Biomarker-based risk model to predict cardiovascular events in patients with acute coronary syndromes — Results from BIPass registry

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Summary

Background Risk models integrating new biomarkers to predict cardiovascular events in acute coronary syndromes (ACS) are lacking. Therefore, we evaluated the prognostic value of biomarkers in addition to clinical predictors and developed a biomarker-based risk model for major adverse cardiovascular events (MACE) within 12 months after hospital admission with ACS.

Methods Patients (n = 4407) consecutively enrolled from November, 2017 to October, 2019 in three hospitals of a prospective Chinese registry (BIomarker-based Prognostic Assessment for Patients with Stable Angina and Acute Coronary Syndromes, BIPass) were designated as the risk model development cohort. Validation was performed in 1409 patients enrolled in two independent hospitals. Cox proportional hazards regression analysis was used to generate a risk prediction model and evaluate the incremental prognostic value of each biomarker.

Findings Over 12 months, 196 patients experienced MACE (5.1%/year). Among twelve candidate biomarkers, N-terminal pro-B-type natriuretic peptide (NT-proBNP) measured at baseline showed the most prognostic capability independent of clinical predictors. The developed BIPass risk model included age, hypertension, previous myocardial infarction, stroke, Killip class, heart rate, and NT-proBNP. It displayed improved discrimination (C-statistic 0.79, 95% CI 0.73-0.85), calibration (GOF = 9.82, p = 0.28) and clinical decision curve in the validation cohort, outperforming the GRACE and TIMI risk scores. Cumulative rates for MACE demonstrated good separation in the BIPass predicted low, intermediate, and high-risk groups.

Interpretation The BIPass risk model, integrating clinical variables and NT-proBNP, is useful for predicting 12-month MACE in ACS. It effectively identifies a gradient risk of cardiovascular events to aid personalized care.

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Keywords: Acute coronary syndromes; Prognosis; Biomarker; Risk prediction model

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Research in context

Evidence before this study

Several biomarkers have been proven to carry prognostic information for the risk of cardiovascular events in patients with acute coronary syndromes (ACS). However, instruments integrating clinical risk factors and candidate biomarkers to accurately predict the occurrence of cardiovascular events, thus facilitating individualization of ACS care are lacking. We have performed systematic literature review on the topic of risk prediction models as well as the associations between biomarkers and cardiovascular events in patients with ACS. We searched Pubmed without language or date restrictions for publications up to December, 2021, using free-text search terms "acute coronary syndrome (s)", "biomarker", "cardiovascular events", "major adverse cardiac events", "cardiovascular disease", "cardiac biomarker", "troponin", "NT-proBNP" in various combinations. GRACE and TIMI are the most notable risk scores which were developed over 20 years ago. Although accumulating evidences showed that biomarkers such as NT-proBNP, cardiac troponin, et al. were associated with cardiovascular events, development and validation of a risk prediction model including the candidate biomarkers and clinical characteristics for cardiovascular event risk in Chinse ACS patients has not been done.

Added value of this study

In this study of Chinese patients with ACS, we provided evidence supporting baseline NT-proBNP as the most prognostic biomarker for cardiovascular events. No additional biomarkers further improved the discrimination once NT-proBNP was included in the clinical model. Furthermore, we developed and validated a BIPass risk prediction model for major cardiovascular events in the first year after hospitalization. The BIPass risk model included biomarkers of NT-proBNP, and clinical variables of age, hypertension, previous myocardial infarction, previous stroke, Killip class and heart rate. This novel risk algorithm showed better discrimination, calibration, and clinical decision curve than GRACE and TIMI risk scores. The C-statistic of BIPass was higher for predicting MACE that happened in one month or later, but lower for predicting MACE in less than one month, indicating that this model be more accurate in predicting mid-term and long-term MACE. The BIPass risk model effectively identified a gradient risk of cardiovascular events, and thus providing a useful instrument to personalize patient care ranging from conservative treatments, intense antiplatelet therapy to more aggressive coronary angiography.

Implications of all the available evidence

This study provides an improved risk stratification tool to aid clinical decision making by integrating clinical variables and biomarkers in the setting of ACS. These data should be useful in informing future studies aiming to develop risk prediction models in patients with other cardiovascular diseases.

Introduction

Acute coronary syndromes (ACS), the acute and severe manifestation of coronary artery disease, represent the major cause of morbidity and mortality worldwide.[1] Although the majority of patients presenting with ACS have a common pathological possess within coronary arteries, i.e. atherosclerotic plaque and thrombosis formation, the risk for future ischemic cardiovascular events is highly heterogeneous. Consequently, patients with ACS may differ in the magnitude of absolute benefit received from proven therapies.[2,3] For instance, high risk patients may gain greater benefit from the intense antiplatelet therapy and aggressive coronary revascularization strategies where the risk of adverse effects (i.e. major bleeding) is exceeded, while such benefit may not exceed the risk among low risk patients.[4,5] To appropriately tailor the intensity of existing treatments, there is a need for implementing risk stratification instruments in patients with ACS.

To date, the most guideline-recommended risk prediction tools include GRACE and TIMI risk scores.[6–8] These risk models include six to eight clinical and lab variables and yield acceptable discrimination for death or recurrent myocardial infarction (MI) over 14 days or 6 months. However, both GRACE and TIMI risk scores were developed over 20 years ago. The established treatments and clinical practices in the management of ACS have undergone tremendous changes since then, which may affect the risk prediction for cardiovascular events in current practice. Furthermore, neither GRACE nor TIMI risk score has been validated in a large Chinese ACS patient population.

During the recent decades, circulating biomarkers have been increasingly recognized to provide objective and accurate information with prognostic significance in the wake of deeper insights into the pathophysiology of cardiovascular diseases.[9,10] Beyond diagnostic utility, initial cardiac troponins add prognostic information in terms of short- and long-term risk for cardiovascular events in patients with ACS.[11,12] Analogously, B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), the biomarkers for myocardial wall tension, show prognostic value in addition to cardiac troponins.[13] Other biomarkers, such as growth differentiation factor 15 (GDF-15) may also have prognostic value.[14,15] Despite the accumulated evidence in literature, the routine measurement of these biomarkers for the prognostic purposes is not recommended by European Society of Cardiology (ESC) guidelines, with the exception of

NT-proBNP.[16] Moreover, it is less clear whether these candidate biomarkers provide additional information when they are integrated in a risk prediction model for cardiovascular events in Chinese ACS patient population.

The aims of this study were to (1) evaluate the incremental prognostic value of each candidate biomarker in addition to clinical characteristics, (2) develop and validate a useful risk prediction model using clinical variables and biomarkers, (3) compare the performance of the developed risk model with the GRACE and TIMI risk scores in Chinese patients with ACS.

Methods

Study design. BIomarker-based Prognostic Assessment for patients with Stable angina and Acute coronary Syndromes (BIPass) was a prospective, multicenter registry study in which eligible patients admitted to a coronary care unit were consecutively enrolled at five tertiary, teaching, and comprehensive hospitals in north China. The BIPass study was aimed to identify the biomarkers with the most prognostic significance, and develop new risk prediction models for cardiovascular and bleeding events by combining biomarkers and clinical characteristics, respectively. For the risk model of ischemic cardiovascular events, we used patients with ACS from the BIPass cohort. Patients from three hospitals (Qilu Hospital, Jinan; Chinese PLA General Hospital, Beijing; Peking University First Hospital, Beijing) were designated as the risk model development cohort. Patients from two independent hospitals (Peking University Third Hospital, Beijing; Zibo Central hospital, Zibo) were designated as the validation cohort.

The BIPass study was approved by the research ethics committee of Qilu Hospital, which was accepted by all the collaborating hospitals. The study complied with the Declaration of Helsinki.

Study population and definitions. Patients were enrolled from November, 2017 to October, 2019. Patients had to be at least 18 years of age, be admitted to participating hospitals with ACS including unstable angina (UA) and MI. The definitions for each subset of ACS are provided in Online methods. All patients with possible cardiovascular diseases who admitted to the participating hospitals were screened twice for eligibility. Initial screening for possible inclusion was performed by the local cardiologists once a patient was admitted. Confirmatory screening was conducted by both the local cardiologists and an independent Eligibility Committee at the time of patient discharge. Patients with non-cardiac comorbidities with life expectancy less than 12 months were excluded. The study schematic is summarized in Online Figure 1. All patients provided written informed consent to participate.

We collected the baseline clinical data including demographic characteristics (age, gender, ethnicity body mass index (BMI)), risk factors and medical history, presenting symptoms and signs (heart rate, Killip class, systolic blood pressure (SBP), diastolic blood pressure (DBP), et al.), electrocardiogram (ECG) recordings, medications, and in-hospital procedures (coronary angiography, et al.). Hypertension was defined as having antihypertensive treatment or at repeated blood pressure measurements >140/90 mm Hg. Current smoking was defined as having smoked within recent 4 weeks. Previous MI was defined as having a history of MI (with or without revascularization). Previous revascularization was defined as having a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) procedures. Previous stroke was defined as having a history of ischemic stroke. Electronic Case Report Form system was used to assist data collection. An independent eletrocardiographic core laboratory measured the ECG records.

The primary outcome was major adverse cardiovascular events (MACE) which was defined as the composite of cardiac death, new or recurrent MI, and ischemic stroke after enrollment through 12 months. Definitions of the primary outcome are provided in Online methods. Follow-up was scheduled via telephone by trained research assistants at each participant site at 30 days, 6 months, and 12 months after admission. Source medical documents were obtained for event adjudication by an independent clinical events committee.

Biomarker analyses. Once the initial screening was completed, we collected fasting blood samples of patients in EDTA tubes and centrifuged them immediately. Plasma samples were stored at -80 °C for approximate 6 months until biomarker analyses were performed centrally at Qilu Hospital, Jinan, China.

A total of twelve candidate biomarker were analyzed, whose pathophysiological classification is provided in Online Table 1. The assay characteristics for each specific biomarker are provided in Online methods. Briefly, NT-proBNP, high-sensitivity cardiac troponin T (hs-cTnT), and Cystatin C concentrations were determined using electrochemiluminescence immunoassays on the Cobas e602 analyzer (Roche Diagnostics, Mannheim, Germany). GDF-15, lipoprotein-associated phospholipase A2 (Lp-PLA2), and dickkopf-related protein 1 (DKK1) concentrations were determined using in a monoclonal antibody sandwich assay on a Luminex 200 platform (R&D systems, Minneapolis, MN). Heart-type fatty acid binding protein (H-FABP) and midregional proadrenomedullin (MR-proADM) concentrations were determined using a specific ELISA assay (Abbexa company, Cambridge, UK). The plasma levels of lipids (triglycerides and LDL-C), hemoglobin, and white blood cells (WBC) were determined under routine working conditions immediately after blood draw with the regular quality assurance control.

Statistical analysis. Continuous variables are summarized as median (interquartile range, IQR), and

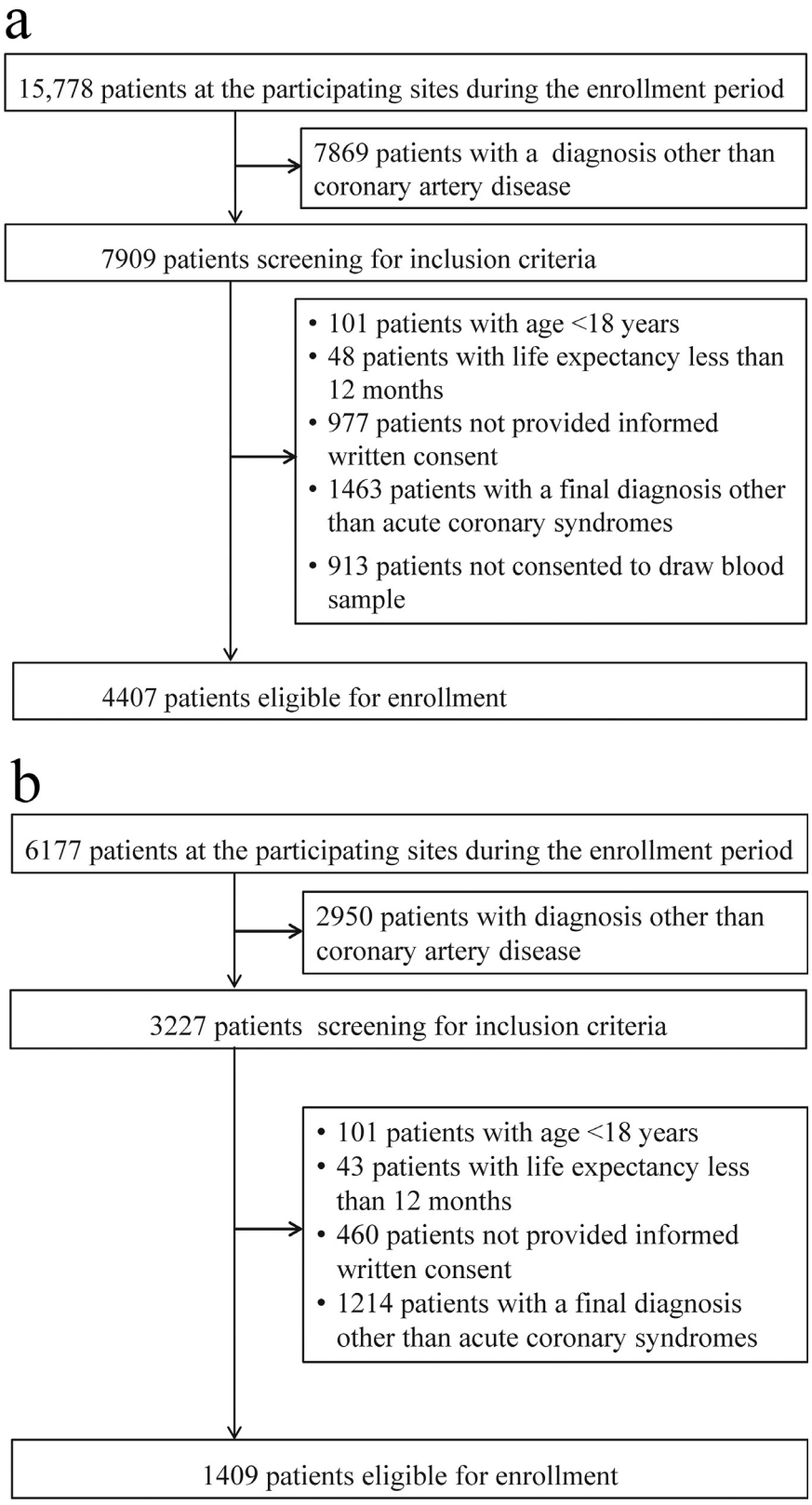

Figure 1. Flowcharts of patient enrollment in the BIPass risk model development (a) and validation cohort (b).

	Development cohort (*n* = 4407)	Validation cohort (*n* = 1409)
Demographics		
Age, years	64 (56, 70)	65 (57, 72)
Female	1490 (34)	541 (38)
Han nationality	4298 (98)	1382 (98)
Body mass index, kg/m^2	26 (23, 28)	25 (23, 28)
Risk factors and medical history		
Hypertension	2799 (64)	889 (63)
Dyslipidemia	532 (12)	495 (35)
Diabetes mellitus	1379 (31)	466 (33)
Previous myocardial infarction	533 (12)	186 (13)
Current smoking	1120 (25)	313 (23)
Previous smoking	1167 (27)	282 (21)
Never smoked	2118 (48)	777 (57)
Peripheral arterial disease	86 (2)	78 (6)
Previous stroke	514 (12)	228 (16)
Congestive heart failure	31 (1)	21 (2)
Previous revascularization	961 (22)	331 (24)
Previous percutaneous coronary intervention	898 (20)	315 (22)
Previous coronary artery bypass grafting	95 (2)	28 (2)
Previous coronary stenosis ≥ 50%	1305 (30)	395 (28)
Renal dysfunction	36 (1)	55 (4)
Presenting characteristics		
Cardiac arrest	4 (0.1)	0 (0.0)
Cardiogenic shock	16 (0.4)	5 (0.4)
Killip class I	4227 (95.9)	1369 (97.2)
Killip class II	153 (3.5)	30 (2.1)
Killip class III	11 (0.3)	5 (0.4)
Killip class IV	16 (0.4)	5 (0.4)
Heart rate, beats/min	72 (65, 80)	71 (65, 79)
SBP, mmHg	133 (120, 146)	137 (125, 150)
DBP, mmHg	75 (67, 83)	77 (70, 85)
Electrocardiographic findings		
Sinus rhythm	3823 (89)	1249 (91)
ST-segment elevation	579 (14)	107 (8)
ST-segment depression	867 (21)	274 (20)
Previous medications		
Aspirin	2659 (60)	781 (55)
DAPT	2749 (62)	824 (59)
Oral anticoagulant	37 (1)	30 (2)
Statin	291 (7)	389 (28)
β blocker	1505 (34)	396 (30)
ACE inhibitors/ARB	1215 (28)	277 (21)
Index event diagnosis		
Unstable angina	2647 (60)	1002 (71)
Non-ST segment elevation MI	651 (15)	185 (13)
ST-segment elevation MI	553 (13)	125 (9)
Other diagnosis or missing data	556 (13)	97 (7)
Cardiac marker-negative ACS	2647 (60)	1002 (71)
Cardiac marker-positive ACS	1760 (40)	407 (29)

Table 1 *(Continued)*

	Development cohort (*n* = 4407)	Validation cohort (*n* = 1409)
Baseline Biomarkers		
NT-proBNP, ng/L	167.10 (63.86, 635.35)	82.80 (39.00, 213.50)
hs-cTnT, ng/L	13.85 (6.71, 61.98)	10.22 (5.08, 48.89)
GDF-15, ng/L	1094.00 (795.78, 1640.00)	1127.00 (784.74, 1712.75)
Lp-PLA2, ng/mL	125.33 (92.20, 158.48)	131.46 (95.73, 172.36)
H-FABP, ng/mL	1.02 (0.67, 1.55)	1.13 (0.79, 2.07)
DKK1, ng/L	724.05 (488.77, 1083.00)	1029.00 (563.95, 1966.50)
MR-proADM, ng/mL	31.43 (13.30, 76.13)	38.59 (16.38, 102.07)
Cystatin C, mg/L	1.02 (0.88, 1.18)	1.05 (0.92, 1.21)
LDL-C, mmol/L	2.23 (1.77, 2.85)	2.28 (1.78, 2.92)
Triglycerides, mmol/L	1.37 (1.02, 1.90)	1.43 (1.04, 2.01)
Hemoglobin, g/L	137.00 (127.00, 148.00)	135.00 (125.00, 145.00)
White blood cells, 10^9	6.28 (5.22, 7.62)	6.38 (5.28, 7.60)

***Table 1*: Clinical characteristics and biomarker levels in the overall development and validation cohort.**
Data are median (IQR) or number (%). Previous revascularization includes previous percutaneous coronary intervention or coronary artery bypass grafting. DAPT indicates aspirin plus clopidogrel or ticagrelor.
Data are complete (denominator *n* = 4407) for all patients except for nationality (*n* = 4399), body mass index (*n* = 4326), cardiac arrest (*n* = 4404), cardiogenic shock (*n* = 4404), heart rate (*n* = 4403), SBP (*n* = 4402), DBP (*n* = 4402), sinus rhythm (*n* = 4286), ST-segment elevation/depression (*n* = 4199).
ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; DAPT = dual anti-platelet therapy; DBP = diastolic blood pressure; DKK1 = dickkopf-related protein 1; GDF-15 = growth differentiation factor 15; H-FABP = heart-type fatty acid binding protein; hs-cTnT = high-sensitivity cardiac troponin T; LDL-C = low-density lipoprotein cholesterol; Lp-PLA2 = lipoprotein-associated phospholipaseA2; MACE = major adverse cardiovascular events; MI = myocardial infarction; MR-proADM = mid-regional proadrenomedullin; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

categorical variables are summarized as numbers and percentages. We compared continuous variables by Mann-Whitney U tests, and compared categorical variables by chi-square or Fisher's exact tests, as appropriate. Natural logarithmic (log) transformations were performed for continuous variables with skewed distributions. Biomarker levels below the limit of detection were set as the lower limits.

Model development. We used the Cox proportional hazards regression analysis to generate a risk prediction model and evaluate the incremental prognostic value of each candidate biomarker in addition to clinical variables, with time to first occurrence of MACE serving as the dependent outcome. Event-free patients were censored at the time of last contact or study end, whichever came first.

We first generated a clinical multivariable model (CMM) using forward stepwise variable selection until all the remaining clinical variables with $p < 0.05$. We began with an intercept only model, and added one variable at a time until the minimum Akaike information criterion (AIC) was achieved. The candidate clinical variables are provided in Online methods. The discriminatory ability of the CMM was assessed using Harrel's C-statistic.[17]

To assess the independent contribution of biomarkers, we added each candidate biomarker one at a time to the CMM and C-statistic improvement of the corresponding model over that of the CMM was estimated. The biomarkers were ranked by their contributed improvement in C-statistic. We then added the most prognostic biomarker to the CMM and used it as a benchmark model. The remaining biomarkers were then added to the benchmark model one at a time and the C-statistic improvement of the corresponding model over that of the benchmark model was estimated. This process stopped when little improvement was observed, and the resulting one was the final risk model. We tested the two-way interaction terms between the selected variables in the final risk model. All interaction terms were nonsignificant and were therefore not included in the final model. Proportional hazard assumption was verified using the Schoenfeld test and residuals plots.

Less than 5.0% of the clinical data and 3.4–8.8% of biomarker data were missing. We treated missing values as missing completely at random and imputed them by 10 rounds of multiple imputations (Online methods).[18] The CMM included clinical predictors that were significant in all imputations. The C-statistics and improvement in C-statistic were calculated as averages from the imputations. The individual risk prediction score was averaged from the 10 imputations for performance assessment. We repeated the model selection process with complete data only as a sensitivity analysis.

Model assessment and validation. Discrimination (C-statistic), calibration and clinical decision curve were calculated to assess the performance of the BIPass risk model in both the development and validation cohort, compared with the GRACE and TIMI risk scores.[6,8]

Calibration was assessed by Hosmer-Lemeshow goodness-of-fit (GOF) chi-square statistic and by plotting the predicted against the observed risk according to the deciles of predicted risk. To recalibrate the GRACE and TIMI risk scores, we updated the baseline survival values by fitting Cox models with the predictive score from the GRACE and TIMI (offset term) in the development cohort. To evaluate clinical utility, we performed a decision curve analysis by estimating the net benefit of BIPass model to stratify patients relative to assuming that no patient will have an event according to a continuum of decision thresholds of risk for 12-month MACE.[17,19] For readers unfamiliar with decision curve analysis, a useful introduction is provided by Vickers et al.[20] Patients with predicted risk thresholds of < 5%, 5-20%, and > 20% were grouped into low, intermediate, and high-risk categories in the development cohort, respectively. Cumulative MACE rates were calculated in each risk category and hazard ratios were compared using the log-rank test.

Subgroup analyses were performed for different age groups, subtypes of ACS, history of diabetes, previous DAPT, and revascularization during hospitalization. Sensitivity analyses were performed for C-statistic using the complete only data.

The development, validation and reporting of this risk prediction model followed TRIPOD statement.[21] The TRIPOD checklist can be found in the Online Appendix. All analyses were conducted using R version 3.6.2 (R Foundation, Vienna, Austria).

Role of the funding source

The study funders had no role in study design, data collection, data analysis, interpretation, or writing of the report.

Results

Study population. A total of 15,778 patients were admitted with definite/possible cardiovascular diseases to a coronary care unit of the participating hospitals in the BIPass development cohort. We excluded 7869 patients with a diagnosis other than coronary artery disease. Among the 7909 patients, 3502 were further excluded, with 1612 not met the inclusion criteria, 977 not provided written consent, and 913 not consented to draw blood sample. Finally, 4407 patients with ACS were included. The flowchart of patient recruitment is provided in Figure 1a.

Baseline characteristics of the included patients are presented in Table 1 and Online Table 2. Overall, patients with MACE were older, had higher prevalence of hypertension, diabetes mellitus, congestive heart failure, previous MI and stroke. Furthermore, patients with MACE were more likely to have cardiogenic shock, higher Killip class, higher heart rate, more ischemic ST changes (elevation or depression), and more use of DAPT. Among the patients, 1747 (40%) admitted with MI and 2660 (60%) with unstable angina, and 582 (13%) had reduced ejection fraction, 3400 (77%) underwent coronary angiography, 2188 (50%) underwent percutaneous coronary intervention, and 109 (3%) underwent coronary artery bypass grafting during hospitalization.

In total, 4344 (99%) patients completed 12-month follow-up. Of these, 196 patients experienced MACE (4.9%), including 99 with cardiac death (2.3%), 93 with MI (2.1%), and 26 with ischemic stroke (0.6%). The incidence rate of MACE was 5.1%/year (Online Table 3).

Biomarkers and clinical outcomes. The majority of biomarkers including NT-proBNP, hs-cTnT, GDF-15, MR-proADM, H-FABP, DKK1, cystatin C, WBC, and hemoglobin were significantly associated with MACE (Table 2). In contrast, triglycerides, LDL-C, and Lp-PLA2 were not significantly associated with MACE.

There were highly positive correlations between NT-proBNP and hs-cTnT (r = 0.54), and GDF-15 and cystatin C (r = 0.51) (Online Table 4). None of the continuous variables showed any sign of non-linear relation with the MACE, and thereafter all were used as linear terms (Online Figure 2).

Incremental prognostic value of biomarkers and risk model development. With the candidate clinical variables, we fitted a CMM which included age, hypertension, previous MI, previous stroke, Killip class, and heart rate as significant predictors of MACE. The CMM achieved a C-statistic of 0.74. The improvement in C-statistics by adding each biomarker to CMM are presented in Figure 2a. NT-proBNP was the most important biomarker with the C-statistic being improved by 0.07 (95% CI 0.03-0.12), followed by hs-cTnT with the reduced improvement in C-statistic (0.03, 95% CI -0.02-0.08). Therefore, NT-proBNP was added to the CMM as a benchmark model.

We then assessed the improvement in discrimination by adding each remaining biomarker to the benchmark model. None of the biomarkers achieved significant and remarkable enhancement in C-statistics beyond the benchmark model. The top ranked biomarker GDF-15 only marginally improved the C-statistic by 0.004 (Figure 2b). In the sensitivity analysis with complete data only, NT-proBNP remained the most prognostic biomarker and no additional biomarkers offered significant improvement of C-statistic once NT-proBNP and clinical variables were included. Thus, the final BIPass risk model included age, hypertension, previous MI, previous stroke, Killip class, heart rate, and NT-proBNP as predictors (Online Figures 3 and 4). The model is represented as a nomogram in Online Figure 5.

Performance of the BIPass risk model. The risk model displayed improved discriminative capability, with a C-statistic of 0.81 (95% CI 0.77-0.85). It significantly

	MACE	No MACE	HR (95% CI)	*p* value
hs-cTnT, ng/L	59.01 (15.63, 668.80)	13.28 (6.52, 55.12)	1.28 (1.19, 1.37)	< 0.001
(*n* = 4030)	(*n* = 190)	(*n* = 3840)		
NT-proBNP, ng/L	1831.00 (362.48, 4141.25)	156.50 (61.29, 567.95)	1.36 (1.31, 1.42)	< 0.001
(*n* = 3788)	(*n* = 178)	(*n* = 3610)		
GDF-15, ng/L	1855.00 (1213.00, 3064.00)	1078.00 (787.08, 1594.75)	1.45 (1.37, 1.54)	< 0.001
(*n* = 4031)	(*n* = 189)	(*n* = 3842)		
Lp-PLA2, ng/mL	123.47 (95.02, 159.61)	125.42 (92.07, 158.44)	1.03 (0.89, 1.18)	0.73
(*n* = 4037)	(*n* = 192)	(*n* = 3845)		
H-FABP, ng/mL	1.48 (0.93, 3.18)	1.%2 (0.67, 1.50)	1.08 (1.03, 1.13)	< 0.001
(*n* = 4017)	(*n* = 193)	2.%2 (*n* = 3824)		
DKK1, ng/L	912.55 (597.44, 1525.75)	721.83 (485.30, 1070.00)	1.31 (1.23, 1.41)	< 0.001
(*n* = 4037)	(*n* = 192)	(*n* = 3845)		
MR-proADM, ng/mL	41.98 (18.10, 94.95)	30.99 (13.10, 74.66)	1.10 (1.03, 1.18)	0.007
(*n* = 4018)	(*n* = 193)	(*n* = 3825)		
Cystatin C, mg/L	1.17 (0.96, 1.46)	1.% 2 (0.88, 1.17)	1.26 (1.20, 1.32)	< 0.001
(*n* = 4034)	(*n* = 193)	2.% 2 (*n* = 3841)		
LDL-C, mmol/L	2.19 (1.66, 2.83)	2.24 (1.77, 2.85)	0.94 (0.80, 1.11)	0.47
(*n* = 4259)	(*n* = 192)	(*n* = 4067)		
Triglycerides, mmol/L	1.29 (0.98, 1.86)	1.37 (1.02, 1.90)	0.98 (0.85, 1.13)	0.79
(*n* = 4256)	(n = 192)	(n = 4064)		
Hemoglobin, g/L	130.00 (115.00, 145.00)	137.00 (128.00, 148.00)	0.66 (0.59, 0.73)	< 0.001
(*n* = 4181)	(*n* = 85)	(*n* = 3996)		
White blood cells, 10^9	7.03 (5.60, 8.63)	6.25 (5.21, 7.57)	1.38 (1.24, 1.54)	< 0.001
(*n* = 4181)	(*n* = 185)	(*n* = 3996)		

***Table 2*: The association of baseline biomarkers with 12-month MACE in the development cohort.**
Data are median (IQR). HR presents as per SD increase HR for each biomarker in the univariate analysis.
CI = confidence interval; DKK1 = dickkopf-related protein 1; GDF-15 = growth differentiation factor 15; H-FABP = heart-type fatty acid binding protein; HR = hazard ratio; hs-cTnT = high-sensitivity cardiac troponin T; LDL-C = low-density lipoprotein cholesterol; Lp-PLA2 = lipoprotein-associated phospholipase A2; MACE = major adverse cardiovascular events; MR-proADM = mid-regional proadrenomedullin; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Subgroups	BIPass risk model	GRACE risk score	TIMI risk score
Age > 65 years (39/681)*	0.76 (0.68, 0.84)	0.73 (0.65, 0.81)	0.65 (0.57, 0.73)
Age ≤ 65 years (18/728)	0.78 (0.68, 0.88)	0.66 (0.54, 0.78)	0.66 (0.56, 0.76)
Biomarker-positive ACS (25/407)	0.77 (0.67, 0.87)	0.72 (0.62, 0.82)	0.68 (0.58, 0.78)
Biomarker-negative ACS** (32/1002)	0.79 (0.71, 0.87)	0.69 (0.59, 0.79)	0.65 (0.55, 0.75)
MI (22/327)	0.77 (0.67, 0.87)	0.71 (0.61, 0.81)	0.67 (0.55, 0.79)
UA with confirmed ischemic ECG changes (19/390)	0.83 (0.75, 0.91)	0.68 (0.56, 0.80)	0.64 (0.52, 0.76)
UA without confirmed ischemic ECG changes (13/612)	0.68 (0.52, 0.84)	0.64 (0.46, 0.82)	0.62 (0.46, 0.78)
Patients with history of diabetes (25/466)	0.74 (0.66, 0.82)	0.70 (0.62, 0.78)	0.63 (0.53, 0.73)
Patients without history of diabetes (25/943)	0.79 (0.69, 0.89)	0.73 (0.63, 0.83)	0.69 (0.59, 0.79)
Patients with previous DAPT (44/824)	0.76 (0.68, 0.84)	0.71 (0.63, 0.79)	0.66 (0.58, 0.74)
Patients without previous DAPT (13/585)	0.85 (0.77, 0.93)	0.77 (0.65, 0.89)	0.73 (0.61, 0.85)
Patients with coronary revascularization (15/568)	0.63 (0.47, 0.79)	0.56 (0.40, 0.72)	0.60 (0.44, 0.76)
Patients without coronary revascularization (42/841)	0.85 (0.81, 0.89)	0.79 (0.73, 0.85)	0.73 (0.65, 0.81)

***Table 3*: C-statistics for the BIPass risk model, GRACE and TIMI risk scores in the subgroups of the validation cohort.**
*Events/sample size in each subgroup are provided. **UA subgroup equals to biomarker-negative ACS.
ACS = acute coronary syndromes; DAPT = dual anti-platelet therapy; ECG = electrocardiogram; MI = myocardial infarction; UA = unstable angina.

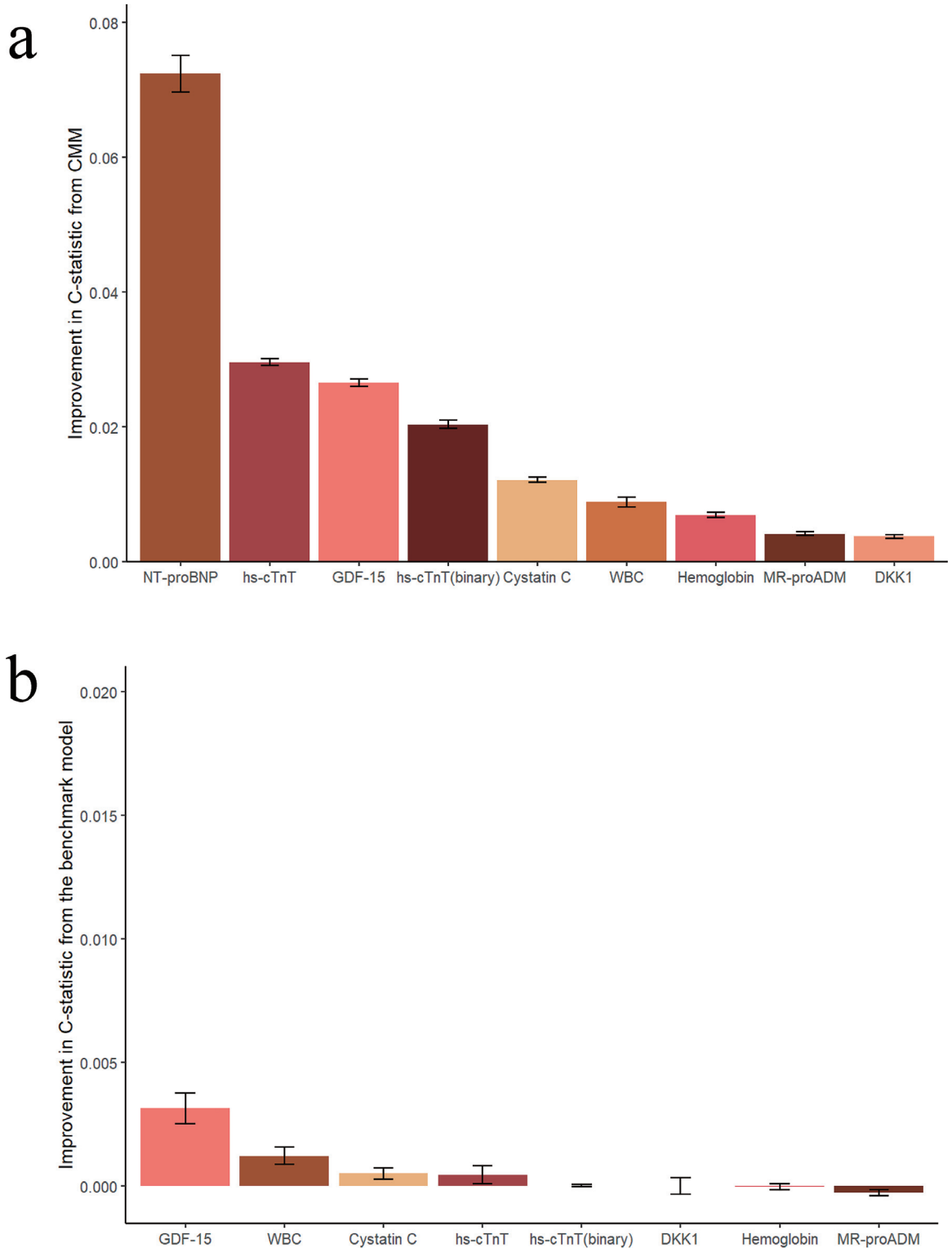

Figure 2. The improvement of discrimination by adding each biomarker to the CMM (a) and the benchmark model (b) in the development cohort.In a, the CMM includes age, hypertension, previous myocardial infarction, stroke, Killip class, and heart rate, with the C-statistic = 0.74. In b, the benchmark model indicates CMM plus NT-proBNP, with the C-statistics = 0.81. Hs-cTnT (binary) indicates that it is dichotomized by a diagnostic cutoff of 14 ng/L. The bars represent the improved C-statistic and 95% CI.CMM = clinical multivariable model; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

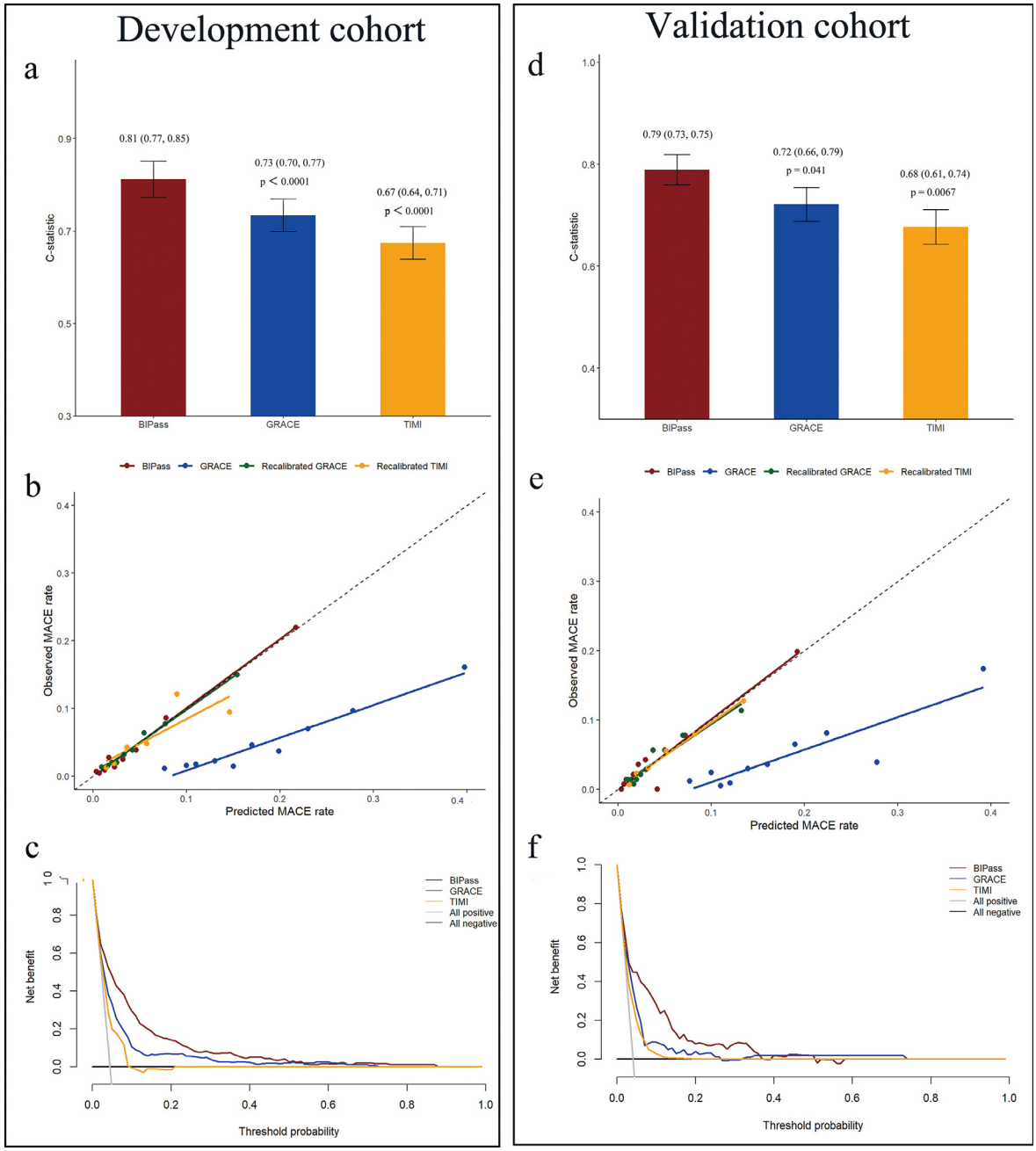

Figure 3. The C-statistics (a,c), calibration plots (b,d) and clinical decision curves (c,f) for the BIPass risk model, GRACE and TIMI risk score in the development and validation cohort.

The bars (a,c) represent the improved C-statistic and 95% CI.

MACE = major adverse cardiovascular events.

outperformed the GRACE risk score (C-statistic 0.73, 95% CI 0.70-0.77; $p < 0.0001$) and TIMI risk score (C-statistic 0.67, 95% CI 0.64-0.71; $p < 0.0001$) (Figure 3a). In the sensitivity analysis with complete data only, BIPass risk model showed the same C-statistic of 0.81. The C-statistics of the BIPass risk model at 0-1 month, 1-6 months, and 6-12 months were also outperformed the GRACE and TIMI risk score at each respective time interval (Online Table 5). The model showed the highest C-statistic for cardiac death, followed by MI and stroke, respectively (Online Table 6). The performance of BIPass risk model was robust in

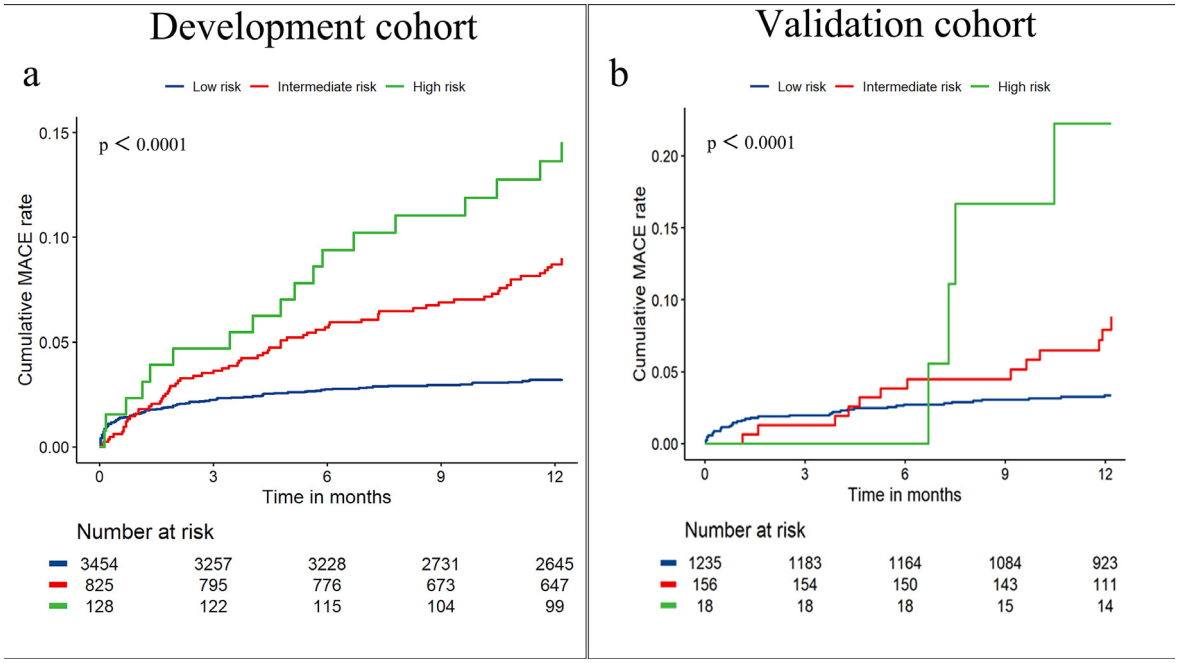

Figure 4. Cumulative rates of MACE by the BIPass risk classes in the development (a) and validation cohort (b).

Patients are classified by their predicted BIPass risk into low (< 5%), intermediate (5-20%), and high (> 20%) groups. The observed MACE cumulative events were plotted for each group. The p value was estimated from the log-rank test.

MACE = major adverse cardiovascular events.

the subgroups with different age categories, history of diabetes, previous DAPT, and revascularization. The C-statistics ranged from 0.79 to 0.82, higher than the GRACE and TIMI risk scores in each subgroup (Online Table 7).

The BIPass risk model showed adequate calibration with comparable observed and predicted MACE risks (GOF chi-square = 9.09, p = 0.33) and each individual event (Online Figure 6). In contrast, GRACE score overestimated the MACE rates across the predicted risk deciles. Recalibration largely improved the prediction of GRACE, however, recalibrated TIMI remained over-estimated the observed MACE risks in the top decile (Figure 3b). In the clinical decision curve analysis, the BIPass risk model provided a larger net benefit across the range of MACE risks, compared with the GRACE and TIMI risk scores (Figure 3c).

Comparison of the cumulative MACE rates between the BIPass predicted risk stratification groups showed significantly increasing event rates from low (3.5%/year), intermediate (9.6%/year) to high-risk (15.9%/year) categories (Figure 4a and Online Table 8). The hazard ratios between the risk classes also demonstrated good separation. Importantly, the BIPass model displayed improved risk stratification within the groups predicted by the GRACE and TIMI risk scores (Online Figure 7).

Validation. The BIPass validation cohort included 1409 patients who were diagnosed as ACS (Figure 1b). Baseline clinical characteristics and biomarkers are provided in Table 1 and Online Table 9. In total, 1386 (98%) patients completed 12-month follow-up and 57 patients experienced MACE (4.4%/year) (Online Table 10).

The BIPass risk model significantly outperformed the GRACE and TIMI risk scores in the overall cohort (BIPass C-statistic 0.79, 95% CI 0.73–0.85; GRACE 0.72, 95% CI 0.66–0.79; TIMI 0.68, 95% CI 0.61-0.74; $p = 0.041$ and $p = 0.0067$, respectively; Figure 3d). The C-statistics of the BIPass risk model were 0.84 (95% CI 0.77–0.91) and 0.81 (95% CI 0.69–0.93) at 1–6 months, and 6–12 months, respectively, both of which outperformed the GRACE and TIMI risk scores. In contrast, the BIPass risk model showed c- statistic of 0.67 (95% CI 0.55–0.79) to predict MACE that happened between 0 and 1 month after hospitalization (Online Table 11). This indicates that the BIPass model may be particularly accurate in predicting MACE in mid-term and long terms, but not as high for predicting early MACE events. The BIPass model showed C-statistic of 0.88 (95% CI 0.81–0.96), 0.77 (95% CI 0.69-0.86), and 0.70 (95% CI 0.55–0.85) for cardiac death, MI and stroke respectively (Online Table 12). The BIPass risk model showed C-statistic of 0.77 (95% CI 0.71–0.83) in the sensitivity analysis with complete data only. The C-statistics of BIPass risk model were consistently higher than the GRACE and TIMI risk scores in subgroups (Table 3).

The BIPass risk model showed excellent calibration (GOF = 9.82, $p = 0.28$) (Figure 3e and Online Figure 6). The clinical decision curve analysis demonstrated that the BIPass risk model was substantially better than the GRACE and TIMI risk scores (Figure 3f). Cumulative MACE rates of the BIPass predicted risk groups demonstrated good separation of observed event rates across the low (3.5%/year), intermediate (8.8%/year) and high-risk (24.1%/year) categories, mainly for events after 6 months (Figure 4b and Online Table 13).

Discussion

In this prospective, multicenter study of Chinese patients with ACS who were admitted to the tertiary and comprehensive hospitals, we develop a BIPass risk model to predict cardiovascular events within the first year after hospitalization. We provide evidence supporting NT-proBNP measured at baseline as the most prognostic biomarker for cardiovascular events, which significantly improves the discriminatory ability by 0.07 from the clinical model. Once NT-proBNP is included in the multivariable risk model with the selected clinical variables, no other biomarkers further improve the discrimination markedly. Therefore, the final BIPass risk model includes NT-proBNP, and clinical variables of age, hypertension, previous MI, previous stroke, Killip class and heart rate. It effectively identifies a gradient risk of cardiovascular events, with adequate calibration, better discrimination and clinical utility characteristics compared to the GRACE and TIMI risk scores. It robustly provides enhanced predictions of MACE over a broad-spectrum of ACS and across clinically important subgroups.

Biomarker predictors and the biological plausibility. NT-proBNP is selected as the most prognostically important biomarker among a wide range of candidate biomarkers in this study. This finding provides evidence supporting with the most recent ESC recommended guidelines.[16] NT-proBNP, reflecting myocardial stretch and increased wall tension, is a well-established prognostic biomarker for cardiovascular events in patients with ACS and stable coronary artery disease.[13,14,22] Recent study has shown that NT-proBNP remained markedly elevated 30 days after ACS.[23] Therefore, NT-proBNP at admission is reliable in the assessment of long-term risk for cardiovascular events. Since NT-proBNP is currently available in most hospitals, we advocate measurement of this biomarker for the prognostic purpose in patients admitted with ACS.

Another biomarker, hs-cTnT, which has been routinely used as a diagnostic instrument in the setting of MI, is not retained in the BIPass risk model. Hs-cTnT is solely released when myocardial necrosis occurs, different from NT-proBNP. Despite hs-cTnT has been the cornerstone of MI diagnosis, evidences regarding its prognostic value have been inconsistent in ACS.[11,24] Furthermore, hs-cTnT has shown to be inferior to NT-proBNP in long-term prognosis.[14,25] In this cohort, we demonstrated that baseline hs-cTnT had less discriminative capability than NT-proBNP in the clinical model, and hs-cTnT showed no significant increase of discrimination once NT-proBNP had been included in the clinical model. Moreover, substituting NT-proBNP with hs-cTnT in the BIPass risk model led to a substantial reduction in discrimination (C-statistic being reduced to 0.77). However, serial measurement of hs-cTnT was not available in our cohort, therefore, the prognostic value of absolute or relative changes of hs-cTnT was not studied.

Our results show that other biomarkers including GDF-15 provides little incremental prognostic values once NT-proBNP has been included in the clinical model, further supporting the guideline recommendations.[16] GDF-15, a member of the transforming growth factor-β cytokine superfamily, reflects distinct pathophysiological pathways contributing to the occurrence of cardiovascular events after ACS.[24] Although previous association studies showed that higher levels of GDF-15 predicted the risk of MACE beyond the established risk factors and biomarkers,[15,26] our study did not show integrating GDF-15 in a risk model which included clinical predictors and NT-proBNP could further improve the discrimination markedly.

Comparison with the GRACE and TIMI risk scores. Among several risk scores for predicting cardiovascular events that have been published in ACS, GRACE and TIMI are the most notable and broadly adopted.[6–8] However, they have not been rigorously assessed for their risk stratification in Chinese ACS patients. In this study, we used TIMI UA/NSTEMI risk score, which had been used in ACS patient population and unspecified suspected ACS (chest pain) population in previous literatures.[27-29] We used GRACE risk score predicting MI and death during 6 months after hospitalization since it was closest to the follow-up duration and outcomes in our study. The results showed that GRACE exhibited higher discrimination than TIMI, which was consistent with previous literature.[27,30]

However, the GRACE score demonstrates only moderate discrimination of cardiovascular risk in our cohort. This may be due to population heterogeneity and/or practice differences. Our cohort had a higher proportion of patients with unstable angina (60% in the development) compared with those reported in other cohorts which ranged from 30 to 50%.[31,32] Several reasons may account for this. First, we enrolled patients in coronary care units, which contain higher proportions of unstable angina patients than those in the coronary intensive care units as recruited in EPICOR cohorts.[31,33] Second, we enrolled patients from the tertiary hospitals, where some patients with chest pain might seek evaluation with coronary angiography. This is typical in Chinese clinical practices, but may increase the likelihood of UA

diagnosis.[32] Accordingly, the observed prevalence of cardiovascular events and distributions of risk factors in our cohort were different from other cohorts.[7,31] For example, the proportion of patients with dyslipidemia was slightly lower in the MACE group (MACE group 8%, No MACE group 12%) in the development cohort, The median concentrations of LDL-C between patients with and without MACE were not significantly different. In addition, temporal changes in ACS treatments over the recent two decades may affect the performance of the GRACE risk score.[34]

It should be noted that when we added NT-proBNP to the GRACE model, the C-statistics were 0.79 (95%CI 0.76–0.83) and 0.80 (95%CI 0.75–0.86) in the development and validation cohorts, respectively. This was similar to those achieved by the BIPass risk model, underlining our findings that NT-proBNP measured at baseline showed the most prognostic capability independent of clinical predictors for both the GRACE score and the derived CMM model in our study. In terms of calibration and clinical utility, the BIPass risk model outperforms the GRACE and TIMI risk scores. In particular, the GRACE risk score tended to overestimate the MACE rate though recalibration could resolve this issue.

Clinical application of the BIPass risk model. With the popularization of web-based tools, an instant and intuitive BIPass risk calculator in portable electronic devices or embedded in an electronic health record system may help physicians obtain the risk estimates at bedside (Risk calculation is provided in the Online results). All variables in the risk model are easily measured in clinical practice. In consideration that Killip class would not be routinely measured for all ACS patients, we generated an alternative risk model in which Killip class was substituted by cardiogenic shock. The resulting model showed comparable discrimination with a C-statistic of 0.81.

Importantly, BIPass risk model showed reasonable predictive performances for patients with older age, different subtypes of ACS, diabetes comorbidity, and DAPT medications. These characteristics make the risk model be generalizable, regardless of these subgroups. The BIPass risk model effectively identifies a gradient risk of cardiovascular events, and thus supporting clinical decisions. For the BIPass predicted high-risk patients whose cardiovascular event rates exceed 20% in the first year, intense antiplatelet therapies and aggressive coronary revascularization are warranted. However, conservative medications may be recommended for patients with the predicted low risk of cardiovascular events. It should be notable that the C-statistic of BIPass is higher for predicting MACE that happened in one month or later, but lower for predicting MACE in less than one month. This is in contrast to the performances of GRACE and TIMI risk scores, both of which show higher discrimination to predict short-term MACE. This indicates that the BIPass risk model may be more accurate in predicting mid-term and long-term MACE, and a complement to GRACE and TIMI in the perspective of time-specific MACE predictions. Further investigations in larger cohorts with longer follow-ups are warranted to confirm this finding and to use the BIPass risk model in concert with GRACE and TIMI to achieve a balance of accurate predictions and easy interpretability.

Limitations

We acknowledge that our study has potential limitations. First, the study population mainly consists of Han Chinese (> 97%). Therefore, it is unknown whether the findings can be extrapolated to other ethnicities in China or other regions of the world. External validation or recalibration of the BIPass risk model in other cohorts are needed to extend its utility. Second, although we evaluate the discriminative performance of the BIPass risk model in various subgroups, including in-hospital revascularization subgroup. We should further incorporate this risk model into prospective trials of ACS therapies to investigate its interaction with treatment effects. Third, BIPass risk model is derived for 12-month MACE. There are differences in the definition of endpoints and follow-up durations between the GRACE and TIMI risk scores and the derived BIPass risk model, which may partially explain the observed difference in prediction performances. Last, the development and validation cohorts were combined in the multiple imputation process, which could lead to biased results. The effect of this limitation can be mitigated as similar findings from the sensitivity analysis using only complete cases were found.

Conclusions

The BIPass risk model, integrating NT-proBNP measured at admission and clinical variables, is useful to predict the risk of 12-month cardiovascular events in Chinese patients with ACS. This model outperformed the GRACE and TIMI risk scores. It offers an improved decision support tool to stratify ACS patients by their risks of cardiovascular events, setting the stage for more personalized treatments.

Contributors

Principal investigator Yuguo Chen and executive committee designed the study.

Jiali Wang, Wei Gao, Guanghui Chen, Ming Chen, and Zhi Wan did literature search and date interpretation.

Wen Zheng, Jingjing Ma, Jiaojiao Pang, Shuo Wang collected the data.

Shuo Wu analyzed the data. Jiali Wang wrote the first draft of the report. Feng Xu, Derek P. Chew, and Yuguo Chen revised the report carefully.

Declaration of interests

The authors declare that there are no competing interests.

Data sharing statement

The coefficient of each predictor is shared in the Supplementary Appendix. All the deidentified participant data for this study, including individual participant data and a data dictionary defining each field in the set will be shared with request.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100479.

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