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Metabolic syndrome and long-term cardiovascular outcomes in NSTEMI with unstable angina

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Abstract *Background and aim:* Metabolic syndrome (MS) is associated with cardiovascular mortality and morbidity in patients with acute coronary syndrome. The purpose of this study was to evaluate the impact of MS on long-term clinical outcomes in patients with pure non-ST segment myocardial infarction (NSTEMI) or unstable angina pectoris (USAP).
Methods and results: We prospectively enrolled 310 consecutive NSTEMI/USAP patients (74 females; mean age, 59.3 ± 11.9 years). The study population was divided into two groups: MS(+) and MS(−). The clinical outcomes of the patients were followed for up to 3 years.

Increased 3-year cardiovascular mortality and reinfarction were observed in the MS(+) group, as compared to the MS(−) group (15 vs. 3.4%, $p = 0.001$, and 22.2 vs. 8.3%, $p = 0.001$, respectively). Hospitalization rates for heart failure and stroke were not significantly different between the two groups on follow-up. By a Cox multivariate analysis, a significant association was noted between MS and the adjusted risk of 3-year cardiovascular mortality (odds ratio 3.4, 95% confidence interval, 1.24–9.1, $p = 0.02$).
Conclusion: These results suggest that MS is associated with an increased risk of 3-year cardiovascular mortality and reinfarction in patients with NSTEMI/USAP.

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Introduction

Metabolic syndrome (MS) is a collection of risk factors, including dysglycemia, high blood pressure, elevated triglyceride (TG) levels, low high-density lipoprotein (HDL) cholesterol levels, and obesity that puts patients at risk for cardiovascular disease and diabetes [1]. Although the exact mechanism of MS is not understood, insulin resistance is the most commonly accepted hypothesis regarding the pathophysiology of MS [2]. MS is associated with an increased risk of cardiovascular mortality and morbidity [3], and it has been identified as a secondary target for risk reduction [4]. In acute coronary syndrome (ACS), the prevalence of MS rises to about 50% [5], and MS predisposes these patients to higher rates of complications (e.g., heart failure, stroke, and mortality) [6]. Many studies have analyzed the impact of MS on acute myocardial infarction (AMI), but none have included patients with pure non-ST segment myocardial infarction (NSTEMI) or unstable angina pectoris (USAP). Our aim was to evaluate the impact of MS using current criteria on long-term clinical outcomes in pure NSTEMI and USAP patients.

Methods

Patient population

Between January and December of 2008, 310 consecutive acute NSTEMI and USAP patients (74 females; mean age, 59.3 $\pm$ 11.9 years) who were admitted to the coronary care unit of Siyami Ersek Thoracic and Cardiovascular Surgery Center within 24 h of the first occurrence of chest discomfort were prospectively evaluated. Patients who were lost to follow-up within 3 years were excluded. The study protocol was approved by the local ethics committee.

Analysis of the data and definitions

A detailed medical history and clinical risk factors were determined for each patient at admission. Hemogram parameters were measured as part of an automated complete blood count using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Biochemical measurements were carried out by the biochemistry department using standard methods. Twelve-hour fasting serum levels of glucose, total cholesterol, triglycerides (TGs), and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were measured by standard enzymatic methods. The glomerular filtration rate (GFR) was estimated by the simplified modification of diet in renal disease equation [7]. A 12-lead electrocardiogram (ECG) was recorded in each patient immediately after hospital admission. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson's rule [8]. A physical examination was done and each patient's waist circumference was measured. The body mass index (BMI) of each patient was calculated as his/her weight in kilograms divided by the square of his/her height in meters.

USAP/NSTEMI was defined by objective evidence of acute myocardial injury/ischemia with prominent T-wave inversion or ST-segment depression on ECG and/or positive biomarkers of necrosis (e.g., troponin and creatine kinase-MB) in the absence of ST segment elevation and in an appropriate clinical setting (i.e., anginal equivalent or chest discomfort). Antiplatelet/anticoagulant agents, β-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, and statins were administered according to current guidelines. The thrombolysis in myocardial infarction (TIMI) risk score was calculated from the initial clinical history, ECG, and laboratory values of each patient on admission. The Global Registry of Acute Coronary Events (GRACE) risk score was calculated from the clinical history, ECG, and laboratory values of each patient upon first arrival [9]. Hypertension (HT) was defined as a resting systolic or diastolic blood pressure of at least 130/85 mmHg or physician-diagnosed HT. Diabetes mellitus (DM) was defined as a previous diagnosis, use of diet or antidiabetic medicines, or a fasting venous blood glucose level of 126 mg/dL on two occasions. Glucose metabolism disorder (GMD) was defined as a fasting glucose level $\geq$ 100 mg/dL and/or DM. Hypercholesterolemia was defined as a total cholesterol level of at least 200 mg/dL. Anemia was defined as a baseline hemoglobin concentration $<$13 mg/dL in males and $<$12 mg/dL in females. The patients were also evaluated according to the Killip classification system [10]. Cardiovascular mortality was defined as unexplained sudden death or death as a result of AMI, heart failure, or arrhythmia. Reinfarction was defined as an AMI occurring as an incident or recurrent MI that was confirmed by the elevation of serum troponin levels with other evidence of myocardial necrosis (European Society of Cardiology definition). Target vessel revascularization (TVR) was defined as either percutaneous or surgical revascularization of the target vessel. Major adverse cardiac events (MACE) was defined as the occurrence of cardiovascular mortality, reinfarction, or TVR. Advanced heart failure was defined as a New York Heart Association classification of at least 3. Heart failure requiring hospitalization was defined by the presence of new symptoms of dyspnea with pulmonary venous congestion requiring hospitalization.

Metabolic syndrome

Metabolic syndrome was diagnosed according to National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) criteria [1] as a complex of three or more of the following:

1. Central obesity: Waist circumference $\geq$ 102 cm (males), $\geq$88 cm (females);
2. Hypertriglyceridemia: TG $\geq$ 150 mg/dL;
3. Low HDL cholesterol: $<$40 mg/dL (males), $<$50 mg/dL (females);
4. HT: Blood pressure $\geq$ 130/85 mmHg or drug treatment for HT;
5. Fasting plasma glucose $\geq$ 100 mg/dL or drug treatment for elevated glucose.

As a side note, we collected blood samples for the measurement of fasting glucose on the second or third day of hospitalization (i.e., the stable period), not at admission.

Follow-up

Patients were followed for up to 3 years after discharge using a standardized protocol that included telephone interviews, outpatient visits, and the recording of recurrent cardiac events. The primary endpoint was cardiovascular mortality. The secondary endpoint was reinfarction, stroke, or heart failure.

Statistical analysis

The study population was classified into two groups: MS(+) and MS(−). Baseline characteristics, In-hospital and follow-up cardiac outcomes of the two groups were compared. Qualitative variables were expressed as percentages; quantitative variables were expressed as mean ± SD. A comparison of parametric values between the two groups was performed using a two-tailed Student's *t*-test. Categorical variables were compared by the likelihood ratio $(chi)^2$ or Fisher's exact test. Correlations between MS and other parameters were assessed using Spearman's rank correlation test. The variables were selected using backward stepwise logistic regression analysis, entering all those with a significant or a borderline ($p < 0.1$) association with MS. A backward stepwise multivariate Cox regression analysis, which included variables with a p value less than 0.1, was performed to identify the independent predictors of long-term cardiovascular mortality. The cumulative survival curves for cardiovascular mortality were constructed using the Kaplan–Meier method, with differences assessed using the log-rank test. A p value less than 0.05 was considered statistically significant. All statistical studies were carried out using the program SPSS (version 15.0; SPSS Inc., Chicago, Illinois, USA).

Results

The baseline characteristics of the two groups are illustrated in Table 1. Patients with MS were more likely to be female, have a history of percutaneous coronary intervention (PCI), and to have a lower LVEF and higher TIMI score. Among the components of MS, the waist circumference measurements were larger, DM and HT were more common, HDL cholesterol levels were lower, and TG and fasting blood glucose levels were higher in patients with MS, as compared to those without MS, as expected.

Table 1 Baseline characteristics of the study patients.

	MS(−) $n = 144$	MS(+) $n = 166$	p
Age (years)	59.1 (11.9)	59.3 (12)	0.85
Female	23 (15.9)	51 (30.7)	0.002
Family history	45 (31.2)	50 (30.1)	0.83
Smoking	69 (47.9)	65 (39.1)	0.12
Alcohol intake	17 (11.8)	16 (9.6)	0.54
MI history	38 (26.3)	53 (31.9)	0.29
PCI history	14 (9.7)	30 (18)	0.04
CABG history	13 (9)	20 (12)	0.4
Stroke history	3 (2)	7 (4.2)	0.29
Peripheral arterial disease history	5 (3.4)	9 (5.4)	0.41
Admission anemia	50 (34.7)	55 (33.1)	0.77
GFR < 60 (MDRD)	32 (22.2)	43 (25.9)	0.34
Hospitalization length (days)	8.8 (5.6)	8.3 (5.5)	0.47
LVEF (%)	53.9 (8)	50.7 (11)	0.007
ST depression > 1 mm	31 (21.5)	50 (34.2)	0.17
TIMI score	3 (1.5)	3.8 (1.6)	<0.001
Grace score	115.9 (30.1)	117.3 (28.9)	0.27
Killip > 1	3 (2)	11 (6.6)	0.06
MS components			
Waist circumference (cm)	93.6 (7.1)	101.9 (8.9)	<0.001
Diabetes mellitus	21(14.5)	70 (42.1)	<0.001
Hypertension	75 (52)	118 (71)	<0.001
HDL cholesterol (mg/dL)	41.2 (10.5)	38.9 (9.5)	0.003
Triglyceride (mg/dL)	156 (85.7)	220 (99.1)	<0.001
Fasting glucose (mg/dL)	96.3 (20.1)	118.9 (28.1)	<0.001
Body mass index (kg/m^2)	26.5 (3.8)	29.9 (4.3)	<0.001
Hyperlipidemia (TC > 200)	66 (45.8)	96 (57.8)	0.08
Treatment (PCI/CABG)	76 (52.7)	84 (50)	0.7

Mean (SD) and *n* (%) are reported for continuous and categorical variables, respectively. MS, metabolic syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease equation; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction; HDL, high density lipoprotein; TC, total cholesterol.

Metabolic syndrome and cardiac outcomes

In-hospital cardiac outcomes were not significantly different between the two groups (Table 2).

The follow-up data, including adverse outcomes at 30 days, 6 months, and 3 years, are depicted in Table 2. Cardiovascular mortality was significantly higher in patients with MS, as compared to those without MS, throughout the follow-up period. At the 3-year follow-up, 5 cardiovascular deaths had occurred in the MS(−) group and 25 cardiovascular deaths had occurred in the MS(+) group. Two noncardiac deaths had occurred, as well. The incidence of the primary endpoint (3-year cardiovascular mortality) was higher in the MS(+) group ($p = 0.001$). Reinfarction was higher at 6 months and at 3 years in the MS(+) group, as compared to the MS(−) group. The rates of hospitalization for heart failure and stroke were not significantly different between the two groups on long-term follow-up.

In a Kaplan–Meier survival analysis, the 3-year cardiovascular mortality rate was higher in the MS(+) group than in the MS(−) group ($p = 0.001$) (Fig. 1).

Individual effects of metabolic syndrome and glucose metabolism disorder on 3-year outcomes

We divided the patient population into four groups as follows: group 1, MS(−) and GMD(−) ($n = 100$); group 2, MS(−)

Table 2 In-hospital cardiac outcomes and follow-up cardiac events.

	MS(−) $n = 144$	MS(+) $n = 166$	p
In hospital mortality	1 (0.6)	3 (1.8)	0.39
Target vessel revascularization	1 (0.6)	0 (0)	0.28
Reinfarction	3 (2)	4 (2.5)	0.85
MACE	4 (2.7)	6 (3.6)	0.69
Stroke	2 (1.3)	1 (0.6)	0.48
Cardiopulmonary resuscitation	1 (0.6)	4 (2.4)	0.23
Renal failure requiring dialysis	2 (1.3)	0 (0)	0.13
Advanced heart failure	6 (4.1)	10 (6)	0.46
İnotrope usage	1 (0.6)	3 (1.8)	0.39
Cardiovascular mortality			
30 days	1 (0.6)	7 (4.2)	0.05
6 months	2 (1.3)	11 (6.6)	0.02
3 years	5 (3.4)	25 ((15)	0.001
Hospitalization for heart failure			
30 days	10 (6.9)	10 (6)	0.74
6 months	11 (7.6)	18 (10.8)	0.33
3 years	13 (9)	22 (13.2)	0.11
Stroke			
30 days	2 (1.3)	2 (1.2)	0.88
6 months	3 (2)	3 (1.8)	0.86
3 years	3 (2)	5 (3)	0.6
Reinfarction			
30 days	3 (2)	8 (4.8)	0.19
6 months	6 (4.1)	20 (12)	0.01
3 years	12 (8.3)	37 (22.2)	0.001

Mean values (SD) and n (%) are reported for continuous and categorical variables, respectively. MS, metabolic syndrome; MACE, major adverse cardiac events (cardiovascular death, reinfarction, target vessel revascularization).

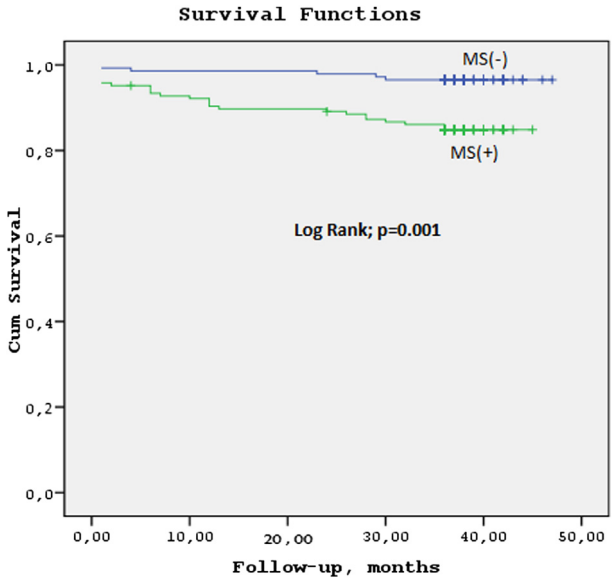

Figure 1 Cumulative event-free survival curves in the Kaplan—Meier survival analysis. 3-year cardiovascular mortality was higher in MS(+) group when compared to MS(−) group ($p = 0.001$).

and GMD(+) ($n = 44$); group 3, MS(+) and GMD(−) ($n = 33$); and group 4, MS(+) and GMD(+) ($n = 133$). Cardiovascular mortality and reinfarction were most common in group 4; however, hospitalization for heart failure was more common in group 2. The incidence of stroke was not significantly different between the groups (Table 3).

Multivariate and univariate predictors of long-term cardiovascular mortality are presented in Table 4. A multivariate logistic regression analysis was performed by including age, DM, HT, smoking, MS, admission anemia, GRACE risk score, GFR < 60 mL/min/1.73 m^2, Killip score > 1, LVEF $< 40\%$, and treatment (PCI and/or coronary artery bypass grafting [CABG]). A significant association was noted between MS and the adjusted risk of long-term cardiovascular mortality (odds ratio [OR] 3.4, 95% confidence interval [CI], 1.24—9.1, $p = 0.02$).

Discussion

The main findings of the present study are that in NSTEMI and USAP patients: 1) Patients with MS were more likely to be female, have a history of PCI, and to have a lower LVEF and higher TIMI score; 2) In-hospital cardiac outcomes were not statistically different between the MS(+) and MS(−) groups; 3) In the MS(+) patients, cardiovascular mortality and reinfarction were significantly more common in the follow-up period, but hospitalization for heart failure and stroke were not; and 3) MS was independently associated with long-term cardiovascular mortality.

The basis of the MS phenomenon was first established by Kylin in 1923 as an assemblage of HT, hyperglycemia, and gout [11]. With time, several other abnormalities (e.g., obesity, microalbuminuria, and abnormalities in fibrinolysis and coagulation) were included in the syndrome [12—14]. This syndrome has been given several other names, including Syndrome X, insulin resistance syndrome, and the deadly quartet [2]. In 1998, the WHO proposed the first set of criteria to define MS [15]. Subsequently, the NCEP ATP III [16], International Diabetes Federation (IDF) [17], and American Heart Association/National Heart, Lung, and Blood Institute [18] defined MS in similar terms. For all of these organizations, MS is defined as consisting of at least three of the five following variables: elevated waist circumference, elevated TG levels, reduced HDL levels, elevated blood pressure, and elevated fasting glucose levels. Initially, the WHO proposed insulin resistance as an obligatory component of MS, while the IDF made abdominal obesity necessary. However, it is currently agreed that there should not be an obligatory component, although waist circumference (with national or regional cut-off points) will continue to be a useful screening tool [1].

The prevalence of MS has risen as more and more people adopt a sedentary lifestyle and become obese. MS contributes to a striking increase in cardiovascular risk factors. Isomaa et al. [3] found that the risks of coronary heart disease, cardiovascular mortality, and stroke were markedly increased in subjects with this syndrome. Also, in patients with manifest vascular disease (coronary heart disease, stroke, peripheral arterial disease, and abdominal aortic aneurysm), the presence of MS is associated with advanced vascular damage based on carotid intima-media

Table 3 Three-year follow-up cardiac events.

	Group 1 MS(−), GMD(−) $n = 100$	Group 2 MS(−), GMD(+) $n = 44$	Group 3 MS(+), GMD(−) $n = 33$	Group 4 MS(+), GMD(+) $n = 133$	p
Cardiovascular mortality	1 (1)	4 (9.1)	4 (12)	21 (15.8)	0.002
Hospitalization for heart failure	4 (4)	7 (15.9)	2 (6)	20 (15)	0.03
Stroke	3 (3)	0 (0)	1 (3)	4 (3)	0.72
Reinfarction	9 (9)	3 (6.8)	6 (18.2)	31 (23.3)	0.008

Mean values (SD) and *n* (%) are reported for continuous and categorical variables, respectively. MS, metabolic syndrome; GMD, glucose metabolism disorder.

thicknesses, ankle brachial pressure indices, and albuminuria [19]. Additionally, it has been shown that non-diabetic individuals with MS have an increased risk of death from all causes, including cardiovascular disease [20]. This finding demonstrates that adverse cardiovascular effects are increased in patients with MS, often independently of DM, and a similar study found that the risk of cardiovascular events was significantly increased in patients with MS following elective PCI, irrespective of DM [21].

Recently, the impact of MS after STEMI was studied, and it was found that in-hospital mortality was higher in STEMI patients with MS when compared to those without MS; however, no difference in the rate of composite MACE was found at the 1-year follow-up assessment [22]. MS was also found to be a predictor of "no-reflow" in STEMI after successful PCI [23].

Although the patient populations in the aforementioned studies were defined specifically as STEMI, in most of the studies associated with AMI and MS the populations were not specified (whether STEMI or NSTEMI/USAP). Therefore, the impact of MS on pure NSTEMI/USAP patients is unknown. Feinberg et al. [6] retrospectively analyzed 1060 ACS patients (STEMI and NSTEMI) with non-clinically diagnosed DM and found MS to be a strong independent predictor of 30-day and 1-year mortality, similar to our findings. Among the components of MS, they found hyperglycemia to be the strongest predictor of 1-year mortality, and they identified the effects of hyperglycemia with and without MS. At 30 days, those hyperglycemic patients with MS had significantly higher mortality rates when compared to patients with hyperglycemia but without MS. These findings are also compatible with ours, as we found higher mortality rates in the MS(+)/GMD(+) group. The aforementioned study used a hyperglycemia cut-off value of $>$140 mg/dL and BMI $>$ 28 kg/m^2, instead of waist circumference, to define central obesity. The actual cardiovascular risk in patients with a fasting glucose level of 100−140 mg/dL must have been underestimated in this study. BMI was a less robust determinant of cardiovascular risk than waist circumference. A previous study revealed that BMI was not predictive of cardiovascular mortality in stable coronary artery disease, but that waist circumference was [24]; therefore, the actual risk in obese patients could be determined in that study. Another study of AMI patients (i.e., STEMI and NSTEMI populations) with a similar design [25] used a BMI $>$ 25 kg/m^2 to define obesity and a fasting glucose level $>$ 110 mg/dL as dysglycemia. In that study, at a median follow-up period of 17.6 months, the incidence of MACE (e.g., cardiac death, nonfatal MI, heart failure, and a need for PCI/CABG) was higher in patients with MS. MS was found to be an independent risk factor for MACE, and dysglycemia was found to be the most important MS component for clinical outcomes. In our study, we found that HT and GMD, among all of the MS components, were

Table 4 Univariate and Multivariate predictors of long-term cardiovascular mortality.

	Univariate			Multivariate		
	OR	CI	p	OR	CI	p
Age	1.073	1.038−1.11	0.005			
GMD	3.92	1.5−10.24	0.004			
HT	4.16	1.45−11.9	0.008			
Smoking	0.32	0.13−0.77	0.01			
MS	4.63	1.77−12.1	0.002	3.4	1.24−9.1	0.02
Killip $>$ 1	9.4	4.18−21.2	$<$0.001			
LVEF $<$ 40%	6.6	2.8−15.4	$<$0.001			
Grace score	1.03	1.02−1.04	$<$0.001	1.03	1.02−1.04	$<$0.001
PCI/CABG	0.28	0.11−0.64	0.003			
GFR $<$ 60	5.9	2.8−12.5	$<$0.001	2.63	0.98−7.1	0.05
Anemia	3.1	1.49−6.4	0.003			

GMD, glucose metabolism disorder; MS, metabolic syndrome; HT, hypertension; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate.

the major predictors of 3-year cardiovascular mortality. Kranjcec et al. [26] reported a larger infarct size and heart failure (Killip $>$ 2) in ACS patients with MS, as compared to those without MS. This finding is contradictory to ours in that we found no differences in in-hospital advanced heart failure (Killip $>$ 3) in patients with or without MS. In addition, we found no differences in hospitalization for heart failure on long-term follow-up. The reasons for this difference may be related to the definition of advanced heart failure (Killip $>$ 2 vs. 3) and patient characteristics.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACLE) trial consisted of NSTEMI/USAP patients and was very similar to ours. Schwartz et al. [27] analyzed the impact of MS on the short-term prognosis in the MIRACLE trial population. However, this protocol did not specify measurements of fasting blood glucose or waist circumference because the importance of MS was unknown at the time of the study (1995—96). Instead, they used a history of DM and a BMI $>$ 30 kg/m^2. They determined that the presence of a low HDL level and a history of DM were associated with an 8% increase in absolute risk. The presence of MS was associated with an increased risk of primary outcomes (death, nonfatal MI, cardiac arrest, and recurrent unstable myocardial ischemia) (19% with MS and 14% without MS at week 16 of follow-up). We similarly discovered that cardiovascular mortality and reinfarction were significantly higher in patients with MS at 3 years of follow-up.

One interesting finding of our study is that MS had no impact on the development of stroke (ischemic and hemorrhagic) in-hospital or during the long-term follow-up period. A previous investigation revealed that patients with MS and without DM exhibited a 1.49-fold increase in the odds of ischemic stroke or transient ischemic attacks (95% CI, 1.20—1.84), whereas those with DM had a 2.29-fold increase in risk (95% CI, 1.88—2.78) [28]. The strongest predictors were an impaired fasting glucose level and HT. Another study assessed insulin resistance and the risk of stroke and stroke subtypes in 5234 participants aged 55 years or older who were stroke- and DM-free at baseline [29]. They found that fasting insulin levels and homeostasis model assessment for insulin resistance were not associated with the risk of stroke, cerebral infarction, or intracerebral hemorrhage. The discrepancy in the data may be related to spontaneous or therapy-induced changes in the components of MS during follow-up.

Study limitations

This single-center study included a small number of patients. We did not assess inflammatory markers (e.g., C-reactive protein, pro-inflammatory/anti-inflammatory cytokines). In addition, we did not assess insulin resistance/hyperinsulinemia. It is known that hyperinsulinemia, as an indicator of insulin resistance that precedes the development of DM, is associated with an increased risk of fatal and non-fatal ischemic heart disease, AMI, and cardiovascular mortality [30]. Although we measured blood fasting glucose levels during the stable period, stress factors may exist and glucose levels may be higher than normal in a hospital environment; therefore, the number of patients with MS may be overestimated.

Clinical implications

MS has a negative long-term impact on cardiovascular mortality and reinfarction in patients with NSTEMI/USAP. Additionally, MS can be used as a marker of cardiovascular mortality in patients with NSTEMI/USAP.

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There are no conflict of interest issues.

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