ORIGINAL RESEARCH

Prognostic Utility of Soluble TREM-1 in Predicting Mortality and Cardiovascular Events in Patients With Acute Myocardial Infarction

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***Background*—**Triggering receptor expressed on myeloid cells-1 (TREM-1) is thought to be critical for inflammatory signal amplification and involved in the development of atherosclerosis. TREM-1 is significantly increased in patients with myocardial infarction. The aim of this study was to investigate the association between soluble TREM-1 (sTREM-1) and mortality and cardiovascular events in patients with acute myocardial infarction.

***Methods and Results*—**We included 838 consecutive patients with acute myocardial infarction from October 7, 2012 to December 5, 2014. Blood samples were collected from patients with acute myocardial infarction immediately after diagnosis. During follow-up, 88 patients died, and 180 patients reached the combined end points of major adverse cardiovascular event (MACE). Patients with high sTREM-1 (higher than the median) had increased risk of all-cause mortality and MACE compared with those with low sTREM-1 (log-rank test, $P<0.001$). After adjustment for confounding risk factors by Cox regression analysis, high sTREM-1 remained an independent predictor of all-cause mortality (hazard ratio, 1.978; 95% confidence interval, 1.462–2.675; $P<0.001$) and MACE (hazard ratio, 2.413; 95% confidence interval, 2.022–2.879; $P<0.001$). After the addition of sTREM-1 to the reference model, the C-statistic for all-cause mortality increased from 0.86 to 0.89, and the difference was 0.023 (95% confidence interval, 0.0009–0.0477), and the C-statistic for MACE increased from 0.71 to 0.80, and the difference was 0.087 (95% confidence interval, 0.053–0.122). sTREM-1 levels were consistently positively associated with risks of all-cause mortality and MACE in various subpopulations, and there was no significant interaction among prespecified subgroups.

***Conclusions*—**sTREM-1 was significantly associated with all-cause mortality and MACE, independent of established conventional risk factors in patients with acute myocardial infarction. **(*J Am Heart Assoc*. 2018;7:e008985. DOI: 10.1161/JAHA.118.008985.)**

Key Words: acute myocardial infarction • all-cause mortality • major adverse cardiac event • prognosis • triggering receptor expressed on myeloid cells-1

Patients with acute myocardial infarction (AMI) still have high morbidity and mortality, despite advances in coronary interventional devices and improvements in pharmacological agents. Inflammation is considered to play a substantial role in the pathophysiological process of cardiac remodeling and results in subsequent adverse events after AMI. Innate immune cells of the neutrophils and monocytes/macrophages are present in the development of atherosclerotic lesions,[1–3] and their activation may contribute significantly to plaque instability.[4–6] Acute myocardial ischemia induces a systemic immediate-phase response of the immune system, leading to cytokine and chemokine production and to the recruitment of neutrophils and mononuclear cells in the infarcted region of the heart.[7,8]

The triggering receptor expressed on myeloid cells-1 (TREM-1), which is an immune receptor initially known to be expressed on neutrophils and monocytes/macrophages, is a recently discovered member of the immunoglobulin superfamily and an amplifier of the innate immune response.[9–13] Not long after the discovery of TREM-1, it was believed that TREM-1 was merely involved in infectious diseases.[10] However, more recent studies have found that TREM-1 and its signaling pathways also lead to several acute and chronic noninfectious inflammatory diseases, including atherosclerosis, colitis, fibrosis, and cancer.[14]

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Clinical Perspective

What Is New?

- We determined the prognostic utility of soluble triggering receptor expressed on myeloid cells-1 in predicting long-term adverse clinical outcomes in patients with acute myocardial infarction after adjustment for conventional risk factors.

What Are the Clinical Implications?

- In patients with acute myocardial infarction, soluble triggering receptor expressed on myeloid cells-1 could serve as a useful marker for long-term all-cause mortality and major adverse cardiovascular events.
- These findings lend support for future research targeting triggering receptor expressed on myeloid cells-1 as a potential new therapeutic approach in patients with acute myocardial infarction.

Furthermore, TREM-1 is constitutively expressed in a-granules and mobilized at the membrane on platelet activation.[15] sTREM-1, a soluble form of TREM-1 shed from the membrane of activated phagocytes, used to be identified as a marker to distinguish infectious from noninfectious inflammatory states, and its significance in infectious diseases is clearly confirmed.[16–19]

Given the prominent role of activated monocytes-macrophages in AMI, the activation of TREM-1 in the context of AMI is believed to trigger upregulation and shedding of sTREM-1. Furthermore, sTREM-1 level is identified to be significantly higher in patients with AMI.[8] Thus, we performed a large-scale prospective study to investigate the prognostic utility of sTREM-1 in patients with AMI.

Methods

The analytic methods will be made available to other researchers. The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

From October 7, 2012 to December 5, 2014, a total of 838 patients with ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction admitted to Zhongshan Hospital, Fudan University, and Shanghai East Hospital, Tongji University School of Medicine (Shanghai, China), were prospectively enrolled in this cohort study. The time from symptom onset to admission had to be within 48 hours. AMI was diagnosed if a patient had a cardiac troponin I level >99th percentile with at least 1 of the following: chest pain lasting >20 minutes or diagnostic serial electrocardiographic changes consisting of new pathological Q waves or ST-segment and T-wave changes. Subjects <18 years old and subjects with known malignancy, renal replacement therapy, or surgery in the previous months were excluded. All patients were managed according to usual practice.

Information on both height and weight was collected for all patients to calculate the body mass index. Hypertension was defined as blood pressure ≥140/90 mm Hg or receiving antihypertensive treatment. Hyperlipidemia was defined as total cholesterol >5.18 mmol/L or receiving lipid-lowering treatment. Patients who smoked regularly were considered as smokers. Diabetes mellitus was defined as a fasting blood glucose >7 mmol/L or current use of diet or medication to lower blood glucose. The left ventricular ejection fraction was visually estimated by expert interpreters guided by strain analyses and wall motion index.

The study was conducted in accordance with the Declaration of Helsinki. The local ethics committee approved the protocol. This study was supported by grants from the National Natural Science Foundation of China (No. 81370390 and No. 81102706).

Data Collection and Follow-Up

All data were prospectively collected and entered into a central database. Clinical follow-up information about the end points was obtained after 24 months (interquartile range, 19–26 months) by reviewing the hospital database and by telephone call to all patients or their families, and these data were verified by reviewing medical records. Follow-up was completed in all patients.

End points were all-cause mortality and major adverse cardiovascular events (MACEs), defined as cardiovascular mortality or admission because of recurrent AMI or heart failure. Recurrent heart failure was defined as a hospital readmission for which heart failure was the primary reason requiring treatment with high-dose diuretics, inotropes, or intravenous nitrate. Recurrent AMI was diagnosed using the universal definition.[20]

Laboratory Methods

Blood samples were drawn from patients with AMI immediately after diagnosis. Serum was centrifuged within 30 minutes, and plasma was stored at 80°C for subsequent analysis. Concentration of sTREM-1 was routinely measured by an established available enzyme linked immunosorbent assay kit (R&D Systems, Minneapolis, MN). Other blood tests, including CRP (C-reactive protein) and troponin I, were assayed by routine

laboratory methods. Troponin I was measured at baseline and after 6 and 12 hours.

Statistical Analysis

Continuous variables are presented as median (interquartile range). Differences in continuous variables were compared by Mann-Whitney *U* test. Categorical data are reported as frequencies. Dichotomous variables were compared by χ^2 test or Fisher's exact test, as appropriate. A penalized spline method was used to allow for nonlinearities in the association between continuous variables and outcomes. Associations between prognostic variables and end points were examined by univariable and multivariable Cox proportional hazards analysis. The factors entered into the Cox regression models for the end points were as follows: age; sex; hypertension; diabetes mellitus; smoker; AMI type; hypercholesterolemia; previous myocardial infarction; previous percutaneous coronary intervention or coronary artery bypass graft; Killip class; percutaneous coronary intervention; body mass index; left ventricular ejection fraction; treatment with dual antiplatelet therapy, statin, β blockers, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker; glycoprotein IIb/IIIa inhibitor; CRP; peak troponin I; and sTREM-1. All biomarker levels were evaluated as continuous and categorical variables, respectively. When these biomarkers were treated as categorical variables, they were $\log_{10}$ transformed, and hazard ratios (HRs) for these values refer to per SD increment of the $\log_{10}$-transformed biomarkers. Results are expressed as HRs for Cox models with 95% confidence intervals (CIs). For the concern of the small sample size, we also used Firth's penalized maximum likelihood bias reduction method for Cox regression to examine whether the bias existed.[21,22] The Kaplan-Meier method was used to demonstrate the timing of events during long-term follow-up in relation to the admission sTREM-1, and the log-rank test was applied. We performed sensitivity analysis for the subgroup of participants, according to the variables listed in Table 1. All analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, IL) and R software, version 3.2.3.

Results

Patient Characteristics

A total of 838 patients with ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction (median age, 64 years; 56.1% men) admitted to the hospitals were enrolled in the present study. On admission, the serum concentration of sTREM-1 in patients with AMI was significantly higher than that detected in healthy controls (165 pg/mL [interquartile range, 108–192 pg/mL]; n=50). The enrolled patients with AMI were divided into 2 groups, according to the median levels of sTREM-1. The baseline characteristics of study population were shown in Table 1. Patients with higher sTREM-1 (higher than the median) were older; had a history of myocardial infarction and percutaneous coronary intervention or coronary artery bypass graft; and had

Table 1. Baseline Characteristics of Patients Stratified According to the Median Levels of sTREM-1

Variable	Low sTREM-1 (<299.9 pg/mL) (n=419)	High sTREM-1 (≥299.9 pg/mL) (n=419)	*P* Value
Age, median (range), y	63 (51–72)	65 (53–73)	0.02
Male sex, n (%)	236 (50.2)	234 (49.8)	0.89
Previous history, n (%)			
Diabetes mellitus	89 (21.2)	103 (24.6)	0.28
Hypertension	233 (55.6)	251 (59.9)	0.24
Hypercholesterolemia	93 (22.2)	79 (18.9)	0.24
Previous or current smoker	219 (52.6)	241 (57.9)	0.14
Previous MI	32 (7.6)	77 (18.4)	<0.001
Prior PCI or CABG	36 (8.6)	85 (20.3)	<0.001
ST-segment–elevation MI, n (%)	260 (49.8)	262 (50.2)	0.94
PCI, n (%)	350 (83.5)	343 (81.9)	0.57
Clinical presentation			
BMI, median (range), kg/m^2	23.5 (21.0–25.7)	23.3 (21.3–26.0)	0.15
LVEF, median (range), %	50 (45–58)	50 (46–58)	0.68
Killip class >1, n (%)	83 (19.8)	108 (25.8)	0.04
Baseline biological examinations			
Peak TnI, median (range), μg/L	7.0 (4.1–17.5)	7.2 (3.2–23.0)	0.71
CRP, median (range), mg/L	7.1 (4.2–14.0)	9.0 (5.0–15.0)	0.03
In-hospital medication, n (%)			
Statins	359 (85.7)	352 (84.0)	0.50
β Blockers	342 (81.6)	324 (77.3)	0.15
ACEI or ARB	348 (83.1)	323 (77.1)	0.04
Dual antiplatelet therapy	392 (93.6)	381 (90.9)	0.17
Glycoprotein IIb/IIIa inhibitor	299 (71.4)	278 (66.3)	0.16

Data presented as n (%) or median (interquartile range) ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; BMI, body mass index; CABG, coronary artery bypass graft; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; TnI, troponin I.

a higher rate of Killip class >1 and treatment with angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist. sTREM-1 level was positively associated with CRP level (9.0 [5.0–15.0] mg/L versus 7.1 [interquartile range, 4.2–14.0] mg/L; P=0.03).

sTREM-1 and Clinical Outcomes

During a median follow-up of 24 months, the rate of all-cause mortality was 10.4% (n=88), and 21.2% of patients (n=180) reached the combined end point of MACE, including cardiovascular mortality or admission attributable to recurrent AMI or heart failure. Figure 1 shows the nonlinear relationships between sTREM-1, CRP, peak troponin I, and log HR (95% CI) using spline curves. Survival analysis using the Cox regression model showed that, after adjustment by variables listed in Tables 2 and 3, multivariate Cox regression analysis showed that log sTREM-1 (per 1 SD) was a significant predictor of all-cause mortality (HR, 1.978; 95% CI, 1.462–2.675; P<0.001) and MACE (HR, 2.413; 95% CI, 2.022–2.879; P<0.001). Compared with the full model with all the previously mentioned variables, the C-statistic for all-cause mortality increased from 0.86 to 0.89, and the difference was 0.023 (95% CI, 0.0009–0.0477) after the addition of sTREM-1. The C-statistic for MACE increased from 0.71 to 0.80, and the difference was 0.087 (95% CI, 0.053–0.122) after the addition of sTREM-1 to the reference model. When treating these biomarkers as continuous variables, sTREM-1 was also a significant predictor of all-cause mortality (HR, 1.004; 95% CI, 1.003–1.005; P<0.001) and MACE (HR, 1.005; 95% CI, 1.004–1.006; P<0.001). Compared with this model, the C-statistic for all-cause mortality increased from 0.88 to 0.90, and the difference was 0.021 (95% CI, 0.003–0.039) after the addition of sTREM-1. The C-statistic for MACE increased from 0.74 to 0.82, and the difference was 0.072 (95% CI, 0.043–0.102) after the addition of sTREM-1 to the second reference model. Firth's penalized maximum likelihood bias reduction method for Cox regression was performed, and the results were similar to the conventional Cox regression analysis.

The log-rank test, based on the Kaplan-Meier curves, showed a significant association between high sTREM-1 (higher than the median) and all-cause mortality (P<0.001) (Figure 2A) and MACE (P<0.001) (Figure 2B).

sTREM-1 and CRP

CRP is a strong predictor of future cardiovascular risk in patients with established coronary artery disease, with or without a previous myocardial infarction. Using a cutoff at the

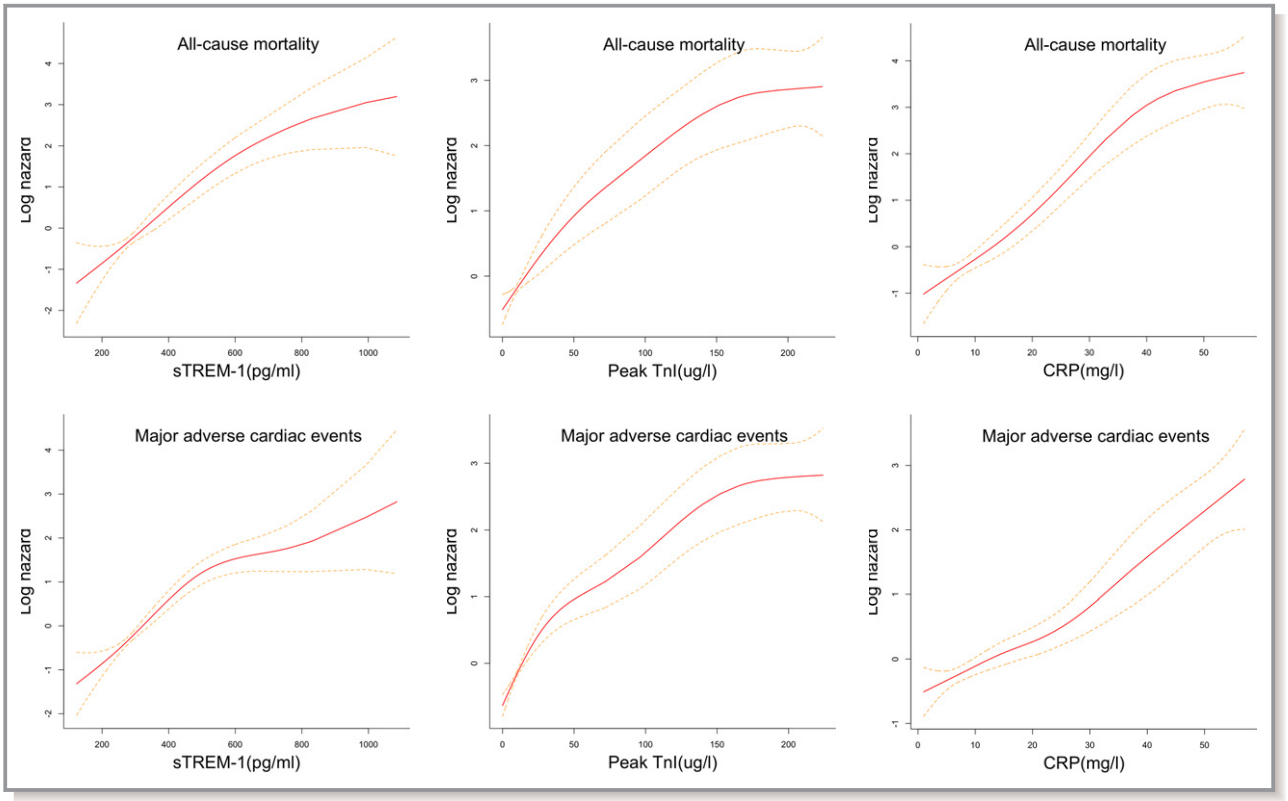

Figure 1. Spline curves between continuous biomarker levels and the hazard ratio of all-cause mortality and major adverse cardiovascular event. CRP indicates C-reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; TnI, troponin I.

Table 2. Multivariable Cox Regression Analyses for All-Cause Mortality

	Univariable		Multivariable Model 1*		Multivariable Model 2†	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.018 (1.001–1.035)	0.035	1.019 (0.996–1.043)	0.092	1.031 (1.008–1.054)	0.008
Male sex	1.306 (0.847–2.014)	0.227	1.020 (0.593–1.756)	0.942	1.013 (0.618–1.662)	0.958
Previous history						
Diabetes mellitus	2.001 (1.294–3.093)	0.003	1.823 (1.045–3.179)	0.034	1.984 (1.166–3.377)	0.012
Hypertension	1.256 (0.812–1.942)	0.305	1.435 (0.779–2.644)	0.247	1.421 (0.774–2.609)	0.258
Hypercholesterolemia	1.240 (0.759–2.026)	0.391	1.337 (0.740–2.417)	0.336	1.468 (1.001–3.123)	0.243
Previous/current smoker	1.634 (1.045–2.555)	0.031	1.181 (0.673–2.074)	0.562	1.078 (0.636–1.827)	0.781
Previous MI	2.059 (1.238–3.424)	0.005	2.249 (1.225–4.128)	0.009	2.354 (1.167–3.566)	0.018
Prior PCI or CABG	1.663 (0.990–2.794)	0.055	1.159 (0.575–2.388)	0.680	1.239 (0.347–2.138)	0.532
STEMI	1.532 (0.963–2.437)	0.072	1.257 (0.705–2.242)	0.438	1.451 (0.800–2.632)	0.22
PCI	0.727 (0.437–1.208)	0.218	0.502 (0.264–0.956)	0.036	0.432 (0.277–1.221)	0.042
Clinical presentation						
BMI	1.036 (0.972–1.104)	0.280	1.115 (1.031–1.207)	0.007	1.096 (1.017–1.180)	0.016
LVEF	0.920 (0.895–0.945)	<0.001	0.938 (0.907–0.970)	<0.001	0.933 (0.902–0.964)	<0.001
Killip class >1	2.310 (1.501–3.553)	<0.001	1.822 (1.050–3.159)	0.033	1.912 (1.118–3.270)	0.018
Baseline biological examinations						
Peak TnI*	1.926 (1.507–2.461)	<0.001	2.375 (1.609–3.506)	<0.001	…	…
CRP*	1.645 (1.291–2.095)	<0.001	1.795 (1.284–2.508)	0.001	…	…
sTREM-1*	2.347 (1.894–2.910)	<0.001	1.978 (1.462–2.675)	<0.001	…	…
Peak TnI†	1.014 (1.011–1.016)	<0.001	…	…	1.011 (1.007–1.015)	<0.001
CRP†	1.067 (1.040–1.096)	<0.001	…	…	1.069 (1.038–1.102)	<0.001
sTREM-1†	1.004 (1.003–1.005)	<0.001	…	…	1.004 (1.003–1.006)	<0.001
In-hospital medication						
Statins	0.455 (0.287–0.719)	0.001	0.856 (0.439–1.669)	0.856	0.682 (0.370–1.255)	0.219
β Blockers	0.291 (0.190–0.444)	<0.001	0.457 (0.231–0.902)	0.024	0.396 (0.218–0.721)	0.002
ACEI or ARB	0.365 (0.237–0.561)	<0.001	0.284 (0.147–0.552)	<0.001	0.388 (0.138–0.622)	0.003
Dual antiplatelet therapy	0.277 (0.172–0.445)	<0.001	0.660 (0.346–1.261)	0.660	0.622 (0.331–1.170)	0.141
Glycoprotein IIb/IIIa inhibitor	0.639 (0.416–0.983)	0.041	0.640 (0.363–1.128)	0.123	0.591 (0.354–0.986)	0.044

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; BMI, body mass index; CABG, coronary artery bypass graft; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation MI; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; TnI, troponin I.

*sTREM-1, peak TnI, and CRP were treated as categorical variables.

†sTREM-1, peak TnI, and CRP were treated as continuous variables.

median for sTREM-1 (299.9 pg/mL) and CRP (8 mg/L), we divided patients into 4 strata, according to the high/low sTREM-1 and high/low CRP. Tables 4 and 5 show a Cox regression analysis for all-cause mortality and MACE, including the 4 groups. By using patients with low sTREM-1/low CRP as the reference group, when both markers were high, the rates of both MACE (HR, 5.712; 95% CI, 3.384–9.640; *P*<0.001) and all-cause mortality (HR, 4.647; 95% CI, 1.912–11.295; *P*<0.001) were significantly increased. Figure 3 shows Kaplan-Meier curves for the 4 groups. As shown in Figure 3A and 3B, patients with high sTREM-1/high CRP had the highest rate of all-cause mortality and MACE, whereas the risk of low sTREM-1/low CRP was the lowest.

Subgroup and Sensitivity Analyses

During the follow-up, higher sTREM-1 levels were consistently associated with higher risks of all-cause mortality and MACE in various subpopulations. There was no significant interaction in the risk of all-cause mortality and MACE among

Table 3. Multivariable Cox Regression Analyses for MACEs

	Univariable		Multivariable Model 1*		Multivariable Model 2†	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.005 (0.993–1.016)	0.415	1.009 (0.997–1.022)	0.129	1.016 (1.002–1.029)	0.121
Male sex	1.046 (0.779–1.406)	0.764	1.316 (0.948–1.826)	0.081	1.043 (0.755–1.439)	0.799
Previous history						
Diabetes mellitus	1.442 (1.044–1.993)	0.026	1.224 (0.854–1.756)	0.271	1.375 (0.971–1.947)	0.072
Hypertension	1.217 (0.898–1.648)	0.205	0.925 (0.647–1.324)	0.344	0.937 (0.662–1.327)	0.716
Hypercholesterolemia	1.306 (0.929–1.836)	0.124	1.120 (0.770–1.628)	0.554	1.336 (0.927–1.926)	0.120
Previous/current smoker	0.829 (0.617–1.112)	0.211	1.190 (0.852–1.664)	0.308	1.135 (0.822–1.566)	0.466
Previous MI	1.757 (1.204–2.565)	0.003	1.888 (1.227–2.905)	0.004	2.003 (1.290–3.110)	0.002
Prior PCI or CABG	1.661 (1.152–2.395)	0.007	1.564 (1.053–2.323)	0.027	1.434 (1.038–2.341)	0.032
STEMI	1.801 (1.291–2.513)	0.001	1.254 (0.873–1.801)	0.220	1.419 (0.989–2.036)	0.058
PCI	0.747 (0.522–1.069)	0.111	0.694 (0.470–1.024)	0.066	0.773 (0.520–1.149)	0.204
Clinical presentation						
BMI	1.007 (0.963–1.054)	0.748	1.047 (0.994–1.102)	0.081	1.046 (0.996–1.098)	0.07
LVEF	0.984 (0.966–1.002)	0.088	0.998 (0.979–1.019)	0.347	0.990 (0.971–1.010)	0.328
Killip class >1	2.003 (1.471–2.726)	<0.001	1.682 (1.197–2.362)	0.003	1.784 (1.285–2.477)	0.001
Baseline biological examinations						
Peak TnI*	2.450 (2.049–2.928)	<0.001	1.874 (1.491–2.354)	<0.001	…	…
CRP*	1.384 (1.195–1.603)	<0.001	1.458 (1.312–1.907)	<0.001	…	…
sTREM-1*	2.155 (1.856–2.503)	<0.001	2.413 (2.022–2.879)	<0.001	…	…
Peak TnI†	1.015 (1.013–1.017)	<0.001	…	…	1.012 (1.009–1.015)	<0.001
CRP†	1.046 (1.025–1.067)	<0.001	…	…	1.050 (1.029–1.072)	<0.001
sTREM-1†	1.004 (1.003–1.005)	<0.001	…	…	1.005 (1.004–1.005)	<0.001
In-hospital medication						
Statins	0.950 (0.634–1.424)	0.804	0.882 (0.577–1.350)	0.564	0.843 (0.391–1.324)	0.756
β Blockers	0.712 (0.502–1.010)	0.057	0.497 (0.327–0.755)	0.001	0.565 (0.365–1.023)	0.012
ACEI or ARB	0.876 (0.598–1.285)	0.499	0.700 (0.490–1.000)	0.050	0.655 (0.465–0.923)	0.016
Dual antiplatelet therapy	0.797 (0.488–1.302)	0.365	0.960 (0.606–1.521)	0.863	1.195 (0.740–1.930)	0.466
Glycoprotein IIb/IIIa inhibitor	0.847 (0.621–1.156)	0.295	0.788 (0.560–1.108)	0.171	0.733 (0.526–1.021)	0.442

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; BMI, body mass index; CABG, coronary artery bypass graft; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation MI; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; TnI, troponin I.

*sTREM-1, peak TnI, and CRP were treated as categorical variables.

†sTREM-1, peak TnI, and CRP were treated as continuous variables.

prespecified subgroups (all *P* values for interaction >0.05; Figure 4).

Discussion

The present study is the first to demonstrate that high sTREM-1 level at admission is an independent predictor of both all-cause mortality and MACE in patients with AMI after adjusting for conventional risk factors. To further confirm the prognostic value of sTREM-1 in AMI, we used a panel of different tests, including Cox survival analysis and Kaplan-Meier analysis. Our findings suggested that sTREM-1 was prognostic for long-term adverse events up to 2 years and could provide important prognostic information for patients with AMI.

TREM-1 is an amplifier of the immune response during various inflammatory diseases.[9] Recently, studies reported that TREM-1 contributes to the development of atherosclerosis through promoting monocytosis, monocyte/macrophage proinflammatory responses, and formation of inflammatory foam cells.[23,24] TREM-1 gene polymorphisms are significantly

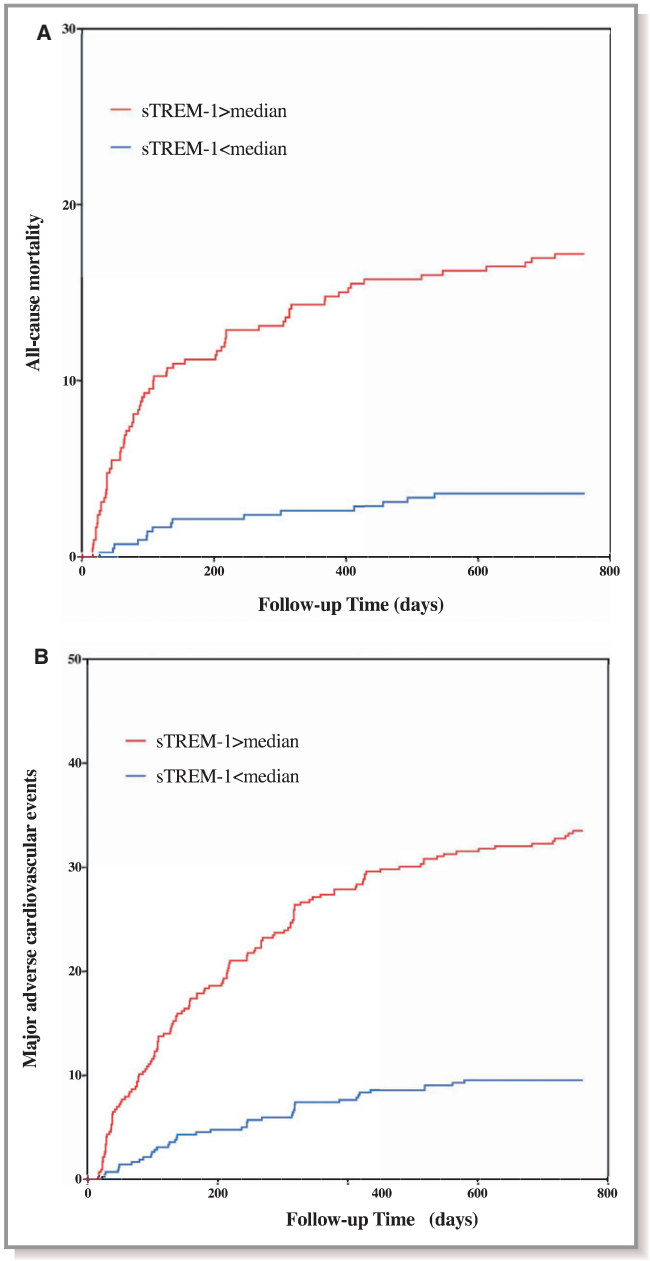

Figure 2. Kaplan-Meier curves for incidence of all-cause mortality (A) and major adverse cardiac events (B) in patients with acute myocardial infarction, stratified according to median levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1).

associated with higher coronary atherosclerosis severity in a Russian population.[25] Moreover, TREM-1 mediates inflammatory injury and cardiac remodeling after myocardial infarction in mice and pigs.[8]

Several pathophysiologic mechanisms could explain the association of TREM-1 with atherosclerosis and AMI. Monocytes/macrophages play a key role in the initiation and progression of atherosclerosis and plaque destabilization, and they lead to cytokine and chemokine production. These

Table 4. Cox Models for Risk of All-Cause Mortality in Groups on the Basis of sTREM-1 and CRP

Variable	HR	95% CI	*P* Value
sTREM-1 < median, CRP < median	1.00	…	…
sTREM-1 < median, CRP > median	1.473	0.525–4.134	0.462
sTREM-1 > median, CRP < median	3.975	1.599–9.882	<0.001
sTREM-1 > median, CRP > median	4.647	1.912–11.295	<0.001

CI indicates confidence interval; CRP, C-reactive protein; HR, hazard ratio; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.

cytokines and chemokines are the primary cause of plaque rupture, coronary artery thrombosis, and recurrent AMI.[26] TREM-1 is an immune receptor expressed by neutrophils, macrophages, and mature monocytes that acts as an amplifier of proinflammatory innate immune response.[9] TREM-1 connected and regulated complicated signals through several pattern recognition receptors induced by specific toll-like receptor agonists in the inflammatory process.[7,8] Li et al[27] identified that TREM-1 was a certain epitope of oxidized low-density lipoprotein in macrophages through the toll-like receptor pathway, which facilitated foam cell formation and activated inflammatory response, suggesting a crucial role in further plaque progression and rupture. Silencing TREM-1 by means of short hairpin RNA or linear plasmid 17 reduced lipid uptake and foam cell formation and impaired inflammatory response to oxidized low-density lipoprotein.[27] The expression of TREM-1 was also mostly found close to cholesterol- and necrotic-rich areas. TREM-1 deficiency/inhibition significantly reduced atherosclerosis growth in mice and induced a less vulnerable plaque phenotype characterized by reduced macrophage infiltration and necrotic core size.[24]

Another potential mechanism of this association was that the role of TREM-1 in orchestrating the inflammatory response triggered by MI lead to poor infarct healing and scar formation.[28] TREM-1 resulted in impaired delicate balance between the type and number of recruited leukocytes. Shortly

Table 5. Cox Models for Risk of MACE in Groups on the Basis of sTREM-1 and CRP

Variable	HR	95% CI	*P* Value
sTREM-1 < median, CRP < median	1.00	…	…
sTREM-1 < median, CRP > median	1.517	0.821–2.803	0.184
sTREM-1 > median, CRP < median	2.951	1.686–5.167	<0.001
sTREM-1 > median, CRP > median	5.712	3.384–9.640	<0.001

CI indicates confidence interval; CRP, C-reactive protein; HR, hazard ratio; MACE, major adverse cardiac event; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.

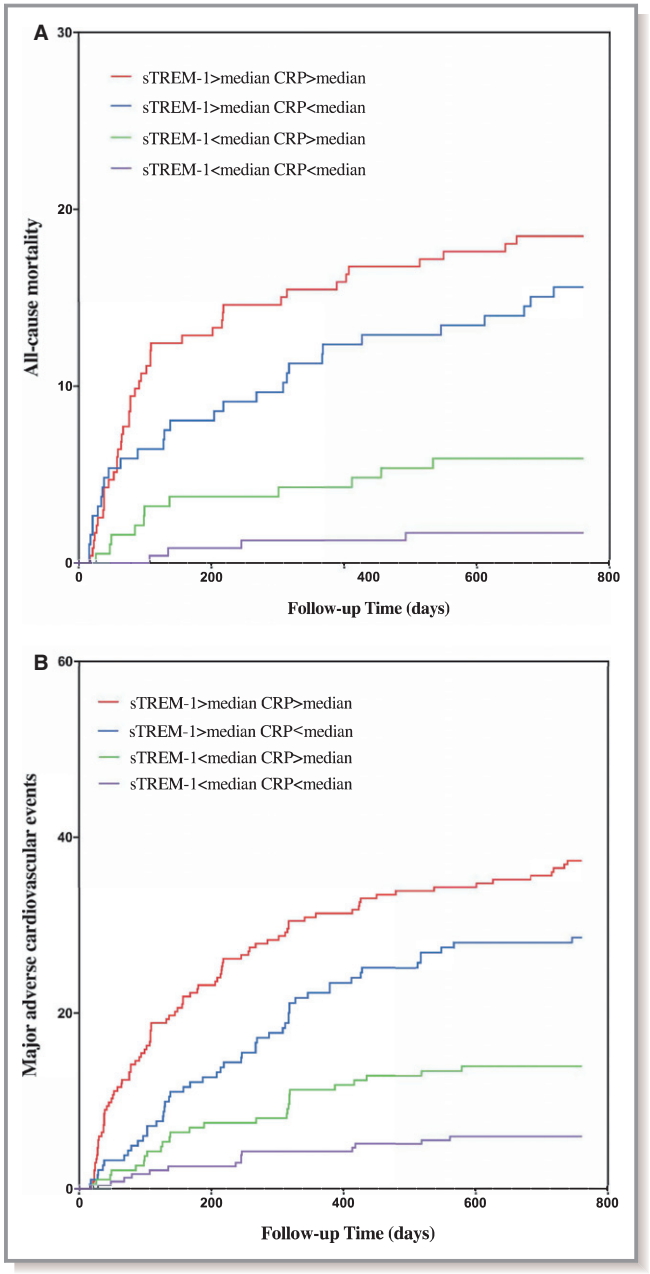

Figure 3. Kaplan-Meier curves for incidence of all-cause mortality (A) and major adverse cardiac events (B) in patients with acute myocardial infarction, stratified according to median levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and C-reactive protein (CRP).

after AMI, excessive neutrophils accumulate in the injured myocardium after ischemia and may lead to further tissue injury. After activation of neutrophils, the inflammatory process is replaced by monocytes. TREM-1 induced the dyslipidemia-induced peripheral blood monocytosis by promoting imbalanced monocyte differentiation from bone marrow hematopoietic stem and progenitor cells, resulting in progression in atherosclerosis and myocardial infiltration.[23] In a recent preclinical study, the genetic invalidation and the pharmacological inhibition of TREM-1 limited the recruitment of inflammatory cells, such as neutrophil and monocyte chemotactic protein-1 production, to the infarcted myocardium and could inhibit the proinflammatory cytokine production. Furthermore, matrix metalloproteinases, whose major source was myeloid cells, especially neutrophils, were associated with the risk of cardiac rupture and remodeling.[29] Inhibition of TREM-1 might prevent the adverse events by reducing myeloid cell infiltration and matrix metalloproteinase 9 expression. These all strongly suggest that TREM-1 is a central player in the inflammatory reactions and development of adverse cardiac remodeling and cardiac function after MI.

sTREM-1 originated from spliced TREM-1 on the cell membrane. Previously published researchers showed that sTREM-1 levels are centrally involved in acute microbial inflammation and are a crucial mediator of septic shock; only 19% of healthy controls had detectable sTREM-1.[9,10] However, the role of sTREM-1 is subject to intensive research in various noninfectious diseases, such as heart surgery, cardiac arrest, anti–neutrophil cytoplasmic antibody–associated vasculitis, and rheumatoid arthritis.[30–35] Therefore, it is reasonable to propose that elevated sTREM-1 in the serum could be derived from activated monocytes/macrophages in atherosclerotic plaque or neutrophils accumulated in the injured myocardium after AMI. Therefore, increased levels of sTREM-1 may, at least partly, reflect progression of atherosclerosis and plaque destabilization; they also may reflect that excessive neutrophils accumulate in the injured myocardium after ischemia and further tissue injury.

Furthermore, TREM-1 inhibition reduces platelet aggregation induced by collagen, ADP, and thrombin in human platelets. In vivo, inhibition of TREM-1 depresses thrombus formation in a carotid artery model and protects mice during pulmonary embolism, without excessive bleeding.[15] Platelet plays a pivotal role in chronic inflammation, leading to development and progression of atherosclerosis and acute coronary events. Therefore, it is possible that TREM-1 is involved, either directly or indirectly, with progression of atherosclerosis, plaque instability, and myocardium injury induced by platelet, and it is also reasonable to propose that elevated concentration of serum sTREM-1 could be partly derived from activated platelets in atherosclerotic plaque.

In addition to the measurements of sTREM-1 levels, we evaluated CRP levels and identified that higher CRP level was a significant predictor of adverse clinical outcomes. In the present study, high sTREM-1 level combined with high CRP level probably indicated a severe inflammatory process. Thus, patients were stratified by high/low sTREM-1 and high/low CRP to 4 groups. The high CRP/high sTREM-1 group significantly associated with the highest event rate, whereas the low CRP/low sTREM-1 group associated with the lowest event rate.

Some limitations should be taken into consideration. First, the present study was the evaluation of TREM-1 levels only once

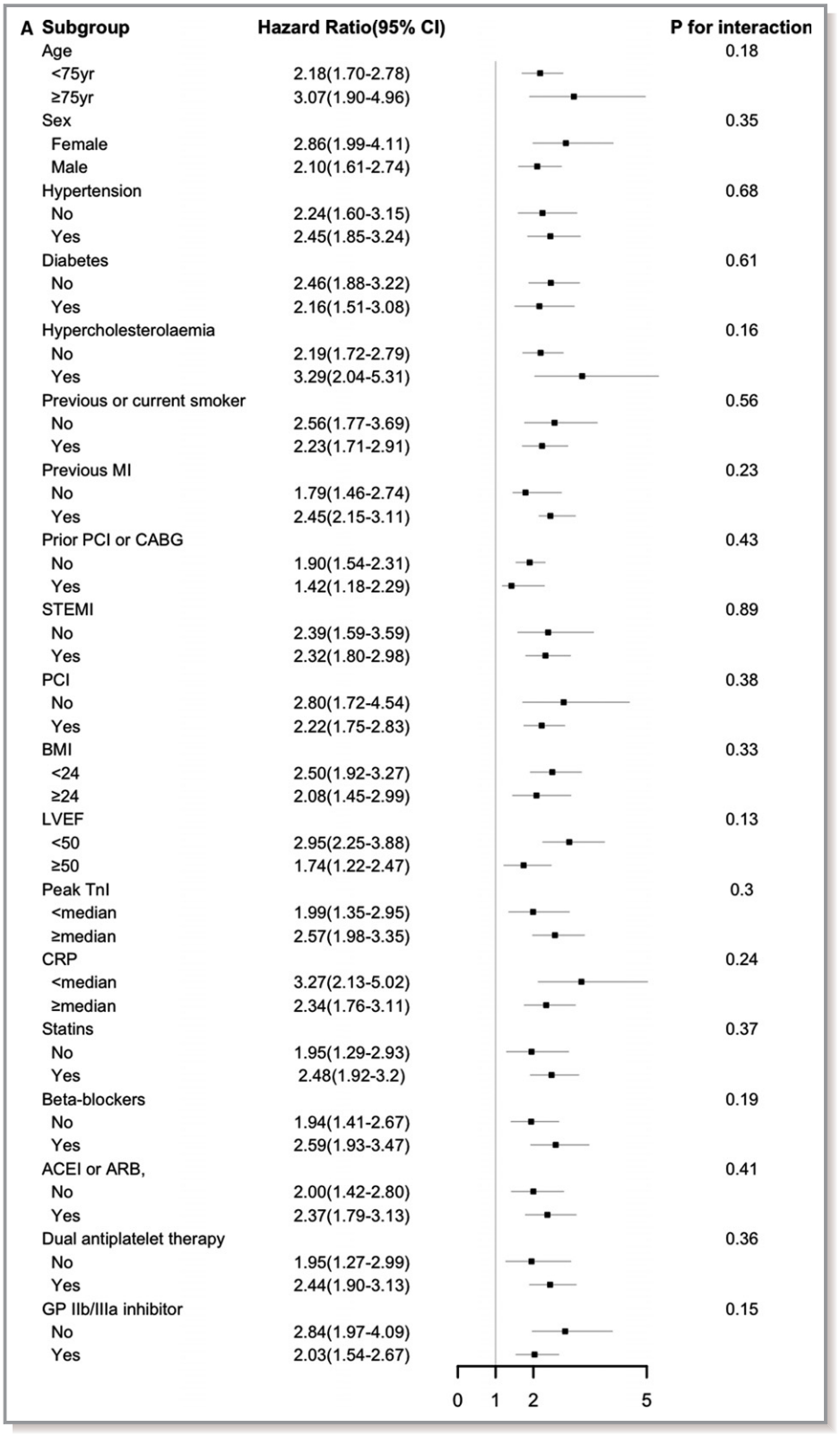

Figure 4. Hazard ratio (HR) and 95% confidence interval (CI) of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) for all-cause mortality (A) and major adverse cardiac events (B) in subgroup analyses. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; BMI, body mass index; CABG, coronary artery bypass graft; CRP, C-reactive protein; GP, glycoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TnI, troponin I.

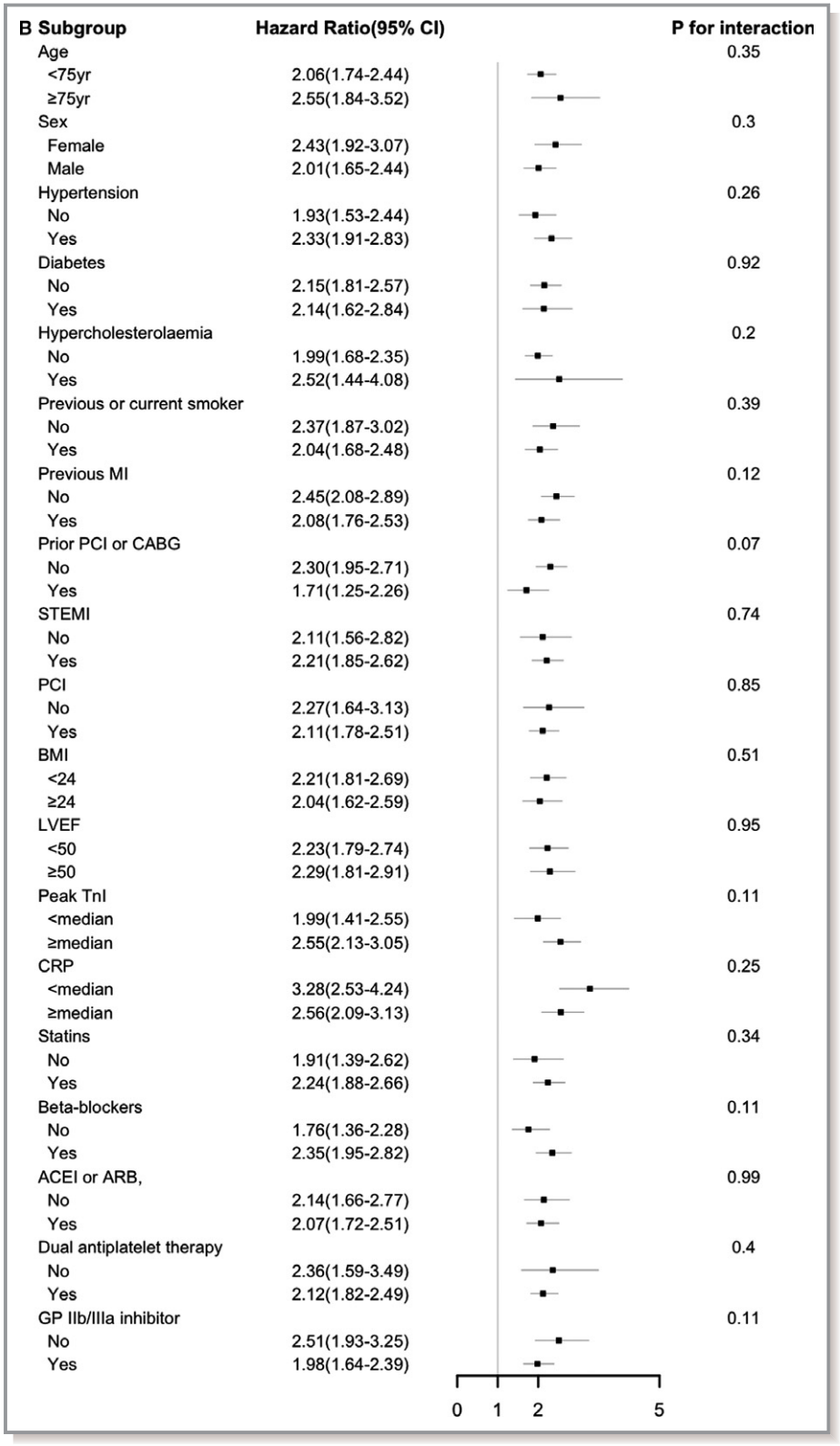

Figure 4. Continued

at admission. Serial measurements after AMI are required to determine the optimum timing of blood collection for predicting the prognosis. Second, our findings are based on a population from 2 admitting hospitals, and the results should be verified in larger populations. Finally, prospective studies on the clinical effectiveness of using this biomarker to distinguish low- or high-risk groups and to choose strategies need to be performed.

In conclusion, the present study is the first to report that elevated levels of circulating sTREM-1 independently predict all-cause mortality and MACE in patients with AMI, independent of established conventional risk factors.

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Disclosures

None.

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