Original Article

The relationship between neutrophil-to-lymphocyte ratio, myeloperoxidase, interleukin-2 and coronary slow flow phenomenon

Xiaoliang Wei[#], Zhizhuang Zou[#^], Bairong Chen, Xinlian Deng, Guo Yang, Huili Liao

Departments of Cardiovascular Disease IV, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China

Contributions: (I) Conception and design: X Wei, Z Zou; (II) Administrative support: B Chen; (III) Provision of study materials or patients: X Wei, X Deng, G Yang, H Liao; (IV) Collection and assembly of data: X Wei, Z Zou; (V) Data analysis and interpretation: X Wei, Z Zou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Bairong Chen, MD, PhD. Departments of Cardiovascular Disease IV, The Fifth Affiliated Hospital of Sun Yat-sen University, No. 52, Meihua East Road, Xiangzhou District, Zhuhai 519000, China. Email: chenbr@mail.sysu.edu.cn.

Background: The precise mechanism of the coronary slow flow (CSF) phenomenon is still ambiguous, but the inflammation is widely convinced as a vital predisposing factor and has been considered in predicting CSF. This study aimed to investigate the relationship between neutrophil-to-lymphocyte ratio (NLR), myeloperoxidase (MPO), interleukin-2 (IL-2) and CSF in patients.

Methods: A total of 100 patients were received in this retrospective study. The CSF group (n=50) and non-CSF group (n=50) were divided according to the corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC). Data on demographics, drug therapy, laboratory measurement, and correct TIMI frame count were compared. The logistics model of the two groups was facilitated to predict the risk factors of CSF.

Results: The proportion of males (64% *vs.* 40%, P=0.012), smoking history (34% *vs.* 16%, P=0.032) and body mass index (BMI) (27.88±3.67 *vs.* 23.65±3.78, P=0.001) was statistically significantly higher in CSF group than the non-CSF group. The medians (25^{th}, 75^{th} percentiles) of NLR [3.46 (2.57, 7.37) *vs.* 1.59 (1.26, 2.28), P<0.001], MPO [59.57 (49.65, 89.25) *vs.* 45.23 (34.19, 56.25), P<0.001], IL-2 [5.35 (2.95, 5.96) *vs.* 2.17 (1.94, 2.94), P<0.001] and CTFC (55.10±11.86 *vs.* 21.67±2.63, P<0.001) were statistically significant higher in CSF group than in non-CSF group. The multivariate logistics regression analysis revealed that NLR [odds ratio (OR) 4.829 (95% CI: 1.235–8.889), P=0.024], IL-2 [OR 5.334 (95% CI: 1.314–21.737), P=0.019] and MPO [1.193 (95% CI: 1.031–1.381), P=0.018] were the independent predictors of CSF. The area under the receiver operating characteristic curve of NLR, IL-2 and MPO were 0.8726, 0.8514 and 0.8678, respectively.

Conclusions: This study suggested that NLR, IL-2 and MPO are associated with CSF, both can be used as promising indicators of CSF.

Keywords: Neutrophil-to-lymphocyte ratio (NLR); myeloperoxidase (MPO); interleukin-2 (IL-2); coronary slow flow phenomenon

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^ ORCID: 0000-0002-7736-7092.

Instruction

The coronary slow flow (CSF) phenomenon is an angiography phenomenon which is characterized by contrast agent passes slowly but no obvious stenosis (1). The definition of CSF was corrected thrombolysis in myocardial infarction frame count (CTFC) less than 27 (2). With the development of non-pharmacological therapy including percutaneous coronary intervention (PCI) and advancement of pharmacological therapy including antiplatelet statin, the rate of CSF has decreased (3). For all this, the incidence of CSF was between 1–7% which can course adverse cardiac events (4), such as coronary hypoperfusion, malignant arrythmia event thought myocardial infarction. Over 80% patients manifested typical angina at rest and admitted with acute coronary syndrome. Accurate identification and diagnosis of CSF is necessary to help clinicians quickly make appropriate treatment decisions for patients.

It is a complex and multifactorial phenomenal involving inflammation, distal embolization, ischemic reperfusion injury and endothelial edema. Although first proposed by Tambe *et al.* (1) in 1972, the mechanism responsible for the CSF phenomenon has not been clearly investigated. A detailed understanding of CSF mechanism may help improve treatment efficiency. Inflammation plays a crucial role in the development of plaque in coronary artery disease (CAD) (5). The principal pathophysiology of CAD is generally considered to be coronary atherosclerosis, an inflammatory disorder caused by the formation of plaque and subsequent obstruction of the coronary arteries. The white blood cell (WBC) count as a clinical marker of inflammation, while the neutrophil-to-lymphocyte ratio (NLR) is use for revealing the systemic balance of inflammatory disruptors and protective factors. Since NLR has been published that increased NLR is associated with major adverse cardiovascular event.

Studies have shown that increased NLR as an independent risk factor in different populations, such as ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) patients with CSF (6,7). Some small studies have suggested that C-reactive protein (CRP) level, uric acid level, lymphocyte-to-monocyte ratio (LMR) are risk factors for CSF patients (8-10). There is evidence that interleukin and myeloperoxidase (MPO) are vital players in the chronic cardiovascular inflammation that is typical for atherosclerosis (11,12). To our knowledge, there is no consensus that the relationship between CSF phenomenon and interleukin-2 (IL-2), MPO, NLR in angina patients. Therefore, the aim of this study was to investigate the inflammation markers as the risk factors for pectoris patients with CSF, with a particular focus on the inflammatory response. We present the following article in accordance with the STROBE reporting checklist (available at https://jxym.amegroups.com/article/view/10.21037/jxym-22-47/rc).

Highlight box

Key findings

- NLR, IL-2 and MPO are associated with CSF, both can be used as promising indicators of CSF.

What is known and what is new?

- The incidence of CSF was between 1–7% which can course adverse cardiac events, inflammation plays a crucial role in the development of plaque in coronary artery disease.
- This study was to investigate the inflammation markers as the risk factors for pectoris patients with CSF, with a particular focus on the inflammatory response.

What is the implication, and what should change now?

- Elevated IL-2, MPO and MPO level were associated with severe inflammation and higher incidence of CSF phenomenon in patients with angina. The aggravated inflammatory response caused by IL-2, MPO and MPO in angina patients needs more attention.

Methods

Study population

This was a retrospectively observational study received from January 2018 to December 2021 at the Department of Cardiology, The Fifth Affiliated Hospital of Sun-Yat Seng University in Zhuhai, China. The patients enrolled in our study who were suspected of having CAD but coronary angiography (CAG) diagnosed with no significant coronary stenosis lesions. The exclusion criteria were as follows: history CAD, isolated coronary artery ectasia, acute coronary syndrome treatment with percutaneous coronary intervention or thrombolysis, chronic or acute heart failure, congenital heart disease, valuer heart disease, cardiomyopathy, acute inflammatory diseases with 1 month and connective tissue disease. A total of 100 continued individuals were included and grouped into the CSF group (n=50) and the non-CSF group (n=50) who were underwent CAG.

Angiography data and frame counting

CAG was performed by two experienced operators who used classic Judkins approach via radial or femoral route and were blinded all information of patients. Ionic-contrast low osmolality contrast medium was used in the procedure and the frames data were collected at a film rate of 30 frames per second. Our study determined using corrected thrombolysis in myocardial infarction (TIMI) frame count to assess CSF as described by Gibson *et al.* (2). In this method, the first frame and the final frame should be calculated, the counts were collected from contrast agent fulfill coronary artery to contrast reach the given distal landmark of certain coronary artery. Due to left anterior descending (LAD) artery longer than left circumflex (LCX), the TIMI frame count (TFC) should divide 1.7 to obtain CTFC (2). Three artery CTFC were summed and divided by 3 to obtain mean CTFC. Published reference frame counts are 36±2.6 for LAD, 20±3 for right coronary artery (RCA) and 22±4 for LCX. CSF phenomenon is diagnosed by a standard deviation greater than 2 declared normal coronary artery flow rates. Gibson *et al.* found that used the CTFC ≥27 frames as a cutoff value of CSF.

Data collection and definition

Age, sex, systolic blood pressure (SBP), diastolic blood pressure, smoking history, diabetes mellitus, hypertension history, body mass index (BMI), drug therapy history, blood count analyses, MPO and IL-2 were obtained at the time of admission. CTFC data was measured and recorded by two experienced operators. Diabetes mellitus was based on the presence of blood glucose concentrations equal to or greater than 7.0 mmol/L after an overnight fast or on the presence of blood glucose concentrations greater than 11.1 mmol/L in general. Hypertension was defined SBP ≥140 mmHg and (or) diastolic blood pressure ≥90 mmHg. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from The Fifth Affiliated Hospital of Sun Yat-sen University Ethics Committee before the commencement of the registry by participating institutions (2022 No. K75-1). Written informed consent was obtained from each subject enrolled in the study.

Statistical analysis

Statistical analysis was performed using the SPSS version 25.0 software (IBM Corp., Armonk, New York, USA). Continuous variables that conform to a normal distribution are expressed as means ± standard deviations, and those that do not conform are expressed as medians (25^{th}, 75^{th} percentiles). Categorical variables are expressed as absolute values and percentages. Kolmogorov-Smirnov test detected whether the variables conform to the normal distribution. Two sample independent *t*-test or Mann-Whitney U test was used to compare the continuous variables of two groups according to whether normally distributed. Comparing two groups of categorical variables were performed using chi-squared test. Spearman correlation analysis screens for risk factors associated with NLR and CSF. Backward stepwise univariate and multivariate logistic regression analysis were performed to screen independent risk factors for CSF. The receiver operating characteristic (ROC) curve determines the sensitivity and specificity of independent predictors of CSF

Results

Two groups of demographics and clinical characteristics were presented at *Table 1*. The proportion of male (64% *vs.* 40%, P=0.012), patients with smoking history (34% *vs.* 16%, P=0.032) and BMI (27.88±3.67 *vs.* 23.65±3.78 kg/m^2, P=0.001) was significantly higher in the CSF group than in the non-CSF group. Besides, the CTFC of LAD (37.06±4.67 *vs.* 20.64±2.62, P<0.001), LCX (35.57±4.61 *vs.* 20.56±2.57, P<0.001) and RCA (33.02±4.26 *vs.* 20.72±2.54, P<0.001) were significantly higher in the CSF group than non-CSF group. However, there was no significant difference between two groups in terms of blood pressure, drug therapy and proportion of diabetes mellitus.

The comparison result of laboratory examinations between two groups was presented at *Table 2*. The terms of CSF group, NLR [3.46 (2.52, 7.37) *vs.* 1.59 (1.26, 2.28), P<0.001], neutrophils counts (5.42±1.86 *vs.* 3.63±1.28, P<0.001), MPO [59.57 (49.65, 89.25) *vs.* 45.23 (34.19, 56.25), P<0.001], IL-2 [5.35 (2.95, 5.96) *vs.* 2.17 (1.94, 2.94), P<0.001] were significantly higher than non-CSF group, but lymphocytes was lower than non-CSF group. However, there was no significant difference in the triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), WBC counts, high-sensitivity CRP and creatinine between two groups.

Spearman correlation analysis was performed using to detect the risk factors between gender, smoking history, BMI, neutrophils count, lymphocytes count, IL-2, NLR, MPO and CSF. Accordingly, there was a significant and

Table 1 Comparison of demographics and clinical characteristics between two groups

Characteristics	CSF (n=50)	Non-CSF (n=50)	P value
Clinical features			
Age (years)	56.67±6.64	55.48±7.74	0.401
Gender (male/female)	32/18	20/30	0.012
SBP (mmHg)	125.56±17.82	127.35±14.42	0.085
DBP (mmHg)	75.15±8.25	77.67±6.40	0.085
Smoking history	17 [34]	8 [16]	0.032
Diabetes mellitus	5 [10]	6 [12]	0.876
Hypertension history	8 [16]	6 [12]	0.537
BMI (kg/m^2)	27.88±3.67	23.65±3.78	0.001
Drug therapy			
β-block	5 [10]	4 [8]	0.703
ACEI/ARB	7 [14]	6 [12]	0.736
CCB	8 [16]	7 [14]	0.747
Statins	15 [30]	14 [28]	0.775
CTFC			
LAD CTFC	37.06±4.67	20.64±2.62	<0.001
LCX CTFC	35.57±4.61	20.56±2.57	<0.001
RCA CTFC	33.02±4.26	20.72±2.54	<0.001

Data were presented as mean ± SD or n [%]. CSF, coronary slow flow; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CTFC, corrected thrombolysis in myocardial infarction frame count; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SD, standard deviation.

positive correlation between CSF and smoking history (r=0.215, P=0.032), BMI (r=0.498, P<0.001), neutrophils count (r=0.475, P<0.001), IL-2 (r=0.613, P<0.001), NLR (r=0.758, P<0.001), MPO (r=0.623, P<0.001), whereas the lymphocytes count had a negative and significant correlation with CSF. On the other hand, the male was found have a positive correlation with CSF but no statistically significant. The correlation analysis was presented at *Table 3*.

Backward stepwise univariate and multivariate logistic regression analysis were performed to detect independent predictors of CSF. Univariable analysis revealed that male, BMI, lymphocytes, neutrophils, IL-2, NLR, MPO correlate with CSF. Whereas these parameters were analyzed by multivariable, only IL-2 [odds ratio (OR) 5.334 (95% confidence interval (CI): 1.314–21.737), P=0.019], NLR [OR 4.829 (95% CI: 1.235–8.889), P=0.024], MPO [OR 1.193 (95% CI: 1.031–1.381), P=0.018] were affirmed as independent predictors of CSF. These analyses were depicted at *Table 4*.

We used ROC curve to determine the sensitivity and specificity of independent predictors of slow coronary blood flow. The ROC curve revealed when an area under the curve (AUC) of 0.8726, using cutoff value of NLR ≥2.47 to predict CSF with sensitivity of 82% and specificity of 78%. The AUC value of IL-2 was 0.8514 with 92% sensitivity and 68% specificity at cutoff value above 3.345 pg/mL. The MPO was found to have AUC value of 0.8678 with an optimal cutoff value ≥46.74 ng/mL, the sensitivity and the specificity was 82% and 78% respectively. The ROC curve was shown at *Figure 1*.

Discussion

In the present study, the pinpoint relationship between CSF

Table 2 Comparison of laboratory examinations between two groups

Characteristics	CSF (n=50)	Non-CSF (n=50)	P value
Laboratory examinations			
TG (mmol/L)	1.64±0.75	1.52±0.48	0.349
TC (mmol/L)	4.67±0.92	4.64±0.93	0.152
HDL-C (mmol/L)	1.03±0.17	1.04±0.14	0.616
LDL-C (mmol/L)	2.85±0.60	2.95±0.51	0.373
NLR	3.46 (2.52, 7.37)	1.59 (1.26, 2.28)	<0.001
LYM (10^9/L)	1.42 (0.76, 1.84)	2.07 (1.86, 2.60)	<0.001
NEU (10^9/L)	5.42±1.86	3.63±1.28	<0.001
WBC (10^9/L)	6.73±2.27	6.86±1.89	0.828
HsCRP (mg/L)	2.41 (1.57, 4.82)	1.92 (1.37, 3.32)	0.057
HGB (g/L)	141.61±15.63	135.9±14.06	0.059
CRE (μmmol/L)	59.67±15.56	57.68±15.26	0.521
MPO (ng/mL)	59.57 (49.65, 89.25)	45.23 (34.19, 56.25)	<0.001
IL-2	5.35 (2.95, 5.96)	2.17 (1.94, 2.94)	<0.001
CTFC			
LAD CTFC	37.06±4.67	20.64±2.62	<0.001
LCX CTFC	35.57±4.61	20.56±2.57	<0.001
RCA CTFC	33.02±4.26	20.72±2.54	<0.001

Data were presented as mean ± SD or medians (25^{th}, 75^{th} percentiles). CSF, coronary slow flow; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NLR, neutrophil-to-lymphocyte ratio; LYM, lymphocyte; NEU, neutrophil; WBC, white blood cell; HsCRP, high-sensitivity C-reactive protein; HGB, hemoglobin; CRE, creatinine; MPO, myeloperoxidase; IL-2, interleukin-2; CTFC, corrected thrombolysis in myocardial infarction frame count; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SD, standard deviation.

Table 3 Correlation analysis between risk factors and CSF

Variables	r	P value
Male	0.061	0.546
Smoking history	0.215	0.032
BMI	0.498	<0.001
LYM	–0.479	<0.001
NEU	0.475	<0.001
IL-2	0.613	<0.001
NLR	0.758	<0.001
MPO	0.623	<0.001

CSF, coronary slow flow; BMI, body mass index; LYM, lymphocyte; NEU, neutrophil; IL-2, interleukin-2; NLR, neutrophil-to-lymphocyte ratio; MPO, myeloperoxidase.

patients and IL-2, MPO, NLR was discussed; our study showed that the NLR, IL-2, and MPO of CSF patients were higher and statistically significant compared to the non-CSF patients. In addition, NLR, IL-2, MPO were not only positively correlated with CSF, but also served as an independent predictor of CSF. The ROC curve revealed that these indicators could well distinguish between CSF and non-CSF patients with a high degree of specificity and sensitivity when the appropriate NLR, IL-2, MPO cut-off values were used.

The exact mechanism of CSF was still not well understood, and present literature suggest that it may be associated with inflammatory response, endothelial dysfunction, microvascular lesions, distal thrombosis, and ischemia-reperfusion injury. Previous studies evidence

Table 4 The independent predictors of coronary slow flow

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Male	3.144 (1.072–9.223)	0.037	6.110 (0.136–9.121)	0.706
BMI	1.650 (1.274–2.137)	<0.001	1.596 (0.889–2.893)	0.124
LYM	0.180 (0.064–0.508)	0.001	1.133 (0.036–36.046)	0.943
NEU	2.857 (1.662–4.912)	<0.001	1.508 (0.415–5.481)	0.533
IL-2	2.930 (1.723–4.983)	<0.001	5.334 (1.314–21.737)	0.019
NLR	4.377 (1.863–9.286)	0.001	4.829 (1.235–8.889)	0.024
MPO	1.112 (1.061–1.165)	<0.001	1.193 (1.031–1.381)	0.018

OR, odds ratio; CI, confidence interval; BMI, body mass index; LYM, lymphocyte; NEU, neutrophil; IL-2, interleukin-2; NLR, neutrophil-to-lymphocyte ratio; MPO, myeloperoxidase.

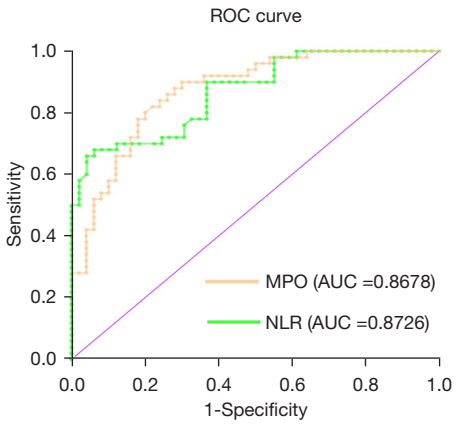

Figure 1 The ROC curve to determine the sensitivity and specificity of independent predictors of slow coronary blood flow. AUC, area under the curve; MPO, myeloperoxidase; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

that the inflammatory response played a vital role in the occurrence and development of cardiovascular disease. For CVD patients, the inflammatory response was involved in the whole process of coronary plaque formation, rupture and embolism (13). Intravascular ultrasound (IVUS) technology was used for those CSF patients could also observe the diffuse intimal thickening and the calcified plaque deposition (14), which revealed that CSF as a subclinical atherosclerosis with normal CAG. Therefore, we hypothesis that various inflammatory factors may affect coronary heart disease also have the potential to influent and predict CSF phenomena.

NLR as a common marker of inflammation that could be easily and quickly obtained in clinical practice. Previous studies had described that in a variety of cardiovascular diseases patients were observed had a significant increase in NLR compared with control patients. Arbel *et al.* divided STEMI patients undergoing emergency PCI into low and high NLR groups, patients in the high NLR group had higher 30-day and 5-year mortality independently associated with lower LVEF (15). Verdoia *et al.* preferred that NLR is independently associated with the occurrence and the severity of CAD in a study of 3,738 patients with stable angina (16). CSF also as a cardiovascular event, hence we hypothesized that NLR was associated with CSF in our study. Through our investigation, further evidence that CSF was associated inflammation, not only that NLR can independently forecast CSF and CSF and non-CSF patients can be distinguished when selected the appropriate cut-off value. Consistent with previously published literature, Doğan *et al.* found that NLR was related to CSF and prognosticate that independently in a study of 82 patients with CSF phenomenal (17).

Inflammation was considered to be the main cause of atherosclerosis through adverse effects on lipoprotein metabolism and arterial walls (18). We hypothesized that CSF is a subclinical atherosclerotic, with IL-1b, IL-6, IL-2 as cytochromes secreted by type 1 CD4 T helper cells, which are considered pro-inflammatory factors and can aggravate atherosclerosis; Ørn *et al.* revealed that high levels of IL-1b and IL-6 were associated with a poor prognosis in patients with STEMI and served as a predictor of myocardial remodeling after myocardial infarction (19). Groot *et al.* followed up with IL-6 tests in STEMI patients undergoing PCI for 1 day to 4 months found that high

IL-6 levels independently predicted a decline in left ventricular systolic function (20). In addition, Li *et al.* revealed a positive correlation between serum IL-6 levels and TFC (21). To our knowledge, there was no study show that whether the difference in serum IL-2 between CSF patients and non-CSF patients is statistically significant. Consequently, we performed our study to reveal IL-2 levels were positively correlated with CSF, and also can be used as an independent predictor of CSF, which is analogous to previous studies of other cytokines. So, we further demonstrated that CSF is a pre-atherosclerotic phenomenal and inflammation involved in the whole line of CSF.

MPO as an important peroxidase formed by activated neutrophil degranulation, which run through the entire process from early endothelial dysfunction to the formation of atherosclerotic plaque inflammatory response in the occurrence and development of cardiovascular disease (22). For patients with stable angina, MPO could produce a series of diffusible strong oxidants *in vivo*, such as hypochlorous acid, superoxide nitrite anions, active aldehydes and other oxidative modifications of LDL and HDL to promote atherosclerosis formation (23). For acute coronary syndrome, MPO is involved in the acute coronary syndromes (ACS) process by perturbation plaque stabilization. Zhang *et al.* performed a study with 2001 CAD patients revealed higher MPO levels than control patients (12). Ndrepepa *et al.* also revealed that MPO distinguished between ACS and non-ACS patients with ROC values of 0.731 (P<0.001) (24). Our research believed that CSF patients had higher MPO concentration than non-CSF patients, and as an independently predictor for CSF, appropriate cut-off values was selected to make a good distinction between CSF and non-CSF. This is consistent with Yurtdas *et al.* (25) investigation and other studies. MPO as an inflammation marker support a new entry point and theoretical basis for future diagnosis of CSF.

This study also has the following limitation: first, this study is a retrospective and observational study conducted in a single research center, with a small sample size. Second, most of the samples were collected at the time of hospitalization prior to angiography examination, and the decision to perform angiography examination depended on different operators, which may not exclude potential selection bias. So, more patients are needed in future studies.

Conclusions

In this study, elevated IL-2, MPO and NLR level were associated with severe inflammation and higher incidence of CSF phenomenon in patients with angina. The aggravated inflammatory response caused by IL-2, MPO and NLR in angina patients needs more attention.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jxym.amegroups.com/article/view/10.21037/jxym-22-47/rc

Data Sharing Statement: Available at https://jxym.amegroups.com/article/view/10.21037/jxym-22-47/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jxym.amegroups.com/article/view/10.21037/jxym-22-47/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from The Fifth Affiliated Hospital of Sun Yat-sen University Ethics Committee before the commencement of the registry by participating institutions (2022 No. K75-1). Written informed consent was obtained from each subject enrolled in the study.

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