Effect of Insulin Resistance on Recurrence after Radiofrequency Catheter Ablation in Patients with Atrial Fibrillation

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Abstract
Background Whether there are many risk factors for recurrence of atrial fibrillation (AF) after ablation is unclear. The aim of this study was to investigate the relationship between insulin resistance (IR) and AF recurrence in patients without diabetes who underwent catheter ablation.

Methods This retrospective study included patients who underwent AF ablation between 2018 and 2019 at the First Affiliated Hospital of Zhengzhou University. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated, and a value of ≥2.69 was defined as IR. The patients were divided into two groups (group 1 HOMA-IR < 2.69, n = 163; group 2 HOMA-IR ≥ 2.69, n = 69). AF recurrence was defined as the occurrence of atrial arrhythmias of more than 30 s after the first 3 months. Univariate and multivariable Cox regression models were used to analyse the risk of AF recurrence.

Results Overall, 232 patients were enrolled (mean age, 59.9 ± 10.2 years old; female, 37.5%; paroxysmal AF, 71.6%). We found that dyslipidaemia, antiarrhythmic drug use, fasting blood glucose and fasting insulin were significantly higher in the IR group (P < 0.05). During the follow-up 1 year after ablation, 62 (26.7%) patients experienced AF recurrence. After adjusting for traditional risk factors, multivariable analysis showed that the HOMA-IR value (HR 1.259, 95% CI 1.086–1.460, P = 0.002) and left atrial diameter (LAD; HR 1.043, 95% CI 1.005–1.083, P = 0.026) were independently associated with AF recurrence.

Conclusions The present results provide evidence that IR patients are more likely to experience AF recurrence. Improving IR status may be a potential target for reducing the postoperative recurrence rate.

Keywords Atrial fibrillation · Insulin resistance · Radiofrequency ablation · Recurrence

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in cardiovascular disease and can significantly increase the risk of heart failure, renal impairment and other diseases [1]. Radiofrequency catheter ablation (RFCA) is the main treatment for AF. However, patients with AF have a certain recurrence rate after ablation. The success rate remained at 70–90% at the 1-year follow-up after RFCA in patients with paroxysmal atrial fibrillation (PAF), and the success rate was even lower at 65–75% for persistent atrial fibrillation (PAF) [2, 3]. Many risk factors, such as hypertension, metabolic syndrome, sleep apnoea syndrome and other diseases, are associated with recurrence of AF after RFCA [4].

Insulin resistance (IR) is a state of decreased insulin response; the signs of IR include obesity, elevated blood glucose, dyslipidaemia and elevated blood pressure [5]. IR
is generally a component of metabolic syndrome and a precursor of diabetes mellitus (DM). Metabolic syndrome and diabetes mellitus are independent risk factors for recurrence after AF ablation [6, 7], and IR could also increase susceptibility to AF [8–10]. At present, the relationship between the recurrence rate after ablation and IR in patients with AF is not clear; thus, the aim of this study was to investigate the effect of IR on AF recurrence after RFCA.

Methods

Study Population

We conducted a retrospective observational study from January 2018 to July 2019 in individual centres in the First Affiliated Hospital of Zhengzhou University. A total of 321 patients with AF who underwent successful RFCA were screened for eligibility. The inclusion criteria were age ≥ 18 years and hospitalization for first RFCA. The exclusion criteria were DM, congenital heart disease, hypertrophic cardiomyopathy, valvular heart disease, treatment with glucocorticoids or nonsteroidal anti-inflammatory drugs, thyroid dysfunction and hepatorenal insufficiency. A participant was considered to have DM if he or she had previously been diagnosed with DM, was currently taking medications for DM or had a glycated haemoglobin (HbA1c) level > 6.5%. The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

Date Collection

Demographic parameters and comorbidities were collected from patients’ medical records and included duration of AF, type of AF, body mass index (BMI), dyslipidaemia, hypertension, cerebrovascular disease, use of antiarrhythmic drugs (AADs) and statins before procedure, left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and heart rate (HR). Blood samples were obtained after at least eight hours of fasting within three days after hospitalization and before ablation; creatinine, uric acid, high-sensitivity C-reactive protein (HS-CRP), erythrocyte sedimentation rate (ESR), Hba1c, fasting plasma glucose (FPG), fasting insulin (FINS), total cholesterol, triglyceride, and high- and low-density lipoprotein cholesterol levels were measured. Intraoperative parameters, including linear ablation and superior vena cava (SVC) ablation, were recorded. The CHA2DS2-VASc score of each patient was calculated [11].

Definition of IR

IR was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = FPG (mmol/L) × FINS (μU/mL)/22.5 [12]. FPG was measured using the hexokinase method, and FINS was measured using the electrochemiluminescence method. In the National Health and Nutrition Examination Survey (NHANES III) study, 8608 people aged ≥20 years with nondiabetic HOMA-IR values ≥ 2.68 were defined as having IR [13]. Moreover, HOMA-IR values ≥ 2.69 in Chinese people were defined as IR [14, 15]. Previous studies have found subtle differences in the defined values of IR, which are attributed to different ethnic groups with different constitutions, and we defined HOMA-IR values ≥ 2.69 as IR according to the physical condition of the Chinese population [16].

Ablation Protocol and Periprocedural Management

Details of the RFCA procedure have been described in published studies [17]. Briefly, circumferential pulmonary vein isolation (CPVI) was performed in all patients with PAF, and isthmus line ablation was performed when typical atrial flutter was documented preoperatively or intraoperatively. For all patients with PeAF, the endpoint of ablation was CPVI, followed by bidirectional block of linear ablation across the left atrial roof, mitral isthmus and cavotricuspid isthmus. If AF could not be terminated after the above ablation, synchronous direct current cardioversion was necessarily converted to sinus rhythm. In addition, electrical isolation of the SVC was performed if induced tachycardia suggested an origin of the SVC or if the potential of the SVC was active in all patients with AF. If no AF induction was confirmed via coronary sinus electrode burst pacing, the procedure was deemed completed.

The patients took AADs for 3 months after ablation to prevent early recurrence of AF. All patients were taking non-vitamin K oral anticoagulants (NOACs) or warfarin (INR of 2.0–3.0) for at least 3 months. Continuation of anticoagulation therapy was determined according to the AHA/ACC/HRS guidelines [18] and was decided jointly by the patient and physician.

Outcome and Follow-Up

The definition of AF recurrence was documented AF, atrial flutter or atrial tachycardia (AT) lasting >30 s recorded on ECG or by 24-h Holter monitoring after a 3-month blanking period. Each participant was followed up at 3, 6, 9 and 12 months after ablation in the outpatient setting or by telephone, and the follow-up endpoint was the recurrence of
AF or up to 1 year. An electrocardiogram (ECG) and/or 24 h Holter monitoring were recommended at each follow-up visit. There was no difference in Holter surveillance for asymptomatic patients between the IR and no IR groups after ablation. Each patient visited the outpatient department of the hospital in a timely manner, and ECG and Holter monitoring were recommended to patients when they experienced any symptoms suggesting AF recurrence. If recurrence occurred, the time of AF recurrence was recorded.

**Statistical Analysis**

Continuous data are described as the mean ± standard deviation or median (IQR, interquartile range), and categorical data are summarized as frequencies (percentages). Continuous variables were compared between the two groups using Student’s t test or Mann–Whitney test depending on whether the data were normally distributed. Categorical variables were compared between two groups by the χ² test or Fisher’s exact test. Kaplan–Meier curves were used to analyse the AF-free survival rate after ablation. Univariate and multivariate Cox regression was used to evaluate the risk of AF recurrence. In the multivariate Cox regression analysis, to address potential confounding, variables with P < 0.01 in the univariate analysis and the important recurrence-related clinical factors AF, AF type, duration of AF, HS-CRP, BMI and CHA2DS2-VASC score ≥ 2 were substituted into the multivariate analysis. Subgroup analyses were performed based on the type of AF. All statistical analyses were performed by SPSS software (version 21.0) and GraphPad Prism (version 9.0). All statistical tests were two-sided, and a value of P < 0.05 was considered indicative of significance.

**Results**

**Patient Characteristics**

Of the 321 AF patients who underwent ablation and were screened, 232 patients were eligible for the study. The participants were divided into two groups, patients (n = 163, 70.3%) with HOMA-IR < 2.69 in group 1 and those with HOMA-IR ≥ 2.69 (n = 69, 29.7%) in group 2 (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. The continuous variables age, BMI, HR, TC, HbA1c, FPG, LAD, LVEF and LVEDD were normally distributed and were therefore analysed by a t test; FINS, HOMA-IR and other continuous data that were not normally distributed were analysed by the Mann–Whitney test. The mean age was 59.9 ± 10.2 years old, and 87 (37.5%) patients were female. The mean BMI was 24.7 ± 2.7 kg/m², 163 (70.3%) patients had PAF, and 69 (29.7%) patients had PeAF. The patients HOMA-IR value was 2.0 (IQR 1.4, 2.9) (Supplementary Material Table 1). Compared to the patients without IR, those with IR were more likely to have dyslipidaemia (63.8% vs. 48.5%, P = 0.033) and to take AADs before the procedure (86, 52.8% vs. 49, 71.0%, P = 0.010). FPG (5.7 ± 1.2 vs. 4.8 ± 0.9, P < 0.001), FINS [13.8 (IQR
The Incidence of AF Recurrence

During the follow-up period of 1 year after ablation, 62 (26.7%) patients experienced recurrence after RFCA. The Kaplan–Meier time-to-event curves revealed a higher recurrence rate in group 2 than in group 1 [40.6% (28/69) vs. 20.9% (34/163) at 1 year, \( P = 0.001 \)], as shown in Fig. 2.

**Table 1** Baseline characteristics of patients with and without insulin resistance

|                       | Group 1 (no IR group, n = 163) | Group 2 (IR group, n = 69) | \( P \)  |
|-----------------------|-------------------------------|-----------------------------|--------|
| Female                | 61 (37.4)                     | 26 (37.7)                   | 0.970  |
| Age, years            | 60.4 ± 10.1                   | 58.9 ± 10.3                 | 0.324  |
| BMI, kg/m\(^2\)       | 24.6 ± 2.8                    | 25.1 ± 2.4                  | 0.220  |
| Smoking habits        | 52 (31.9)                     | 19 (30.2)                   | 0.510  |
| AF type               |                               |                             | 0.906  |
| Paroxysmal            | 117 (71.8)                    | 49 (71.0)                   |        |
| Persistent            | 46 (28.2)                     | 20 (29.0)                   |        |
| Hypertension          | 77 (47.2)                     | 39 (56.5)                   | 0.196  |
| Cerebrovascular disease | 15 (9.2)                   | 8 (11.6)                    | 0.577  |
| Dyslipidemia          | 79 (48.5)                     | 44 (63.8)                   | 0.033  |
| Duration of AF, > 5 years | 37 (22.7)       | 22 (31.9)                   | 0.142  |
| AADs                  | 86 (52.8)                     | 49 (71.0)                   | 0.010  |
| Statins               | 72 (44.2)                     | 28 (40.6)                   | 0.614  |
| HR, bpm               | 78.7 ± 17.4                   | 79.6 ± 19.0                 | 0.743  |
| Cr, µmol/l            | 74 (64, 85)                   | 84 (63, 72)                 | 0.379  |
| UA, mmol/l            | 305 (252, 368)                | 284 (233, 366)              | 0.376  |
| TG, mmol/l            | 1.3 (0.9, 1.9)                | 1.6 (1.0, 2.2)              | 0.136  |
| TC, mmol/l            | 3.7 ± 1.0                     | 3.9 ± 0.9                   | 0.258  |
| HDL-C, mmol/l         | 1.2 (0.9, 1.8)                | 1.7 (1.1, 2.5)              | 0.706  |
| LDL-C, mmol/l         | 2.6 (1.9, 3.3)                | 2.7 (2.0, 3.5)              | 0.712  |
| HS-CRP, mg/l          | 3.1 (1.6, 5.5)                | 3.9 (1.6, 6.2)              | 0.322  |
| ESR, mm/l             | 10.8 (8, 14.0)                | 11.8 (9.7, 13.9)            | 0.134  |
| HbA1c, %              | 5.8 ± 0.6                     | 5.9 ± 0.6                   | 0.625  |
| FPG, mmol/L           | 4.8 ± 0.8                     | 5.8 ± 1.3                   | <0.001 |
| FINS, µU/mL           | 8.2 (6.0, 9.9)                | 13.8 (12.2, 16.3)           | <0.001 |
| HOMA-IR               | 1.7 (1.3, 2.1)                | 3.3 (2.9, 4.0)              | <0.001 |
| LAD, mm               | 39.5 ± 6.5                    | 40.4 ± 6.6                  | 0.356  |
| LVEF, %               | 60.8 ± 6.6                    | 60.5 ± 7.8                  | 0.776  |
| LVEDD, mm             | 47.6 ± 5.3                    | 48.2 ± 6.1                  | 0.418  |

Group 1 was defined as HOMA-IR < 2.69 (no IR group); group 2 was defined as HOMA-IR ≥ 2.69 (IR group); Continuous data are presented as mean±standard deviation (SD) or median (interquartile range), and categorical data were shown as n (%)  

Abbreviations: AF, atrial fibrillation; BM, body mass index; AADs, antiarrhythmic drugs; HR, heart rate; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HS-CRP, high sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter

12.2, 16.3) vs. 8.2 (IQR 6.0, 9.9), \( P < 0.001 \) and HOMA-IR [3.3 (IQR 2.9, 4.0) vs. 1.7 (IQR 1.3, 2.1), \( P < 0.001 \)] were significantly higher in group 2 than in group 1.

**Risk Factors Associated with AF Recurrence**

All patients with AF were divided into the recurrence of AF group (\( n = 62, 26.7\% \)) and the no-recurrence of AF group (\( n = 170, 73.3\% \)) according to the follow-up results, there were 30 (48.4\%) recurrences of AF, 17 (27.4\%) of atrial flutter, and 15 (24.2\%) of AT. In the univariable analysis, patients with recurrence of AF after ablation had higher HOMA-IR values [2.5(IQR1.9, 3.6) vs. 1.8(IQR1.4, 2.6); HR 1.264, 95% CI 1.096 -1.457, \( P = 0.001 \)] and LAD [(41.7 ± 6.6)mm vs. (39.1 ± 6.4) mm; HR 1.046, 95% CI 1.009 -1.084, \( P = 0.015 \)]. There were no
significant differences in the type of AF, dyslipidaemia, duration of AF (>5 years), CHA2DS2-VASc score ≥ 2, HS-CRP, or BMI between the two groups (P > 0.05, Table 2 and Supplementary Material Table 1). In the multivariable Cox regression analysis, HOMA-IR (HR 1.259, 95% CI 1.086–1.460, P = 0.002) and LAD (HR 1.043, 95% CI 1.005–1.083, P = 0.026) remained independent predictive factors for AF recurrence (Table 2).

Subgroup Analysis

Among patients with PAF, 40 (24.1%) patient recurrence of AF after ablation. HOMA-IR (HR 1.219, 95% CI 1.027–1.448, P = 0.023) and LAD (HR 1.052, 95% CI 1.005–1.083, P = 0.026) remained independent predictive factors for AF recurrence (Table 2).

Discussion

The findings of this study provide important information about the risk of AF recurrence in patients without diabetes. IR is associated with a high recurrence rate after ablation in patients with AF. The association between a high HOMA-IR value and recurrence of AF after ablation remained in the subgroup analysis according to the type of AF. This could be important information in clinical decision-making in treating patients with AF ablation. AF ablation has a certain recurrence rate, which may be increased by many risk factors. Previous studies have shown that an increased LAD leads to left atrial remodelling, making recurrence rates higher after ablation in patients with AF [19, 20]. The results of this study also showed that a larger LAD in AF patients was associated with high recurrence rates after ablation, which was consistent with a previous study. However, the impact of IR on recurrence after AF ablation is unclear. A previous study showed that IR was a predictor of PAF recurrence.
after CPVI [21]. Our study is the first to report that high HOMA-IR levels in patients with AF were associated with a higher recurrence rate after ablation, whether for PAF or PeAF, and included 232 AF patients, which was more than the 114 AF patients in a previous study.

IR is a common feature of metabolic syndrome and diabetes mellitus and is a potential mechanism for the development of abnormal glucose metabolism [22]. IR is associated with abnormal obesity, obesity and hyperlipidaemia and can cause excessive fat accumulation in the body, causing the release of cytokines related to IR and resulting in the abnormal production of components of the signalling pathway in which insulin is active [23]. IR combined with obesity can aggravate the cardiac burden of patients, and poor weight control is one of the main causes of IR [24]. In this study, BMI was higher than normal in both groups, possibly because in all patients with AF, obesity is associated with the occurrence and development of AF [25]. There was a significantly higher use of AADs in the group with IR than in the group with no IR \( (P = 0.01) \). This appears to suggest an increased proportion of symptomatic AF in the group with IR, and IR may promote the development of AF and impair glucose tolerance in the body. There was no significant difference in LAD and LVEDD of HS-CRP between the two groups, possibly because IR has little effect on atrial structural remodelling. IR was found to not significantly alter atrial fibrosis and structural remodelling [26].

| Table 2 | Univariable and multivariable Cox regression hazard analysis for AF recurrence |
|---------|-------------------------------------|
|         | Univariable HR 95% CI P Multivariable HR 95% CI P |
| Female  | 1.137 0.684–1.889 0.620 0.644 0.376–1.103 0.109 |
| Smoking habits | 1.293 0.732–2.284 0.376 0.803 0.462–1.396 0.437 |
| Type of AF (PAF vs PeAF) | 0.768 0.401–1.135 0.138 0.981 0.591–1.628 0.941 |
| Hypertension | 0.663 0.401–1.099 0.111 0.985 0.903–1.106 0.999 |
| Dyslipidemia | 1.229 0.744–2.030 0.421 0.985 0.903–1.106 0.999 |
| Duration of AF (> 5 years) | 0.683 0.401–1.163 0.160 0.981 0.591–1.628 0.941 |
| CHA2DS2-VASc score ≥ 2 | 0.882 0.535–1.452 0.621 0.981 0.591–1.628 0.941 |
| Age | 1.007 0.983–1.032 0.561 0.985 0.903–1.106 0.999 |
| BMI | 1.001 0.909–1.103 0.982 1.001 0.909–1.103 0.982 |
| HR | 1.000 0.985–1.014 0.949 1.000 0.985–1.014 0.949 |
| Cr | 0.997 0.982–1.012 0.671 1.000 0.985–1.014 0.949 |
| UA | 0.999 0.997–1.002 0.646 1.000 0.985–1.014 0.949 |
| TG | 1.081 0.819–1.427 0.581 1.081 0.819–1.427 0.581 |
| TC | 1.121 0.864–1.456 0.390 1.121 0.864–1.456 0.390 |
| HDL | 0.771 0.525–1.133 0.185 0.771 0.525–1.133 0.185 |
| LDL | 1.090 0.958–1.241 0.191 1.090 0.958–1.241 0.191 |
| HbAlc | 0.826 0.531–1.286 0.397 0.826 0.531–1.286 0.397 |
| HS-CRP | 1.047 0.984–1.114 0.150 1.047 0.984–1.114 0.150 |
| ESR | 1.016 0.968–1.067 0.514 1.016 0.968–1.067 0.514 |
| LAD | 1.046 1.009–1.084 0.015 1.046 1.009–1.084 0.015 |
| LVEF | 1.002 0.966–1.039 0.935 1.002 0.966–1.039 0.935 |
| LVEDD | 1.004 0.961–1.048 0.874 1.004 0.961–1.048 0.874 |
| Linear ablation | 1.382 0.832–2.296 0.211 1.382 0.832–2.296 0.211 |
| SVC isolation | 0.585 0.278–1.230 0.157 0.585 0.278–1.230 0.157 |
| FPG, mmol/L | 1.165 0.951–1.427 0.139 1.165 0.951–1.427 0.139 |
| HOMA-IR | 1.264 1.096–1.457 0.001 1.264 1.096–1.457 0.001 |

Multivariate Cox regression analysis model included type of AF, duration of AF (> 5 years), CHA2DS2-VASc score ≥ 2, BMI, HS-CRP, LAD and HOMA-IR

Abbreviations: AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; BMI, body mass index; HR, heart rate; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated haemoglobin; HS-CRP, high sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; SVC, superior vena cava; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence interval; HR, hazard ratio
Shigematsu et al. suggested that IR accounted for a significantly higher proportion of nondiabetic hypertrophic cardiomyopathy patients with AF than hypertrophic cardiomyopathy patients with sinus rhythm. IR may be a potential mechanism that mediates the development of AF; impaired fasting glucose and impaired glucose tolerance could lead to interatrial conduction delay and formation of low-voltage areas [27]. Lee et al. found that high HOMA-IR levels were independently associated with an increased risk of AF in patients without diabetes and that high HOMA-IR levels were one of the main causes of AF in a nondiabetic population [28]. The recurrence rate of AF after ablation in patients with diabetes is higher than that in patients without diabetes, and metabolic abnormalities in diabetes play a role in promoting arrhythmia [29]. The recurrence of AF in the abnormal glucose metabolism group after catheter ablation was also significantly higher than that in patients in the normal glucose metabolism group [7]. IR leads to the slowing of conduction velocity in the left atrium and the formation of re-entry, aggravating atrial electrical remodelling and promoting recurrence after AF ablation [21]. In this study, HOMA-IR levels in patients with AF in the recurrence group...
were significantly higher than those in patients without AF recurrence. This may be because IR exacerbates the process of delayed atrial conduction velocity in patients with AF, which leads to continuous atrial electrical remodelling and causes an increase in the recurrence of AF.

At present, there are many patients with IR, but most IR patients do not receive regular treatment. In this study, the measurement of homa IR was performed before ablation. We found that HOMA-IR is helpful for predicting and should be performed before ablation to identify the presence or absence of IR and that regular treatment for IR may be given to decrease the recurrence rate of AF after ablation. Whether patients with IR should be followed up, if it is prudent to screen the glucose status and whether intervention of IR helps to reduce the recurrence rate after AF ablation has not been clarified. In clinical work, we insist that it is of great importance to AF patients with IR and treat patients with IR as early as possible. Further prospective research is also needed to clarify whether interventions to treat IR are beneficial in preventing the recurrence of AF.

Limitations

Several limitations existed in our study. First, the insulin clamp is the gold standard method for measuring IR, and HOMA IR is not the gold standard but a surrogate for IR, which may produce a bias. Second, this was a retrospective study that could not avoid information bias. The duration of AF was sometimes reported by the patients themselves, and there was no record of obstructive sleep apnoea (OSA) or drug treatment after ablation. In addition, this was a single-centre study with a small sample size, which may limit the generalizability of the results. Finally, the lack of a standardized arrhythmia detection strategy may limit the detection of asymptomatic recurrences. Whether IR is an independent predictor of recurrence of AF needs to be supported by more evidence in the future.

Conclusions

HOMA-IR and LAD were independent risk factors for AF recurrence after RFCA in AF patients without diabetes. IR in patients with AF is associated with a high recurrence rate after ablation.

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Author Contributions ZW: Designed the study and wrote the manuscript. YJW, ZYL, and QL: Contributed to writing of the manuscript. YWK: Participated in data analysis. YWC and YHS: Supervised the data acquisition, data analysis and interpretation. JZD: Verified the data extraction and reviewed the manuscript. All authors read and approved the final manuscript.

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Data Availability The data supporting the findings of this study are available on request.

Declarations

Conflict of Interest The authors declare that they have no conflicts of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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