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Involvement of Serum Matrix Metalloproteinase-9 in the Pathogenesis of Acute Myocardial Infarction

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Objectives: Prior studies indicate that matrix metalloproteinase-9 (MMP-9) plays a key role in pathogenesis of plaque rupture. The objective of this study was to evaluate the involvement of serum MMP-9 enzyme at pathogenesis of the plaque rupture in coronary atherosclerosis. **Methods:** The study enrolled 80 consecutive patients who underwent percutaneous coronary intervention in our institution. Inclusion in the case group (n = 40) required a ruptured coronary atherosclerotic plaque confirmed by conventional angiography, whereas inclusion in the control group (n = 40) required stable coronary atherosclerosis. Serum MMP-9 levels were determined by ELISA. Cardiac Infarction Injury Score (CIIS) by electrocardiogram and Gensini score (Coronary Angiographic Scoring System) were utilized for assessing the severity of coronary artery disease. **Results:** The average level of MMP-9 was significantly higher in the case group than in the control group (396±155 ng/mL vs. 223±87 ng/mL, $p<0.001$) with further demonstration that MMP-9 is an independent predictor of plaque rupture ($\beta = 0.985$, $p<0.001$). MMP-9 is well correlated with Gensini and CIIS score ($r = 0.552$, $p <0.01$ and $r = 0.340$, $p<0.01$, respectively). Furthermore, serum MMP-9 enzyme significantly increased in accordance with the severity of the myocardium damage ($p <0.01$) by CIIS score. **Conclusion:** MMP-9 plays a role at pathogenesis of plaque rupture in coronary atherosclerosis.

Keywords: Matrix Metalloproteinase 9, Myocardial Infarction, Coronary Atherosclerosis, Coronary Angiography

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide (31% of total deaths) [1]. In the last 20 years, CVD has also been the leading cause of all deaths in the Mongolian population, which accounts for one of every three cases [2]. Thrombogenesis and plaque rupture of coronary atherosclerosis is an important pathogenesis mechanism of acute myocardial

infarction (AMI). Myocardial perfusion suddenly deficit from thrombogenesis leads to unstable angina, myocardial infarction and sudden death [3].

The enzyme matrix metalloproteinase-9 (MMP-9) is one of the 25 subgroups of MMP enzymes and MMPs 2 and 9 appear specialized for non-fibrillar collagens, including type IV, which is a major component of basement membranes [4]. Coronary atherosclerotic plaque has been known to contain MMP-1, MMP-2, MMP-8, MMP-9, MMP-13 enzymes and their mRNA. MMP-9 is more frequently synthesized from foam cell and other inflammation cells in the coronary atherosclerotic plaque than other MMPs. Serum levels of MMP-9 have been shown to be correlated with plaque rupture ($p < 0.005$), a marker for plaques vulnerable to rupture. The MMP-9 participates in the plaque rupture of coronary atherosclerosis in AMI [5].

For all of these reasons, there has been interest in developing an assay for the measurement of MMP-9 in peripheral blood in patients with AMI. A previous investigation showed that patients with AMI had either very increased or normal MMP-9 concentrations (6 with high and 7 with normal concentrations) on day 1, whereas patients with unstable angina all had high concentrations initially. The authors hypothesized that the increased concentrations were related to inflammation in the plaques, which in aggregate might be related to the extent of coronary artery disease (CAD). MMP-9 plasma levels in the coronary circulation of patients with unstable angina were significantly increased, as compared to stable angina [6]. Overexpression of MMP-9 promotes intravascular thrombus formation by degrading the fibrous cap and coagulation is further enhanced by MMP-9-mediated cleavage of the tissue factor pathway inhibitor [7]. Serum MMP-9 levels have been directly associated with the complications of coronary atherosclerotic plaque [8]. Some researchers reported the clinical applicability of this enzyme as a marker of prognosis in patients with AMI [9]. The purpose of this study is to evaluate the involvement of serum MMP-9 enzyme at pathogenesis of plaque rupture in coronary atherosclerosis.

Materials and Methods

This study was conducted using a case-control design within February 2014 to May 2015. Initially, 80 patients who had coronary angiography were included from the departments of cardiovascular diseases at Songdo Hospital and Shastin National Hospital in Ulaanbaatar, Mongolia. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The main inclusion criteria for the case group were that the 40 patients had a ruptured coronary atherosclerotic plaque. Also 40 stable angina patients with coronary stenosis or chronic occlusion without ruptured plague were included in the control group confirmed by a conventional coronary angiography. The level of serum MMP-9 was determined by the enzyme-linked immunosorbent assay (ELISA). We used Cardiac Infarction Injury Score (CIIS) by electrocardiogram (ECG) and Gensini score system (Coronary Angiographic Scoring System) for assessing the severity of coronary heart disease.

1. Case group

The case group involved participants who had type 1 AMI according to the 2014 European Society of Cardiology Guidelines for the management of AMI in patients presenting with ST-segment elevation [10]. Type 1 AMI is characterized by atherosclerotic plaque rupture, ulceration, fissure, erosion or dissection with resulting intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow or distal embolization and subsequent myocardial necrosis. Type 1 AMI patients met the following criteria: (1) symptoms of acute coronary syndromes occurred suddenly and lasted for more than 2 hours, (2) acute myocardial ischemic syndrome was detected on new or presumed new significant ST-T wave changes or left bundle branch block on 12 lead ECG, (3) the serum troponin I was increased (serum troponin I or T was positive) and (4) intracoronary thrombus related to plaque rupture was detected by coronary angiography in epicardial arteries.

2. Control group

The control group included patients that had stable coronary atherosclerosis according to the 2013 European Society of Cardiology Guidelines on the management of stable coronary artery disease [11]. The patients were collected according to the following criteria: (1) chronic coronary disease (Rose angina questionnaire had specificity of 80-95%), (2) no signs of acute coronary syndrome on the ECG, (3) enzymes of myocardial

infarction were not detected in the serum and (4) atherosclerotic stable stenosis (no plaque rupture and new thrombus formation) were detected at coronary angiography.

3. ECG and Cardiac Infarction Injury Score (CIIS)

ECG was performed using a standard ECG apparatus (Schiller AT, Schiller Inc., USA) with a conventional 12 lead ECG. CIIS was calculated in accordance with the standard evaluation (Table 1). For the evaluation of the myocardial infarction damage level CIIS's sensitivity is 85% and specificity is 95% [13].

4. Coronary angiography

The surgery area was sterilized according the proper procedure; radial and femoral artery were punctured with the Seldinger technique approach. At the punctured section, the 6F introducer was located and with the help of the guide, JR catheters and JL catheters (B. Braun Medical Inc., Germany) were placed in the left and the right coronary arteries, respectively. Diagnostic coronary angiography was performed by injecting ultravist contrast solution (Iopromide, Bayer HealthCare Inc., USA). Right and left coronary artery stenosis was evaluated based on

Table 1. Cardiac infarction injury score classifier for practical visual coding of electrocardiograms

Component	Lead	Feature	Threshold	Score[c]
1	aVL	Q duration in seconds (measured to nearest threshold)	Q absent	5
			0.010	1
			0.020	3
			0.030	9
			0.040	10
			0.050	12
2	aVL	T amplitude in mm[a], if T negative add 2 points for each mm[b]	≤0.5 or	
			≥3	3
			2	
3	-aVR	R amplitude in mm = R (subtract 1 point for each mm)	-1	-R
4	-aVR	T amplitude (positive phase) in mm, subtract 2 additional points for each mm exceeding 4	0	6
			1	3
			2	0
			3	-2
			4	-5
5	II, aVF	Largest Q:R amplitude ratio	≥1/20	12
6	III, -aVL	Largest Q duration in seconds	≥0.040	5
7	III	T amplitude (negative phase) in mm	>1	5
8	V1	T amplitude (positive phase) in mm	>2	5
9	V2	R amplitude in mm	<3 or ≥14	5
10	V2	T amplitude (negative phase) in mm	≥1/4	5
11	V3	Q:R amplitude ratio	>1/20	9
12	V5	S amplitude in mm	<2	5

[a]Absolute values of negative amplitudes are used. The T amplitude (positive and negative phase) is measured as the absolute value of the largest deflection above and below the PR baseline in a window spanning from 80 milliseconds after the end of QRS to the end of T. [b]The amplitudes are measured in standard millimeters (1 mm = 0.l mV). [c]CIIS severity levels: level A, CIIS 20, probable injury; level B, CIIS 15, possible injury: level C, CIIS 10, borderline abnormality.

the angiographic image and coronary intervention treatment indicated when necessary. Consequently, the treatment procedure involving stent placement with appropriate balloon expansion was performed when required.

5. Gensini score

First, the section and the degree of the stenosis in the right and left coronary arteries were evaluated based on the coronary angiography using Gensini score [14, 15]. Second, the severity of the coronary atherosclerosis was estimated using the Gensini score (Figure 1). For example, if there was 50% stenosis in the middle section of the right coronary artery and 75% stenosis in the proximal section of the left anterior descending artery, the Gensini score would be 12 calculated as follows: [2 (right coronary artery – 50%) x 1 (middle site)] + [4 (left anterior descending – 75%) x 2.5 (proximal site)] = 2 x 1 + 4 x 2.5 = 2 + 10 = 12.

6. Matrix metalloproteinase-9 (MMP-9)

From the patient who underwent diagnostic or treatment coronary angiography, 5 mL of peripheral blood was collected. The serum was separated after using a centrifuge with a speed of 1000 rpm for 15 minutes and it was stored at -20°C. Serum MMP-9 level was identified according to the protocol recommended by the manufacturer of the ELISA kit (Human MMP-9 Quantikine, R and D Systems Inc., USA). The concentrations were measured at 450 nm and the calibration was done using a standard curve.

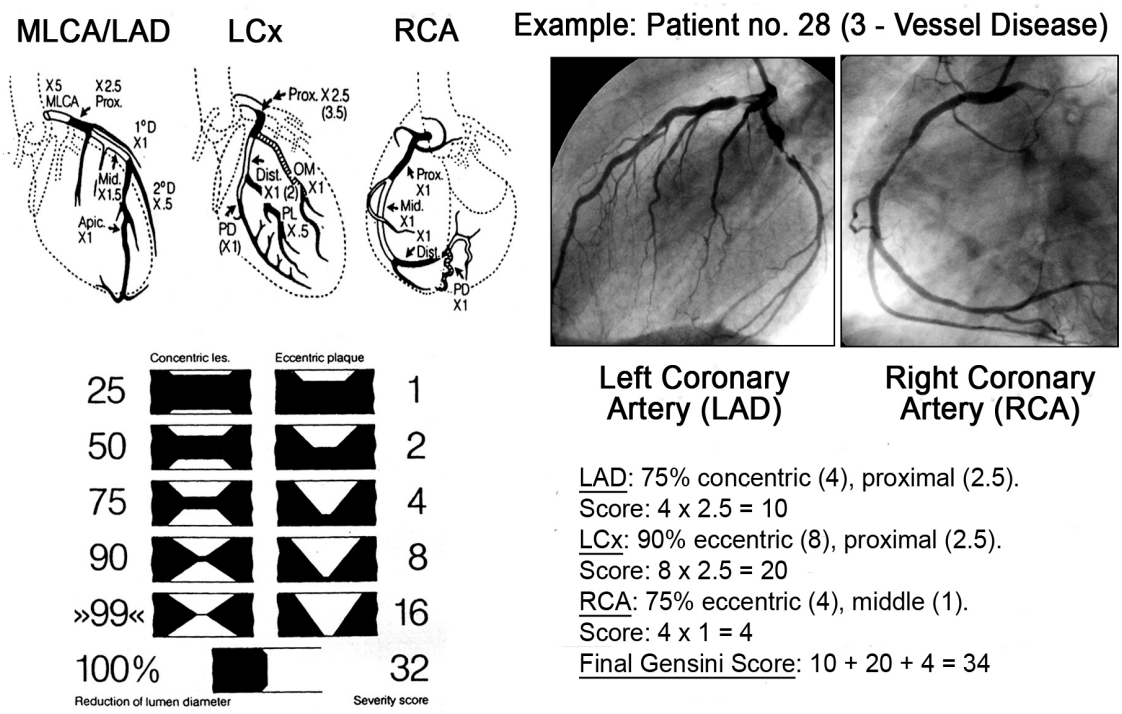

Figure 1. Drawing of the Gensini score. This method evaluates a total score depending on the degree of stenosis, its location (proximal, middle or distal site) in the vessel and the type of coronary vessel involved (left anterior descending (LAD), left circumflex (LCx) or right coronary artery (RCA)). An example of Gensini score calculation is shown on the right part of the figure. MLCA = main left coronary artery.

7. Statistical analysis

For the statistical analysis, the mean and standard deviations (SD) were calculated and the independent sample t-test, one-way analysis of variance (ANOVA) test, binary logistic regression, and receiver operating curve (ROC) were applied to the data using SPSS (version 21, SPSS Inc., Chicago, IL, USA) computer application. Statistical significance was considered as $p < 0.05$.

Results

A total of 80 subjects participated in this research, 40 in the case group and 40 in the control group. The mean age was 58.2 ±11.3 years old. The indicators or variables such as white blood cells, segmented neutrophils, smoking index, physical activity, body mass index, heart rate, systolic heart rate, and diastolic rate was not statistically different between the case and control groups (p >0.05, Table 2).

Table 2. Mean and standard deviation for the characteristics of each group

Variables	Case group (n = 40)	Control group (n = 40)	p-value
Age (years)	57.6 ±9.89	58.8 ±12.6	0.612
Smoking index (pack/day)	32.8 ±15.5	30.2 ±17.1	0.120
Physical activity (score)	13.4 ±14.0	12.6 ±14.4	0.881
Body mass index (kg/m^2)	30.1 ±4.4	27.1 ±4.7	0.759
Heart rate (beats/min)	75.3 ±12.7	71.1 ±11.1	0.118
Systolic blood pressure (mm Hg)	124.4 ±19.2	126.5 ±19.8	0.706
Diastolic blood pressure (mm Hg)	77.3 ±14.3	77.3 ±14.3	0.397
White blood cell count (1 x 10^6)	5.9 ±1.13	5.7 ±0.87	0.475
Segmented neutrophils (%)	57.2 ±3.11	52 ±1.01	0.269
CIIS score	17 ±6.4	10.8 ±6.2	<0.001
Gensini score	49.5 ±35.4	8.84 ±14.3	<0.001
MMP-9 (ng/mL)	396 ±155	223 ±87	<0.001

However, CIIS and Gensini scores were statistically higher in the case group than in the control group (p <0.001, Table 2). A moderate correlation was observed between myocardial infarction injury score and Gensini score (r = 0.34, p <0.01) showing that the myocardial injury is directly related to the coronary stenosis stage.

Serum MMP-9 level in the case group (396 ±155 ng/mL) was higher than that in the control group (223 ±87 ng/mL) (p <0.001). The binary logistic regression analysis indicated that the serum MMP-9 level was an independent predictor of coronary plaque rupture (β = 0.985, CI: 0.97-0.99, p <0.001). When the serum MMP-9 levels increased by approximately 1 ng, the risk of plague rupture increased by 0.1%.

By receiver operating curve analysis it was determined that serum MMP-9 enzyme area was equal to 0.85 (approximately, sensitivity is 80% and specificity is 85%) while being used as a diagnostic test for the rupture of coronary atherosclerosis plaque and formation of thrombosis (Figure 2). Therefore, the enzyme is not only a factor for causing the complication but also it can be used as a marker in diagnosing of such complications. Moreover serum MMP-9 enzyme level has a direct moderate correlation with Gensini score with statistical significance (r = 0.552, p <0.01).

Coronary atherosclerosis changes are divided into four main groups. These are: (1) coronary arteries with no stenosis or unchanged (left main, left descending artery, circumflex and right coronary arteries, no significant severe stenosis or <75% stenosis); (2) coronary artery has one significant severe stenosis (one of the vessels has >75% stenosis); (3) coronary artery has two significant severe stenoses (two of the vessels have >75% stenosis); (4) coronary artery has three significant severe stenoses (three of the vessels has >75% stenosis). As the number of the arteries with stenosis increased, the MMR-9 enzyme serum titer increased along with it and was significant (p <0.001, one-way ANOVA test, Table 3, Figure 3).

The cardiac injury cases were divided into three groups according to the CIIS: (1) ischemic injury (CIIS <10, [MMP-9] 227 ±99 ng/mL), (2) infarction injury (CIIS 10-15, [MMP-9] 315

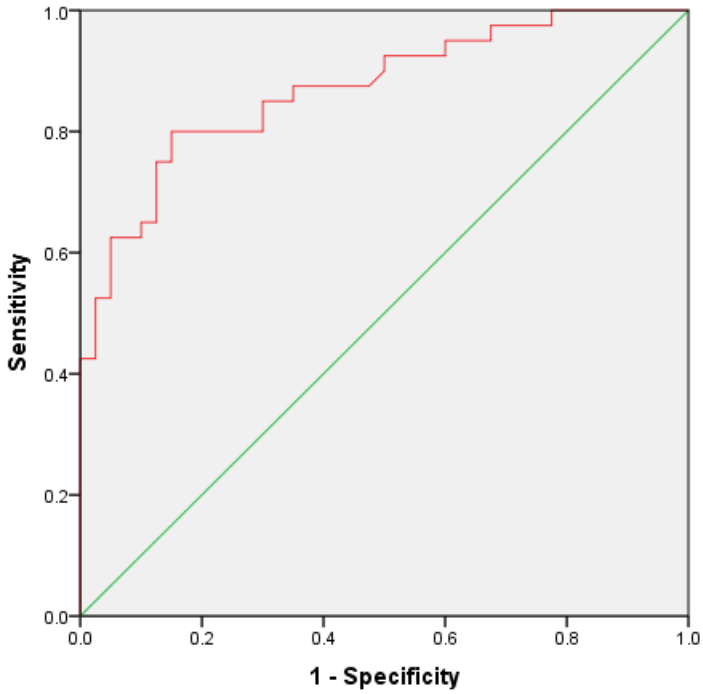

Figure 2. Receiver operating characteristic curve showing the diagnostic validity of serum MMP-9 in plaque rupture of coronary atherosclerosis. The diagonal line segment was produced by ties.

Table 3. One-way ANOVA test of serum MMP-9 enzyme in coronary atherosclerosis changes

Variable	n	Mean ±SD (ng/mL)	95% Confidence interval		F	p-value
			Lower bound	Upper bound		
No significant stenosis	23	245 ±85.9	208.3	282.6	4.176	0.001
1 significant stenosis vessels	32	312 ±23.4	264.7	360.2		
2 significant stenosis vessels	19	157 ±35.9	272.9	423.9		
3 significant stenosis vessels	6	133 ±14.9	304.2	540.1		

±116 ng/mL), (3) infarction severe injury (CIIS >15, [MMP-9] 376 ±132 ng/mL). The average serum MMP-9 was calculated in each group and it was determined that the more severe the cardiac injury, the higher the MMP-9 level was ($p<0.05$, one-way ANOVA test).

Discussion

The main findings of this observational study are two: (1) the serum MMP-9 level was higher in patients with AMI than in those with stable coronary disease, (2) the degree of increase in serum MMP-9 was well correlated with the degree of coronary stenosis as well as myocardial injury score.

The MMP-9 level in the case group (patients with the coronary atherosclerotic plaque rupture in the myocardial infarction) was significantly higher than those in the control group (396 ±155 ng/mL vs. 223 ±87 ng/mL; $p<0.001$) which is in line with the result by Fiotti et al. [16] and Koizumi et al. [17]. In addition, the probability of plaque rupture increased by 0.1% as the MMP-9 levels in serum increased by 1 ng ($\beta = 0.985$, $p<0.001$) [18].

One human study has suggested that circulating levels of MMP-9 are released from the culprit lesion in acute coronary syndrome and our results showed that high levels of MMP-9 in the case group and control groups might correpsond to event-related ruptured plaque at the culprit site. The MMP-9 enzyme is

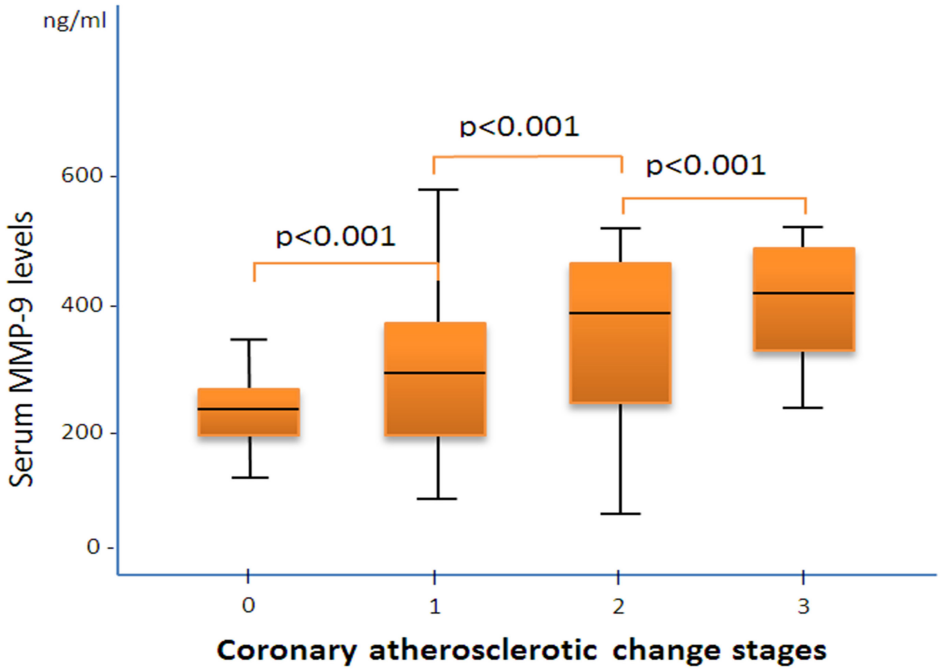

Figure 3. Change of serum MMP-9 levels by coronary atherosclerotic change group.

released from foam cells and macrophage cells in the plaque and it is possible that it might help breakdown collagen components and connective tissue within the plaque [19].

The receiver operating curve analysis (area = 0.87) shows that the serum MMP-9 enzyme level can be a diagnostic indicator of complications of plaque rupture and thrombosis in the coronary arteries. This conclusion confirms result of the Popović et al. [18] and Kobayashi et al. [20]. Also, our research results show that the serum MMP-9 levels increase in accordance to the coronary stenosis stage ($p < 0.001$), which was a similar outcome shown by Phatharajaree et al. [8].

Gensini score showing the coronary atherosclerotic stage was directly dependent on the serum MMP-9 levels ($r = 0.552$, $p < 0.01$). This is similar to the result by Zhou et al. ($r = 0.225$, $p < 0.05$) [21] and Wang et al. [22]. Increasing evidence indicates that MMPs have been identified in the vascular remodeling process and play important roles in the pathogenesis and progression of atherosclerosis, especially plaque formation and rupture [23]. MMP-9, which belongs to the gelatinase subclass of the MMP family, has the potency for collagen-cleaving and disintegrating extracellular plaque matrix, thus causing instability and rupture to collagens containing plaque [24]. Clinical studies have shown that the serum MMP-9 level could also be correlated to the severity of CAD [25] and to the rapid luminal narrowing of the coronary artery in patients with stable angina [26]. Furthermore, the expression of serum MMP-9 has been found to be increased in patients with acute coronary syndrome (ACS) [27]. These results indicate that an elevation of these enzymes accompanies processes such as plaque rupture that precipitate ACS. A recent study also indicates that the serum level of MMP-9 might be a sensitive marker and a predictor of cardiovascular mortality in patients with CAD [28].

In our study there was no significant difference between the case and control group in the coronary heart disease risk factors such as smoking, hypertension, exercise level, body mass index, age and sex. In our opinion, it was because both groups of patients had already been diagnosed with coronary atherosclerosis disease. Also, these coronary risk factors do not affect the rupture of coronary atherosclerotic plaque. MMP-9, a biomarker for plaque rupture or vulnerability, but not for myocardial damage, is more useful for diagnosing the earliest stage of ACS than biomarkers of myocardial damage [29].

The present study only compared MMP-9 levels between patients with AMI (mostly ST-elevation myocardial infarction - STEMI) and stable CAD. MMP-9 levels might be utilized to distinguish ACS with ACS-mimicking non-coronary disease.

Furthermore, the effects of percutaneous coronary intervention procedures on MMP-9 level during the acute stage of STEMI need to be further clarified. Due to the limitation of the present study, that is, the relatively small sample size, the present findings need to be confirmed by multicenter studies with larger cohorts. An increase in serum MMP-9 enzyme levels is a risk factor of the coronary atherosclerotic plaque rupture. MMP-9 is also well correlated with the degree of coronary stenosis and myocardial injury, suggesting it has value as a novel prognostic marker in these patients.

Conflict of Interest

The authors state no conflict of interest.

Acknowledgements

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