 2020, and all methods were carried out in accordance with Helsinki Declaration.

Informed Consent
Informed consent was obtained from participants and/or their legal guardians for participation in the study.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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None.

Authors' Contribution
B.D. confirmed the authenticity of all the raw data and edited the manuscript, YH.Y. collected data and processed the data. JH.H. and S.C. conducted the statistics. HH.M. revised the article. All authors read and approved the final manuscript.

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