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Clinical Research

Circulating MIF Levels Predict Clinical Outcomes in Patients With ST-Elevation Myocardial Infarction After Percutaneous Coronary Intervention

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See editorial by Haitjema and Hoefer, pages 1281–1282 of this issue.

ABSTRACT

Background: The purpose of the study was to assess the value of admission macrophage migration inhibitory factor (MIF) levels in predicting clinical outcomes in ST-elevation myocardial infarction (STEMI) patients.

Methods: For this study we recruited 498 STEMI patients after they received percutaneous coronary intervention (PCI), 40 with stable angina pectoris and 137 healthy participants. Plasma MIF levels were measured at admission and after PCI. The primary end points were in-hospital mortality and major adverse cardio-and/or cerebrovascular events (MACCE) during hospitalization and 3.2-year follow-up period.

RÉSUMÉ

Contexte : L'étude visait à évaluer l'utilité du dosage du facteur d'inhibition de la migration des macrophages (MIF) effectué lors de l'admission à l'hôpital aux fins de pronostic des résultats cliniques chez les patients ayant souffert d'un infarctus du myocarde avec élévation du segment ST (STEMI).

Méthodologie : Pour les besoins de cette étude, nous avons recruté 498 patients ayant souffert de STEMI après qu'ils eurent subi une intervention coronarienne percutanée (ICP), 40 patients atteints d'angine de poitrine stable et 137 sujets en bonne santé. Les concentrations plasmatiques de MIF ont été mesurées lors de

Acute myocardial infarction (AMI) is the leading cause of cardiac mortality worldwide.[1] The prognosis of AMI patients depends on clinical manifestation, disease severity, and clinical management. A range of risk factors and clinical biomarkers have been reported to bear prognostic values for AMI.[2] Recently, biomarkers from peripheral blood have become a major focus for early diagnosis and outcome prediction in AMI patients. Although several myocardial injury biomarkers including creatine kinase and its cardiomyocyte-specific isoform CK-MB,[3] troponins,[4-6] myoglobin,[7] and N-terminal probrain natriuretic peptide (NT-proBNP)[8] have been shown to be promising for predicting clinical outcomes, some of these biomarkers require repeat testing and they have limitations in clinical sensitivity and/or specificity.[4,9] Identification of novel biomarkers for early prediction of post-myocardial infarction (MI) prognosis could significantly improve the risk stratification and subsequent patient management and long-term outcomes.

Macrophage migration inhibitory factor (MIF) is a pleotropic cytokine associated with a variety of inflammatory disorders.[10,11] The role of MIF in the progress of atherosclerosis

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Results: Admission MIF levels were elevated in 88.4% of STEMI patients over the upper reference limit of healthy controls and it was 3- to 7-fold higher than that in stable angina pectoris and control groups (122 ± 61 vs 39 ± 19 vs 17 ± 8 ng/mL; $P < 0.001$). Admission MIF levels were significantly higher in patients who died after myocardial infarction vs survivors. For predicting in-hospital mortality using the optimal cutoff value (127.8 ng/mL) of MIF, the area under the receiver operating characteristic curve for MIF was 0.820, similar area under the receiver operating characteristic curve values for predicting short-term outcomes were observed for high-sensitivity troponin T, CK-MB, N-terminal probrain natriuretic peptide, and **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) score. Although peak high-sensitivity troponin T and N-terminal probrain natriuretic peptide also predicted MACCE during the follow-up period, only higher admission MIF levels predicted in-hospital mortality and MACCE during the 3.2-year follow-up. Multivariate regression analysis showed the independent predictive value of a higher admission MIF level ($\geq$ 127.8 ng/mL) on in-hospital mortality (odds ratio, 9.1; 95% confidence interval, 1.7-47.2) and 3.2-year MACCE (hazard ratio, 2.8; 95% confidence interval, 1.5-5.6).

Conclusions: A higher admission MIF level is an independent predictor for in-hospital mortality and long-term MACCE in STEMI patients who underwent PCI.

Résultats : Lors de l'admission à l'hôpital, les concentrations de MIF étaient élevées chez 88,4 % des patients qui avaient souffert de STEMI; elles se situaient au-delà de la limite supérieure de référence mesurée chez les sujets témoins en bonne santé et étaient de 3 à 7 fois plus élevées que celles notées chez les patients atteints d'angine de poitrine stable et les sujets témoins (122 ± 61 vs 39 ± 19 vs 17 ± 8 ng/ml, $p < 0{,}001$). Les concentrations de MIF lors de l'admission à l'hôpital étaient significativement plus élevées chez les patients qui sont décédés après avoir souffert d'un infarctus du myocarde que chez les survivants. Pour le pronostic de mortalité intrahospitalière en fonction de la concentration de MIF constituant la valeur seuil optimale (127,8 ng/ml), l'aire sous la courbe ROC était de 0,820. Une aire sous la courbe ROC similaire a été observée pour le pronostic des résultats à court terme en fonction des concentrations de troponine T hypersensible, de CK-MB et de NT-proBNP (propeptide natriurétique de type B N-terminal) et en fonction du score GRACE (***G**lobal **R**egistry of **A**cute **C**oronary **E**vents*). Même si les concentrations maximales de troponine T hypersensible et de NT-proBNP étaient aussi prédictives des MACCE durant la période de suivi, seules les concentrations plus élevées de MIF lors de l'admission à l'hôpital constituaient un marqueur pronostique de mortalité intrahospitalière et de MACCE durant la période de suivi de 3,2 ans. L'analyse de régression multivariée a montré qu'une concentration plus élevée de MIF lors de l'admission à l'hôpital ($\geq$ 127,8 ng/ml) constitue un marqueur pronostique indépendant de mortalité intrahospitalière (rapport des risques instantanés de 9,1; intervalle de confiance à 95 % de 1,7 à 47,2) et de MACCE sur une période de 3,2 ans (rapport de cotes de 2,8; intervalle de confiance à 95 %, de 1,5 à 5,6).

Conclusions : Une concentration plus élevée de MIF lors de l'admission à l'hôpital constitue un marqueur pronostique indépendant de mortalité intrahospitalière et de MACCE à long terme chez les patients qui ont souffert d'un STEMI et subi une ICP.

has been intensively studied.[11,12] Previous studies showed that MIF was produced abundantly by various cells in all types of human atherosclerotic lesions and thus plays an important role in plaque development and lesion progression.[12] Elevated circulating MIF level was observed in patients with AMI and a higher MIF level was associated with plaque rupture.[13] Recent preclinical and clinical studies have revealed that MIF also plays a critical role in AMI and ischemia/reperfusion injury.[14-18] In a murine cardiac ischemic model, MIF was reported to be rapidly increased upon cardiac ischemia and infarction and this early increase of plasma MIF occurs before an elevation of troponin level.[14] Importantly, the increase of MIF levels in the blood was proportional to the mass of myocardial damage.[14] Notably, abundant MIF protein is preformed and stored in cardiomyocytes and the rapid elevation of circulating MIF levels indicates the possibility of direct cardiac release after myocardial ischemic insult.[14,19] We previously showed that the MIF level at the earliest available time point correlated with acute and chronic infarct size according to magnetic resonance imaging (MRI) and the degree of left ventricular (LV) remodelling.[14] These findings imply that MIF might have the potential to be a promising biomarker to predict outcomes of AMI patients.

Further clinical research is warranted to establish MIF as a predictor for the prognosis of AMI patients. In the present study, we aimed to investigate the association between admission plasma MIF level and in-hospital mortality and long-term outcomes in patients with ST-elevation MI (STEMI).

Methods

Study design and participants

This was a single-centre, prospective cohort study designed to assess whether admission MIF levels could predict in-hospital and long-term outcomes in patients with STEMI treated with primary percutaneous coronary intervention (PCI). The study complied with the Declaration of Helsinki, and the study protocol was approved by the Human Ethical Committee of the First Affiliated Hospital of Xinjiang Medical University. All participants in this study provided written informed consent.

We consecutively recruited adult patients with STEMI who attended the Department of Cardiology, the First Affiliated Hospital of Xinjiang Medical University during the period of January 2013 to June 2017 and underwent PCI

within 12 hours after the onset of chest pain. The diagnosis of STEMI was defined as a plasma CK-MB level > twofold than the normal value or a cardiac high-sensitivity troponin T (hs-TnT) > 0.1 μg/mL after symptom onset together with at least 1 of the following: (1) chest pain persisting for > 20 minutes; (2) electrocardiograph (ECG) exhibiting elevation of the ST segment > 1 mm or a new pathological Q wave.[20] Patients having 1 or more of the following conditions were excluded: malignancy, thrombolysis therapy, chronic inflammation, chronic renal failure, or serum creatinine level > 2.5 mg/dL, and other serious diseases.

The sex- and age-matched control subjects were recruited from the Health Physical Examination Centre of our hospital, and had no evidence of cardiovascular and other systemic disease as determined according to history, physical examination, blood test, and ECG recording. Patients with stable angina pectoris (SAP) were diagnosed according to 2013 European Society of Cardiology guidelines[21] and were recruited during routine outpatient visits. A total of 498 STEMI patients, 137 healthy participants, and 40 SAP patients were included in this study.

All STEMI patients received standard medical treatment including 300 mg of aspirin and a 300-mg loading dose of clopidogrel at admission and 70 U/kg of standard intravenous heparin before the PCI. All PCI procedures were performed by experienced interventional cardiologists using a radial artery approach and drug-eluting stents. Thereafter, all patients received dual antiplatelet therapy: 100 mg aspirin daily, and 75 mg clopidogrel daily for at least 1 year. Other cardiac medications were given at the discretion of the attending physician.

Blood collection and laboratory tests

Venous blood samples were drawn at different time points after admission in STEMI patients. Plasma MIF levels at admission, 4 hours, and 24 hours after PCI were measured, in duplicate, using Quantikine MIF ELISA kits (R&D Systems, Minneapolis, MN) according to manufacturer's specifications at Xinjiang Key Laboratory of Cardiovascular Disease Research. All routine full blood examinations and blood biochemistry were performed using the commercially available automated platform, in the Central Laboratory of the First Affiliated Hospital of Xinjiang Medical University. These tests included white blood cell (WBC) count, total cholesterol (TC), triglyceride, low-density lipoprotein cholesterol (LDL-C) or high-density lipoprotein cholesterol (HDL-C), creatinine, and CK-MB. CK-MB was tested at admission every 4 hours before 12 hours, and then every 12 hours until 48 hours after admission to determine the peak values and the area under the curve (AUC). hs-TnT and NT-proBNP (Roche Diagnostics, Indianapolis, IN) was tested at admission and then every 4 hours before 12 hours, and 24 hours after admission to determine the peak values.

Coronary angiography and PCI

Angiograms were independently reviewed by 2 interventional cardiologists who were blinded to patient information. Multivessel disease was defined as visually assessed > 50% diameter stenosis in more than 1 major epicardial artery in relation to the infarct area. According to the Gensini scoring system,[22,23] the angiographic severity of the lesion was rated as follows: 1 point = 0%-25%, 2 points = 25%-50%, 4 points = 50%-75%, 8 points = 75%-90%, 16 points = 90%-99%, and 32 points = 99%-100% (a completely occluded vessel). The rate was multiplied by the segment location multiplying factors to obtain the Gensini score for each patient.[22,23] All primary PCI procedures were performed by experienced interventional cardiologists using a radial artery approach and drug-eluting stents. The procedure was considered successful if postinterventional grade 3 of **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) flow in the target vessel and a postprocedural residual stenosis < 20% were achieved.[24]

Definition of Cardiovascular Risk Factors

Body mass index (BMI) was calculated by dividing body weight (in kilograms) by the height in metres squared. Overweight/obesity was classified as a BMI ≥ 25.[25] Persons reporting regular tobacco use in the previous 6 months were considered as current smokers. Hypertension was defined as history of hypertension and/or repeated systemic blood pressure measurements exceeding 140/90 mm Hg. Diabetes was defined as history or presence of diabetes and/or a fasting plasma glucose level > 7.0 mmol/L (126 mg/dL) on 2 separate occasions, or a random glucose value > 11.1 mmol/L (200 mg/dL) on at least 1 occasion before the present admission. Concentrations of TC > 6.22 mmol/L, triglyceride level > 2.26 mmol/L, LDL-C > 4.14 mmol/L, and HDL-C < 1.04 mmol/L were defined as hypercholesterolemia, hypertriglyceridemia, high LDL-C, or low HDL-C, respectively, according to Chinese dyslipidemia guidelines.[26] Dyslipidemia was defined as any of the 4 lipid abnormalities noted. The **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) risk score is recognized as a validated predictor of adverse cardiovascular events in AMI patients.[27,28] It is calculated on the basis of age, heart rate, systolic blood pressure, creatinine level, history of congestive heart failure, PCI, MI, ST-segment changes on admission ECG, and elevated levels of cardiac enzymes or markers.

Echocardiography

All patients were assessed using transthoracic echocardiography within 48 hours after primary PCI using a Vivid7 ultrasound system (GE Medical Systems, Oslo, Norway). Standard echocardiographic views were acquired and analyzed by 2 experienced cardiologists who were unaware of grouping information. LV ejection fraction (LVEF) and LV **W**all **M**otion **S**core **I**ndex (WMSI) were measured using a standard 16-segment model from parasternal long and short axes, and apical 2- and 4-chamber views.[29] Each LV segment was scored as 0 = hyperkinetic, 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The total score divided by the number of segments analyzed gave an overall score for assessment of LV dysfunction.

Study End Points

In-hospital end points

In-hospital end points were: (1) in-hospital mortality; and (2) major adverse cardiovascular events (MACE) during hospitalization including cardiac death, cardiogenic shock, malignant arrhythmia, severe heart failure, and recurrence of MI.

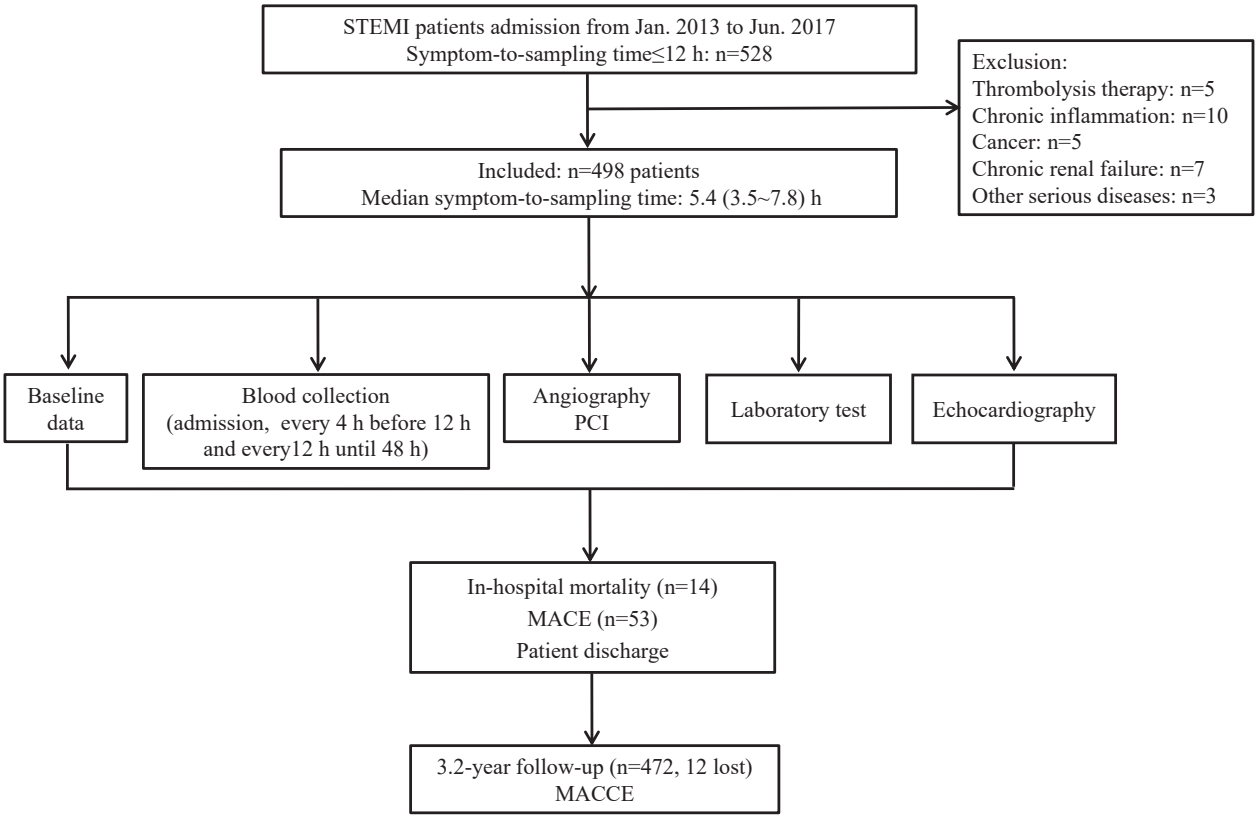

Figure 1. The flow chart of study design with inclusion and exclusion procedures. MACE/MACCE, major adverse cardio- and/or cerebrovascular events; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Long-term follow-up end points

Long-term follow-up end points were major adverse cardio- and cerebrovascular events (MACCE) including cardiac death, nonfatal MI, target lesion revascularization, rehospitalization, stent thrombosis, and stroke.[30] The protocol included phone interview, outpatient visiting, and in-hospital clinical records of patients who were rehospitalized. Information of deceased patients was obtained from hospital records or phone contact with relatives of the patients.

Statistical analysis

For details on statistical analysis, please see the Supplemental Methods.

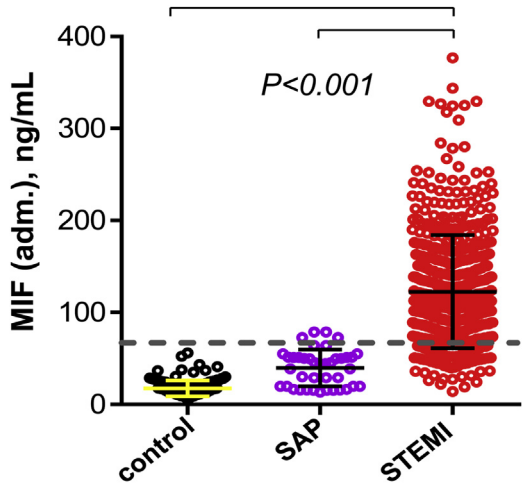

Figure 2. Admission (adm.) levels of macrophage migration inhibitory factor (MIF) in patients with ST-elevation myocardial infarction (STEMI; n = 498) and in healthy participants (control; n = 137) and stable angina pectoris (SAP; n = 40).

Results

Basic characteristics

During January 2013 to June 2017, we consecutively recruited 528 adult STEMI patients who underwent primary PCI within 12 hours after onset of chest pain. Of these patients, 30 were excluded from the study because of thrombolysis therapy, chronic inflammation, cancer, chronic renal failure, or other serious diseases. Finally, a total of 498 STEMI patients who met the inclusion criteria and 137 healthy participants and 40 SAP patients matched with the case group in age and sex were included in this study. In-hospital all-cause mortality occurred in 14 patients (2.8%). We lost contact with 12 (2.4%) patients during the follow-up period. Thus, 472 STEMI patients were followed-up during the 3.2-year period for assessment of long-term clinical outcomes. Figure 1 depicts the flow chart of the study design. Baseline characteristics of study participants at the time of enrollment are presented in Supplemental Table S1. Age, sex, and BMI were comparable among the 3 groups. STEMI patients had a

Table 1. Comparison of characteristics and biomarkers at admission between fatality and nonfatality group during hospitalization

Variable	Fatality (n = 14)	Nonfatality (n = 484)	*P*
Age, years	62 ± 10	57 ± 11	0.094
Male sex, n (%)	8 (57.1)	415 (85.7)	0.003
BMI	25.6 ± 3.5	24.3 ± 2.8	0.090
Hypertension, n (%)	8 (57.1)	231 (47.7)	0.487
Diabetes mellitus, n (%)	2 (14.3)	116 (24.0)	0.401
Previous MI, n (%)	1 (7.1)	34 (7.0)	0.986
Current smoker, n (%)	9 (64.3)	281 (58.1)	0.641
Admission heart rate, bpm	84 ± 16	82 ± 13	0.573
Admission SBP	112 ± 22	120 ± 18	0.104
WBC, 10^9/L	13.3 ± 4.8	11.2 ± 3.4	0.030
TC, mmol/L	4.8 ± 1.4	4.7 ± 1.0	0.716
TG, mmol/L	2.0 ± 0.5	1.8 ± 0.9	0.408
LDL-C, mmol/L	2.8 ± 0.8	3.0 ± 0.8	0.357
Creatinine, mg/dL	123 (76-186)	74 (64-86)	0.001
Admission MIF, ng/mL	211.4 ± 82.7	120.0 ± 58.8	< 0.001
Admission hs-TnT, μg/mL	8.56 (0.97-10.00)	0.15 (0.04-1.11)	0.003
Peak hs-TnT, μg/mL	10.00 (8.97-10.00)	4.13 (1.88-8.14)	< 0.001
Peak CK-MB, U/L	849 (255-981)	244 (129-400)	0.004
CK-MB AUC, U/L	14,121 (9577-18,235)	4931 (2770-7713)	< 0.001
Admission NT-proBNP, ng/L	3176 (226-8046)	129 (46-414)	0.033
Peak NT-proBNP, ng/L	5499 (1330-6790)	422 (95-1293)	< 0.001
GRACE score	176 ± 26	127 ± 29	< 0.001
Gensini score	98 ± 43	65 ± 34	0.001
TIMI grade after PCI	2.7 ± 0.4	2.9 ± 0.2	< 0.001
LVEF, %	48 ± 7	58 ± 6	< 0.001
LV, WMSI	1.32 ± 0.10	1.17 ± 0.09	< 0.001
Medications, n (%)			
Aspirin	14 (100)	480 (99.2)	0.733
Clopidogrel/ticagrelor	14 (100)	484 (100)	–
β-Blocker	9 (64.3)	380 (78.5)	0.204
ACEI/ARB	9 (64.3)	367 (75.8)	0.322
Statin	14 (100)	477 (98.6)	0.650

Values are expressed as mean ± SD or median (25th-75th percentiles), or exact number and percentage.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AUC, area under the curve; BMI, body mass index; bpm, beats per minute; GRACE, **G**lobal **R**egistry of **A**cute **C**oronary **E**vents; hs-TnT, high-sensitivity troponin T; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MIF, macrophage migration inhibitory factor; NT-proBNP, N-terminal probrain natriuretic peptide; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TIMI, **T**hrombolysis **I**n **M**yocardial **I**nfarction; WBC, white blood cell count; WMSI, **W**all **M**otion **S**core **I**ndex.

higher prevalence of smoking, hypertension, diabetes, and dyslipidemia than healthy participants, but comparable with SAP patients. Angiographic data showed that STEMI patients had the higher prevalence of triple-vessel disease whereas most of the SAP patients had a single-vessel disease. The distribution of culprit arteries was comparable between SAP and STEMI groups.

MIF levels elevated in STEMI patients and correlated with conventional biomarkers of myocardial injury

The median symptom-to-sampling time was 5.4 hours (25th-75th percentile, 3.5-7.8 hours). In total, 18.3% of patients had the first blood sampling within 3 hours after the onset of chest pain, 55.4% within 6 hours, and 79.5% within 8 hours. In 88.4% of STEMI patients, admission MIF levels were above the upper reference limit (56.0 ng/mL) of healthy controls (Fig. 2), and the MIF levels in STEMI patients were 3- and 7-fold higher than in SAP patients and healthy participants (122.6 ± 61.4 vs 39.8 ± 19.8 and 17.5 ± 8.8 ng/mL, respectively; $P < 0.001$). A serial plasma test showed that MIF levels at 4 hours after PCI was slightly further increased (133.3 ± 70.4 ng/mL), and then declined back to the admission level at 24 hours after PCI (120.8 ± 64.8 ng/mL). These changes did not reach statistical significance compared with admission MIF values.

Associations between common cardiovascular risk factors and MIF levels were analyzed in STEMI patients. Admission MIF levels were higher in smoking than nonsmoking patients (127.2 ± 60.4 vs 116.2 ± 62.3 ng/mL; $P = 0.040$) and correlated with peak hs-TnT and CK-MB, AUC of CK-MB, and Gensini score (Supplemental Fig. S1). MIF levels showed lack of association with other risk factors (ie, sex, overweight/obesity, hypertension, dyslipidemia, diabetes, multiple vessel disease, and NT-proBNP; all P = not significant).

Elevated admission MIF levels predicts clinical outcomes

In-hospital mortality and MACE. During 1- to 15-day hospitalizations, 53 patients developed MACE including cardiac death (14; 26.4%), cardiogenic shock (12; 22.6%), malignant arrhythmia (18; 34.0%), severe heart failure (6; 11.3%), and recurrence of MI (3; 5.7%). The causes of cardiac death were cardiogenic shock for 11 patients (78.6%), malignant arrhythmia for 2 (14.3%), and cardiac rupture for 1 (7.1%). The MIF levels in deceased patients was significantly higher than that in survivors (Table 1) with the highest level in the patient who died from cardiac rupture (329.4 ng/mL).

Comparison of clinical characteristics between in-hospital fatality and nonfatality groups in STEMI patients are

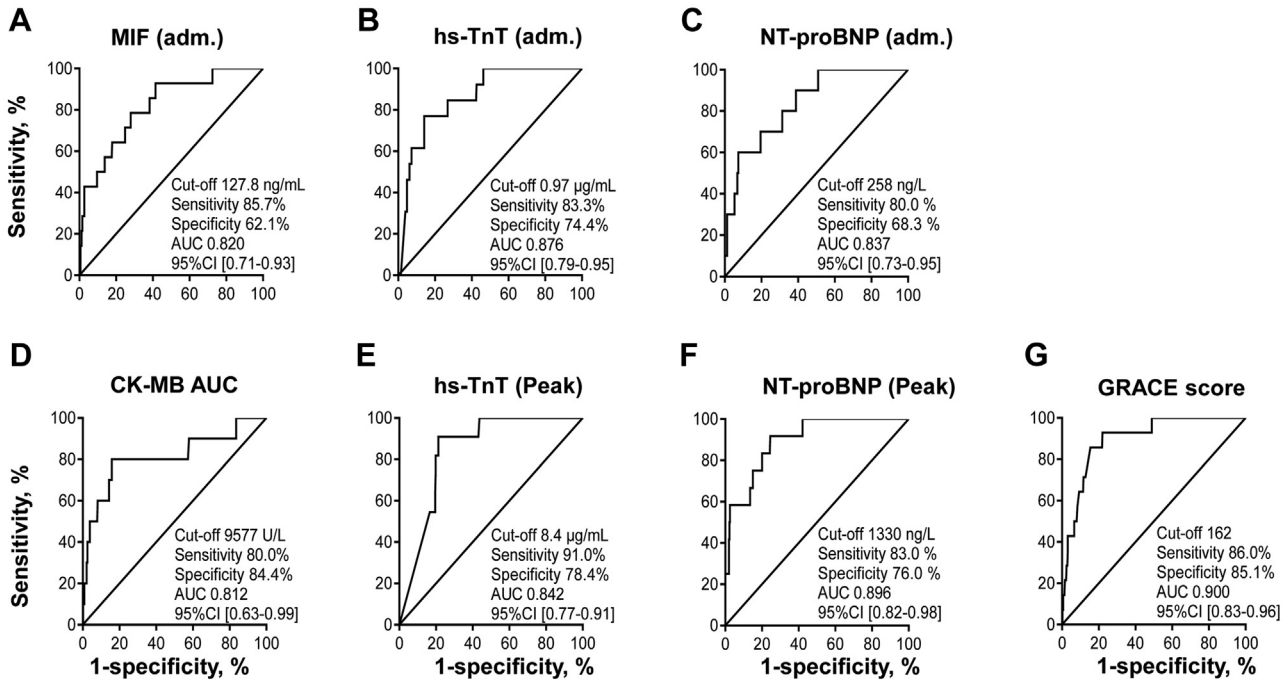

Figure 3. The receiver operating characteristic (ROC) curve analyses of (**A**) admission (adm.) migration inhibitory factor (MIF), (**B**) adm. high-sensitivity troponin T (hs-TnT), (**C**) adm. N-terminal probrain natriuretic peptide (NT-proBNP), (**D**) area under the curve (AUC) of CK-MB, (**E**) peak hs-TnT, (**F**) peak NT-proBNP, and (**G**) **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) score for in-hospital death. CI, confidence interval.

presented in Table 1. The fatality group had fewer male patients than the nonfatality group. The admission MIF level was markedly higher in deceased patients than in survivors ($P < 0.001$). The patients who died in-hospital had greater levels of WBC, creatinine, admission and peak levels of hs-TnT and NT-proBNP, and peak level and AUC of CK-MB (all $P < 0.05$ vs survivors). The fatality group also had higher Gensini score and GRACE score (both $P < 0.001$) and lower TIMI grade post-PCI. Echocardiography performed within 48 hours post-MI revealed that the fatality group had significantly lower LVEF, but higher LV WMSI compared with the nonfatality group (both $P < 0.001$). Medication within 24 hours after admission was comparable between the 2 groups. There were no statistical differences in other examined variables between the 2 groups.

Receiver operating characteristics (ROC) of MIF for predicting in-hospital mortality in STEMI patients is presented in Figure 3A. The area under the ROC curve for MIF predicting mortality was 0.820. The recommended cutoff value for MIF on the basis of the maximum of Youden index on the ROC curve was 127.8 ng/mL and it had 85.7% sensitivity and 62.1% specificity in predicting in-hospital mortality. For a comparison, admission and peak hs-TnT and NT-proBNP, AUC of CK-MB, and GRACE score were also similarly studied (Figure 3B-G). The values of area under the ROC plot were similar among these parameters (P = not significant). The cutoff values of these parameters had a comparable sensitivity for predicting in-hospital mortality, whereas MIF had the lowest specificity.

A 24-hour serial monitoring of hs-TnT showed a typical temporal change with the peak level reached at 4 hours after admission and gradually returned back to the admission level by 12 hours (Figure 4A). The peak of CK-MB was reached at 8 hours after admission and gradually returned back to the admission level by 36 hours in 48-hour serial monitoring (Figure 4B). On the basis of the MIF cutoff value (127.8 ng/mL), STEMI patients were further divided into the high- and low-MIF level groups. As shown in Figure 4 and Supplemental Table S2, patients with high MIF levels had a greater peak value and AUC of hs-TnT and CK-MB (Figure 4C and D) and Gensini score than those with low MIF levels ($P < 0.01$). Other clinical characteristics were similar between the 2 groups. A further stepwise multivariable logistic regression analysis was performed to assess the association between in-hospital mortality and potential confounding factors (Supplemental Table S3). The admission MIF levels either as a continuous variable (odds ratio, 1.6; 95% confidence interval [CI], 1.29-2.06) or as a categorical variable (the cutoff value of 127.8 ng/mL: odds ratio, 9.1; 95% CI, 1.75-47.25) was an independent predictor for in-hospital mortality. We further analyzed the relationship between admission MIF levels and MACE in-hospital. In spline regression models, higher admission MIF level was also associated with a greater risk of adverse outcomes, MACE (Fig. 5).

Kaplan-Meier curves showed that STEMI patients with higher cutoff values of admission MIF, hs-TnT, and NT-proBNP, AUC of CK-MB, peak hs-TnT and NT-proBNP, and GRACE score also had a greater in-hospital mortality (Fig. 6A-G; all $P < 0.01$). The predictive values for in-hospital mortality using generated cutoff values of these 7 parameters were comparable.

Long-term outcomes. After discharge from the hospital, 484 STEMI patients were followed-up with the median duration of follow-up of 39 months (range, 12-67 months). During the

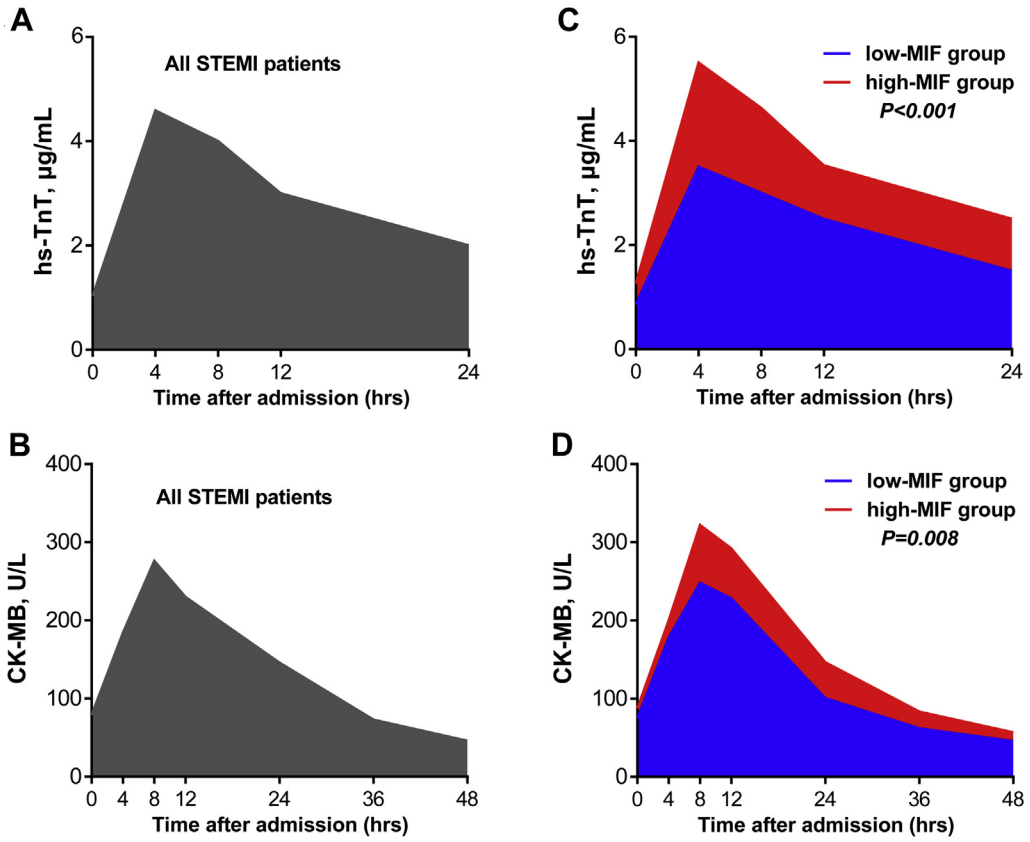

Figure 4. Temporal changes of traditional tissue injury biomarkers in ST-elevation myocardial infarction (STEMI) patients after admission. The area under the curve of (**A**) high-sensitivity troponin T (hs-TnT), and (**B**) CK-MB in all STEMI patients (n = 495). The area under the curve of (**C**) hs-TnT and (**D**) CK-MB in low (n = 303) and high migration inhibitory factor (MIF) level (n = 195) groups on the basis of the cutoff value of MIF (127.8 ng/mL) at admission.

follow-up period, 12 patients lost contact and 137 patients (29.0%) developed MACCE, including cardiac death, nonfatal MI, rehospitalization because of recurrent angina or heart failure, target lesion revascularization, stent thrombosis, and stroke (Supplemental Table S4). Patients with MACCE had higher admission MIF levels than those without MACCE (137.7 ± 67.8 vs 112.8 ± 53.5 ng/mL; $P < 0.001$).

STEMI patients discharged from hospital were separated into 2 groups according to the MIF cutoff value of 127.8 ng/mL. Kaplan-Meier curves showed that the prevalence of MACCE was significantly higher in patients with high MIF levels than those with low MIF levels during the 3.2-year follow-up period (Figure 6H; $P < 0.001$). The higher peak levels of hs-TnT ($P = 0.036$) and NT-proBNP ($P = 0.004$)

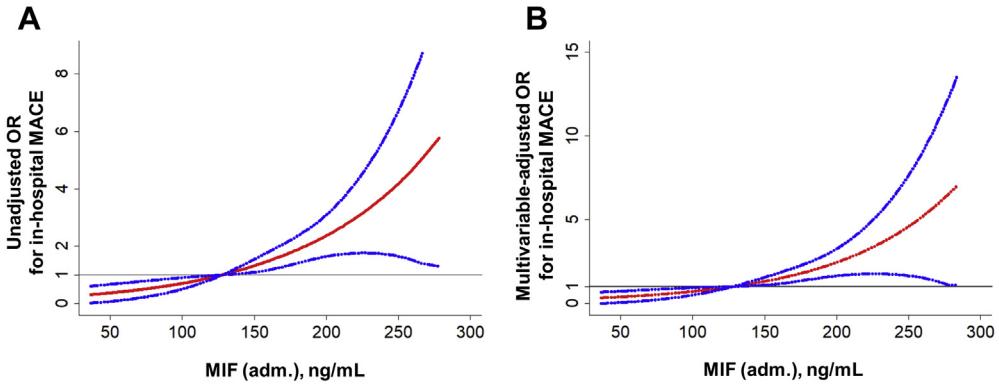

Figure 5. Cubic spline plots showing the relative odds ratios (OR) for in-hospital major adverse cardiovascular events (MACE) in ST-elevation myocardial infarction patients according to admission (adm.) migration inhibitory factor (MIF) level: (**A**) unadjusted; (**B**) the multivariable model adjusted for sex, age, smoking status, blood pressure, heart rate, Gensini score, and MIF levels at admission. The **solid red lines** indicate the odds ratio (OR) points estimation and the **dashed blue lines** indicate 95% confidence intervals. The OR value corresponding to the admission MIF level (127.8 ng/mL) was set as 1 for reference.

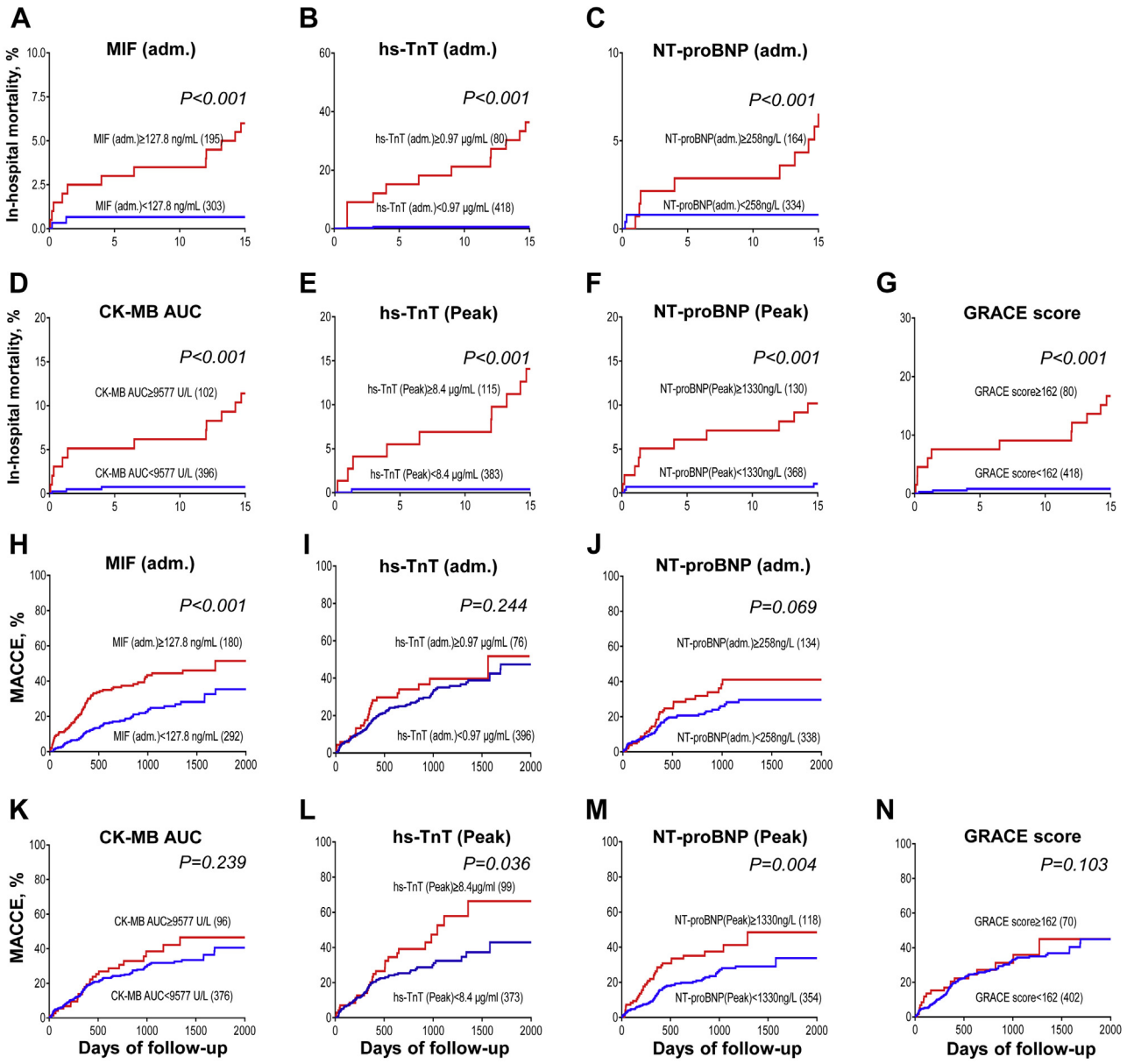

Figure 6. Prediction of migration inhibitory factor (MIF), high-sensitivity troponin T (hs-TnT), N-terminal probrain natriuretic peptide (NT-proBNP), CK-MB area under the curve (AUC) and **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) score for clinical outcomes after ST-elevation myocardial infarction. Kaplan-Meier curves showing in-hospital mortality on the basis of the cutoff values of (**A**) admission (adm.) MIF levels, (**B**) adm. hs-TnT level, (**C**) adm. NT-proBNP, (**D**) CK-MB AUC, (**E**) peak hs-TnT, (**F**) peak NT-proBNP, and (**G**) adm. GRACE score. Kaplan-Meier curves showing the prevalence of major adverse cardio- and cerebrovascular events (MACCE) in patients during a 3.2-year follow-up period on the basis of the cutoff values of (**H**) adm. MIF, (**I**) adm. hs-TnT, (**J**) adm. NT-proBNP, (**K**) CK-MB AUC, (**L**) peak hs-TnT, (**M**) peak NT-proBNP, and (**N**) adm. GRACE score. Numbers in brackets indicate group size.

also predicted MACCE during the follow-up (Figure 6L and M). However, for admission hs-TnT and NT-proBNP, AUC of CK-MB and GRACE score, Kaplan-Meier analyses showed no differences in the prevalence of MACCE between patients with high and low cutoff values of the 4 parameters during the follow-up period (Figure 6I-K and N; all $P > 0.05$). Multivariate analysis using stepwise Cox proportional hazards regression analysis (incorporating as putative predictors including age, sex, BMI, hypertension, diabetes, smoking status, TC, LDL-C, peak of CK-MB, peak hs-TnT and NT-proBNP, Gensini sore, LVEF, and TIMI classification post-PCI) confirmed that admission MIF levels (either as a continuous variable, natural square-transformed variable, or in binary fashion according to the MIF cutoff value $\geq$ 127.8 ng/mL) remained as an independent predictor of MACCE (hazard ratio, 1.2 [95% CI, 1.06-1.33] or hazard ratio, 2.8 [95% CI, 1.49-5.57], respectively; Table 2).

Discussion

In the present study we investigated whether admission plasma MIF level could predict the in-hospital and long-term

Table 2. Unadjusted and adjusted Cox proportional hazards models for major adverse cardio- and/or cerebrovascular events

	Unadjusted		Adjusted for clinical variables	
	HR (95% CI)	*P*	HR (95% CI)	*P*
MIF level, square	1.1 (1.07-1.21)	< 0.001	1.2 (1.06-1.33)	0.003
MIF level ≥ 127.8 ng/mL (according to ROC curve analysis)	2.1 (1.52-2.98)	< 0.001	2.8 (1.49-5.57)	0.002

The final model adjusted for age, sex, history of hypertension or diabetes, smoking status, total cholesterol, low-density lipoprotein cholesterol, peak levels of CK-MB, high-sensitivity troponin T; N-terminal probrain natriuretic peptide, Gensini score, left ventricular ejection fraction, and **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) classification after percutaneous coronary intervention.

HR, hazard ratio; CI, confidence interval; MIF, macrophage migration inhibitory factor; ROC, receiver operating characteristics.

clinical outcomes in STEMI patients. Several major findings were made. First, elevation of plasma MIF level was observed in 88.4% of patients at the earliest available samples after admission compared with healthy controls, and patients who died in the hospital had higher admission MIF levels than survivors. Admission MIF levels in STEMI patients correlated with the established biomarkers (ie, hs-TnT and CK-MB) for assessment of the severity of myocardial damage. Second, patients with higher admission MIF levels had greater in-hospital mortality and MACE than those with low MIF levels. Third, incidence of MACCE during a 3.2-year follow-up period was also significantly greater in patients with higher admission MIF levels. Thus, our results suggest that the admission MIF level bears prognostic value for short- and long-term clinical outcomes in STEMI patients.

Clinical studies have reported an elevation of circulating MIF in patients after cardiac ischemic injury including AMI or open-heart surgery either at earliest available sampling time or after reperfusion.[13,14,31,32] The admission MIF level in STEMI patients of our cohort increased by 3- to 7-fold relative to the levels of SAP patients or healthy participants. We also detected that 88.4% patients exhibited MIF levels above the upper reference limit of the healthy controls. A previous study reported that AMI patients with multiple complex lesions had significantly higher MIF levels than those with single/no complex lesion.[33] In our study, 67% of patients had multiple diseased arteries but their MIF levels were comparable with that of patients with single-vessel disease. However, using the Gensini score, a comprehensive index for the severity of diseased arteries, we found that higher MIF levels were associated with greater Gensini scores. Although some clinical studies reported a burst increase in MIF levels during cardiac surgery, especially after reperfusion,[32,34,35] we did not observe such fluctuation of MIF levels within 4 hours after PCI. This is likely because of the different etiologies that are associated with different degree and duration of cardiac ischemia.

Although MIF is known as a proinflammatory cytokine, whether elevation of MIF reflects inflammatory status or the severity of myocardial injury remains elusive. In the present study, we found lack of correlation between WBC counts and MIF levels although WBC counts were higher in the fatality group. However, we observed that STEMI patients with high admission MIF levels had a greater AUC of CK-MB. MIF levels were correlated with the established myocardial injury biomarkers (ie, peak or cumulative release of CK-MB). These results are correlated with our previous report, which showed a close association between admission MIF levels and MRI-derived infarct size.[14] We previously also reported that except for MIF, other conventional biomarkers of cardiac injury such as hs-TnT, creatine kinase, and myoglobin measured at the earliest available sampling time did not correlate with MRI-derived infarct size.[14] However, because MRI was not used to assess infarct size in the current study, future studies on the relationships between admission MIF levels, other myocardial injury biomarkers, and infarct size measured using MRI are warranted to substantiate our findings. The association between MIF and plaque instability or the severity of coronary artery lesion has been documented.[13,36] Furthermore, elevated MIF levels measured at 1-2 days after AMI, when regional inflammatory response surged, were related to established inflammatory biomarkers such as C-reactive protein, interleukin-6, and/or matrix metalloproteinase-9,[13,14,37] whereas MIF levels were not correlated with C-reactive protein measured at admission after AMI.[14] The early increases of circulating MIF levels after cardiac ischemic insult reflect cellular/tissue damage rather than inflammatory status. This was also supported by a rapid increase of MIF levels in patients with stress-induced chest pain.[31] These findings show the dynamic feature of the relationship between MIF levels and the extent of tissue injury or inflammatory status. Therefore, our data suggest the early elevation of MIF level as a biomarker for prediction of the extent of myocardial injury.

Currently, the predictive value of MIF levels for future cardiac events in patients with coronary artery disease (CAD) remains ambiguous. In CAD patients with impaired glucose tolerance or type 2 diabetes mellitus, high plasma MIF level is an independent predictor for adverse long-term outcomes.[38] However, in population-based studies, MIF levels either have no predictive value for the risk of CAD[39] or are only weakly associated with cardiac death due to CAD.[40] In patients with cardiac arrest, increased MIF level was associated with 60-day mortality, but not with inflammatory status.[16] Although the predictive value of admission MIF level for clinical outcomes in STEMI patients is less studied, our cohort study revealed that a higher admission MIF level of ≥ 127.8 ng/mL predicts in-hospital mortality, MACE, and long-term MACCE in STEMI patients treated with PCI. Our results are consistent with the findings in a recent clinical study showing that STEMI patients with high admission MIF levels experienced poorer recovery of cardiac function and worse outcomes during 64-month follow-up.[41] These findings were further supported by the comparison between deceased patients and survivors in the current study. In the fatality group, all traditional myocardial injury markers, GRACE and Gensini scores, and WMSI, were significantly higher and LVEF was lower than in the nonfatality group. Overall, STEMI patients who died in-hospital had markedly higher admission MIF levels than survivors. Compared with MIF, the cutoff values of

admission and peak hs-TnT and NT-proBNP, AUC of CK-MB, or GRACE score had a similar sensitivity for predicting in-hospital mortality and better specificity. Notably, a higher admission MIF level also predicted long-term MACCE; other parameters such as admission levels of hs-TnT and NT-proBNP, AUC of CK-MB, and GRACE score failed in predicting long-term MACCE. Although peak levels of hs-TnT and NT-proBNP also had a similar predictive value in long-term MACCE, the detection of the peak levels of these 2 parameters requires repeating tests. These results highlight the unique power of a single MIF measurement at the earliest sampling time after onset of AMI in prediction of short- and long-term clinical outcomes. Our results also suggest that the mechanisms underlying the prognostic power of admission MIF might not only relate to the extent of cardiac injury, but also link to other actions of MIF such as proinflammatory properties.[11,42] This warrants further investigation.

There are some limitations in our study. First, this was an observational study from a single-centre that limited STEMI patient enrollment. The number of in-hospital events was small. Therefore, the number of covariates entered in the multivariable regression model was limited. However, power calculation indicates sufficient sample size and event numbers in our study. Second, in our study only STEMI patients who received primary PCI were included. The predictive value of admission MIF levels in all patients with acute coronary artery syndrome should be investigated in the future. Third, we did not use MRI to assess infarct size. Instead we only applied the well recognized cardiac enzymatic biomarker (ie, AUC of CK-MB and hs-TnT) as a surrogate for assessment of the degree of myocardial injury.[43-45] However, the goal of this study was to assess the predictive value of admission MIF levels for clinical outcomes post-AMI, a natural extension from our previous study.[14]

In conclusion, significantly increased plasma MIF levels become evident at the earliest available sampling time after onset of AMI. Patients with higher admission MIF levels had greater risk of in-hospital death as well as MACCE during the 3.2-year follow-up period. After adjustment for traditional risk factors, a higher admission MIF level remains as an independent predictor for in-hospital mortality and long-term MACCE in STEMI patients who received PCI.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.04.028.