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Dynamic risk prediction in patients following acute myocardial infarction

Running title: Dynamic risk prediction after AMI

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Abstract

Objectives: The risk of adverse events and prognostic factors are changing in different time phases after acute myocardial infarction (AMI). The incidence of adverse events is considerable in the early period after AMI hospitalization. Therefore, dynamic risk prediction is needed to guide post-discharge management of AMI. This study aimed to develop an dynamic prognostic instrument for patients following AMI.

Design: Prospective cohort.

Setting: 108 hospitals in China.

Participants: A total of 23887 patients after AMI in the China Acute Myocardial Infarction registry were included in this analysis.

Primary outcome measures: All-cause mortality.

Results: In multivariable analyses, age, prior stroke, heart rate, Killip class, left ventricular ejection fraction (LVEF), in-hospital percutaneous coronary intervention (PCI), recurrent myocardial ischemia, recurrent myocardial infarction, heart failure (HF) during hospitalization, antiplatelet therapy, and statins at discharge were independently associated with 30-day mortality. Variables related to mortality between 30 days and 2 years included age, prior renal dysfunction, history of HF, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, HF during hospitalization, HF worsening within 30 days after discharge, antiplatelet therapy, β blocker, and statins use within 30 days after discharge. The inclusion of adverse events and medications significantly improved the predictive performance of models without these indexes (likelihood ratio test P<0.0001). These two sets of predictors were used to establish dynamic prognostic nomograms for predicting survival in patients with AMI. The C indexes of 30-day and 2-year prognostic nomograms were 0.85 (95% confidence interval [CI]: 0.83-0.88) and 0.83 (95% CI: 0.81-0.84) in derivation cohort,

and 0.79 (95% CI: 0.71-0.86) and 0.81 (95% CI: 0.79-0.84) in validation cohort, with satisfying calibration.

Conclusions: We established dynamic prognostic models incorporating adverse event and medications. The nomograms may be useful instruments to help prospective risk assessment and management of AMI.

Trial registration number: NCT01874691.

Keywords: Myocardial infarction, risk prediction, model, prognosis

Strengths and limitations of this study

- We developed and validated dynamic prognostic nomograms, which might help prospective risk evaluation and management of patients after acute myocardial infarction (AMI) hospitalization.
- The study demonstrated that both in-hospital and post-discharge adverse events as well as medications were independently associated with mortality, and provided incremental prognostic value over traditional predictors.
- The predictive performance of dynamic prognostic nomograms would be further improved if included more follow-up variables.
- The dynamic prognostic models should be further validated in independent cohorts.

Introduction

Although in-hospital mortality of acute myocardial infarction (AMI) has been decreased in many countries,[1,2] risk of adverse events remains considerable in survivors after AMI hospitalization.[3] Previous studies have indicated unsatisfying and imbalanced quality of secondary prevention medications in clinical practice,[4,5] which could cause negative impact on prognosis of AMI patients. Individualized risk assessment may aid in decision making of long-term therapeutic strategies for patients after AMI. However, the existing risk prediction tools, which are mainly based on data collected at admission, fail to consider the changing nature of adverse events and medications after AMI hospitalization,[6,7] and therefore may not be appropriate to guide long-term management. Dynamic risk assessment may help improve the quality of long-term management for patients following AMI.

Although several studies sought to forecast mortality dynamically in patients with acute coronary syndromes,[8-11] prognostic components of these models were obtained during hospitalization, without taking follow-up adverse events and medications into consideration. Dynamic prognostic instruments designed to help risk reassessment should include post-discharge information which is associated with outcomes. In this study, we aimed to establish and validate dynamic risk prediction models, visualized by nomograms, which included in-hospital and post-discharge adverse events and medications, to assist in prognostic evaluation and decision-making of secondary prevention strategies in patients following AMI.

Methods

Study population

The data for the present study were from the China Acute Myocardial Infarction (CAMI) registry. The design of the CAMI registry has been described and published elsewhere.[12] Briefly, 108 hospitals from 31 provinces and municipalitis throughout Mainland China were included in this prospective, nationwide, multicenter registry. Consecutive patients with AMI were enrolled in the registry and the final diagnosis of patients must meet the third Universal Definition for Myocardial Infarction (2012).[13] All types of AMI were eligible for the CAMI registry, except type 4a and type 5. Presenting characteristics, medical history, laboratory results, medications, and clinical outcomes were collected according to the ACC/AHA Task Force on clinical data standards and NCDR-ACTION-GWTG element dictionary.

Patients registered in the CAMI registry from January 2013 to September 2014 were included in this study. Those with invalid diagnosis (n=1312), who were transferred out (n=1181) or died during hospitalization (n=1690) were excluded. The remaining population (n=23887) was divided randomly according to 2:1 ratio into derivation (n=15925) and validation (n=7962) cohorts for developing and validating a 30-day risk prediction model. After further excluding patients who died within 30 days after discharge (n=293) and those with missing data on 30-day medication use (n=5391), the remaining derivation (n=12136) and validation (n=6067) cohorts were used for establishing and testing a 2-year risk prediction model (online supplemental figure 1).

Definitions

Standard definitions of adverse events have been described elsewhere in detail.[14] Taking a medication within 30 days means using the medication during this period after discharge without discontinuation.

Follow-up and endpoints

Patients were followed by clinical visits or telephone call at 30 days, 6 months, 12 months, 18 months, and 24 months. Adverse events (such as death, recurrent myocardial infarction, and heart failure worsening) and medications at follow-up time points were collected by trained cardiologists or cardiovascular fellows. The primary endpoints of this analysis were all-cause mortality within 30 days after AMI hospitalization (for establishing 30-day risk prediction model) and mortality between 30 days and 2 years (for establishing 2-year risk prediction model).

Statistical analysis

Categorical variables were summarized as frequencies and percentages, and compared by chi-square or Fisher exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation or medians (interquartile range) according to data distributions, and compared by student t or nonparametric test. Kaplan-Meier curve and density plots were used to depict the changing nature of risk after AMI hospitalization.

The derivation cohort was used to screen predictors of 30-day mortality and mortality between 30 days and 2 years. The associations between variables, including age, sex, body mass index (BMI), diabetes, hypertension, hyperlipidemia, smoking, prior angina pectoris, prior myocardial infarction, prior heart failure, prior stroke, prior peripheral artery disease, prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), prior renal dysfunction, chronic obstructive pulmonary disease, symptom onset to admission time, heart rate, systolic blood pressure, Killip class, cardiac arrest at admission, diagnosis, anterior wall involvement, creatinine clearance, hemoglobin, leukocyte count, left ventricular ejection fraction (LVEF), in-hospital PCI, in-hospital CABG, heart failure, recurrent

myocardial ischemia, recurrent myocardial infarction, stroke, other bleeding events (bleeding events not including cerebral heamorrhage) during hospitalization, antiplatelet therapy at discharge, statins at discharge, β blockers at discharge, and angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) at discharge, and 30-day mortality were first assessed in univariable Cox regression models. For obtaining prognostic factors of mortality between 30 days and 2 years, the associations of adverse events within 30 days (recurrent myocardial infarction and heart failure worsening) and 30-day medications (antiplatelet therapy, statins, β blockers, and ACEI/ARB) with mortality were also assessed in univariable Cox models besides variables mentioned previously. Subsequently, the least absolute shrinkage and selection operator (LASSO) method was adopted to select predictors of short-term and long-term mortality respectively from variables with $P \leq 0.1$ in univariable analysis. The selected predictors were used to establish dynamic risk prediction models by multivariable Cox regression model. The relative importance of these variables was ranked according to the proportion of explainable log-likelihood ratio χ^2 statistics.

To analyze the incremental prognostic value of adverse events and medications over traditional predictive indexes, we compared the predictive performance between models with or without adverse events and medications using C index, net reclassification index (NRI), integrated discrimination improvement index (IDI), likelihood ratio test, and Bayesian information criteria (BIC). The clinical utilities of models were compared by decision curve analysis. Predictive performance was also compared between 30-day risk model or 2-year risk model and the Global Registry of Acute Coronary Events (GRACE) risk score to further analyze the additional value of the dynamic models beyond existing prognostic tool.

Two prognostic nomograms, which could make complex predictive formulas friendly to use in clinical practice, were constructed based on the regression coefficients of predictors for mortality using the “rms” package of R software. Discrimination and calibration of the

nomograms were assessed by C index and calibration curves presenting the relationship between observed and predicted survival probabilities in both derivation and validation cohorts. Predictive performance of models was also evaluated in subgroups of patients according to age, sex, diabetes, AMI classification, and in-hospital PCI.

Before multivariable analysis, we calculated variance inflation factor to examine multicollinearity issue. Multiple imputation was used to generate 5 datasets without missing values. The LASSO method was performed in each dataset. Only variables selected by LASSO method in all 5 datasets were included in final dynamic prognostic models. Results of Cox regression models were reported as hazard ratios (HR) with 95% confidence intervals (CI). A two-tailed $P<0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and public involvement

Patients or the public were not involved directly in the design, conduct, reporting or dissemination plans of our research.

Results

Baseline characteristics, medications, and outcomes of derivation and validation cohorts were summarized in table 1 and online supplemental table 1. Variables were comparable between derivation and validation cohorts except β blockers at discharge. Rates of 30-day mortality among hospital survivors in derivation and validation cohorts were 1.2% (190/15925 patients) and 1.3% (103/7962 patients), respectively. Rates of mortality between 30 days and 2 years

were 6.1% (740/12136 patients) and 5.7% (345/6067 patients). The Kaplan-Meier curve and density plots showed the changing risk of death and recurrent myocardial infarction within 2 years after AMI hospitalization (online supplemental figure 2 and 3).

Predictors of 30-day mortality in patients after AMI

Univariable analysis of the associations between variables and 30-day mortality was presented in online supplemental table 2. In the LASSO-based Cox regression model, age, prior stroke, heart rate, Killip class, LVEF, in-hospital PCI, in-hospital recurrent myocardial ischemia, in-hospital recurrent myocardial infarction, in-hospital heart failure, antiplatelet therapy, and statins at discharge were independently associated with 30-day mortality (online supplemental figure 4 to 8; table 2). The relative importance of these predictors was ranked and shown in online supplemental figure 9.

Predictors of 2-year mortality for 30-day survivors after AMI hospitalization

Univariable analysis of mortality between 30 days and 2 years after AMI hospitalization was shown in online supplemental table 3. In the LASSO-based Cox regression model, age, prior renal dysfunction, history of heart failure, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, in-hospital heart failure, heart failure worsening within 30 days, antiplatelet therapy, β blocker, and statins within 30 days were identified as predictors of mortality (online supplemental figure 10 to 14; table 3). The relative importance of these predictors was ranked and presented in online supplemental figure 15.

Incremental prognostic value of adverse events and medications

The inclusion of in-hospital recurrent myocardial ischemia, in-hospital recurrent myocardial infarction, in-hospital heart failure, antiplatelet therapy, and statins at discharge significantly improved the predictive power of 30-day risk prediction model (table 4; 30-day model 1 vs 30-day model 0, C index, 0.855 [0.830-0.879] vs 0.822 [0.796-0.848]; NRI [95%CI], 0.445 [0.339-0.523], P<0.0001; IDI [95%CI], 0.040 [0.025-0.074], P<0.0001; likelihood ratio test P<0.0001; BIC, 3434.091 vs 3350.882). In the 2-year risk prediction model, heart failure worsening within 30 days, antiplatelet, β blocker, and statins within 30 days also provided additional prognostic value over predictive indexes obtained during hospitalization (table 5). The decision curve analysis further demonstrated better clinical utilities after adding adverse events and medications into 30-day and 2-year risk models (online supplemental figure 16).

Comparisons of prognostic models and GRACE risk score

For predicting 30-day mortality, the 30-day risk prediction model showed significantly better predictive performance than the GRACE risk score (30-day risk model vs GRACE score, C index, 0.855 [0.830-0.879] vs 0.771 [0.740-0.802]; NRI [95%CI], 0.412 [0.307-0.485], P<0.0001; IDI [95%CI], 0.048 [0.032-0.090], P<0.0001; BIC, 3267.271 vs 3402.578). Similarly, when predicting 2-year mortality, the 2-year risk prediction model also performed better than the GRACE risk score (2-year risk model vs GRACE score, C index, 0.825 [0.811-0.839] vs 0.798 [0.783-0.813]; NRI [95%CI], 0.191 [0.147-0.257], P<0.0001; IDI [95%CI], 0.041 [0.031-0.057], P<0.0001; BIC, 12540.559 vs 12697.527). The decision curve analysis further demonstrated better clinical utilities of both 30-day and 2-year risk models than CRACE score (online supplemental figure 17).

Nomograms for dynamic risk prediction

Two nomograms were created by assigning a weighted score based on regression coefficients of each prognostic index for calculating 30-day and 2-year survival probabilities respectively. All observed values of a prognostic index corresponded vertically to points on the top scale. The sum of points for each index was plotted on the "Total points" scale, and corresponded to survival probability at the bottom (figure 1 and 2).

The 30-day prognostic nomogram achieved high discrimination in both derivation and validation cohorts, with C indexes of 0.85 (95% CI: 0.83-0.88) and 0.79 (95% CI: 0.71-0.86) respectively. The calibration curves presenting the concordance between observed and predicted 30-day survival probability in two cohorts also showed satisfying calibration of the model (online supplemental figure 18). In addition, the 30-day prognostic nomogram achieved moderate to high discrimination (C indexes: 0.74 to 0.83) in subsets according to age, sex, diabetes, AMI classification, and PCI (online supplemental table 4).

The C indexes of 2-year prognostic nomogram were 0.83 (95% CI: 0.81-0.84) and 0.81 (95% CI: 0.79-0.84) in derivation and validation cohorts, respectively. The calibration curves demonstrated excellent calibration of the nomogram in both derivation and validation cohorts (online supplemental figure 19). In aforementioned subgroups of patients, the model discrimination was acceptable (C index: 0.66 to 0.83, online supplemental table 5).

Discussion

Using data from a large, prospective, multicenter registry, we screened eleven predictors of 30-day mortality, and fourteen variables, including heart failure worsening and medications within 30 days, related to mortality between 30 days and 2 years in patients after AMI hospitalization. These two sets of predictors were used to develop prognostic nomograms which could predict post-discharge mortality for AMI patients in different time phases. The

nomograms showed satisfying discrimination and calibration in both derivation and validation cohorts. This is a novel dynamic prognostic tool which can serve for prospective risk assessment and guide long-term management of patients after AMI.

A series of risk models have been developed to predict mortality in patients with acute coronary syndromes.[6,7,15] These models mainly included prognostic factors obtained at admission, and provided a fixed estimate of survival probability for a given patient. This working mode of prognostic models was helpful for screening high-risk patients and determining therapeutic strategies after admission. However, the incidence of adverse cardiovascular events remained considerable after in-hospital management of AMI. Accumulating evidence has implied that a larger proportion of adverse events occurred in the early phase after AMI hospitalization,[16] which reflected the changing risk following AMI and highlighted the importance of risk reassessment during follow-up. Although some prognostic models, such as the Global Registry of Acute Coronary Events (GRACE) risk score and dynamic Thrombolysis In Myocardial Infarction (TIMI) risk score, could be used to assess survival at discharge,[6,9] none of them could improve survival estimates during follow-up. Considering the higher risk of adverse events in the early period than that at the late stage after AMI hospitalization (online supplemental figure 2 and 3), we chose 30 days, which was also one of routine follow-up points after AMI hospitalization in clinical practice, as the time point of risk reassessment to establish dynamic risk prediction models.

The first model, which was developed to assess 30-day survival at discharge in patients after AMI, included variables related to patients' demographics, hemodynamics, left ventricular systolic function, treatment, in-hospital adverse events, and medications at discharge. Previous studies have established several prognostic models, such as Platelet glycoprotein IIb/IIIa in Unstable agina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) and Zwolle risk scores,[17,18] to predict 30-day mortality in patients with

acute coronary syndromes. However, these models mainly used patient characteristics, clinical presentations at admission as well as angiographic features as prognostic indexes. The present study showed that recurrent myocardial ischemia, recurrent myocardial infarction, heart failure during AMI hospitalization, antiplatelet therapy, and statins use at discharge were independently associated with short-term mortality after discharge, and provided significantly incremental prognostic information over traditional predictive indexes. Therefore, these adverse events and medications were included in the novel 30-day prognostic model, which might assist in decision-making of post-discharge management.

For the second model assessing 2-year survival in 30-day survivors, we screened new predictors including heart failure worsening within 30 days, antiplatelet therapy, β blocker, and statins use within 30 days after discharge. A prior study showed that mortality rate of patients with an early recurrent myocardial infarction (recurrent myocardial infarcction within 90 days of discharge) was nearly 50% within 5 years.[19] In the present study, we observed that the recurrent myocardial infarction and heart failure worsening within 30 days after discharge were associated with >3-fold and >4.5-fold increase of 2-year mortality risk respectively in univariable analysis, and heart failure worsening, which was included in 2-year prognostic nomogram, was a statistically significant prognostic index in multivariable analysis. To our best knowledge, this is the first prognostic instrument taking follow-up adverse event after AMI into consideration. In addition, although some studies analyzed the prognostic impact of secondary prevention implementation in patients after AMI,[20,21] follow-up medications have not been considered as predictive indexes in risk models for AMI so far. For some patients, not taking optimal medical care within 30 days after discharge could be explained by poor medication adherence after AMI, which was a problem for both developed and developing countries.[21-23] A study found that about 30% of patients with myocardial infarction who underwent PCI in the United States reported suboptimal adherence to prescribed medications

in six weeks after hospitalization.[23] Data from the China PEACE Prospective AMI study also showed a similar percentage of AMI patients did not take medications as prescribed in the first month after discharge.[21] Patients with early medication nonadherence not only suffered a higher risk of early adverse events, but might not comply with long-term secondary prevention measures, and therefore had poorer long-term prognosis. Another situation was that patients were not prescribed with some medications by physicians, due to contraindications or high risk of side effects. However, lack of secondary prevention medications after AMI still meant a higher risk of cardiovascular adverse events in these patients. Indeed, our analysis showed that insufficient use of antiplatelet therapy, β blocker, and statins within 30 days after AMI hospitalization had significant negative impact on 2-year survival. The inclusion of follow-up medications and adverse events improved risk prediction of 2-year prognostic model.

The present study showed that the dynamic prognostic nomograms achieved satisfying discrimination and calibration, and performed well in subgroups of patients according to age, sex, diabetes, AMI classification, and PCI. The clinical usefulness of nomograms was confirmed by decision curve analysis. Prognostic nomograms have been used for risk prediction of cancer and cardiovascular diseases.[24-28] The nomograms in this study could assist in dynamic prognostic evaluation in routine clinical practice. Using the nomogram for prediction of 30-day survival, physicians can identify high-risk patients at discharge. Then, the second nomogram can be used to reassess survival probabilities of 30-day survivors, and may guide decision-making of long-term follow-up intensity and strategies of medical care.

Limitations

Several important limitations in this study should be mentioned. First, besides variables during hospitalization, heart failure worsening and medications within 30 days after discharge were included in the model for prediction of 2-year mortality. However, laboratory or echocardiographic indexes, such as biomarkers of inflammation, N-terminal pro-B-type natriuretic peptide, or LVEF, were not obtained during follow-up. These variables may further improve the predictive performance of dynamic models. Second, although the present study showed the feasibility of assessing 2-year prognosis at 30 days after discharge, risk reassessment was a serial process and should be done repeatedly beyond early phase after AMI hospitalization. Finally, our dynamic models were only validated in the CAMI registry. Further tests for generalizability in external cohorts are needed.

Conclusions

The dynamic risk prediction tool consisted of a short-term prognostic model and a long-term prognostic model for patients following AMI. Taking the changing nature of adverse events and medications into consideration, the models can serve prospective risk stratification and guide post-discharge management of AMI. Dynamic risk prediction may play an important role in therapeutic decision-making and quality improvement of secondary prevention after AMI hospitalization.

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Contributors

HX and YYang contributed significantly to the conception, design, and conduction of this study. JL and CW wrote the initial manuscript. CW, YZ, and YW provided strong support in statistical analysis. JL, CW, XG, JY, XZ, YYe, QD, RF, HS, XY, YZ, YW, HX, and YYang contributed significantly to revisions of manuscript, analysis, and interpretation of data. All authors contributed substantially to this study and approved its submission.

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Competing Interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The CAMI registry conformed to the ethical guidelines of the Declaration of Helsinki, and was approved by the institutional review board central committee at Fuwai Hospital, National Center for Cardiovascular Diseases of China. Written informed consents were given by eligible patients before registration.

Data Availability Statement

Data are available on reasonable request from the corresponding authors.

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Table 1. Baseline characteristics, medications, and outcomes of cohorts for developing and validating 30-day prognostic model

Variables	Derivation cohort (n=15925)	Validation cohort (n=7962)	P value
Demographics			
Age, yrs	62.27±12.36	62.54±12.29	0.1122
Female	3878 (24.4)	1940 (24.4)	0.9809
BMI, kg/m^2	24.13±3.05	24.08±3.04	0.2475
Medical history			
Diabetes	2943 (19.6)	1505 (20.0)	0.4491
Hypertension	7873 (51.2)	3897 (50.8)	0.4970
Hyperlipidemia	1154 (8.5)	569 (8.3)	0.6198
Current smoker	7083 (45.7)	3483 (44.8)	0.2257
Prior angina pectoris	4044 (27.8)	1994 (27.4)	0.4987
Prior myocardial infarction	1083 (7.4)	553 (7.5)	0.7122
Prior heart failure	329 (2.2)	169 (2.3)	0.7723
Prior stroke	1330 (8.8)	711 (9.4)	0.1367
Prior peripheral artery disease	96 (0.6)	46 (0.6)	0.8073
Prior PCI	753 (5.0)	381 (5.1)	0.8669
Prior CABG	56 (0.4)	36 (0.5)	0.2450

Prior renal dysfunction	197 (1.3)	94 (1.3)	0.6985
COPD	279 (1.9)	142 (1.9)	0.8702
Presenting characteristics			
Symptom onset to admission time			0.1515
0-6h	7398 (47.0)	3625 (46.0)	
>6h	8330 (53.0)	4247 (54.0)	
Heart rate, beats/min	77.45±18.07	77.84±18.03	0.1131
Systolic blood pressure	129.48±25.01	129.94±25.26	0.1865
Killip class			0.5017
I	11836 (76.2)	5903 (75.8)	
II-IV	3694 (23.8)	1883 (24.2)	
Cardiac arrest at admission	128 (0.8)	77 (1.0)	0.2092
AMI classification			0.4680
STEMI	12051 (75.7)	5991 (75.2)	
NSTEMI	3874 (24.3)	1971 (24.8)	
Anterior wall involvement	7406 (47.7)	3696 (47.5)	0.8342
Laboratory results			
Creatinine, μmol/L	74.90 (62.00, 90.00)	74.60 (62.00, 90.40)	0.9110
Creatinine clearance, ml/min	83.83 (61.61, 109.00)	83.70 (61.52, 108.71)	0.3404

Hemoglobin, g/L	136.23±21.09	136.07±20.94	0.5897
Leukocyte count, $\times 10^9$/L	10.09±3.69	10.04±3.60	0.4052
LVEF, %	53.84±10.07	53.81±10.08	0.8202
In-hospital treatment			
PCI	8951 (57.9)	4432 (57.2)	0.3550
CABG	127 (0.8)	76 (1.0)	0.2190
Adverse events during hospitalization			
New-onset heart failure	2082 (13.5)	1035 (13.4)	0.8803
Recurrent myocardial ischemia	384 (2.5)	166 (2.2)	0.1124
Recurrent myocardial infarction	61 (0.4)	22 (0.3)	0.1781
Stroke	90 (0.6)	40 (0.5)	0.5349
Other bleeding events	236 (1.5)	121 (1.6)	0.8112
Medications at discharge			
Antiplatelet therapy			0.4017
Dual antiplatelet therapy	13212 (87.6)	6571 (87.1)	
Single antiplatelet therapy	1261 (8.4)	648 (8.6)	
None	603 (4.0)	327 (4.3)	
Statins	13846 (91.8)	6976 (92.4)	0.1115
β blockers	10341 (68.6)	5006 (66.3)	0.0006

ACEI/ARB	8642 (57.3)	4326 (57.3)	0.9937

Values are shown as mean ± standard deviation, median (interquartile range), or number (%) without imputation of missing data. BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2. Multivariable analysis of 30-day mortality in the derivation cohort

	All-cause death	
	Adjusted HR (95% CI)	**P value**
Age (per 1 year increase)	1.035 (1.021, 1.049)	<0.0001
Prior stroke (vs no)	1.560 (1.091-2.231)	0.0148
Heart rate (per 1beat/min increase)	1.006 (1.000-1.012)	0.0497
Killip class Ⅱ-Ⅳ(vs Ⅰ)	1.528 (1.115-2.094)	0.0083
LVEF (per 1% increase)	0.969 (0.955, 0.982)	<0.0001
In-hospital PCI (vs no)	0.441 (0.307, 0.634)	<0.0001
In-hospital recurrent myocardial ischemia (vs no)	1.711 (1.019-2.871)	0.0421
In-hospital recurrent myocardial infarction (vs no)	4.572 (2.121-9.859)	0.0001
In-hospital heart failure (vs no)	2.869 (2.065-3.986)	<0.0001
Antiplatelet therapy at discharge (vs dual antiplatelet therapy)		
Single antiplatelet therapy	0.791 (0.491-1.275)	0.3358
None	2.363 (1.395-4.003)	0.0014
Statins at discharge (vs no)	2.009 (1.258-3.208)	0.0035

LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval.

Table 3. Multivariable analysis of mortality after 30 days in the derivation cohort

	All-cause death	
	Adjusted HR (95% CI)	**P value**
Age (per 1 year increase)	1.052 (1.045-1.060)	<0.0001
Prior renal dysfunction (vs no)	1.539 (1.076-2.201)	0.0181
History of heart failure (vs no)	1.501 (1.160-1.943)	0.0020
STEMI (vs NSTEMI)	0.747 (0.639-0.873)	0.0002
Heart rate (per 1 beat/min increase)	1.008 (1.005-1.011)	<0.0001
Killip class Ⅱ-Ⅳ(vs Ⅰ)	1.330 (1.129-1.566)	0.0006
Hemoglobin (per 1g/L increase)	0.993 (0.990-0.996)	<0.0001
LVEF (per 1% increase)	0.971 (0.964-0.978)	<0.0001
In-hospital PCI (vs no)	0.423 (0.351-0.510)	<0.0001
In-hospital heart failure(vs no)	1.287 (1.085-1.525)	0.0037
Heart failure worsening within 30 days (vs no)	1.675 (1.258-2.229)	0.0004
Antiplatelet therapy within 30 days (vs dual antiplatelet therapy)		
Single antiplatelet therapy	1.107 (0.911-1.345)	0.3084
None	1.430 (1.055-1.937)	0.0211
β blocker within 30 days (vs yes)	1.271 (1.085-1.491)	0.0031
Statins within 30 days (vs yes)	1.191 (0.908-1.561)	0.2075

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval.

Table 4. Comparison of 30-day prognostic models with or without adverse events and medications

	30-day model 0	30-day model 1
C index	0.822 (0.796-0.848)	0.855 (0.830-0.879)
NRI (95%CI)	0.445 (0.339-0.523)	
P value	<0.0001	
IDI (95%CI)	0.040 (0.025-0.074)	
P value	<0.0001	
Likelihood ratio test (P value)	<0.0001	
BIC	3434.091	3350.882

30-days Model 0: age, prior stroke, heart rate, Killip class, LVEF, and in-hospital PCI. 30-day Model 1: age, prior stroke, heart rate, Killip class, LVEF, in-hospital PCI, in-hospital recurrent myocardial ischemia, in-hospital recurrent myocardial infarction, in-hospital heart failure, antiplatelet therapy, and statins at discharge. LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; NRI, net reclassification index; CI, confidence interval; IDI, integrated discrimination improvement index; BIC, Bayesian information criteria.

Table 5. Comparison of 2-year prognostic models with or without adverse events and medications

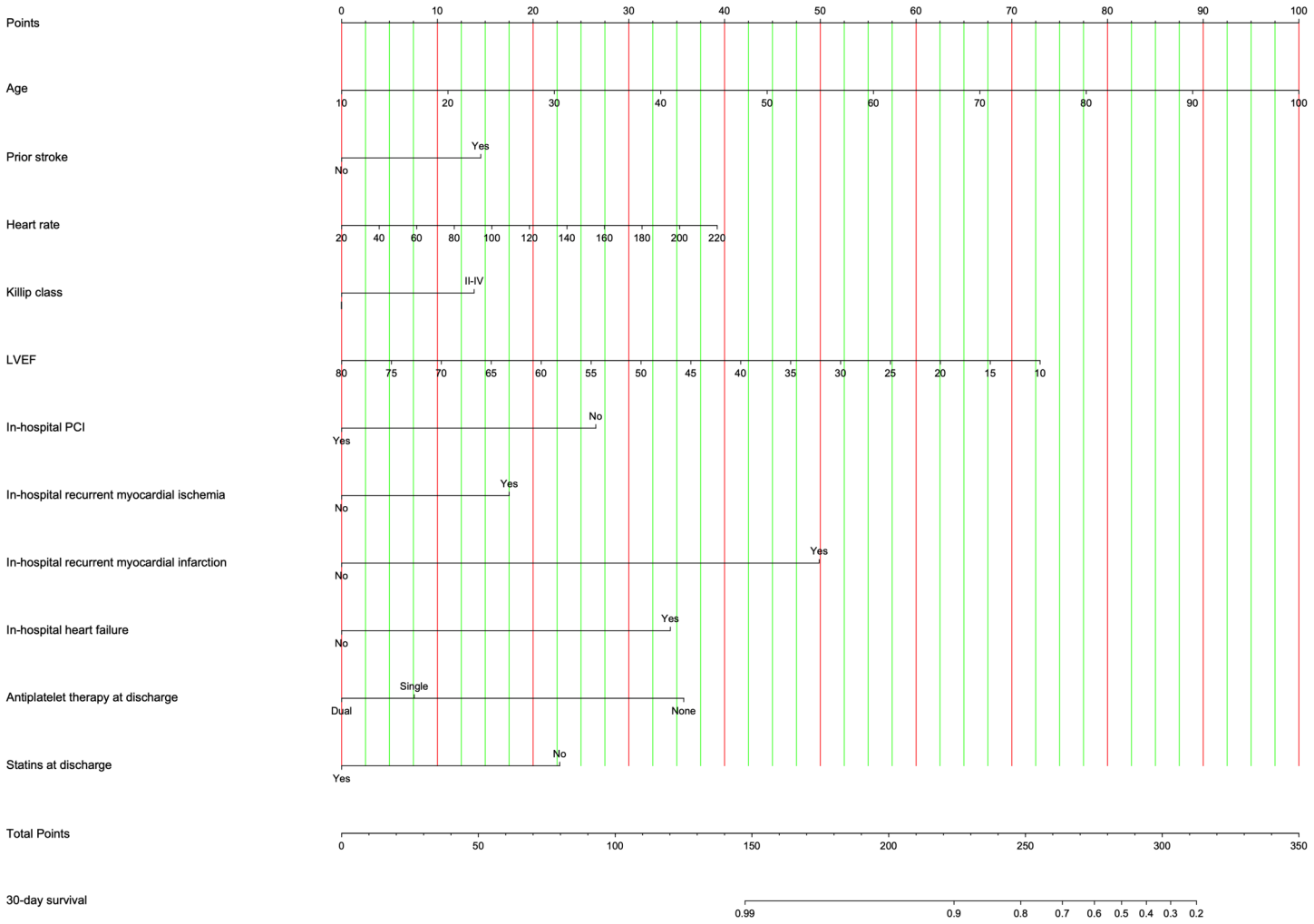
	2-year model 0	2-year model 1
C index	0.822 (0.807-0.836)	0.825 (0.811-0.839)
NRI (95%CI)	0.119 (-0.045-0.176)	
P value	0.126	
IDI (95%CI)	0.008 (0.004-0.017)	
P value	0.007	
Likelihood ratio test (P value)	<0.0001	
BIC	12792.602	12785.706

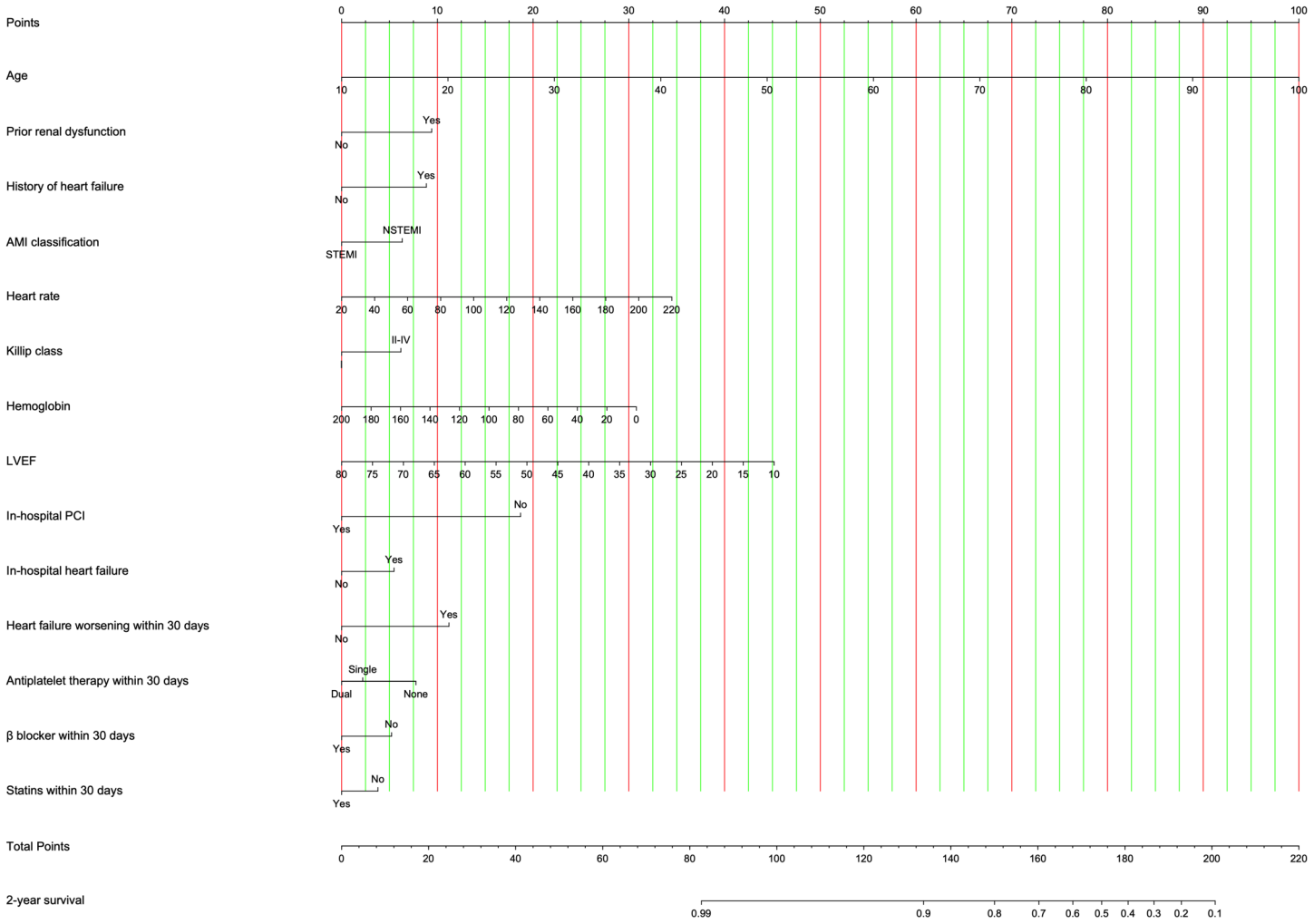
2-year Model 0: age, prior renal dysfunction, prior heart failure, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, and in-hospital heart failure. 2-year Model 1: age, prior renal dysfunction, prior heart failure, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, in-hospital heart failure, heart failure worsening within 30 days, antiplatelet therapy, β blockers, and statins within 30 days. AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; NRI, net reclassification index; CI, confidence interval; IDI, integrated discrimination improvement index; BIC, Bayesian information criteria.

FIGURE LEGENDS

Figure 1. Nomogram for predicting 30-day survival probability. The observed value of a prognostic index was assigned a point by drawing a perpendicular line towards the top scale. The sum of points for each index was plotted on the "Total points" scale, and corresponded to the probability of 30-day survival at the bottom with a vertical line. LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Figure 2. Nomogram for predicting 2-year survival probability. The observed value of a prognostic index was assigned a point by drawing a perpendicular line towards the top scale. The sum of points for each index was plotted on the "Total points" scale, and corresponded to the probability of 2-year survival at the bottom with a vertical line. AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.




Points
Age
Prior renal dysfunction
No
Yes
History of heart failure
No
Yes
AMI classification
STEMI
NSTEMI
Heart rate
Killip class
I
II-IV
Hemoglobin
LVEF
In-hospital PCI
Yes
No
In-hospital heart failure
No
Yes
Heart failure worsening within 30 days
No
Yes
Antiplatelet therapy within 30 days
Dual
Single
None
β blocker within 30 days
Yes
No
Statins within 30 days
Yes
No
Total Points
2-year survival

Supplemental Materials

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I. Supplemental Tables.

Supplemental Table 1. Baseline characteristics, medications, and outcomes of cohorts for developing and validating 2-year prognostic model.

Supplemental Table 2. Univariable analysis of 30-day mortality.

Supplemental Table 3. Univariable analysis of mortality after 30 days.

Supplemental Table 4. Discrimination of 30-day prognostic nomogram in subgroups of patients.

Supplemental Table 5. Discrimination of 2-year prognostic nomogram in subgroups of patients.

II. Supplemental Figures.

Supplemental Figure 1. Flowchart of this study. AMI, acute myocardial infarction.

Supplemental Figure 2. Kaplan-Meier curve for patients after AMI hospitalization. AMI, acute myocardial infarction.

Supplemental Figure 3. Density plots for all-cause death and recurrent myocardial infarction during follow-up. (A) Density plot for all-cause death. (B) Density plot for recurrent myocardial infarction.

Supplemental Figure 4. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 1. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute

shrinkage and selection operator; SE, standard error.

Supplemental Figure 5. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 2. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 6. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 3. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 7. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 4. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 8. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 5. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 9. Relative importance of selected predictors for 30-day mortality. Relative importance of variables selected by LASSO method was ranked according to the proportion of explainable log-likelihood ratio χ^2 statistics. LASSO, least absolute shrinkage and selection operator; Mi, myocardial ischemia; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; HF, heart failure.

Supplemental Figure 10. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 1. (A) The plot showing partial likelihood deviance values

versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 11. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 2. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 12. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 3. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 13. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 4. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 14. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 5. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 15. Relative importance of selected predictors for 2-year mortality. Relative importance of variables selected by LASSO method was ranked according to the proportion of explainable log-likelihood ratio χ^2 statistics. LASSO, least absolute shrinkage and selection operator; HF, heart failure; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Supplemental Figure 16. Comparisons of clinical utilities between models with or without adverse events and medications. The red and green lines represent the assumption that all or none patients at high risk with different thresholds. The lines in the upper right represent the risk prediction models. (A) Comparison of clinical utilities between 30-day model with or without adverse events and medications. (B) Comparison of clinical utilities between 2-year model with or without adverse events and medications.

Supplemental Figure 17. Comparisons of clinical utilities between models and GRACE risk score. The red and green lines represent the assumption that all or none patients at high risk with different thresholds. The lines in the upper right represent the risk prediction models. (A) Comparison of clinical utilities between 30-day model and GRACE risk score. (B) Comparison of clinical utilities between 2-year model and GRACE risk score. GRACE, Global Registry of Acute Coronary Events.

Supplemental Figure 18. Calibration curves of 30-day prognostic nomogram. Calibration curves present the relationship between observed and predicted survival probabilities by 30-day prognostic nomogram in both derivation and validation cohorts. (A) Calibration curve of 30-day prognostic nomogram in derivation cohort. (B) Calibration curve of 30-day prognostic nomogram in validation cohort.

Supplemental Figure 19. Calibration curves of 2-year prognostic nomogram. Calibration curves present the relationship between observed and predicted survival probabilities by 2-year prognostic nomogram in both derivation and validation cohorts. (A) Calibration curve of 2-year prognostic nomogram in derivation cohort. (B) Calibration curve of 2-year prognostic nomogram in validation cohort.

I. Supplemental Tables.

Supplemental Table 1. Baseline characteristics, medications, and outcomes of cohorts for developing and validating 2-year prognostic model

Variables	Derivation cohort (n=12136)	Validation cohort (n=6067)	P value
Demographics			
Age, yrs	62.08±12.28	62.26±12.20	0.3634
Female	2967 (24.4)	1459 (24.0)	0.5531
BMI, kg/m^2	24.12±3.02	24.11±3.01	0.8755
Medical history			
Diabetes	2213 (19.0)	1146 (19.6)	0.2974
Hypertension	6021 (50.6)	3011 (50.7)	0.8935
Hyperlipidemia	760 (7.2)	382 (7.2)	0.9871
Current smoker	5565 (46.3)	2737 (45.5)	0.3511
Prior angina pectoris	3173 (28.0)	1571 (27.8)	0.7999
Prior myocardial infarction	821 (7.2)	420 (7.3)	0.6981
Prior heart failure	243 (2.1)	120 (2.1)	0.9227
Prior stroke	1038 (8.8)	572 (9.7)	0.0503
Prior peripheral artery disease	72 (0.6)	30 (0.5)	0.3967
Prior PCI	562 (4.8)	293 (5.0)	0.5356
Prior CABG	38 (0.3)	25 (0.4)	0.2883
Prior renal dysfunction	130 (1.1)	56 (1.0)	0.3474
COPD	221 (1.9)	114 (2.0)	0.7794
Presenting characteristics			
Symptom onset to admission time			0.1659
0-6h	5725 (47.6)	2798 (46.5)	
>6h	6298 (52.4)	3216 (53.5)	
Heart rate, beats/min	77.37±18.06	77.63±18.04	0.3710
Systolic blood pressure	129.61±25.30	130.00±25.52	0.3250
Killip class			0.8824
I	9163 (76.2)	4589 (76.3)	
II-IV	2859 (23.8)	1424 (23.7)	
Cardiac arrest at admission	95 (0.8)	62 (1.0)	0.1055

AMI classification			0.2540
STEMI	9215 (75.9)	4560 (75.2)	
NSTEMI	2921 (24.1)	1507 (24.8)	
Anterior wall involvement	5743 (47.7)	2843 (47.2)	0.5888
Laboratory results			
Creatinine, μmol/L	74.00 (61.80, 89.10)	73.90 (61.40, 89.60)	0.7455
Creatinine clearance, ml/min	84.53 (62.60, 109.58)	84.92 (63.22, 110.16)	0.9369
Hemoglobin, g/L	136.37±20.82	136.39±20.79	0.9582
Leukocyte count, $\times 10^9$/L	10.09±3.65	10.02±3.52	0.1737
LVEF, %	54.08±10.00	54.01±9.94	0.7200
In-hospital treatment			
In-hospital PCI	6998 (58.4)	3468 (57.7)	0.4281
In-hospital CABG	87 (0.7)	50 (0.8)	0.4388
Adverse events during hospitalization			
New-onset heart failure	1616 (13.5)	805 (13.5)	0.9477
Recurrent myocardial ischemia	281 (2.3)	125 (2.1)	0.2736
Recurrent myocardial infarction	37 (0.3)	18 (0.3)	0.9259
Stroke	65 (0.5)	29 (0.5)	0.6109
Other bleeding events	183 (1.5)	94 (1.6)	0.8199
Medications within 30 days			
Antiplatelet therapy			0.4345
Dual antiplatelet therapy	10518 (86.7)	5287 (87.1)	
Single antiplatelet therapy	1292 (10.6)	610 (10.1)	
None	326 (2.7)	170 (2.8)	
Statins	11486 (94.6)	5736 (94.5)	0.7789
β blockers	8751 (72.1)	4347 (71.6)	0.5171
ACEI/ARB	7221 (59.5)	3591 (59.2)	0.6866

Values are shown as mean ± standard deviation, median (interquartile range), or number (%) without imputation of missing data. BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II

receptor blocker.

Supplemental Table 2. Univariable analysis of 30-day mortality

	Unadjusted HR (95% CI)	P value
Age (per 1 year increase)	1.066 (1.052, 1.080)	<0.0001
Women (vs men)	1.662 (1.233, 2.241)	0.0009
BMI (per 1kg/m^2 increase)	0.893 (0.850, 0.939)	<0.0001
Diabetes (vs no)	1.545 (1.123, 2.126)	0.0075
Hypertension (vs no)	1.289 (0.958, 1.734)	0.0930
Hyperlipidemia (vs no)	0.749 (0.406, 1.384)	0.3547
Current smoking (vs no)	0.406 (0.293, 0.563)	<0.0001
Prior angina pectoris (vs no)	1.324 (0.972, 1.803)	0.0754
Prior myocardial infarction (vs no)	1.177 (0.709, 1.954)	0.5284
Prior heart failure (vs no)	5.078 (3.166, 8.144)	<0.0001
Prior stroke (vs no)	2.627 (1.842, 3.747)	<0.0001
Prior PCI (vs no)	0.814 (0.400, 1.659)	0.5717
Prior CABG (vs no)	—	—
Prior renal dysfunction (vs no)	1.596 (0.587, 4.338)	0.3591
COPD (vs no)	3.208 (1.744, 5.901)	0.0002
Prior peripheral artery disease (vs no)	—	—
Symptom onset to admission time (vs 0-6h)		
>6h	1.947 (1.431, 2.649)	<0.0001
Heart rate (per 1 beat increase)	1.024 (1.018, 1.029)	<0.0001
Systolic blood pressure (per 1mmHg increase)	0.994 (0.988, 1.000)	0.0358
Killip class (vs I)		
II-IV	3.980 (2.990, 5.298)	<0.0001
Cardiac arrest at admission (vs no)	1.921 (0.614, 6.011)	0.2620
NSTEMI (vs STEMI)	1.230 (0.898, 1.686)	0.1977
Anterior wall involvement (vs no)	1.255 (0.943, 1.671)	0.1185
Creatinine clearance (vs >90 ml/min)		
60-90	1.805 (1.222, 2.666)	0.0030
≤60	4.252 (2.985, 6.058)	<0.0001
Hemoglobin (per 1g/L increase)	0.988 (0.983, 0.993)	<0.0001
Leukocyte count (per 10^9/L increase)	1.055 (1.023, 1.088)	0.0006

LVEF (per 1% increase)	0.938 (0.923, 0.952)	<0.0001
In-hospital PCI (vs no)	0.220 (0.157, 0.308)	<0.0001
In-hospital CABG (vs no)	1.277 (0.317, 5.145)	0.7308
New-onset heart failure during hospitalization (vs no)	7.204 (5.414, 9.585)	<0.0001
Recurrent myocardial ischemia during hospitalization (vs no)	6.028 (3.938, 9.228)	<0.0001
Recurrent myocardial infarction during hospitalization (vs no)	13.299 (6.752 26.195)	<0.0001
Stroke during hospitalization (vs no)	2.908 (0.934, 9.052)	0.0654
Other bleeding events during hospitalization (vs no)	4.109 (2.235, 7.558)	<0.0001
Antiplatelet therapy at discharge (vs dual therapy)		
Single antiplatelet therapy	1.344 (0.762, 2.372)	0.3024
none	5.158 (3.468, 7.672)	<0.0001
Statins at discharge (vs no)	3.180 (2.246, 4.502)	<0.0001
β blockers at discharge (vs no)	1.483 (1.105, 1.991)	0.0087
ACEI/ARB at discharge (vs no)	1.481 (1.088, 2.017)	0.0128

BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HR, hazard ratio; CI, confidence interval.

Supplemental Table 3. Univariable analysis of mortality after 30 days

	Unadjusted HR (95% CI)	P value
Age (per 1 year increase)	1.084 (1.076, 1.092)	<0.0001
Women (vs men)	1.947 (1.679, 2.259)	<0.0001
BMI (per 1kg/m^2 increase)	0.895 (0.872, 0.919)	<0.0001
Diabetes (vs no)	1.571 (1.328, 1.857)	<0.0001
Hypertension (vs no)	1.533 (1.321, 1.779)	<0.0001
Hyperlipidemia (vs no)	0.631 (0.443, 0.900)	0.0111
Current smoking (vs no)	0.423 (0.359, 0.498)	<0.0001
Prior angina pectoris (vs no)	1.318 (1.131, 1.536)	0.0004
Prior myocardial infarction (vs no)	2.064 (1.657, 2.570)	<0.0001
Prior heart failure (vs no)	5.964 (4.685, 7.594)	<0.0001
Prior stroke (vs no)	2.013 (1.651, 2.455)	<0.0001
Prior PCI (vs no)	1.122 (0.817, 1.540)	0.4770
Prior CABG (vs no)	1.656 (0.618, 4.433)	0.3156
Prior renal dysfunction (vs no)	4.383 (2.969 6.470)	<0.0001
COPD (vs no)	2.897 (2.076, 4.044)	<0.0001
Prior peripheral artery disease (vs no)	2.273 (1.197, 4.314)	0.0122
Symptom onset to admission time (vs 0-6h)		
>6h	1.497 (1.287, 1.742)	<0.0001
Heart rate (per 1 beat increase)	1.021 (1.018, 1.024)	<0.0001
Systolic blood pressure (per 1mmHg increase)	1.005 (1.002, 1.008)	0.0005
Killip class (vs I)		
II-IV	3.225 (2.792, 3.726)	<0.0001
Cardiac arrest at admission (vs no)	1.068 (0.478, 2.388)	0.8724
NSTEMI (vs STEMI)	2.395 (2.070, 2.771)	<0.0001
Anterior wall involvement (vs no)	1.210 (1.047, 1.398)	0.0096
Creatinine clearance (vs >90 ml/min)		
60-90	1.725 (1.405, 2.119)	<0.0001
≤60	5.193 (4.328, 6.231)	<0.0001
Hemoglobin (per 1g/L increase)	0.980 (0.978, 0.983)	<0.0001
Leukocyte count (per 10^9/L increase)	1.010 (0.990, 1.030)	0.3333

LVEF (per 1% increase)	0.948 (0.941, 0.955)	<0.0001
In-hospital PCI (vs no)	0.207 (0.175, 0.246)	<0.0001
In-hospital CABG (vs no)	0.421 (0.106, 1.674)	0.2184
New-onset heart failure during hospitalization (vs no)	3.418 (2.932, 3.984)	<0.0001
Recurrent myocardial ischemia during hospitalization (vs no)	2.653 (1.949, 3.610)	<0.0001
Recurrent myocardial infarction during hospitalization (vs no)	1.773 (0.659, 4.771)	0.2565
Stroke during hospitalization (vs no)	3.455 (1.991, 5.996)	<0.0001
Other bleeding events during hospitalization (vs no)	2.233 (1.486, 3.356)	0.0001
Recurrent myocardial infarction within 30 days (vs no)	3.032 (1.130-8.134)	0.0276
Heart failure worsening within 30 days (vs no)	4.790 (3.631, 6.319)	<0.001
Antiplatelet therapy within 30 days (vs dual antiplatelet therapy)		
Single antiplatelet therapy	2.147 (1.779, 2.591)	<0.0001
none	4.371 (3.385, 5.643)	<0.0001
Statins within 30 days (vs no)	2.454 (1.960, 3.073)	<0.0001
β blockers within 30 days (vs no)	1.594 (1.374, 1.850)	<0.0001
ACEI/ARB within 30 days (vs no)	1.153 (0.997, 1.333)	0.0546

BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HR, hazard ratio; CI, confidence interval.

Supplemental Table 4. Discrimination of 30-day prognostic nomogram in subgroups of patients

Subgroup	Sample size	C statistic (95% CI)
Age, yrs		
≤75	4766	0.74 (0.65-0.84)
>75	935	0.83 (0.71-0.94)
Sex		
Male	4359	0.79 (0.69-0.88)
Female	1342	0.75 (0.62-0.88)
Diabetes		
Yes	1106	0.81 (0.62-1.00)
No	4431	0.78 (0.70-0.87)
Diagnosis		
STEMI	4302	0.77 (0.68-0.86)
NSTEMI	1399	0.83 (0.72-0.93)
In-hospital PCI		
Yes	3498	0.76 (0.63-0.88)
No	2203	0.76 (0.66-0.85)

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CI, confidence interval.

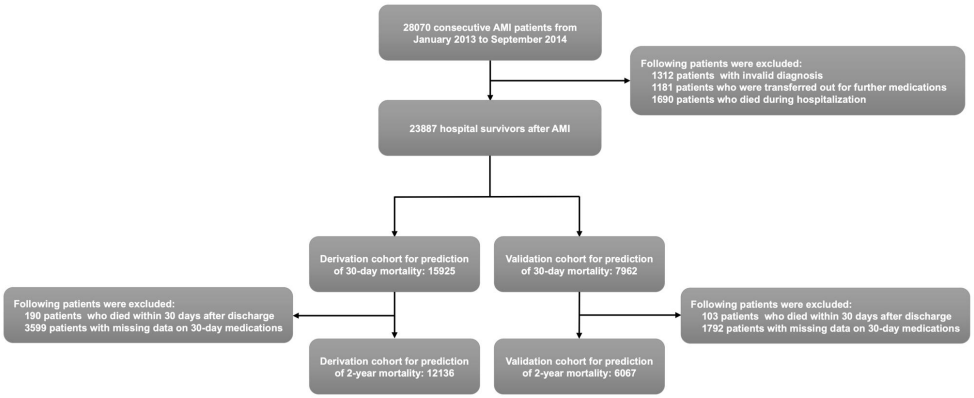
Supplemental Table 5. Discrimination of 2-year prognostic nomogram in subgroups of patients

Subgroup	Sample size	C statistic (95% CI)
Age, yrs		
≤75	3766	0.79 (0.75-0.83)
>75	695	0.66 (0.62-0.71)
Sex		
Male	3412	0.83 (0.80-0.86)
Female	1049	0.75 (0.70-0.80)
Diabetes		
Yes	845	0.81 (0.76-0.86)
No	3496	0.81 (0.78-0.84)
AMI classification		
STEMI	3364	0.81 (0.78-0.84)
NSTEMI	1097	0.81 (0.76-0.85)
In-hospital PCI		
Yes	3104	0.82 (0.78-0.87)
No	1357	0.72 (0.68-0.76)

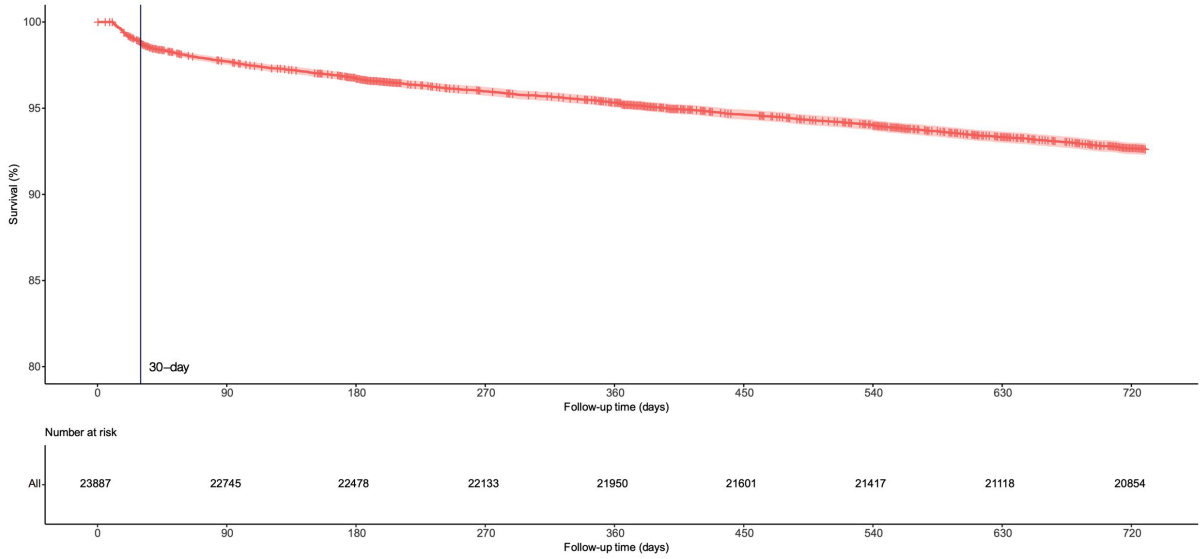
AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CI, confidence interval.

II. Supplemental Figures.

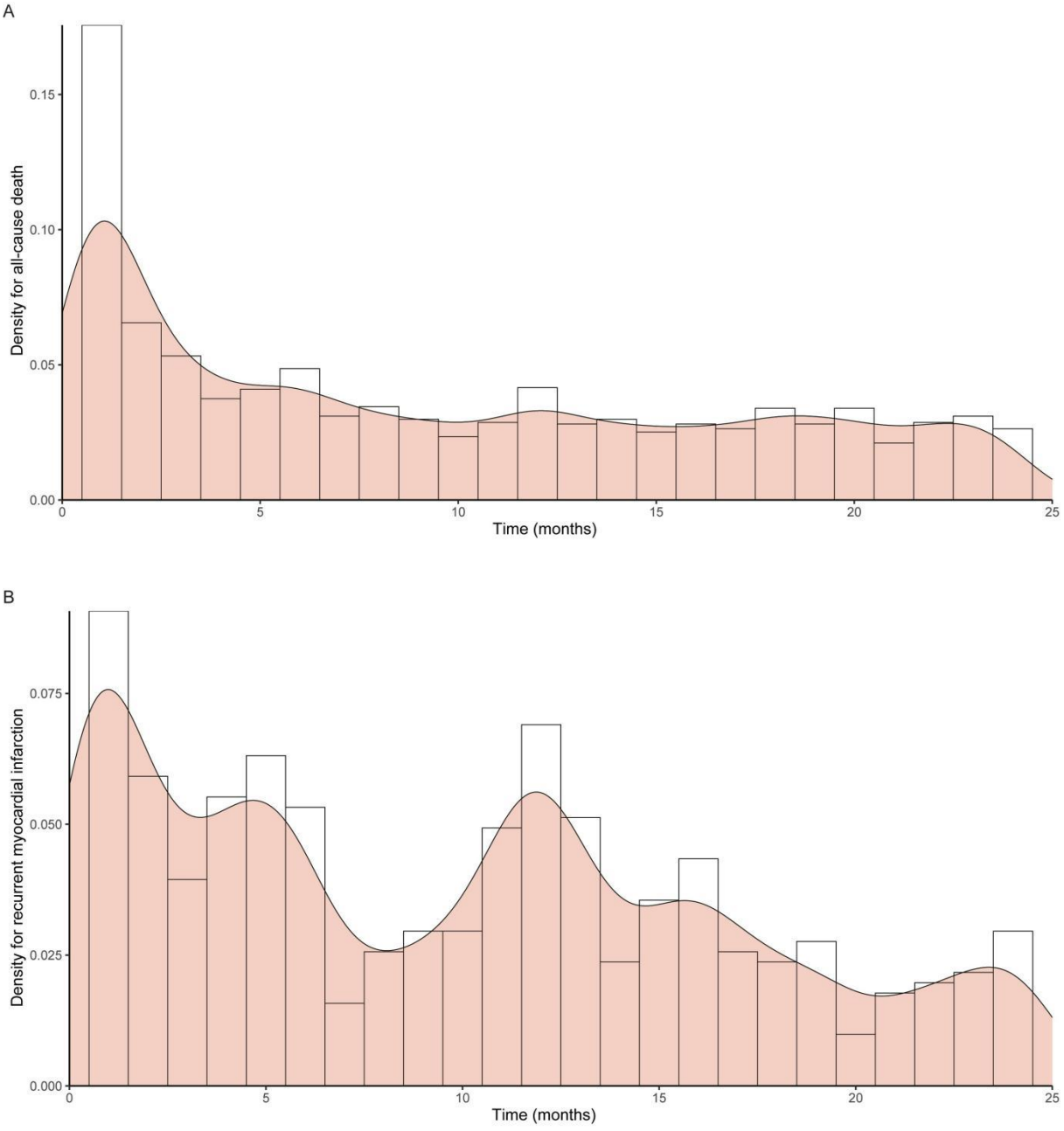
Supplemental Figure 1. Flowchart of this study



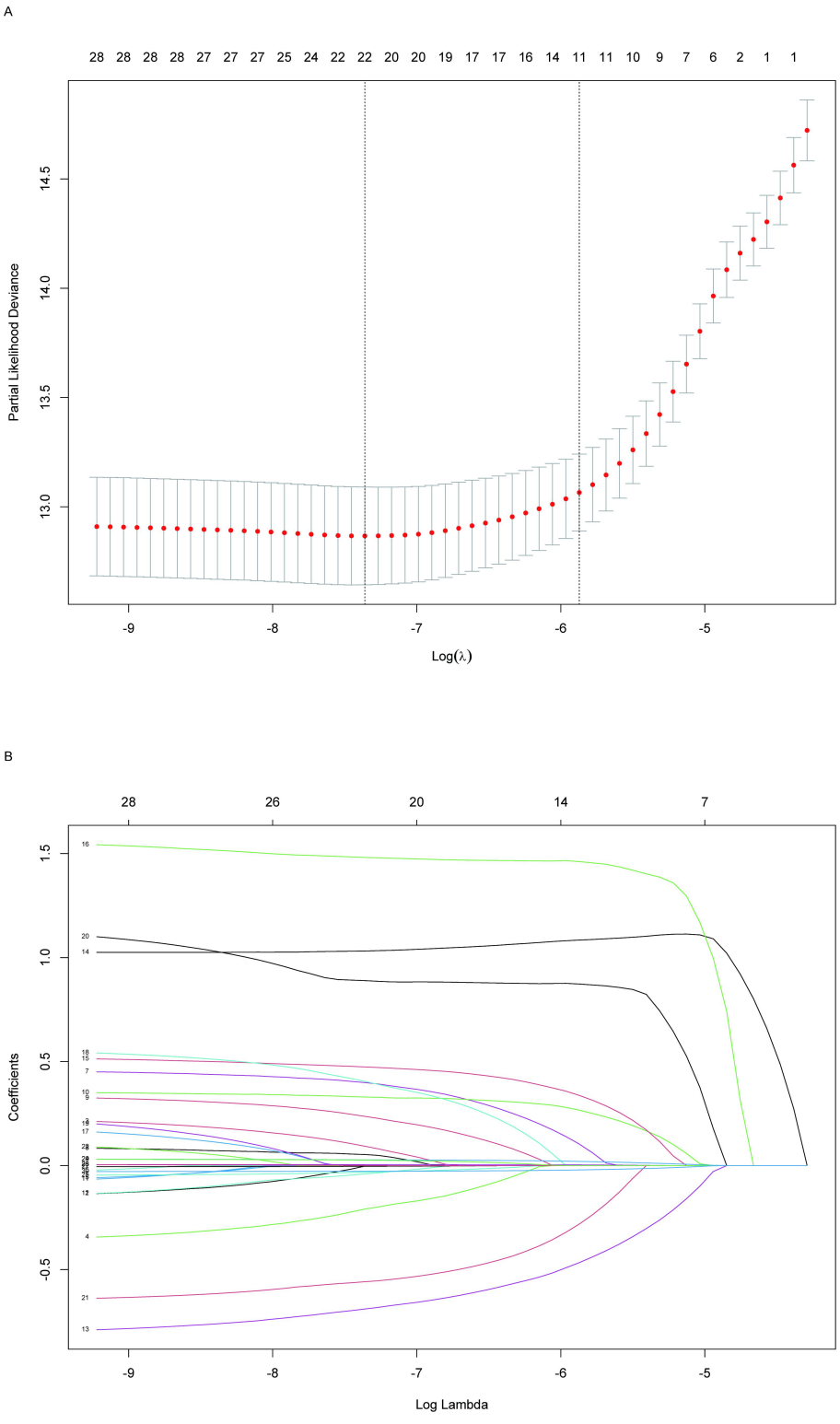
Supplemental Figure 2. Kaplan-Meier curve for patients after AMI hospitalization



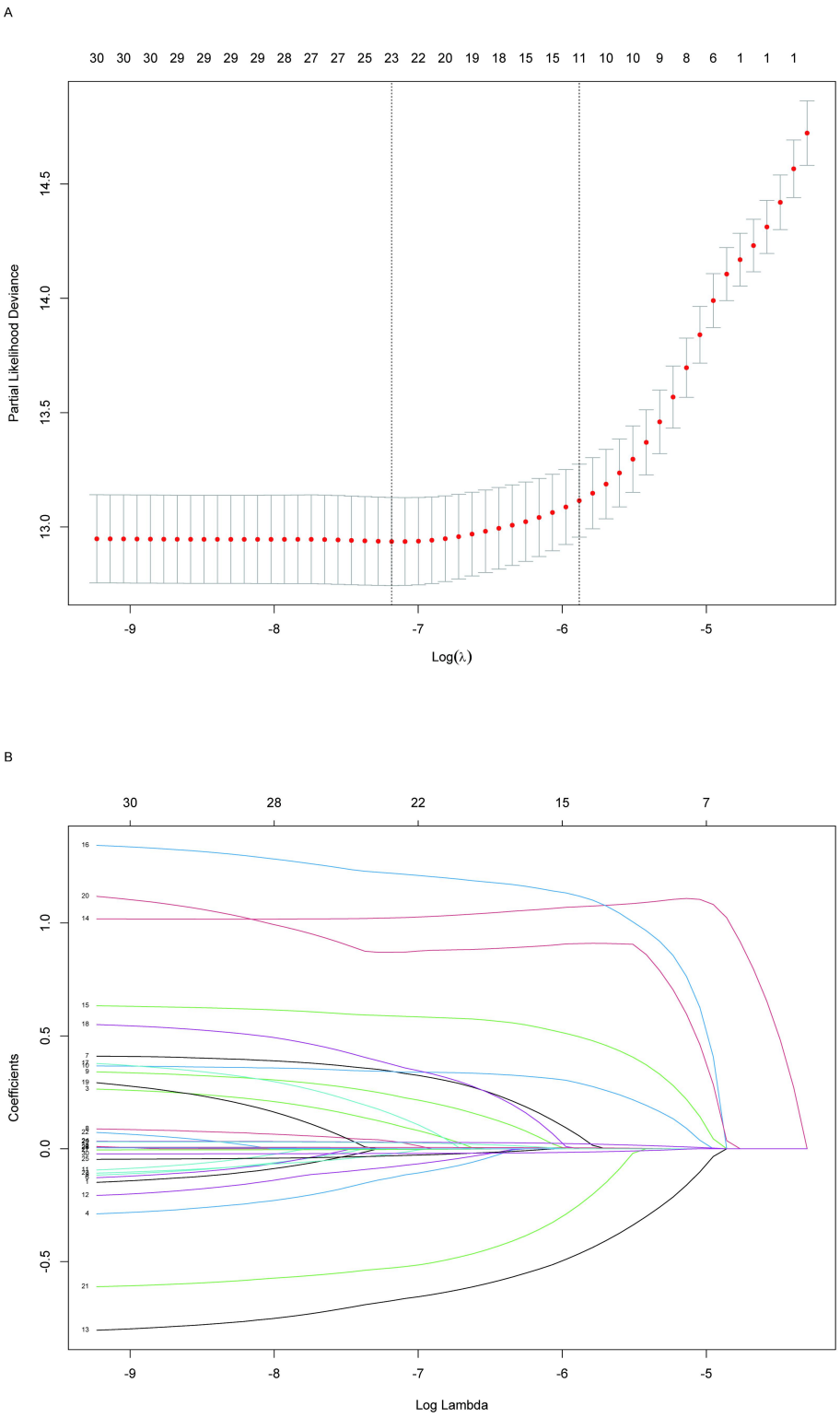
Supplemental Figure 3. Density plots for all-cause death and recurrent myocardial infarction during follow-up



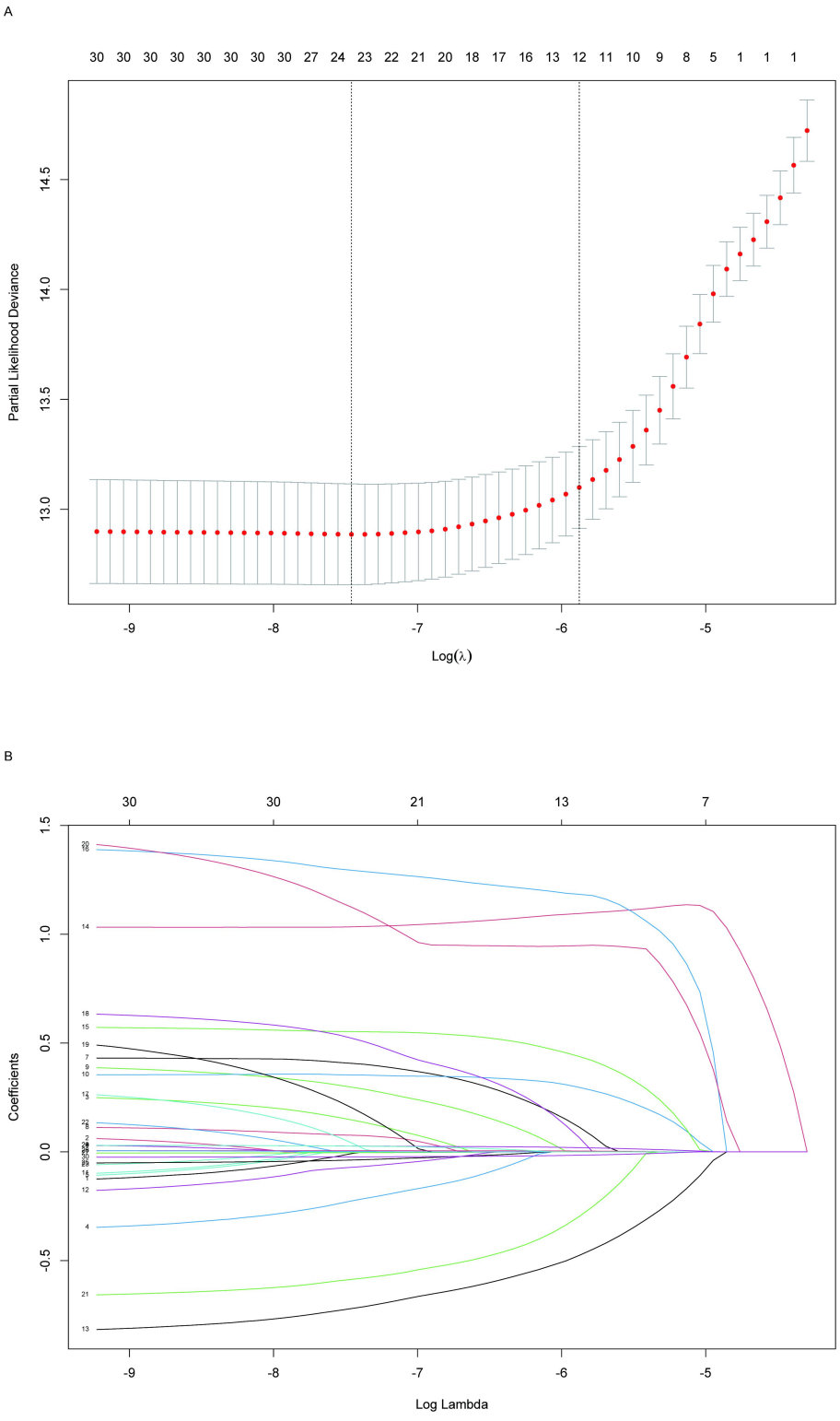
Supplemental Figure 4. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 1



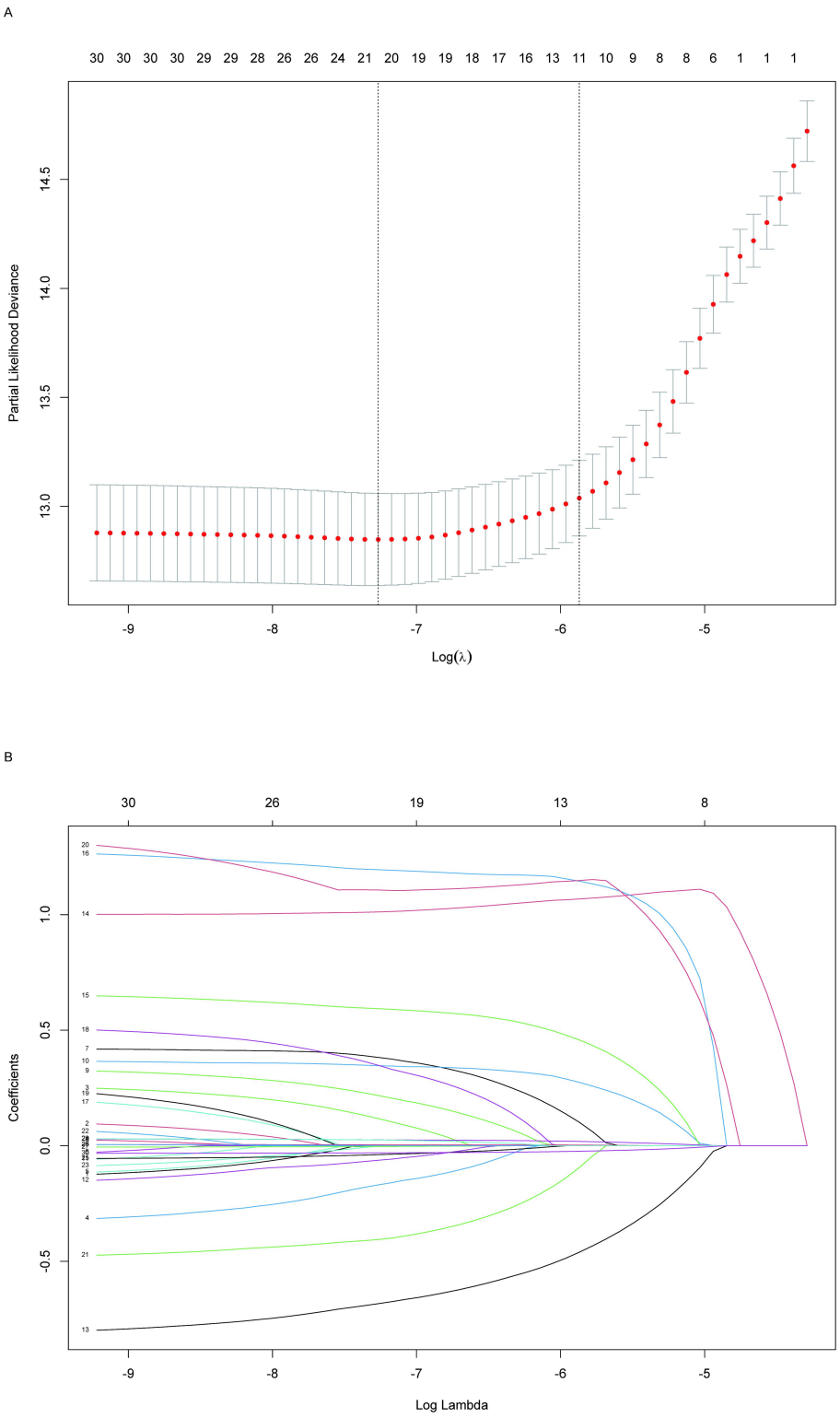
Supplemental Figure 5. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 2



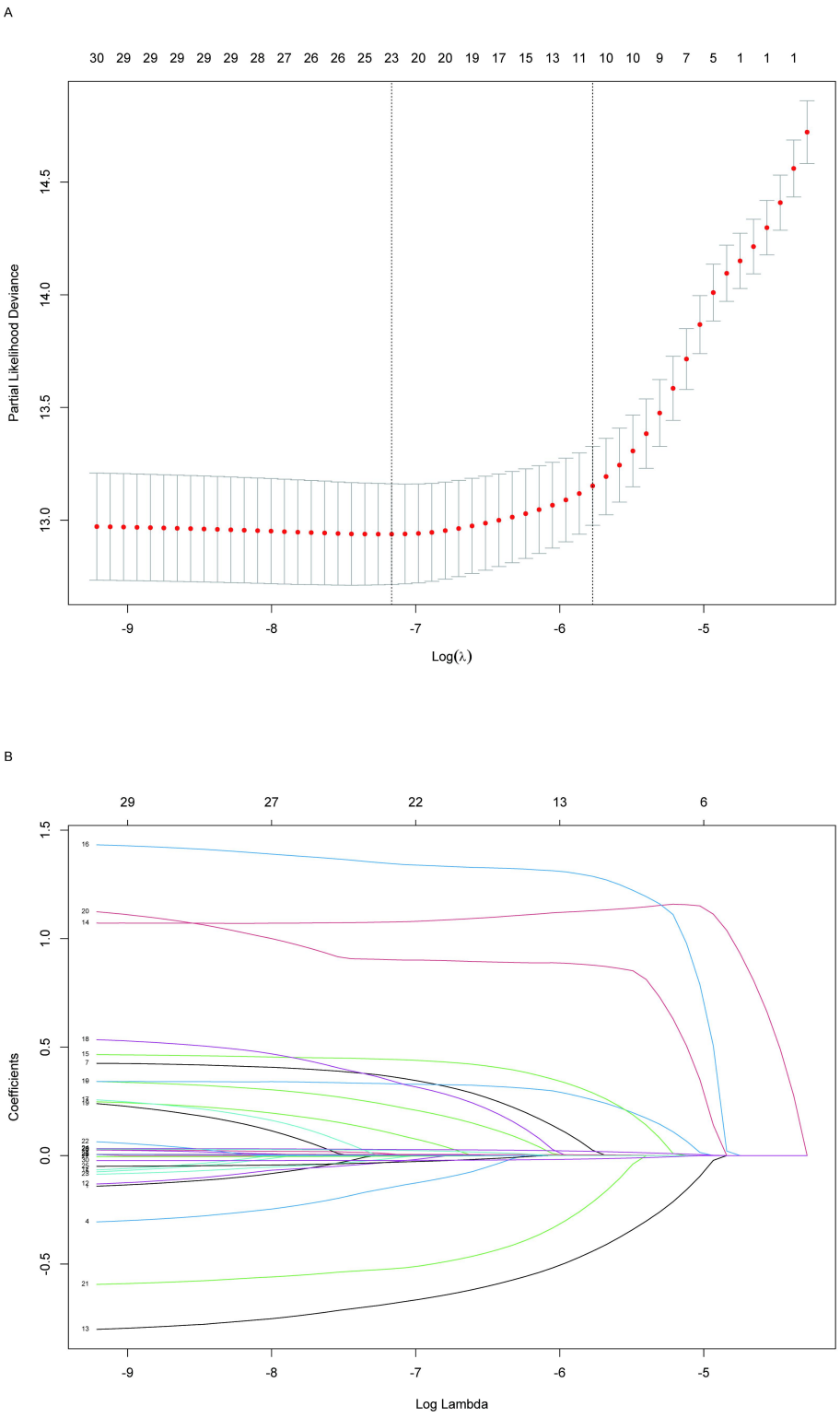
Supplemental Figure 6. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 3



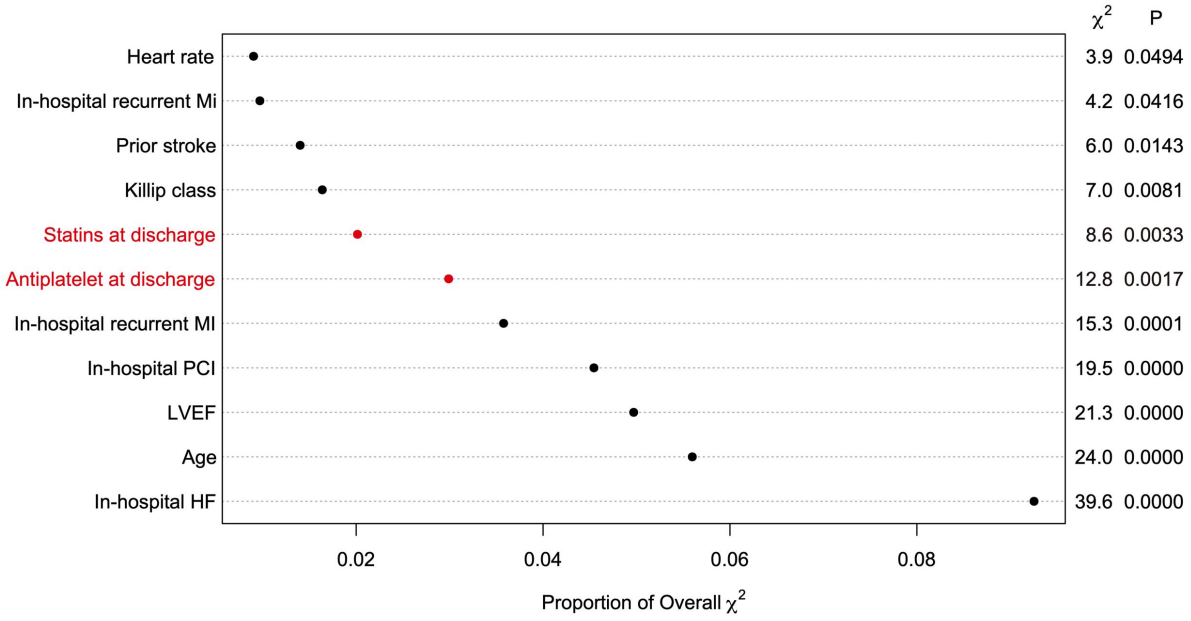
Supplemental Figure 7. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 4



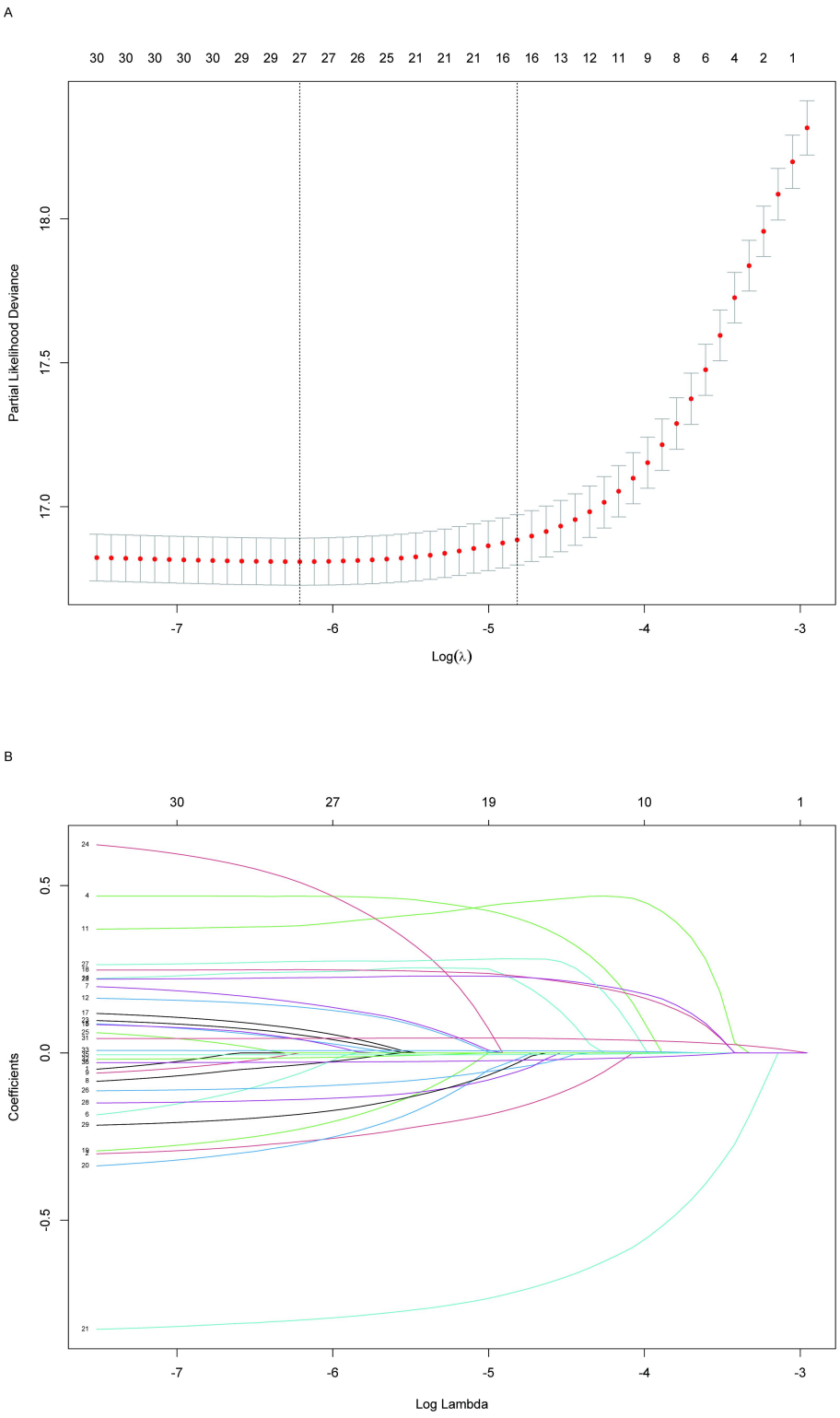
Supplemental Figure 8. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 5



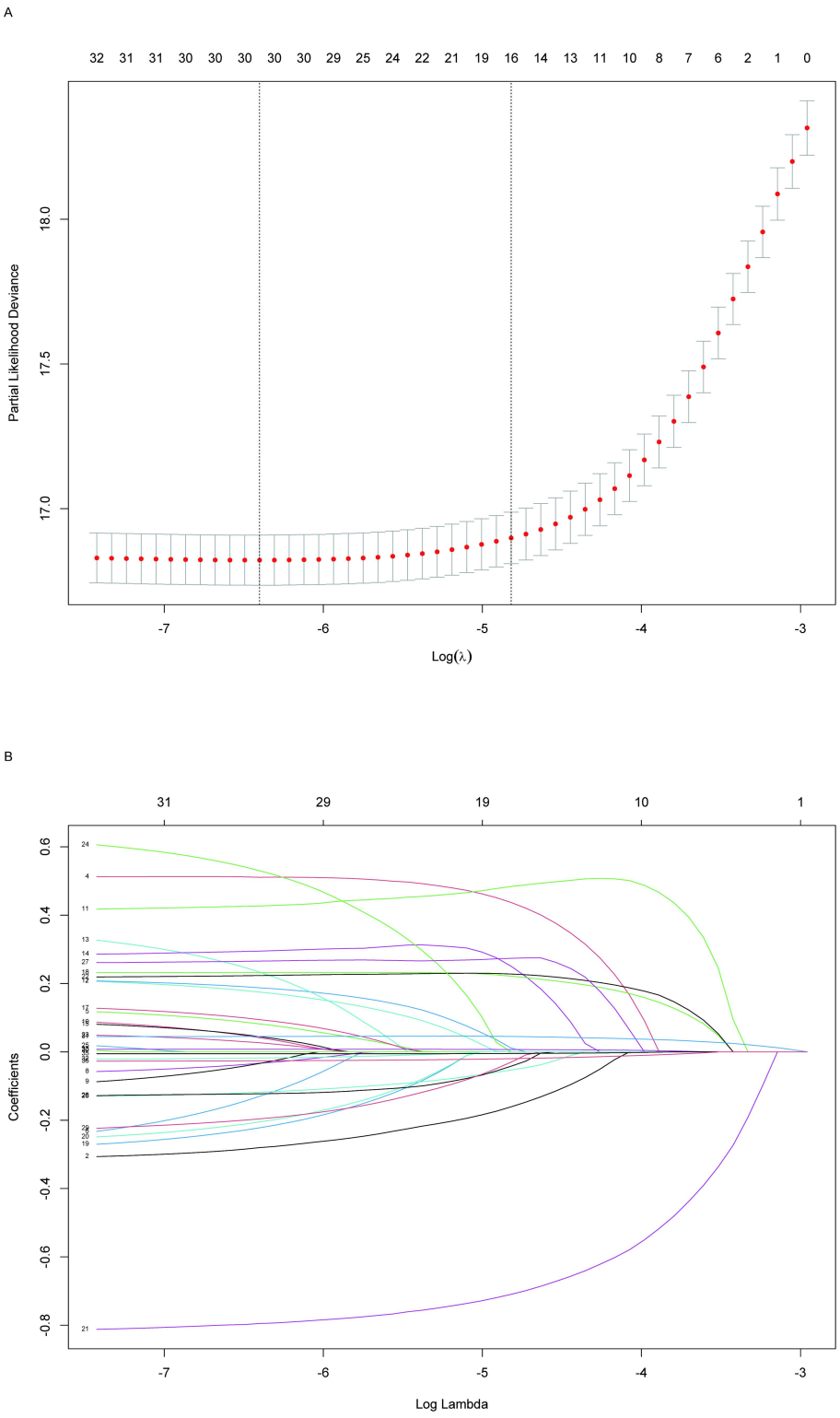
Supplemental Figure 9. Relative importance of selected predictors for 30-day mortality



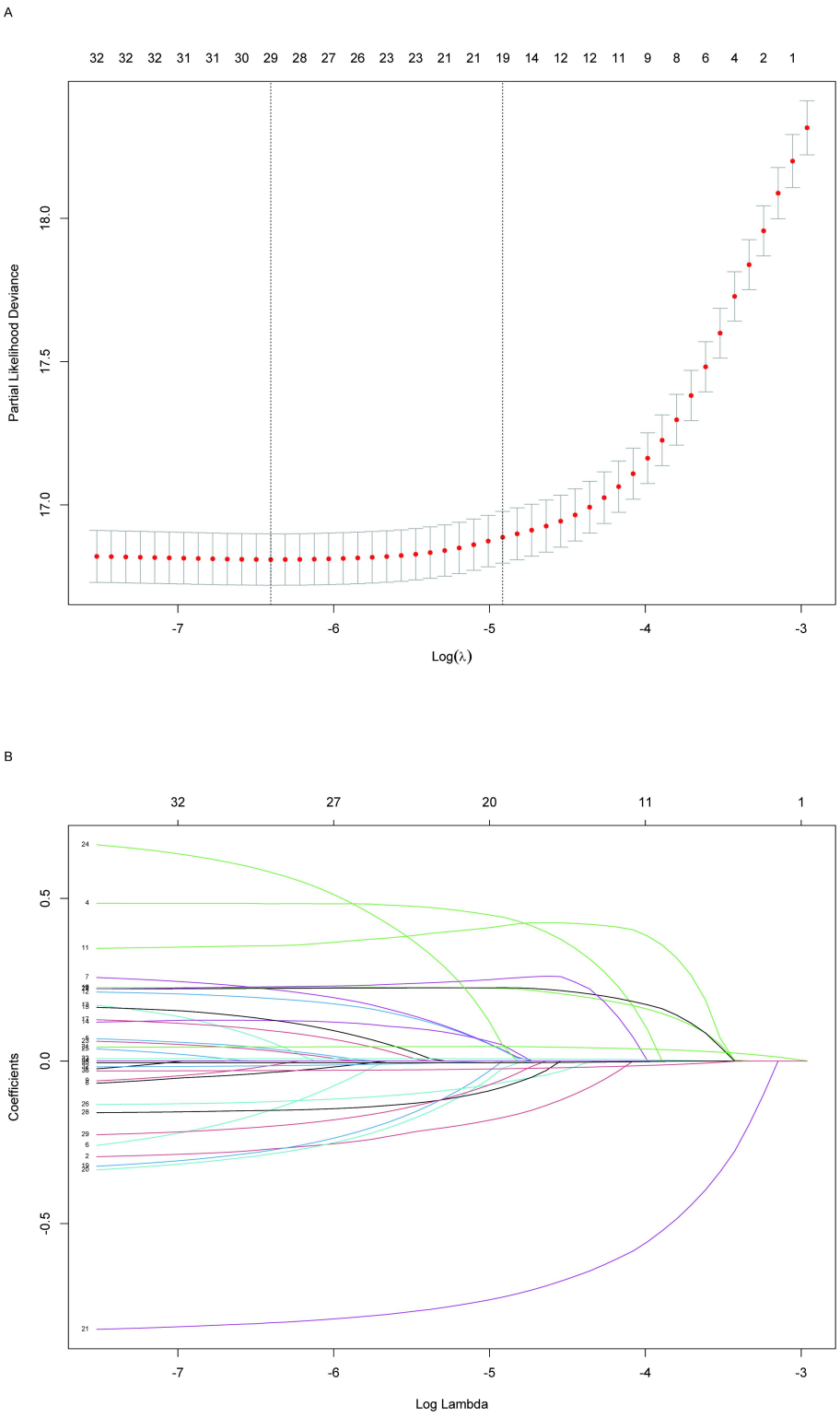
Supplemental Figure 10. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 1



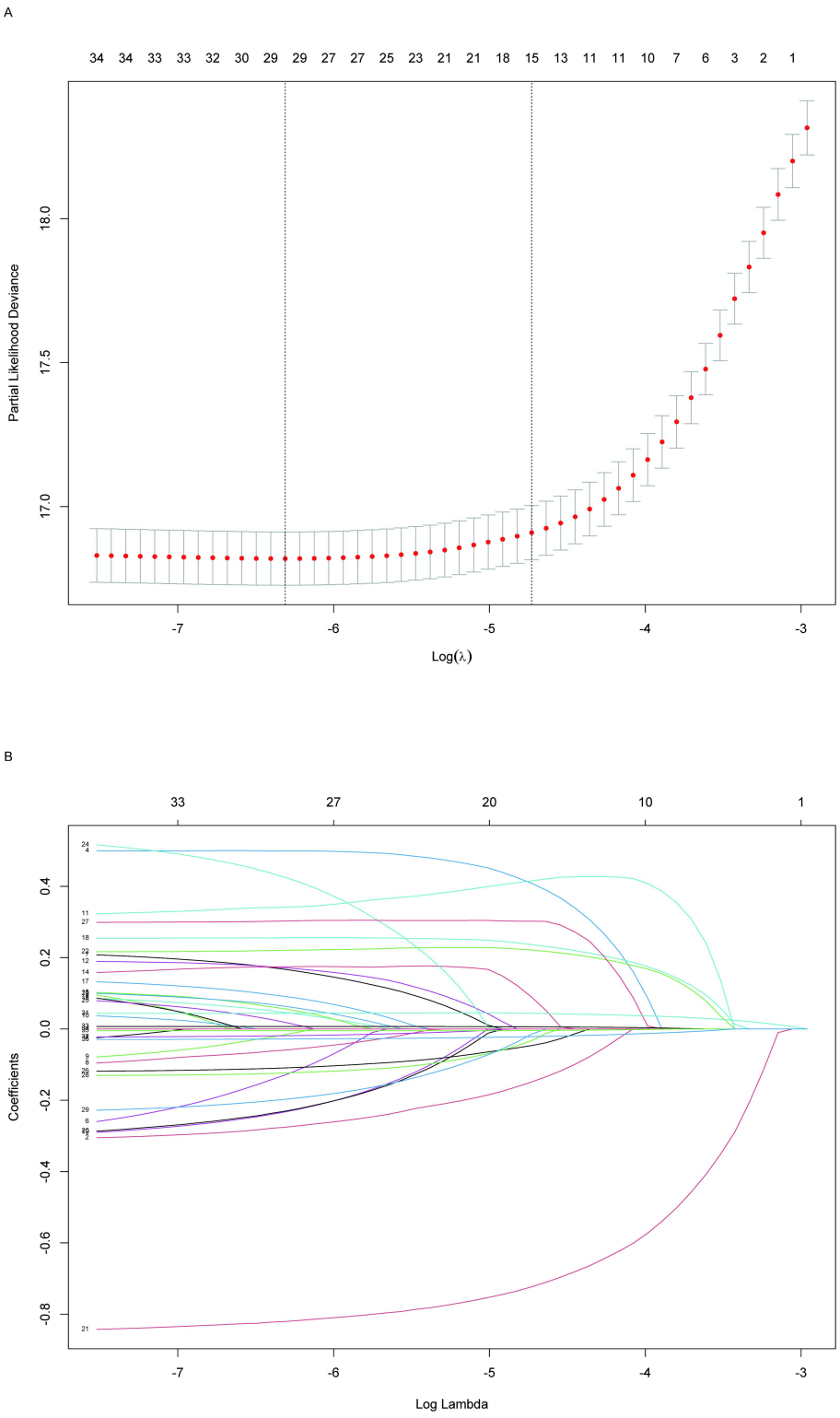
Supplemental Figure 11. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 2



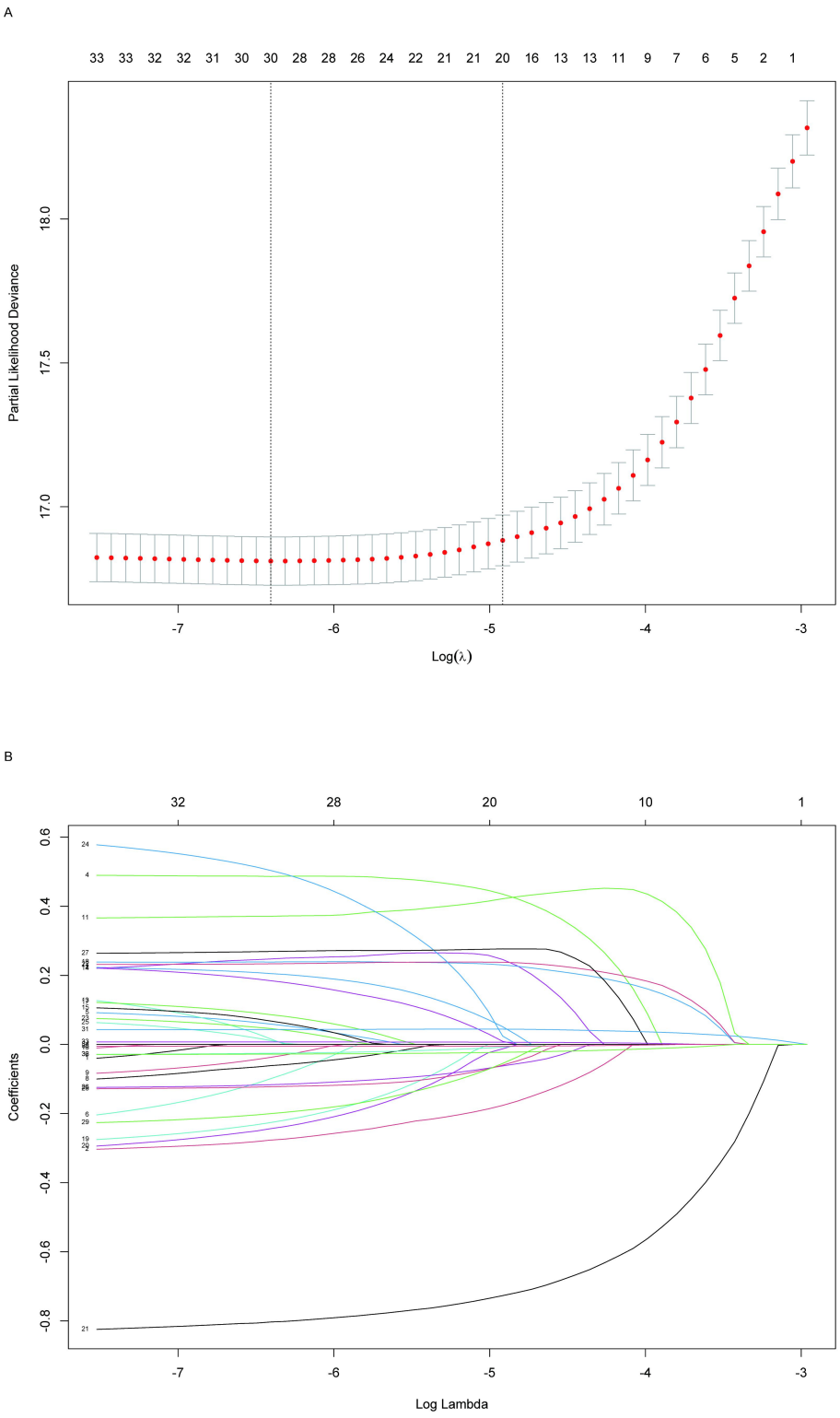
Supplemental Figure 12. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 3



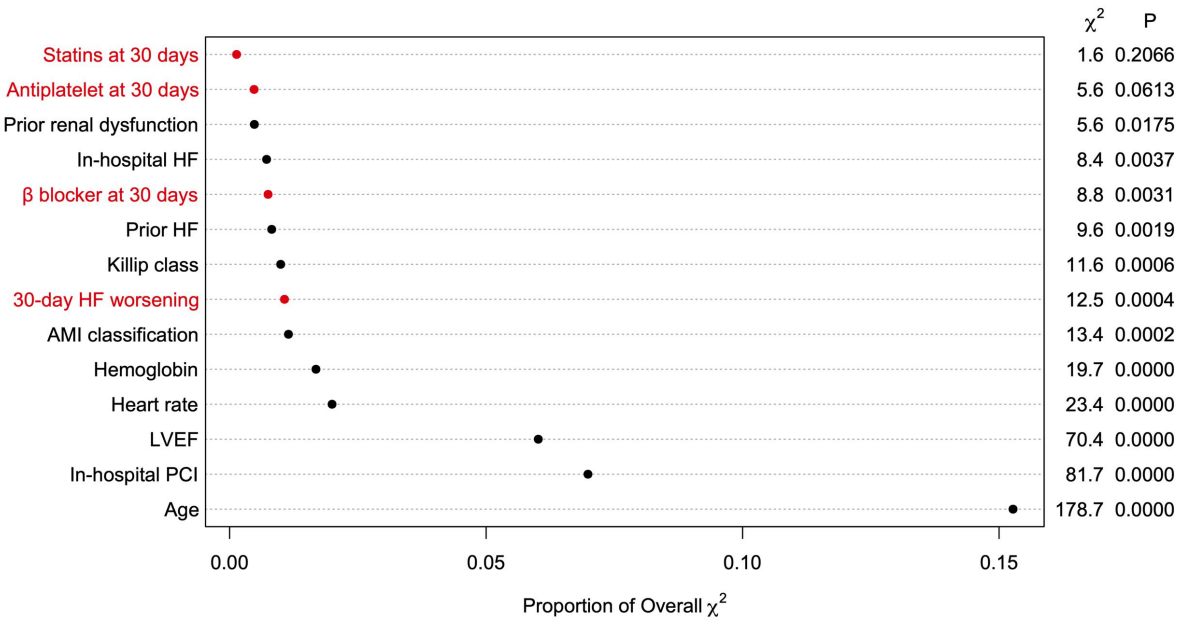
Supplemental Figure 13. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 4



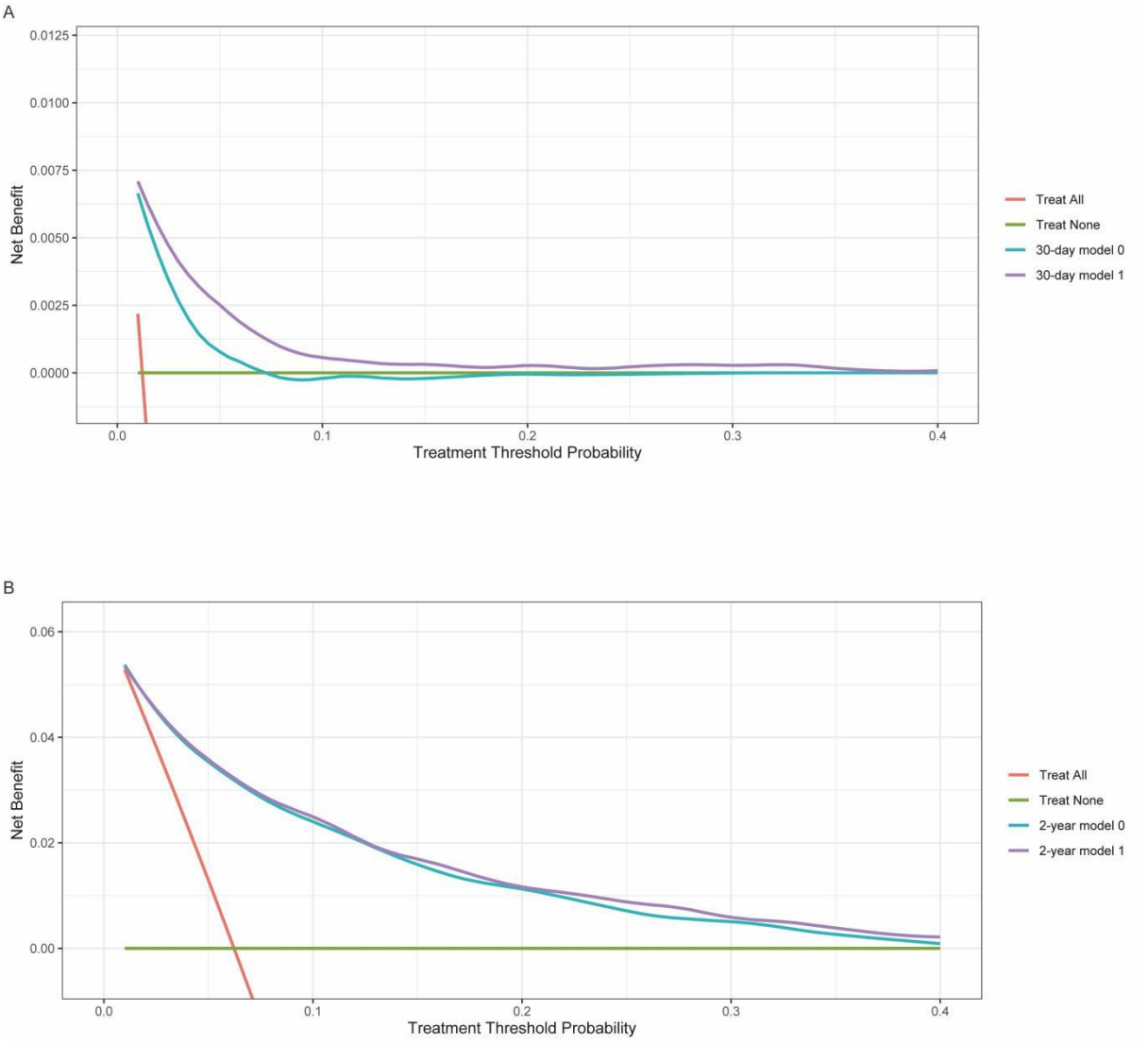
Supplemental Figure 14. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 5



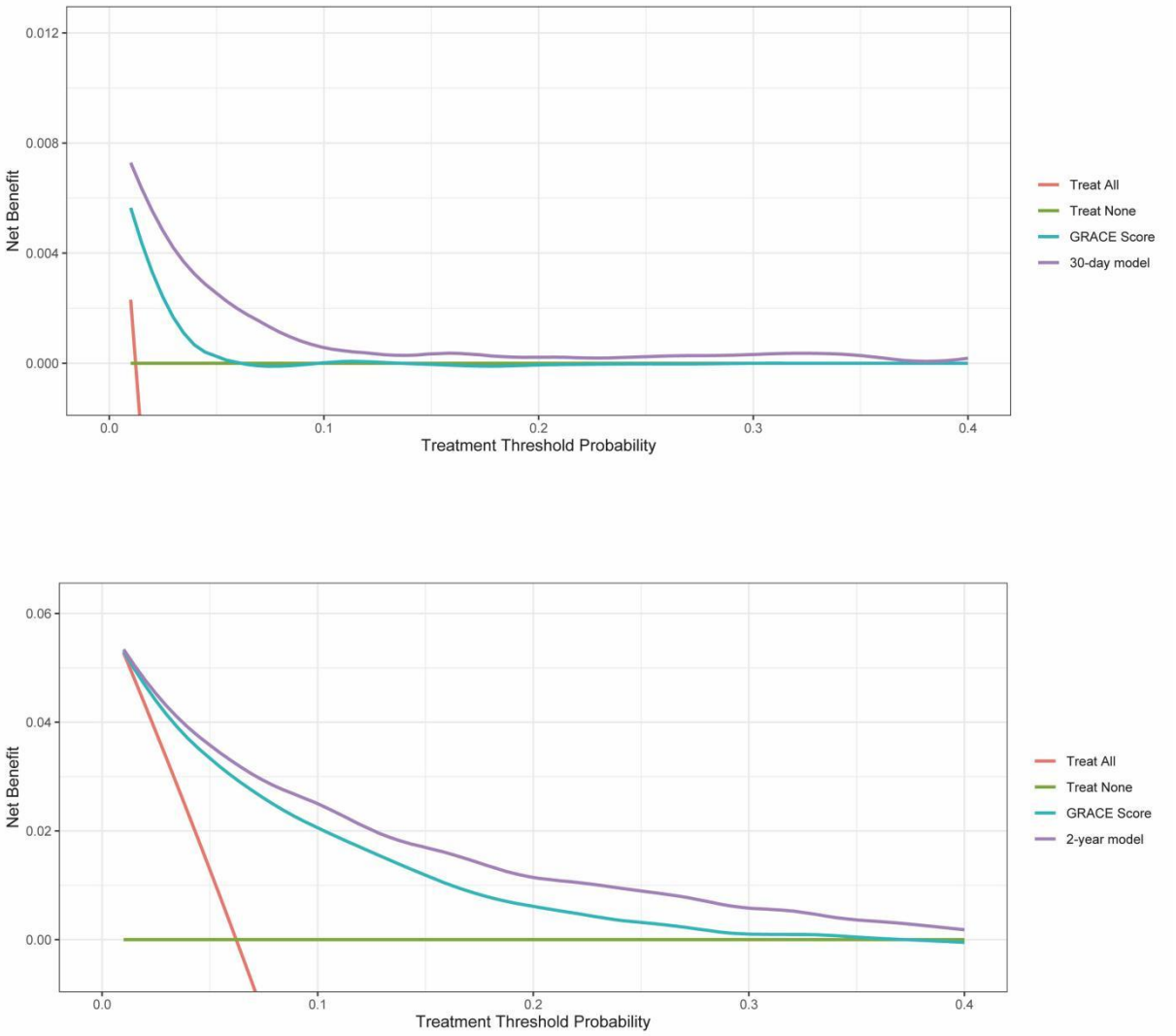
Supplemental Figure 15. Relative importance of selected predictors for 2-year mortality



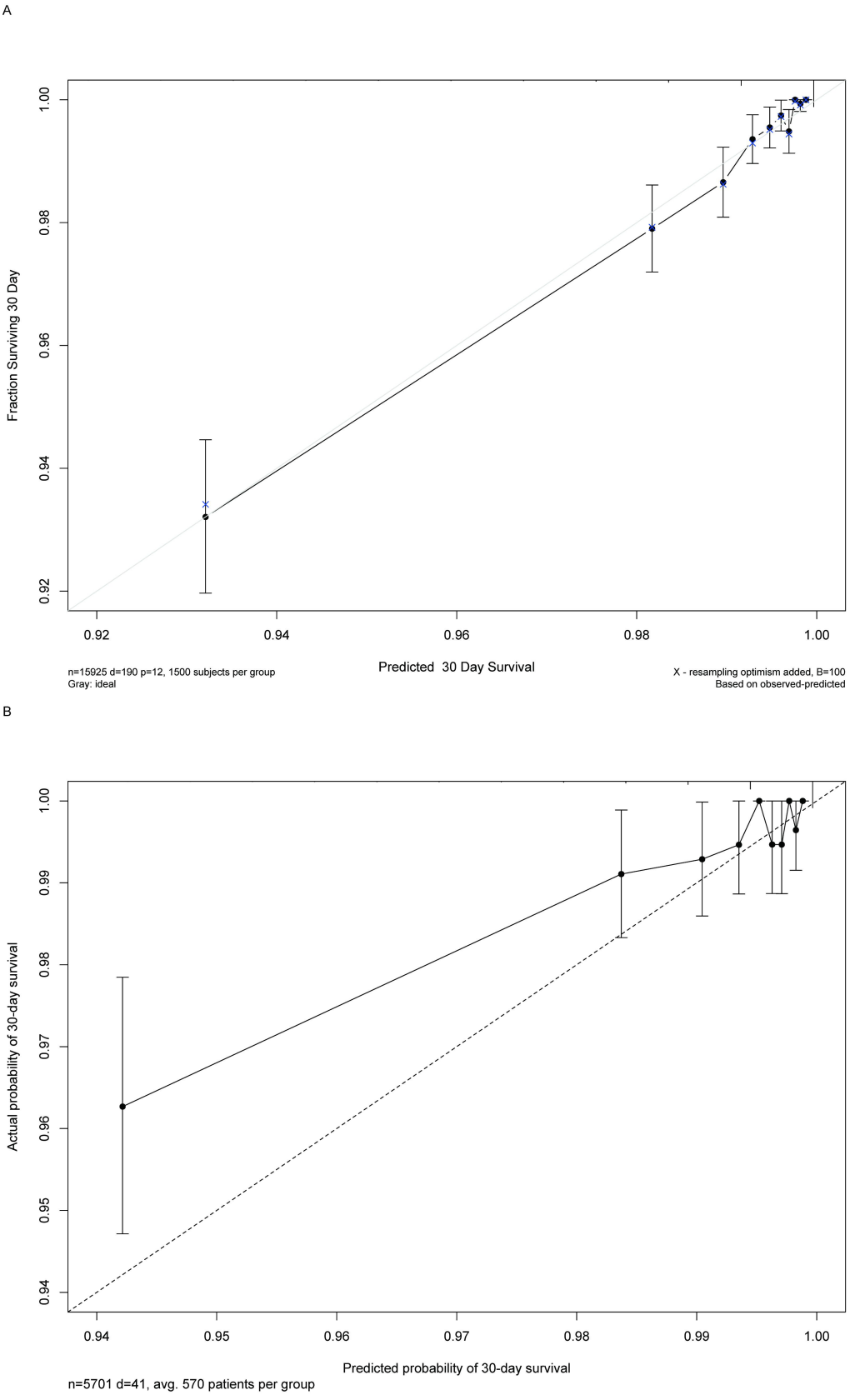
Supplemental Figure 16. Comparisons of clinical utilities between models with or without adverse events and medications



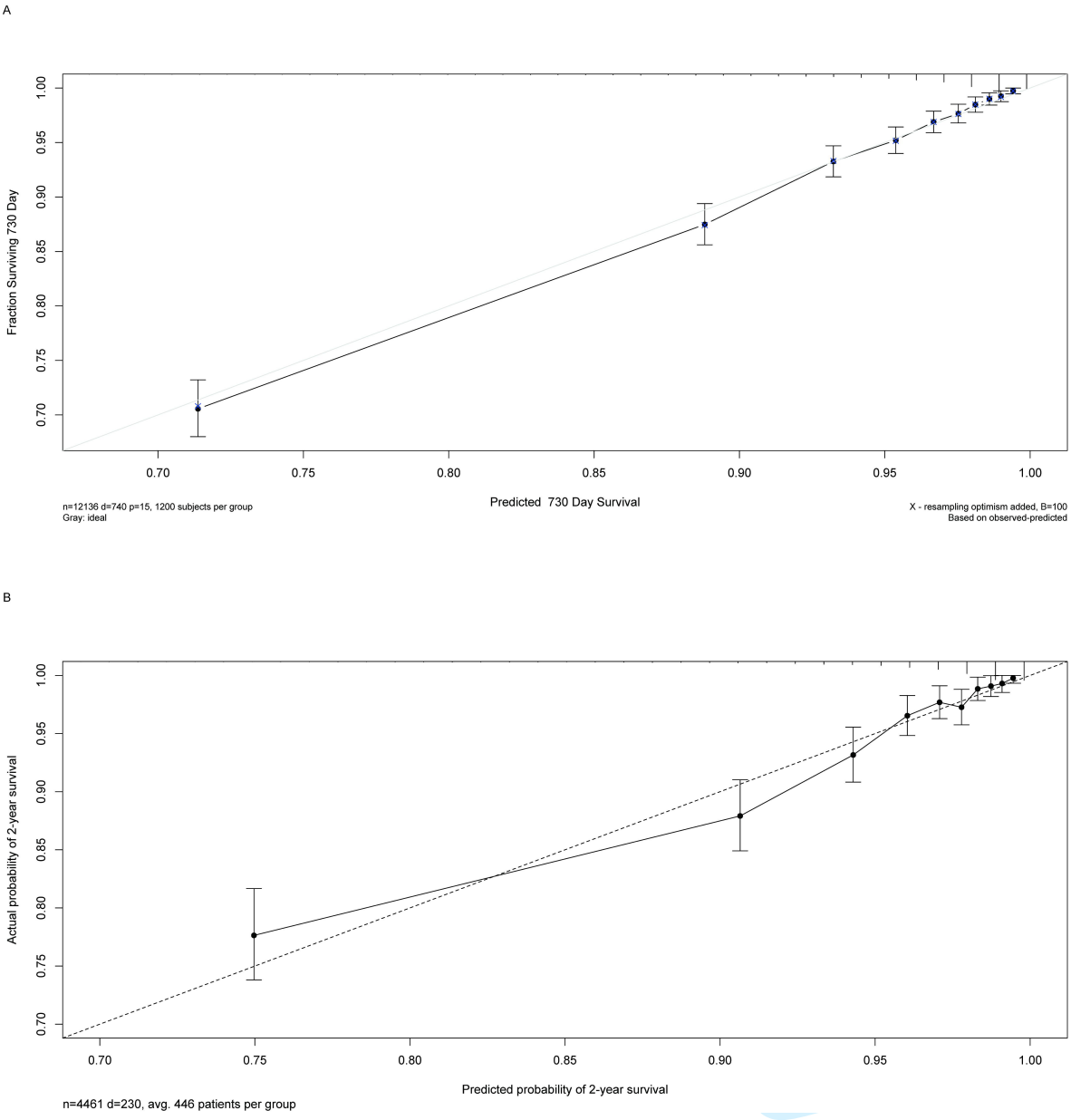
Supplemental Figure 17. Comparisons of clinical utilities between models and GRACE risk score



Supplemental Figure 18. Calibration curves of 30-day prognostic nomogram



Supplemental Figure 19. Calibration curves of 2-year prognostic nomogram



TRIPOD Checklist: Prediction Model Development

Section	Item	Checklist description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract				
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.		
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.		
Introduction				
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.		
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.		
Methods				
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, ifapplicable.		
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.		
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.		
	5b	Describe eligibility criteria for participants.		
	5c	Give details of treatments received, if relevant.		
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.		
	6b	Report any actions to blind assessment of the outcome to be predicted.		
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.		
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.		
Sample size	8	Explain how the study size was arrived at.		

Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.		
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.		
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.		
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.		
Risk groups	11	Provide details on how risk groups were created, if done.		
Results				
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.		
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.		
Model development	14a	Specify the number of participants and outcome events in each analysis.		
	14b	If done, report the unadjusted association between each candidate predictor and outcome.		
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).		
	15b	Explain how to the use the prediction model.		
Model performance	16	Report performance measures (with CIs) for the prediction model.		
Discussion				
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).		
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.		
Implications	20	Discuss the potential clinical use of the model and implications for future research.		
Other information				
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.		
Funding	22	Give the source of funding and the role of the funders for the present study.		

BMJ Open

Development and validation of dynamic models to predict post-discharge mortality risk in patients with acute myocardial infarction: results from China Acute Myocardial Infarction registry

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Myocardial infarction < CARDIOLOGY, Coronary heart disease <

	CARDIOLOGY, Coronary intervention < CARDIOLOGY, Prognosis

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Development and validation of dynamic models to predict post-discharge mortality risk in patients with acute myocardial infarction: results from China Acute Myocardial Infarction registry

Running title: Dynamic models in patients with AMI

Junxing Lv, MD[1,*], Chuangshi Wang, PhD[2,*], Xiaojin Gao, MD, PhD[1], Jingang Yang, MD, PhD[1], Xuan Zhang, MD[1], Yunqing Ye, MD[1], Qiuting Dong, MD, PhD[1], Rui Fu, MD[1], Hui Sun, MD[1], Xinxin Yan, MD, PhD[1], Yanyan Zhao, PhD[2], Yang Wang, PhD[2], Haiyan Xu, MD, PhD[1,†], and Yuejin Yang, MD, PhD[1,†]; on behalf of the China Acute Myocardial Infarction Registry study group

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Word count

Abstract: 299 **Main text (not including references, tables, and figure legends):** 3775

Abstract

Objectives: The risk of adverse events and prognostic factors are changing in different time phases after acute myocardial infarction (AMI). The incidence of adverse events is considerable in the early period after AMI hospitalization. Therefore, dynamic risk prediction is needed to guide post-discharge management of AMI. This study aimed to develop an dynamic risk prediction instrument for patients following AMI.

Design: A retrospective analysis of a prospective cohort.

Setting: 108 hospitals in China.

Participants: A total of 23887 patients after AMI in the China Acute Myocardial Infarction registry were included in this analysis.

Primary outcome measures: All-cause mortality.

Results: In multivariable analyses, age, prior stroke, heart rate, Killip class, left ventricular ejection fraction (LVEF), in-hospital percutaneous coronary intervention (PCI), recurrent myocardial ischemia, recurrent myocardial infarction, heart failure (HF) during hospitalization, antiplatelet therapy, and statins at discharge were independently associated with 30-day mortality. Variables related to mortality between 30 days and 2 years included age, prior renal dysfunction, history of HF, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, HF during hospitalization, HF worsening within 30 days after discharge, antiplatelet therapy, β blocker, and statins use within 30 days after discharge. The inclusion of adverse events and medications significantly improved the predictive performance of models without these indexes (likelihood ratio test $P<0.0001$). These two sets of predictors were used to establish dynamic prognostic nomograms for predicting mortality in patients with AMI. The C indexes of 30-day and 2-year prognostic nomograms were 0.85 (95% confidence interval

[CI]: 0.83-0.88) and 0.83 (95% CI: 0.81-0.84) in derivation cohort, and 0.79 (95% CI: 0.71-0.86) and 0.81 (95% CI: 0.79-0.84) in validation cohort, with satisfying calibration.

Conclusions: We established dynamic risk prediction models incorporating adverse event and medications. The nomograms may be useful instruments to help prospective risk assessment and management of AMI.

Trial registration number: NCT01874691.

Keywords: Myocardial infarction, risk prediction, model, prognosis

Strengths and limitations of this study

- We developed and validated a dynamic risk prediction tool using data from a large, prospective, multicenter registry.
- We analyzed the incremental prognostic value of in-hospital and post-discharge adverse events as well as medications over traditional predictors in patients following acute myocardial infarction.
- We compared the predictive performance of our models with existing risk prediction tools, including the Global Registry of Acute Coronary Events 1.0 and 2.0 scores.
- The predictive performance of the dynamic risk prediction tool can be further improved if including more follow-up information.
- The dynamic risk prediction tool should be further validated in external cohorts.

Introduction

Although in-hospital mortality of acute myocardial infarction (AMI) has been decreased in many countries,[1,2] risk of adverse events remains considerable in survivors after AMI hospitalization.[3] Previous studies have indicated unsatisfying and imbalanced quality of secondary prevention medications in clinical practice,[4,5] which can cause negative impact on prognosis of AMI patients. Individualized risk assessment may aid in decision making of long-term therapeutic strategies for patients after AMI. However, the existing risk prediction tools, which are mainly based on predictive indexes collected at admission, fail to consider the changing nature of adverse events and medications after AMI hospitalization,[6,7] and therefore may not be appropriate to guide long-term management. Dynamic risk assessment may help improve the quality of long-term management for patients following AMI.

Although several studies sought to forecast mortality dynamically in patients with acute coronary syndromes,[8-11] the prognostic components of these models were obtained during hospitalization, without taking follow-up adverse events and medications into consideration. Dynamic prognostic instruments designed to help risk reassessment should include post-discharge information which is associated with outcomes. In this study, we aimed to develop and validate dynamic risk prediction models, visualized by nomograms, which included in-hospital and post-discharge adverse events and medications, to assist in prognostic evaluation and decision-making of secondary prevention strategies in patients following AMI.

Methods

Study population

The data for the present study were from the China Acute Myocardial Infarction (CAMI) registry. The design of the CAMI registry has been described and published elsewhere.[12]

Briefly, 108 hospitals from 31 provinces and municipalitis throughout Mainland China were included in this prospective, nationwide, multicenter registry. Consecutive patients with AMI were enrolled in the registry and the final diagnosis of patients must meet the third Universal Definition for Myocardial Infarction (2012).[13] All types of AMI were eligible for the CAMI registry, except type 4a and type 5. Presenting characteristics, medical history, laboratory results, medications, and clinical outcomes were collected according to the American College of Cardiology/American Heart Association Task Force on clinical data standards and NCDR-ACTION-GWTG element dictionary.

Patients registered in the CAMI registry from January 2013 to September 2014 were included in this study. Those with invalid diagnosis (n=1312), who were transferred out (n=1181) or died during hospitalization (n=1690) were excluded. The remaining population (n=23887) was divided randomly according to 2:1 ratio into derivation (n=15925) and validation (n=7962) cohorts for developing and validating a 30-day risk prediction model. After further excluding patients who died within 30 days after discharge (n=293) and those with missing data on 30-day medication use (n=5391), the remaining derivation (n=12136) and validation (n=6067) cohorts were used for establishing and testing a 2-year risk prediction model (online supplemental figure 1).

Definitions

Standard definitions of adverse events have been described elsewhere in detail.[14] Taking a medication within 30 days means using the medication during this period after discharge without discontinuation.

Follow-up and endpoints

Patients were followed by clinical visits or telephone call at 30 days, 6 months, 12 months, 18 months, and 24 months. Adverse events (such as death, recurrent myocardial infarction, and heart failure worsening) and medications at follow-up time points were collected by trained cardiologists or cardiovascular fellows. The primary endpoints of this analysis were all-cause mortality within 30 days after AMI hospitalization (for establishing 30-day risk prediction model) and mortality between 30 days and 2 years (for establishing 2-year risk prediction model).

Statistical analysis

Categorical variables were summarized as frequencies and percentages, and compared by chi-square or Fisher exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation or medians (interquartile range) according to data distributions, and compared by student t or nonparametric test. Kaplan-Meier curve and density plots were used to depict the changing nature of risk after AMI hospitalization. In the derivation cohort, 190 deaths occurred within 30 days after discharge, which could ensure at most 19 predictor parameters (greater than 12 predictor parameters finally included) in the 30-day risk prediction model based on the rule of thumb that 10 events per candidate predictor parameters (EPP). Similarly, 740 deaths occurred between 30 days and 2 years, which could ensure at most 74 predictor parameters (greater than 15 predictor parameters finally included) in the 2-year risk prediction model.[15]

The derivation cohort was used to identify predictors of 30-day mortality and mortality between 30 days and 2 years. The associations between variables, including age, sex, body mass index (BMI), diabetes, hypertension, hyperlipidemia, smoking, prior angina pectoris, prior myocardial infarction, prior heart failure, prior stroke, prior peripheral artery disease, prior

percutaneous coronary intervention (PCI), prior coronary artery bypass graft (CABG), prior renal dysfunction, chronic obstructive pulmonary disease (COPD), symptom onset to admission time, heart rate, systolic blood pressure, Killip class, cardiac arrest at admission, diagnosis, anterior wall involvement, creatinine clearance, hemoglobin, leukocyte count, left ventricular ejection fraction (LVEF), in-hospital PCI, in-hospital CABG, heart failure, recurrent myocardial ischemia, recurrent myocardial infarction, stroke, other bleeding events (bleeding events not including cerebral heamorrhage) during hospitalization, antiplatelet therapy at discharge, statins at discharge, β blockers at discharge, and angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) at discharge, and 30-day mortality were first assessed in univariable Cox regression models. For obtaining prognostic factors of mortality between 30 days and 2 years, the associations of adverse events within 30 days (recurrent myocardial infarction and heart failure worsening) and 30-day medications (antiplatelet therapy, statins, β blockers, and ACEI/ARB) with mortality were also assessed in univariable Cox models besides variables mentioned previously. Subsequently, the least absolute shrinkage and selection operator (LASSO) method was adopted to select predictors of short-term and long-term mortality respectively from variables with $P \leq 0.1$ in univariable analysis. The selected predictors were used to establish dynamic risk prediction models by multivariable Cox regression model. The relative importance of these variables was ranked according to the proportion of explainable log-likelihood ratio χ^2 statistics.

To analyze the incremental prognostic value of adverse events and medications over traditional predictive indexes, we compared the predictive performance between models with or without adverse events and medications using C index, net reclassification index (NRI), integrated discrimination improvement index (IDI), likelihood ratio test, and Bayesian information criteria (BIC). The clinical utility of models were compared by decision curve analysis. Predictive performance was also compared between 30-day risk model or 2-year risk

model and the Global Registry of Acute Coronary Events (GRACE) risk scores (version 1.0 and 2.0) to further analyze the additional value of the dynamic models beyond existing prognostic tool.[6,16]

Two prognostic nomograms, which could make complex predictive formulas friendly to use in clinical practice, were constructed based on the regression coefficients of predictors for mortality using the "rms" package of R software. Discrimination and calibration of the nomograms were assessed by C index and calibration curves presenting the relationship between observed and predicted survival probabilities in both derivation and validation cohorts. Subgroup analyses were performed in patients with complete data on model predictors in the validation cohort according to age, sex, diabetes, AMI classification, in-hospital PCI, and hospital level (province level, prefecture level, and county level).

Before regression analysis, we used Martingale residual plots to check the linearity assumption for continuous variables (online supplemental figure 2 and 3). We also calculated variance inflation factor to examine multicollinearity issue. The proportional hazards assumptions were tested by inspection of Schoenfeld residual plots (online supplemental figure 4 and 5). Multiple imputation was used to generate 5 datasets without missing values. The LASSO method was performed in each dataset. Only variables selected by LASSO method in all 5 datasets were included in final dynamic risk prediction models. Number of missing values for selected predictors were shown in online supplemental table 1. Results of Cox regression models were reported as hazard ratios (HR) with 95% confidence intervals (CI). A two-tailed $P<0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and public involvement

Patients or the public were not involved directly in the design, conduct, reporting or dissemination plans of our research.

Results

Baseline characteristics, medications, and outcomes of derivation and validation cohorts were summarized in table 1, online supplemental table 2 and online supplemental table 3. Rates of 30-day mortality among hospital survivors in derivation and validation cohorts were 1.2% (190/15925 patients) and 1.3% (103/7962 patients), respectively. Rates of mortality between 30 days and 2 years were 6.1% (740/12136 patients) and 5.7% (345/6067 patients). The Kaplan-Meier curve and density plots showed the changing risk of death and recurrent myocardial infarction within 2 years after AMI hospitalization (online supplemental figure 6 and 7).

Predictors of 30-day mortality in patients after AMI

Univariable analysis of the associations between variables and 30-day mortality was presented in online supplemental table 4. In the LASSO-based Cox regression model, age, prior stroke, heart rate, Killip class, LVEF, in-hospital PCI, in-hospital recurrent myocardial ischemia, in-hospital recurrent myocardial infarction, in-hospital heart failure, antiplatelet therapy, and statins at discharge were independently associated with 30-day mortality (online supplemental figure 8 to 12; table 2). The relative importance of these predictors was ranked and shown in online supplemental figure 13.

Predictors of 2-year mortality for 30-day survivors after AMI hospitalization

Univariable analysis of mortality between 30 days and 2 years after AMI hospitalization was shown in online supplemental table 5. In the LASSO-based Cox regression model, age, prior renal dysfunction, history of heart failure, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, in-hospital heart failure, heart failure worsening within 30 days, antiplatelet therapy, β blocker, and statins within 30 days were identified as predictors of mortality (online supplemental figure 14 to 18; table 3). The relative importance of these predictors was ranked and presented in online supplemental figure 19.

Incremental prognostic value of adverse events and medications

The inclusion of in-hospital recurrent myocardial ischemia, in-hospital recurrent myocardial infarction, in-hospital heart failure, antiplatelet therapy, and statins at discharge significantly improved the predictive power of 30-day risk prediction model (table 4; 30-day model 1 vs 30-day model 0: C index, 0.855 [0.830-0.879] vs 0.822 [0.796-0.848]; NRI [95%CI], 0.445 [0.339-0.523], P<0.0001; IDI [95%CI], 0.040 [0.025-0.074], P<0.0001; likelihood ratio test P<0.0001; BIC, 3434.091 vs 3350.882). In the 2-year risk prediction model, heart failure worsening within 30 days, antiplatelet, β blocker, and statins within 30 days also provided additional prognostic value over predictive indexes obtained during hospitalization (table 5). The decision curve analysis further demonstrated better clinical utility after adding adverse events and medications into 30-day and 2-year risk models (online supplemental figure 20). Notably, the hospital level provided no incremental value to 30-day or 2-year risk models (the inclusion of hospital level to 30-day model, likelihood ratio test P=0.4174; to 2-year model, likelihood ratio test P=0.5621; online supplemental figure 21).

Comparisons of prognostic models and GRACE risk scores

For predicting 30-day mortality, the 30-day risk prediction model showed significantly better predictive performance than both GRACE 1.0 and 2.0 scores (30-day risk model vs GRACE 1.0 score: C index, 0.855 [0.830-0.879] vs 0.771 [0.740-0.802]; NRI [95%CI], 0.412 [0.307-0.485], P<0.0001; IDI [95%CI], 0.048 [0.032-0.090], P<0.0001; BIC, 3267.271 vs 3402.578; 30-day risk model vs GRACE 2.0 score: C index, 0.855 [0.830-0.879] vs 0.752 [0.720-0.784]; NRI [95%CI], 0.569 [0.500-0.624], P<0.0001; IDI [95%CI], 0.061 [0.044-0.101], P<0.0001; BIC, 3247.357 vs 3492.004). Similarly, when predicting 2-year mortality, the 2-year risk prediction model also performed better than the GRACE risk scores (2-year risk model vs GRACE 1.0 score: C index, 0.825 [0.811-0.839] vs 0.798 [0.783-0.813]; NRI [95%CI], 0.191 [0.147-0.257], P<0.0001; IDI [95%CI], 0.041 [0.031-0.057], P<0.0001; BIC, 12540.559 vs 12697.527; 2-year risk model vs GRACE 2.0 score: C index, 0.825 [0.811-0.839] vs 0.769 [0.752-0.786]; NRI [95%CI], 0.486 [0.456-0.529], P<0.0001; IDI [95%CI], 0.115 [0.098-0.143], P<0.0001; BIC, 12257.375 vs 12934.783). The decision curve analysis further demonstrated better clinical utility of both 30-day and 2-year risk models than GRACE scores (online supplemental figure 22 and 23).

Nomograms for dynamic risk prediction

Two nomograms were created by assigning a weighted score based on regression coefficients of each prognostic index for evaluating 30-day and 2-year mortality risk respectively. All observed values of a prognostic index corresponded vertically to points on the top scale. The sum of points for each index was plotted on the "Total points" scale, and corresponded to mortality risk at the bottom (figure 1 and 2).

The 30-day prognostic nomogram achieved high discrimination in both derivation and validation cohorts, with C indexes of 0.85 (95% CI: 0.83-0.88) and 0.79 (95% CI: 0.71-0.86)

respectively. The calibration curves presenting the concordance between observed and predicted 30-day survival probability in two cohorts also showed satisfying calibration of the model (online supplemental figure 24). In addition, the 30-day prognostic nomogram achieved moderate to high discrimination (C indexes: 0.74 to 0.83) in subsets according to age, sex, diabetes, AMI classification, PCI, and hospital level (online supplemental table 6).

The C indexes of 2-year prognostic nomogram were 0.83 (95% CI: 0.81-0.84) and 0.81 (95% CI: 0.79-0.84) in derivation and validation cohorts, respectively. The calibration curves demonstrated excellent calibration of the nomogram in both derivation and validation cohorts (online supplemental figure 25). In aforementioned subgroups of patients, the model discrimination was acceptable (C index: 0.66 to 0.83, online supplemental table 7).

Discussion

Using data from a large, prospective, multicenter registry, we screened eleven predictors of 30-day mortality, and fourteen variables, including heart failure worsening and medications within 30 days, associated with mortality between 30 days and 2 years in patients after AMI hospitalization. These two sets of predictors were used to develop prognostic nomograms which could predict post-discharge mortality for AMI patients in different time phases. The nomograms showed satisfying discrimination and calibration in both derivation and validation cohorts. This is a novel dynamic risk prediction tool which can serve for risk assessment and guide long-term management of patients after AMI.

A series of risk models have been developed to predict mortality in patients with acute coronary syndromes.[6,7,17] These models mainly included prognostic factors obtained at admission, and provided a fixed estimate of survival probability for a given patient. This working mode of prognostic models was helpful for screening high-risk patients and

determining therapeutic strategies after admission. However, the incidence of adverse cardiovascular events remained considerable after AMI hospitalization. Accumulating evidence has implied that a larger proportion of adverse events occurred in the early phase after AMI hospitalization,[18] which reflected the changing risk following AMI and highlighted the importance of risk reassessment during follow-up. Although some risk prediction models, such as the GRACE risk score and dynamic Thrombolysis In Myocardial Infarction (TIMI) risk score, could be used to assess mortality risk at discharge,[6,9] none of them could improve prognostic evaluation during follow-up. Considering the higher risk of adverse events in the early period than that at the late stage after AMI hospitalization (online supplemental figure 6 and 7), we chose 30 days, which was also one of routine follow-up points after AMI hospitalization in clinical practice, as the time point of risk reassessment to establish dynamic risk prediction models.

The first model, which was developed to assess 30-day mortality risk at discharge in patients after AMI, included variables related to patients' demographics, hemodynamics, left ventricular systolic function, treatment, in-hospital adverse events, and medications at discharge. Previous studies have established several risk prediction models, such as Platelet glycoprotein IIb/IIIa in Unstable agina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) and Zwolle risk scores,[19,20] to predict 30-day mortality in patients with acute coronary syndromes. However, these models mainly used patient characteristics, clinical presentations at admission as well as angiographic features as prognostic indexes. The present study showed that recurrent myocardial ischemia, recurrent myocardial infarction, heart failure during AMI hospitalization, antiplatelet therapy, and statins use at discharge were independently associated with short-term mortality after discharge, and provided significantly incremental prognostic information over traditional predictive indexes. Therefore, these

adverse events and medications were included in the novel 30-day risk prediction model, which might assist in decision-making of post-discharge management.

For the second model assessing 2-year mortality risk in 30-day survivors, we screened new predictors including heart failure worsening within 30 days, antiplatelet therapy, β blocker, and statins use within 30 days after discharge. A prior study showed that mortality rate of patients with an early recurrent myocardial infarction (recurrent myocardial infarcction within 90 days of discharge) was nearly 50% within 5 years.[21] In the present study, we observed that the recurrent myocardial infarction and heart failure worsening within 30 days after discharge were associated with >3-fold and >4.5-fold increase of 2-year mortality risk respectively in univariable analysis, and heart failure worsening, which was included in 2-year prognostic nomogram, was a statistically significant prognostic index in multivariable analysis. To our best knowledge, this is the first prognostic instrument taking follow-up adverse event after AMI into consideration. In addition, although some studies analyzed the prognostic impact of secondary prevention implementation in patients after AMI,[22,23] follow-up medications have not been considered as predictive indexes in risk models for AMI so far. For some patients, not taking optimal medical care within 30 days after discharge could be explained by poor medication adherence after AMI, which was a problem for both developed and developing countries.[23-25] A study found that about 30% of patients with myocardial infarction who underwent PCI in the United States reported suboptimal adherence to prescribed medications in six weeks after hospitalization.[25] Data from the China PEACE Prospective AMI study also showed that a similar percentage of AMI patients did not take medications as prescribed in the first month after discharge.[23] Patients with early medication nonadherence not only suffered a higher risk of early adverse events, but might not comply with long-term secondary prevention measures, and therefore had poorer long-term prognosis. Another situation was that patients were not prescribed with some medications by physicians, due to contraindications or high risk of side

effects. However, lack of secondary prevention medications after AMI still meant a higher risk of cardiovascular adverse events in these patients. Indeed, our analysis showed that insufficient use of antiplatelet therapy, β blocker, and statins within 30 days after AMI hospitalization had significant negative impact on 2-year survival. The inclusion of follow-up medications and adverse events improved risk prediction of 2-year risk prediction model.

Although a previous study from CAMI registry showed that there were significant variations in in-hospital mortality among three levels of hospitals in China,[14] hospital level was not used as a predictive index in the present risk prediction models, for the improvement of care quality in relatively low-level hospitals was likely to weaken its prognostic value. Besides, the hospital level was showed to provide no additional prognostic information beyond current predictors in the risk prediction models. Socioeconomic factors, which were known as risk factors for survival following myocardial infarction,[26-29] were not included in the present models because we sought to develop models based on predictors directly reflecting patients' clinical conditions. Notably, these factors were also not included in existing risk prediction tools.[6,7,9,16] The rates of COPD and prior heart failure in our cohort were lower than the United Kingdom population of AMI.[30] However, the rates in the present study were similar with data from the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome project, which was also a nationwide registry in China.[31,32] The distinct prevalence of comorbidity in patients with myocardial infarction between countries highlighted the importance of developing risk prediction model for specific population.

The present study showed that the dynamic prognostic nomograms achieved satisfying discrimination and calibration, and performed well in subgroups of patients according to age, sex, diabetes, AMI classification, PCI, and hospital level. The clinical utility of nomograms was further confirmed by decision curve analysis. Prognostic nomogram is a graphical presentation format for complex predictive regression model.[33] A series of prognostic

nomograms have been established for risk prediction in patients with cancer or cardiovascular diseases.[34-39] For patients with myocardial infarction, previous prognostic nomograms mainly focused on evaluating short-term risk of mortality or other adverse events.[37,38] There also existed nomogram developed to predict risk of adverse events beyond 1 year.[36] However, without consideration of changing nature of event risk or medications, the nomogram might not play roles in post-discharge management of patients. Our prognostic nomograms, which took into account follow-up adverse event as well as medications, could assist in risk reassessment at 30 days after discharge. In detail, using the nomogram for prediction of 30-day mortality, physicians can identify high-risk patients at discharge. At 30-day follow up, the second nomogram can be used to reassess mortality risk of 30-day survivors, and may guide decision-making of long-term follow-up intensity and strategies of medical care.

Limitations

Several important limitations in this study should be mentioned. First, as a retrospective analysis of a prospective cohort, this study only used data which had been collected in the CAMI registry. Although the present risk prediction tool has achieved satisfying discrimination and calibration, it may be further improved by including other prognostic factors of AMI, such as details of angiographic characteristics, which were not available in a large proportion of the cohort. Heart failure worsening and medications within 30 days after discharge were included in the 2-year risk prediction model. However, lifestyle interventions and cardiac rehabilitation programmes, which were associated with lower risk of adverse events in patients with coronary artery disease,[40,41] as well as laboratory and echocardiographic indexes were not collected during follow up. These variables may also improve the predictive performance of the models. Second, although the present study showed the feasibility of assessing 2-year prognosis at 30 days after discharge, risk reassessment is a serial process and ideally performed at more time

points beyond the early phase after discharge. Models which can ensure more dynamic and accurate risk prediction are still needed. Third, the distribution of AMI types (types 1, 2, 3, 4b, and 4c) was not collected in the CAMI registry. Results of the present study could have biased if a certain type was more represented than another. However, the CAMI registry enrolled patients consecutively from 108 hospitals, which meant that it was representative of AMI population in routine clinical practice. It is plausible that the impact of distribution of AMI types is relatively limited. Fourth, there existed some missing values which needed to be imputed before regression analysis. However, almost all predictors had missing values of <6%. Finally, our dynamic models were only internally validated in Chinese patients. Further validations in external cohorts including patients of other races are needed.

Conclusions

The dynamic risk prediction tool consisted of a short-term prognostic model and a long-term prognostic model for patients after AMI hospitalization. Taking the changing nature of adverse events and medications into consideration, the models can serve prospective risk stratification and guide post-discharge management of AMI. Dynamic risk prediction may play an important role in therapeutic decision-making and quality improvement of secondary prevention after AMI hospitalization.

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Contributors

HX and YYang contributed significantly to the conception, design, and conduction of this study. JL and CW wrote the initial manuscript. CW, YZ, and YW provided strong support in statistical analysis. JL, CW, XG, JY, XZ, YYe, QD, RF, HS, XY, YZ, YW, HX, and YYang contributed significantly to revisions of manuscript, analysis, and interpretation of data. All authors contributed substantially to this study and approved its submission.

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Competing Interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The CAMI registry conformed to the ethical guidelines of the Declaration of Helsinki, and was approved by the institutional review board central committee at Fuwai Hospital, National Center for Cardiovascular Diseases of China (Approval No. 2012-431). Written informed consent was given by eligible patients before registration.

Data Availability Statement

Data are available on reasonable request from the corresponding authors.

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Table 1. Baseline characteristics of cohorts for developing and validating 30-day prognostic model

Variables	Derivation cohort (n=15925)	Validation cohort (n=7962)
Demographics		
Age, yrs	62.27±12.36	62.54±12.29
Female	3878 (24.4)	1940 (24.4)
BMI, kg/m^2	24.13±3.05	24.08±3.04
Medical history		
Diabetes	2943 (19.6)	1505 (20.0)
Hypertension	7873 (51.2)	3897 (50.8)
Hyperlipidemia	1154 (8.5)	569 (8.3)
Current smoker	7083 (45.7)	3483 (44.8)
Prior angina pectoris	4044 (27.8)	1994 (27.4)
Prior myocardial infarction	1083 (7.4)	553 (7.5)
Prior heart failure	329 (2.2)	169 (2.3)
Prior PCI	753 (5.0)	381 (5.1)
Prior CABG	56 (0.4)	36 (0.5)
Prior renal dysfunction	197 (1.3)	94 (1.3)
COPD	279 (1.9)	142 (1.9)

Presenting characteristics		
Symptom onset to admission time		
0-6h	7398 (47.0)	3625 (46.0)
>6h	8330 (53.0)	4247 (54.0)
Heart rate, beats/min	77±18	78±18
Systolic blood pressure	129.48±25.01	129.94±25.26
Killip class		
I	11836 (76.2)	5903 (75.8)
II-IV	3694 (23.8)	1883 (24.2)
Cardiac arrest at admission	128 (0.8)	77 (1.0)
AMI classification		
STEMI	12051 (75.7)	5991 (75.2)
NSTEMI	3874 (24.3)	1971 (24.8)
Anterior wall involvement	7406 (47.7)	3696 (47.5)

Values are shown as mean ± standard deviation, median (interquartile range), or number (%) without imputation of missing data. BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

Table 2. Multivariable analysis of 30-day mortality in the derivation cohort

	All-cause death	
	Adjusted HR (95% CI)	**P value**
Age (per 1 year increase)	1.035 (1.021, 1.049)	<0.0001
Prior stroke (vs no)	1.560 (1.091-2.231)	0.0148
Heart rate (per 1beat/min increase)	1.006 (1.000-1.012)	0.0497
Killip class Ⅱ-Ⅳ(vs Ⅰ)	1.528 (1.115-2.094)	0.0083
LVEF (per 1% increase)	0.969 (0.955, 0.982)	<0.0001
In-hospital PCI (vs no)	0.441 (0.307, 0.634)	<0.0001
In-hospital recurrent myocardial ischemia (vs no)	1.711 (1.019-2.871)	0.0421
In-hospital recurrent myocardial infarction (vs no)	4.572 (2.121-9.859)	0.0001
In-hospital heart failure (vs no)	2.869 (2.065-3.986)	<0.0001
Antiplatelet therapy at discharge (vs dual antiplatelet therapy)		
Single antiplatelet therapy	0.791 (0.491-1.275)	0.3358
None	2.363 (1.395-4.003)	0.0014
Statins at discharge (vs no)	2.009 (1.258-3.208)	0.0035

LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval.

Table 3. Multivariable analysis of mortality after 30 days in the derivation cohort

	All-cause death	
	Adjusted HR (95% CI)	**P value**
Age (per 1 year increase)	1.052 (1.045-1.060)	<0.0001
Prior renal dysfunction (vs no)	1.539 (1.076-2.201)	0.0181
History of heart failure (vs no)	1.501 (1.160-1.943)	0.0020
STEMI (vs NSTEMI)	0.747 (0.639-0.873)	0.0002
Heart rate (per 1 beat/min increase)	1.008 (1.005-1.011)	<0.0001
Killip class Ⅱ-Ⅳ(vs Ⅰ)	1.330 (1.129-1.566)	0.0006
Hemoglobin (per 1g/L increase)	0.993 (0.990-0.996)	<0.0001
LVEF (per 1% increase)	0.971 (0.964-0.978)	<0.0001
In-hospital PCI (vs no)	0.423 (0.351-0.510)	<0.0001
In-hospital heart failure(vs no)	1.287 (1.085-1.525)	0.0037
Heart failure worsening within 30 days (vs no)	1.675 (1.258-2.229)	0.0004
Antiplatelet therapy within 30 days (vs dual antiplatelet therapy)		
Single antiplatelet therapy	1.107 (0.911-1.345)	0.3084
None	1.430 (1.055-1.937)	0.0211
β blocker within 30 days (vs yes)	1.271 (1.085-1.491)	0.0031
Statins within 30 days (vs yes)	1.191 (0.908-1.561)	0.2075

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval.

Table 4. Comparison of 30-day prognostic models with or without adverse events and medications

	30-day model 0	30-day model 1
C index	0.822 (0.796-0.848)	0.855 (0.830-0.879)
NRI (95%CI)	0.445 (0.339-0.523)	
P value	<0.0001	
IDI (95%CI)	0.040 (0.025-0.074)	
P value	<0.0001	
Likelihood ratio test (P value)	<0.0001	
BIC	3434.091	3350.882

30-days Model 0: age, prior stroke, heart rate, Killip class, LVEF, and in-hospital PCI. 30-day Model 1: age, prior stroke, heart rate, Killip class, LVEF, in-hospital PCI, in-hospital recurrent myocardial ischemia, in-hospital recurrent myocardial infarction, in-hospital heart failure, antiplatelet therapy, and statins at discharge. LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; NRI, net reclassification index; CI, confidence interval; IDI, integrated discrimination improvement index; BIC, Bayesian information criteria.

Table 5. Comparison of 2-year prognostic models with or without adverse events and medications

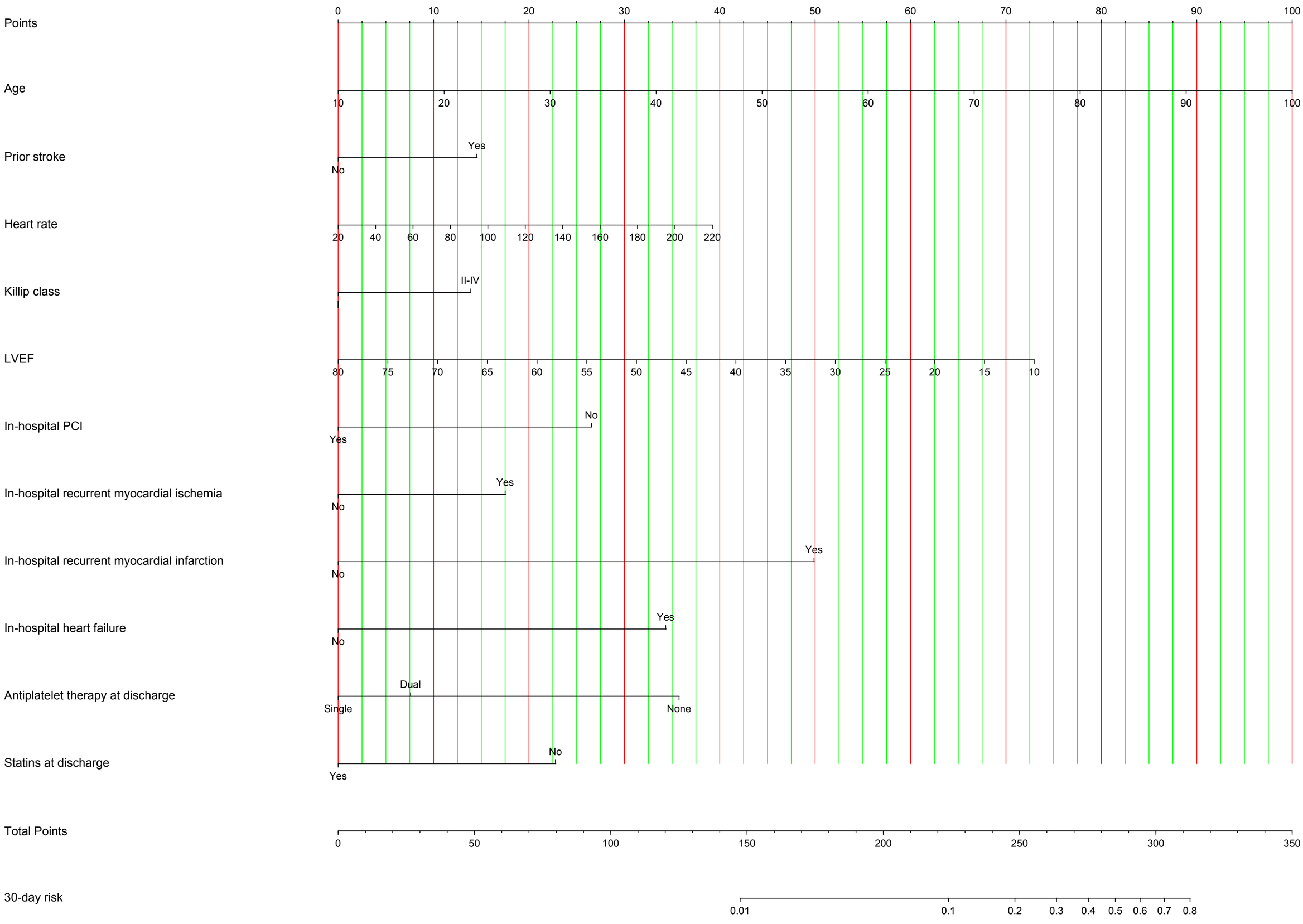
	2-year model 0	2-year model 1
C index	0.822 (0.807-0.836)	0.825 (0.811-0.839)
NRI (95%CI)	0.119 (-0.045-0.176)	
P value	0.126	
IDI (95%CI)	0.008 (0.004-0.017)	
P value	0.007	
Likelihood ratio test (P value)	<0.0001	
BIC	12792.602	12785.706

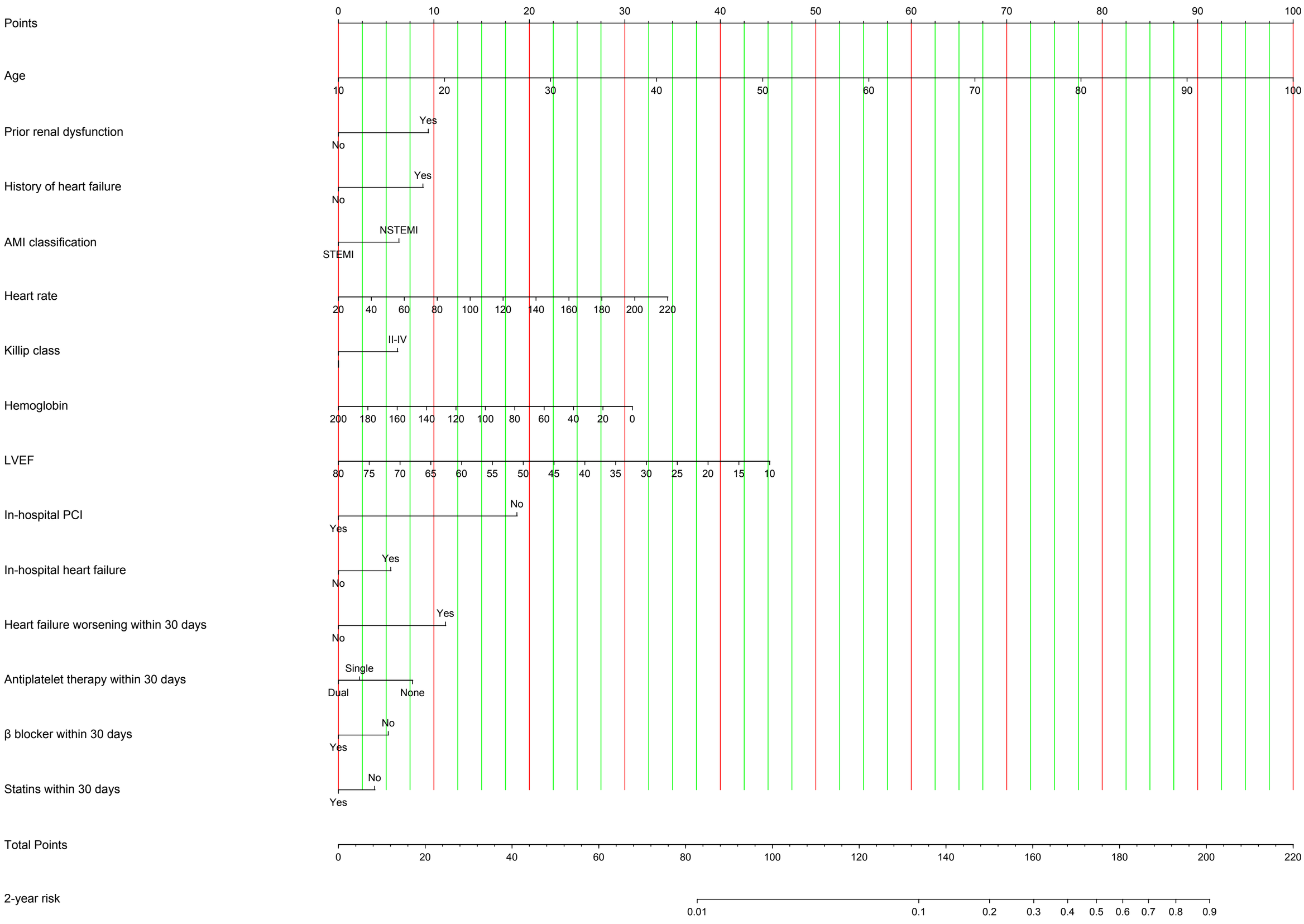
2-year Model 0: age, prior renal dysfunction, prior heart failure, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, and in-hospital heart failure. 2-year Model 1: age, prior renal dysfunction, prior heart failure, AMI classification, heart rate, Killip class, hemoglobin, LVEF, in-hospital PCI, in-hospital heart failure, heart failure worsening within 30 days, antiplatelet therapy, β blockers, and statins within 30 days. AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; NRI, net reclassification index; CI, confidence interval; IDI, integrated discrimination improvement index; BIC, Bayesian information criteria.

FIGURE LEGENDS

Figure 1. Nomogram for predicting 30-day mortality risk. The observed value of a prognostic index was assigned a point by drawing a perpendicular line towards the top scale. The sum of points for each index was plotted on the "Total points" scale, and corresponded to the risk of 30-day mortality at the bottom with a vertical line. LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Figure 2. Nomogram for predicting 2-year mortality risk. The observed value of a prognostic index was assigned a point by drawing a perpendicular line towards the top scale. The sum of points for each index was plotted on the "Total points" scale, and corresponded to the risk of 2-year mortality at the bottom with a vertical line. AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.


Points
0 10 20 30 40 50 60 70 80 90 100
Age
10 20 30 40 50 60 70 80 90 100
Prior stroke
Yes
No
Heart rate
20 40 60 80 100 120 140 160 180 200 220
Killip class
II-IV
I
LVEF
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
In-hospital PCI
No
Yes
In-hospital recurrent myocardial ischemia
Yes
No
In-hospital recurrent myocardial infarction
Yes
No
In-hospital heart failure
Yes
No
Antiplatelet therapy at discharge
Dual
Single
None
Statins at discharge
No
Yes
Total Points
0 50 100 150 200 250 300 350
30-day risk
0.01 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8


Points
0 10 20 30 40 50 60 70 80 90 100
Age
10 20 30 40 50 60 70 80 90 100
Prior renal dysfunction
Yes
No
History of heart failure
Yes
No
AMI classification
NSTEMI
STEMI
Heart rate
20 40 60 80 100 120 140 160 180 200 220
Killip class
II-IV
I
Hemoglobin
200 180 160 140 120 100 80 60 40 20 0
LVEF
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
In-hospital PCI
No
Yes
In-hospital heart failure
Yes
No
Heart failure worsening within 30 days
Yes
No
Antiplatelet therapy within 30 days
Single
Dual
None
β blocker within 30 days
No
Yes
Statins within 30 days
No
Yes
Total Points
0 20 40 60 80 100 120 140 160 180 200 220
2-year risk
0.01 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

Supplemental Materials

Junxing Lv et al. Development and validation of dynamic models to predict post-discharge mortality risk in patients with acute myocardial infarction: results from China Acute Myocardial Infarction registry.

I. Supplemental Tables.

II. Supplemental Figures.

Supplemental Figure 3. Martingale residual plots for testing the linearity assumption before developing the 2-year model. LVEF, left ventricular ejection fraction.

Supplemental Figure 4. Schoenfeld residual plots for testing the proportional hazards assumption before developing the 30-day model. LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; HF, heart failure; reMI, recurrent myocardial infarction.

Supplemental Figure 5. Schoenfeld residual plots for testing the proportional hazards assumption before developing the 2-year model. LVEF, left ventricular ejection fraction; HF, heart failure; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention.

Supplemental Figure 6. Kaplan-Meier curve for patients after AMI hospitalization. AMI, acute myocardial infarction.

Supplemental Figure 7. Density plots for all-cause death and recurrent myocardial infarction during follow-up. (A) Density plot for all-cause death. (B) Density plot for recurrent myocardial infarction.

Supplemental Figure 8. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 1. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 9. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 2. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 10. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 3. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The

lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 11. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 4. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 12. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 5. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 13. Relative importance of selected predictors for 30-day mortality. Relative importance of variables selected by LASSO method was ranked according to the proportion of explainable log-likelihood ratio χ^2 statistics. LASSO, least absolute shrinkage and selection operator; Mi, myocardial ischemia; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; HF, heart failure.

Supplemental Figure 14. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 1. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 15. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 2. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 16. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 3. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 17. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 4. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 18. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 5. (A) The plot showing partial likelihood deviance values versus log(λ). Tuning parameter λ selection used 10-fold cross-validation. The vertical lines were drawn at optimal values by the minimum criteria and the 1 SE of minimum criteria. The lambda with 1 SE of minimum deviance was used for variable selection. (B) The coefficient profile plot. The plot was produced against the log(λ) sequence. LASSO, least absolute shrinkage and selection operator; SE, standard error.

Supplemental Figure 19. Relative importance of selected predictors for 2-year mortality. Relative importance of variables selected by LASSO method was ranked according to the proportion of explainable log-likelihood ratio χ^2 statistics. LASSO, least absolute shrinkage and selection operator; HF, heart failure; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Supplemental Figure 20. Comparisons of clinical utility between models with or without adverse events and medications. The red and green lines represent the assumption that all or none patients at high risk with different thresholds. The lines in the upper right represent the risk prediction models. (A) Comparison of clinical utility between 30-day model with or without adverse events and medications. (B) Comparison of clinical utility between 2-year model with or without adverse events and medications.

Supplemental Figure 21. Comparisons of clinical utility between models with or without hospital level. The red and green lines represent the assumption that all or none patients at high risk with different thresholds. The lines in the upper right represent the risk prediction models. (A) Comparison of clinical utility between 30-day model with or without hospital

level. (B) Comparison of clinical utility between 2-year model with or without hospital level.

Supplemental Figure 22. Comparisons of clinical utility between models and GRACE 1.0 score. The red and green lines represent the assumption that all or none patients at high risk with different thresholds. The lines in the upper right represent the risk prediction models. (A) Comparison of clinical utility between 30-day model and GRACE 1.0 score. (B) Comparison of clinical utility between 2-year model and GRACE 1.0 score. GRACE, Global Registry of Acute Coronary Events.

Supplemental Figure 23. Comparisons of clinical utility between models and GRACE 2.0 score. The red and green lines represent the assumption that all or none patients at high risk with different thresholds. The lines in the upper right represent the risk prediction models. (A) Comparison of clinical utility between 30-day model and GRACE 2.0 score. (B) Comparison of clinical utility between 2-year model and GRACE 2.0 score. GRACE, Global Registry of Acute Coronary Events.

Supplemental Figure 24. Calibration curves of 30-day prognostic nomogram. Calibration curves present the relationship between observed and predicted survival probabilities by 30-day prognostic nomogram in both derivation and validation cohorts. (A) Calibration curve of 30-day prognostic nomogram in derivation cohort. (B) Calibration curve of 30-day prognostic nomogram in validation cohort.

Supplemental Figure 25. Calibration curves of 2-year prognostic nomogram. Calibration curves present the relationship between observed and predicted survival probabilities by 2-year prognostic nomogram in both derivation and validation cohorts. (A) Calibration curve of 2-year prognostic nomogram in derivation cohort. (B) Calibration curve of 2-year prognostic nomogram in validation cohort.

I. Supplemental Tables.

Supplemental Table 1. Number of missing values for selected predictors in derivation and validation cohorts

	Number of missing values (%)
Derivation cohort	
30-day prognostic model	
Age	336 (2.1)
Prior stroke	820 (5.1)
Heart rate	391 (2.5)
Killip class	395 (2.5)
LVEF	3370 (21.2)
In-hospital PCI	435 (2.7)
In-hospital recurrent myocardial ischemia	518 (3.3)
In-hospital recurrent myocardial infarction	518 (3.3)
In-hospital heart failure	502 (3.2)
Antiplatelet therapy at discharge	849 (5.3)
Statins at discharge	849 (5.3)
2-year prognostic model	
Age	242 (2.0)
Prior renal dysfunction	510 (4.2)
History of heart failure	490 (4.0)
AMI classification	0 (0.0)
Heart rate	107 (0.9)
Killip class	114 (0.9)
Hemoglobin	327 (2.7)
LVEF	2307 (19.0)
In-hospital PCI	130 (1.1)
In-hospital heart failure	155 (1.3)
Heart failure worsening within 30 days	8 (0.1)
Antiplatelet therapy within 30 days	0 (0.0)
β blockers within 30 days	0 (0.0)
Statins within 30 days	0 (0.0)

Validation cohort	
30-day prognostic model	
Age	144 (1.8)
Prior stroke	404 (5.1)
Heart rate	197 (2.5)
Killip class	176 (2.2)
LVEF	1678 (21.1)
In-hospital PCI	216 (2.7)
In-hospital recurrent myocardial ischemia	267 (3.4)
In-hospital recurrent myocardial infarction	261 (3.3)
In-hospital heart failure	254 (3.2)
Antiplatelet therapy at discharge	416 (5.2)
Statins at discharge	416 (5.2)
2-year prognostic model	
Age	106 (1.7)
Prior renal dysfunction	260 (4.3)
History of heart failure	254 (4.2)
AMI classification	0 (0.0)
Heart rate	75 (1.2)
Killip class	54 (0.9)
Hemoglobin	135 (2.2)
LVEF	1161 (19.1)
In-hospital PCI	60 (1.0)
In-hospital heart failure	83 (1.4)
Heart failure worsening within 30 days	9 (0.1)
Antiplatelet therapy within 30 days	0 (0.0)
β blockers within 30 days	0 (0.0)
Statins within 30 days	0 (0.0)

LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction.

Supplemental Table 2. Baseline characteristics, medications, and outcomes of cohorts for developing and validating 30-day prognostic model

Variables	Derivation cohort (n=15925)	Validation cohort (n=7962)
Demographics		
Age, yrs	62.27±12.36	62.54±12.29
Female	3878 (24.4)	1940 (24.4)
BMI, kg/m^2	24.13±3.05	24.08±3.04
Medical history		
Diabetes	2943 (19.6)	1505 (20.0)
Hypertension	7873 (51.2)	3897 (50.8)
Hyperlipidemia	1154 (8.5)	569 (8.3)
Current smoker	7083 (45.7)	3483 (44.8)
Prior angina pectoris	4044 (27.8)	1994 (27.4)
Prior myocardial infarction	1083 (7.4)	553 (7.5)
Prior heart failure	329 (2.2)	169 (2.3)
Prior stroke	1330 (8.8)	711 (9.4)
Prior peripheral artery disease	96 (0.6)	46 (0.6)
Prior PCI	753 (5.0)	381 (5.1)
Prior CABG	56 (0.4)	36 (0.5)
Prior renal dysfunction	197 (1.3)	94 (1.3)
COPD	279 (1.9)	142 (1.9)
Presenting characteristics		
Symptom onset to admission time		
0-6h	7398 (47.0)	3625 (46.0)
>6h	8330 (53.0)	4247 (54.0)
Heart rate, beats/min	77±18	78±18
Systolic blood pressure	129.48±25.01	129.94±25.26
Killip class		
I	11836 (76.2)	5903 (75.8)
II-IV	3694 (23.8)	1883 (24.2)
Cardiac arrest at admission	128 (0.8)	77 (1.0)

AMI classification		
STEMI	12051 (75.7)	5991 (75.2)
NSTEMI	3874 (24.3)	1971 (24.8)
Anterior wall involvement	7406 (47.7)	3696 (47.5)
Laboratory results		
Creatinine, μmol/L	74.90 (62.00, 90.00)	74.60 (62.00, 90.40)
Creatinine clearance, ml/min	83.83 (61.61, 109.00)	83.70 (61.52, 108.71)
Hemoglobin, g/L	136.23±21.09	136.07±20.94
Leukocyte count, $\times 10^9$/L	10.09±3.69	10.04±3.60
LVEF, %	53.84±10.07	53.81±10.08
In-hospital treatment		
PCI	8951 (57.9)	4432 (57.2)
CABG	127 (0.8)	76 (1.0)
Adverse events during hospitalization		
New-onset heart failure	2082 (13.5)	1035 (13.4)
Recurrent myocardial ischemia	384 (2.5)	166 (2.2)
Recurrent myocardial infarction	61 (0.4)	22 (0.3)
Stroke	90 (0.6)	40 (0.5)
Other bleeding events	236 (1.5)	121 (1.6)
Medications at discharge		
Antiplatelet therapy		
Dual antiplatelet therapy	13212 (87.6)	6571 (87.1)
Single antiplatelet therapy	1261 (8.4)	648 (8.6)
None	603 (4.0)	327 (4.3)
Statins	13846 (91.8)	6976 (92.4)
β blockers	10341 (68.6)	5006 (66.3)
ACEI/ARB	8642 (57.3)	4326 (57.3)
Hospital level		
Province level	5516 (34.6)	2728 (34.3)
Prefecture level	8740 (54.9)	4371 (54.9)
County level	1668 (10.5)	863 (10.8)

Values are shown as mean ± standard deviation, median (interquartile range), or number (%)

without imputation of missing data. BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Supplemental Table 3. Baseline characteristics, medications, and outcomes of cohorts for developing and validating 2-year prognostic model

Variables	Derivation cohort (n=12136)	Validation cohort (n=6067)
Demographics		
Age, yrs	62.08±12.28	62.26±12.20
Female	2967 (24.4)	1459 (24.0)
BMI, kg/m^2	24.12±3.02	24.11±3.01
Medical history		
Diabetes	2213 (19.0)	1146 (19.6)
Hypertension	6021 (50.6)	3011 (50.7)
Hyperlipidemia	760 (7.2)	382 (7.2)
Current smoker	5565 (46.3)	2737 (45.5)
Prior angina pectoris	3173 (28.0)	1571 (27.8)
Prior myocardial infarction	821 (7.2)	420 (7.3)
Prior heart failure	243 (2.1)	120 (2.1)
Prior stroke	1038 (8.8)	572 (9.7)
Prior peripheral artery disease	72 (0.6)	30 (0.5)
Prior PCI	562 (4.8)	293 (5.0)
Prior CABG	38 (0.3)	25 (0.4)
Prior renal dysfunction	130 (1.1)	56 (1.0)
COPD	221 (1.9)	114 (2.0)
Presenting characteristics		
Symptom onset to admission time		
0-6h	5725 (47.6)	2798 (46.5)
>6h	6298 (52.4)	3216 (53.5)
Heart rate, beats/min	77±18	78±18
Systolic blood pressure	129.61±25.30	130.00±25.52
Killip class		
I	9163 (76.2)	4589 (76.3)
II-IV	2859 (23.8)	1424 (23.7)
Cardiac arrest at admission	95 (0.8)	62 (1.0)
AMI classification		

STEMI	9215 (75.9)	4560 (75.2)
NSTEMI	2921 (24.1)	1507 (24.8)
Anterior wall involvement	5743 (47.7)	2843 (47.2)
Laboratory results		
Creatinine, μmol/L	74.00 (61.80, 89.10)	73.90 (61.40, 89.60)
Creatinine clearance, ml/min	84.53 (62.60, 109.58)	84.92 (63.22, 110.16)
Hemoglobin, g/L	136.37±20.82	136.39±20.79
Leukocyte count, $\times 10^9$/L	10.09±3.65	10.02±3.52
LVEF, %	54.08±10.00	54.01±9.94
In-hospital treatment		
In-hospital PCI	6998 (58.4)	3468 (57.7)
In-hospital CABG	87 (0.7)	50 (0.8)
Adverse events during hospitalization		
New-onset heart failure	1616 (13.5)	805 (13.5)
Recurrent myocardial ischemia	281 (2.3)	125 (2.1)
Recurrent myocardial infarction	37 (0.3)	18 (0.3)
Stroke	65 (0.5)	29 (0.5)
Other bleeding events	183 (1.5)	94 (1.6)
Medications within 30 days		
Antiplatelet therapy		
Dual antiplatelet therapy	10518 (86.7)	5287 (87.1)
Single antiplatelet therapy	1292 (10.6)	610 (10.1)
None	326 (2.7)	170 (2.8)
Statins	11486 (94.6)	5736 (94.5)
β blockers	8751 (72.1)	4347 (71.6)
ACEI/ARB	7221 (59.5)	3591 (59.2)
Hospital level		
Province level	3876 (31.9)	1956 (32.2)
Prefecture level	6947 (57.2)	3461 (57.0)
County level	1313 (10.8)	650 (10.7)

Values are shown as mean ± standard deviation, median (interquartile range), or number (%) without imputation of missing data. BMI, body mass index; PCI, percutaneous coronary

intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Supplemental Table 4. Univariable analysis of 30-day mortality

	Unadjusted HR (95% CI)	P value
Age (per 1 year increase)	1.066 (1.052, 1.080)	<0.0001
Women (vs men)	1.662 (1.233, 2.241)	0.0009
BMI (per 1kg/m^2 increase)	0.893 (0.850, 0.939)	<0.0001
Diabetes (vs no)	1.545 (1.123, 2.126)	0.0075
Hypertension (vs no)	1.289 (0.958, 1.734)	0.0930
Hyperlipidemia (vs no)	0.749 (0.406, 1.384)	0.3547
Current smoking (vs no)	0.406 (0.293, 0.563)	<0.0001
Prior angina pectoris (vs no)	1.324 (0.972, 1.803)	0.0754
Prior myocardial infarction (vs no)	1.177 (0.709, 1.954)	0.5284
Prior heart failure (vs no)	5.078 (3.166, 8.144)	<0.0001
Prior stroke (vs no)	2.627 (1.842, 3.747)	<0.0001
Prior PCI (vs no)	0.814 (0.400, 1.659)	0.5717
Prior CABG (vs no)	—	—
Prior renal dysfunction (vs no)	1.596 (0.587, 4.338)	0.3591
COPD (vs no)	3.208 (1.744, 5.901)	0.0002
Prior peripheral artery disease (vs no)	—	—
Symptom onset to admission time (vs 0-6h)		
>6h	1.947 (1.431, 2.649)	<0.0001
Heart rate (per 1 beat increase)	1.024 (1.018, 1.029)	<0.0001
Systolic blood pressure (per 1mmHg increase)	0.994 (0.988, 1.000)	0.0358
Killip class (vs I)		
II-IV	3.980 (2.990, 5.298)	<0.0001
Cardiac arrest at admission (vs no)	1.921 (0.614, 6.011)	0.2620
NSTEMI (vs STEMI)	1.230 (0.898, 1.686)	0.1977
Anterior wall involvement (vs no)	1.255 (0.943, 1.671)	0.1185
Creatinine clearance (vs >90 ml/min)		
60-90	1.805 (1.222, 2.666)	0.0030
≤60	4.252 (2.985, 6.058)	<0.0001
Hemoglobin (per 1g/L increase)	0.988 (0.983, 0.993)	<0.0001
Leukocyte count (per 10^9/L increase)	1.055 (1.023, 1.088)	0.0006

LVEF (per 1% increase)	0.938 (0.923, 0.952)	<0.0001
In-hospital PCI (vs no)	0.220 (0.157, 0.308)	<0.0001
In-hospital CABG (vs no)	1.277 (0.317, 5.145)	0.7308
New-onset heart failure during hospitalization (vs no)	7.204 (5.414, 9.585)	<0.0001
Recurrent myocardial ischemia during hospitalization (vs no)	6.028 (3.938, 9.228)	<0.0001
Recurrent myocardial infarction during hospitalization (vs no)	13.299 (6.752 26.195)	<0.0001
Stroke during hospitalization (vs no)	2.908 (0.934, 9.052)	0.0654
Other bleeding events during hospitalization (vs no)	4.109 (2.235, 7.558)	<0.0001
Antiplatelet therapy at discharge (vs dual therapy)		
Single antiplatelet therapy	1.344 (0.762, 2.372)	0.3024
none	5.158 (3.468, 7.672)	<0.0001
Statins at discharge (vs no)	3.180 (2.246, 4.502)	<0.0001
β blockers at discharge (vs no)	1.483 (1.105, 1.991)	0.0087
ACEI/ARB at discharge (vs no)	1.481 (1.088, 2.017)	0.0128

BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HR, hazard ratio; CI, confidence interval.

Supplemental Table 5. Univariable analysis of mortality after 30 days

	Unadjusted HR (95% CI)	P value
Age (per 1 year increase)	1.084 (1.076, 1.092)	<0.0001
Women (vs men)	1.947 (1.679, 2.259)	<0.0001
BMI (per 1kg/m^2 increase)	0.895 (0.872, 0.919)	<0.0001
Diabetes (vs no)	1.571 (1.328, 1.857)	<0.0001
Hypertension (vs no)	1.533 (1.321, 1.779)	<0.0001
Hyperlipidemia (vs no)	0.631 (0.443, 0.900)	0.0111
Current smoking (vs no)	0.423 (0.359, 0.498)	<0.0001
Prior angina pectoris (vs no)	1.318 (1.131, 1.536)	0.0004
Prior myocardial infarction (vs no)	2.064 (1.657, 2.570)	<0.0001
Prior heart failure (vs no)	5.964 (4.685, 7.594)	<0.0001
Prior stroke (vs no)	2.013 (1.651, 2.455)	<0.0001
Prior PCI (vs no)	1.122 (0.817, 1.540)	0.4770
Prior CABG (vs no)	1.656 (0.618, 4.433)	0.3156
Prior renal dysfunction (vs no)	4.383 (2.969 6.470)	<0.0001
COPD (vs no)	2.897 (2.076, 4.044)	<0.0001
Prior peripheral artery disease (vs no)	2.273 (1.197, 4.314)	0.0122
Symptom onset to admission time (vs 0-6h)		
>6h	1.497 (1.287, 1.742)	<0.0001
Heart rate (per 1 beat increase)	1.021 (1.018, 1.024)	<0.0001
Systolic blood pressure (per 1mmHg increase)	1.005 (1.002, 1.008)	0.0005
Killip class (vs I)		
II-IV	3.225 (2.792, 3.726)	<0.0001
Cardiac arrest at admission (vs no)	1.068 (0.478, 2.388)	0.8724
NSTEMI (vs STEMI)	2.395 (2.070, 2.771)	<0.0001
Anterior wall involvement (vs no)	1.210 (1.047, 1.398)	0.0096
Creatinine clearance (vs >90 ml/min)		
60-90	1.725 (1.405, 2.119)	<0.0001
≤60	5.193 (4.328, 6.231)	<0.0001
Hemoglobin (per 1g/L increase)	0.980 (0.978, 0.983)	<0.0001
Leukocyte count (per 10^9/L increase)	1.010 (0.990, 1.030)	0.3333

LVEF (per 1% increase)	0.948 (0.941, 0.955)	<0.0001
In-hospital PCI (vs no)	0.207 (0.175, 0.246)	<0.0001
In-hospital CABG (vs no)	0.421 (0.106, 1.674)	0.2184
New-onset heart failure during hospitalization (vs no)	3.418 (2.932, 3.984)	<0.0001
Recurrent myocardial ischemia during hospitalization (vs no)	2.653 (1.949, 3.610)	<0.0001
Recurrent myocardial infarction during hospitalization (vs no)	1.773 (0.659, 4.771)	0.2565
Stroke during hospitalization (vs no)	3.455 (1.991, 5.996)	<0.0001
Other bleeding events during hospitalization (vs no)	2.233 (1.486, 3.356)	0.0001
Recurrent myocardial infarction within 30 days (vs no)	3.032 (1.130-8.134)	0.0276
Heart failure worsening within 30 days (vs no)	4.790 (3.631, 6.319)	<0.001
Antiplatelet therapy within 30 days (vs dual antiplatelet therapy)		
Single antiplatelet therapy	2.147 (1.779, 2.591)	<0.0001
none	4.371 (3.385, 5.643)	<0.0001
Statins within 30 days (vs no)	2.454 (1.960, 3.073)	<0.0001
β blockers within 30 days (vs no)	1.594 (1.374, 1.850)	<0.0001
ACEI/ARB within 30 days (vs no)	1.153 (0.997, 1.333)	0.0546

BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HR, hazard ratio; CI, confidence interval.

Supplemental Table 6. Discrimination of 30-day prognostic nomogram in subgroups of patients

Subgroup	Sample size	C statistic (95% CI)
Age, yrs		
≤75	4766	0.74 (0.65-0.84)
>75	935	0.83 (0.71-0.94)
Sex		
Male	4359	0.79 (0.69-0.88)
Female	1342	0.75 (0.62-0.88)
Diabetes		
Yes	1106	0.81 (0.62-1.00)
No	4431	0.78 (0.70-0.87)
Diagnosis		
STEMI	4302	0.77 (0.68-0.86)
NSTEMI	1399	0.83 (0.72-0.93)
In-hospital PCI		
Yes	3498	0.76 (0.63-0.88)
No	2203	0.76 (0.66-0.85)
Hospital level		
Province level	1984	0.78 (0.66-0.90)
Prefecture level	3168	0.80 (0.70-0.90)
County level	549	0.74 (0.51-0.97)

STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CI, confidence interval.

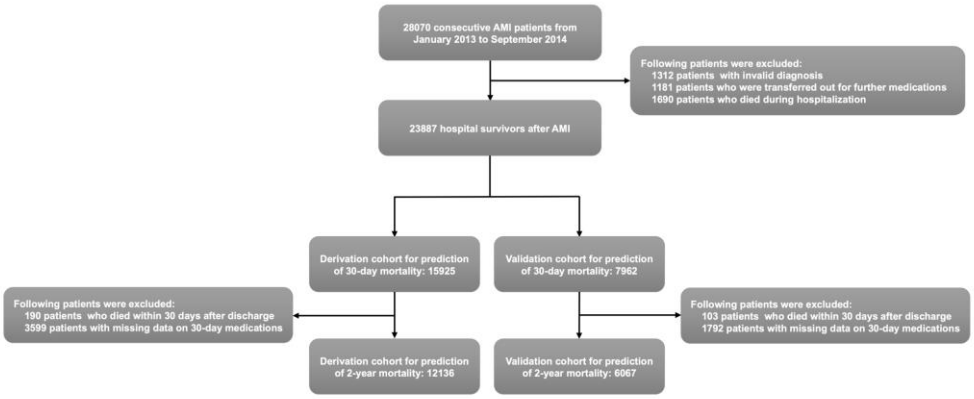
Supplemental Table 7. Discrimination of 2-year prognostic nomogram in subgroups of patients

Subgroup	Sample size	C statistic (95% CI)
Age, yrs		
≤75	3766	0.79 (0.75-0.83)
>75	695	0.66 (0.62-0.71)
Sex		
Male	3412	0.83 (0.80-0.86)
Female	1049	0.75 (0.70-0.80)
Diabetes		
Yes	845	0.81 (0.76-0.86)
No	3496	0.81 (0.78-0.84)
AMI classification		
STEMI	3364	0.81 (0.78-0.84)
NSTEMI	1097	0.81 (0.76-0.85)
In-hospital PCI		
Yes	3104	0.82 (0.78-0.87)
No	1357	0.72 (0.68-0.76)
Hospital level		
Province level	1460	0.83 (0.78-0.88)
Prefecture level	2552	0.81 (0.77-0.84)
County level	449	0.78 (0.70-0.85)

AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CI, confidence interval.

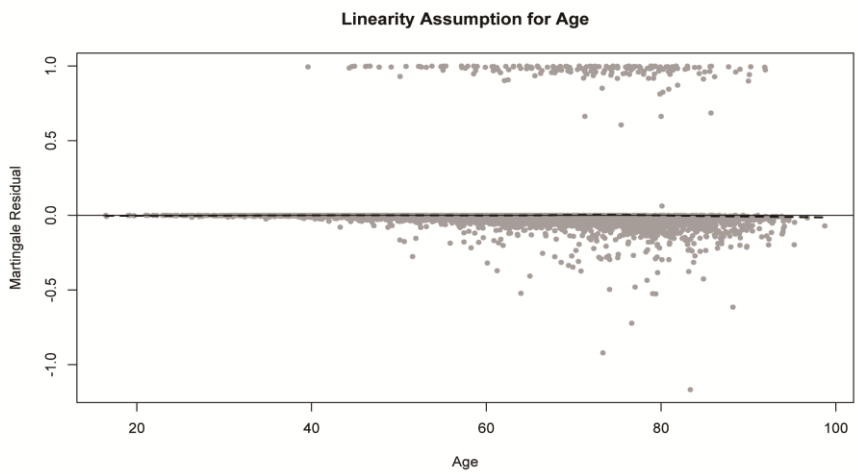
II. Supplemental Figures.

Supplemental Figure 1. Flowchart of this study

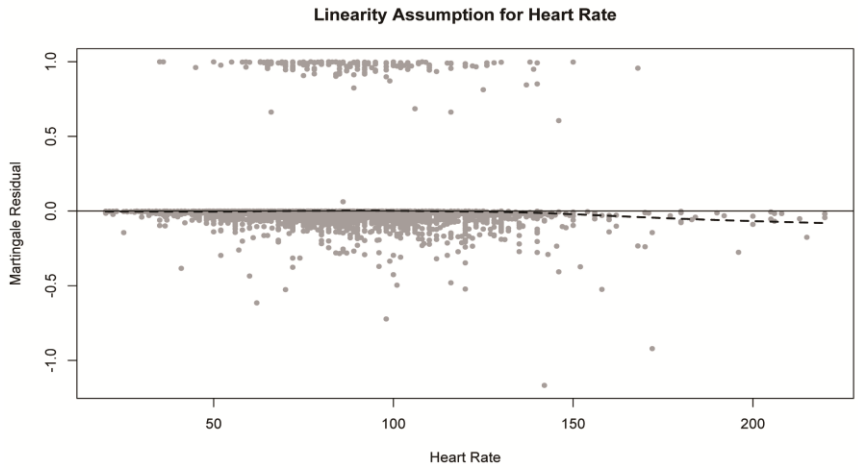


Supplemental Figure 2. Martingale residual plots for testing the linearity assumption before developing the 30-day model

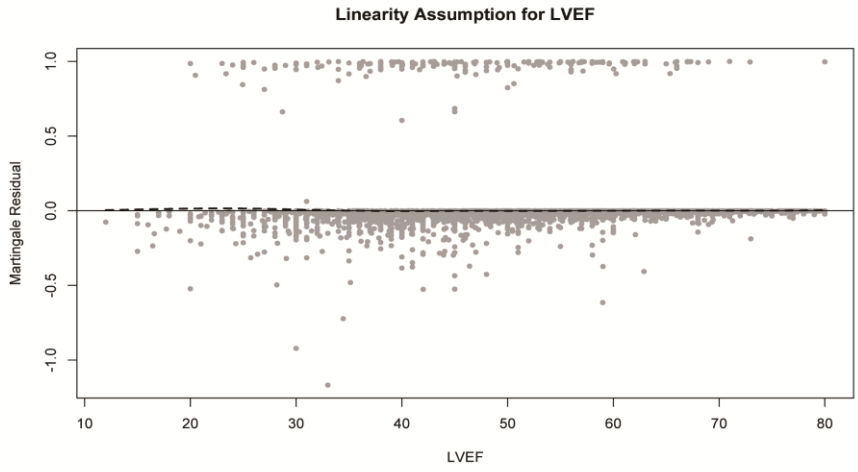
A



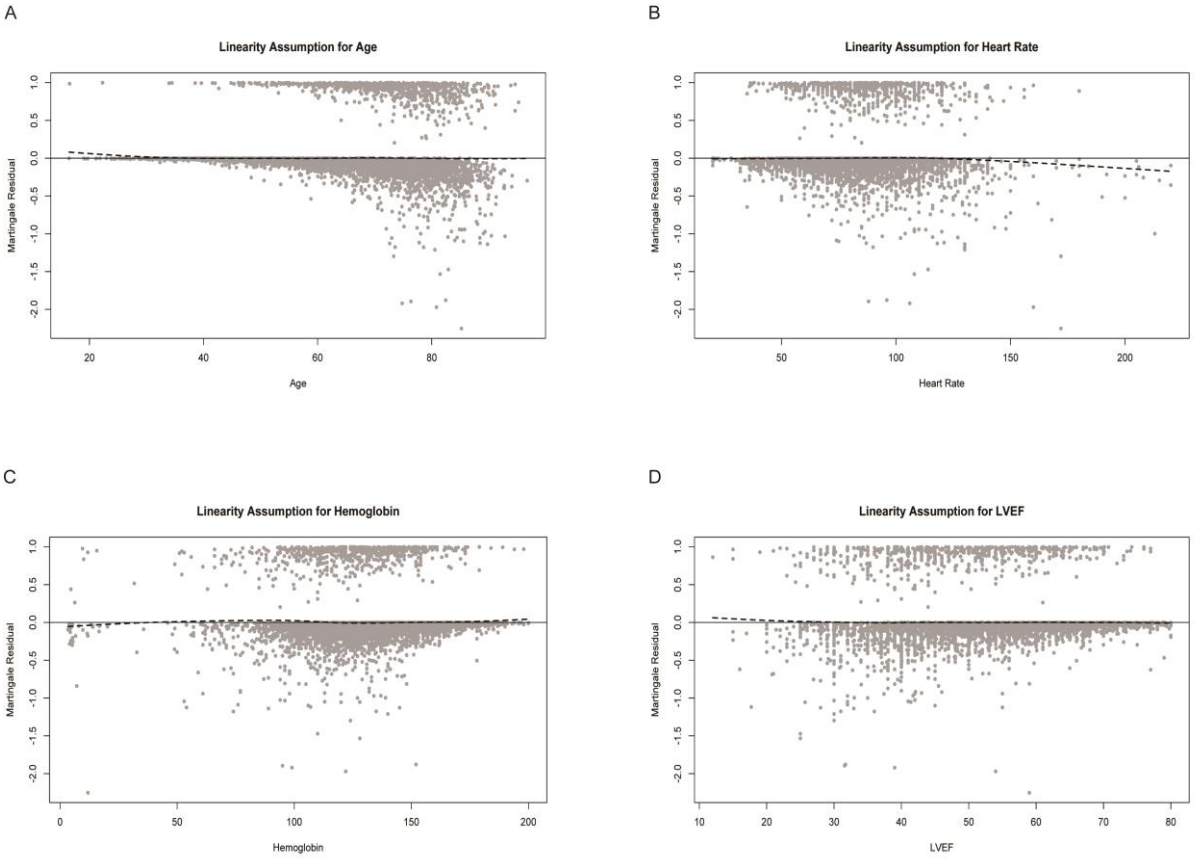
B



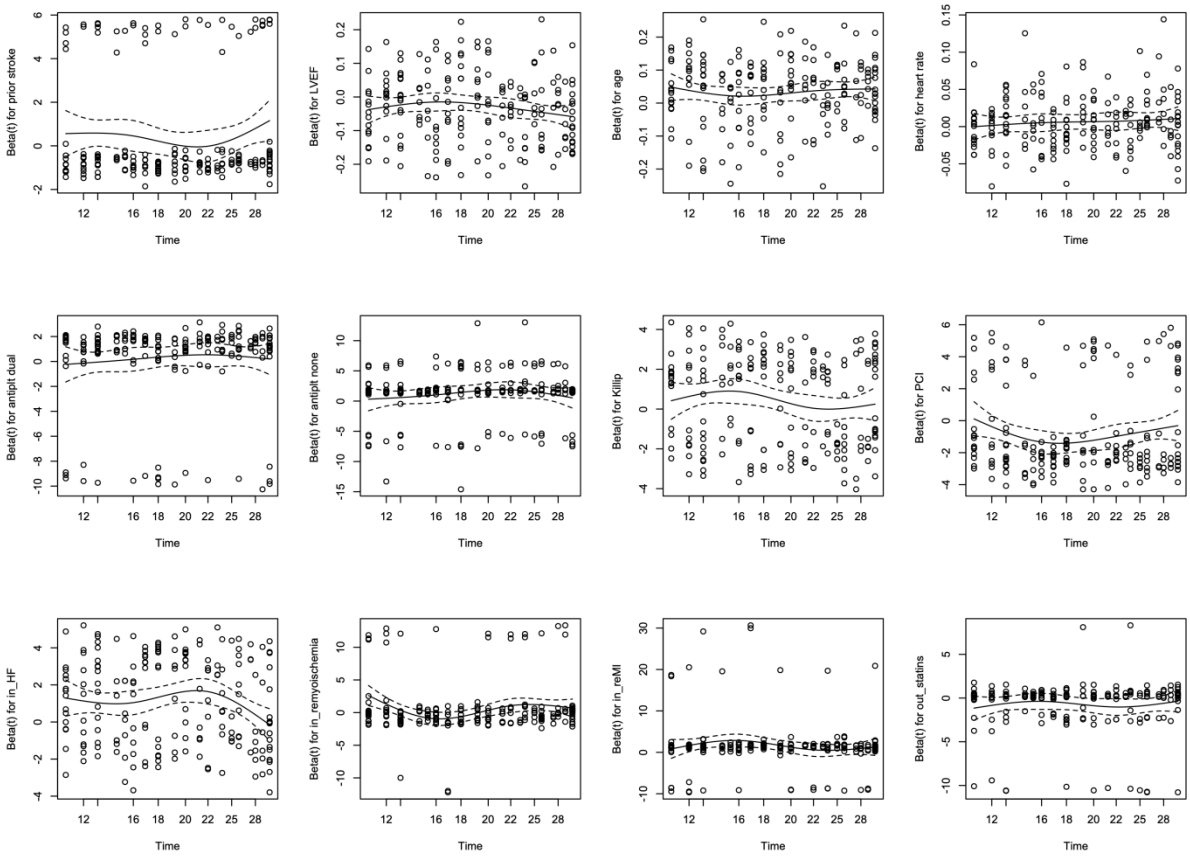
C



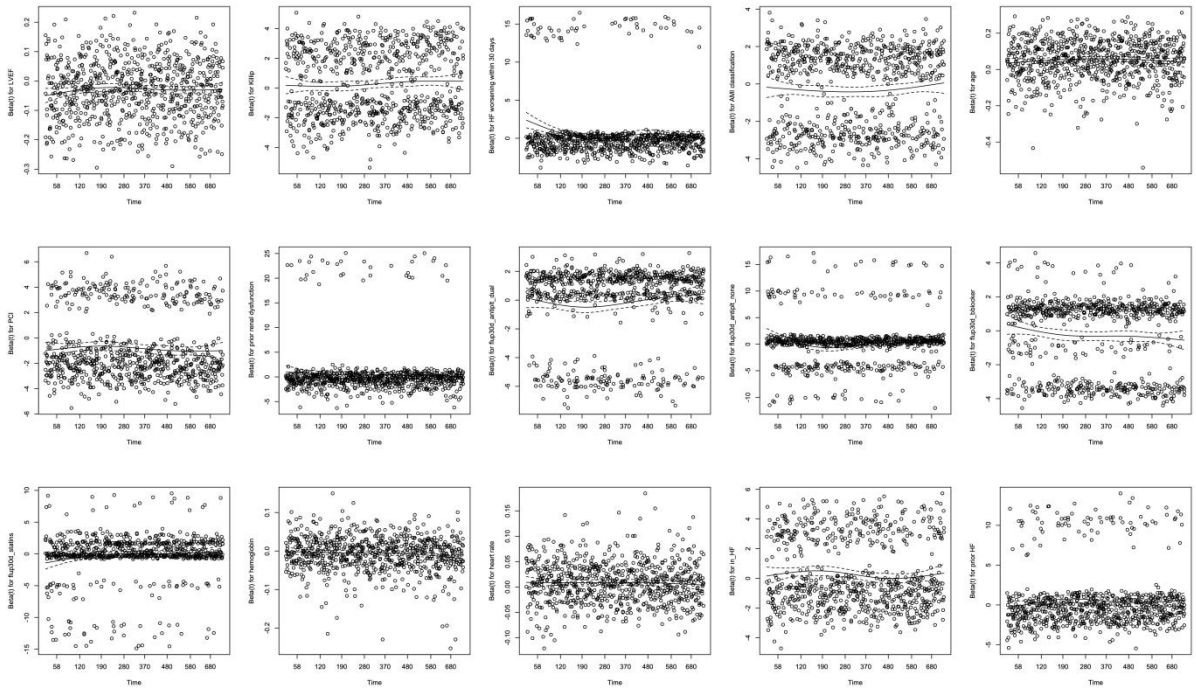
Supplemental Figure 3. Martingale residual plots for testing the linearity assumption before developing the 2-year model



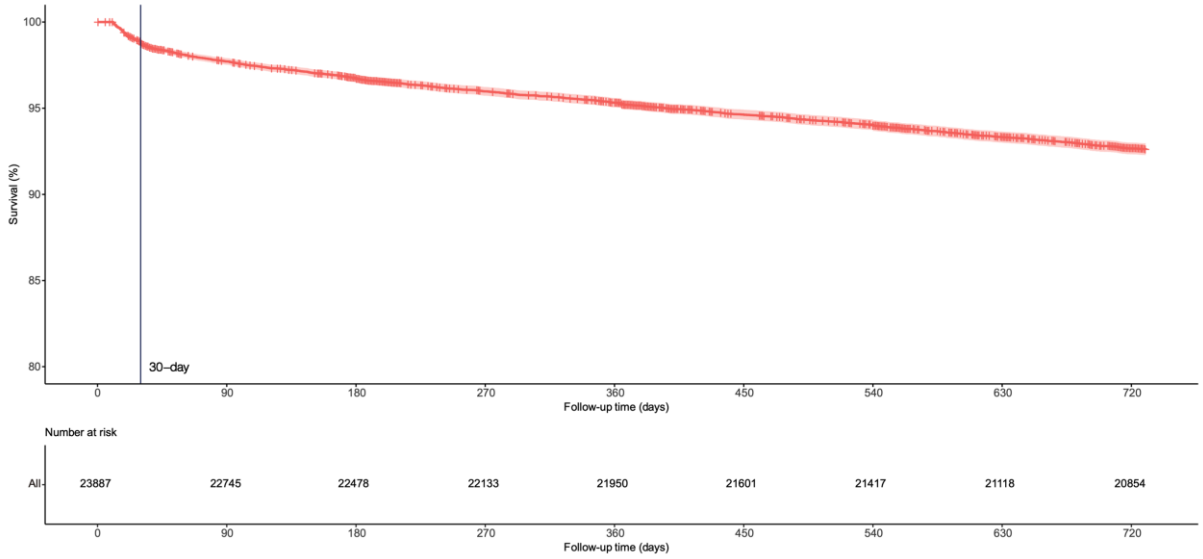
Supplemental Figure 4. Schoenfeld residual plots for testing the proportional hazards assumption before developing the 30-day model



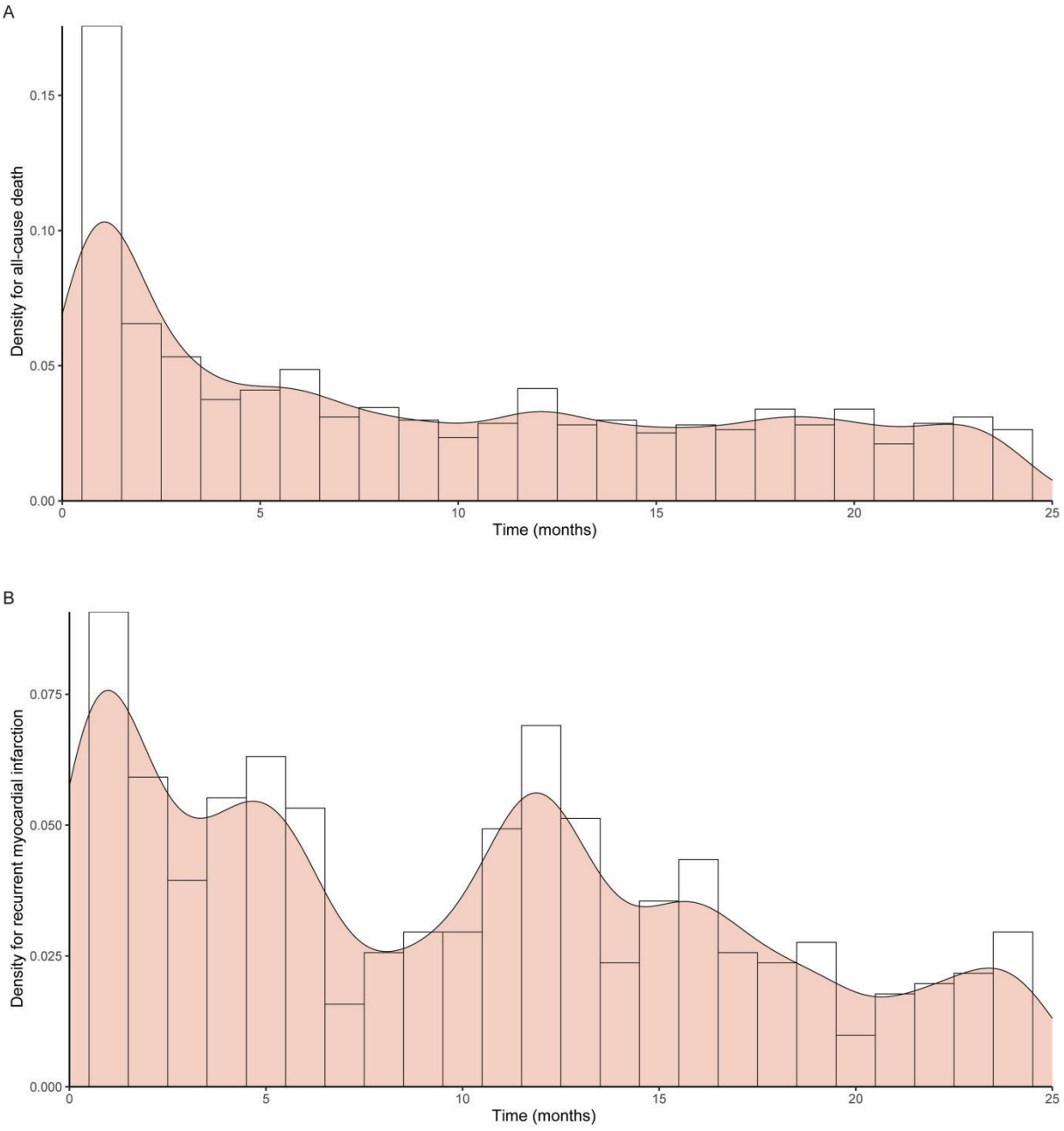
Supplemental Figure 5. Schoenfeld residual plots for testing the proportional hazards assumption before developing the 2-year model



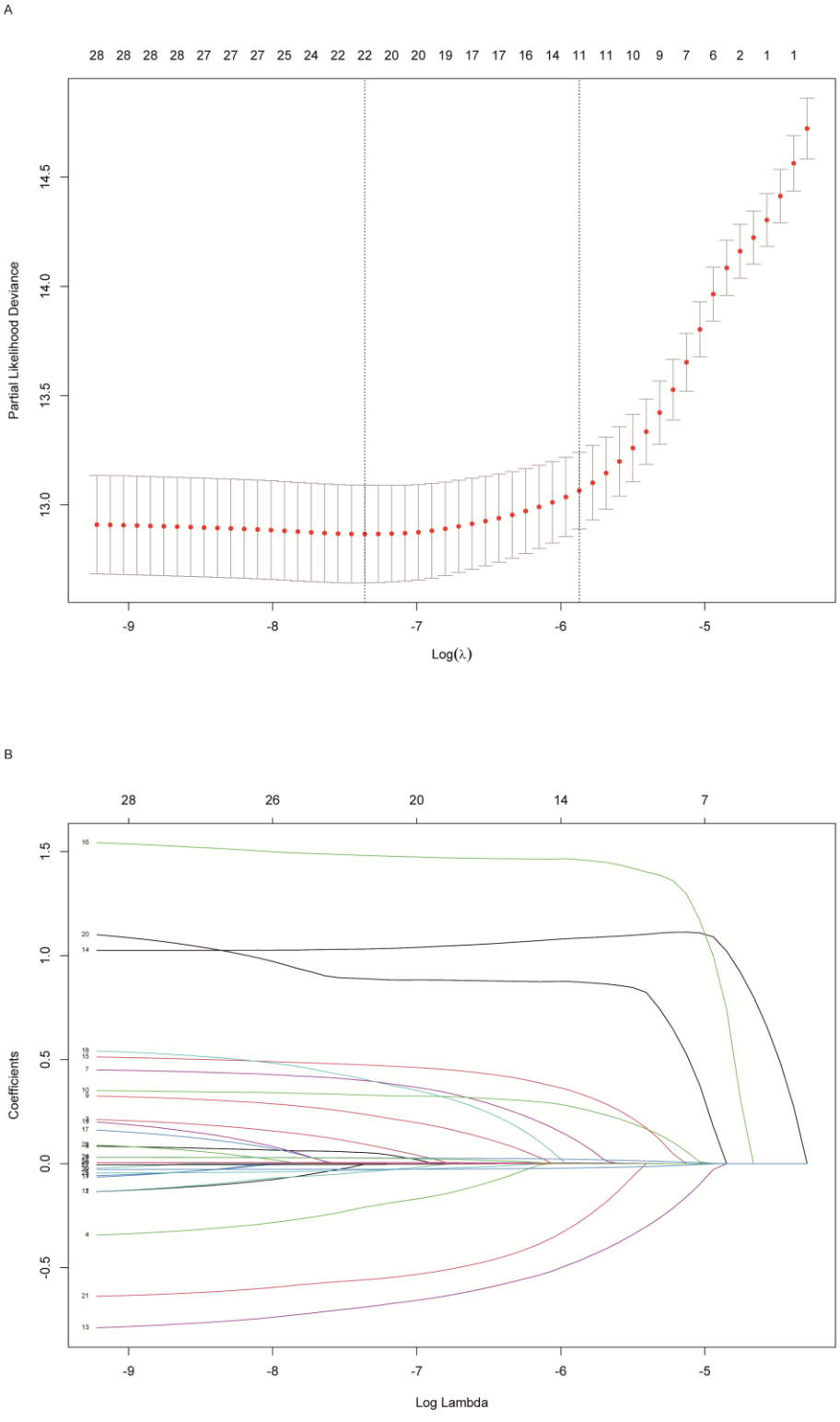
Supplemental Figure 6. Kaplan-Meier curve for patients after AMI hospitalization



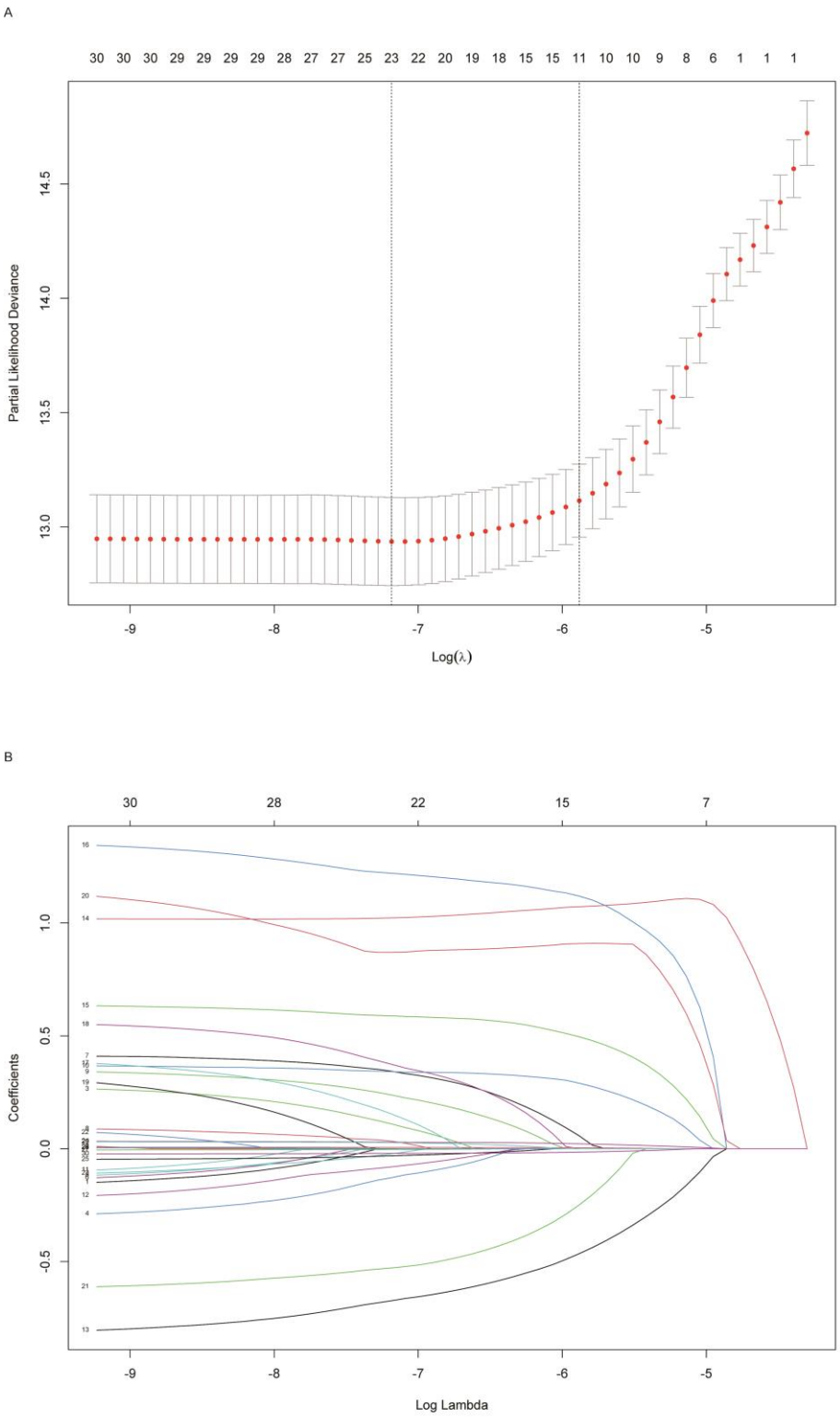
Supplemental Figure 7. Density plots for all-cause death and recurrent myocardial infarction during follow-up



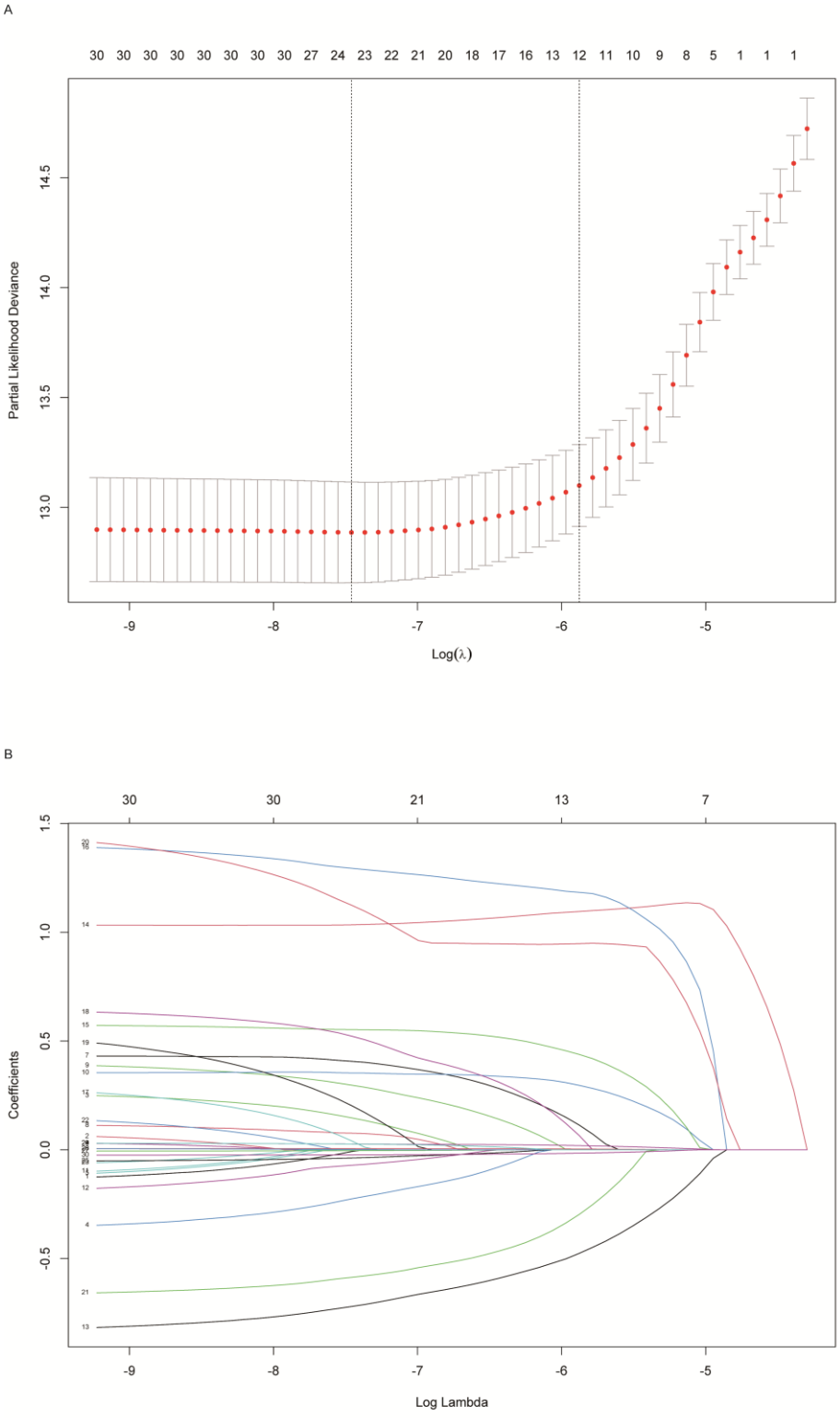
Supplemental Figure 8. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 1



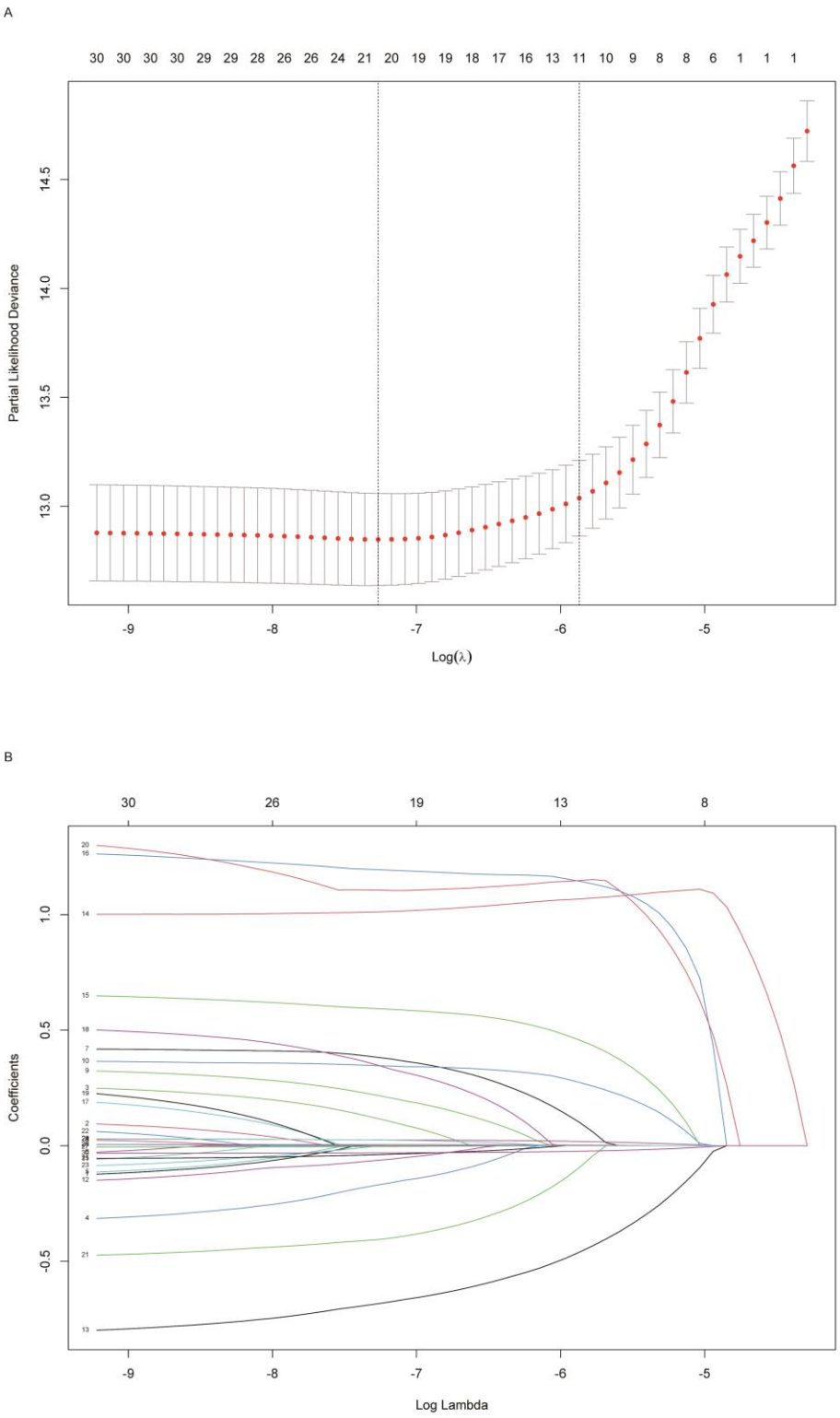
Supplemental Figure 9. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 2



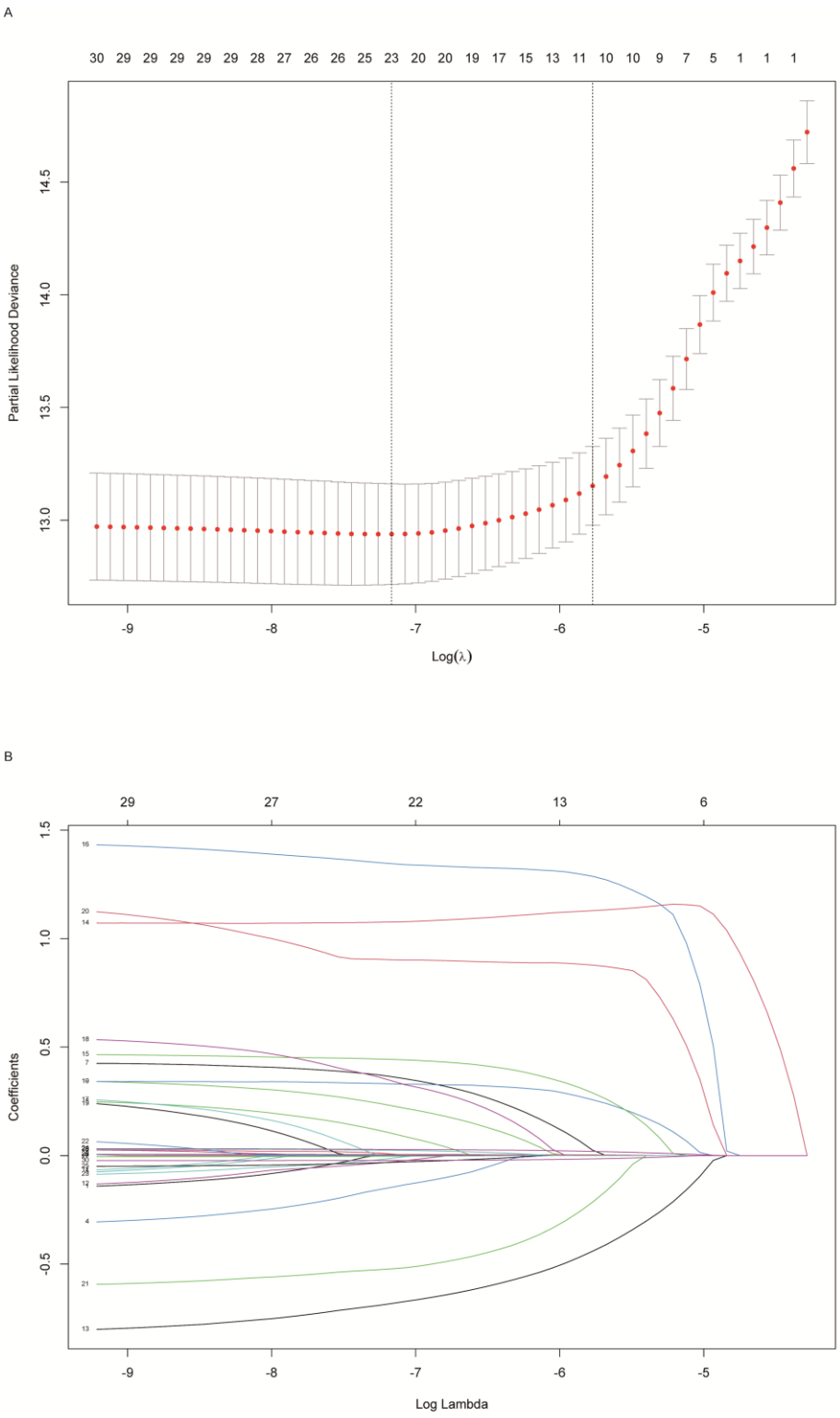
Supplemental Figure 10. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 3



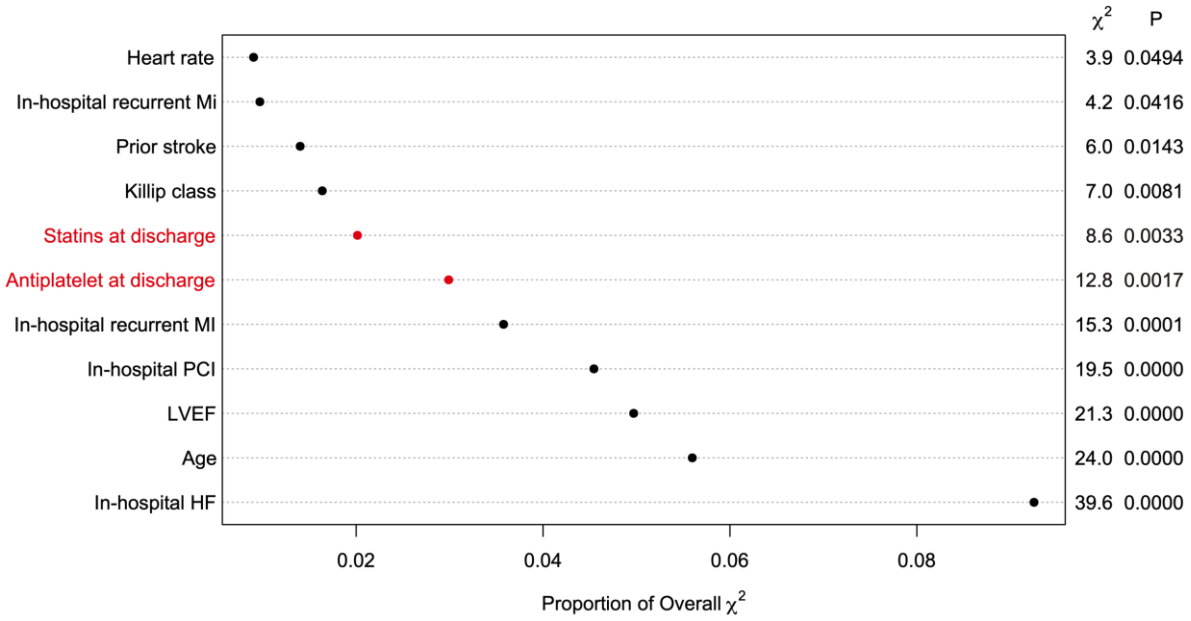
Supplemental Figure 11. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 4



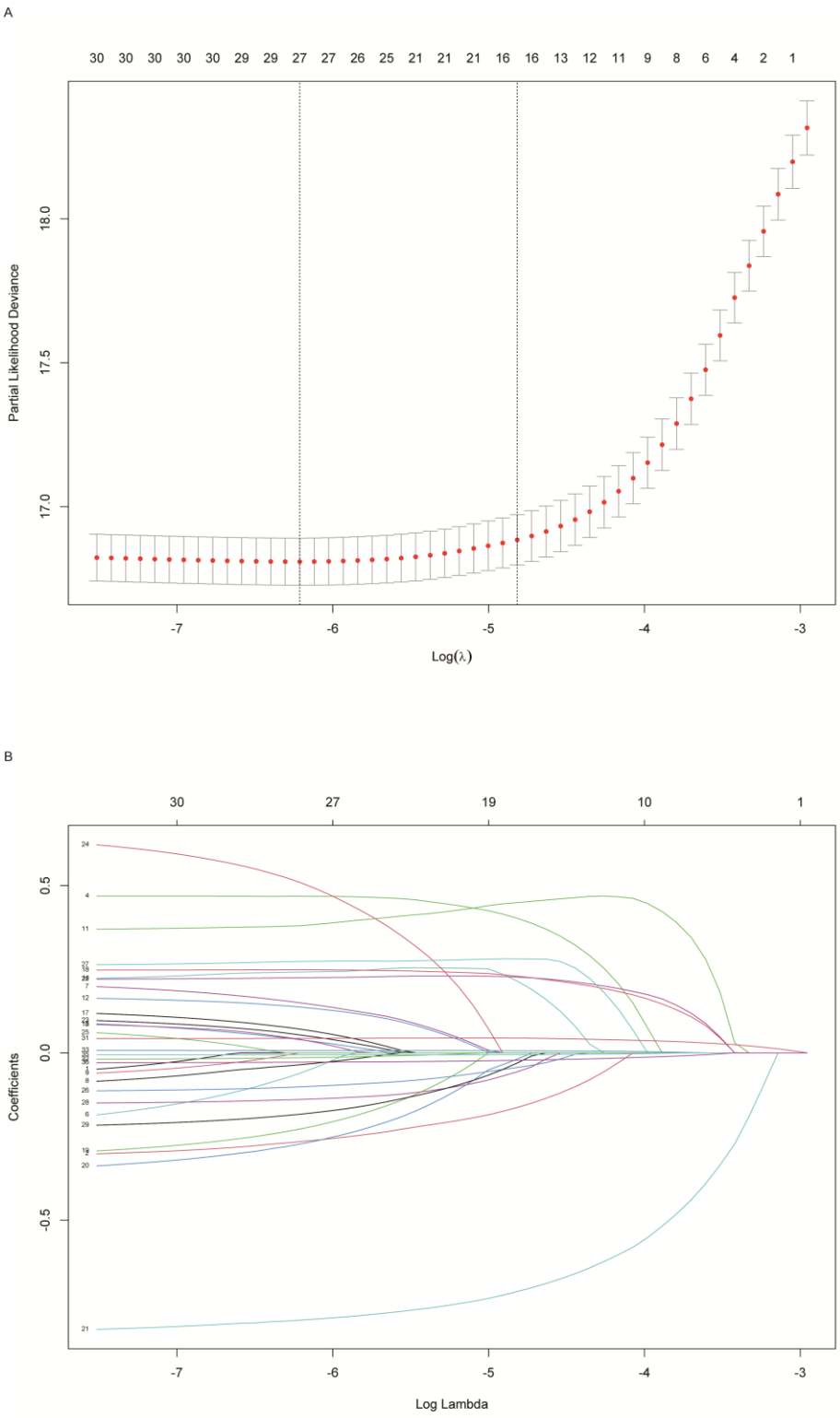
Supplemental Figure 12. Variable selection by LASSO method for 30-day prognostic model in imputation dataset 5



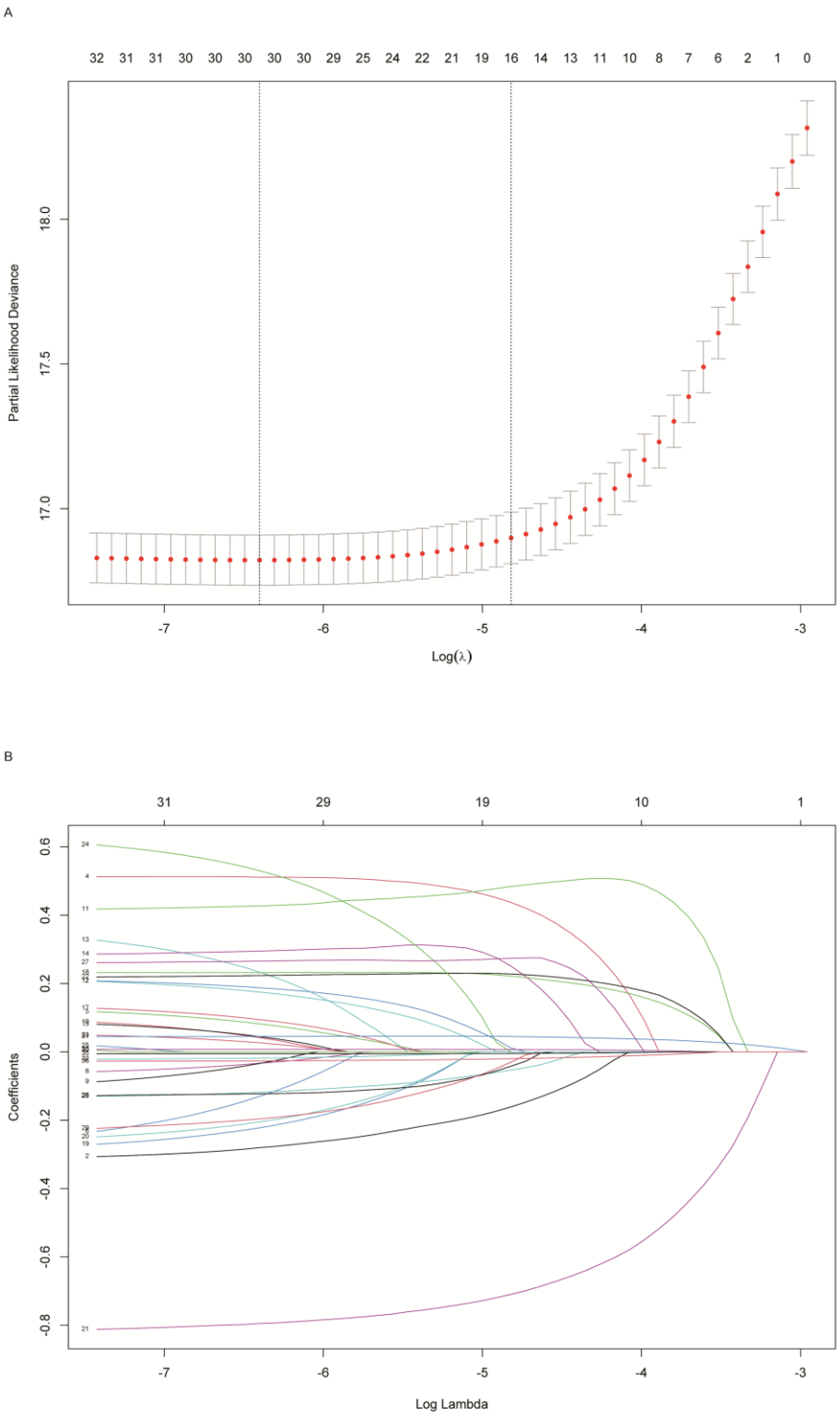
Supplemental Figure 13. Relative importance of selected predictors for 30-day mortality



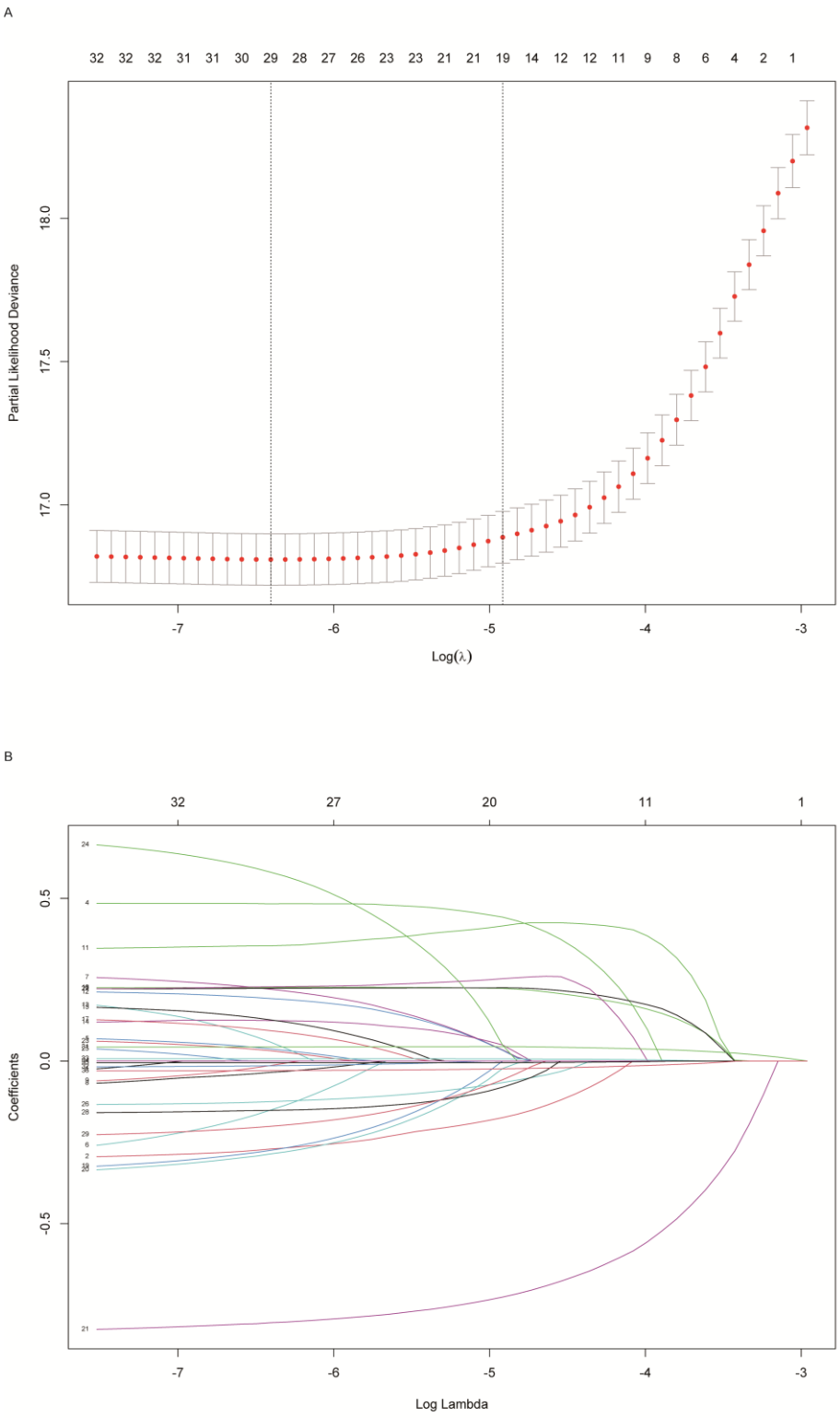
Supplemental Figure 14. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 1



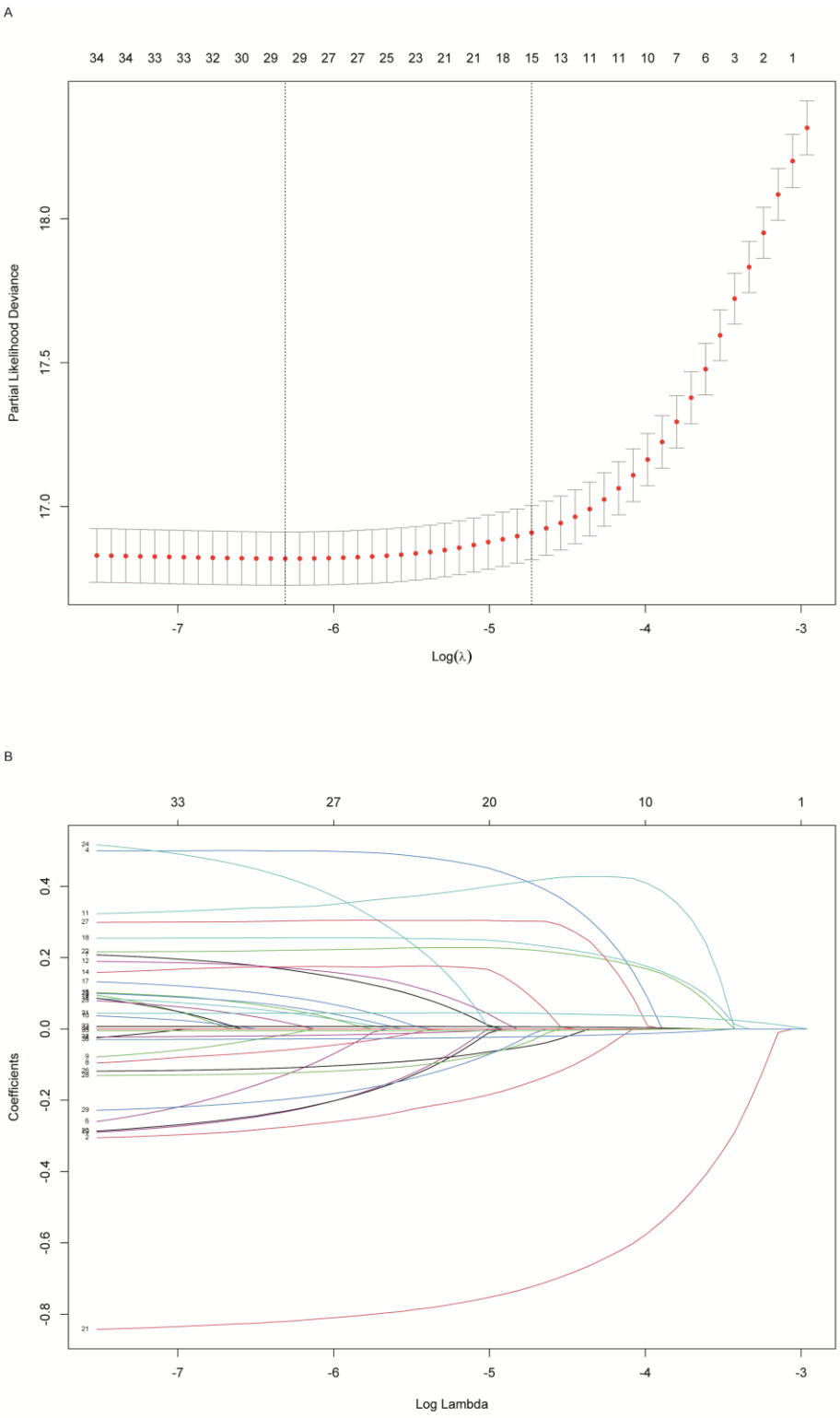
Supplemental Figure 15. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 2



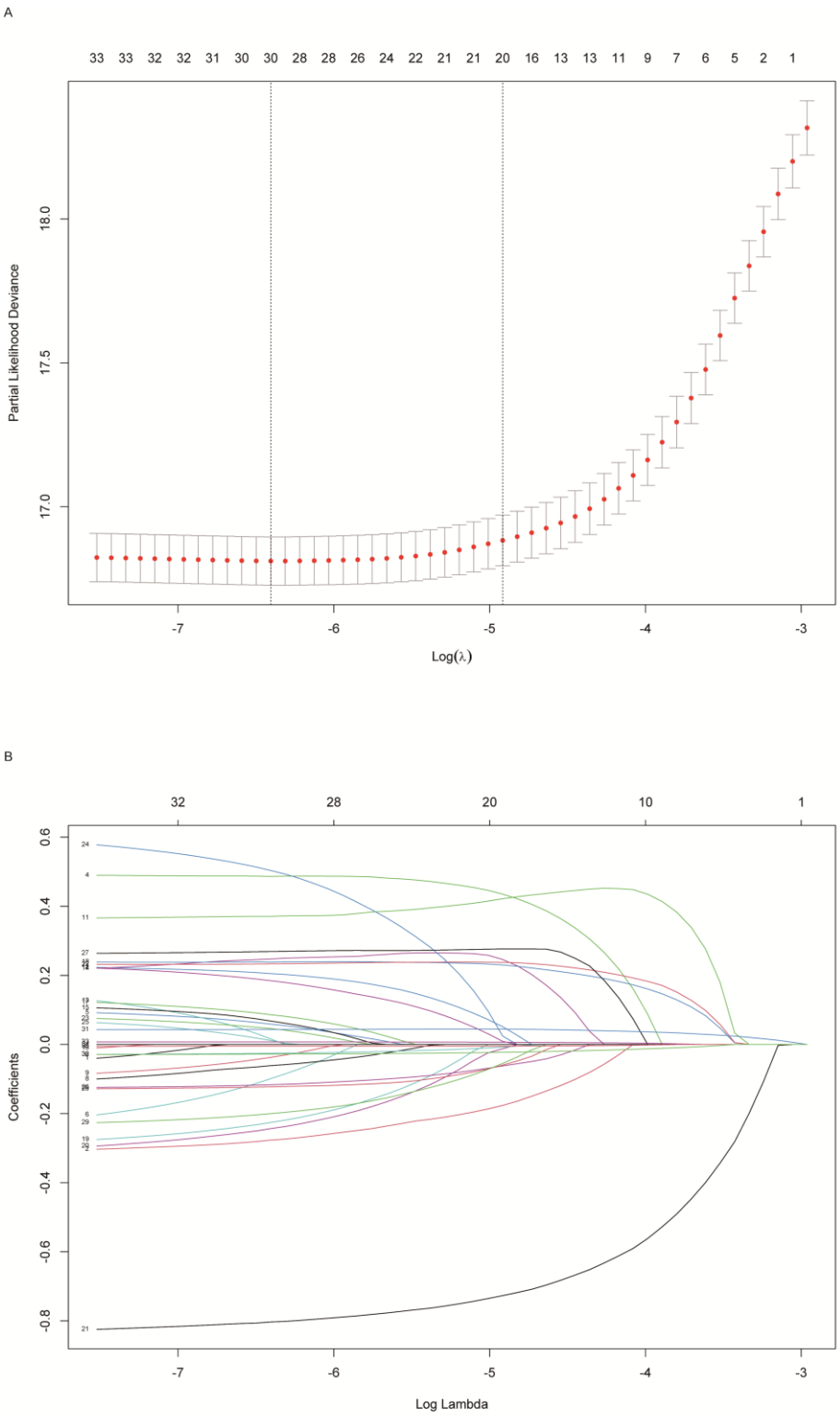
Supplemental Figure 16. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 3



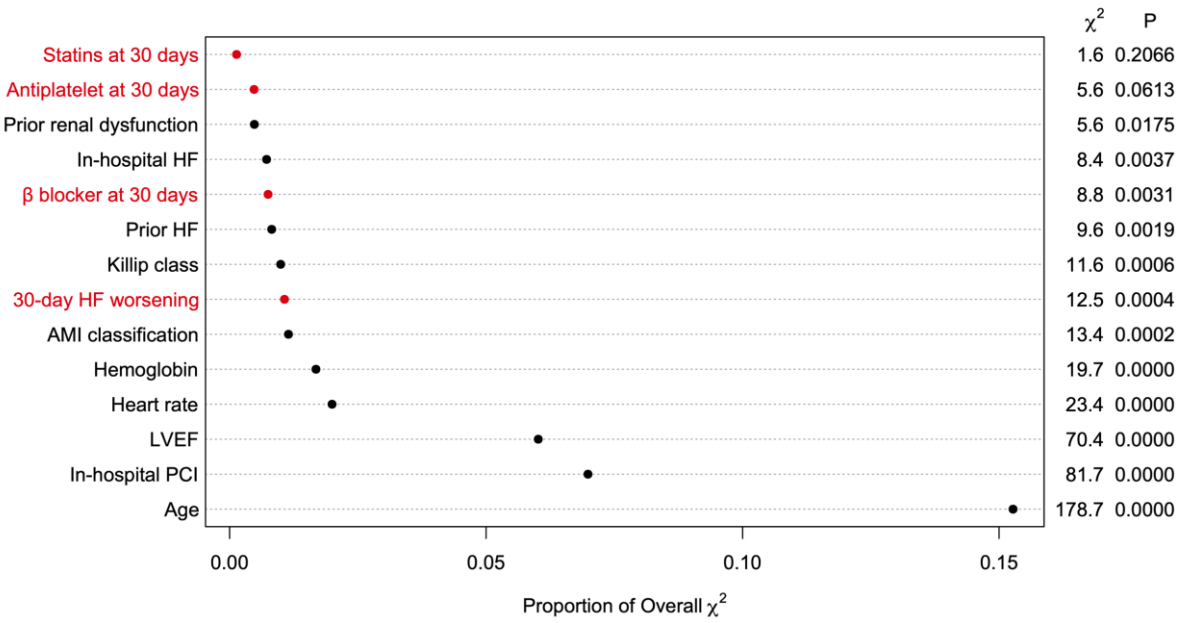
Supplemental Figure 17. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 4



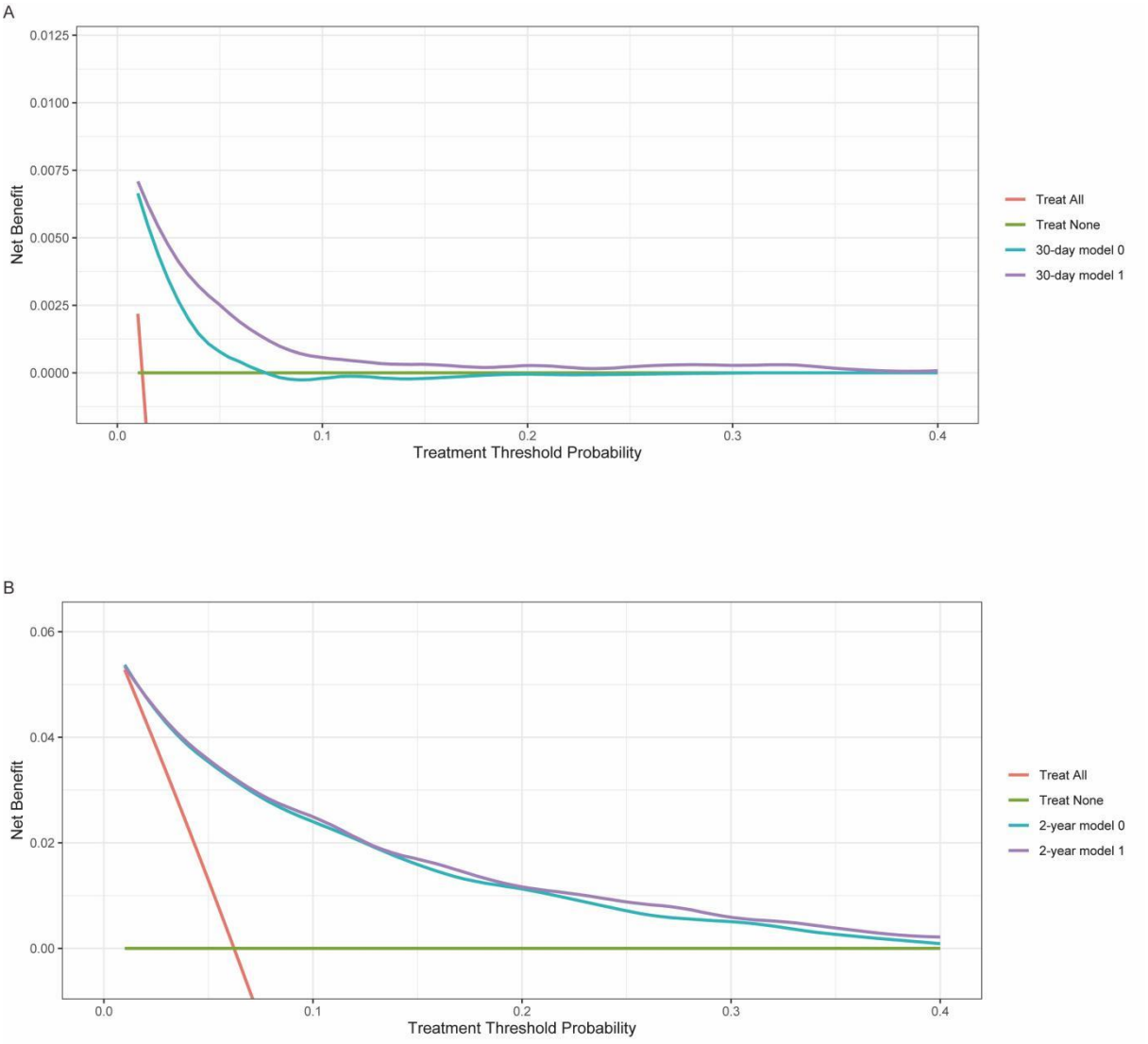
Supplemental Figure 18. Variable selection by LASSO method for 2-year prognostic model in imputation dataset 5



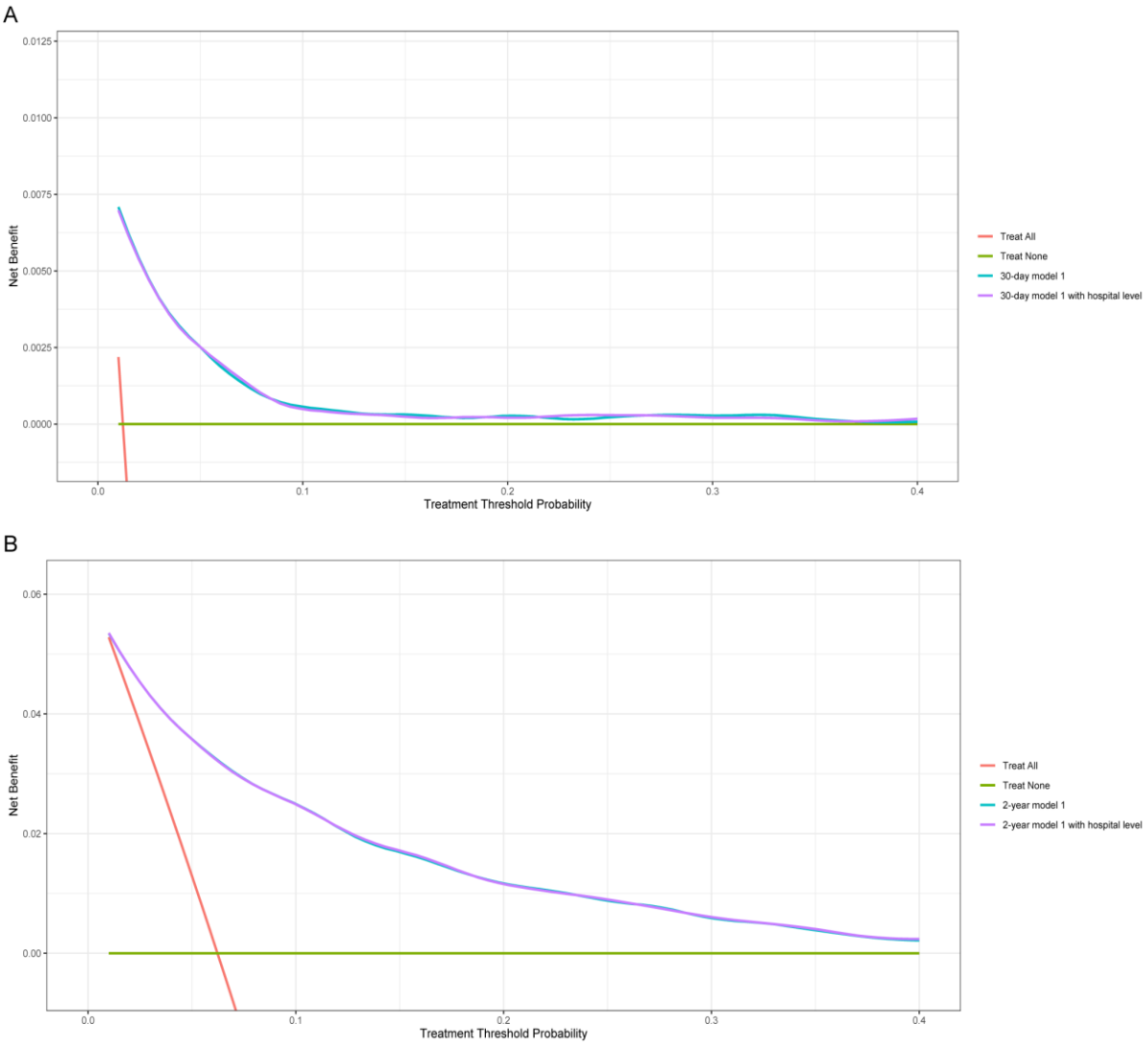
Supplemental Figure 19. Relative importance of selected predictors for 2-year mortality



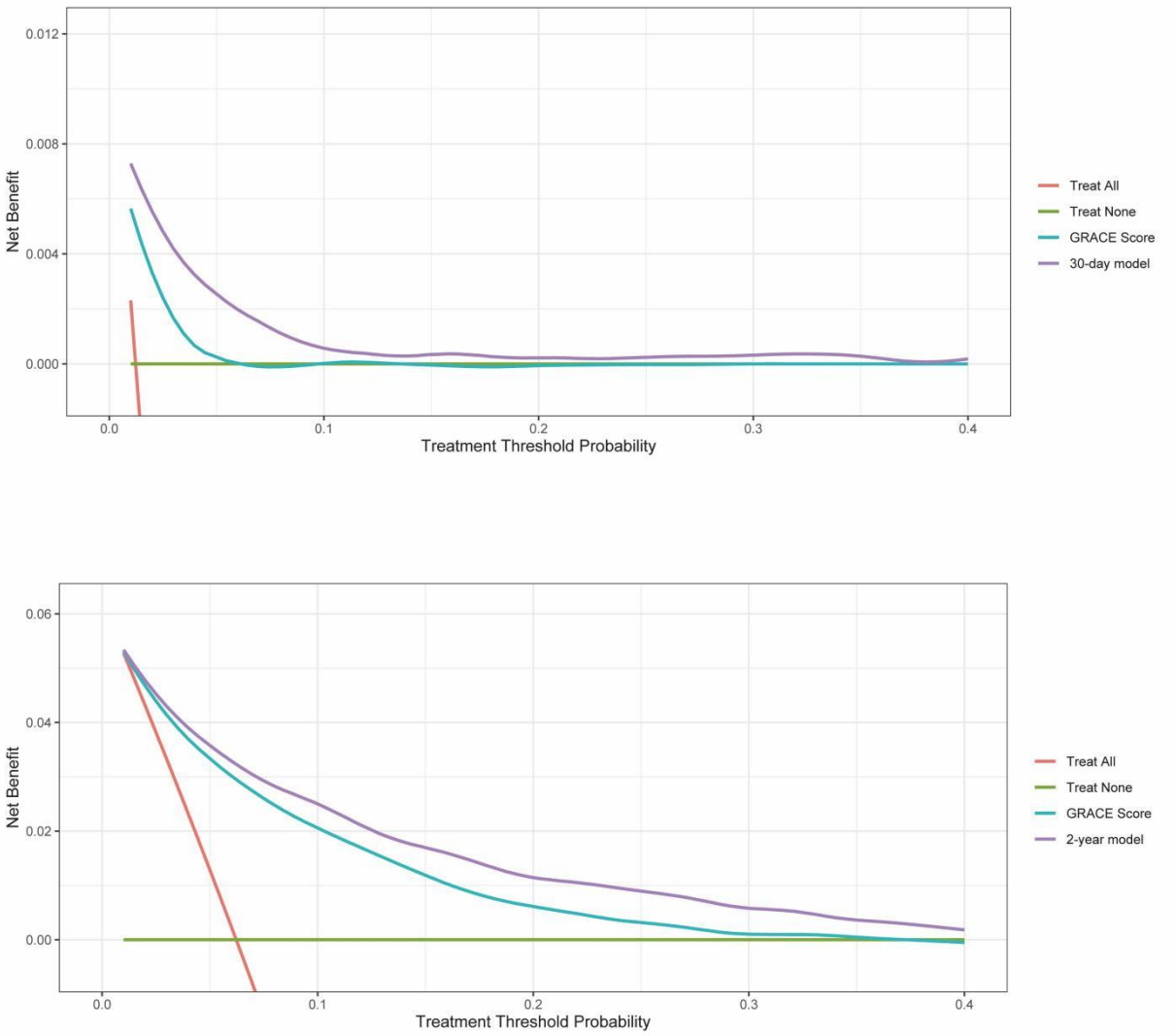
Supplemental Figure 20. Comparisons of clinical utility between models with or without adverse events and medications



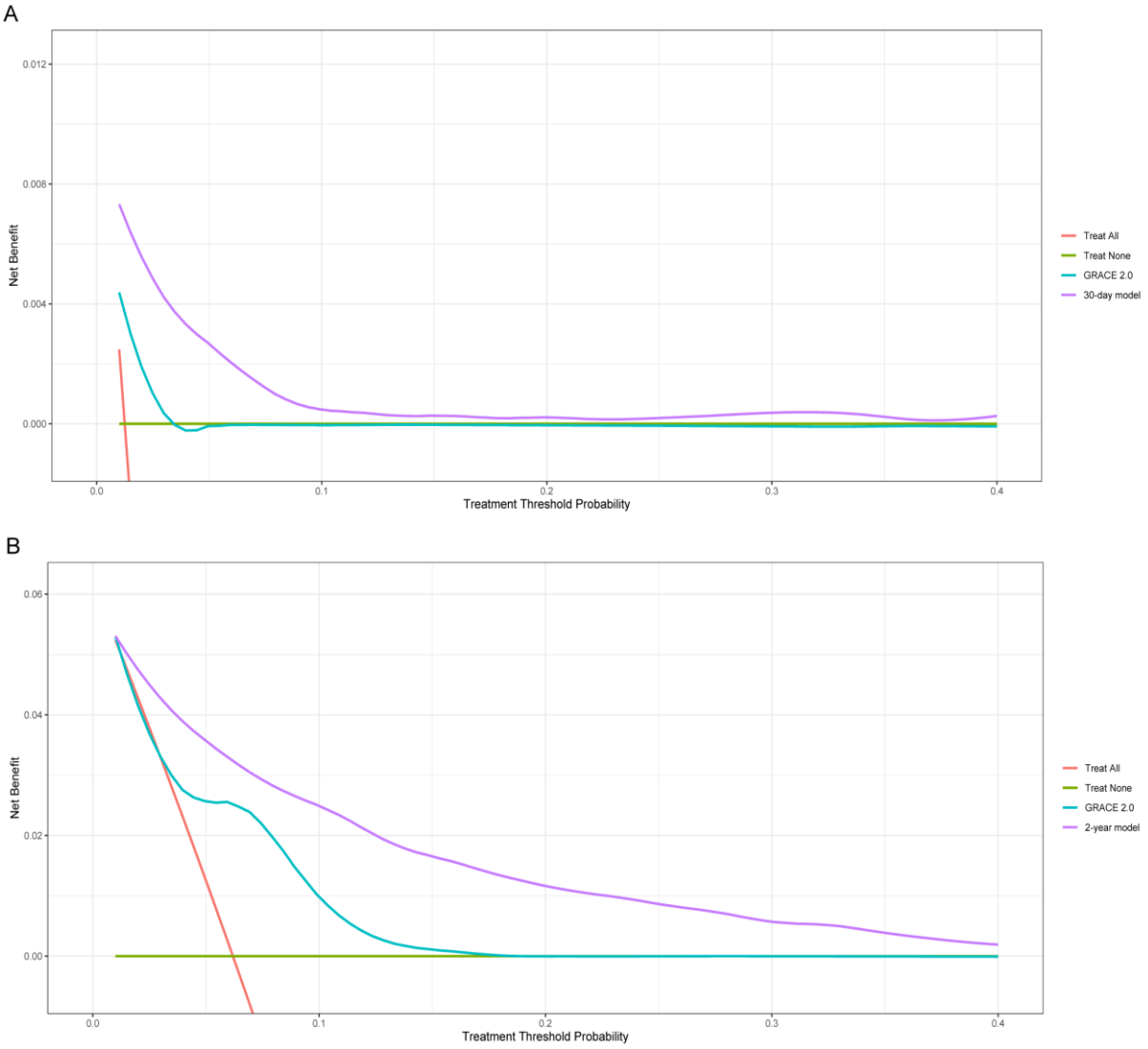
Supplemental Figure 21. Comparisons of clinical utility between models with or without hospital level



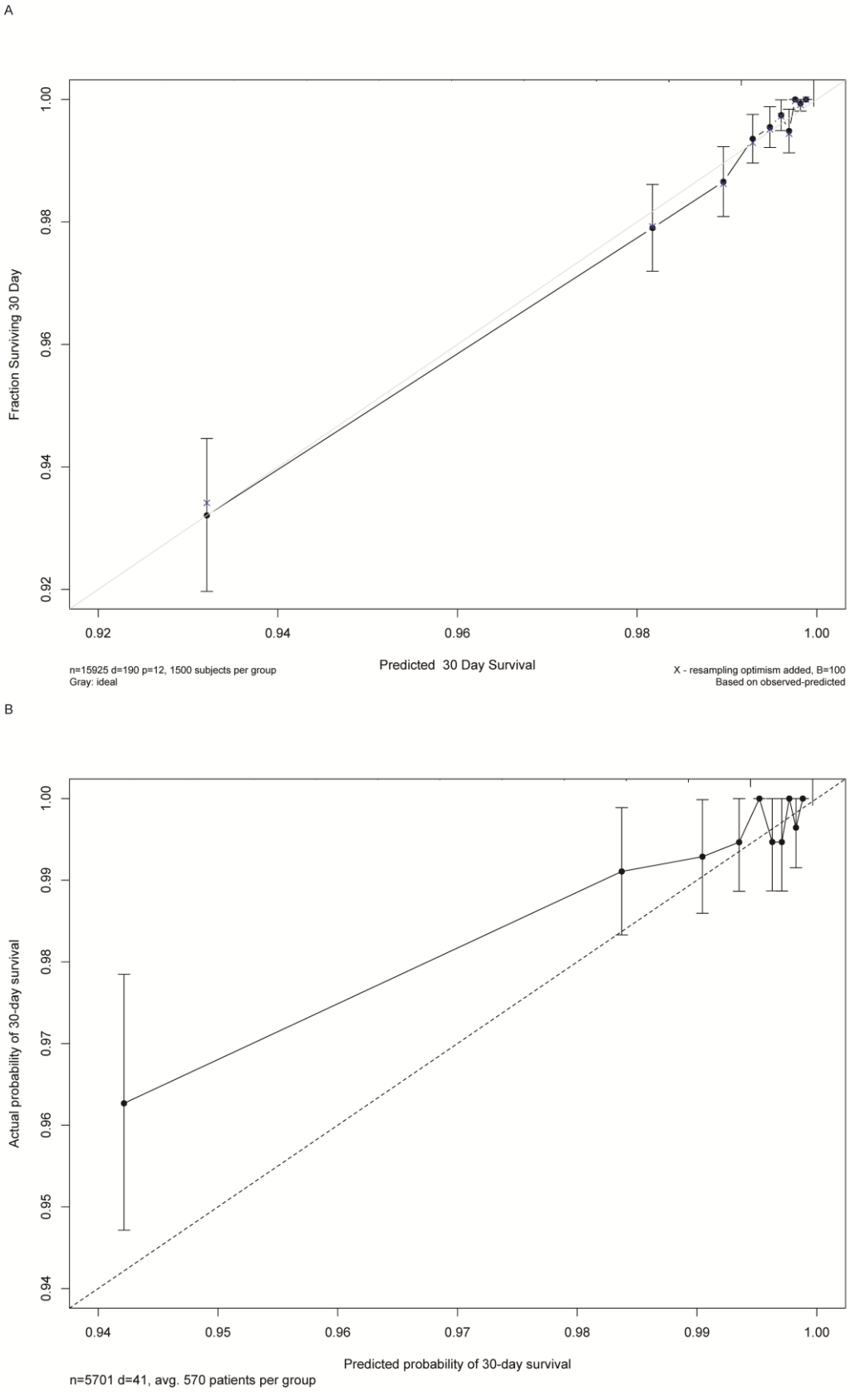
Supplemental Figure 22. Comparisons of clinical utility between models and GRACE 1.0 score



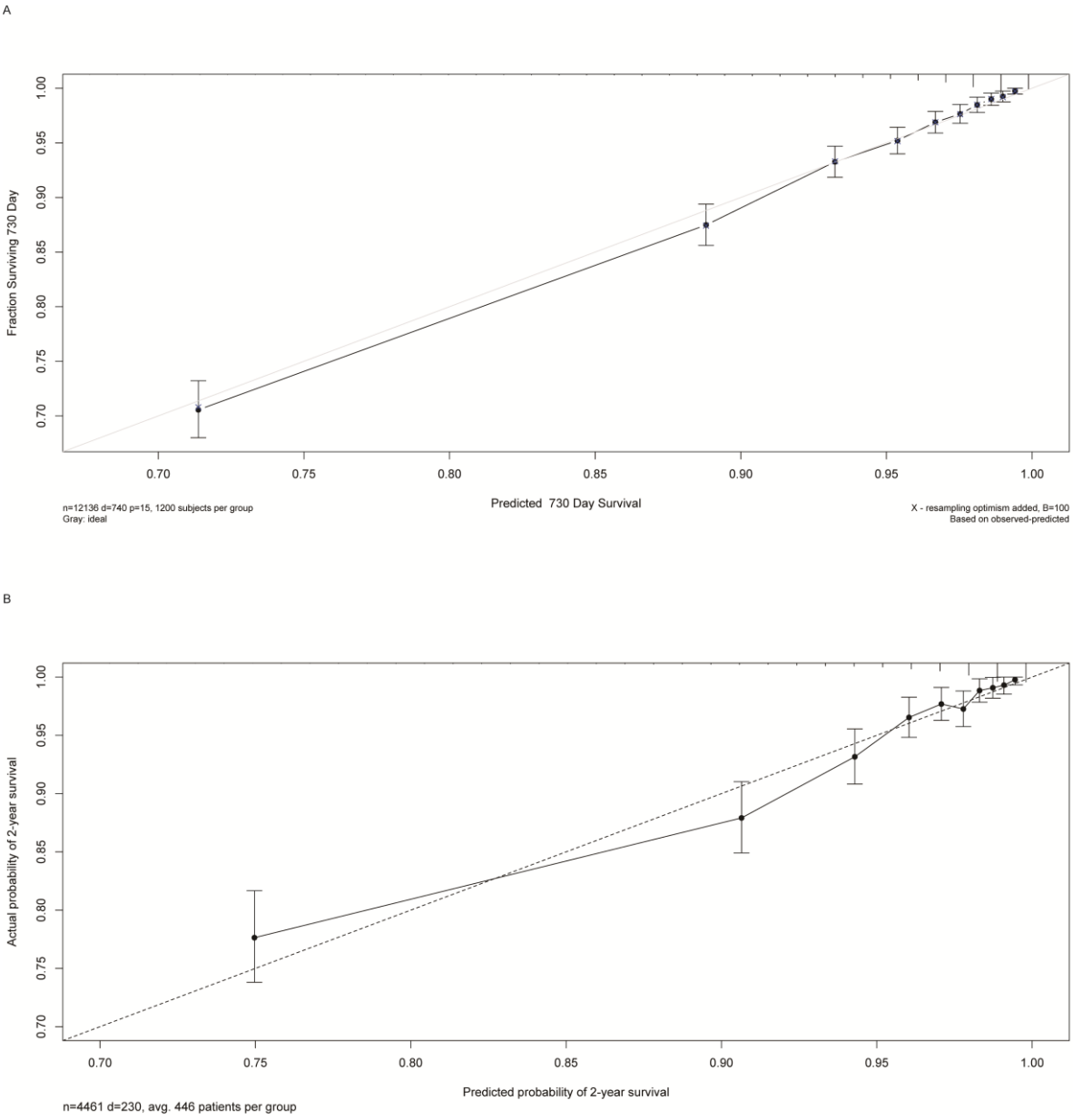
Supplemental Figure 23. Comparisons of clinical utility between models and GRACE 2.0 score



Supplemental Figure 24. Calibration curves of 30-day prognostic nomogram



Supplemental Figure 25. Calibration curves of 2-year prognostic nomogram



TRIPOD Checklist: Prediction Model Development

Section	Item	Checklist description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title and abstract				
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.		
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.		
Introduction				
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.		
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.		
Methods				
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, ifapplicable.		
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.		
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.		
	5b	Describe eligibility criteria for participants.		
	5c	Give details of treatments received, if relevant.		
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.		
	6b	Report any actions to blind assessment of the outcome to be predicted.		
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.		
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.		
Sample size	8	Explain how the study size was arrived at.		

Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.		
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.		
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.		
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.		
Risk groups	11	Provide details on how risk groups were created, if done.		
Results				
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.		
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.		
Model development	14a	Specify the number of participants and outcome events in each analysis.		
	14b	If done, report the unadjusted association between each candidate predictor and outcome.		
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).		
	15b	Explain how to the use the prediction model.		
Model performance	16	Report performance measures (with CIs) for the prediction model.		
Discussion				
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).		
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.		
Implications	20	Discuss the potential clinical use of the model and implications for future research.		
Other information				
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.		
Funding	22	Give the source of funding and the role of the funders for the present study.