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# Correlation between perivascular adipose tissue surrounding coronary arteries measured on coronary artery CT Angiography and the presence and severity of CAD

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► ***Original article***

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## ABSTRACT

***Background:*** The aim of this study was to explore the relationship between peri-coronary adipose tissue volume (V-PCAT), as assessed via coronary artery CT angiography (CCTA), and the presence and severity of coronary artery disease (CAD). ***Materials and Methods:*** A retrospective analysis was conducted on 160 individuals with suspected CAD who underwent CCTA from June 2020 to December 2021. Quantification of both epicardial adipose tissue volume (V-EAT) and V-PCAT was performed. Clinical data, lipid metrics, and differences in adipose tissue volume between CAD and non-CAD groups were assessed. Variables influencing CAD were analyzed using univariate and multivariate logistic regression. The diagnostic accuracy of adipose tissue volume in predicting CAD was determined through receiver operating characteristic curves. The association between adipose tissue volume and coronary artery stenosis severity was investigated. ***Results:*** The analysis included 100 patients with CAD and 60 without CAD. V-EAT and V-PCAT were notably higher in the CAD group than the without CAD group. After adjustments for confounding factors, V-EAT and V-PCAT showed a positive association with CAD. The area under the curve of V-PCAT was 0.875. ***Conclusions:*** V-PCAT, measured via CCTA was substantial associated with CAD while serving as an independent risk determinant. Additionally, V-PCAT, notably correlated with the severity of coronary artery stenosis.

## INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of global mortality [1]. In 2016, CAD accounted for 17.6 million deaths worldwide, surpassing cancer-related deaths by twofold, according to the Global Burden of Disease study. The mortality from cardiovascular disease also witnessed a 14.5% increase between 2006 and 2016 [2,3]. Reducing the incidence and severity of CAD is an imperative in global healthcare, necessitating continued research into prevention, early detection, and treatment to improve patient outcomes and alleviate the burden imposed by this disease.

In clinical practice, coronary CT angiography (CCTA) is a highly sensitive technique for screening asymptomatic CAD and cardiac events while diagnosing the symptomatic obstructive CAD [4,5]. Compared to coronary angiography, CCTA is a non-invasive imaging technique that evaluate not only the vessel lumen but also the vessel walls and adjacent tissue [6]. Furthermore, an increasing number of studies employ CCTA to measure the epicardial adipose tissue volume (V-EAT) to assess the occurrence and severity of CAD [7,9]. Kim *et al.* [10] have indicated that V-EAT was correlated with the presence and severity of CAD. Shan *et al.* [11] have demonstrated that the volume of EAT was positive correlated with high-risk plaque. Epicardial adipose tissue (EAT), a metabolically active tissue that produces both anti-inflammatory and pro-inflammatory adipokines, which have a significant impact on cardiac function and morphology [12, 13]. In addition, it regulates vascular tone through release of various molecules [14,15]. Despite of various advantages of EAT, it has some limitations that restrict its role as an accurate predictor for CAD. It is important to note that various therapeutic or daily factors can also have a significant impact on the V-EAT. Not only the health of coronary arteries, but also season, demographic, and clinical factors could influence the V-EAT [16,19]. Utilizing EAT as a predictor for CAD may be less accurate.

Peri-coronary adipose tissue (PCAT) is part of the EAT, but it exhibits distinct pathophysiological features and roles in the development of atherosclerosis [20]. Recent studies have shown that PCAT produces harmful pro-inflammatory adipokines, which contribute to the formation of atherosclerosis [21]. Compared with EAT, the PCAT is located closer to coronary artery and can communicate cytokines directly with it. This provides PCAT with more advantages in reflecting the condition of the coronary artery. Several studies have



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examined the relationship between mean attenuation of PCAT (PCATMA) and occurrence or severity of CAD. Yuvaraj *et al*. [22] found that patients with stable CAD exhibit higher values of PCATMA. Hoshino *et al*. [23] indicated an association between PCATMA and intermediate epicardial stenosis. Chen *et al*. [24] demonstrated that high-risk plaques are associated with elevated levels of PCATMA. However, using mean attenuation as an indirect criterion for describing PCAT may not provide accurate assessment results. A more direct and precise measure is the volume of PCAT (V-PCAT). To the best of our knowledge, no studies have reported on the correlation between V-PCAT and the severity of CAD. This was the first study that aimed to assess the relationship between the V-PCAT, as measured by CCTA, and the presence and severity of CAD.

## MATERIALS AND METHODS

### *Study population*

160 suspected CAD patients who underwent CCTA at our hospital between June 2020 and December 2021 were retrospectively included in this study. A scan of the heart using CCTA was performed. Further coronary angiography examination and treatment were conducted for patients with unclear diagnosis or moderate to severe stenosis. Exclusion criteria for the study were as follows 1) History of myocardial revascularization or old myocardial infarction 2) Presence of complications such as heart failure, severe arrhythmia, thyroid disease, chronic liver or kidney disease, inflammatory disease, malignant tumor, etc.

### *Acquisition of relevant clinical data*

Clinical data were obtained from the electronic medical record system, including age, gender, height, weight, body mass index, smoking history, drinking history, hypertension, diabetes, hyperlipidemia, and blood lipid indicators such as total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

### *Coronary CT angiography examination*

The examination was performed using the Optima CT680 64-row 128-slice CT scanner (GE Company, USA). The scanning range extended from below the tracheal prominence to below the diaphragm, approximately 1 cm. The scanning parameters were as follows: collimation of 64 × 0.625 mm, slice thickness of 0.625 mm, tube voltage of 120 kV, tube current of 300 mAs, and pitch ranging from 0.16 to 0.5. Patients with a normal heart rate of ≥60 beats per minute received oral administration of metoprolol at a dosage of 50 mg before examination. Additionally, all patients were required to place 2.5 mg of isosorbide dinitrate sublingually 2 minutes before image acquisition. During the examination, 1 ml/kg of iodinated contrast medium (370 mg I/ml) was initially administered intravenously at a flow rate of 5 ml/s, followed by the injection of 40 ml of saline at the same rate. The region of interest was placed at the level of the aortic root, and image acquisition commenced 5 seconds after the attenuation within the region of interest reached 150 Hounsfield units.

### *Measurement of adipose tissue* [25]

CCAT and post-processing software (GEoptemo680, United Imaging) were used to measure the V-EAT and V-PCAT (figure 1). EAT was defined as the adipose tissue between the visceral pericardium and the parietal pericardium, and the measurement range was from the pulmonary artery bifurcation to the pulmonary artery apex. The region containing EAT was manually selected from the multi -planar reconstruction image, and the threshold method was employed to specify EAT as adipose tissue within the range of -200 to -30 HU. Finally, the V-EAT was automatically calculated using volume measurement function provided by software. Coronary arteries were volumetrically and planar reconstructed using coronary artery analysis software.

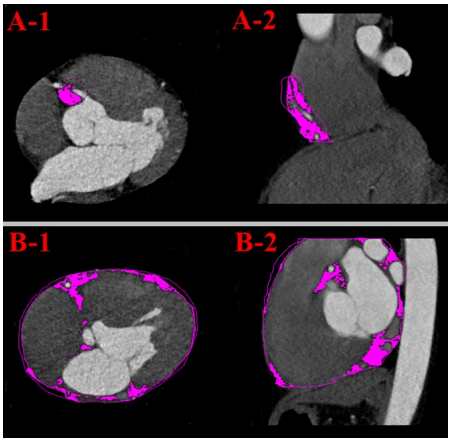


**Figure 1.** Measurement of adipose tissue. **(A)** Measurement of V-PCAT of RCA (1. Axial view; 2. Sagittal view) **(B)** Measurement of epicardial adipose tissue (1. Axial view, 2. Sagittal view).

Using coronary artery analysis software, the coronary arteries were volumetrically and planar reconstructed. The exact length of the coronary artery was measured using the software's automatic vessel analysis function. The left main artery (LM), left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) were continuously segmented from the ostium, with each segment being 10 mm long. The measurement results 50 mm from the ostium were marked as LM-LAD1-5, LCX1-5, and RCA1-5, respectively. The short axis of each vessel segment was reconstructed using multi-planar reconstruction. Meanwhile, the region of interest containing the vessel segment and PCAT was manually outlined. The threshold method (threshold



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set to -200 to -30 HU) and automatic volume measurement software were used to determine the V-PCAT of each segment. The sum of the V-PCAT of the 5 segments was calculated as V-PCAT for the coronary artery.

### *Coronary angiography*

All patients undergo invasive coronary angiography through femoral or radial artery puncture after fasting. CAD is defined as any coronary artery stenosis equal to or greater than 50%. The major coronary arteries were defined as the LM, LAD, LCX, and RCA. Based on the results of coronary angiography, patients were classified into three groups: mild stenosis (single branch stenosis with a stenosis rate of 50% to 75%), moderate stenosis (two branches or single branch stenosis with a stenosis rate exceeding 75%), and severe stenosis (left main artery or 3-vessel stenosis). The evaluation of the coronary angiography results was performed quantitatively using the Gensini score by two experienced cardiologists who are blinded to the CCTA results [26].

### *Statistical analysis*

Statistical analysis was performed using Statistic Package for Social Science (SPSS) Statistics (version 25; IBM, Armonk, NY, USA) and MedCalc (version 20.015). The normality of metric data was tested using the Kolmogorov-Smirnov test. Normally distributed metric data were presented as mean ± standard deviation (□ ± □), and comparative analysis was using the independent sample t-test. Non-normally distributed metric data were presented as median (P25, P75), and comparative analysis was using the Mann-Whitney U test. Count data were presented as frequency and percentage (%), and comparative analysis was using the chi-square test.

To identify the factors associated with CAD, a univariate logistic regression analysis was performed. Variables with a P-value less than 0.1 in the univariate analysis, as well as demographic characteristics such as age, gender, and body mass index, were included in the multivariate logistic regression analysis model for adjustment. The independent risk factors for CAD were determined by analyzing the results of the multivariate logistic regression.

The predictive value of V-EAT and V-PCAT in the occurrence of CAD was evaluated using the receiver operating characteristic (ROC) curve and area under the curve (AUC). The optimal cut-off value for diagnosing CAD was determined by identifying the maximum Youden index (sensitivity + specificity - 1) on the ROC curve. The relationship between V-EAT, V-PCAT, and Gensini score was assessed using scatterplots and correlation analysis. The repeatability of V-EAT and V-PCAT measurements among inter and intra-ratters was assessed using the intraclass correlation coefficient (ICC). A statistically significant difference was defined as $P < 0.05$.

## RESULTS

Clinical and imaging characteristics of the study population were analyzed. As shown in table 1, 100 cases of CAD and 60 cases of non-CAD were finally included. The mean age of the CAD group was (63.57 ± 7.62) years, with 57 male cases (57.0%). The mean age of the non-CAD group was (62.88 ± 7.57) years, with 29 male cases (48.3%). There were no statistically significant differences in age or gender between the two groups ($P > 0.05$ for both). There were also no statistically significant differences in body mass index, smoking, alcohol consumption, hypertension, diabetes, or blood lipid parameters (total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol) between the two groups ($P > 0.05$ for all). Compared with the non-CAD group, the CAD group had significantly higher V-EAT, LM-LAD PCAT, LCX PCAT, RCA PCAT, and V-PCAT levels, and the differences were all statistically significant ($P < 0.05$).

**Table 1.** Comparison of Clinical and Imaging Characteristics between CAD Group and Non-CAD Group.

| Characteristics | CAD(n=100) | Non-CAD(n=60) | t/Z/χ2 | P |
|---|---|---|---|---|
| Age(year) | 63.57 ± 7.62 | 62.88 ± 7.57 | 0.553 | 0.581 |
| Male | 57 (57.0) | 29 (48.3) | 1.133 | 0.287 |
| BMI(kg/m2) | 23.18 ± 3.32 | 22.34 ± 3.01 | 1.600 | 0.112 |
| Smoking | 45 (45.0) | 18 (30.0) | 3.535 | 0.060 |
| Drinking | 19 (19.0) | 14 (23.3) | 0.430 | 0.512 |
| Hypertension | 46 (46.0) | 27 (45.0) | 0.015 | 0.902 |
| Diabetes | 25 (25.0) | 10 (16.7) | 1.524 | 0.217 |
| Hyperlipidemia | 31 (31.0) | 17 (28.3) | 0.127 | 0.722 |
| TC(mmol/L) | 4.48 ± 0.82 | 4.24 ± 0.94 | 1.746 | 0.083 |
| HDL-C(mmol/L) | 1.21 (0.93-1.79) | 1.05(0.92-1.85) | 0.707 | 0.480 |
| LDL-C(mmol/L) | 2.32 ± 0.48 | 2.17 ± 0.65 | 0.111 | 0.111 |
| TG(mmol/L) | 1.30 1.07-1.51) | 1.31(1.01-1.81) | 0.404 | 0.687 |
| V-EAT(cm3) | 137.99 ± 37.15 | 98.84 ± 11.16 | 7.405 | <0.001* |
| LM-LAD PCAT (cm3) | 6.76 ± 1.11 | 5.35 ± 0.74 | 8.715 | <0.001* |
| LCX PCAT(cm3) | 5.20 ± 0.90 | 4.21 ± 0.58 | 7.547 | <0.001* |
| RCA PCAT(cm3) | 8.19 ± 1.24 | 6.83 ± 0.75 | 7.705 | <0.001* |
| V-PCAT(cm3) | 20.19 ± 2.96 | 16.40 ± 2.03 | 8.786 | <0.001* |
| Gensini score | 5.00 (2.00-8.00) | 31.50 (16.0-65.20) | 11.025 | <0.001* |

*P<0.05. BMI, Body mass index; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, Triglycerides; V-EAT, Volume of epicardial adipose tissue; LM-LAD, left main-left anterior descending artery; PCAT, Peri-coronary adipose tissue; LCX, Left circumflex artery; RCA, Right coronary artery; V-PCAT, Volume of peri-coronary adipose tissue.

Univariate and multivariate logistic regression analyses identifying factors associated with CAD. Univariate logistic regression analysis showed that smoking, total cholesterol, V-EAT, and V-PCAT were all significantly associated with CAD ($P < 0.1$). After



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stratifying by age, gender, body mass index, smoking, and total cholesterol, the results showed that V-EAT (OR = 1.028, 95% CI 1.011-1.046, P = 0.001) and V-PCAT (OR = 1.824, 95% CI 1.422-2.340, P < 0.001) were positively associated with CAD (table 2).

**Table 2.** Results of univariate and multivariate logistic regression analyses on factors influencing CAD.

| | Factors Univariate Analysis | | Multivariate Analysis* | |
|---|---|---|---|---|
| | OR value(95%CI) | P | OR value(95%CI) | P |
| **Smoking** | 1.909 (0.969-3.762) | 0.062 | 1.712 (0.679-4.313) | 0.254 |
| **TC** | 1.400 (0.955-2.053) | 0.085 | 1.117 (0.642-1.943) | 0.696 |
| **V-EAT** | 1.043 (1.028-1.059) | <0.001* | 1.028 (1.011-1.046) | 0.001* |
| **V-PCAT** | 2.066 (1.636-2.611) | <0.001* | 1.824 (1.422-2.340) | <0.001* |

*P<0.05. *Stratified by age, gender, BMI. TC, Total cholesterol; V-EAT, Volume of epicardial adipose tissue; V-PTCA, Volume of peri-coronary adipose tissue.

ROC curve for the diagnosis of CAD with V-EAT and V-PCAT. The ROC curve analysis of V-EAT for the diagnosis of CAD, the results showed an AUC of 0.811 (95% CI 0.74-0.868, P<0.001), with the optimal threshold at 101.84 (sensitivity and specificity of 76.0% and 75.0%, respectively). Similarly, the ROC curve analysis for the diagnosis of CAD using V-PCAT showed an AUC of 0.875 (95% CI 0.814-0.922, P<0.001), with the optimal threshold being 17.86 (sensitivity and specificity of 78.0% and 85.0%, respectively) (figure 2).

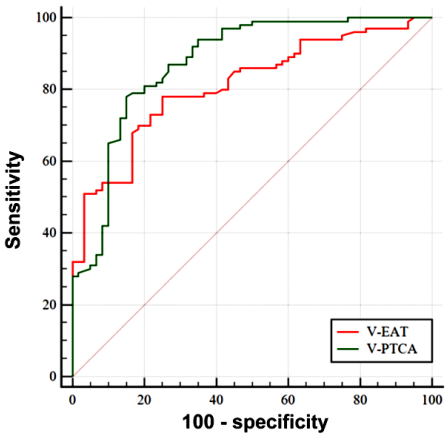


**Figure 2.** ROC Curve of V-EAT and V-PCAT for Diagnosis of Coronary Artery Disease. V-EAT, Volume of epicardial adipose tissue; V-PCAT, Volume of peri-coronary adipose tissue.

Correlation analysis between CAD and V-PCAT. Based on the results of coronary angiography, the patients were divided into three groups: mild lesion group with 33 cases, moderate lesion group with 36 cases, and severe lesion group with 31 cases. There was a certain correlation between CAD and V-EAT. The Pearson correlation analysis showed a moderate positive correlation between V-PCAT and Gensini score (r=0.797, P < 0.001). Figure 3 shows that LM-LAD PCAT, LCX PCAT, RCA PCAT, and V-PCAT increased with the severity of CAD (figure 3).

Reproducibility analysis for the measurement of CCTA results. Both intra- and inter-operator measurements of V-EAT and V-PCAT showed good consistency (ICC>0.8). Specifically, the intra-operator ICC value for V-EAT was 0.986 (95%CI: 0.981-0.990), and the inter-operator ICC value was 0.983 (95%CI: 0.978-0.988). Similarly, the intra-operator ICC value for V-PCAT was 0.987 (95%CI: 0.982-0.992), and the inter-operator ICC value was 0.984 (95%CI: 0.980-0.990). Finally, the intra-operator ICC value for Gensini score measurement was 0.985 (95%CI: 0.979 -0.990), and the inter-operator ICC value was 0.981 (95%CI: 0.976-0.985) (table 3).

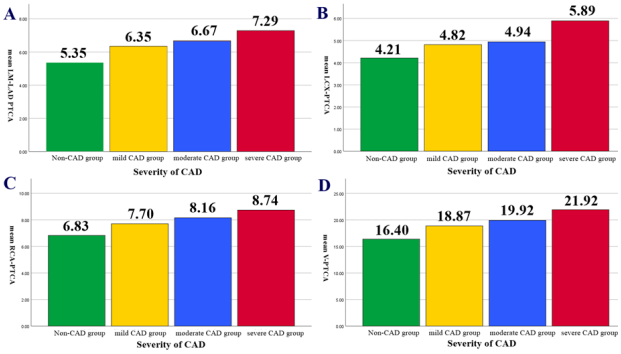


**Figure 3.** The relationship between the V-PCAT and the severity of coronary artery stenosis. LM-LAD, left main-left anterior descending artery; PCAT, Peri-coronary adipose tissue; LCX, Left circumflex artery; RCA, Right coronary artery; V-PCAT, Volume of peri-coronary adipose tissue.

**Table 3.** Reproducibility Analysis for the Measurement of CCTA Results.

| | Inter-rater | | Intra-rater | |
|---|---|---|---|---|
| | ICC (95% CI) | P value | ICC (95% CI) | P value |
| **V-EAT** | 0.986 (0.981-0.990) | <0.001* | 0.983 (0.978-0.988) | <0.001* |
| **LM-LAD PCAT** | 0.988 (0.983-0.994) | <0.001* | 0.986 (0.980-0.992) | <0.001* |
| **LCX PCAT** | 0.982 (0.978-0.989) | <0.001* | 0.983 (0.979-0.991) | <0.001* |
| **RCA PCAT** | 0.991 (0.987-0.995) | <0.001* | 0.989 (0.985-0.993) | <0.001* |
| **V-PCAT** | 0.987 (0.982-0.992) | <0.001* | 0.984 (0.980-0.990) | <0.001* |
| **Gensini Score** | 0.985 (0.979-0.990) | <0.001* | 0.981 (0.976-0.985) | <0.001* |

*P<0.001. V-EAT, Volume of epicardial adipose tissue; LM-LAD, left main-left anterior descending artery; PCAT, Peri-coronary adipose tissue; LCX, Left circumflex artery; RCA, Right coronary artery; V-PCAT, Volume of peri-coronary adipose tissue.

## DISCUSSION

EAT shares embryological and morphological similarities with visceral fat and is located between the myocardium and the visceral pericardium. Histological analysis has revealed that EAT contains a significant amount of adipose and inflammatory cells, capable of producing and secreting biologically active factors such as adiponectin, resistin, and pro-inflammatory cytokines [27,28]. Furthermore, EAT can disrupt vascular homeostasis, impair endothelial function, accelerate vascular wall inflammation and



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intima-media damage, and promote the formation of atherosclerotic plaques [29,30]. In recent years, numerous studies have demonstrated the significant role of EAT in the development and progression of CAD, making it an emerging therapeutic target.

In our study, V-EAT was greater in the CAD group than the non-CAD group, and was moderately correlated with the degree of coronary artery stenosis. Previous studies have utilized imaging techniques, such as ultrasound and CT, to demonstrate a close relationship between the volume and thickness of EAT and CAD risk. Sanjay *et al*. [31] used multi-source CT to measure the V-EAT while identifying an increased risk for CAD associated with elevated levels of EAT. Furthermore, they also emphasized its clinical significance as an important non-invasive indicator, in addition to calcium scoring and coronary angiography. A large-scale study involving over 4,000 patients discovered that V-EAT was independently associated with cardiovascular mortality and non-fatal coronary artery events regardless of traditional cardiovascular risk factors [32]. These finding was consistent with our results.

In our study, we measured V-PCAT through CCTA, V-PCAT was significantly higher in the CAD group and independently associated with the presence of CAD. Additionally, there was a moderate correlation between V-PCAT and the degree of coronary artery stenosis, with an increase in V-PCAT corresponding to an increase in stenosis. Previous study has found that V-PCAT was significantly associated with the extent and severity of coronary atherosclerosis [33]. This was similar to our finding. The evidence of the correlation between the V-PCAT and the degree of coronary artery stenosis was limited. DeVos *et al*. [34] demonstrated that the thickness of PCAT was closely more related to cardiovascular risk factors and coronary artery calcium scores. Another study of patients with acute myocardial infarction showed that V-PCAT was closely related to the degree of coronary artery segmental lesions, indicating that PCAT may play an important role in coronary atherosclerosis and lead to myocardial infarction [35]. Different from fat in other areas, PCAT was a part of EAT that located proximal to arteries. PCAT can release various inflammatory factors, such as TNF-α, IL-6, promoting the formation and the development of coronary atherosclerosis while directly affect the vessel wall.

Currently, there are few studies on the application of CCTA for measuring V-PCAT in CAD patients. This non-invasive imaging method can accurately guide further percutaneous coronary intervention therapy. The quantitative measurement of V-PCAT does not require additional radiation exposure in routine CCTA.

This study has some limitations. Firstly, it is a single-center, retrospective study with a relatively small sample size. In the future, larger-scale, multicenter, prospective studies should be conducted with increased sample size and collaboration among multiple centers. Secondly, this study was a cross-sectional study. It only indicates the correlation of V-PCAT and V-EAT. Even though the multiple logistic regression analysis has been conducted, the causal relationship is unknown. Finally, the influence of different image acquisition parameters and CT scanners on PCAT quantification requires further investigation.

## CONCLUSION

In our study, V-PCAT may be a noteworthy risk factor for CAD, which may potentially serve as a more sensitive and specific indicator of cardiovascular risk than other adiposity measures. Measuring V-PCAT using routine CCTA can provide a non-invasive imaging approach to identifying CAD.

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*Not applicable.*

***Conflict of Interests:*** The authors declared no conflict of interest.

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***Ethical consideration:*** This study was approved by the Ethics Committee of Shaoxing City Shangyu People's Hospital (ID: SRY-20200501-0002)

***Author contribution:*** S.Y: (Shanshan Yuan): Design of the work; acquisition, analysis and interpretation of data; drafted the work; Q.Y. (Quan Yuan): Conceptualization and design; F.X (Fuyi Xing): analysis of data; Y.W (Yiqun Wang): and substantively revised the work.

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