

Incorporating the erythrocyte sedimentation rate for enhanced accuracy of the global registry of acute coronary event score in patients with ST-segment elevated myocardial infarction

A retrospective cohort study

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Abstract

There is scarce evidence that the erythrocyte sedimentation rate (ESR) could efficiently improve the prediction accuracy of the Global Registry of Acute Coronary Events (GRACE) risk score in cases of ST-elevation myocardial infarction (STEMI).

A cohort of 1094 STEMI patients undergoing primary percutaneous coronary intervention was retrospectively recruited. Patients were categorized based on the ESR values. Final endpoints included cardiovascular death and major adverse cardiovascular event (MACE) occurrence. The predictive value of combined models with the GRACE score and ESR was assessed by receiver operating characteristic (ROC) analysis, net reclassification improvement (NRI), and integrated discrimination improvement.

During the mean follow-up of 23 months, 34 patients died and 190 experienced MACEs, of which 23 patients died in the first year; both endpoints were more frequent in the higher group. The ESR and high-sensitivity C-reactive protein (hs-CRP) were independent risk factors of 1-year cardiovascular death, together with the GRACE score (ESR: hazard ratio=1.03, $P=.006$ hs-CRP: hazard ratio=1.00, $P=.001$; GRACE: 1.03, $P=.012$). Although no statistical improvement in the area under the ROC curve was observed in either the GRACE/ESR or the GRACE/hs-CRP model (GRACE/ESR models: 0.8073 vs GRACE: 0.7714, $P=.22$; GRACE/ESR models: 0.7815 vs GRACE: 0.7714, $P=.61$), the GRACE score and ESR together significantly improved the NRI (0.633; $P<.001$) compared with the GRACE alone. Regarding the mid-term mortality, adding the ESR to the GRACE score not only improved the NRI (0.8433; $P<.001$), but also increased the integrated discrimination improvement (0.0509; $P=.04$).

The ESR is an independent risk factor of cardiovascular death and MACE in STEMI patients receiving primary percutaneous coronary intervention. The ESR comparatively enhanced the predictive values of the prognostic model, including the GRACE risk score.

Abbreviations: ACS = acute coronary syndrome, AIC = Akaike information criterion, AUC = area under receiver operating characteristic curve, ESR = erythrocyte sedimentation rate, GRACE = global registry of acute coronary event, HR = hazard ratio, Hs-CRP = high sensitivity C-reactive protein, IDI = integrated discrimination improvement, MACE = major adverse cardiovascular events, NRI = net reclassification improvement, PCI = percutaneous coronary intervention, STEMI = acute ST-elevated myocardial infarction.

Keywords: erythrocyte sedimentation rate, global registry of acute coronary events risk scores, major adverse cardiovascular events, ST-elevated myocardial infarction

Editor: Wen-Jun Tu.

CL and YW, These authors contributed to the work equally and should be regarded as co-first authors.

The datasets generated and analyzed during the current study are not publicly available due to the restrictions by the Beijing Chaoyang Hospital, who owns the data. The authors used this dataset under an agreement with the Beijing Chaoyang Hospital for the current study.

The work was supported by the National Key Research and Development Project [grant number 2016YFC1301100 and 2016YFC1301102]. It funded the collection of the data and the patients' follow-up.

This study was approved by the institutional review board of Beijing Chaoyang Hospital and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent forms were obtained from all patients or their legal relatives.

The authors have no conflicts of interest to disclose.

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How to cite this article: Li C, Wang Y, Zhang Q, Wang L, Li K, Yang X. Incorporating the erythrocyte sedimentation rate for enhanced accuracy of the global registry of acute coronary event score in patients with ST-segment elevated myocardial infarction: a retrospective cohort study. *Medicine* 2020;99:41(e22523).

Received: 12 July 2020 / Received in final form: 14 August 2020 / Accepted: 2 September 2020

<http://dx.doi.org/10.1097/MD.00000000000022523>

1. Introduction

Patients with acute ST-segment elevated myocardial infarction (STEMI) are vulnerable to a higher risk of long-term cardiovascular mortality and adverse clinical events. Risk stratification is crucial in the management and treatment of patients with STEMI. In contrast to other risk scores used for assessment of prognosis,^[1,2] the Global Registry of Acute Coronary Event (GRACE) risk score is predictive of discharge mortality and re-infarction and has been recommended as the preferred risk score in acute coronary syndrome (ACS).^[3,4] However, the scant number of biological markers included in the GRACE risk score (GRS) may contribute to the insufficient discriminatory performance. Recent studies have focused on improving discrimination of GRS by integrating other biomarkers.^[5,6]

Chronic inflammatory processes are related to the pathogenesis and extension of atherosclerosis in coronary artery disease.^[7] Several studies show that inflammatory markers, such as C-reactive protein (CRP),^[8,9] neutrophil counts,^[10] mean platelet volume,^[11] platelet-to-lymphocyte ratio,^[12] and neutrophil-to-lymphocyte ratio,^[13,14] correlate with GRS and adversely predict short- and long-term prognosis. However, none of these works demonstrates the independent predictive value of the erythrocyte sedimentation rate (ESR) on clinical adverse outcomes. A few previous studies that investigate the association of the elevated ESR with an increased risk of fatal cardiovascular events yield some positive results.^[15,16] Moreover, the increased ESR in aggressive forms of coronary artery disease (CAD) could be regarded as an index to predict coronary artery disease mortality.^[17] However, few studies elucidate the additional value of ESR on improving risk prediction and risk-guide therapy in the setting of STEMI.

Given the above considerations, the objective of the present study is to investigate the predictive values of the ESR for major adverse cardiovascular events (MACE) and the incremental prognostic value of the ESR combined with the GRS on cardiovascular mortality in STEMI patients undergoing primary percutaneous coronary intervention (PCI).

2. Materials and Methods

2.1. Study setting and inclusion

We retrospectively recruited consecutive patients with STEMI admitted to the Department of Cardiology at the Beijing Chaoyang Hospital in China between January 2014 and December 2018. STEMI patients received primary PCI were eligible for the study. STEMI was defined according to the 2013 American College of Cardiology Foundation/American Heart Association Guidelines. The diagnostic criteria included the following:

- (1) persistent symptoms of ischemia for at least 30 minutes;
- (2) ST-segment elevation of at least 1 mm in at least 2 adjacent limb leads, or of at least 2 mm in at least 2 contiguous precordial leads, or a new left bundle branch block in the electrocardiography; and
- (3) elevated serum cardiac troponin-I and creatine kinase-myocardial band more than twice the upper limit of normal level.

The excluded criteria included valvular heart disease, malignant tumors, severe liver dysfunction and end stage renal disease.

2.2. Demographic feature and biochemical measurements

Clinical and demographic characteristics of all patients were recorded and included age, sex, comorbidities, vital signs, and results of auxiliary examinations. Additionally, previous myocardial infarction (MI), previous PCI, and presence of congestive heart failure and cardiac arrest were recorded. The GRACE risk predicting model was calculated by 2 senior doctors (Dr. Chuang Li and Dr. YuXing Wang) blinded to the clinical outcomes using the web-based tool (<https://www.outcomes-umassmed.org/grace>). The related variables including age, heart rate, systolic blood pressure, level of creatinine, history of congestive heart failure, revascularization (primary PCI), previous MI, ST-segment depression, and elevated cardiac markers were entered into the GRS to estimate the cumulative risks of the MACE. The ESR and high-sensitivity CRP (hs-CRP) were detected using an analytical instrument (Monitor 100, Italy) method and a turbidimetric inhibition immune-assay within 24 hours of admission, respectively.

2.3. Definition of endpoint and follow-up

Patients were followed for up for major adverse outcomes. The follow-up records were completed by telephone contacts and hospital documents. The primary endpoint was defined as the cardiovascular death. The secondary endpoint was defined as a composite of the MACE consisting of cardiovascular mortality, rehospitalization due to acute heart failure, recurrent MI, revascularization due to unstable angina pectoris and non-fatal stroke. The follow-up information of all included participants was collected by 1 of the authors (Dr. Qian Zhang). This study was approved by the institutional review board of the Chaoyang Hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients or their legal relatives.

2.4. Statistical analysis

Continuous variables are presented as mean \pm standard deviation (mean \pm standard deviation) if the data distribution fits both normal distribution and homogeneity of variance. The distribution of the data was tested using the skewness and Kurtosis normality tests. The continuous variables not satisfying these criteria are presented as median (interquartile range, IQR). Categorical variables are presented as frequency (percentage). Statistical differences between the continuous variables was examined using 1-way analysis of variance or the Kruskal–Wallis rank test according to the distribution and characteristics of the data. Differences among the categorical variables were determined by the Pearson χ^2 test or the Fisher exact test. The Kaplan–Meier method was used to calculate adverse clinical outcomes and the log-rank test was used to conduct intergroup comparisons. The multivariate Cox proportional hazard regression analysis was performed to identify predictors for adverse clinical outcomes.

The χ^2 likelihood ratio tests were used with nested models to determine whether the logistic regression model in combination with the GRS and the ESR or hs-CRP would provide significantly better prediction probabilities of the outcomes than could the GRS would alone. Comparisons of the nested and non-nested models including the GRS or its combination with the ESR or the

hs-CRP were performed using corrected Akaike information criterion (AICc), delta-AICc (Δ -AICc), and Akaike weights (wi) to estimate the “best” fitting model.^[18]

Three models that could assess and quantify the improvement of risk prediction, including increase in the area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI >0), and integrated discrimination improvement (IDI), were used to analyze the incremental predictive value of the combinations of the ESR and hs-CRP with the GRS.^[19] The event NRI (NRI_e) was defined as the net percentage of persons with the event of interest correctly assigned to a higher predicted risk, and non-event NRI (NRI_{ne}) was defined as the net percentage of persons without the event of interest correctly assigned to a lower predicted risk. The overall NRI was equal to the net proportion of persons with events of interest plus those without events of interest (NRI = NRI_e + NRI_{ne}). The IDI was used to examine the differences between the average sensitivity and specificity for the models combined GRS with or without the ESR or the hs-CRP.^[20] All statistical analyses were calculated using STATA (version 15.0).

3. Results

3.1. Study population and demographic feature

Initially, 1094 patients were enrolled in this retrospective cohort study. According to the excluded criteria, a total of 1036 patients were recruited and followed up. The final eligible population were categorized into 2 groups according to the values of ESR (Q1: <15 mm/h; Q2 ESR ≥15 mm/h). The patient baseline characteristics, history of disease, and discharge medication are listed in Table 1. As generally reported in similar cohorts of patients, patients in the higher group had a relatively lower hemoglobin count, significantly elevated level of admission heart rate, lower ejection fraction, and more frequent history of smoking, hypertension and diabetes mellitus. The value of hs-CRP was significantly higher in the higher ESR group than in the lower ESR group ($P < .001$), whereas no difference was seen in the discharge GRS ($P = .22$). There was no significant difference in other variables between the 2 groups.

3.2. Relation of the ESR and GRS to clinical outcomes

During the average follow-up period of 23 months, a total of 99 MACE (9.6%) occurred in the first year, including 23 cardiovascular deaths (2.2%), 51 acute heart failures (4.9%), 11 recurrent MIs (1.1%), 28 revascularizations (2.7%), and 8 non-fatal strokes (0.8%), while the sum of mid-term mortality and MACE were 34 (3.3%) and 190 (18.3%), respectively (Table 1). Cardiovascular death and MACE were both more frequently presented in the higher quartiles (One-year cardiovascular death: 4.4% vs 1.5%, $P = .01$; One-year MACE: 20.0% vs 6.2%, $P < .001$; mid-term cardiovascular death: 7.2% vs 2.0%, $P < .001$; mid-term MACE: 38.0% vs. 12.1%, respectively). The cumulative incidence of 1-year and mid-term cardiovascular death and MACE among different ESR groups evaluated using the Kaplan-Meier survival curves are shown in Figures 1 and 2, respectively. The incident of cardiovascular death and MACE increased significantly in the higher ESR group compared with the lower 1.

The multivariate Cox proportional hazard regression analysis suggested that the GRS hazard ratio [HR]=1.03

Table 1

Baseline clinical characteristics according to the ESR.

	Q1 (<15 mm/h)	Q2 (≥15 mm/h)	P-value
Number	786	250	
Age (yr)	62 (12.7)	62 (12.6)	.90
Male (n %)	638 (81.2%)	202 (80.8%)	.93
Admission HR (bpm)	76.5 (20)	80 (18)	<.01
Discharge HR (bpm)	70 (11)	71 (11)	.04
Admission SBP (mm Hg)	124 (27)	123 (29)	.82
Discharge SBP (mm Hg)	120 (18)	120 (22)	.13
HGB (g/L)*	139 (21)	124 (21)	<.001
Cholesterol (mmol/L)	4.6 (1.4)	4.6 (1.5)	.76
LDL (mmol/L)	2.9 (1.2)	2.9 (1.4)	.77
hs-CRP (mg/L)*	4.07 (7.86)	11.42 (8.17)	<.001
Creatinine (umol/L)	74.1 (21.3)	76 (36.2)	.06
Fasting Glucose (mmol/L)	6.5 (3.41)	6.8 (4.57)	.10
EF (%)*	60 (15)	58 (14)	<.001
Hypertension (n%)*	453 (57.5%)	178 (71.2%)	<.001
Diabetes mellitus (n%)*	237 (30.2%)	113 (45.2%)	<.001
Hyperlipemia (n%)*	428 (54.5%)	125 (50.4%)	.26
Smoking (n%)*	559 (71.1%)	132 (52.8%)	<.001
Precious PCI (n%)	94 (12.0%)	21 (8.4%)	.12
Precious MI (n%)	81 (10.3%)	24 (9.6%)	.74
Admission GRACE score	124 (39)	130 (43)	.02
Discharge GRACE score	96 (37)	96 (37)	.22
Discharge medications			
Aspirin, n(%)	779 (99.1%)	244 (97.6%)	.06
Clopidogrel, n(%)	777 (98.9%)	247 (98.8%)	.94
Beta-blockers, n(%)	497 (63.2%)	148 (59.2%)	.25
ACEI/ARB, n(%)	401 (51.0%)	118 (47.2)	.29
Statin, n(%)	639 (81.3%)	191 (76.4%)	.09
One-year endpoint			
Mortality, n(%)	12 (1.5%)	11 (4.4%)	.01
Recurrent MI, n(%)	7 (0.9%)	4 (1.6%)	.34
Revascularization, n(%)*	13 (1.7%)	14 (5.6%)	<.001
Heart failure, n(%)*	20 (2.5%)	31 (12.4%)	<.001
Stroke, n(%)	5 (0.6%)	3 (1.2%)	.37
MACE, n(%)*	49 (6.2%)	50 (20.0%)	<.001
Mid-term endpoint			
Follow-up time (mo)	24 (13)	23 (18)	.03
Mortality, n(%)*	16 (2.0%)	18 (7.2%)	<.001
Recurrent MI, n(%)	20 (2.5%)	8 (3.2%)	.58
Revascularization, n(%)*	44 (5.6%)	32 (12.8%)	<.001
Heart failure, n(%)*	27 (3.4%)	50 (20.0%)	<.001
Stroke, n(%)	6 (0.8%)	9 (3.6%)	.001
MACE, n(%)*	95 (12.1%)	95 (38.0%)	<.001

There is some difference in some cardiovascular risk factors and baseline clinical characteristics between 2 ESR groups. The values are expressed as median (IQR) or number (percentage).

ACEI = angiotensin converting enzyme inhibitor, EF = ejection fraction, ESR = erythrocyte sedimentation rate, GRACE = Global Registry of Acute Coronary Event, HDL = high density lipoprotein, HGB = Hemoglobin, HR = heart rate, hs-CRP = high sensitivity C-reactive protein, LDL = low density lipoprotein, MACE = major adverse cardiovascular events, MI = myocardial infarction, SBP = systolic blood pressure.

* $P < .001$.

(1.01–1.05), $P = .012$), ESR [HR = 1.03 (1.01–1.07), $P = .006$], and hs-CRP [HR = 1.00 (1.00–1.01), $P < .001$] were independent predictors of the 1-year cardiovascular death after adjusting for the potential confounding factors (Table 2). When included in the same regression model, ESR [HR = 1.02 (1.01–1.03), $P = .013$] and hs-CRP [HR = 1.00 (1.00–1.00), $P < .001$], but not GRS [HR = 1.00 (0.99–1.01), $P = .957$], were independent predictors of the 1-year MACE at the final follow-up (Table 2).

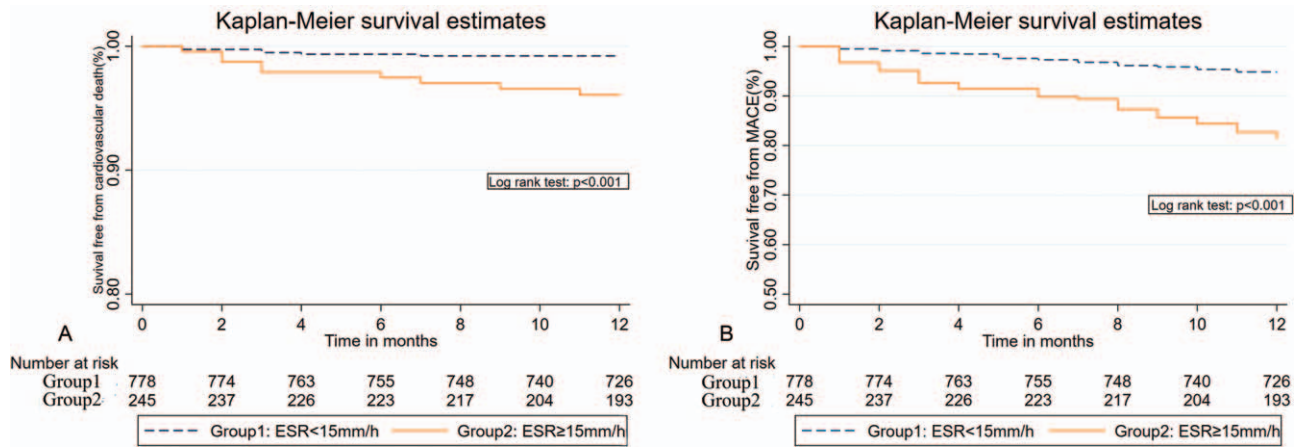


Figure 1. Kaplan-Meier survival curves indicating 1-year cardiovascular death and MACE according to values of the ESR.

3.3. Evaluating the impact of the ESR on GRS model

Given the negative results of GRS over MACE, we conducted the likelihood ratio tests which could provide a positively better predictive probability regarding the 1-year cardiovascular death among the 3 models. The results indicated that the models combining the GRS with the ESR, rather than with hs-CRP levels, allowed for more accurate prediction of cardiovascular death by means of quantitative comparison of the AICc, Δ-AICc, and Akaike weights (Table 3). Evidently, examination of Akaike weights revealed that models containing the GRS and the ESR is 5.445 times more likely to be superior compared with the models containing GRS alone.

The ROC analysis was performed to assess which of the prognostic models integrating GRS with the ESR or hs-CRP levels could better predict 1-year and mid-term mortality. There was no statistical difference in the AUC between the GRS and 2 inflammatory makers (GRS: 0.6932 vs ESR: 0.6973 vs hs-CRP: 0.6552, $P = .72$). The AUC of the ROC moderately increased when the GRS was coupled with the ESR (AUC=0.8073 vs 0.7714, $P = .22$), but not with the hs-CRP level (AUC=0.7815 vs

0.7714, $P = .61$) (Fig. 3). Regarding the mid-term mortality, the AUC of the ROC significantly elevated when the ESR was integrated into the GRS (AUC=0.8399 vs 0.7965, $P = .012$) (Fig. 4).

When incorporated into a logistic regression model containing the GRS, the ESR could enhance the net reclassification of the new model in predicting the 1-year cardiovascular death during follow-up (Table 4). In the analysis of NRI, the ESR could improve reclassification by 10.0% for those with events of interest and by 53.3% for those with events of not of interest, respectively. Finally, under the equation mentioned above, the total NRI was 0.633 ($P = .01$). However, the integrated discrimination during follow-up was seldomly improved by the addition of the ESR into the GRACE scoring system (IDI: 4.16%, $P = .16$). In contrast, models combining GRACE with hs-CRP couldn't improve reclassification and discrimination compared with models containing GRACE alone (NRI=0.3116, $p = 0.17$; IDI=4.77%, $P = .27$). However, in the mid-term duration, while the ESR could progressively improve the net reclassification by 84.33% and integrated discrimination by 5.09% for the GRS (NRI: 0.8433, $P < .001$; IDI: 0.0509, $P = .04$).

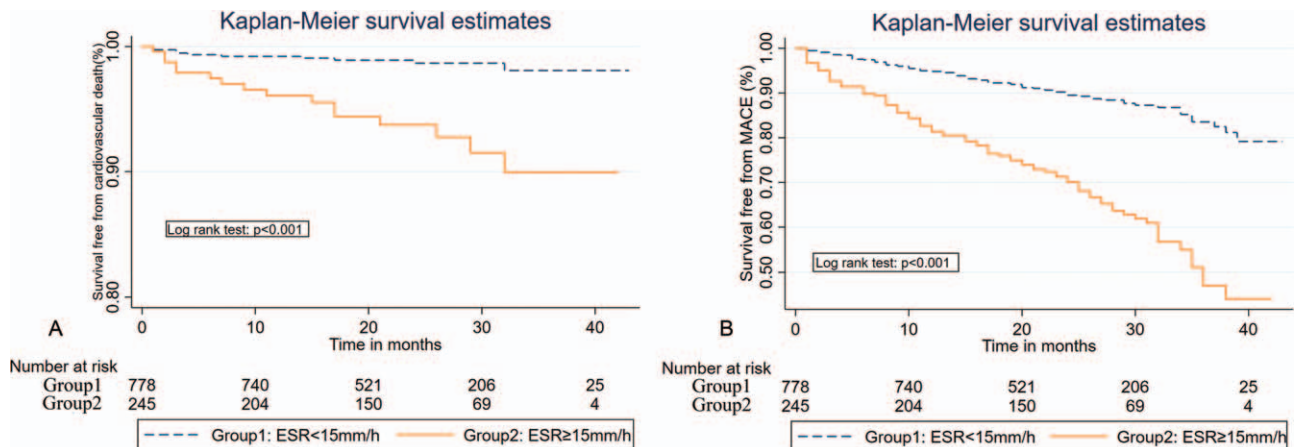


Figure 2. Kaplan-Meier survival curves indicating 1-year cardiovascular death and MACE during the mean follow-up time of 23 months according to values of the ESR.

Table 2**Cox proportional hazard regression analysis for 1-year cardiovascular death and MACE.**

Variables	Cardiovascular death		MACE	
	HR (95% CI)	P-value	HR (95% CI)	P-value
GRACE RS	1.03 (1.01, 1.05)	.012	1.00 (0.99, 1.01)	.957
ESR	1.03 (1.01, 1.07)	.006	1.02 (1.01, 1.03)	.013
hs-CRP	1.00 (1.00, 1.01)	.001	1.00 (1.00, 1.00)	<.001
Female	0.49 (0.47, 2.64)	.408	0.75 (0.39, 1.45)	.339
HGB	0.98 (0.95, 1.02)	.463	0.98 (0.97, 1.00)	.072
LDL	1.29 (0.67, 2.51)	.438	1.16 (0.91, 1.48)	.229
EF	0.96 (0.93, 0.99)	.015	0.98 (0.96, 0.99)	<.001
Creatinine	1.23 (0.74, 2.03)	.413	1.21 (0.96, 1.54)	.102
Fasting Glucose	1.12 (1.02, 1.23)	.018	1.05 (1.00, 1.11)	.039
Hypertension	3.01 (0.57, 15.8)	.194	2.16 (1.26, 3.70)	.005
Diabetes mellitus	0.64 (0.15, 2.65)	.541	1.56 (0.93, 2.60)	.091
Previous MI	1.34 (0.28, 6.39)	.706	1.37 (0.74, 2.53)	.307
Smoking	0.62 (0.18, 2.04)	.431	1.27 (0.78, 2.08)	.318
Discharged with BB	0.37 (0.09, 1.49)	.165	1.06 (0.67, 1.67)	.803
Discharged without ACEI	1.56 (0.46, 5.23)	.469	0.75 (0.47, 1.18)	.223
Discharged without statin	2.70 (0.76, 9.50)	.122	1.16 (0.68, 1.96)	.582

Cox proportional hazard regression analysis for cardiovascular death and major adverse cardiovascular events. Under the cox hazard regression, we can identify independent risk factors related to clinical adverse events.

ACEI = angiotensin converting enzyme inhibitor, BB = beta-blockers, CI = confidence interval, EF = ejection fraction, ESR = erythrocyte sedimentation rate, GRACE = Global Registry of Acute Coronary Event, HGB = hemoglobin, HR = hazard ratio, hs-CRP = high sensitivity C-reaction protein, LDL = low density lipoprotein, MACE = major adverse cardiovascular events, MI = myocardial infarction, SE = standard error.

4. Discussion and Conclusions

This retrospective cohort study of STEMI patients demonstrated that

- (1) GRS remains accurate for the prediction of 1-year and mid-term cardiovascular mortality under the current management of patients with STEMI, similar to a previous study^[21];
- (2) the ESR as well as hs-CRP collected during the first 24-hour after admission are independent risk factors for cardiovascular mortality and adverse clinical events; and
- (3) the additive value of the ESR on models based on the GRS could efficiently enhance the predictive probability of cardiovascular death.

To the best of our knowledge, the present study is the first to demonstrate that the ESR could enhance the predictive probability of the GRACE risk model in STEMI patients undergoing primary PCI.

The ESR is a simple and inexpensive test and influenced by plasma constituents, such as fibrinogen, globulins, and hemoglobin, but generally varies with age and sex.^[17,22,23] In the present study, after adjusting for gender and conventional risk factors, the independent association we observed between the ESR and cardiovascular death remained, as has been previously sug-

gested.^[15–17,24] Destabilization and rupture of plaque in the pathophysiology of STEMI may primarily be presented as an intimal hemorrhage. In this circumstance, the accumulation of erythrocytes, which participate in the necrotic-core enlargement within the lesions, may be the proinflammatory factor that increases the risk of plaque rupture.^[25] On the other hand, increased ESR correlates with increased red blood cell adhesiveness and aggregation. A previous study by Sargento et al^[26] demonstrated that lower erythrocyte aggregation is associated with a lower incidence of long-term recurrent cardiovascular events in survivors with STEMI. Moreover, the recent study by Yunoki et al indicates that hyper-aggregability induced by severe oxidative stress elicits erythrocyte-rich thrombus, which is proportional to the extent of myocardial necrosis and deterioration of ventricular function and remodels from the acute to recovery phase in the setting of re-perfused STEMI.^[27] Our findings provide the cumulative evidence that increased ESR can lead to worse prognosis in the course of STEMI.

Clinical studies show that both ESR and hs-CRP are associated with incremental MI and stroke risk in the general population,^[15,24,28,29] particularly in patients with chronic inflammation disorders.^[30,31] Notably, a large amount of published data indicate that hs-CRP is significantly associated with the extent of

Table 3**Akaike's information criteria and likelihood ratio test to determine the best fitting model for predicting 1-year cardiovascular death.**

Model	Likelihood ratio test			Akaike's information criteria			
	χ^2	P-value	AICc	Δ -AICc	Relative likelihood	wi	wj/wi
GRS			191.8076	8.4702	0.1837	0.1145	1.00
GRS+ ESR	10.47	.001	183.3374	0.00	1.00	0.6234	5.445
GRS+ hs-CRP	6.33	.01	187.4737	4.3339	0.4203	0.2620	2.288

Outcome Akaike's information criteria and likelihood ratio test used to determine the best fitting model for predicting MACE. The combined model with the GRACE score and ESR is a better predictive model for MACE than the other two models.

Δ -AICc = delta AICc is a measure of each model relative to the best model, AICc = corrected Akaike's information criteria, wi = Akaike weights, the ratio of Δ AICc values for each model relative to the whole set, wj/wi = evidence ratios of Akaike weights for comparison between model i and model j.

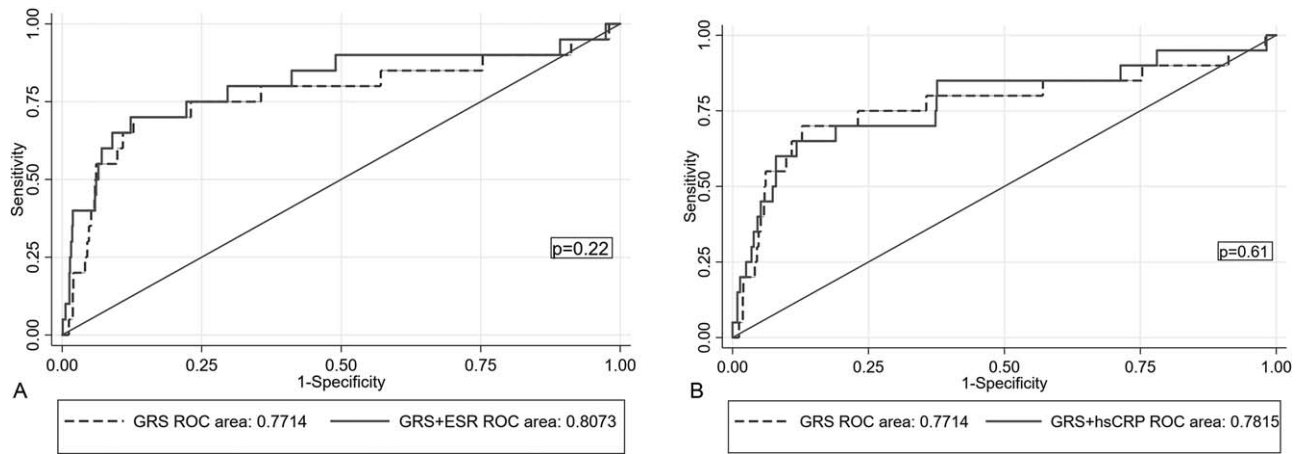


Figure 3. Receiver-operating characteristic (ROC) curves comparing 2 combined models and the GRS alone in predicting one-year cardiovascular mortality.

coronary stenosis and prognosis in patients with ACS and may even improve some risk stratifications.^[5,32] In a previous meta-analysis by He *et al.*, CRP is correlated with the long-term risk of recurrent cardiovascular events or death in patients with ACS.^[33] However, this meta-analysis does not clarify the association between hs-CRP and the clinical prognosis in patients with acute MI. Our present study also found that there is no significant increase in the C-statistics of the GRS when hs-CRP is incorporated into the routine assessment of patients with STEMI, similar to 2 previous studies.^[9,34] In recent genetic studies and meta-analyses,^[35,36] published data cannot confer any evidence of a causal association between CRP and atherogenesis and indicates that it is likely to be a bystander rather than a true risk factor. In another study by Van Toorenburg *et al*^[5] the addition of other biomarkers, including hs-CRP, to the GRS improves the AUC over GRS alone; however, the final model is excessively complicated and it is not certain if the relationship between hs-CRP and mortality contributes to this increment. Meanwhile, investigations by Sumayya *et al* find that the GRS of MI patients nearly correlates with hs-CRP and inflammation markers.^[8] This intimate interaction between the hs-CRP and GRS can provide some rational explanation about the negative consequences of

the new model, which combines the hs-CRP and GRS, in our study.

In this study, we excluded patients, who had tumors, but not those with inflammatory or metabolic diseases. There is a possibility that other potential disorders can influence the ESR and confound its association with mortality. In the HDDRISC study, Gosland *et al* show that elevated ESR could predict death from cardiovascular disease during a period of 18 to 20 years, independent of metabolic syndrome.^[37] Meanwhile, prior studies indicate that patients with chronic inflammation disorders, such as rheumatoid arthritis, psoriasis, and chronic obstructive pulmonary disease, are vulnerable to a higher risk of MACE.^[38–40] Moreover, in this circumstance, increased ESR is associated with an increased prevalence of future MACE risk. Therefore, we assume that the fluctuation in rheology could offer a possible mechanism to mediate the higher prevalence of cardiovascular morbidity and mortality in patients with inflammatory disorders.

Finally, our findings of this retrospective study indicate that the GRS is only an independent risk factor for mortality, but not for MACE. A number of previous studies show that the GRS has a predictable probability for MACE composited of death and

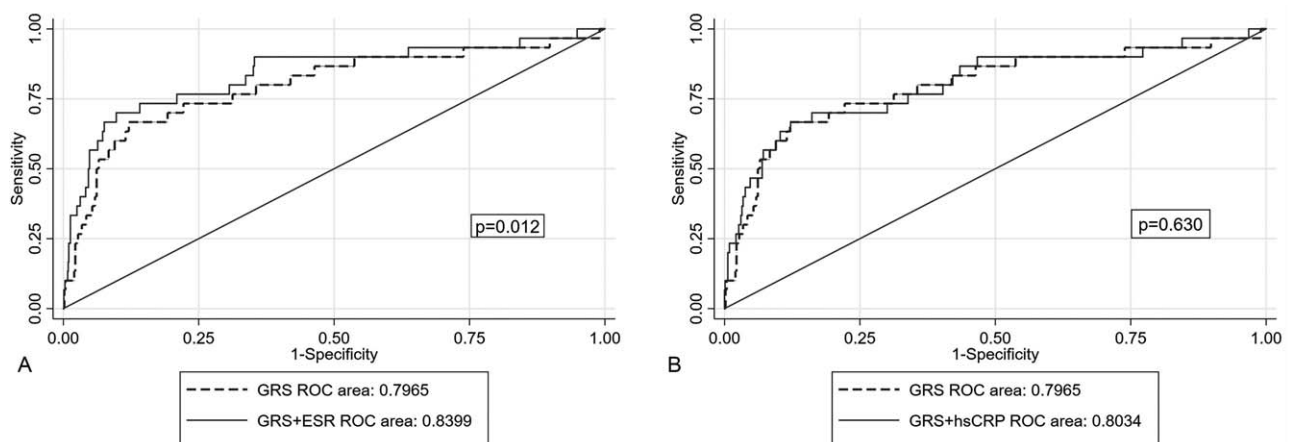


Figure 4. Receiver-operating characteristic (ROC) curves comparing 2 combined models and the GRS alone in predicting mid-term cardiovascular mortality.

Table 4**Net reclassification improvement for model improvement with the addition of ESR or hs-CRP into GRS on cardiovascular mortality.**

	GRS vs GRS + ESR				GRS score vs GRS + hs-CRP			
	NRIe	NRIne	Total	P-value	NRIe	NRIne	Total	P-value
One-year	0.1000	0.5330	0.6330	.01	0.1000	0.2116	0.3116	.17
Mid-term	0.2666	0.5766	0.8433	<.001	0.2000	0.2358	0.4359	.02
	IDle	IDIne	Total	P-value	IDle	IDIne	Total	P-value
One-year	0.0406	−0.001	0.0416	.16	0.0467	−0.001	0.0477	.27
Mid-term	0.0494	−0.0015	0.0509	.04	0.0401	−0.0012	0.0413	.14

Net reclassification improvement for model improvement with the addition of ESR or hs-CRP to the GRACE score. The combined model of the GRS with ESR significantly improved the predictive ability of the GRS model alone.

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, GRACE = Global Registry of Acute Coronary Event, NRI = net reclassification improvement.

MI.^[5,10,14,41] Although the study by Fan et al of Chinese STEMI patients finds some association between the GRS and complex cardiovascular events,^[42] our study finds the predictive ability of the GRS on multiple major adverse events to remain inadequate and further work is required. Nevertheless, the disparity between our and Fan et al results could be due to the lower rate of cardiovascular death and MACE in our center, which is owed by the timely reperfusion and complete revascularization in accordance with current guidelines and management of STEMI.

Several limitations exist in this study and should be considered. First, our study did not clarify the status and extent of chronic inflammation disorders, which may influence the ESR and confounded the association with clinical adverse endpoints. From the viewpoint of prior studies, severe diseases, which have inflammatory properties, do not significantly influence the association between ESR and MACE.^[28] However, the severity and classification of different chronic inflammation disorders may ultimately interfere with the final results of this study. Secondly, it must be stated that the number of eligible patients with STEMI from only 1 cardiac center is relatively small, and this low prevalence of 1-year mortality could also contribute to the negative result of the models containing the ESR and GRS seen here. Accordingly, in cases of higher cardiovascular deaths, the improvement of integrated discrimination was seen in the models combining the ESR and GRS. Thirdly, in the mean period of 23 months, we did not report the details of patients, who could not be followed up or did not consent to the study. This could inevitably result in selection bias. While we propose that the ESR to be used as a predictor of clinical prognosis, future study with multiple centers and larger numbers of patients should be conducted to support our results.

In conclusion, the present study showed that the ESR is a strong predictor of cardiovascular death and adverse clinical outcomes in STEMI patients undergoing primary PCI after adjustment for traditional cardiovascular risk factors. Moreover, the ESR enhanced the predictability of the GRS with regard to the mortality of the STEMI patients. This study provides support for future investigations aiming to evaluate the value of ESR on risk prediction and risk-guided therapy.

Author contributions

Chuang Li: Conceptualization, Software, Validation, Writing-Original Draft; YuXing Wang: Methodology, Investigation, Data Curation, Writing-Original Draft; Qian Zhang: Software, Writing-Original Draft, Visualization; LeFeng Wang: Resources, Supervision, Funding acquisition; KuiBao Li: Formal analysis,

Writing-Review and Editing; XinChun Yang: Writing-Review and Editing, Visualization, Project administration.

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