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Original Article

Association between serum MFG-E8 levels and coronary severity index in patients with acute coronary syndrome

Akut koroner sendrom hastalarında koroner arter hastalığı ciddiyeti ile serum MFG-E8 düzeyleri arasındaki ilişki

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ABSTRACT

Aim: MFG-E8 (milk fat globule-epidermal growth factor 8, also known as lactaderin) plays an important role in many adverse clinical conditions such as atherosclerosis, angiogenesis, ischemia/reperfusion injury, and cancers. The present study aims to investigate the association of serum MFG-E8 levels at admission with the severity of coronary artery disease (CAD) in patients with acute coronary syndrome (ACS).

Material and Methods: A total of 88 patients were enrolled in the study. Patients were divided into two groups according to SYNTAX score as low SYNTAX score <23 (n=75) and high SYNTAX score ≥23 (n=13).

Results: In correlation analysis, there was no statistically significant correlation between serum MFG-E8 levels and SYNTAX score (r = 0.029; p>0.05). However, there was a moderate and negative correlation between MFG-E8 levels and Thrombolysis In Myocardial Infarction (TIMI) risk score (r = -0.365, p = 0.001). A slightly negative association between serum uric acid level and MFG-E8 was also determined (r = -0.232, p = 0.03). In addition, diabetes mellitus (p = 0.031), monocyte to HDL ratio (p = 0.049), TIMI risk score (p = 0.004) and SYNTAX II (p = 0.012) score were significantly higher in the high SYNTAX group with a significantly lower LVEF (p = 0.014).

Conclusion: The serum levels of MFG-E8 were not found to be correlated with the SYNTAX score, an indicator of worsening clinical cardiovascular event risk and the severity of coronary artery stenosis. However, MFG-E8 levels were found to be correlated with TIMI risk score, which is one of the most commonly used risk stratification model for patients presenting with non-ST segment elevation myocardial infarction (NSTEMI).

Key words: Myocardial infarction, SYNTAX score, Inflammation, MFG-E8, Acute coronary syndrome, TIMI risk score

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ÖZ

Amaç: MFG-E8 (süt yağı globül-epidermal büyüme faktörü 8, laktaderin olarak da bilinir) ateroskleroz, anjiyogenez, iskemi/reperfüzyon hasarı ve kanserler gibi birçok olumsuz klinik durumda önemli rol oynamaktadır. Bu çalışmada, akut koroner sendrom (ACS) hastalarında başvuru sırasında serum MFG-E8 düzeyinin koroner arter hastalığı (CAD) ciddiyeti ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya toplam 88 NSTEMI hastası alındı. Hastalar SYNTAX skorlama sistemine göre düşük SYNTAX skoru olanlar <23 (n=75) ve yüksek SYNTAX skoru olanlar ≥23 (n=13) olarak iki gruba ayrıldı.

Bulgular: Korelasyon analizinde, MFG-E8 ile SYNTAX skoru arasında ilişki saptanmadı (r = 0.029, p>0.05). Ancak, MFG-E8 ve TIMI risk skoru arasında orta derece negatif korelasyon saptandı (r = -0.365, p = 0.001). Ek olarak, MFG-E8'in serum ürik asit düzeyi ile hafif negatif ilişkisi vardı (r = -0.232, p = 0.03). Ayrıca SYNTAX skoru yüksek olan grupta diyabetes mellitus (p = 0.031), monosit/HDL oranı (p = 0.049), TIMI risk skoru (p = 0.004) ve SYNTAX II (p = 0.012) skoru daha yüksek saptanırken, LVEF anlamlı olarak daha düşüktü (p = 0.014).

Sonuç: NSTEMI hastalarında MFG-E8 düzeyleri, daha kötü klinik kardiyovasküler olay riski ve koroner arter hastalığı ciddiyeti göstergesi olan SYNTAX skoru ile ilişkili değildir. Ancak, NSTEMI ile başvuran hastalarda en sık kullanılan risk sınıflandırma modellerinden biri olan TIMI risk skoru ile serum MFG-E8 seviyeleri arasında negatif ilişki bulunmaktadır.

Anahtar Kelimeler: Miyokard enfarktüsü, SYNTAX skoru, İnflamasyon, MFG-E8, Akut koroner sendrom, TIMI risk skoru

Introduction

Acute myocardial infarction (AMI) is an important cause of morbidity and mortality all around the world. Atherosclerosis plays a significant role in the development of the majority of cardiovascular diseases [1,2]. In atherosclerosis, a gradual accumulation of fibrous tissue and cholesterol in the form of plaques results in narrowing of the arterial lumen and it is the main cause of non-ST segment elevation acute myocardial infarction (NSTEMI). Inflammation is a component of the atherosclerotic process [3,4]. It is now widely accepted that all developmental stages of atherosclerosis are mediated, in large part, by inflammatory factors, including increasing plaque instability, resulting in subsequent clinical events such as unstable angina, myocardial infarction, sudden death, and stroke [5,6].

MFG-E8 is a peripheral glycoprotein that acts as a bridge molecule between phosphatidylserine on apoptotic cells and integrin receptors on phagocytes, thus playing a major role in the phagocytosis of apoptotic cells in necrotic tissues [7,8]. It is secreted by activated macrophages and dendritic cells and performs a wide variety of functions in cellular physiology [8,9]. As an anti-inflammatory factor, it provides defense against the adverse effects of inflammation. Therefore, MFG-E8 is a protective factor in coronary artery disease (CAD). Membranes of apoptotic cells are particularly rich in pro-inflammatory oxidized phospholipids. Macrophage-derived MFG-E8 specifically binds apoptotic cells by recognizing aminophospholipids such as phosphatidylserine. Phagocytosis of apoptotic cells has immunosuppressive effects on phagocytes; it has been reported that proinflammatory cytokine production (eg, IL-6) decreases in macrophages after phagocytosis of apoptotic cells, whereas anti-inflammatory cytokine production (eg, IL-10, TGF-β) increases [10,11]. In addition to its critical role in efferocytosis, MGF-E8 possesses a known pro-angiogenic effect supporting vascular endothelial growth factor (VEGF) function in adult neovascularization [12]. However, a few studies have been reported on the relationship between MFG-E8 and CAD.

In this study, we aimed to evaluate the association between MFG-E8 levels and coronary severity index assessed by SYNTAX score in patients with NSTEMI. Thus, we can estimate the extent of CAD without invasive coronary intervention.

Material and Methods

Study Population

A total of 88 patients who presented to our emergency department with a first episode of NSTEMI between December 2021 and February 2022 were consecutively enrolled in this cross-sectional, single-center study. Exclusion criteria included previous PCI or coronary artery bypass grafting history, presence of decompensated heart failure, severe liver and kidney diseases, autoimmune diseases, malignancies, hematological disorders, severe valvular disease, and inflammatory or infectious diseases. A definitive NSTEMI diagnosis was made according to current guidelines [13,14].

Written informed consent was obtained from each patient and the study protocol was approved by the Yozgat Bozok University Ethics Committee. The study was conducted by the principles of the Declaration of Helsinki.

Age, gender, history of CAD and cardiovascular risk factors of the patients were recorded in their files. The patients with repeated blood pressure measurements >140/90 mm Hg and those on antihypertensive drugs were considered hypertensive patients. The patients with fasting plasma glucose levels >126 mg/dL on multiple measurements and those on antidiabetic medications were considered diabetic. The family history of the patients with CAD was considered positive if 1 member of the patient's immediate family died suddenly before the age of 65 years in the case of women or 55 years in the case of men or there was a positive history of CAD.

Laboratory Measurements

Peripheral venous blood samples were obtained from the patients by atraumatic puncture from the antecubital vein at the time of diagnosis, before sending to the catheter laboratory. Levels of blood biochemical parameters including urea, creatinine, uric acid, sodium, potassium, lipid panel, and high-sensitivity C-reactive protein (hs-CRP) were measured using the Beckman Coulter AU 5800 autoanalyzer. Low-density lipoprotein (LDL) was calculated using the Friedewald equation. An automated blood cell counter (Beckman Coulter LH 750; Beckman Coulter Inc., USA) was used to analyze complete blood count variables.

The serum samples taken to measure the level of MFG-E8 were centrifuged at 2000 rpm for 20 minutes at 4 °C. The serum samples were separated and stored at -80°C until analysis. Serum MFG-E8 levels were measured using a commercial ELISA (SunRed Biotechnology Campany, Shanghai Sunred Biological Technology Co., Ltd. Hu Tai Road. Baoshan District. Sanghani, China.) kit.

Transthoracic echocardiography was performed in all patients and Simpson's method was used to calculate left ventricular ejection fraction (LVEF).

Angiographic Analysis

Standard Judkins technique (Expo; Boston Scientific Corporation, Natick, Massachusetts, USA) and Siemens Axiom Sensis XP device (Munich, Germany) were used for coronary angiography. Each coronary artery was visualized in at least two perpendicular planes. All coronary angiographic images were digitally recorded for quantitative analysis. According to clinical practice standards, percutaneous coronary intervention (PCI) was performed using iopromide (low osmolarity and non-ionic contrast agent). Before the intervention, all patients received 180 mg of ticagrelor or 600 mg of a loading dose of clopidogrel and 300 mg of acetylsalicylic acid. Unfractionated heparin was administered during the intervention. The use of the stent type (naked or drug-coated) and the glycoprotein IIb/IIIa receptor inhibitor tirofiban is left to the discretion of the operator.

Two independent and experienced interventional cardiologists, unaware of the patient's clinical data, reviewed the digital angiograms and calculated the SYNTAX scores. There was no difference between interventional cardiologists for the calculated SYNTAX scores. Each lesion 1.5 mm in diameter and 50% stenosis was scored using the online SYNTAX Score Calculator version 2.1 (www.syntaxscore.com). According to this scoring system, the study population was divided into two groups as those with low SYNTAX score <23 (n=75) and those with high SYNTAX score ≥23 (n=13).

Statistical Analysis

Statistical analysis was performed using SPSS software version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the distribution pattern of the data. Normally distributed continuous data were shown as mean ± standard deviation and abnormally distributed continuous data as median (Interquartile range 25-75). On the other hand, categorical variables were presented as percentages and numbers. A t-test was used to compare parametric continuous variables. Mann-Whitney U test was used for non-parametric continuous variables. Categorical variables were compared using Pearson's chi-square and Fisher's exact test. Spearman correlation analysis was used to determine the correlation of MFG-E8 levels with the SYNTAX score. A value of $p<0.05$ was considered statistically significant.

Results

A total of 88 NSTEMI patients were included in this study. The average age of 88 patients was 61.6 ± 10.1 and 65.9% (58) of the patients were male. The baseline demographic, clinical, laboratory, and angiographic characteristics of study patients are shown in Table 1.

In correlation analysis, there was no statistically significant correlation between serum MFG-E8 levels and SYNTAX score (Spearman's Rho: 0.029; $p>0.05$, Figure 1). In addition, no correlation was found between inflammation biomarkers (such as platelet/lymphocyte ratio, monocyte/HDL ratio, systemic inflammation index, hs-CRP), LVEF, pro-brain natriuretic peptide (pro-BNP) and serum MFG-E8 levels (Table 2). However, there was a moderate and negative correlation between MFG-E8 levels and TIMI score (Spearman's Rho: -0.365, $p = 0.001$, Table 2). Moreover, a slightly negative association between serum uric acid level and MFG-E8 was also determined (Spearman's Rho: -0.232, $p = 0.03$, Table 2).

Table 1. Baseline Demographic, Clinical, Laboratory and Angiographic characteristics of study patients

	All patients (n=88)	Low SYNTAX score (n=75)	High SYNTAX score (n=13)	p value
Age [year]	61.6 ± 10.1	61.8 ± 10.1	60.4 ± 10.3	0.654
Male gender [n (%)]	58 (65.9)	48 (64)	10 (76.9)	0.529
Diabetes mellitus [n (%)]	37 (42)	28 (37.3)	9 (69.2)	0.031
Hypertension [n (%)]	44 (50)	40 (53.3)	4 (30.8)	0.133
Smoking [n (%)]	33 (37.5)	27 (36)	6 (46.2)	0.747
Family history of CAD [n (%)]	18 (20.5)	16 (21.3)	2 (15.4)	0.624
LVEF [%]	50 (45-55)	52 (46-55)	40 (35-50)	0.014
Urea [mg/dl]	34 (27.2-44.7)	33 (28-44)	36 (26-45.5)	0.874
Creatinine [mg/dl]	0.75 (0.64-0.91)	0.76 (0.64-0.92)	0.71 (0.63-0.79)	0.394
Uric acid [mg/dl]	5.3 (4.4-6.4)	5.3 (4.5-6.4)	5.5 (4.1-6.7)	0.685
Sodium [mmol/L]	136 (134-138)	136 (134-138)	136 (136-137.5)	0.319
Potassium [mmol/L]	4 (3.8-4.3)	4 (3.7-4.3)	4.2 (3.9-4.4)	0.169
Total cholesterol [mg/dl]	193 (163-227)	192.5 (162.5-221)	212 (170-258.5)	0.180
Triglyceride [mg/dl]	109 (72-193)	126 (69.7-186.2)	90 (79-224.5)	0.721
LDL cholesterol [mg/dl]	121 (105-154)	119 (105-152)	153 (102-159)	0.325
HDL cholesterol [mg/dl]	43 (36-47)	42.1 (36.7-47)	46 (36-51)	0.356
White blood cell count [10^3/µL]	9 ± 2.4	9 ± 2.4	9.2 ± 2.3	0.709
Neutrophil count [10^3/µL]	5.3 (4.6-6.9)	5.3 (4.6-6.7)	6.2 (4.3-7.6)	0.663
Lymphocyte count [10^3/µL]	2.1 (1.5-2.9)	2.1 (1.5-3)	2.3 (1.7-2.8)	0.685
Platelet count [10^3/µL]	232 (192-276)	234 (204-274)	216 (186-331)	0.897
Hemoglobin [g/dl]	13.8 (13-14.7)	13.9 (13-14.7)	13.7 (12.7-14.9)	0.841
High-sensitivity CRP [mg/L]	0.45 (0.28-0.83)	0.45 (0.28-0.83)	0.5 (0.29-1.56)	0.560
Pro-BNP [ng/ml]	326 (169-1019)	310 (165-710)	789 (189-2265)	0.091
MFG-E8 [ng/L]	156.4 (137.1-203.7)	159.5 (136.7-210)	151.6 (138.4-187)	0.814
SYNTAX II score	25.5 (19-33.3)	24.8 (18.5-32.5)	32.4 (25.5-37.9)	0.012
TIMI score	3 (2-4)	3 (2-4)	4 (3-5.5)	0.004
Systemic inflammation index	561.6 (408.7-971.3)	603 (402-978)	527 (422-1062)	0.746
Monocyte to HDL-C ratio	14.7 (11.1-18.7)	13.7 (10.8-17.9)	15.6 (15.2-24.4)	0.049
Platelet to Lymphocyte ratio	110.4 (77.2-171)	111.4 (77.8-179.1)	96.6 (66.6-162.1)	0.545

Numerical parameters were expressed as mean ± standard deviation or median (min-max). Categorical variables were expressed as numbers and percentage. BNP, Brain natriuretic peptide; CAD, Coronary artery disease; CRP, C-reactive protein; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; LVEF, Left ventricular ejection fraction; TIMI, Thrombolysis in myocardial infarction. Bold values means statistically significant.

Table 2. Correlation between serum MFG-E8 levels and laboratory findings

Variables	r	p value
Monocyte to HDL-C ratio	0.017	0.872
Platelet to Lymphocyte ratio	-0.149	0.167
Systemic inflammation index	-0.108	0.317
Uric acid	-0.232	0.03
Hs-CRP	0.097	0.371
Pro-BNP	-0.196	0.079
SYNTAX score	0.029	0.791
SYNTAX II score	-0.138	0.199
TIMI score	-0.365	0.001
LVEF	0.09	0.403

BNP, Brain natriuretic peptide; CRP, C-reactive protein; HDL, High-density lipoprotein; LVEF, Left ventricular ejection fraction; TIMI, Thrombolysis in myocardial infarction. Bold values means statistically significant.

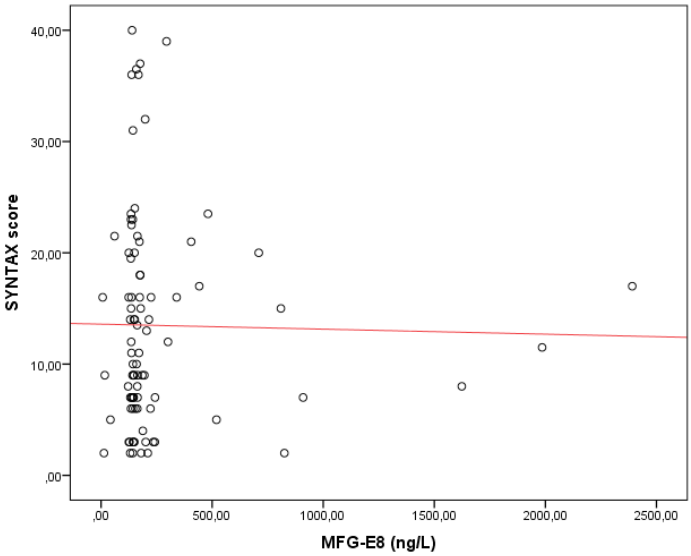

Figure 1. Correlation of MFG-E8 levels and SYNTAX score

Patients were divided into two groups according to the SYNTAX scoring system as those with low SYNTAX score <23 (n=75) and those with high SYNTAX score ≥23 (n=13). There were no statistically significant differences in age, gender, hypertension, and smoking status between the two groups ($p > 0.05$). Diabetes mellitus ($p = 0.031$), monocyte/HDL ratio ($p = 0.049$), TIMI risk score ($p = 0.004$) and SYNTAX II ($p = 0.012$) score were significantly higher in the high SYNTAX group with a significantly lower LVEF ($p = 0.014$, Table 1). And also, there was no significant difference between the groups in MFG-E8 levels (159.5 ng/L vs. 151.6 ng/L; $p = 0.814$, Figure 2).

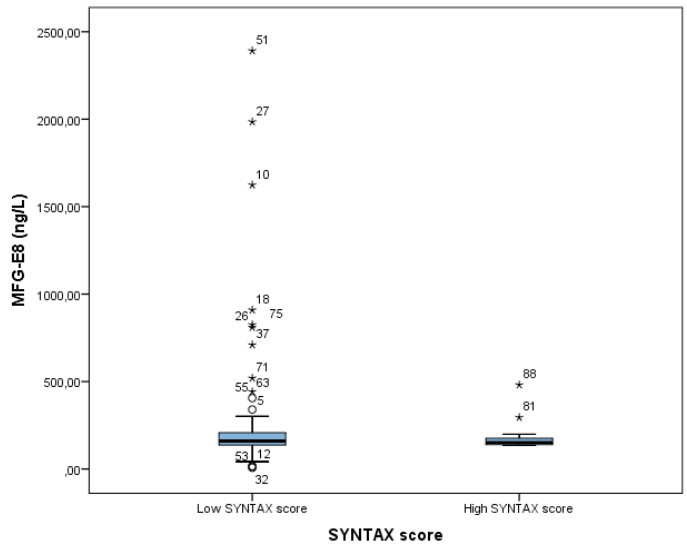

Figure 2. The relationship between SYNTAX groups and serum MFG-E8 level

Discussion

Our results indicated that there was no statistical correlation between serum MFG-E8 levels and SYNTAX score, which is an indicator of higher hospital mortality and more severe coronary atherosclerosis, in patients with NSTEMI. In addition, no correlation was found between MFG-E8 levels and inflammation biomarkers (systemic inflammation index, platelet/lymphocyte ratio, monocyte/HDL ratio, hs-CRP), LVEF, and pro-BNP. However, MFG-E8 levels were found to be correlated with TIMI risk score.

Coronary atherosclerosis is the most important cause of CAD. Intracoronary thrombus formation, which results from the rupture or erosion of the atherosclerotic coronary plaque and the incorporation of thrombogenic core and matrix materials from the plaque into the circulation, is the initiating mechanism of ACS [15]. In this process, inflammation plays a role along with many other risk factors. In addition, cardiac inflammation is a life-threatening complication of NSTEMI that causes mortality and morbidity in the general population [16].

MFG-E8 plays important role in phagocytosis by maintaining normal tissue and blood vessel integrity under inflammation and other associated stress conditions [17]. To date, MFG-E8 studies have been conducted in various animal models to demonstrate the potentially beneficial effects of inflammatory diseases (eg, colitis, renal, hepatic, and intestinal ischemia/reperfusion) [18,19]. In the majority of cases, MFG-E8 is differently expressed from the basal level under pathophysiological stress. In sepsis, intestinal injury, and neurodegenerative disease, most studies have reported down-regulation of MFG-E8 [20-22]. Inconsistent with the above findings, other studies have demonstrated increased production of MFG-E8 in human systemic lupus erythematous [23] and melanoma [24].

In a study by Ait-Oufella et al, it was shown that MFG-E8 production decreased in atherosclerotic plaques [25]. In the previous study, MFG-E8-deficient mice revealed greater numbers of apoptotic cells, increased plaque necrosis, and increased indices of inflammation (especially increased interferon-gamma) in atheroma plaques compared with the control group. Similarly, in another study, Dai et al showed that the serum level of MFG-E8 was lower in CAD (n=295) compared to controls (n=176) [26]. They also showed that MFG-E8 concentration decreased from stable angina to acute MI, thus MFG-E8 had a negative association with the clinical classification of CAD [26]. Moreover, they found a significantly negative correlation between Gensini score and the level of MFG-E8 in patients with CAD [26]. This observation may provide evidence that MFG-E8 has a role in predicting the

severity of coronary artery stenosis. In our study, contrary to previous studies, there was no correlation between serum MFG-E8 levels and SYNTAX score. One of the reasons for this result may be that our study population consisted of an isolated NSTEMI group. In addition, the power of our study may be low due to the small number of patients. Moreover, pre-hospital medication such as statin used in our study population may have affected serum MFG-E8 levels.

Hs-CRP level is an independent risk factor for CAD [27]. Several studies have reported that increased hs-CRP levels are associated with an increased risk of stroke as well as an increased rate of atherosclerosis progression in the carotid vessels [28]. Dai et al reported that serum levels of MFG-E8 were negatively correlated with hs-CRP [26]. Because of its protective effects, some studies have also focused on treatment strategies using exogenous MFG-E8. These studies determined that exogenous MFG-E8 can reduce inflammation in sepsis and renal, hepatic, intestinal ischemia/reperfusion injury by reducing proinflammatory cytokines, including tumor necrosis factor-a, interleukin (IL)-6 and IL-1b [19]. Although these results come from animal experiments, large-scale studies are still needed for clinical application.

Hyperuricemia is associated with increased mortality and poor prognosis in patients with ischemic heart disease [29]. In a study by Ndrepepa et al, high serum uric acid levels were found to be associated with increased one-year mortality in 5000 patients treated for acute coronary syndrome [30]. In another study by Kojima et al, it was shown that serum uric acid levels were an important marker in predicting heart failure and long-term mortality [31]. In our study, in accordance with other studies, a slightly significant negative correlation was found between the anti-inflammatory factor MFG-E8 and serum uric acid levels. High serum uric acid levels play an important role in oxidative stress and free radical formation [32]. The fact that membranes of apoptotic cells are rich in pro-inflammatory oxidized phospholipids and MFG-E8 interacts with phospholipids on these cells may explain the negative correlation between serum uric acid levels and MFG-E8 in our study.

Another important feature of our study was that we found a moderate and negative correlation between serum MFG-E8 levels and TIMI risk score. TIMI risk score has been demonstrated to be an effective risk stratification tool for predicting in-hospital mortality or 14-day mortality in patients with NSTEMI. A score of 3 or more on the TIMI model is recommended to have early invasive management with cardiac angiography and revascularization if necessary. The TIMI risk score is predictive of the severity of the vascular disease making it a good tool to predict the potential of coronary circulation involvement in chest pain cases [33].

Conclusion

The serum levels of MFG-E8 were not found to be correlated with the SYNTAX score. However, MFG-E8 levels were found to be correlated with the TIMI risk score, which is one of the most commonly used risk stratification model for patients presenting with NSTEMI. We are of the opinion that further, large-scale prospective studies are needed to determine the role of MFG-E8 levels in acute coronary syndrome patients.

Limitations of the study

Nonetheless, there are some limitations to this study. First, the sample size is relatively small due to the selection of patients from a single hospital, and follow-up data are not available due to the cross-sectional design of the study. Second, we were only able to measure MFG-E8 levels at admission and we could not perform serial measurements due to financial concerns. Measurement of MFG-E8 levels after the acute phase of MI will provide additional information. Third, there were no patients with obstructive CAD without NSTEMI. Finally, we did not gather any data about pre-hospital medication such as statin use that can affect the inflammatory process.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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