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Correlation of oxidative stress and vascular endothelial dysfunction with hippocampal perfusion in atrial fibrillation patients with cognitive impairment

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Abstract

Objectives: To evaluate the correlation of oxidative stress and vascular endothelial dysfunction with hippocampal perfusion in patients with atrial fibrillation and cognitive impairment.

Methods: In total, 41 atrial fibrillation patients with cognitive impairment were compared to 45 atrial fibrillation patients without cognitive impairment. Oxidative stress, vascular endothelial dysfunction, hippocampal perfusion, and cognitive function were measured.

Results: Serum level of oxidized low-density lipoprotein was significantly higher in the atrial fibrillation + cognitive impairment group than in the atrial fibrillation group. Serum levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 were significantly higher, and nitric oxide was lower, in the atrial fibrillation + cognitive impairment group than in the atrial fibrillation group. The regional cerebral blood volume, mean transit time, and time to peak were significantly higher in the atrial fibrillation + cognitive impairment group than in the atrial fibrillation group. Moreover, regional cerebral blood flow was significantly lower in the atrial fibrillation + cognitive impairment group than in the atrial fibrillation group. Age, left atrial diameter, and regional cerebral blood volume were negatively correlated with the cognitive function score in the atrial fibrillation + cognitive impairment group. Serum levels of oxidized low-density lipoprotein, regional cerebral blood volume, regional cerebral blood flow, mean transit time, and time to peak were significantly correlated with cognitive impairment in atrial fibrillation patients after multivariate logistic regression analysis.

Conclusion: Hippocampal perfusion and oxidative stress were significantly correlated with cognitive impairment in atrial fibrillation patients.

Keywords

Oxidative stress, endothelial dysfunction, hippocampal perfusion, atrial fibrillation, cognitive impairment

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Introduction

Atrial fibrillation (AF) can occur in all patients with organic heart disease and some patients with non-organic heart disease. AF can threaten the health of patients and affect their quality of life due to its serious complications such as stroke and heart failure. It also increases the medical and financial burden on society and families. The Framingham study[1] found that the annual incidence of stroke in patients with AF was 3% to 5%, which was five times that of the normal population. AF is an independent risk factor for Alzheimer's disease, especially in elderly patients with AF.[2] Even in the absence of stroke, AF is an important risk factor for cognitive decline[3] and is associated with dementia and depression.[4]

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The hippocampus is located in the medial temporal lobe of the brain and is an important part of the limbic system of the brain. The hippocampus is closely involved in learning, memory, control of emotional behavior, and neuroendocrine function. Cognitive impairment (CI) refers to the impairment of any aspect of mental and intellectual activity in the brain, such as perception, memory, speech, abstract thinking, and other higher functions. CI is an important early symptom of dementia. In patients with amnestic mild CI (MCI), hippocampal atrophy is associated with memory decline and the risk of Alzheimer's disease progression.[5] Therefore, whether AF has abnormal hippocampal perfusion and whether it is correlated with CI has become a research hotspot.

Oxidative stress and endothelial dysfunction play important roles in the pathogenesis of AF.[5,6] Abnormal oxidative stress is closely associated with AF,[6] while endothelial dysfunction is closely associated with atrial remodeling, thereby increasing the susceptibility to AF.[7] In this study, oxidative stress levels, changes in endothelial injury markers, and hippocampal perfusion status in AF patients with or without CI were examined to investigate their correlations with CI in AF patients.

Materials and methods

Clinical data

Our case–control study population included 86 patients with AF who were hospitalized at the First Affiliated Hospital of Guangxi Medical University from December 2017 to July 2020. All patients underwent detailed medical history inquiry and physical examination, and routine biochemical examinations were performed on all patients in the morning. All patients underwent a 12-lead electrocardiogram after admission. The duration of AF was calculated from its signs on the electrocardiogram when the patient described sudden palpitations. The study protocol was approved by the hospital ethics committee of the First Affiliated Hospital of Guangxi Medical University (approval No. 2022-KY-E-(176)). Patients with coronary artery disease, valvular heart disease, chronic renal failure, or persistent systemic inflammation (such as infection, cancer, rheumatoid arthritis, liver fibrosis, or chronic obstructive pulmonary disease) were excluded. Patients who had undergone surgery within 60 days or had an ejection fraction (EF) of less than 40% were also excluded.

Methods

All methods were performed in strict accordance with the relevant guidelines and regulations in China. Informed consent was obtained from all subjects, according to the World Medical Association Declaration of Helsinki, revised in 2013. Written consent was obtained, including CT and laboratory testing. Statistical software was used to estimate the required sample size based on the parameters. We followed the STROBE guidelines for case–control studies. Patient characteristics were collected and included demographic information such as age, gender, body mass index (BMI), smoking status, as well as the presence of diabetes mellitus and hypertension. A preoperative transthoracic echocardiography was used to assess the left atrial diameter (LAD) and left ventricular EF. Blood samples were taken and centrifuged at 1000 relative centrifugal force for 10 min at 4°C, and blood samples were frozen at −80°C. After all the specimens were collected, they were processed in a unified manner. Enzyme-linked immunosorbent assay was used to detect endothelin-1 (ET-1), nitric oxide (NO), intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and oxidized low-density lipoprotein (ox-LDL). Plasma malondialdehyde (MDA) and superoxide dismutase (SOD) were measured by the colorimetric method.

Measurement of hippocampal perfusion: (1) The brain was scanned using SOMATOM Definition Flash dual-source CT. After conventional scanning of the frontal-side positioning image, whole-brain perfusion examination was performed with the scanning parameters of a tube voltage of 80 kV, tube current of 80 mas, rotation time of 0.28 s, and 4D range of 100 mm, 1.5 s. Scanning was started 5 s after the injection of the contrast agent. Scans were performed every 1.5 s for a total of 30 times. A Nemoto high-pressure syringe was used. The injection site was the anterior vein of the right elbow. A 20-gauge trocar was used for venepuncture. The flow rate of contrast agent injection was 5.0 ml/s, and the total amount was 40 ml. After the contrast agent was injected, 40 ml of normal saline was added at the same flow rate. The scan range was the entire brain. (2) Image postprocessing: The whole-brain perfusion images were transferred to a Siemens workstation, and the VPCT neuro software package was used for data postprocessing to obtain the perfusion parameters regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF), mean transit time (MTT), and time to peak (TTP) in the brain and hippocampus.

Cognitive function assessment: All enrolled patients were evaluated with the Montreal Cognitive Assessment (MoCA) scale, and patients with MCI or worse were included in the study. The MoCA-B test lasts approximately 15 min, and it has a total score of 30 points. Starting time: The time (hour–minute–second) was calculated and recorded when the subject was introduced to the first part of the test (executive function). The full score of the MoCA scale is 30 points: $\geqslant$26 points are normal, 18–26 is mild, 10–17 is moderate, and $<$10 is severe. If the subject has $\leqslant$12 years of schooling (or high school level), 1 point can be added to the results, but the total score cannot exceed 30 points. If the patient is illiterate or has a very low level of education, the basic test can be given. If the patient is unable to write due to disability (e.g., hemiplegia), the full score is recorded out of 25 points, and the final score is converted to the 30-point scale.

Statistical analysis

The measurement data are expressed as the mean ± standard deviation (mean ± SD) and were analyzed with SPSS

Table 1. Baseline of characteristics, biochemical parameters, and cognitive assessment in all patients.

Characteristics	All patients ($n=86$)	AF group ($n=45$)	AF + CI group ($n=41$)	p Value
Age (years)	65.86 ± 7.291	65.27 ± 7.542	66.51 ± 7.040	0.4320
Male gender (n, %)	56 (65.1%)	27(60%)	29 (70.7%)	0.3671
BMI (kg/m^2)	21.46 ± 1.188	21.46 ± 1.136	21.45 ± 1.256	0.9729
Smoking (n, %)	30 (34.9%)	14 (31.1%)	16 (39.0%)	0.5010
DM (n, %)	9 (10.5%)	4 (8.9%)	5 (12.2%)	0.7309
Hypertension (n, %)	68 (79.1%)	33 (73.3%)	35 (85.4%)	0.6580
LAD (mm)	41.80 ± 3.487	40.53 ± 2.727	43.20 ± 3.723	0.0003
EF (%)	62.15 ± 3.035	62.49 ± 3.210	61.78 ± 2.824	0.2823
Cognitive assessment	25.45 ± 4.205	29.09 ± 1.276	21.46 ± 2.146	<0.0001
Biochemical parameters				
ET-1 (ng/L)	65.42 ± 6.903	66.78 ± 5.339	63.94 ± 8.097	0.0559
NO (μmol/L)	55.04 ± 6.029	56.65 ± 5.656	53.28 ± 5.997	0.0088
ICAM-1 (mg/L)	230.9 ± 37.89	222.4 ± 37.38	240.1 ± 36.68	0.0295
VCAM-1 (mg/L)	610.4 ± 74.99	572.4 ± 57.70	652.2 ± 69.79	<0.0001
MDA (nmol/ml)	5.010 ± 1.252	4.961 ± 1.339	5.063 ± 1.164	0.7083
SOD (U/ml)	83.86 ± 6.728	83.41 ± 6.916	84.35 ± 6.564	0.5198
ox-LDL (U/L)	69.68 ± 6.316	68.09 ± 6.705	71.42 ± 5.422	0.0138
Hippocampal perfusion				
rCBV (ml/100 g)	3.378 ± 0.6941	2.937 ± 0.6204	3.862 ± 0.3760	<0.0001
rCBF (ml/100 g/min)	45.89 ± 1.900	46.72 ± 1.532	44.97 ± 1.857	<0.0001
MTT (s)	4.784 ± 0.8702	4.080 ± 0.5632	5.557 ± 0.2997	<0.0001
TTP (s)	14.99 ± 1.693	13.73 ± 1.104	16.37 ± 0.9993	<0.0001

AF: atrial fibrillation; CI: cognitive impairment; BMI: body mass index; DM: diabetes mellitus; LAD: left atrial diameter; EF: ejection fraction; ET-1: endothelin-1; NO: nitric oxide; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; MDA: malondialdehyde; SOD: superoxide dismutase; ox-LDL: oxidized low-density lipoprotein; rCBV: regional cerebral blood volume of hippocampus; rCBF: regional cerebral blood flow of hippocampus; MTT: mean transit time of hippocampus; TTP: the time to peak blood flow of hippocampus.

22.0. Samples were tested for normal distribution by the Shapiro–Wilk test. The independent-sample t-test was used to compare the means between the two groups. Pearson correlation coefficient analysis was used to measure correlations between the two groups of data. Count data are expressed as rates or percentages, and the chi-squared test or Fisher's exact probability test was used for comparisons between groups. $p<0.05$ was considered statistically significant.

Results

Comparison of clinical data and cognitive function scores between the two groups

The average age of the AF group and the AF + CI group was 65.27 ± 7.542 years and 66.51 ± 7.040 years, respectively. The LAD of the AF + CI group was significantly longer than that of the AF group (43.20 ± 3.723 mm vs 40.53 ± 2.727 mm, $p=0.0003$). There were no significant differences in age, sex, BMI, number of smokers, number of diabetics, number of hypertensives, or EF between the two groups (all $p>0.05$). The cognitive function score of the AF + CI group was 21.46 ± 2.146 points, which was significantly lower than the 29.09 ± 1.276 points of the AF group ($p<0.0001$) (Table 1).

Comparison of oxidative stress levels between the two groups

The AF + CI group had significantly higher ox-LDL than the AF group (71.42 ± 5.422 U/L vs 68.09 ± 6.705 U/L) ($p=0.0138$). There was no significant difference in MDA or SOD (both $p>0.05$) (Table 1).

Comparison of vascular endothelial function between the two groups

The levels of ICAM-1 and VCAM-1 in the AF + CI group were significantly higher than those in the AF group (240.1 ± 36.68 mg/L vs 222.4 ± 37.38 mg/L and 652.2 ± 69.79 mg/L vs 572.4 ± 57.70 mg/L, respectively, $p=0.0295$ and $p<0.0001$, respectively), while NO was lower in the AF + CI group (53.28 ± 5.997 μmol/L vs 56.65 ± 5.656 μmol/L, $p=0.0088$). There was no significant difference in ET-1 ($p=0.0559$) (Table 1).

Comparison of hippocampal perfusion level between the two groups

rCBV, MTT, and TTP were higher in the AF + CI group than the AF group (3.862 ± 0.3760 ml/100 g vs

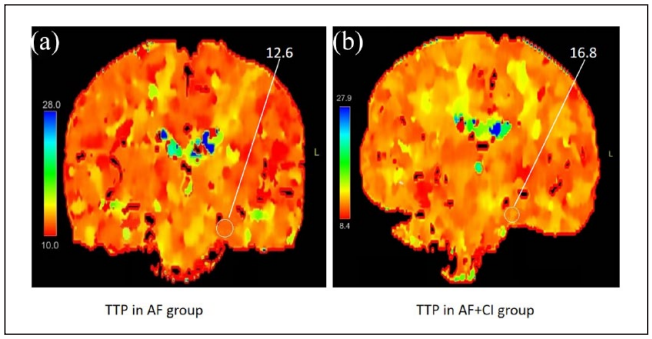

Figure 1. TTP in patients with and without CI.

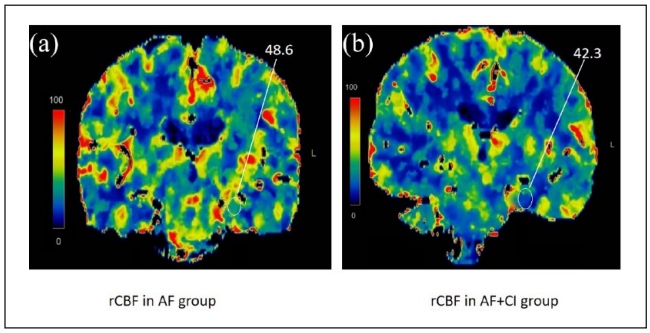

Figure 2. rCBF in patients with and without CI.

2.937 ± 0.6204 ml/100 g, 5.557 ± 0.2997 s vs 4.080 ± 0.5632 s, and 16.37 ± 0.9993 s vs 13.73 ± 1.104 s, respectively), while rCBF was lower in the AF + CI group (44.97 ± 1.857 ml/100 g/min vs 46.72 ± 1.532 ml/100 g/min) (all $p < 0.0001$). The results are shown in Table 1 and Figures 1 and 2.

Correlation analysis of oxidative stress level, vascular endothelial function, and hippocampal perfusion with cognitive function in patients with AF

Linear correlation analysis of the AF + CI group showed that age ($r = -0.3570$, $p = 0.0219$), LAD ($R = -0.3089$, $p = 0.0494$), and rCBV ($r = -0.3533$, $p = 0.0234$) were negatively correlated with the cognitive function score, while ox-LDL ($R = -0.3721$, $p = 0.0118$) and rCBV ($r = -0.4214$, $p = 0.0039$) were negatively correlated with the cognitive function score in the AF group (Tables 2 and 3). After adjustment for age, sex, BMI, smoking, diabetes, and hypertension, multiple regression analysis showed that rCBV (OR: 0.1552; 95% CI: 0.08122–0.2292; $p < 0.0001$), rCBF (OR: −0.03709; 95% CI: −0.06321 to −0.01098; $p = 0.0060$), MTT (OR: 0.1997; 95% CI: 0.1210–0.2784; $p < 0.0001$), TTP (OR: 0.1394; 95% CI: 0.09579–0.1830; $p < 0.0001$), and ox-LDL (OR: 0.007275; 95% CI: 0.0003507–0.01420; $p = 0.0397$) were significantly correlated with CI.

Table 2. Linear correlation analysis of oxidative stress level, vascular endothelial function, and hippocampal perfusion with cognitive function in AF patients with CI.

AF + CI group ($n = 41$)	Cognitive assessment r value	p Value
Age (years)	−0.3570	0.0219
BMI (kg/m^2)	0.08744	0.5867
LAD (mm)	−0.3089	0.0494
EF (%)	0.2977	0.0587
ET-1 (ng/L)	−0.03226	0.8413
NO (μmol/L)	0.1320	0.4105
ICAM-1 (mg/L)	0.1797	0.2609
VCAM-1 (mg/L)	−0.01060	0.9476
MDA (nmol/ml)	0.1951	0.2215
SOD (U/ml)	0.06580	0.6827
ox-LDL (U/L)	0.1841	0.2492
rCBV (ml/100 g)	−0.3533	0.0234
rCBF (ml/100 g/min)	0.1425	0.3742
MTT (s)	−0.09053	0.5735
TTP (s)	−0.1206	0.4526

AF: atrial fibrillation; CI: cognitive impairment; BMI: body mass index; DM: diabetes mellitus; LAD: left atrial diameter; EF: ejection fraction; ET-1: endothelin-1; NO: nitric oxide, ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; MDA: malondialdehyde; SOD: superoxide dismutase; ox-LDL: oxidized low-density lipoprotein; rCBV: regional cerebral blood volume of hippocampus; rCBF: regional cerebral blood flow of hippocampus; MTT: mean transit time of hippocampus; TTP: the time to peak blood flow of hippocampus.

Discussion

The results of this study found that oxidative stress and vascular endothelial function biomarkers were significantly increased in AF patients with CI. Hippocampal perfusion in AF patients with CI was significantly lower than in AF patients without CI and correlated with cognitive function scores. Hippocampal perfusion and oxidative stress were significantly correlated with CI in patients with AF.

Many clinical studies have found that AF is associated with an increased risk of CI and cognitive functional decline and may lead to dementia.[8] A study from Taiwan conducted a 1:1 comparison between 332,665 AF patients without dementia and the same number of individuals with neither dementia nor AF. The endpoint of the study was the occurrence of dementia, and the value of CHADS2 and CHA2DS2 VASc scores in predicting dementia were analyzed. The results showed that patients with AF had a higher annual incidence of dementia than non-AF patients. The CHADS2 and CHA2DS2 VASc scores are important predictors of dementia in AF patients.[8] Marzona et al.[9] used the Mini-Mental State Examination to evaluate the cognitive function of patients with AF at baseline and 2 and 5 years later. They also recorded sudden dementia, loss of independence in daily life activities, and entry into long-term care

Table 3. Linear correlation analysis of oxidative stress level, vascular endothelial function, and hippocampal perfusion with cognitive function in AF patients without CI.

AF group ($n=45$)	Cognitive assessment *r* value	*p* Value
Age (years)	0.07777	0.6116
BMI (kg/m^2)	0.01348	0.9300
LAD (mm)	−0.1119	0.4643
EF (%)	−0.03305	0.8294
ET−1 (ng/L)	−0.07075	0.6442
NO (μmol/L)	−0.1442	0.3445
ICAM-1 (mg/L)	0.07470	0.6258
VCAM-1 (mg/L)	−0.1261	0.4091
MDA (nmol/ml)	−0.04925	0.7480
SOD (U/ml)	0.01384	0.9281
ox-LDL (U/L)	−0.3721	0.0118
rCBV (ml/100 g)	−0.4214	0.0039
rCBF (ml/100 g/min)	−0.05696	0.7102
MTT (s)	−0.09077	0.5532
TTP (s)	0.03700	0.8093

AF: atrial fibrillation; CI: cognitive impairment; BMI: body mass index; DM: diabetes mellitus; LAD: left atrial diameter; EF: ejection fraction; ET-1: endothelin-1; NO: nitric oxide, ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; MDA: malondialdehyde; SOD: superoxide dismutase; ox-LDL: oxidized low-density lipoprotein; rCBV: regional cerebral blood volume of hippocampus; rCBF: regional cerebral blood flow of hippocampus; MTT: mean transit time of hippocampus; TTP: the time to peak blood flow of hippocampus.

facilities. Multivariate regression analysis showed that cognitive and functional decline was an important consequence of AF, even in the absence of an obvious stroke.[9] Myserlis et al.[10] evaluated the relationship between AF and cognitive decline in adults with heart failure through a systematic review and meta-analysis. They found that the presence of AF was associated with a higher risk of CI in patients with heart failure, and concomitant AF may exacerbate CI in patients with heart failure. Our study showed that the cognitive function score in AF patients with CI was significantly lower than in AF patients without CI by evaluating the MoCA scale.

The hippocampus is important in learning, memory, control of emotional behavior, and neuroendocrine function. The hippocampus can be damaged by Alzheimer's disease, hypertension, traumatic brain injury, hypoxia, and extreme stress.[11] Knecht et al.[12] used a stepwise multiple regression model to compare the cognitive scores and brain imaging changes in patients with and without AF. They found that AF patients without stroke performed significantly poorer in learning and memory tasks as well as attention and executive functions than the normal control group. Compared with paroxysmal AF, patients with chronic AF also showed a worse trend in learning and memory tasks. Our study found that rCBV, MTT, and TTP were higher, while rCBF was lower, in AF patients with CI when compared to AF patients without CI. Hippocampal perfusion was correlated with the cognitive function scores in AF patients.

Oxidative stress plays an important role in the pathogenesis of AF. Yoo et al.[13] found that in a canine heart failure model, oxidative stress via calmodulin-dependent protein kinase II signaling led to AF-related changes in the atrial matrix. Ren et al.[14] summarized several possible reactive oxygen species pathways based on atrial electrical remodeling and structural remodeling data and proposed that the clearance of oxidative stress markers might be a therapeutic target for AF. Our study showed that the levels of ox-LDL, ICAM-1, and VCAM-1 were significantly higher, and the level of NO was significantly lower, in AF patients with CI than those in AF patients without CI. In our study, multivariate logistic regression analysis found that a decrease in hippocampal perfusion and an increase in serum level of ox-LDL were significantly correlated with CI in AF patients, which suggests it could serve as a predictor for CI.

Our study also found that patients with both AF and CI often exhibit a larger LAD compared to those without CI. This can be attributed to several potential factors. First, AF itself contributes to structural changes in the heart, causing atrial remodeling and dilation. The irregular and rapid electrical activity in the atria during AF leads to stretching and enlargement of the atrial walls, including the left atrium. The extent of atrial enlargement is often proportional to the duration and severity of AF, and more advanced stages of AF are associated with CI. Second, AF and CI share common risk factors such as advanced age, hypertension, diabetes, and vascular disease. These risk factors individually contribute to atrial enlargement. Hypertension, specifically, is linked to both CI and LAD enlargement. Lastly, a bidirectional relationship exists between AF and CI. AF-related cerebral microembolism and reduced cerebral blood flow adversely affect cognitive function. Conversely, CI can result in reduced physical activity, poor medication adherence, and increased systemic inflammation, all of which can exacerbate AF and contribute to LAD enlargement. It should be understood that while a larger LAD is observed in patients with AF and CI, the precise mechanisms behind this association are still under investigation. Further research is necessary to fully comprehend the intricate relationship between CI, AF, and LAD enlargement.

This study has several limitations. First, the number of patients in our study was relatively small, and sample size calculation was performed by statistical software. Further studies are expected to confirm our result on a bigger sample size. Second, patients with all types of AF were selected, and no subgroup analysis of AF was performed. Therefore, this study cannot provide information on the impact of different types of AF on the results. Third, since the purpose of this study was to explore the related factors of CI in patients with AF, we grouped and analyzed AF patients according to the conditions with or without CI, while non-AF patients with or without CI were not included in this study. Therefore, our results failed to identify the related factors of CI in non-AF patients. Finally, CT and CT perfusion imaging were performed using ionizing radiation and iodine contrast agents in this study. Brain MRI

can be perfused with ASL (without gadolinium contrast). Those are some limitations of this study.

Conclusion

AF patients with CI displayed significantly elevated levels of oxidative stress and vascular endothelial function biomarkers. Moreover, these patients exhibited significantly lower hippocampal perfusion compared to AF patients without CI. The hippocampal perfusion reduction was found to be correlated with cognitive function scores. In addition, a significant correlation was observed between hippocampal perfusion, oxidative stress, and CI among AF patients.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics approval

The study protocol was approved by the hospital ethics committee of the First Affiliated Hospital of Guangxi Medical University (approval No. 2022-KY-E-(176)).

Informed consent

All patients signed an informed consent approved by the institutional guidelines.

Trial registration

Not applicable.

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