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Prognostic significance and dynamic change of plasma macrophage migration inhibitory factor in patients with acute ST-elevation myocardial infarction

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Abstract

Macrophage migration inhibitory factor (MIF) has been reported as an inflammatory cytokine in many inflammatory diseases, including rheumatoid arthritis and ischemic diseases. However, dynamic changes of MIF within the first 24 hours on admission and potential prognostic significance following ST-elevation myocardial infarction (STEMI) have been little known. In this study, we examined the dynamic change of MIF level and its potential diagnostic and prognostic value after the onset of STEMI. Plasma MIF levels were evaluated in symptomatic subjects who received coronary angiogram with a median 27 months follow-up for the development of major adverse cardiovascular events (MACEs).

Of all 993 subjects, patients with STEMI showed a significantly higher MIF levels than in patients with non-ST elevation acute coronary syndrome, stable angina, and normal coronary artery, respectively ($P < .01$). Plasma MIF levels elevated as early as 12 hours post-onset of STEMI and peaked rapidly within 24 hours, and remained elevated from about day 5 till day 9 during hospitalization. In multivariate analysis, MIF was associated with a decreased risk of MACEs occurrence in STEMI patients after adjustment for traditional cardiovascular risk factors [hazard ratio 0.81, (0.72–0.90), $P < .001$]. The ROC curve for MACEs was 0.72 (95% CI 0.62–0.80, $P < .001$) and 0.85 (95% CI 0.80–0.90, $P < .001$) using Framingham risk factors only and combined with MIF, individually.

Measurement of MIF adds potential information for the early diagnosis of acute STEMI and significantly improves risk prediction of MACEs when added to a prognostic model with traditional Framingham risk factors.

Abbreviations: AMI = acute myocardial infarction, AUCs = areas under the curves, CAD = coronary artery disease, CHD = coronary heart disease, CK-MB = creatine kinase-MB, CRP = C-reactive protein, cTnI = cardiac troponin I, cTnT = ardiac troponin T, ECG = electrocardiographic, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, MACEs = major adverse cardiovascular events, MI = myocardial infarction, MIF = macrophage migration inhibitory factor, NCA = negative coronary angiography, NSTE-ACS = non-ST elevation acute coronary syndrome, NSTEMI = non-ST elevation myocardial infarction, PCI = percutaneous coronary intervention, SA = stable angina, STEMI = ST-elevation myocardial infarction, TVR = target vessel revascularization, WBC = white blood cells.

Keywords: MACEs, MIF, prognostic significance, STEMI

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Key Points

- What is already known about this subject?
  Few clinical studies have previously reported the relationship of circulating MIF levels in patients with coronary heart disease. And MIF has been suggested to have cardio-protective role in the pathogeneses of acute myocardial infarction (AMI) in animal models.
- What does this study add?
  In this study, we measured the dynamic MIF level in STEMI patients who did coronary angioplasty within 24 hours after chest-pain symptom and examined the association of MIF and various cardiovascular outcomes.
- How might this impact on clinical practice?
  MIF within 24 hours post-STEMI was a significant predictor of MACEs in STEMI patients. It is a good and early biomarker for STEMI risk stratification.

1. Introduction

Myocardial infarction (MI) is 1 of the clinical manifestations of coronary heart disease (CHD).[1] By 2030, it is estimated 23.3 million will die annually from cardiovascular disease.[2] ST-segment elevation myocardial infarction (STEMI) is a severe heart attack caused by a prolonged period of blocked blood supply that affects a large area of myocardium and is linked to high incidence of persistent and total coronary occlusion.[3] Survivors of the initial STEMI still face risks of various further cardiovascular events, including recurrent MI, heart failure, angina, stroke, and even death.[4] The prognosis of STEMI varies among patients and is largely dependent on risk factors and inflammatory station (i.e. systemic or local).[5] Although clinical features, such as ST-segment deviation, elevation of cardiac markers and hemodynamic parameters may be useful as earliest markers for STEMI diagnosis prediction, the sensitivity and specificity is relatively poor,[6] and it still remains a challenge in the evaluation of patients with suspected acute myocardial infarction (AMI) despite the emergence of high sensitivity troponins or creatine kinase (CK)-MB.[7] Therefore, more specific and sensitive biomarkers are urgently needed to optimize the prediction and prognosis in STEMI.

As a unique cytokine, macrophage migration inhibitor factor (MIF) inhibits random migration of macrophage with pleiotropic actions[8] and has been suggested cardio-protective in the pathogenesis of AMI.[9] Several types of research observed that MIF-deficient mice had greater heart contractile dysfunction than wild-type, and it is explained that both AMP-activated protein kinase (AMPK) activation and the enhancement of glucose uptake induced by ischemia/reperfusion (I/R) may have metabolic protective effects and ultimately reduced infarct size.[10,11,12] Furthermore, the infarct size was significantly reduced after injected MIF agonist directly into left ventricular cavity before reperfusion in an animal model, supporting the protective role of MIF in AMI.[13]

To date, some studies have noted the relationship between circulating MIF level and clinical outcomes in patients with coronary heart disease (CHD), finding that MIF is an independent risk factor for cardiovascular events in CHD patients with impaired glucose tolerance or type 2 diabetes mellitus.[14,15,16,17] However, the dynamic change and the correlation between plasma MIF level and major adverse cardiovascular events (MACEs) have not been examined extensively in patients with STEMI treated by coronary angiogram. The present study assessed the serial change of circulating MIF level during hospitalization and the association between MIF and MACEs in STEMI and non-ST elevation acute coronary syndrome (NSTE-ACS) subjects who underwent coronary angiogram.

2. Methods

2.1. Patients

Patients were admitted to the First Affiliated Hospital of Xi'an Jiaotong University due to chest pain and all treated by coronary angiogram or combined with emergency percutaneous coronary intervention (PCI) according to patients' condition from November 2013 to February 2014; Total 993 participants were enrolled and analyzed in the current study after exclusion of 34 patients. The median follow-up was 27 months, while the longest was 39 months. The First Affiliated Hospital of Xi'an Jiaotong University is a tertiary hospital providing secondary care cardiology with annual attendances of 90,000 per annum to Accident and Emergency.

993 participants were divided into 4 groups including STEMI, NSTE-ACS, stable angina (SA), and control group mainly according to the results of coronary angiogram. In the STEMI group, along with the evidence of coronary angiogram, STEMI was also diagnosed if electrocardiographic (ECG) showed an ST elevation ≥2 mm in some precordial leads and/or pathological Q waves in at least 2 consecutive precordial leads or ST elevation≥1 mm in limb leads, and a typical rise of CK-MB and cardiac troponin T (cTnT).[18] In the NSTE-ACS group, which including non-ST elevation MI (NSTEMI) and unstable angina (UA), was ascertained by angiographically documented manifestation, ECG signs and cardiac biomarkers above.[19] Each ECG was read by an experienced clinician/researcher, with a second reading if there was troponin elevation to adjudicate the type of MI. In the SA group, patients showed effort-related angina without any change in the clinical pattern in the preceding 2 months.[20] Finally, patients in the control group only showed discontinuous atypical precordial chest pain, no previous history of heart disease, and represent negative coronary angiography (NCA) results. Additionally, among STEMI group, we randomly chose 39 patients who received PCI within 12 hours after the onset of chest pain were respectively measured circulating MIF levels at different time points to observe dynamic change during hospitalization. Because of these 39 patients were all chosen from STEMI group, we named this subgroup as "dynamic change STEMI subgroup" (DCS subgroup) in order to easily analyse and distinguish. Patients having any of the following criteria were excluded:

1) Infectious diseases;
2) Any type of cancer;
3) Surgical treatment in recent 2weeks;
4) Autoimmune disease;
5) Severe renal insufficiency (estimated glomerular filtration rate $< 30\,mL/min/1.73m^2$);
6) Persistence of impaired liver function or liver disease (alanine aminotransferase >2 times the upper limit);
7) Non-coronary vascular inflammatory and thrombotic diseases (vasculitis, aortic dissection, abdominal aortic aneurysm and transient ischemic attack);
8) Usage of immunosuppressants.

Individual written informed consent was obtained from all patients before enrollment in the study, which was approved by ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University. This study was performed in keeping with the requirements of the Declaration of Helsinki.

2.2. Data collection and blood samples

Venous blood was collected from all the patients into anticoagulant heparin tubes in the following morning of the admission day. While for the DCS subgroup above, the venous blood was extracted every 2 hours within the first 24 hours (day 1) soon after admission, and then every other day until day 9 (in other words the blood samples were collected in day 1, day 3, day 5 day 7, and day 9 for DCS subgroup). Plasma was separated and stored at -80°C until analysis. MIF levels were determined by ELISA with commercially available kits (Human MIF, Quantikine, R&D Systems, Minneapolis, USA). The levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), cTnT, CK-MB, CK, B-type natriuretic peptide (BNP) and white blood cells (WBC) were assayed by our hospital's centre clinical laboratory.

Table 1

Basic characteristics of the 993 subjects.

	ACS			
	STEMI (n = 336)	NSTE-ACS (n = 307)	SA (n = 54)	NCA (n = 296)
MIF, pg/mL	2055.42 (968.29, 3799.96)*,†,‡	1731.56 (1226.60, 2834.2)	1588.48 (868.39, 2352.75)	1380.43 (860.24, 1923.86)
Age, years	57.74 ± 14.14*,†	62.73 ± 10.25*	59.90 ± 10.61	59.33 ± 11.81
Male gender, n (%)	280 (83.33%)*,†	201 (65.74%)	39 (72.22%)	172 (58.11%)
Body mass index, kg/m^2	22.58 (20.81, 25.71)	22.49 (20.76, 24.80)	21.19 (20.76, 23.67)	22.49 (20.76, 24.80)
Cardiovascular risk factors				
Hypertension, n (%)	145 (43.15%)	191 (62.21%)*,‡	20 (37.04%)	129 (43.58%)
Diabetes, n (%)	81 (24.11%)*,‡	64 (20.85%)*,‡	2 (3.70%)	28 (9.46%)
Current smoker, n (%)	218 (64.88%)*	139 (45.28%)*	26 (48.15%)	104 (35.14%)
LDL-C, ng/mL	2.38 (1.94, 2.88)†	2.26 (1.71, 2.78)	2.36 (1.70, 3.22)	2.33 (1.76, 2.79)
HDL-C, ng/mL	0.92 (0.77, 1.08)*	0.91 (0.80, 1.13)	1.02 (0.80, 1.24)	0.99 (0.83, 1.18)
eGFR (mL/min/1.73m^2)	72.73 (46.48, 93.42)*,†,‡	66.61 (42.00, 90.09)	54.02 (11.70, 90.00)	65.27 (42.43, 86.15)
WBC (^9 /L)	7.65 (5.83, 10.31)*,†,‡	6.23 (5.05, 7.59)	6.50 (5.11, 8.68)	6.88 (5.43, 8.36)
CRP, mg/L	6.09 (2.28, 10.07)*,†,‡	1.69 (0.66, 5.23)	1.57 (0.51, 10.20)	0.98 (0.34, 2.77)
LVEF on admission				
Normal (EF>55%)	165 (49.1%)*	124 (40.4%)*	22 (40.7%)	280 (94.6%)
Impaired (EF<55%)	171 (50.9%)*	183 (59.6%)*	32 (59.3%)	16 (5.4%)
Grace score	66.00 (60.00, 72.00)	66.00 (59.00, 72.00)		
Gensini score	26.50 (12.00, 69.00)	32.00 (22.00, 74.00)	38.00 (12.77, 82.250)	

[a]Data are expressed as the mean value ± SD, number (%) of patients or median (inter quartile ranges).

[b]Definitions and abbreviations: smoking, >10 cigarettes/day for >1 year; Hypertension, blood pressure >140/90mmHg or taking anti-hypertensive medication. CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, HDL-C = high-density-lipoprotein cholesterol, LDL-C = low-density-lipoprotein cholesterol, LVEF = left ventricular ejection fraction on echocardiography, WBC = white blood cell.

[c]Values from t-test for continuous variables and from Chi-square-test for categorical variables.

[d]. *: STEMI versus NCA $P < .05$; †STEMI versus NSTE-ACS, $P < .05$; ‡STEMI versus SA, $P < .05$.

2.3. Follow-up and Statistical analysis

All patients were prospectively followed up to November 2016 for development of MACEs. The predefined MACEs were a composite of sudden cardiac death, non-fatal cardiac MI, target vessel revascularization (TVR). TVR was defined as recurrent and more aggravating angina that led to revascularization.

Data were expressed as mean values ± SD, median and inter-quartile range (25th and 75th percentiles) or frequencies (%). Comparisons were performed with analysis of variance (ANOVA) for parametric variables, Kruskal–Wallis test for non-parametric variables, and chi-square test for categorical variables. Both CK-MB and Gensini score (coronary artery stenosis marker) were used for analyzing the tendency of MIF.[21] In survival analysis, Kaplan–Meier was used to identify development of MACEs among groups. The association between MIF level and MACEs in patients with STEMI and NSTE-ACS was estimated by Cox proportional hazards regression models. ROC analysis was used to assess the performance of Framingham risk factors[22] alone and combined with MIF for the prediction of the clinical endpoint. The areas under the curves (AUCs) acquired in different subsets were compared using the Hanley and McNeil method.[23] Logistic-regression analysis was used to estimate the MIF and cardiac factors with the probability of MACEs, expressed as hazard ratio (HR) with 95% CI. Results were considered statistically significant at a level of $P < .05$. All analyses were performed with PASW Statistics 20.0 software (SPSS Inc, Chicago, IL).

3. Result

Table 1 displays the basic characteristics of 993 patients. Plasma MIF levels were significantly higher in patients with STEMI than those with NSTE-ACS, SA and NCA only ($P < .01$). MIF level in NSTE-ACS patients was slightly higher than that in SA and NCA groups, while there was no significant difference between patients with SA and NCA (Fig. 1). Furthermore, MIF levels in patients with STEMI displayed a obvious correlation with CK-MB release using Pearson correlation test (r = 0.114, $P = .036$) but showed no correlation utilizing Gensini score (r = -0.036, $P = .515$) (Supplement Figure 1, http://links.lww.com/MD/C591). Compared with NCA patients, patients in STEMI group were younger (57.74 ± 14.14 vs 59.33 ± 11.81, $P < .01$), and had higher WBC count [7.65 (5.83, 10.31) vs 6.88 (5.43, 8.36), $P < .01$] and CRP levels [6.09 (2.28, 10.07) vs 0.98 (0.34, 2.77), $P < .01$]. Patients with STEMI also showed higher prevalence of diabetes [81 (24.11%) vs 28 (9.46%), $P < .01$], higher current smokers [18 (64.88%) vs 104 (35.14%), $P < .05$], and lower HDL-C levels [0.92 (0.77, 1.08) vs 0.99 (0.83, 1.18), $P < .01$].

During the follow-up period of 27.87 ± 7.23 months (10–39 months), MACEs occurred in total 115 patients (11.6%), coming from 79 (68%) STEMI, 33 (29%) NSTE-ACS, and 3 (3%) SA patients, respectively. To further analyze the incremental prognostic value of MIF level regarding to established risk predictors and MACEs prevalence, we stratified all STEMI and NSTE-ACS patients into subgroups by the tertiles of MIF value respectively, and the baseline characteristics were shown in supplement Table 1, http://links.lww.com/MD/C591. The incidence of MACEs was lower in the highest tertile subgroup (log-rank test, $P < .001$) in STEMI patients (Fig. 2A), whereas there was no statistical significance among the 3 tertile subgroups in patients with NSTE-ACS (Fig. 2B). Similar analysis was failed in patients with SA due to the very low incidence of MACEs (n = 3). Then we further analyzed the possible prognostic value of MIF in patients with STEMI, MIF (HR 0.81, 95% CI (0.72–0.90), $P < .001$) was a significant predictor of MACEs in a stepwise Cox proportional hazard analysis after adjustment for coronary risk factors (Fig. 3). AUCs for MACEs incidence using Framingham risk factors only and combined with MIF were 0.72 (95% CI

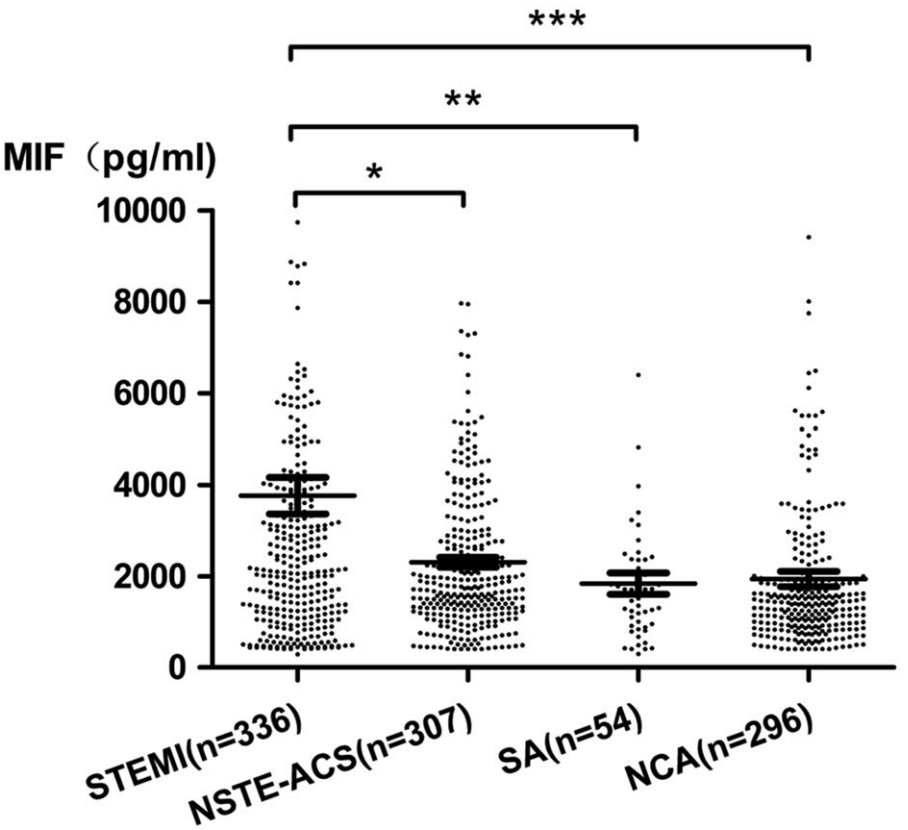

Figure 1. Levels of plasma MIF in presentation. Baseline levels of circulating MIF in the following morning of the admission day in 993 patients with STEMI, NSTE-ACS, SA, and NCA. Non parametric Friedman Rank test was used. MIF = macrophage migration inhibitor factor, NCA = normal coronary artery, NSTE-ACS = non-ST elevation acute coronary syndrome, SA = stable angina, STEMI = ST-elevation myocardial infarction. *: STEMI versus NSTE-ACS $p < 0.01$, **: STEMI versus SA $P < .01$; ***: STEMI versus NCA $P < .01$.

0.62–0.80, $P < .001$) and 0.85 (95% CI 0.80–0.90, $P < .001$), individually (Fig. 4), suggesting the incremental effect of MIF on the prognosis of MACEs in patients with STEMI.

Serial dynamic change of MIF levels at different time points in DCS subgroup was shown in coherent scatter diagram (Fig. 5). We observed a clear tendency that MIF level rose as early as 3 to 6 hours soon after admission and then peaked rapidly within 24 hours, especially the level on admission and the following the first 12 hours. After a transient decrease, MIF level restarted to rise slowly from day 3 and remained elevated ultimately till day 9 during hospitalization.

4. Discussion

In this study, we show as our key message that plasma MIF quickly increase then rose to peak value within 12 hours after symptoms onset, and the MIF level was significantly higher in STEMI patients than that in patients with NSTE-ACS, SA and NCA, which consistent with previous cross-sectional studies.[17,21,24] Furthermore, MIF was associated with better outcomes according to the follow-up study, supporting a protective regulatory role of MIF in STEMI. The survival analysis suggested the incremental effect of MIF on the prediction of MACEs in patients with STEMI.

Early non-invasive diagnosis of AMI relies on the history, symptoms, ECG, and cardiac biomarkers. ECG lacks sensitivity and it is insufficient diagnosis of NSTEMI,[25] thus it is a clearly unreliable test for observing early coronary artery obstruction. Over the past decades for cardiac biomarkers, cTnT, CK-MB, and myoglobin have been admittedly used to distinguish chest pain and identify suspected AMI.[26] However, cTnT and cardiac troponin I (cTnI) are considered as more specific and sensitive than CK-MB or myoglobin for both STEMI and NSTEMI.[27] Basically, cTnT and cTnI rise to peak approximately 1 to 2 days after onset of MI and remain in the circulation about more than 10 days[28] and the use of high-sensitivity troponin T (hsTnT) test significantly enhance the sensitivity for early AMI diagnosis.[29,30] However, the release of troponins into the circulation is mainly based on cell degradation due to they are structural components of cardiomyocyte sarcomeres and thus plasma troponin only rise several hours after onset of chest pain in AMI patients as well as even with contemporary assays, peak levels in plasma may not be reached until 6 to 8 hours after symptom onset,[9,31] let along other biomarkers (CK-MB, CRP, heart-type fatty acid binding protein) that unable to increase as rapidly or specifically as troponin.[32,33,34] All of these suggest the development of new devices and technologies to detect cTnT and other new biomarkers are needed.

In this study, we observed the serial dynamic change of MIF levels in 39 patients among STEMI group, and found a markedly elevated trend of MIF on admission as well as a quick MIF peak was reported within 12 hours. Müller et al[16] found the expression of MIF is significantly enhanced in patients with ACS at an early phase during the event, though CRP and other inflammatory markers did not increase even though the MIF level was elevated at admission in patients with AMI, and there was no

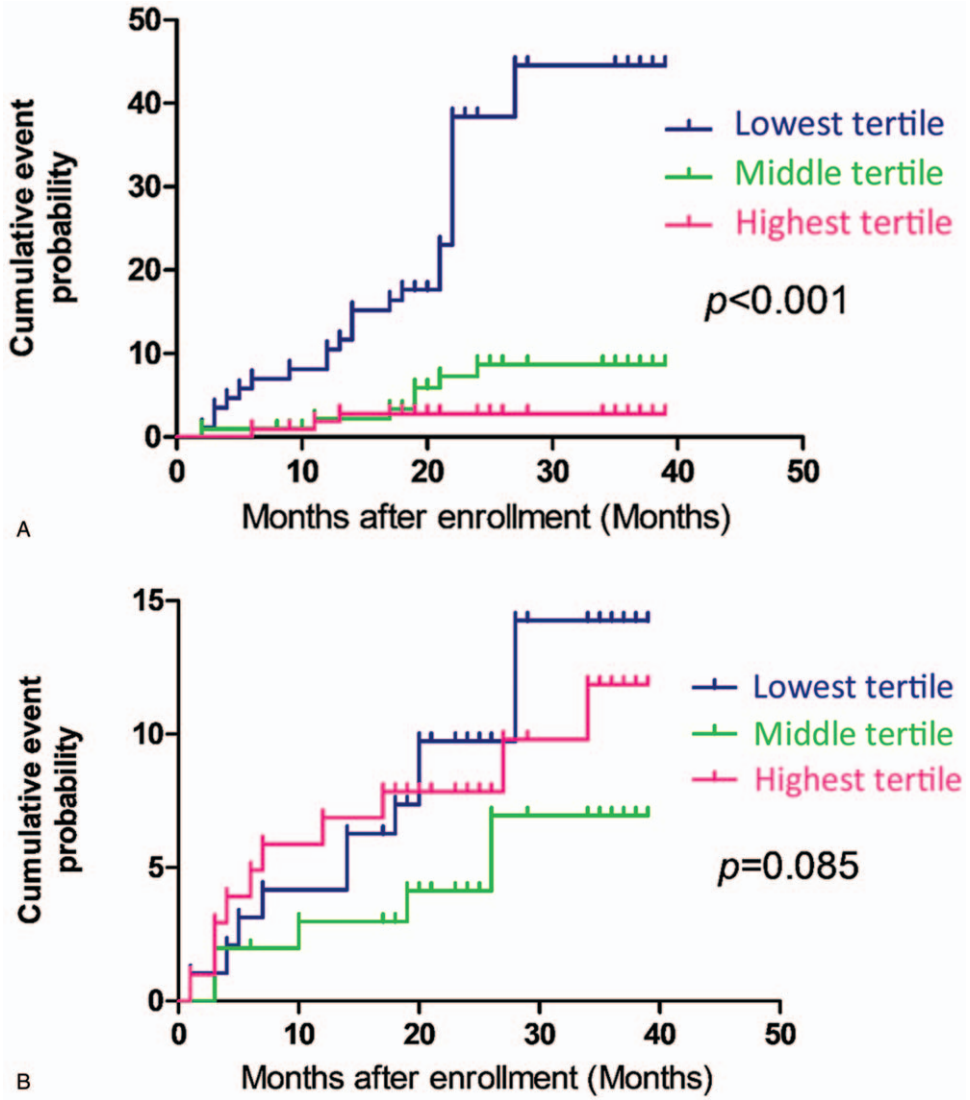

Figure 2. Kaplan–Meier curves show incidence of MACEs within median 27 months follow-up, comparing patients with highest tertile, middle tertile and lowest tertile of circulating MIF. Tertiles of MIF were divided based on the 67th and 33th percentiles of the distribution of the baseline MIF levels. (A) Prognostic impact of different MIF levels in *STEMI* group (n = 336) for probability of developing MACEs. (B) Prognostic impact of different MIF levels in NSTE-ACS group (n = 307) for probability of developing MACEs. Statistical analysis was performed by log rank test. MACEs = major adverse cardiovascular events, MIF = macrophage migration inhibitor factor, NSTE-ACS = non-ST elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction.

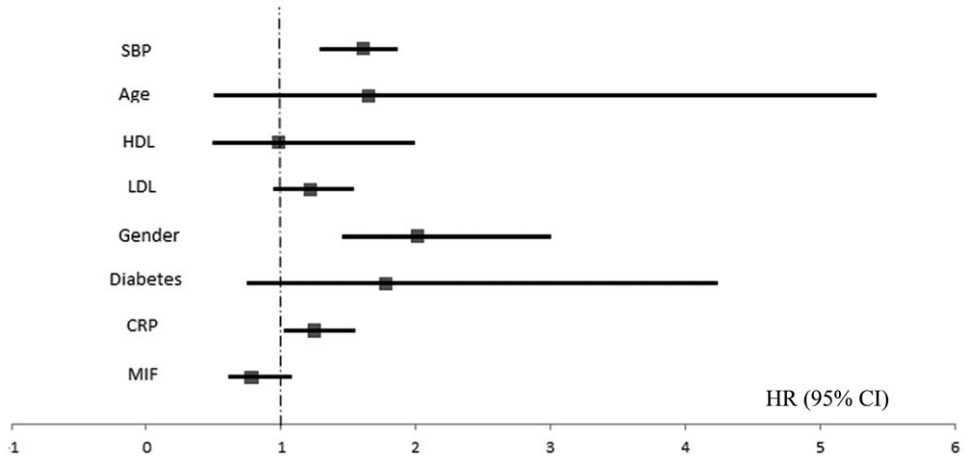

Figure 3. Multivariate Cox Regression Analysis for the prediction of MACEs in patients with STEMI (n = 336). Box centers represent HR and bars represent 95% CI. CI = confidence intervals, HR = hazard ratio.

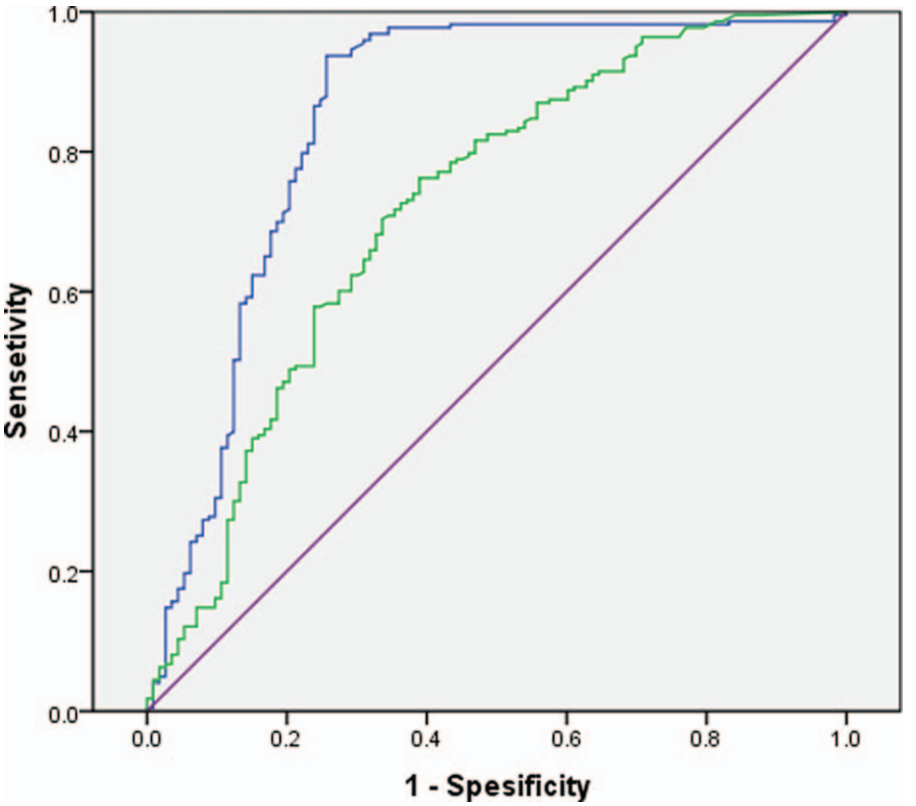

Figure 4. ROC curves at presentation for the incidence of MACEs events in STEMI group. ROC curves were performed by logistic models using Framingham risk score model (age, gender, smoking, DM, LDL-C, HDL-C levels, and SBP) alone (green line) and the combination of Framingham risk factor with MIF level (blue line). CRP = C-reactive protein, DM = diabetes mellitus, HDL = high density lipoprotein, LDL = low density lipoprotein, MACEs = major adverse cardiovascular events, MIF = macrophage migration inhibitor factor, SBP = systolic blood pressure, STEMI = ST-elevation myocardial infarction.

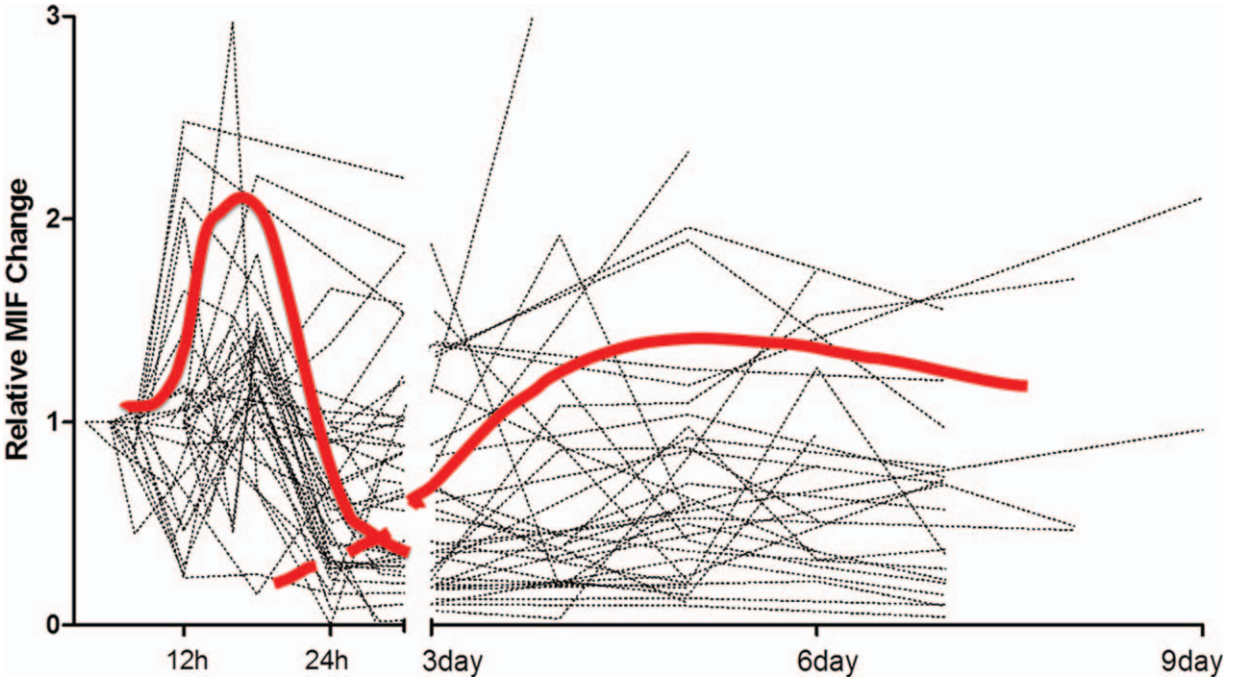

Figure 5. Serial dynamic change of plasma MIF level at different time points of 39 patients among STEMI group during hospitalization. Plasma MIF level rose as early as 3 to 6 hours soon after admission and then peaked rapidly within 12 hours. After a transient decrease, MIF level restarted to rise slowly from day 3 and remained elevated ultimately till day 9. MIF = macrophage migration inhibitory factor, STEMI = ST-elevation myocardial infarction.

correlation between levels of MIF and CRP. In comparison with CK-MB and troponin, MIF is expressed from either intracellular pools of cardiomyocytes[11] or immune cells[35] and can be activated released by viable and stressed cardiomyocytes[36,37] as a mechanism of self-salvage while the 2 above enter into circulation by leakage through the disintegrated cellular membrane of dead cells.[9,30] Chan et al[17] found that plasma MIF level increased 2.5-fold in AMI mice model for 15 or 60 minutes following coronary artery occlusion. However, 15 minutes after occlusion only detected a modest elevation in plasma troponin and then it robustly elevated after 60 minutes. Moreover, they further made analyses in a cohort of acute myocardial ischemia patients, observing that a remained elevation of MIF while TnT and CRP did not increase in stress-induced acute myocardial ischemia. Based on previous animal studies, ischaemia triggers cardiac MIF release into the coronary venous effluent and may exert cardio-protective role in the "super acute stage" of a mouse heart ischemic event.[35,38] It is suggested that plasma MIF is an early marker for acute myocardial ischemia in a short period of time after occlusion which is not sufficient to cause cardiomyocyte death.

We made a large-sample size analysis of MIF level within 24 hours after diagnosis of STEMI and NSTE-ACS patients, the observed maximum MIF level within 12 hours post-STEMI indicates the source of cardiac origin and MIF can be readily released without requiring de novo synthesis by myocardium, which is supported by findings in several experimental studies.[11,12,35,38] In addition to survival analysis, we found that MIF had a strong predictive value for MACEs in patients with STEMI, but had absent or weak prognostic value in patients with NSTE-ACS. The possible reasons for ineffective prognostic value between MIF and NSTE-ACS are as follows. First, oxidized LDL-C was found promoting migration of macrophage and other inflammatory cells into the vessel wall as well as upregulating expression of MIF in endothelial cells in vitro, suggesting its expression is upregulated from early atherosclerotic plaques progress to advanced stages.[39] Therefore, MIF can be greatly released due to large infarct size, ischaemic insult[9] and plenty of necrosis myocardiocytes and immune cells at the onset of STEMI. Second, it reported in rabbit and apolipoprotein E (ApoE) -deficient mouse models that MIF expression was associated with severity of atherosclerotic disease, lesion size within plaques and disease progression.[39,40] Obviously, STEMI is known as the most critical and emergency stage among all types of acute coronary syndrome in comparison with NSTE-ACS, thus the increase of MIF among STEMI patients may perform a more significant tendency than that in patients with NSTE-ACS. Finally, our study found that plasma MIF levels correlated with CK-MB release using Pearson correlation test, but showed no relationship with the Gensini score. It may further indicate that the expression of MIF was associated with the mass of ischemic and infarcted myocardium,[17] and this was an important evidence implicating the involvement of this cytokine in the pathogenic process of AMI where myocardial cell necrosis is substantial.

Despite that in some experimental studies, the protective effect of cardiac-derived MIF has been repeatedly found in ischaemia.[9,12,13,38] However, under prolonged ischaemia, cardiac-derived MIF may activate circulating leucocytes, resulting in increased expression of MIF (PBMC-derived wave) and other inflammatory molecules with potential noxious effects.[9] Therefore, more studies on MIF level post-STEMI for a longer period in human are needed. In our study, MIF level remained relatively stable after 24 hours. We hypothesized that MIF level may be affected by various factors, such as anti-inflammatory drugs and genetic factors. For example, MIF – 173G/C polymorphism is associated with higher MIF expression in human/animal and higher MIF level in Chinese patients with coronary artery disease (CAD).[41] In patients with a history of ischemic stroke, carriers of MIF CATT7 (compared with CATT5–6) – 173C allele (compared with MIF – 173G/G) were associated with severity of CAD.[42] Therefore, more genetic studies of MIF polymorphism on the cardiac injury in STEMI are needed.

4.1. Limitations

There are several limitations in our study. We only detected the MIF level within 24 hours post STEMI in a small sample, and the level and effect of MIF at additional time points still remains unknown. All patients enrolled in our study came from a single center and were limited to native Chinese individuals. It limits the generalizability of our findings.

5. Conclusion

In summary, Measurement of MIF adds potential information for the early diagnosis of acute STEMI and significantly improved risk prediction of MACEs when added to a prognostic model with traditional Framingham risk factors. More studies measuring MIF level in different time point is needed to better understand the role of MIF in the pathogenesis of atherosclerosis.

Author contributions

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Writing – original draft: Fuxue Deng, Qiang Zhao.
Writing – review & editing: Fuxue Deng, Juan Zhou.
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