Optimization of GRACE Risk Stratification by N-Terminal Pro-B-type Natriuretic Peptide Combined With D-Dimer in Patients With Non-ST-Elevation Myocardial Infarction

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We aimed to explore the utility of multiple biomarkers with GRACE risk stratification for non-ST-elevation myocardial infarction (NSTEMI). A total of 1,357 patients diagnosed with NSTEMI were enrolled in this study at multiple medical centers in Tianjin, China. The outcomes were 1-year all-cause death and major adverse cardiac events (MACE: all-cause death, hospital admission for unstable angina, hospital admission for heart failure, nonfatal recurrent myocardial infarction, and stroke). C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated to verify that the biomarkers improve the predictive accuracy of the GRACE score. A total of 57 participants died, while 211 participants experienced 231 MACEs during follow-up (mean: 339 days). For all-cause death, the combination of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and D-dimer improved the predictive accuracy of GRACE the most, with C-index, IDI, and NRI values of 0.88, 0.085, and 1.223, respectively. For MACE, trigeminal combination of NT-proBNP, fibrinogen, and D-dimer resulted in C-index, IDI, and NRI values of 0.80, 0.079, and 0.647, respectively. As a result, NT-proBNP, D-dimer, fibrinogen, and GRACE comprise a new scoring system for assessing 1-year clinical events. Kaplan-Meier analysis revealed a significant increase in 1-year mortality (score ≥3.85 vs <3.85, $p < 0.0001$) and 1-year MACE (score ≥1.72 vs <1.72, $p < 0.0001$) between different score groups. In conclusion, the combination of NT-proBNP and D-dimer added prognostic value to GRACE for all-cause death. Combining NT-proBNP, fibrinogen, and D-dimer increased the prognostic value of GRACE for MACE. This newly developed scoring system is strongly correlated with all-cause mortality and MACE, and can be easily utilized in clinical practice. **(Am J Cardiol 2021;140:13−19)**

Acute myocardial infarction is defined as cardiomyocyte necrosis with clinical evidence of acute myocardial ischemia.[1] Acute myocardial infarction is divided into non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). NSTEMI has a higher long-term mortality than STEMI, which is probably due to a greater burden of co-morbidities and coronary artery disease.[2,3] Current guidelines recommend using a risk score to assess prognosis in patients with NSTEMI for stratified management.[4,5] The Global Registry of Acute Coronary Events (GRACE) risk score provides the most accurate stratification of ischemic risk, and an estimation of mortality rate and incidence of myocardial infarction.[6] Moreover, the "TACSO" trial has demonstrated that in NSTEMI with a GRACE score >140, undergoing coronary angiography within 12 hours of admission could reduce the risk of death and myocardial infarction at 180 days.[7] However, some challenges remain unaddressed. First, the GRACE risk score mainly assesses the occurrence of death and myocardial infarction in acute coronary syndrome (ACS). Nevertheless, other cardiovascular adverse events, including heart failure and revascularization still seriously affect patient quality of life and should be considered in the risk assessment. Second, GRACE risk score only incorporates cardiac biomarkers (troponin T/I or CK-MB) and serum creatinine. Some biomarkers have been shown to have a high predictive value for prognosis, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), and D-dimer.[8−10] NT-proBNP, hsCRP, and growth differentiation factor 15 have been recognized to enhance the predictive power of GRACE risk score.[11−15] However, the models constructed using these

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studies have some drawbacks, including the inconvenience associated with using biomarkers that are not routinely monitored in clinical practice. In addition, no studies have evaluated whether the addition of D-dimer to the GRACE risk score could improve the ability to predict cardiovascular events. Therefore, there is a need to evaluate the prognostic value of multiple biomarkers simultaneously focused on NSTEMI patients and explore if these integrated biomarkers provide additional information for the GRACE risk score. The present study first investigated whether biomarkers such as D-dimer combined with GRACE can improve risk prediction for all-cause mortality and major adverse cardiac events (MACE) in patients with NSTEMI.

Methods

This research represents a real-world, multicenter, prospective, cohort study on the prognostic value of multiple biomarkers in patients with NSTEMI. Research populations were recruited at Tianjin Medical Center (Tianjin Chest Hospital, Tianjin Fourth Central Hospital, Tianjin Medical University General Hospital, Tianjin Third Center Hospital, and Tianjin People's Hospital) between January 2018 and December 2018. All hospitals were required to enroll participants continuously. MACE that occurred within 1 year were censored. Inclusion criteria: (1) age >18 years; (2) NSTEMI was defined as acute MI without ST-segment elevation in electrocardiography at presentation and meeting the following criteria: (1) clinical presentation was compatible with myocardial ischemia; (2) dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals. Exclusion criteria: (1) Electrocardiogram with persistent ST-segment elevation; (2) chest pain caused by noncardiac causes, such as aortic dissection and pulmonary embolism. The study was approved by the ethical committee of each hospital and all patients signed the informed consent forms. This study is listed at ClinicalTrials.gov (identifier: NCT03600259).

GRACE was used to assess risk stratification when NSTEMI patients were admitted to the hospital. Eight variables were collected for all patients upon admission, including age, systolic blood pressure, heart rate, serum creatinine, Killip class, cardiac arrest, elevated cardiac biomarkers, and ST deviation. These variables were then included in the GRACE risk calculator (https://www.outcomes-umassmed.org/ risk_models_grace_orig.aspx) to determine the final score.

Treatment therapy was systematically determined using current clinical guidelines,[5] physicians' judgment, and patient's preference. All patients were expected to receive the best medical treatment. The timing of coronary angiography and revascularization strategy was determined by at least two experienced operators.

Blood was collected within the first 12 hours after admission. All samples were centrifuged at 3000 g for 10 min to obtain serum samples. Aliquots were stored at −80°C until measurement. Common clinical indicators (NT-proBNP, hsTnT, CK, hsCRP, fibrinogen, and D-dimer) were measured using Roche Diagnostics (Mannheim, Germany).

The primary study outcome was 1-year all-cause mortality, including cardiac, vascular, and noncardiovascular causes of death. The secondary outcome was 1-year MACE, consisting of all-cause death, hospital admission for unstable angina, hospital admission for heart failure, nonfatal recurrent myocardial infarction, and stroke. Heart failure was diagnosed according to the current guidelines[16] from the European Society of Cardiology. The recurrent myocardial infarction diagnosis was defined by the fourth universal definition of myocardial infarction.[1] Stroke was identified by CT and/or MRI with signs of ischemia or bleeding. Reviews of clinic visits and telephone interviews were conducted for the 6-month and 1-year outcomes. Clinical follow-up was performed at 1, 3, 6, and 12 months for each participant.

The biomarker value was determined using logarithmic transformation for normal distributions. Patient characteristics were described according to quartiles for continuous variables, and absolute and relative frequency for categorical variables. In univariate analysis, parametric *t* tests, nonparametric Wilcoxon-rank tests, and Wald Chi-squared tests were used dependent on their distribution to examine the difference between groups. Pearson's correlation coefficient was calculated for the biomarkers. Since there is no standard method for accessing the discrimination ability for time-to-event data, receiver operating characteristic (ROC) analyses were utilized to calculate the corresponding C-statistic, sensitivity, and specificity at optimal cutoff point based on the Youden index maximization principle for every biomarker.

Cox proportional hazards regression was used to evaluate the biomarker effect on both primary and secondary outcomes. In multivariable regression, the stepwise method was utilized to reveal independent significant biomarkers. The Kaplan-Meier curves for patients at risk were plotted stratified by the optimal cutoff value for the calculated risk score based on GRACE combined with biomarkers, and compared with the log-rank test.

C-index was used to evaluate the discrimination of different models. However, comparing C-index is inefficient to evaluate the relative merits of the new models. Thus, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) based on logistic regression were calculated to evaluate added predictive ability of biomarkers to the GRACE score. NRI involves classifying patients into binary outcomes and evaluates how the new model, updated using biomarkers, reclassifies these patients compared with a previous model.[17] IDI is a more sensitive metric because it is free of arbitrary boundaries delineating discrete categories of risk.[18] Moreover, the subgroup analyses were performed based on age (<75 or ≥75 years), sex, left ventricular ejection fraction (left ventricular eject fraction, <40 or ≥40%), and Killip classification (Killip <2 or ≥2). Analyses were performed using the SAS software (version 9.4, SAS Institute, Cary, NC) and R version 3.4.3. A 2-sided $p < 0.05$ was considered statistically significant.

Results

The study included 1,357 patients with NSTEMI, 93 of whom were lost to follow-up. The mean follow-up time was 339 days. A total of 57 (4.2%) all-cause death and 211 (15.6%) MACE cases were observed during 1-year follow-

up (all-cause death in 57 patients, hospital admission for unstable angina in 58 patients, hospital admission for heart failure in 81 patients, nonfatal recurrent myocardial infarction in 29 patients, and stroke in 6 patients). Presentation characteristics and biomarkers across different primary outcome groups are shown in Table 1. NT-proBNP, hsTnT, CK, hsCRP, fibrinogen, and D-dimer were significantly higher in all-cause death patients than in patients without all-cause death.

ROC analysis was used to assess the discrimination of each univariate biomarker for a fundamental exploration of biomarker prognostic value. NT-proBNP and D-dimer exhibited good performance, with a C-index >0.7 in both primary and secondary outcomes (Additional file, Table S1). Logarithmic transformation was performed prior to correlation analysis. Correlation among the biomarkers was medium or low. The most correlated biomarkers were hs-TnT and CK, with a correlation coefficient of 0.53 (Additional file, Figure S1).

Dichotomized biomarkers were used based on optimal cutoff points (Additional file, Table S2) for the Cox regression in both crude and adjusted models for clinical convenience (Table 2). NT-proBNP and D-dimer were significant independent biomarkers for all-cause death. NT-proBNP, fibrinogen, and D-dimer were significant independent biomarkers for MACE. The quartiles and continuous (logarithmic transformation) form were also used to validate the results. The regression results were robust for both all-cause death and MACE (Additional file, Tables S3 and S4).

Considering the robustness of NT-proBNP and D-dimer for the prediction of all-cause death, all possible combinations of NT-proBNP, D-dimer, and fibrinogen were tested for MACE to evaluate the added predictive ability of biomarkers (Table 3). Prespecified subgroup analyses revealed

Table 1
Characteristics and biomarkers of NSTEMI patients upon presentation

Characteristics	All (n = 1357)	All-cause death at 1 year		Statistic	pValue
		NO Event (n = 1300)	Event (n = 57)		
Age(years)	65 ± 12	64 ± 11	76 ± 8	7.96	<0.0001
Men	945 (69.6%)	921 (70.9%)	24 (42.1%)	21.33	<0.0001
Smoker	811 (59.8%)	773 (59.5%)	38 (66.7%)	1.16	0.2806
Hypertension	917 (67.6%)	879 (67.6%)	38 (66.7%)	0.02	0.8809
Diabetes mellitus	460 (33.9%)	433 (33.3%)	27 (47.4%)	4.82	0.0282
Hyperlipermia	994 (76.8%)	959 (77.2%)	35 (68.6%)	2.00	0.1574
No. of narrowed coronary arteries					
1	177 (16.5%)	175 (16.7%)	2 (8.3%)	0.66	0.4160
2	245 (22.9%)	240 (22.9%)	5 (20.8%)	0.06	0.8115
3	623 (58.1%)	606 (57.8%)	17 (70.8%)	1.63	0.2015
LVEF (%)	51.33 ± 9.86	51.62 ± 9.73	44 ± 10.53	4.81	<0.0001
Prior PCI	219 (16.1%)	212 (16.3%)	7 (12.3%)	0.65	0.4186
Prior CABG	73 (5.4%)	69 (5.3%)	4 (7.0%)	0.31	0.5755
Baseline Medication					
DAPT	1335 (98.4%)	1279 (98.4%)	56 (98.3%)	-	0.6139
β-blockers	1041 (76.7%)	995 (76.5%)	46 (80.7%)	0.53	0.4667
ACEI or ARB	862 (63.5%)	834 (64.2%)	28 (49.1%)	5.32	0.0210
Statins	1310 (96.5%)	1256 (96.6%)	54 (94.7%)	-	0.4442
Anticoagulants	1334 (98.3%)	1278 (98.3%)	56 (98.3%)	-	>0.9999
Treatment therapy				48.50	<0.0001
Conservative treatment	472 (34.8%)	428 (32.9%)	44 (77.2%)		
PCI	770 (56.7%)	761 (58.5%)	9 (15.8%)		
CABG	115 (8.5%)	111 (8.5%)	4 (7.0%)		
TC (mg/dl)	171.05 (144.74, 197.757)	171.83 (145.51, 198.14)	188.08 (160.61, 215.56)	1.87	0.0608
TG (mg/dl)	138.22 (105.43, 193.15)	139.99 (106.32, 194.92)	113.41 (93.03, 139.10)	3.61	0.0003
HDL (mg/dl)	37.54 (32.12,44.89)	37.54 (32.12,44.89)	38.7 (31.73,46.05)	0.33	0.7419
LDL (mg/dl)	114.17 (89.78, 138.55)	114.55 (90.17, 139.32)	105.65 (86.69, 127.71)	1.72	0.0848
GRACE score	127.48 ± 34.32	125.66 ± 33.34	169.04 ± 30.04	8.54	<0.0001
NT-proBNP (pg/mL)	913.3 (366.5, 2471.0)	878.5 (355.45, 2236.5)	9373 (3715, 15042)	9.11	<0.0001
HsTnT (μg/L)	0.54 (0.24, 1.22)	0.53 (0.23, 1.17)	1.54 (0.43, 2.56)	4.55	<0.0001
CK (U/L)	209 (103, 489)	207 (103, 483)	252 (136, 585.5)	2.05	0.0400
hsCRP (mg/L)	5.47 (2.26, 16.58)	5.33 (2.22, 15.08)	32.89 (5.86, 102.96)	5.68	<0.0001
Fibrinogen (g/L)	3.59 (3.13, 4.27)	3.57 (3.12, 4.23)	4.49 (3.65, 5.26)	4.63	<0.0001
D-dimer (μg/mL)	0.38 (0.27, 0.65)	0.37 (0.26, 0.60)	0.95 (0.50, 2.00)	6.81	<0.0001

Quantitative data are expressed as mean ± SD (normal distribution) or median (Q1, Q3; non-normal distribution). *t* test was used for normal distribution homoscedasticity data. In other cases, Wilcoxon test was used. Category data were described by absolute and relative frequency and tested by Wald Chi-squared test.

LVEF = left ventricular eject fraction; TC = total cholesterol; TG = triglyceride; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CK = creatine kinase; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; DAPT = dual antiplatelet therapy; ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blocker; hsCRP = hypersensitive C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; hs-TnT = hypersensitive troponin T.

Table 2
COX proportional hazards model for 1-year all-cause death and MACE

Biomarkers	Crude		Adjusted*	
	HR (95%CI)	p Value	HR (95%CI)	p Value
All-cause death				
NT-proBNP	18.80 (9.74, 36.30)	<0.0001	10.85 (4.19, 28.11)	<0.0001
Hs-TnT	4.04 (2.39, 6.83)	<0.0001		
CK	1.88 (1.10, 3.20)	0.0207		
hsCRP	5.67 (3.21, 10.00)	<0.0001		
Fibrinogen	4.41 (2.60, 7.49)	<0.0001		
D-dimer	6.70 (3.71, 12.07)	<0.0001	2.44 (1.10, 5.38)	0.0092
MACE				
NT-proBNP	5.71 (4.35, 7.49)	<0.0001	3.06 (2.12, 4.42)	<0.0001
Hs-TnT	2.30 (1.75, 3.03)	<0.0001		
CK	1.41 (1.08, 1.85)	0.0125		
hsCRP	2.65 (2.02, 3.47)	<0.0001		
Fibrinogen	2.62 (2.00, 3.43)	<0.0001	1.43 (1.05, 1.97)	0.0177
D-dimer	3.69 (2.81 ,4.86)	<0.0001	2.12 (1.50, 2.99)	<0.0001

* Adjusted significant baseline variables in Table 1 (age, gender, diabetes, left ventricular eject fraction, angiotensin converting enzyme inhibitors or angiotensin receptor blocker, treatment therapy, total cholesterol, triglyceride, and GRACE) and other biomarkers. In multivariable Cox stepwise regression, 0.05 level for entry was adapted.

MACE = major adverse cardiac events; CK = creatine kinase; hsCRP = hypersensitive C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; hs-TnT = hypersensitive troponin T.

consistent results for all subgroups (Additional file, Tables S4 and S5). Quartile results are shown in the Additional file, Table S6.

Four variables (GRACE, NT-proBNP, fibrinogen, and D-dimer) were used to build a new scoring system. The cutoff points for all biomarkers were determined using the Youden index. Group information and risk score assignments are presented in Figure 1. Survival curves for different risk score groups based on GRACE augmented with biomarkers are represented in Figure 1. The number of clinical events in the high-risk categories (score ≥3.85 for all-cause death or score ≥1.72 for MACE) was significantly higher than that in the low-risk categories ($p < 0.0001$).

Discussion

Using prospectively collected data for NSTEMI patients, the present study demonstrated that multiple biomarkers (NT-proBNP and D-dimer) measured upon hospital admission can enhance the ability of the GRACE risk score to predict 1-year all-cause mortality. Moreover, the addition of NT-proBNP, D-dimer, and fibrinogen improved risk discrimination for 1-year MACE (all-cause death, hospital admission for unstable angina, hospital admission for heart failure, nonfatal recurrent myocardial infarction, and stroke) beyond that achieved by GRACE score alone. In addition, a new scoring system that can successfully identify high-risk groups was developed based on the GRACE score.

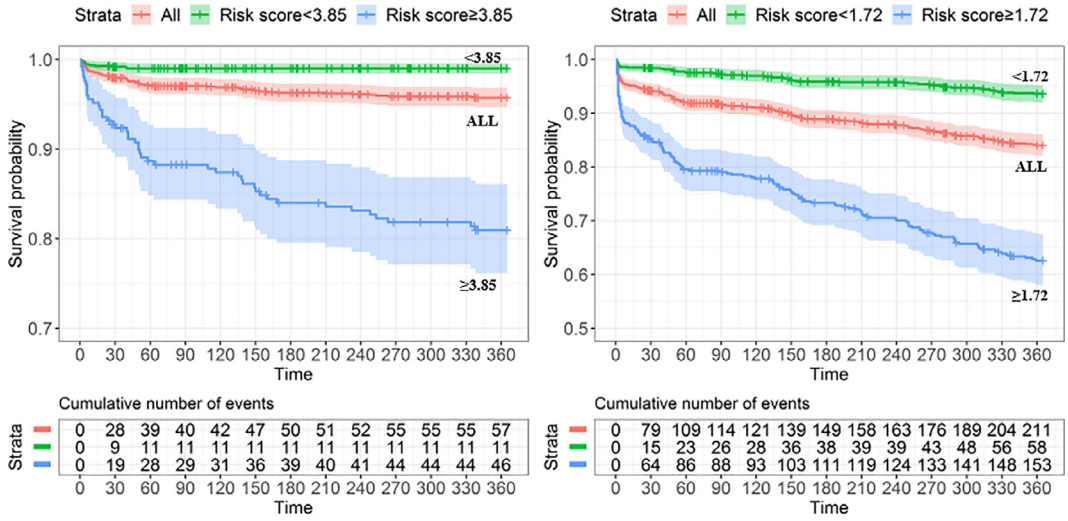
Table 3
C-index, IDI, and NRI for GRACE augmented by biomarkers

	C-index	IDI	NRI
All-cause death at 1 year			
GRACE	0.77	Ref	Ref
GRACE+ NT-proBNP	0.86	0.077 (0.061, 0.092)	1.208 (1.068, 1.486)
GRACE+ D-dimer	0.82	0.024 (0.012 ,0.035)	0.903 (0.669, 1.137)
GRACE+ NT-proBNP+ D-dimer	0.88	0.085 (0.065, 0.105)	1.223 (1.014, 1.433)
MACE at 1 year			
GRACE	0.73	Ref	Ref
GRACE+ NT-proBNP	0.78	0.062 (0.044, 0.080)	0.783 (0.643, 0.924)
GRACE+ Fibrinogen	0.76	0.022 (0.012, 0.033)	0.455 (0.313, 0.598)
GRACE+ D-dimer	0.76	0.029 (0.018, 0.040)	0.660 (0.518, 0.802)
GRACE+ NT-proBNP+ Fibrinogen	0.79	0.070 (0.051, 0.089)	0.719 (0.579, 0.860)
GRACE+ NT-proBNP+ D-dimer	0.79	0.074 (0.055, 0.094)	0.700 (0.559, 0.842)
GRACE+ Fibrinogen + D-dimer	0.77	0.040 (0.027,0.053)	0.617 (0.477, 0.757)
GRACE+NT-proBNP+ Fibrinogen+ D-dimer	0.80	0.079 (0.059,0.099)	0.647 (0.505, 0.788)

The added predictive ability of all significant biomarker combinations in multivariable Cox regression was measured using C-index, IDI, and NRI. NRI was designated continuous NRI (ranging from −2 to 2) in this manuscript.

All-cause death at 1year	
Items	**Risk Score**
GRACE	
≤108	0
108~140	1.65
> 140	2.32
NT-proBNP>3338	2.20
D-dimer>0.54	0.82

MACE at 1 year	
Item	**Risk Score**
GRACE	
≤108	0
108~140	0.84
> 140	1.61
NT-proBNP>3338	1.16
Fibrinogen>4.27	0.46
D-dimer>0.54	0.56



The left panel was survival curve for all-cause death, the red curve was all 1357 patients, the green curve was for the patients whose risk score greater than or equal 3.85 and the blue curve was for the patients whose risk score less than 3.85. Similarly, the right panel was survival curve for MACE, the red curve was all 1357 patients, the green curve was for the patients whose risk score greater than or equal 1.72 and the blue curve was for the patients whose risk score less than 1.72. P<0.0001 in log-rank test.

Figure 1. Risk score assignment table and survival curve for different risk score groups.

The condition of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) can range from asymptomatic to life-threatening. Therefore, risk stratification is critical for the management of NSTE-ACS, especially NSTEMI.[5] The GRACE risk score is the most powerful tool for the risk assessment of patients with NSTE-ACS. However, the C-statistic for predicting 1-year death or myocardial infarction is only 0.715 (95% CI: 0.672 to 0.756).[19] Other studies that validated the GRACE score also showed that the C-statistic to predict 1-year mortality was 0.78 to 0.79.[20–22] The predictive ability was similar (area under the receiver-operating characteristic curve, AUC: 0.77) in the present study. Beyond that, the predictive power of GRACE score for MACE was not ideal (AUC: 0.73), suggesting that there is room for further improvement. Biomarkers that are readily available in clinical practice may offer additive prognostic value to the GRACE score. The present study demonstrated that NT-proBNP and D-dimer provided a better predictive power based on the GRACE score.

The present study showed that both NT-proBNP and D-dimer have excellent predictive powers (C-index >0.7) in ROC analysis. The AUC for NT-proBNP predicting 1-year mortality reached 0.85. NT-proBNP has been studied extensively and its clinical value is thoroughly understood.[5,8] Additionally, the predictive value of D-dimer for the prognosis of stable coronary heart disease and ACS is gradually becoming recognized.[23,24] D-dimer is associated with a composite event of cardiovascular death, myocardial infarction, or stroke in ACS (OR: 1.13, 95% CI: 1.00 to 1.28, p = 0.048). In the present study, univariate ROC analysis revealed a prognostic value for NT-proBNP and D-dimer, while multivariable Cox regression analysis indicated that they were independent risk factors for 1-year mortality.

NRI and IDI were calculated for each combination of biomarkers significant in the time-to-event analysis. The positive NRI and IDI values suggested that the combination of NT-proBNP and/or D-dimer with GRACE might improve the accuracy of GRACE. For the secondary outcome, MACE, fibrinogen might prove to be another potential biomarker with prognostic value, in addition to NT-proBNP and D-dimer, due to its MACE hazard ratio of 1.43 (1.05, 1.97) in multivariable Cox regression analysis. Trigeminal combination of NT-proBNP, D-dimer, and fibrinogen with GRACE improved the predictive accuracy the most for MACE.

Several previous studies have explored biomarkers to improve GRACE risk stratification of NSTE-ACS.[12–14,22,25] Widera et al.[25] explored 9 biomarkers (NT-proBNP, GDF-15, cardiac troponin T, C-reactive protein, fibroblast

growth factor 23, and others) in 1,146 patients with NSTE-ACS and found that the two most promising biomarkers to improve the performance of GRACE model were NT-proBNP and GDF-15. The addition of NT-proBNP and GDF-15 to GRACE enhanced model discrimination with an increase in AUC from 0.79 (95% CI, 0.71 to 0.88) to 0.86 (95% CI, 0.78 to 0.94).[25] Compared with the present study, this study only evaluated the 6-month all-cause mortality or nonfatal myocardial infarction. In addition, GDF-15 that was eventually included in the model was not clinically easy to obtain. Similarly, although the final model (heart-type fatty acid-binding protein plus NT-proBNP plus GRACE) to predict 1-year MACE (death and cardiovascular events) had an AUC of 0.83 (0.77 to 0.89), it is inconvenient to obtain in clinical practice.[22] Both Toorenburg et al.[22] and Klingenberg et al.[13] have studied some of the common clinical biomarkers. Their final models incorporated more indicators, but the model's ability to predict all-cause mortality or myocardial infarction was lower than the present model. More importantly, the present study is the first to evaluate the role of D-dimer in improving the predictive ability of GRACE. Adding D-dimer to NT-proBNP and GRACE can increase the AUC for 1-year all-cause death from 0.86 to 0.88, which is higher than the AUC for models using GRACE and biomarkers reported in the previously-mentioned literature. Whether it is 1-year MACE or 1-year mortality and myocardial infarction, the final model had an AUC >0.8. Therefore, the present study is the first to reveal the value of D-dimer in improving GRACE risk stratification.

In addition, a new scoring system was developed based on GRACE that can distinguish between low-risk and high-risk groups. All biomarkers were readily available upon admission and were easily assessed. This simple and easy-to-use scoring system quickly identifies high-risk groups so that the medical team can provide more aggressive treatments. Compared with the current risk stratification of NSTE-ACS management,[13] the score is more specific to NSTEMI and has objective indicators to evaluate. In addition to referencing patient's physiological state and co-morbidities, medical professionals can also refer to this score when making clinical decisions.

Study limitations were reflected in four aspects of this research. First, the included sample size was relatively small. Therefore, follow-up studies will need to recruit more patients with NSTEMI. Second, due to the nature of observational studies, it is impossible to verify the guiding value of the scoring system for clinical treatments. Third, the added predicted value of biomarkers was based on the dichotomous form for clinical convenience, which might miss some information. Nevertheless, result robustness was evaluated in quartered and continuous forms. Fourth, although this research was carried out at multiple medical centers, the patients were mainly form Tianjin, China. Thus, it is necessary to validate these findings in multiple regions.

In conclusion, the present study demonstrates that NT-proBNP and D-dimer are closely related to prognosis and can be used to optimize GRACE risk stratification. The newly developed scoring system based on GRACE shows a good ability to distinguish between high-risk and low-risk patients, which may provide guidance for the management of NSTEMI.

Author Contribution

Peng-Ju Lu: Conceptualization, Data curation, Writing - original draft, Writing - review & editing. Xiao-Wen Gong: Software, Writing - original draft, Formal analysis, Methodology. Yin Liu: Conceptualization, Supervision, Funding acquisition, Resources. Feng-Shi Tian: Resources. Wen-Juan Zhang: Resources. Ying-Wu Liu: Resources. Zhu-Hua Yao: Resources. Ji-Xiang Wang: Resources. Peng Han: Investigation. Ya-Nan Yang: Investigation. Zhuang Cui: Methodology, Data curation, Writing - review & editing. Jing Gao: Conceptualization, Funding acquisition, Project administration, Supervision, Writing - review & editing.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.050.

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