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Research Article

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Proposal of a prediction model for prognosis of patients with acute myocardial infarction after percutaneous coronary intervention based on galectin-3 and soluble growth stimulating expressed gene 2 levels

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Abstract

Background: To study the correlations of serum galectin-3 (Gal-3) and soluble growth stimulating expressed gene 2 (sST2) levels with prognosis of patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI).

Methods: A total of 112 patients diagnosed from August 2015 to October 2017 were selected. They were followed up for 3 years. Based on major adverse cardiovascular events (MACEs) during follow-up, they were divided into MACE and non-MACE groups. Multivariate logistic regression analysis was performed to explore the independent risk factors for MACEs. A nomogram model was established using the factors and validated. The optimal cut-off values of Gal-3 and sST2 levels were determined by receiver operating characteristic curves. Kaplan-Meier method was used for survival analysis.

Results: MACEs occurred in 78 patients during follow-up. Patients in the MACE group were more often hypertensive, had higher total cholesterol, uric acid, sST2 and Gal-3, and lower left ventricular ejection fraction (LVEF) ($P<0.05$). CK-MB, sST2, Gal-3 and LVEF were the independent risk factors for MACEs ($P<0.05$). The nomogram model established with these factors had high accuracy for predicting overall survival, and its concordance index (C-index) was 0.768 (95% confidence interval: 0.692-0.865). The prognosis of the patients with Gal-3 ≥12.57 μg/mL and sST2 ≥18.56 ng/mL was poorer 3 years after PCI.

Conclusions: The levels of serum Gal-3 and sST2 are the independent risk factors for MACEs in AMI patients following PCI, with high prognostic value.

***Keywords**: acute myocardial infarction, galectin-3, soluble growth stimulating expressed gene 2, percutaneous coronary intervention, prognosis, model*

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Introduction

Acute myocardial infarction (AMI) is one of the common critical cardiovascular diseases. The rupture, erosion and endothelial damage of coronary atherosclerotic plaques lead to secondary thrombosis under the action of various inflammatory mediators, causing vascular occlusion and subsequent myocardial necrosis and inflammatory response. According to the *Report on Cardiovascular Diseases in China 2018*, the mortality rate of AMI has been rising rapidly in China since 2005 (1). Extensive data from previous research demonstrated that direct emergency percutaneous coronary intervention (PCI) can effectively reduce the mortality rate of AMI patients, save the dying myocardium and protect the cardiac function of MI patients, becoming the most efficacious therapeutic method for AMI at present (2). However, reperfusion may induce cardiac ischemia/reperfusion injury (3,4).

As a member of the galectin protein family, galectin-3 (Gal-3) is a powerful pro-inflammatory cytokine secreted by macrophages. It possesses a carbohydrate recognition domain and participates in cell growth, angiogenesis, inflammation, and other physiological and pathological processes on the surface of the cells, inside the cells or in the extracellular matrix (5). Growth stimulating express gene 2 (ST2), a member of the interleukin-1 (IL-1) receptor family, can be mainly classified into membrane-bound ST2 (ST2L) and soluble ST2 (sST2); the latter is a decoy receptor of IL-33, able to competitively bind to IL-33 and inhibit the IL-33/ST2 signaling pathway (6). Studies in recent years have illustrated that both Gal-3 (7) and sST2 (8) are vital markers of cardiovascular disease, with high predictive values for major cardiovascular events. However, the prognostic value of the two markers for AMI patients after PCI is rarely researched. In this study, therefore, the levels of serum Gal-3 and sST2 in AMI patients after PCI and their correlations with major adverse cardiovascular events (MACEs) were explored.

Materials and methods

This study was approved by the ethics committee of Zhongda hospital, and the patients and their families signed the informed consent. A total of 112 AMI patients diagnosed with AMI in the Department of Cardiology of our hospital from August 2015 to October 2017 were enrolled in the study group. The group included 57 males and 55 females, aged 24-76 years, and (56.32±17.48) years old on average. All patients were hospitalized at 1-12 h after onset. AMI was diagnosed according to the criteria in the *Guidelines for the Diagnosis and Management of Patients with ST-Segment Elevation Myocardial Infarction* (2015) (9) by electrocardiography and coronary angiography. In detail, the levels of myocardial biochemical indices (mainly troponin) increase and/or decrease by at least over 99% of the upper limit of reference value, accompanied by at least one of the following manifestations: 1) symptoms of ischemia; 2) new ST-T changes or left bundle branch block on ECG; 3) pathological Q waves on ECG; 4) imaging discloses loss of viable myocardium or abnormal local movement of the myocardial wall; 5) coronary angiography or autopsy shows thrombosis in the coronary artery lumen. The selected cases should meet the above-mentioned diagnostic criteria for acute myocardial infarction. Diabetes mellitus was diagnosed according to the WHO criteria (10).

The exclusion criteria were set as follows: 1) patients with known heart failure before the acute coronary event; 2) those with autoimmune disorders; 3) those with malignant tumors; 4) those with a history of trauma requiring major surgery within the last 6 months; 5) those with severe hepatic (Child Pugh class B and C) or renal dysfunction (serum creatinine ≥160 μmol/L is renal insufficiency, 200-450 μmol/L is azotemia, and

>450 μmol/L is renal failure). 6) those with incomplete clinical data.

After enrollment, the patients were queried about medical history and subjected to physical examination, so as to review their general data and obtain the age, gender and medical history. The presence and severity of coronary artery disease was assessed by coronary angiography. Then the blood pressure of patients was measured in a resting state after admission, and the systolic pressure and diastolic pressure were recorded. Fasting (deprived of food for 8-12 h) venous blood specimens were acquired from the patients on the next morning after admission-and were placed in blood collection tubes containing separation gel and coagulant. Next, the serum was immediately separated for detection of such biochemical indices as Gal-3, sST2 and routine blood tests. Specifically, sST2 concentration was determined using enzyme-linked immunosorbent assay (ELISA), and Gal-3 concentration was detected by a full-automatic immuno-analyzer I-2000. The kits were purchased from R&D Systems (USA). Routine blood tests were performed using Sysmex XE-2100. Moreover, Beckman Coulter AU5400 Analyzer was employed to measure other biochemical indices. Color Doppler echocardiography was performed at 24 f after onset to assess and record the left ventricular ejection fraction (LVEF).

All AMI patients treated by PCI were followed up for 3 years (once every 3 months) by means of telephone inquiry, clinic reexamination and medical record inquiry, with a follow-up rate of 100%. The patients were assigned into MACE group and non-MACE group based on the occurrence of MACEs. The MACEs included all-cause mortality, recurrent angina, fatal or nonfatal MI, malignant arrhythmia, heart failure and target vessel revascularization (11).

SPSS 23.0 software was used for statistical analysis of all data. The normally distributed measurement data were presented as mean ± standard deviation ($\bar{\chi} \pm s$), the measurement data not in line with normal distribution were expressed by median [M (Q1, Q3)], and the enumeration data were presented as frequency (%). Independent-samples *t*-test was conducted for inter-group comparison of data in line with normal distribution, while Mann-Whitney U test was performed for inter-group comparison of data not in line with normal distribution; the inter-group comparison of enumeration data was implemented using the chi-square test. The statistical test on the separate diagnosis with sST2 and Gal-3 was implemented using receiver operating characteristic (ROC) curves, and the results were expressed by the area under the ROC curve (AUC) and 95% confidence interval (CI). The optimal cut-off values of sST2 and Gal-3 for predicting MACEs were further determined based on the ROC curves, and survival curves were plotted for survival analysis using the Kaplan-Meier method. The independent risk factors for MACEs within 36 months were analyzed through univariate and multivariate logistic regression models and the factors with $P<0.05$ in the univariate analysis were subjected to multivariate analysis. Finally, the rms package of R software was adopted to construct a nomogram model, followed by internal validation and calculation of concordance index (C-index). $P<0.05$ was set as the threshold of significance.

Results

Among the 112 AMI patients in this study, 57 had acute ST-segment elevation MI, and 55 had non-ST-segment elevation MI. During the 3 years of follow-up, there were 78 cases (69.64%) of MACEs, including 15 cases (19.23%) of recurrent angina, 46 cases (58.97%) of target vessel revascularization, 8 cases (10.26%) of all-cause mortality, 3 cases (3.85%) of fatal or nonfatal MI, 4 cases (5.13%) of heart failure and 2 cases (2.56%) of malignant arrhythmia. Through com-

paring the clinical data between MACE group and non-MACE group, it was found that the proportion of hypertensive patients, lipoprotein A, total cholesterol (TC), creatine kinase-MB (CK-MB), blood uric acid, sST2, Gal-3 and LVEF were higher in MACE group than those in non-MACE group (P<0.05) (**Table 1**).

The occurrence of MACEs in AMI patients during follow-up and the clinical features with statistical differences (P<0.05) in univariate analysis were incorporated into multivariate logistic regression analysis. The results of stepwise regression method showed that CK-MB, sST2, Gal-3 and LVEF were the independent risk factors for MACEs (P<0.05) (**Table 2**).

AUC of Gal-3 for predicting MACEs was 0.724 (95% CI: 0.625-0.826, P<0.001), the cut-off value was 12.57 μg/mL, and the sensitivity and specificity at the cut-off value were 73.7% and 85.4%, respectively. As for sST2, AUC for predicting MACEs, cut-off value, sensitivity and specificity at the cut-off value were 0.765

Table 1. Clinical data of patients

Item	MACE group (n=78)	Non-MACE group (n=34)	Statistical value	P
Age (Y)	57.38±14.37	55.48±16.34	-0.805[a]	0.370
Male [n (%)]	41 (52.56)	16 (47.06)	0.815	0.365
BMI (kg/m^2)	23.43±1.32	23.25±1.08	0.951	0.253
Hypertension [n (%)]	53 (67.95)	18 (52.94)	3.002	0.046
Diabetes mellitus [n (%)]	26 (33.33)	9 (26.47)	3.562	0.057
Smoking history [n (%)]	48 (61.54)	19 (55.88)	2.633	0.105
Systolic blood pressure (mmHg)	136.54±18.71	132.93±20.54	0.758[a]	0.540
Diastolic blood pressure (mmHg)	96.64±11.32	93.28±9.73	1.947[a]	0.053
History of myocardial infarction [n (%)]	8 (10.26)	3 (8.82)	0.446	0.459
Previous stent placement [n (%)]	7 (8.97)	2 (5.88)	0.743	0.328
TC (mmol/L)	4.48±1.34	4.20±1.28	-1.078[a]	0.006
TG (mmol/L)	1.47±0.91	1.55±0.85	0.524[a]	0.601
HDL-C (mmol/L)	1.13±0.33	1.20±0.21	1.741[a]	0.098
LDL-C (mmol/L)	2.64±0.87	2.48±0.71	1.427[a]	0.156
CK-MB (U/L)	45.72 (16.38,105.79)	24.46 (10.54,58.74)	36.745[b]	<0.01
Blood urea nitrogen (mmol/L)	5.71±1.86	5.45±1.47	-1.259[a]	0.189
Blood creatinine (μmol/L)	77.43±24.28	74.69±14.31	-1.187[a]	0.236
Blood uric acid (μmol/L)	377.92±92.00	354.33±87.64	-1.982[a]	0.048
Blood glucose (mmol/L)	8.24±1.97	7.93±2.01	0.880[a]	0.384
HbA1c (%)	6.77±1.65	6.39±1.42	-1.198[a]	0.246
FFA (mmol/L)	0.53 (0.36,0.67)	0.45 (0.32,0.65)	-1.734[b]	0.139
Hcy (mmol/L)	16.28±0.89	16.04±0.95	-0.297[a]	0.967
Hs-CRP (mmol/L)	3.81 (1.58,13.98)	3.28 (1.06,8.26)	-1.163[b]	0.243
Lipoprotein A (mmol/L)	0.18 (0.09,0.54)	0.12 (0.06,0.26)	-2.258[b]	0.024
sST2 (ng/mL)	24.66 (18.26,27.83)	15.49 (12.38,18.64)	19.845[b]	<0.01
Gal-3 (μg/L)	16.58 (12.16,21.74)	10.03 (8.86,12.93)	9.687[b]	<0.01
LVEF	41.5 (32.00,51.25)	60.24 (50.25,65.00)	-2.729[b]	0.007

1 mmHg = 0.133 kPa, BMI = body mass index, TC = total cholesterol, TG = triglyceride, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, CK-MB = creatine kinase-MB, HbA1c = glycosylated hemoglobin, FFA = free fatty acid, Hcy = homocysteine, hs-CRP = high-sensitivity C-reactive protein, sST2 = soluble growth stimulating expressed gene 2, Gal-3 = galectin-3, and LVEF = left ventricular ejection fraction. [a]: *t* value, [b]: Z value, and others: χ^2 value.

Table 2. Multivariate logistic regression analysis results of factors affecting prognosis

Variable	Regression coefficient	Standard error	Wald χ^2	P	OR	95% CI
Lipoprotein A	0.139	0.325	0.208	0.728	1.092	0.535-2.782
TC	0.419	0.357	1.516	0.302	1.423	0.715~3.293
CK-MB	0.054	0.014	7.653	0.002	1.162	0.862~1.293
sST2	1.134	0.187	28.326	0.000	2.783	2.111~4.492
Gal-3	1.367	0.245	21.954	0.000	4.502	2.623~7.723
LVEF	-0.054	0.023	10.273	0.002	0.911	0.825~0.973

TC = total cholesterol, CK-MB = creatine kinase-MB, sST2 = soluble growth stimulating expressed gene 2, Gal-3 = galectin-3, and LVEF = left ventricular ejection fraction.

(95% CI: 0.657-0.846, P<0.001), 18.56 ng/mL, 68.34% and 95.7%, respectively (**Figure 1**).

The nomogram model was established with the independent risk factors in the multivariate logistic regression analysis as predictors (**Figure 2**).

The calibration and validity of the established nomogram model were evaluated (**Figure 3**). With A indicating the reference curve and B standing for fitting curve, the shadow on both sides represented the 95% CI. According to the nomogram model, the risk was underestimated by the model when the event rate was below 35% and at 55-100%, while it was overestimated when the event rate was 35-55%; the predicted value of the model was completely concordant with the observed value when the event rate was 35% and 55%. On the whole, the model had relatively high accuracy. The results of internal data validation showed that the C-index was 0.768

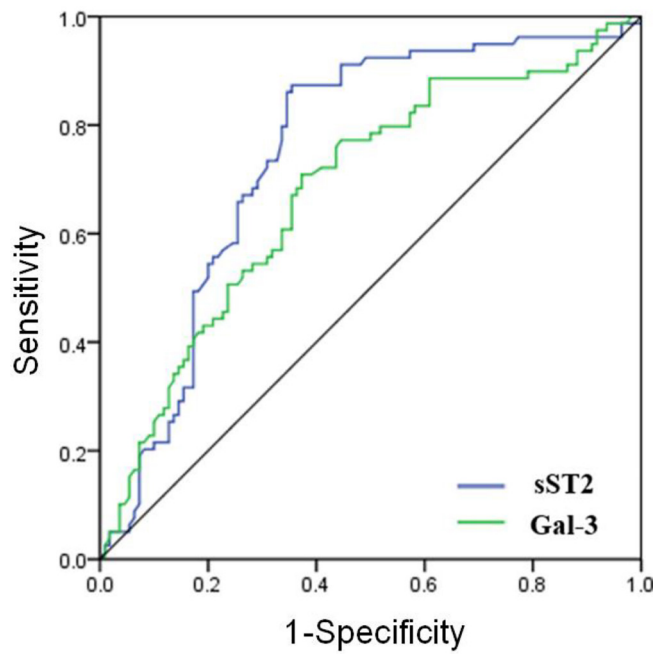

Fig. 1. ROC curves of serum Gal-3 and sST2 levels for predicting MACEs. Gal-3: Galectin-3; MACE: major adverse cardiovascular event; ROC: receiver operating characteristic; sST2: soluble growth stimulating expressed gene 2.

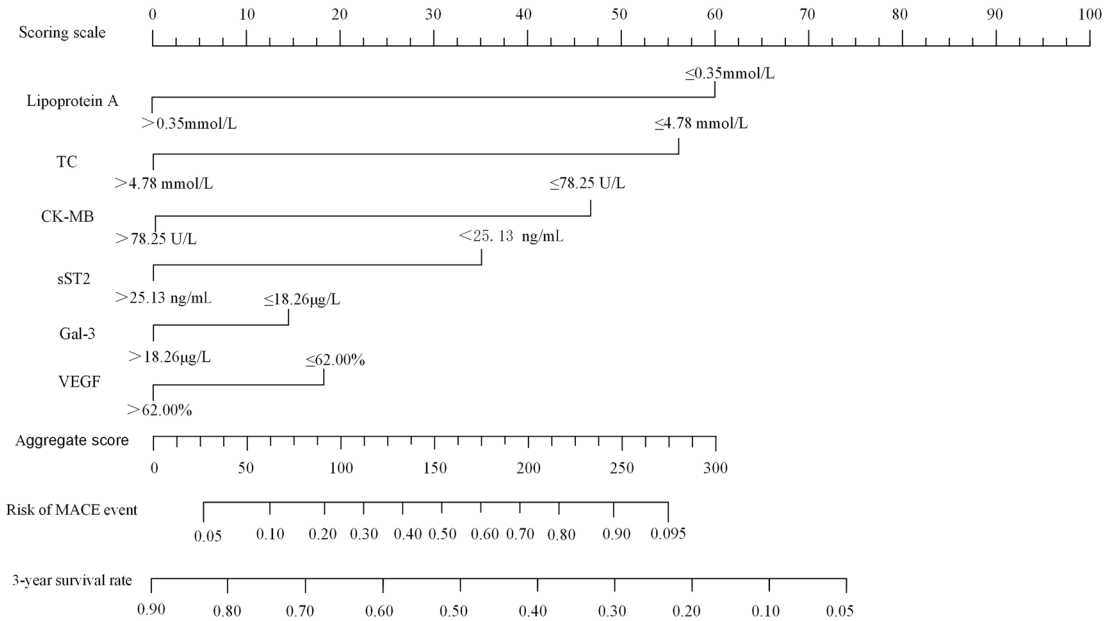

Fig. 2. Nomogram model for MACEs in AMI patients after PCI. AMI: Acute myocardial infarction; CK-MB: creatine kinase-MB; Gal-3: Galectin-3; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular event; PCI: percutaneous coronary intervention; sST2: soluble growth stimulating expressed gene 2.

(95% CI: 0.692-0.865), and the standard curve fitted well with the prediction curve in the calibration chart, suggesting that the incidence of MACEs predicted by the nomogram model was consistent with the observed value.

Discussion

The morbidity rate of AMI, an acute cardiovascular disease characterized by high death rate, disability rate and medical expenses, is increasing year by year, and the patients become young-

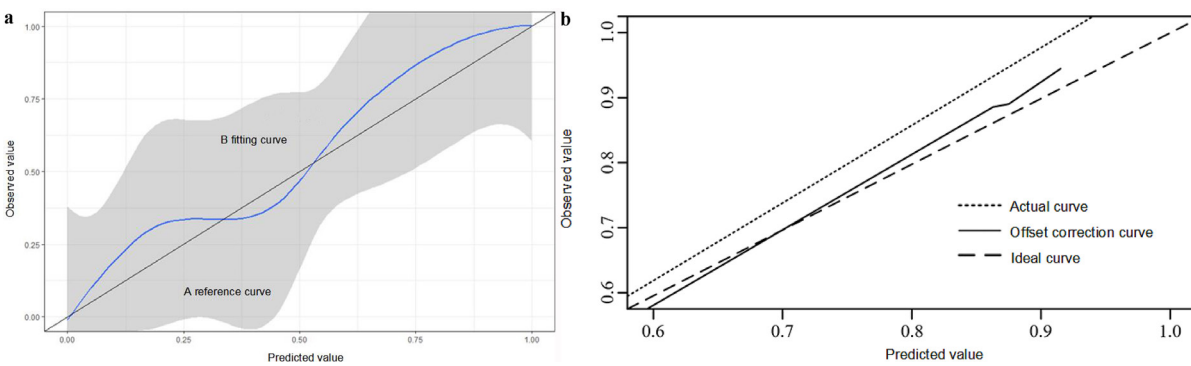

Fig. 3. (a) Calibration and (b) internal calibration of nomogram model for MACEs in AMI patients after PCI. AMI: Acute myocardial infarction; MACE: major adverse cardiovascular event; PCI: percutaneous coronary intervention.

er and younger (12). Accordingly, AMI has been recognized as a prominent public health problem and social problem. Despite optimal medical treatment and PCI, MI-induced myocardial necrosis, myocardial remodeling and irreversible damage of cardiac function may still occur. Hence, seeking for prognosis-related risk factors is of important significance for clinically improving the survival rate of AMI patients.

The development and progression of AMI involve a significant inflammatory response (13), in which Gal-3 and sST2 are crucial inflammatory factors. Inflammation activation is a pivotal regulatory mechanism of Gal-3 and sST2, and they can induce the expression of inflammatory mediators (*e.g.* TNF-α, IL-1β and IL-6) to promote the progression of cardiac fibrosis and acute and chronic heart failure by regulating inflammatory cell functions and downstream signaling pathways (14). It has been reported in studies that Gal-3 and sST2 levels play a favorable prognostic role in cardiovascular diseases. For example, Luo et al. (15) investigated the Gal-3 expression changes in the serum of patients with MI-induced chronic heart failure, and discovered that the serum Gal-3 level was elevated in such patients, with a positive correlation with inflammatory response and a negative correlation with cardiac function. Arora et al. (16) reported that the levels of serum Gal-3 and sST2 were remarkably raised in patients with dilated cardiomyopathy and heart failure, and the sST2 level was related to the severity of cardiac function deterioration. In addition, the studies of Weir et al. (4,17) revealed that the Gal-3 level had a correlation with coronary thrombus burden of AMI patients and was involved in ventricular remodeling following MI. In the present study, it was shown that the serum Gal-3 and sST2 levels after PCI were higher in MACE group than those in non-MACE group, implying that Gal-3 and sST2 can serve as the prognostic factors for AMI patients after PCI. Besides, patients in the MACE group had higher cholesterol, uric acid, cholesterol, lipoprotein A, and sST2 and galectin-3 levels, and lower LVEF. Furthermore, the results of multivariate logistic regression analysis demonstrated that hypertension history, CK-MB, sST2, Gal-3 and LVEF were the independent risk factors for MACEs. According to the Kaplan-Meier survival analysis on the correlations of serum Gal-3 and sST2 levels with survival rate of patients, the prognosis of patients with Gal-3 ≥12.57 μg/mL or sST2 ≥118.56 ng/mL was poorer at 3 years after operation.

Based on the multivariate logistic regression analysis results in this study, the nomogram model for MACEs after PCI was established using the independent risk factors, and its accuracy was validated by discrimination (*i.e.* C-index). C-index refers to the property of precisely screening the possibility of postoperative MACEs, ranging from 0.5 (no predictive ability) to 1 (complete predictive ability) (18-20). The C-index of the nomogram model prepared in this study was 0.768 (95% CI: 0.692-0.865), illustrating good concordance between predicted value and observed value, as well as preferable predictive value, so the nomogram model can be used as an auxiliary prediction tool for clinical AMI patients after PCI to some extent. In terms of the accuracy and validity evaluation of the established nomogram model, the risk was underestimated by the model when the event rate was less than 35% and at 55-100%, while it was overestimated when the event rate was 35-55%, and the predicted value of the model was completely concordant with the observed value when the event rate was 35% and 55%. In general, the accuracy of the model was relatively high. Nevertheless, the clinical practice value of the nomogram model needs to be validated by more clinical data because of limited sample size of this study.

In conclusion, the levels of serum Gal-3 and sST2 are the independent risk factors for MACEs

in AMI patients following PCI, with good prognostic value. The nomogram model constructed based on the independent risk factors for MACEs can predict the MACE risk in such patients. However, this study still has limitations. BUN may not be the best parameter for describing kidney function; glomerular filtration rate should be calculated and included in the analysis, considering that both the sST2 and galectin-3 levels, and outcomes may be influenced by the RFG. Besides, patients with STEMI and non-STEMI have been analyzed together, but they may exhibit different inflammatory patterns. Moreover, the sample size of this single-center study is small, which may induce bias in multivariate logistic regression analysis. Further in-depth multicenter studies with larger sample sizes are ongoing to validate the findings herein.

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Authors'contribution

FZ: designed the study; FY and SS: conceived and supervised the study; HY and LS: performed and analyzed the experiments; JT: drafted the paper.

Conflict of interest

The authors report no conflicts of interest.

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