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Biomarkers enhance the long-term predictive ability of the KAMIR risk score in Chinese patients with ST-elevation myocardial infarction

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Abstract

Background: The Global Registry of Acute Coronary Events (GRACE) score is recommended by current ST-elevation myocardial infarction (STEMI) guidelines. But it has inherent defects. The present study aimed to investigate the more compatible risk stratification for Chinese patients with STEMI and to determine whether the addition of biomarkers to the Korea Acute Myocardial Infarction Registry (KAMIR) score could enhance its predictive value for long-term outcomes.

Methods: A total of 1093 consecutive STEMI patients were included and followed up 48.2 months. Homocysteine, hypersensitive C-reactive protein (hs-CRP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were detected. The KAMIR score and the GRACE score were calculated. The performance between the KAMIR and the GRACE was compared. The predictive power of the KAMIR alone and combined with biomarkers were assessed by the receiver-operating characteristic (ROC) curve.

Results: The KAMIR demonstrated a better risk stratification and predictive ability than the GRACE (death: AUC = 0.802 vs. 0.721, $P < 0.001$; major adverse cardiovascular events (MACE): AUC = 0.683 vs. 0.656, $P < 0.001$). It showed that the biomarkers could independently predict death [homocysteine: HR = 1.019 (1.015–1.024), $P < 0.001$; hs-CRP: HR = 1.052 (1.000–1.104), $P = 0.018$; NT-pro BNP: HR = 1.142 (1.004–1.280), $P = 0.021$] and MACE [homocysteine: HR = 1.019 (1.015–1.024), $P < 0.001$; hs-CRP: HR = 1.012 (1.003–1.021), $P = 0.020$; NT-pro BNP: HR = 1.136 (1.104–1.168), $P = 0.006$]. When they were used in combination with the KAMIR, the area under the ROC curve (AUC) significantly increased for death [homocysteine: AUC = 0.802 vs. 0.890, Z = 5.982, $P < 0.001$; hs-CRP: AUC = 0.802 vs. 0.873, Z = 3.721, $P < 0.001$; NT-pro BNP: AUC = 0.802 vs. 0.871, Z = 2.187, $P = 0.047$; homocysteine, hs-CRP and NT-pro BNP: AUC = 0.802 vs. 0.940, Z = 6.177, $P < 0.001$] and MACE [homocysteine: AUC = 0.683 vs. 0.771, Z = 6.818, $P < 0.001$; hs-CRP: AUC = 0.683 vs. 0.712, Z = 2.022, $P = 0.031$; NT-pro BNP: AUC = 0.683 vs. 0.720, Z = 2.974, $P = 0.003$; homocysteine, hs-CRP and NT-pro BNP: AUC = 0.683 vs. 0.789, Z = 6.900, $P < 0.001$].

Conclusion: The KAMIR is better than the GRACE in risk stratification and prognosis prediction in Chinese STEMI patients. A combination of above-mentioned biomarkers can develop a more predominant prediction for long-term outcomes.

Keywords: ST-elevation myocardial infarction; the Korea Acute Myocardial Infarction Registry risk score; the Global Registry of Acute Coronary Events risk score; homocysteine; hypersensitive C-reactive protein; N-terminal pro-B-type natriuretic peptide

Introduction

Patients with ST-elevation myocardial infarction (STEMI) face various risks of adverse cardiovascular events.[1] Risk stratification, therefore, is a cornerstone in the modern management and treatment of STEMI.[2,3] Several models have been developed to perform risk stratification, such as the Thrombolysis in Myocardial Infarction (TIMI), Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and Global Registry of Acute Coronary Events (GRACE).[4] However, these models have inherent defects.[5] Even the GRACE risk scoring system,[6] which is recommended by current STEMI management guidelines,[2,3] is developed for short-term prognosis and its calculation is tedious. Furthermore, the GRACE risk scoring system was validated on the basis of early data. Patients and procedural characteristics in STEMI have been changing,[7] thus current clinical treatments may no longer fit the GRACE score. Moreover, the GRACE risk scoring system

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was developed based on patients in Europe and America, whose characteristics may differ from the Asians.

Recently, a new risk prediction model, the Korea Acute Myocardial Infarction Registry (KAMIR) score, is developed to assess risks of clinical outcomes in acute myocardial infarction (AMI).[8] This model has advantages in simplicity and accuracy simultaneously for both short- and long-term risk assessment, and has the potential to be a powerful predictive tool for prognosis of AMI.[9] Research has already shown that the KAMIR score does a better job than the GRACE score in predicting the clinical outcomes in AMI patients in Korea.[9] It will be valuable to see if this advantage also exists in patients in other areas. Up to now, no studies have been found to compare the effects of the KAMIR score and the GRACE score in Chinese STEMI patients.

Extensive research has been conducted to evaluate the effectiveness of risk prediction models and to explore how to improve the effectiveness. It is already confirmed that biomarkers can strengthen the predictive capability of the models. For example, homocysteine,[10] neutrophil count,[11] mean platelet volume (MPV),[12] cystatin C (Cys C),[13] hypersensitive C-reactive protein (hs-CRP),[14] N-terminal pro-B-type natriuretic peptide (NT-proBNP),[15] growth differentiation factor 15 (GDF-15),[16] and red blood cell fatty acid[17] are reported to be able to reinforce risk assessment beyond the GRACE score. This suggests room and possibility for improvement in the KAMIR scoring system. The biomarkers, being considered in the system, are limited to creatinine and glucose. However, studies have found that homocysteine,[18] hs-CRP,[19] and NT-pro BNP[20] have a vigorous response following AMI and their plasma levels are related to mortality. These biomarkers help to reveal the pathological process of AMI in terms of metabolism, inflammation, and neuroendocrine. In spite of the important values of these biomarkers in AMI, they are not included in the KAMIR score, and there are by far no reports on whether they could enhance the predictive ability of the KAMIR score. In particular, no studies have been conducted to evaluate the potential influences of these biomarkers on the KAMIR score in STEMI. In the present study, we compared the predictive ability of the GRACE score and the KAMIR score in Chinese STEMI patients and investigated whether combination of the above-mentioned 3 biomarkers with the KAMIR score could better predict the long-term clinical outcomes in the Chinese patients. The aim of our analyses was to identify a risk prediction model that fits Chinese STEMI patients better.

Methods

Ethical approval

The study was approved by the Ethics Committees of Gansu Provincial Hospital and the First Affiliated Hospital of Xi'an Jiaotong University School of Medicine. It was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients.

Study population

From January 2010 to December 2012, 1093 consecutive patients upon a confirmed diagnosis of STEMI were admitted to the Department of Cardiology in the two hospitals with facilities for primary percutaneous coronary intervention (PCI) and on-site cardiac surgery in China. The diagnostic criteria followed the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines of STEMI.[2,3] Patients with malignant tumors or severe liver or kidney dysfunction were excluded. These patients have all received PCI treatment.

Biomarker detection

Blood samples were collected from the patients, and then the serum was obtained by centrifugation at 4°C and stored in aliquots at −80°C. All laboratory parameters, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C), plasma glucose, creatinine, uric acid, Cys C, creatine kinase (CK), creatine kinase-myocardial band (CK-MB), cardiac troponin, homocysteine, hs-CRP, and NT-pro BNP, were detected in the Biochemical Departments of the two hospitals where the same laboratory standards were followed.

Echocardiography

Comprehensive echocardiographic analysis of cardiac structure and function was performed by a single experienced physician following the echocardiography guidelines[21] to achieve measurement stability. All measurements were averaged over 3 cardiac cycles. The indexes of left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) were normalized according to body surface area. Left ventricular mass was calculated using the recommended formula of the American Society of Echocardiography,[21] and the left ventricular mass index was also normalized. Regional wall motion was assessed using a left ventricular 16-segment model and a 4-point grading scale.[21] The wall-motion score index was calculated as the sum of the score of each segment divided by the number of segments scored. A higher index corresponds to weaker wall motion.

Coronary angiography

Coronary angiography was performed according to the standard method.[22] The images were analyzed by a single specialist. Coronary single-vessel disease was defined as >50% stenosis in a major coronary artery (eg, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) and/or their main branches. Multiple-vessel disease was defined as >50% stenosis in more than 1 major coronary artery.[22] The Gensini score[23] was calculated to assess the severity of stenosis. The higher the score, the more severe the coronary artery lesion would be.

Risk score calculation

Baseline data, including demographic information, clinical data, and medication usage, were collected using a standard case report form. The KAMIR risk score was calculated as described in the literature.[8] Six independent variables related to cardiovascular events, namely age, Killip class, serum creatinine, no in-hospital PCI, left ventricular ejection fraction (LVEF), and admission glucose, were involved via a multivariable Cox proportional hazard regression analysis. The GRACE risk score was also calculated as described previously.[6] Values of variables, including age, heart rate, systolic blood pressure, serum creatinine level, history of congestive heart failure, in-hospital PCI, in-hospital coronary artery bypass graft surgery (CABG), previous MI, ST-segment depression, and elevated cardiac markers, were entered into the GRACE risk calculator to obtain the score.

Follow-up

Patient follow-up was performed by a group of medical staff. All patients were followed up by telephone calls or interviews to track the occurrence of cardiovascular events and medication adherence. The major adverse cardiovascular events (MACE) included all-cause death, rehospitalization due to heart failure or angina symptoms, recurrent nonfatal MI, repeated coronary revascularization, and stroke.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (inter-quartile range). Categorical variables are presented as frequency (percentage). The data were checked for normality using the Kolmogorov-Smirnov test. Independent-samples *t* test or Mann-Whitney *U* test was used to examine the differences between continuous variables, as appropriate. The Pearson χ^2 test or Fisher exact test was used to determine the differences between categorical variables, as appropriate. Univariate and multivariate Cox proportional hazard regression analysis was performed to identify predictors for adverse clinical outcomes. The outcomes were further evaluated by the Kaplan-Meier curve, and intergroup comparisons were conducted with the log-rank test. The potential correlation between the 3 biomarkers, homocysteine, hs-CRP, and NT-pro BNP, and the KAMIR risk score were analyzed by Spearman rank correlation. The predictive value of combining these biomarkers into the KAMIR risk scoring system was estimated by the receiver-operating characteristic (ROC) curve. Discrimination was assessed by the area under ROC curve (AUC), and the increase in AUC was tested for significance using the method previously proposed.[24] Calibration was assessed with Hosmere Lemeshow goodness-of-fit.[24] Statistical analyses were performed using SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA), MedCalc for Windows (version 9.6.4.0), and R-programming language (version 3.1.2). All the analyses were two-tailed, and a P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of patients

Altogether 1093 patients were included and follow-up data were obtained from all the patients. The patients (85% male) had a median age of 58 years (interquartile range [IQR], 50–67 years) and a median follow-up period of 48.2 months (IQR, 39.6–58.0 months). The baseline characteristics, including demographic and clinical characteristics, biomarker concentrations, and medication during hospitalization, are shown in Table 1.

Comparison of baseline data between patients with and without MACE

During the period of follow-up, 278 (25.4%) patients reached the clinical endpoint, including 109 (10.0%) deaths, 77 (7.0%) heart failures, 54 (4.9%) unstable anginas, 34 (3.1%) MIs, 54 (4.9%) coronary revascularizations, and 18 (1.6%) strokes. The baseline data of the patients with or without MACE are demonstrated in Table 2. Compared with patients without adverse events, patients with such events were older, more often females, and with a higher frequency of smoking, hypertension, and family history of coronary heart disease. Moreover, these patients had higher heart rate, blood glucose, uric acid, Killip classification, left ventricular size and mass, and the Gensini score, and had worse left ventricular systolic function and wall motion. Moreover, the homocysteine, hs-CRP, and NT-pro BNP levels, the KAMIR score, and the GRACE score were significantly higher in patients with MACE.

Analysis of factors correlated with clinical outcomes

Cox proportional hazard regression analyses were performed to identify the predictive factors for clinical outcomes. Tables 3 and 4 summarize the results of univariate and multivariate Cox proportional hazard regression analyses for all-cause death or MACE in these patients. Univariate analysis showed that the aforementioned 3 biomarkers (homocysteine, hs-CRP, and NT-pro BNP), the KAMIR risk score, and the GRACE risk score were associated with higher risks of all-cause death and MACE. After adjusted for potential confounding factors, such as age, gender, body mass index, heart rate, blood pressure, smoking, hypertension, dyslipidemia, diabetes, and Killip classification, homocysteine, hs-CRP, NT-pro BNP, the KAMIR risk score, and the GRACE risk score remained to be significant predictors for all-cause death [homocysteine: HR = 1.019 (1.015–1.024), $P < 0.001$; hs-CRP: HR = 1.052 (1.000–1.104), $P = 0.018$; NT-pro BNP: HR = 1.142 (1.004–1.280), $P = 0.021$; KAMIR score: HR = 1.547 (1.268–1.887), $P < 0.001$; GRACE score: HR = 1.015 (1.005–1.025), $P = 0.003$] and MACE [homocysteine: HR = 1.019 (1.015–1.024), $P < 0.001$; hs-CRP: HR = 1.012 (1.003–1.021), $P = 0.020$; NT-pro BNP: HR = 1.136 (1.104–1.168), $P = 0.006$; KAMIR score: HR = 1.566 (1.421–1.726), $P < 0.001$; GRACE score: HR = 1.010 (1.007–1.012), $P < 0.001$].

Table 1: Baseline characteristics of patients with ST-elevation myocardial infarction

Clinical characteristics	Results
Male gender, *n* (%)	929 (85)
Age (years)	58.45 ± 11.45
Body mass index (kg/m^2)	23.94 ± 2.78
Heart rate (beats/min)	76.06 ± 15.48
Systolic blood pressure (mmHg)	121.85 ± 20.46
Diastolic blood pressure (mmHg)	76.92 ± 13.24
Smoking, *n* (%)	771 (70.5)
Hypertension, *n* (%)	477 (43.6)
Dyslipidemia, *n* (%)	192 (17.6)
Diabetes, *n* (%)	157 (14.4)
History of myocardial infarction, *n* (%)	69 (6.3)
History of revascularization, *n* (%)	29 (2.7)
History of cerebrovascular disease, *n* (%)	80 (7.3)
Family history of coronary heart disease, *n* (%)	101 (9.2)
Anterior wall infarct, *n* (%)	626 (57.3)
Killip classification, *n* (%)	
Class I	701 (64.1)
Class II	296 (27.1)
Class III	57 (5.2)
Class IV	39 (3.6)
Laboratory examinations	
Triglycerides (mmol/L)	1.63 ± 0.92
Total cholesterol (mmol/L)	4.09 ± 1.21
Low-density lipoprotein cholesterol (mmol/L)	2.38 ± 0.82
Blood glucose (mmol/L)	7.82 ± 4.00
Uric acid (μmol/L)	305.69 ± 91.72
Cystatin C (mg/L)	1.07 ± 0.97
Homocysteine (μmol/L)	21.45 ± 15.09
Hypersensitive C-reactive protein (mg/L), median (IQR)	9.28 (3.80, 25.80)
N-terminal pro-B-type natriuretic peptide (pg/mL), median (IQR)	877.20 (360.95, 1751.0)
Creatine phosphokinase-myocardial band (U/L), median (IQR)	63.99 (15.03, 191.20)
eGFR (mL·min^{-1}·1.73 m^{-2})	113.55 ± 46.20
Ultrasound cardiogram parameters	
Left ventricular end-diastolic dimension index (cm/m^2)	3.02 ± 0.41
Left ventricular end-systolic dimension index (cm/m^2)	2.15 ± 0.45
Left ventricular end-diastolic volume index (mL/m^2)	58.66 ± 14.08
Left ventricular end-systolic volume index (mL/m^2)	30.82 ± 11.75
Left ventricular mass index (g/m^2)	90.63 ± 23.28
Left ventricular fraction shortening (%)	29.33 ± 7.79
Left ventricular ejection fraction (%)	53.42 ± 11.09
Wall motion score index	1.27 ± 0.19
Coronary angiography characteristics	
Multiple-vessel disease, *n* (%)	633 (57.9)
Gensini score	69.76 ± 39.86
Risk score	
KAMIR risk score	1.87 ± 1.21
GRACE risk score 1	98.08 ± 28.83
GRACE risk score 2	128.25 ± 44.08
Medicine, *n* (%)	
Aspirin	1043 (95.4)
Clopidogrel/Ticagrelor	1087 (99.5)
Statin	1040 (95.2)
Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker	1010 (92.4)
β-Blocker	999 (91.4)
Platelet glycoprotein IIbIIIa receptor antagonist	773 (70.7)

eGFR: estimated glomerular filtration rate; KAMIR risk score: the Korea Acute Myocardial Infarction Registry risk score; GRACE risk score: the Global Registry of Acute Coronary Events risk score (GRACE risk score 1: the algorithms of probability for death at admission; GRACE risk score 2: the algorithms of probability for death or myocardial infarction at admission). eGFR is calculated according to the MDRD formula: eGFR (mL·min^{-1}·1.73 m^{-2} of body surface area) = 186 × (SCr)–1.154 × (Age)–0.203 (× 0.742 for females). SCr is reported in mg/dL.

Table 2: Baseline data of patients with or without MACE

Items	With MACE ($n=278$)	Without MACE ($n=815$)	Statistics	*P* value
Clinical characteristics				
Male gender	220 (79.1)	709 (87.0)	10.035†	0.002
Age (years)	62.94±11.56	56.91±11.00	7.596*	<0.001
Body mass index (kg/m^2)	23.93±2.72	23.95±2.80	–0.117*	0.907
Heart rate (beats/min)	80.28±19.10	74.62±13.76	4.562*	<0.001
Systolic blood pressure (mmHg)	120.76±22.22	122.22±19.83	–0.973*	0.331
Diastolic blood pressure (mmHg)	75.73±14.32	77.32±12.84	–1.642*	0.101
Smoking	201 (72.3)	530 (65.0)	5.293†	0.021
Hypertension	136 (48.9)	341 (41.8)	4.225†	0.040
Dyslipidemia	59 (21.2)	133 (16.3)	3.443†	0.064
Diabetes	36 (12.9)	121 (14.8)	0.606†	0.436
History of myocardial infarction	22 (7.9)	47 (5.8)	1.615†	0.204
History of revascularization	7 (2.5)	22 (2.7)	0.026†	0.871
History of cerebrovascular disease	25 (9.0)	55 (6.7)	1.539†	0.215
Family history of coronary heart disease	29 (10.4)	47 (5.8)	1.239†	0.020
Anterior wall infarct	166 (59.7)	460 (56.4)	0.906†	0.341
Killip classification	82.274†	<0.001		
Class I	140 (50.4)	561 (68.8)		
Class II	78 (28.1)	218 (26.7)		
Class III	33 (11.9)	24 (2.9)		
Class IV	27 (9.7)	12 (1.5)		
Laboratory examinations				
Triglycerides (mmol/L)	1.58±0.95	1.64±0.90	–1.043*	0.297
Total cholesterol (mmol/L)	4.14±1.48	4.07±1.11	0.807*	0.420
Low-density lipoprotein cholesterol (mmol/L)	2.43±0.81	2.36±0.82	1.262*	0.208
Blood glucose (mmol/L)	8.32±4.88	7.65±3.63	2.107*	0.036
Uric acid (μmol/L)	324.50±109.46	299.28±83.95	3.506*	0.001
Cystatin C (mg/L)	1.11±0.76	1.06±1.03	0.821*	0.412
Homocysteine (μmol/L)	29.82±22.38	18.59±10.14	8.086*	<0.001
Hypersensitive C-reactive protein (mg/L), median	625.15	520.34	5.368†	<0.001
N-terminal pro-B-type natriuretic peptide (pg/mL), median	697.54	495.65	6.671†	<0.001
Creatine phosphokinase-myocardial band (U/L), median	541.28	548.95	–0.375†	0.726
eGFR (mL·min^{-1}·1.73m^{-2})	116.53±66.15	112.53±37.02	0.957*	0.339
Ultrasound cardiogram parameters				
Left ventricular end-diastolic dimension index (cm/m^2)	3.09±0.44	3.00±0.40	3.141*	0.002
Left ventricular end-systolic dimension index (cm/m^2)	2.24±0.49	2.12±0.43	3.842*	<0.001
Left ventricular end-diastolic volume index (mL/m^2)	60.36±14.66	58.07±13.84	2.346*	0.019
Left ventricular end-systolic volume index (mL/m^2)	33.07±12.44	30.06±11.41	3.711*	<0.001
Left ventricular mass index (g/m^2)	95.02±24.80	89.13±22.56	3.665*	<0.001
Left ventricular fraction shortening (%)	27.75±7.96	29.87±7.66	–4.106*	<0.001
Left ventricular ejection fraction (%)	51.08±11.37	54.22±10.89	–3.951*	<0.001
Wall motion score index	1.29±0.21	1.27±0.19	1.813*	0.070
Coronary angiography characteristics				
Multiple-vessel disease	157 (56.5)	469 (57.5)	4.785†	0.323
Gensini score	82.00±42.12	66.13±38.45	5.504*	<0.001
Risk score				
KAMIR risk score	2.61±1.56	1.62±0.93	9.995*	<0.001
GRACE risk score 1	113.32±31.95	92.88±25.71	9.653*	<0.001
GRACE risk score 2	147.04±46.06	121.84±41.51	8.070*	<0.001

* *t* value. † χ^2 value. eGFR: estimated glomerular filtration rate; KAMIR risk score: the Korea Acute Myocardial Infarction Registry risk score; GRACE risk score: the Global Registry of Acute Coronary Events risk score; MACE: major adverse cardiovascular events.

Performance of the KAMIR risk score precedes the GRACE risk score

The accuracy of predicting all-cause death by the KAMIR score was AUC 0.802 (95% CI: 0.753–0.852) and that by the GRACE score was 0.721 (95% CI: 0.672–0.770) ($P<0.001$). For MACE, the accuracy was AUC 0.683 (95% CI: 0.644–0.723) by the KAMIR score and 0.656 (95% CI: 0.618–0.693) by the GRACE score ($P<0.001$). Figure 1 demonstrates the greater power of the KAMIR score, as

Table 3: Cox proportional hazard regression analyses for all-cause death

Items	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.085 (1.065–1.107)	<0.001	1.070 (1.048–1.092)	<0.001
Female gender	2.443 (1.611–3.705)	<0.001	1.835 (1.147–2.936)	0.011
Heart rate	1.028 (1.019–1.037)	<0.001	1.018 (1.008–1.028)	<0.001
Diastolic blood pressure	0.982 (0.968–0.997)	0.020		
Killip classification	2.178 (1.826–2.597)	<0.001		
eGFR	1.004 (1.001–1.007)	0.003		
Blood glucose	1.060 (1.029–1.091)	<0.001		
Uric acid	1.004 (1.002–1.006)	<0.001		
Homocysteine	1.025 (1.021–1.029)	<0.001	1.019 (1.015–1.024)	<0.001
Hypersensitive C-reactive protein	1.070 (1.005–1.135)	<0.001	1.052 (1.000–1.104)	0.018
N-terminal pro-B-type natriuretic peptide	1.181 (1.024–1.338)	<0.001	1.142 (1.004–1.280)	0.021
Left ventricular end-diastolic dimension index	1.885 (1.271–2.794)	0.002		
Left ventricular end-diastolic volume index	1.013 (1.001–1.025)	0.029		
Left ventricular mass index	1.011 (1.004–1.018)	0.003		
Left ventricular ejection fraction	0.954 (0.938–0.971)	<0.001	0.970 (0.951–0.990)	0.004
Gensini score	1.011 (1.006–1.016)	<0.001		
KAMIR risk score	2.213 (1.977–2.478)	<0.001	1.547 (1.268–1.887)	<0.001
GRACE risk score	1.039 (1.032–1.045)	<0.001	1.015 (1.005–1.025)	0.003

CI: confidence interval; eGFR: estimated glomerular filtration rate; GRACE risk score: the Global Registry of Acute Coronary Events risk score; HR: hazard ratio; KAMIR risk score: the Korea Acute Myocardial Infarction Registry risk score.

compared with the GRACE score, in predicting adverse clinical outcomes in the patients.

Risk stratification of the KAMIR risk score

Patients were divided into 3 categories according to the KAMIR risk score: 0–1 point as low risk ($n=507$), 2–3 points as intermediate risk ($n=469$), and over 4 points as high risk ($n=117$)[8]. This risk scoring system displayed good predictive values for all-cause death (Chi-square = 158.579, $P<0.001$) and MACE (Chi-square = 147.731, $P<0.001$) in the study population [Figure 2].

Biomarkers as independent predictors for adverse clinical outcomes

The patients were categorized into 3 groups according to the tertiles of biomarker levels: homocysteine (Tertile 1: <

Table 4: Cox proportional hazard regression analyses for MACE

Items	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.045 (1.034–1.057)	<0.001	1.027 (1.015–1.040)	<0.001
Female gender	1.737 (1.300–2.320)	<0.001	1.370 (1.023–1.836)	0.035
Heart rate	1.019 (1.012–1.025)	<0.001		
Hypertension	1.318 (1.041–1.668)	0.022		
Killip classification	1.798 (1.589–2.034)	<0.001	1.450 (1.258–1.672)	<0.001
Blood glucose	1.037 (1.011–1.063)	0.004		
Uric acid	1.006 (1.001–1.011)	<0.001		
Homocysteine	1.022 (1.018–1.026)	<0.001	1.019 (1.015–1.024)	<0.001
Hypersensitive C-reactive protein	1.015 (1.007–1.023)	<0.001	1.012 (1.003–1.021)	0.020
N-terminal pro-B-type natriuretic peptide	1.179 (1.124–1.234)	<0.001	1.136 (1.104–1.168)	0.006
Left ventricular end-diastolic dimension index	1.643 (1.259–2.146)	<0.001		
Left ventricular end-diastolic volume index	1.011 (1.003–1.019)	0.005		
Left ventricular mass index	1.009 (1.004–1.014)	<0.001		
Left ventricular ejection fraction	0.976 (0.966–0.986)	<0.001	0.982 (0.971–0.993)	0.001
Wall motion score index	1.782 (1.023–3.105)	0.041		
Gensini score	1.009 (1.006–1.011)	<0.001		
GRACE risk score	1.012 (1.009–1.015)	<0.001	1.010 (1.007–1.012)	<0.001
KAMIR risk score	1.788 (1.647–1.941)	<0.001	1.566 (1.421–1.726)	<0.001

CI: confidence interval; GRACE risk score: the Global Registry of Acute Coronary Events risk score; HR: hazard ratio; KAMIR risk score: the Korea Acute Myocardial Infarction Registry risk score; MACE: major adverse cardiovascular events.

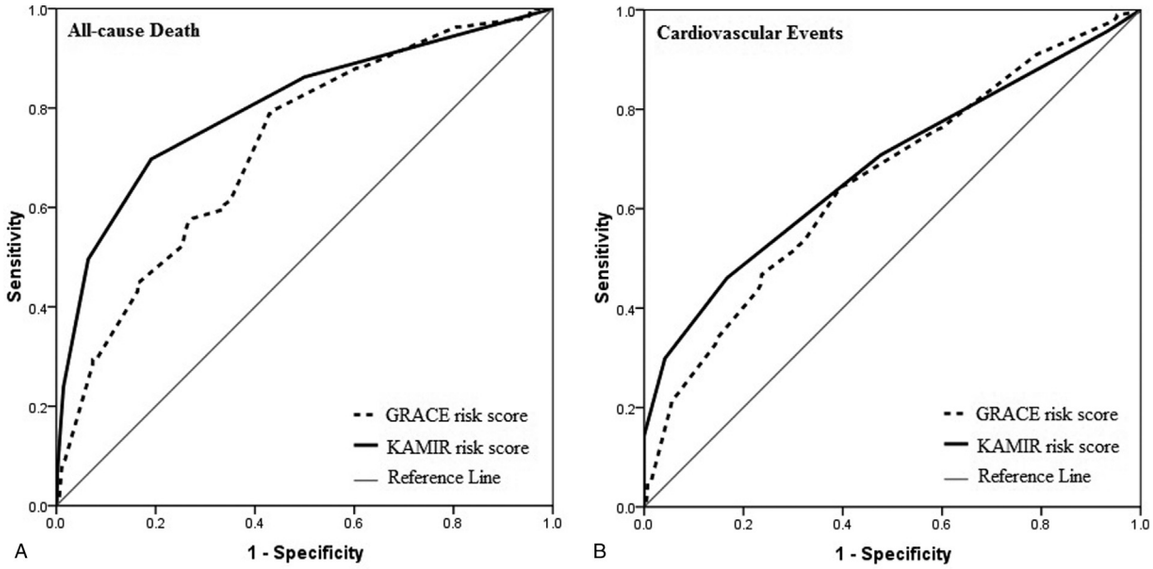


Figure 1: Receiver-operating characteristic curve analysis. The accuracy for all-cause death (A) and MACE (B) between the KAMIR risk score and the GRACE risk score. GRACE: the Global Registry of Acute Coronary Events risk score; KAMIR: the Korea Acute Myocardial Infarction Registry risk score; MACE: major adverse cardiovascular events.

14.70 μmol/L; Tertile 2: 14.70–24.50 μmol/L; Tertile 3: >24.50 μmol/L), hs-CRP (Tertile 1: <5.00 mg/L; Tertile 2: 5.00–17.40 mg/L; Tertile 3: >17.40 mg/L), and NT-pro BNP (Tertile 1: <488.20 pg/mL; Tertile 2: 488.20–1254.37 pg/mL; Tertile 3: >1254.37 pg/mL). The cumulative incidences of all-cause death and MACE in these groups of patients are illustrated by the Kaplan-Meier survival curves in Figure 3. The curves revealed significantly worse clinical outcomes with the increase of homocysteine, hs-CRP, or NT-pro BNP level. Log-rank test on the curves identified remarkable differences among these groups in all-cause death (homocysteine: Chi-square = 94.974, $P < 0.001$; hs-CRP: Chi-square = 13.229, $P = 0.001$; NT-pro BNP: Chi-square = 89.695, $P < 0.001$) and MACE (homocysteine: Chi-square = 88.604, $P < 0.001$; hs-CRP: Chi-square = 8.302, $P = 0.016$; NT-pro BNP: Chi-square = 97.027, $P < 0.001$).

Association of the biomarkers with the KAMIR risk score

The associations of homocysteine, hs-CRP, and NT-pro BNP with the KAMIR risk score were analyzed by Spearman rank correlation respectively. The results showed that all the 3 biomarkers were significantly and

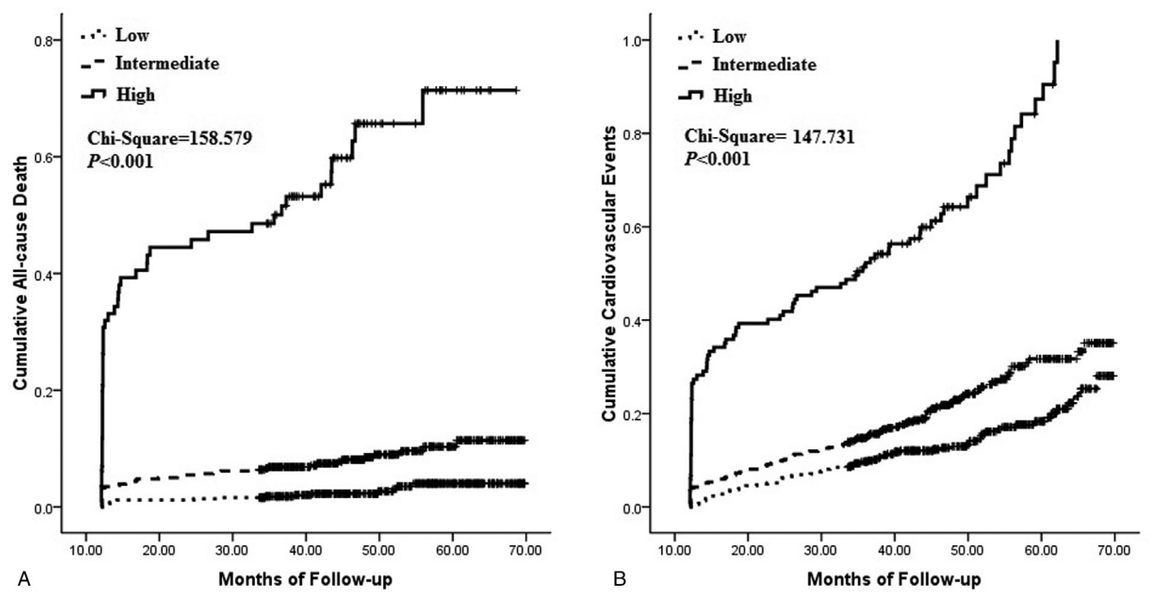


Figure 2: Kaplan-Meier survival curve analysis. The probability of all-cause death (A) and MACE (B) among groups divided in terms of the KAMIR risk score. KAMIR: the Korea Acute Myocardial Infarction Registry risk score.

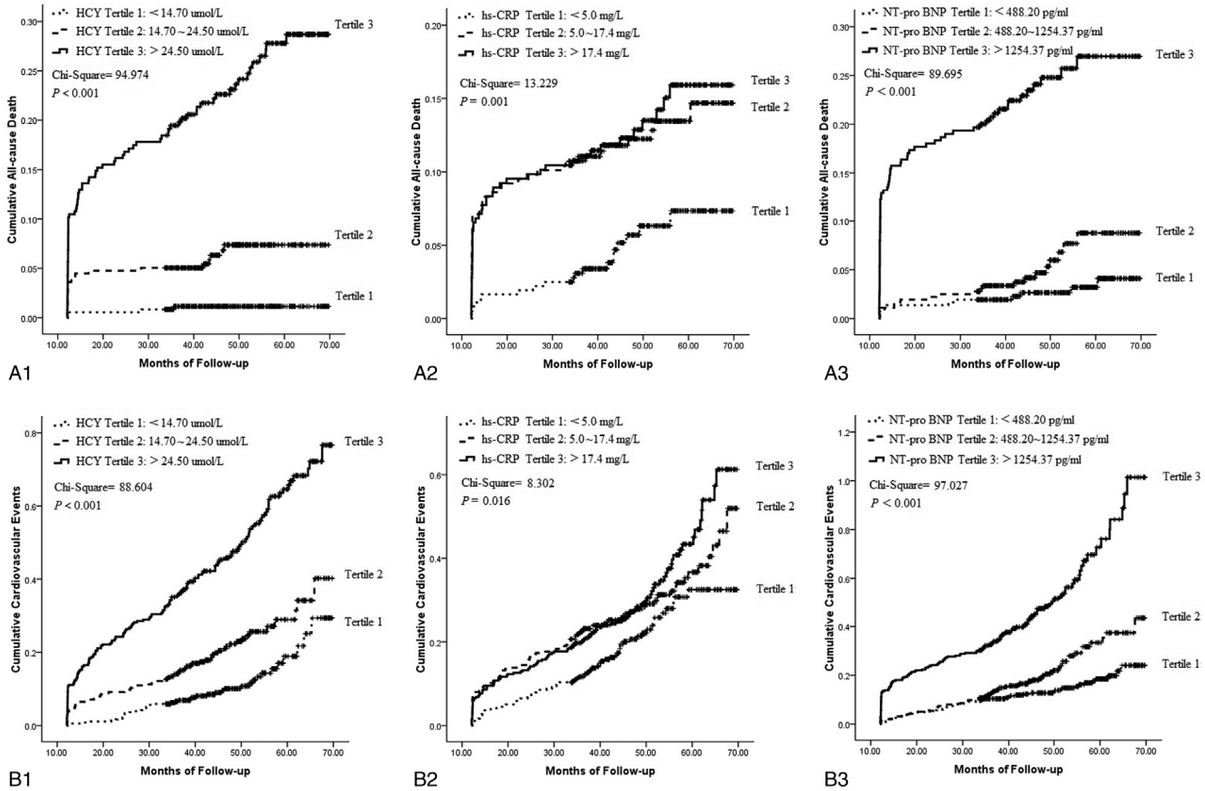


Figure 3: Kaplan-Meier survival curve analysis. The probability of all-cause death (A) and MACE (B) increased with the increase of homocysteine (1), hs-CRP (2), and NT-pro BNP (3). MACE: major adverse cardiovascular events.

positively correlated with the KAMIR score (homocysteine: r = 0.135, $P < 0.001$; hs-CRP: r = 0.149, $P < 0.001$; and NT-pro BNP: r = 0.362, $P < 0.001$).

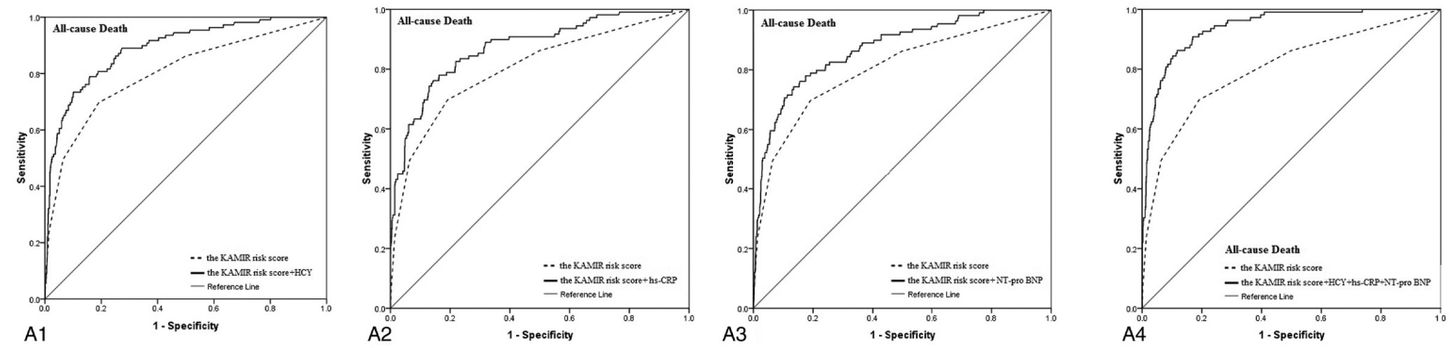
Combination of the KAMIR risk score with the biomarkers

ROC analysis was performed to assess whether combination of the KAMIR risk score with homocysteine, hs-CRP, or NT-pro BNP could better predict the adverse clinical outcomes. As shown in Figure 4, the AUC increased significantly when the KAMIR score was coupled with homocysteine (all-cause death: AUC = 0.802 vs. 0.890, 95% CI = 0.059–0.012, Z = 5.982, $P < 0.001$; MACE: AUC = 0.683 vs. 0.771, 95% CI = 0.062–0.113, Z = 6.818, $P < 0.001$), hs-CRP (all-cause death: AUC = 0.802 vs. 0.873, 95% CI = 0.012–0.039, Z = 3.721, $P < 0.001$; MACE: AUC = 0.683 vs. 0.712, 95% CI = 0.651–0.730, Z = 2.022, $P = 0.031$), or NT-pro BNP (all-cause death: AUC = 0.802 vs. 0.871, 95% CI = 0.0002–0.002, Z = 2.187, $P = 0.047$; MACE: AUC = 0.683 vs. 0.720, 95% CI = 0.007–0.032, Z = 2.974, $P = 0.003$). Moreover, the AUC increased even more significantly when all the 3 biomarkers were included in the KAMIR score (all-cause death: AUC = 0.802 vs. 0.940, 95% CI = 0.066–0.128, Z = 6.177, $P < 0.001$; MACE: AUC = 0.683 vs. 0.789, 95% CI = 0.071–0.127, Z = 6.900, $P < 0.001$).

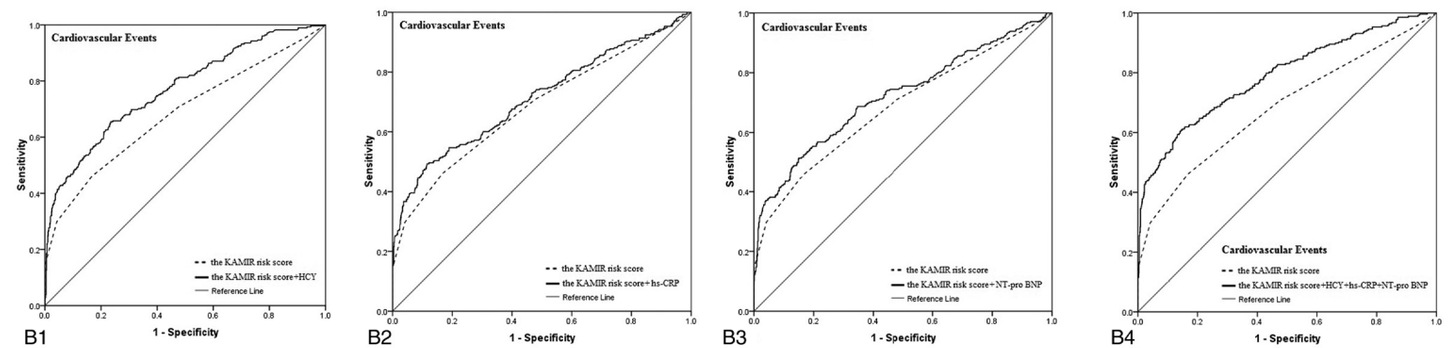
Discussion

In the present study, we compared the predictive ability of the KAMIR risk scoring system and the GRACE risk scoring system in 1093 Chinese patients with STEMI. Our data showed that the KAMIR score is more effective in predicting the clinical outcomes in this cohort of patients. We then evaluated the relationships of the KAMIR score and 3 biomarkers – homocysteine, hs-CRP, and NT-pro BNP. Our hypothesis was that the predictive power of the KAMIR risk score in STEMI could be enhanced by the addition of these biomarkers. This hypothesis was verified by our results. Homocysteine, hs-CRP, and NT-pro BNP were found to be able to serve as independent predictors for cardiovascular events in STEMI, proved by our findings that the increased level of any of them was significantly associated with increased risks of all-cause death and MACE in the patients. The calibration and discriminatory capacity of the KAMIR risk scoring were improved significantly when these biomarkers were also considered. Our data suggest that measurement of homocysteine, hs-CRP, and NT-pro BNP on admission reinforces the predictive power of the KAMIR score for long-term adverse cardiovascular events in Chinese patients with STEMI.

Risk stratification is an important and integral part of the management of patients following STEMI. The GRACE score is an oft-recommended tool for clinical risk stratification in ACS.[2,3] However, this score is developed for short-term prognosis, but vital in STEMI patients is long-term prognosis prediction.[2,3] The composite endpoint evaluated by the GRACE score limits to death and MI, while other cardiovascular events, such as heart failure, angina symptoms, and stroke, also indicate adverse clinical out-



	KAMIR score vs. KAMIR score+HCY	KAMIR score vs. KAMIR score+hs-CRP	KAMIR score vs. KAMIR score+NT-pro BNP	KAMIR score vs. KAMIR score+HCY+hs-CRP+NT-pro BNP
The area under ROC (AUC)	0.802 vs. 0.890, Z=5.982, P<0.001	0.802 vs. 0.873, Z=3.721, P<0.001	0.802 vs. 0.871, Z=2.187, P=0.047	0.802 vs. 0.940, Z=6.177, P<0.001
Hosmere Lemeshow				
KAMIR score	Chi-square=3.839, P=0.279	Chi-square=3.839, P=0.279	Chi-square=3.839, P=0.279	Chi-square=3.839, P=0.279
KAMIR score+HCY	Chi-square=2.836, P=0.944			
KAMIR score+ hs-CRP		Chi-square=5.835, P=0.666		
KAMIR score+ NT-pro BNP			Chi-square=7.499, P=0.484	
KAMIR score+HCY+hs-CRP+ NT-pro BNP				Chi-square=2.366, P=0.967



	KAMIR score vs. KAMIR score+HCY	KAMIR score vs. KAMIR score+hs-CRP	KAMIR score vs. KAMIR score+NT-pro BNP	KAMIR score vs. KAMIR score+HCY+hs-CRP+NT-pro BNP
The area under ROC (AUC)	0.683 vs. 0.771, Z=6.818, P<0.001	0.683 vs. 0.712, Z=2.022, P=0.031	0.683 vs. 0.720, Z=2.974, P=0.003	0.683 vs. 0.789, Z=6.900, P<0.001
Hosmere Lemeshow				
KAMIR score	Chi-square=4.341, P=0.247	Chi-square=4.341, P=0.247	Chi-square=4.341, P=0.247	Chi-square=4.341, P=0.247
KAMIR score+HCY	Chi-square=2.531, P=0.829			
KAMIR score+ hs-CRP		Chi-square=6.109, P=0.505		
KAMIR score+ NT-pro BNP			Chi-square=5.909, P=0.661	
KAMIR score+HCY+hs-CRP+ NT-pro BNP				Chi-square=2.337, P=0.872

Figure 4: ROC curve analysis. The addition into the KAMIR score with homocysteine (1), hs-CRP (2), and NT-pro BNP (3) and a combination of the three (4). The addition of homocysteine, hs-CRP, and NT-pro BNP improved the predictive power of the KAMIR risk scoring system for all-cause death (A) and MACE (B). KAMIR: the Korea Acute Myocardial Infarction Registry risk score; ROC: receiver-operating characteristic.

comes and are used in clinical researches extensively. Moreover, calculation of the GRACE score is complex. The variables included in the score are age, heart rate, systolic blood pressure, creatinine level, history of congestive heart failure, in-hospital PCI, in-hospital coronary artery bypass graft surgery, previous MI, ST-segment depression, and elevated cardiac markers. It is very difficult to obtain estimates of the cumulative risks of adverse cardiovascular events if without special Web-based calculator or software. Furthermore, existing research on the GRACE scoring recruited predominantly Western patients. It is not clear if this risk prediction model performs as well in Chinese patients. Recently, a novel risk scoring system, the KAMIR score, has been developed in an Asian country, Korea. The model is reported to be simple in calculation and accurate in risk stratification and prediction for long-term prognosis of AMI.[9] Some studies have suggested a greater risk predictive power of the KAMIR score as compared to the GRACE score.[9] This is proved by our observation that the KAMIR score demonstrated a better risk stratification and predictive ability than the GRACE score for long-term clinical outcomes in our STEMI patient population (all-cause death: AUC = 0.802 vs. 0.721, $P < 0.001$; MACE: AUC = 0.683 vs. 0.656, $P < 0.001$). Our study, together with the aforementioned studies, suggests that the KAMIR risk scoring system may be more suitable for patients in Asian countries.

Previous studies have shown that biomarkers, particularly homocysteine,[25] hs-CRP,[19] and NT-pro BNP,[26] are significantly associated with adverse cardiovascular events in AMI. Homocysteine can induce endothelial dysfunction, vascular smooth muscle proliferation, cholesterol and triglyceride metabolism dysregulation, inflammatory activation, collagen synthesis and arterial wall elastic deterioration, and thrombus formation.[27-29] Therefore, homocysteine plays an important role in the pathogenesis of atherosclerosis and coagulation.[30,31] Recently, hyperhomocysteine is identified as an intensive and independent risk factor for atherosclerotic diseases.[32] Prospective research has demonstrated that hyperhomocysteine can predict cardiovascular events in coronary artery disease.[33] Hs-CRP, which is synthesized by liver, is a non-specific marker of systemic inflammatory response in acute period. Elevated plasma hs-CRP level is considered as linked to inflammation, thrombosis, decrease in nitric oxide synthesis, expression of adhesion molecules, and inhibition of the physiologic fibrinolysis.[34,35] Due to its important role in the immune response, hs-CRP is implicated in the development and complications of atherosclerosis.[19] Clinical research has illuminated that hs-CRP is a strong predictor of clinical events in patients with AMI.[36] NT-pro BNP is a neurohormone synthesized predominantly in ventricular myocardium, which reveals cardiac neurohormonal activation after myocardial damage.[20] As an important indicator of heart function, NT-pro BNP can reflect the systolic and diastolic function of the left and right ventricle,[37] and can reflect the degree of myocardial injury.[37] The association of plasma NT-pro BNP level with mortality in AMI patients has been confirmed.[26]

The biomarkers discussed above reveal the pathological process of STEMI from multiple dimensions including metabolism, inflammation, and neuroendocrine. However, they are not involved in the KAMIR scoring system. The comparison of the baseline data between patients with and without MACE in this study showed that the levels of homocysteine, hs-CRP, and NT-pro BNP were significantly higher in patients who experienced such events. Both univariate and multivariate Cox proportional hazard regression analysis revealed that homocysteine, hs-CRP, and NT-pro BNP were independent risk factors and strong predictors for adverse cardiovascular events. Kaplan-Meier survival curves also verified that the probability of all-cause death and MACE significantly rose with the increase of homocysteine, hs-CRP, or NT-pro BNP level. Moreover, these biomarkers were found positively correlated with the KAMIR risk score, which means that the predictive power of the KAMIR score could be enhanced when combined with either homocysteine (AUC: 0.802 to 0.890 for all-cause death, 0.683 to 0.771 for MACE), hs-CRP (AUC: 0.802 to 0.873 for all-cause death, 0.683 to 0.712 for MACE), NT-pro BNP (AUC: 0.802 to 0.871 for all-cause death, AUC = 0.683 to 0.720 for MACE), or all of them (AUC: 0.802 to 0.940 for all-cause death, AUC: 0.683 to 0.789 for MACE) for long-term clinical outcomes in patients with STEMI.

Study limitations

The patients included in this study were from only two hospitals. Our findings need to be further proved by large multicenter research. Since our study is based exclusively on Chinese patients, the results should be applied cautiously to other ethnic populations.

Conclusions

In conclusion, our study confirms that the KAMIR score performs better than the GRACE score in risk stratification and prediction for adverse prognosis in Chinese STEMI patients. The biomarkers, including homocysteine, hs-CRP, and NT-pro BNP, can independently predict adverse cardiovascular events in STEMI. Using these biomarkers in combination with the KAMIR system derives a more robust predictive power for long-term clinical outcomes in patients with STEMI.

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Conflict of interest

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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