A retrospective study on the relationship between fibrosis-4 index and all-cause mortality in patients with acute myocardial infarction

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Abstract. The fibrosis-4 (FIB-4) index is a non-invasive score used to determine liver fibrosis. The present study aimed to assess the predictive ability of FIB-4 for all-cause mortality in patients with acute myocardial infarction (AMI). It retrospectively analyzed a total of 797 patients who were diagnosed with AMI. The patients were equally divided into three tertiles based on the values of the FIB-4 index scores: Group A (FIB-4 index <3.19; n=265), group B (3.19 ≤FIB-4 <8.14; n=267) and group C (FIB-4 index ≥8.14 group; n=265). Kaplan-Meier curves were used to analyze the incidence of all-cause mortality among the three groups. Multivariate Cox regression analysis was used to assess the association of risk of all-cause mortality in the patients. The Kaplan-Meier curves showed that the incidence of all-cause mortality was statistically significantly higher in group C than in groups A and B (P<0.001). After adjusting for confounding factors, multivariate Cox analysis demonstrated the risk of all-cause mortality in group C was significantly higher than in group A (hazard ratio: 2.898, 95% confidence interval: 1.069-7.857, P=0.037). In receiver-operating characteristics (ROC) analysis, an FIB-4 index of 6.647 and a Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score of 26.75 had sensitivities of 67.3 and 55.8% and specificities of 63 and 71.9%, respectively. Comparing the area under the ROC curve revealed no statistical differences between the FIB-4 index and SYNTAX score (0.654 vs. 0.661; P=0.864). Higher FIB-4 index were associated with increased risks of all-cause mortality among AMI patients. The FIB-4 index, a noninvasive and convenient tool, plays a potential role in the prognosis of AMI.

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Introduction

Acute myocardial infarction (AMI) remains a major cause of mortality worldwide, despite the development and popularity of primary percutaneous coronary intervention (1-3). Early risk stratification of patients helps to improve disease prognosis through early interventions (4). Multiple clinical scoring systems are available to identify high-risk patients. Fox *et al* (5) validated the GRACE score that assesses the short- and long-term prognoses among patients with coronary artery disease. However, this evaluation system was mainly derived from and therefore applied for, non-ST acute coronary syndrome patients.

The Gensini score and The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) scores are the most common assessment system today (6). However, both are based on an arbitrary ranking of coronary lesion complexity. Another limitation of the scores is that they take into account the presence of lesions in very small vessels (1.5 mm), which are almost always functionally insignificant and in which the benefit of revascularization is uncertain (7).

The liver-heart axis is a growing field of interest (8). Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder. NAFLD is a part of cardiac metabolic disorder, rather than a dependent disease (8). NAFLD and cardiac metabolic disorders are different organ reflections of systemic metabolic syndrome. There is a significant connection between NAFLD and cardiovascular disease, which have same risk factors including obesity, hypertension and insulin resentence (8).

The fibrosis-4 (FIB-4) index is a simple, convenient, non-invasive tool that uses patient age and levels of platelets (PLT), aspartate transaminase (AST) and alanine transaminase (ALT) in the blood for its estimation. Initially, the FIB-4 index was used to detect liver impairment and liver fibrosis in NAFLD. It can also evaluate the prognosis of NAFLD. Previous studies have demonstrated that the FIB-4 index could be used to assess the risk of cardiovascular events, such as myocardial infarction and heart failure, in patients with NAFLD (9,10). In the cardiovascular field, FIB-4 index can help predict adverse outcomes, ranging from readmission to all-cause mortality, in patients with heart failure (10-12). In heart failure patients, those with a FIB-4 index >3.01 had 3.5-fold higher all-cause mortality compared with patients

with a FIB-4 index <3.01 (10). To date, it is unclear whether the FIB-4 index can also help to predict poor outcomes after AMI. Therefore, this study aimed to investigate the relationship between the FIB-4 index and prognoses of AMI.

Patients and methods

Study population. This retrospective study included 896 patients from Yongchuan Hospital of Chongqing Medical University, a tertiary hospital in Southwest China, between January 2016 and January 2019. The inclusion criteria were age >18 years and AMI according to the relevant guidelines (13). The exclusion criteria were a history of chronic viral hepatitis; previous or current diagnosis of bile duct obstruction; excessive alcohol consumption (>21 drinks/week in men and >14 drinks/week in women); severe renal insufficiency; severe heart valvular disease, severe hematological diseases, incomplete data and/or being lost to follow-up. Based on these criteria, the data of 797 patients was finally analyzed. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethical Committee of the Yongchuan Hospital of Chongqing Medical University approved this retrospective study (approval no. 2019029). The requirement for informed consent was waived due to the retrospective design.

Measurements. The sociodemographic, lifestyle characteristics, medical history, comorbidity and laboratory data of all the participants was collected. Smoking was defined as at least one cigarette per day for half a year before admission and alcohol intake was defined as drinking any types of alcoholic beverages at least once a week for more than six months before admission. Blood samples for evaluating the liver functions, including AST, ALT, gamma-glutamyl transpeptidase, total bilirubin (TBIL), direct bilirubin (DBIL) and fasting blood glucose level, were collected after ≤8 h of fasting. Other items were obtained soon after the admission, including white blood cell (WBC), hemoglobin, PLT, uric acid, creatinine, total cholesterol, hypertriglyceridemia (TG), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, cardiac troponin I (cTn I) and N-terminal B-type natriuretic peptide. Details of the discharge medication prescription of all patients, including antiplatelet agents, statins, β-receptor blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers (depending on their individual situation), was also collected through the medical record system.

FIB-4 index. The FIB-4 index was calculated using the following equation (14):

$$\frac{\text{Age (years)} \times \text{AST (U/l)}}{\text{platelet count } (10^9/\text{l}) \times \sqrt{\text{ALT(U/l)}}}$$

The patients were equally divided into three tertiles based on the values of the FIB-4 index scores: first tertile (FIB-4 index <3.19, n=265); second tertile (3.19 ≤FIB-4 <8.14, n=267); and third tertile (FIB-4 index ≥8.14, n=265) (15).

Follow-up and endpoints. The patients were followed up via annual telephone interviews after discharge. The last follow-up conducted in January 2020. Data were obtained through the inpatient medical records, outpatient medical records and telephone interviews. The primary endpoint was all-cause mortality.

Statistical analysis. Continuous normally distributed variables are presented as mean ± standard deviation and were compared between groups using one-way analysis of variance. Non-normally distributed variables are presented as median and interquartile range and were compared using the Kruskal-Wallis H test. Categorical variables are presented as number (percentage) and were analyzed via the Chi-squared test. Kaplan-Meier curves were plotted for the incidences of events and the log-rank test was used to compare the differences between groups. Multivariate Cox's regression was used to analyze the relationship between the FIB-4 index and the occurrence of the endpoint. Pearson correlation analysis was used to analyze the correlation of data. The receiver-operating characteristics (ROC) curve was used to determine the sensitivity and specificity of the FIB-4 index and the optimal cut-off value for predicting the outcome of patients with AMI. All statistical analyses were performed using SPSS v20.0 (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. Table I summarizes the sociodemographic data and clinical characteristics of patients; the mean age was 66.3±11.7 years and 72.4% of the cohort were male. The 50% median time from onset chest pain symptom to sample collection was 22.1 h. Compared with those other in other two groups, the participants in the group C were older and had a higher prevalence of Killip class. Moreover, group C had the highest levels of WBC count and serum levels of AST, ALT, γ-GT, TBIL, DBIL and cTn I; However, the serum levels of PLT and TG and amount of discharge medication were lowest in the group C (P<0.05).

Clinical outcomes. During a median follow-up period of 13 months, 113 deaths occurred: 19 (7.2%) patients in group A, 33 (12.4%) in group B and 61 (23.0%) in group C. The Kaplan-Meier curves indicated that group C had significantly lower cumulative event-free survival rates than the other two groups (log-rank test, P<0.001; Fig. 1).

The FIB-4 index of groups B and C indicated 1.773-fold and 3.36-fold higher risk of all-cause mortality compared to that of group A, respectively. After adjusting for hypertension, diabetes, sex, smoking, Killip class, total cholesterol, WBC, creatinine, cardiac troponin I, left ventricular ejection fraction, SYNTAX score, complete revascularization (excluding the variables included in the FIB-4 index formula), the increased risk of all-cause mortality risk for group C was higher than that for group A patients [hazard ratio, (HR): 2.898, 95% confidence interval (CI): 1.069-7.857, P=0.037]. Patients in group B had an increased risk of all-cause mortality compared with those in group A; however, the difference was not significant (HR: 1.587, 95% CI: 0.542-4.649, P=0.400; Table II).

Table I. Baseline characteristics of the participants.

Item	Group A (n=265)	Group B (n=267)	Group C (n=265)	P-value
Male sex	187 (70.6)	195 (73.0)	195 (73.6)	0.71
Age, years	63.7±11.9	66.0±11.8	69.2±10.7[a,b]	<0.001
Smoking	169 (63.8)	162 (60.7)	167 (63.0)	0.743
CAD	17 (6.4)	10 (3.7)	16 (6.0)	0.336
Hypertension	128 (48.3)	123 (46.1)	137 (51.9)	0.400
Diabetes	62 (23.5)	55 (20.6)	44 (16.6)	0.141
Stroke	13 (4.9)	18 (6.7)	24 (9.1)	0.168
Killip class ≥2	101 (38.1)	122 (45.7)	156 (58.9)[a,b]	<0.001
Laboratory indicators				
WBC(x10^9/l)	6.3 (4.7,8.6)	7.7 (5.6,10.4)[a]	8.5 (6.8,11.1)[a,b]	<0.001
Hb, g/l	136 (123, 148)	134 (123, 146)	134 (121, 146)	0.506
Plt, x10^9/l	220 (180, 263)	193 (150, 236)[a]	170 (138, 207)[a,b]	<0.001
ALT, U/l	24 (16, 38)	32 (21, 52)[a]	57 (38, 81)[a,b]	<0.001
AST, U/l	30 (22, 41)	78 (49, 141)[a]	256 (175, 384)[a,b]	<0.001
γ-GT, U/l	32 (22, 61)	31 (20, 53)	29 (18, 48)	0.056
ALB, g/l	38.7 (36.1, 42.0)	38.5 (36.1, 41.2)	38.8 (35.9, 40.9)	0.772
TBIL, μmol/l	8.6 (6.1, 11.4)	10.1 (7.4,13.3)[a]	13.1 (10.0, 18.5)[a,b]	<0.001
DBIL, μmol/l	2.8 (2.0, 3.9)	3.4 (2.3, 4.5)[a]	4.1 (2.8, 6.0)[a,b]	<0.001
CR, μmol/l	75 (62, 93)	74 (62, 93)	79 (65, 96)	0.115
TC, mmol/l	4.6 (3.9, 5.4)	4.4 (3.8, 5.2)	4.6 (3.8, 5.2)	0.391
TG, mmol/l	1.5 (1.1, 2.1)	1.4 (1.0, 2.0)	1.3 (1.0,1.8)[a,b]	<0.001
LDL-C, mmol/l (mmol/l)	2.7 (2.1, 3.2)	2.5 (2.1, 3.2)	2.6 (2.0, 3.1)	0.449
HDL-C, mmol/l (mmol/l)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	0.616
cTn I, ng/ml	1.4 (0.3, 7.0)	5.2 (0.8, 18.1)[a]	20.0 (2.4, 25.0)[a,b]	<0.001
NT-proBNP, pg/ml	3,539 (414, 3,555)	3,538 (393, 3,549)	3,520 (1,110, 3,547)	0.869
LVEF, %	59 (58, 62)	59 (58, 60)	59 (57, 60)	0.344
Number of lesions				0.600
1	50 (19.1)	55 (20.8)	42 (15.8)	
2	78 (29.8)	81 (30.7)	79 (29.8)	
≥3	134 (51.1)	128 (48.5)	144 (54.3)	
SYNTAX score	12.5 (20.0, 28.8)	21.5 (13.0, 29.00)	23.0 (16.0, 30.5)[a]	0.034
Complete revascularization	153 (57.7)	151 (56.6)	137 (51.7)	0.333
Discharge medication				
Aspirin	245 (92.5)	246 (92.1)	226 (85.3)[a,b]	0.008
Clopidogrel/ticagrelor	248 (93.6)	248 (92.9)	229 (86.4)[a,b]	0.006
Statins	245 (92.5)	241 (90.3)[a]	224 (84.5)[a,b]	0.010
β-blocker	224 (84.5)	205 (76.8)[a]	201 (75.8)[a,b]	0.026
ACEI/ARB	178 (67.2)	166 (62.2)[a]	140 (52.8)[a,b]	0.003

Values are presented as mean ± standard deviation, median (interquartile range) or n (%). [a]P<0.05 vs. First tertile, [b]P<0.05 Second tertile vs. Third tertile. CAD, coronary artery disease; WBC, white blood cell; Hb, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transpeptidase; TBIL, total bilirubin; DBIL, direct bilirubin; UA, uric acid; CR, creatinine; TC, total cholesterol; TG, hypertriglyceridemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; cTn I, cardiac troponin I; NT-pro BNP, N-terminal B-type natriuretic peptide; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

In the ROC curve, an FIB-4 index of 6.647 predicted all-cause mortality with 67.3% sensitivity and 63% specificity; The area under the ROC curve (AUC) of the FIB-4 index was 0.654 (95% CI: 0.602-0.707, P<0.001). A SYNTAX score of 26.75 predicted all-cause mortality with 55.8% sensitivity and 71.9% specificity. The AUC of the SYNTAX score was 0.661 (95% CI: 0.607-0.715, P<0.001). No difference was observed between the AUC of the FIB-4 index and SYNTAX score (0.654 vs. 0.661, P=0.864; Fig. 2). The FIB-4 index had a weak positive correlation with SYNTAX scores (r=0.117, P=0.001; Fig. 3).

Table II. Cox's proportional hazard analysis for all-cause mortality.

	Unadjusted			Adjusted[a]		
Group	HR	95% CI	P-value	HR	95% CI	P-value
A	Ref	Ref	Ref	Ref	Ref	Ref
B	1.773	1.008-3.118	0.047	1.587	0.542-4.649	0.400
C	3.336	2.993-5.583	<0.001	2.898	1.069-7.857	0.037

[a]Models were adjusted for hypertension, diabetes, gender, smoking, Killip class, total cholesterol, white blood cell, creatinine, cardiac troponin I, left ventricular ejection fraction, SYNTAX score and complete revascularization as categorical variables, other than the variables included in the Fibrosis-4 index formula. CI, confidence interval; HR, hazard ratio.

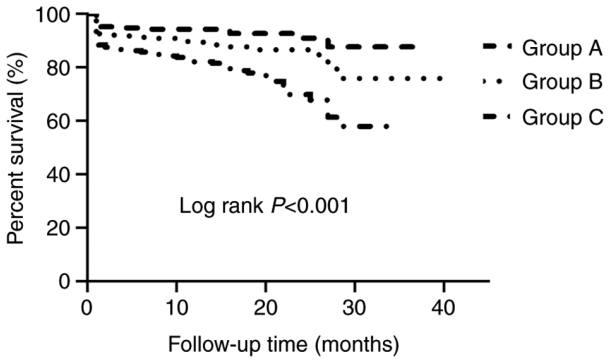

Figure 1. Kaplan-Meier curves to compare the incidences of all-cause mortality in the three patient groups that different group of fibrosis-4 index. Group C had significantly lower cumulative event-free survival rates than the other two groups.

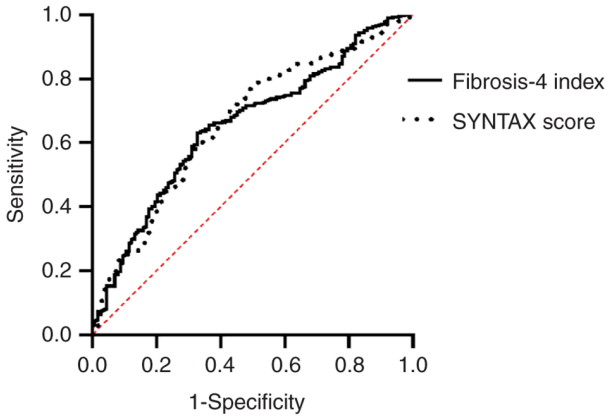

Figure 2. Receiver-operating characteristic curve of FIB-4 index in predicting all-cause mortality. The area under receiver-operating characteristics curve signifies no difference between FIB-4 index and SYNTAX score. FIB-4, fibrosis-4.

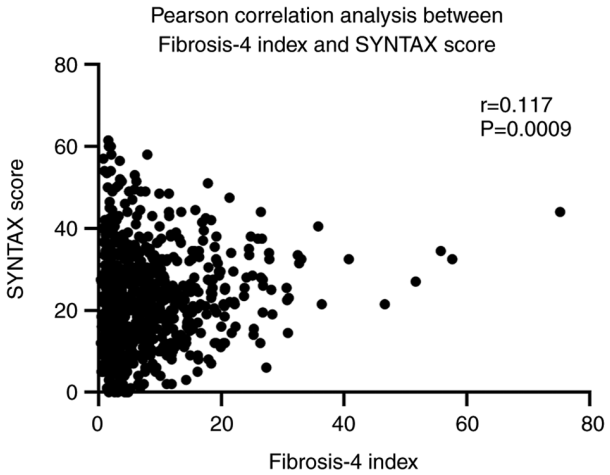

Figure 3. Pearson correlation analysis revealed the correlation between FIB-4 index and SYNTAX score.

Discussion

Increasing research has demonstrated that liver diseases are associated with poor cardiovascular outcome (16,17) and both coronary atherosclerotic heart disease and NAFLD have common risk factors, such as obesity, hypertension, type 2 diabetes, metabolic syndrome and dyslipidemia (18). Patients with NAFLD are at an increased risk of developing atherosclerosis, cardiomyopathy and arrhythmia, which clinically result in cardiovascular morbidity and mortality (16). This may be due to several mechanisms including low-grade systemic inflammation, oxidative stress, cytokines and insulin resistance (19,20), which can promote atherosclerosis.

Early identification of patients at high risk of AMI is important. A simple, convenient and effective scoring method is conducive to active interventions, which can improve the prognosis. Some of the available prediction scoring systems include the SYNTAX score, GRACE score, Gensini score, TIMI score and EUROSCORE scores; however, all of them require a detailed medical history, laboratory tests and invasive coronary angiography. The FIB-4 index, as a simple, convenient, non-invasive tool, is widely used to assess the probability of liver fibrosis and/or cirrhosis in patients with NAFLD and has been recommended by several guidelines (21,22). A meta-analysis compared laboratory tests, ultrasound and magnetic resonance elastography to detect fibrosis in patients with NAFLD; among four noninvasive tools, FIB-4 index offered the best diagnostic performance for detecting advanced fibrosis (23). The FIB-4 index can even be used to stage fibrosis and diagnose cirrhosis (24). Generally, it is useful tool for identifying patients with no to minimal fibrosis (F0) or advanced fibrosis (F3 to F4) but is less accurate at distinguishing early or intermediate stages of liver disease (F1 to F2).

The present study found that the FIB-4 index was independently associated with an increased risk of all-cause mortality in patients with AMI; the higher the FIB-4 index, the higher incidence of all-cause mortality. To the best of the authors' knowledge, this is the first study to evaluate the association between the FIB-4 index and all-cause mortality in patients with AMI. The present study supported the use of the FIB-4 index for evaluations in patients with AMI for its convenient and non-invasive feature. The FIB-4 index has the same predictive power as the SYNTAX score.

Myocardial fibrosis is the most important pathophysiology after AMI, resulting in complications such as heart failure and arrhythmia which can affect disease prognosis of patients. The degree of liver fibrosis is closely related to the cardiac structure and function (25,26), such as left ventricular ejection fraction (27) and myocardial remodeling (28). Additionally, heart failure is a common complication in patients with AMI. Following myocardial infarction, congestion of the systemic circulation can lead to congestive liver disease, causing abnormal liver function. A previous study demonstrated that liver stiffness can reflect heart failure even in the compensatory phase (29). This may be due to residual congestion, which correlates with the risk of readmission due to heart failure and all-cause mortality (11). Furthermore, decreased cardiac output and insufficient arterial perfusion lead to ischemic hepatitis (30), which is associated with systemic inflammation.

The liver is an essential metabolic organ involved with systemic inflammation via the secretion of inflammatory markers and cytokines, such as IL-6 and C-reactive protein (CRP). IL6 and CRP are involved in the onset and progression of atherosclerosis, as well as the progression of cardiovascular diseases, such as myocardial remodeling and myocardial fibrosis following AMI (19,31). Moreover, arrhythmia is common following myocardial infarction. Liver diseases were independently associated with a higher risk for QTc prolongation (32) and ventricular arrhythmias (33), while a prospective, observational, multicenter study indicated that the FIB-4 index was independently associated with the risks of cardiovascular events and all-cause mortality in patients with nonvalvular AF even after adjusting for the CHA_2DS_2-VASc score (34).

To the best of the authors' knowledge, no studies have demonstrated a relationship between the FIB-4 index and the prognosis among patients with AMI. In the present study, it was confirmed for the first time that the FIB-4 index can predict poor outcomes in patients with AMI. As demonstrated by the Kaplan-Meier curves, the higher the FIB-4 index, the higher was the incidence of all-cause mortality. After adjusting for traditional risk factors, multivariate Cox regression analysis revealed that the FIB-4 index was an independent risk factor for all-cause mortality. Furthermore, based on the ROC curve, it was found that the FIB-4 index has a certain predictive power for all-cause mortality.

However, to date, the underlying mechanisms between the baseline FIB-4 index and long- and short-term prognoses have not been clearly determined. It was hypothesized that the composition of the FIB-4 index can reflect the association more accurately. The FIB-4 index includes patient age, PLT, AST and ALT levels, which are independently correlated with arteriosclerotic cardiovascular disease. Age is an independent risk factor of coronary atherosclerotic heart disease and studies have demonstrated that elevated serum levels of AST and ALT are associated with short-term and long-term all-cause mortality among patients with AMI (31,32,35). Additionally, increases in serum AST/ALT ratio are reported to be related to the long-term prognosis of patients with AMI (19). Serum PLT count exhibits a U-shaped curve of its association with all-cause and cause-specific mortality and cardiovascular events (36-38).

The present study had some limitations. First, this was a retrospective study with a small sample size; thus, prospective studies with larger sample sizes are needed to validate its findings. Second, the blood samples were acquired 22.1 h after the onset of chest pain. Due to the dynamic fluctuations in liver function, the present study did not compare the liver functions during and after the hospitalization of patients and hence could not confirm when the FIB-4 index was the most valuable for predicting all-cause mortality. Third, although patients with AMI patients with distinct liver disease were excluded, the possibility of potential liver disease in the patients who were included in the current study cannot be ruled out completely. The relationship between the FIB-4 index and other evaluations of fibrosis, such as liver biopsy, should also be assessed, which is not generally performed in patients with AMI.

In conclusion, the FIB-4 index, a simple and convenient non-invasive scoring method, was independently associated with an increased risk of all-cause mortality among patients with AMI. It is thus a useful tool to predict poor outcomes for the risk assessment of patients with AMI.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MC and ZC performed the conception and design of the study. MC, TL, ZL FG and ZC performed the experiments. MC and TL analyzed and checked the data and drafted the manuscript. MC and TL prepared figures. ZC edited and revised manuscript. ZC was primarily responsible for final content. MC, TL and ZC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The methods of treatment meet the criteria of Helsinki declaration for human rights and the study was approved by

the Yongchuan Hospital of Chongqing Medical University (approval no. 2019029).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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