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Clinical characteristics, prognosis, and risk prediction model for adverse outcomes in patients suspected of coronary artery diseases and no significant stenosis on angiography

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Abstract

Background and objectives

Although patients with suspected coronary artery disease and no significant stenosis on angiography are thought to have a better prognosis, some still experience adverse outcomes. This study aims to develop a predictive model for these adverse outcomes.

Methods

We retrospectively enrolled patients diagnosed with angina with nonobstructive coronary arteries (ANOCA) between January 2019 and June 2023, collecting relevant clinical data. We employed LASSO regression to select adverse prognostic risk factors, which were then integrated into a Cox proportional hazards regression model. Subsequently, we created a nomogram. Model performance was assessed for discrimination and calibration using the areas under the curve (AUC) and calibration plots, along with internal validation. The nomogram was utilized to categorize patients into high- and low-risk groups, and we compared their survival differences using the log-rank test.

Results

4,452 patients were included in the training cohort, and 1,482 in the testing cohort. The nomogram incorporated eight variables: age, hemoglobin, serum urea, serum sodium, ALT/AST ratio, NT-proBNP, left atrial diameter, and LVEF. It showed good predictive performance for 1-year, 2-year, and 3-year event-free survival probabilities in both the training cohorts (AUC 0.82, 0.90, and 0.89) and testing cohorts (AUC 0.75, 0.77, and 0.78). Calibration plots revealed close alignment between

predicted and actual event-free survival probabilities in both cohorts. Significant survival differences were observed among risk groups (log-rank $p < 0.0001$).

Conclusions

This study has successfully established a predictive model for adverse outcomes in ANOCA patients using clinically accessible variables, which could serve as a valuable tool to risk-stratify patients and customize their management and treatment strategies.

Key word

angina, coronary artery disease, MINOCA, prognosis, nomogram.

Backgrounds

Chest pain is a common symptom among patients seeking medical services, often raising concerns about potentially life-threatening conditions such as coronary artery disease (CAD) [1,2]. Timely and accurate diagnostic assessments, including electrocardiography, coronary computed tomography angiography, and coronary angiography, are frequently recommended for individuals presenting with chest pain to rule out severe conditions such as myocardial infarction (MI) [3,4]. However, in the cohort of patients undergoing diagnostic workup, approximately half exhibit nonobstructive coronary arteries (stenosis less than 50%)[5,6], a condition known as angina with nonobstructive coronary arteries (ANOCA) [7].

ANOCA patients often seek medical care due to symptoms and undergo repetitive invasive examinations, leading to significant healthcare resource utilization and imposing individual burdens and additional risks [8–10]. In a randomized controlled trial involving over 10,000 patients suspected of CAD with intermediate pretest likelihood, only approximately 12% of them yielded a positive result in the final coronary artery functional tests [11]. Patients with a low pretest probability exhibit an exceedingly low positivity rate in diagnostic workup and experience fewer adverse outcomes [12]. Therefore, clinical guidelines recommend delaying diagnostic testing for patients at low risk for CAD[13,14]. However, patients without obstructive coronary arteries confirmed by coronary angiography (CAG) or coronary computed tomography angiography (CCTA) have been observed to experience more adverse outcomes compared to the general population[15–17]. Identifying high-risk patients remains a challenge.

There is limited research on predicting adverse outcomes in ANOCA patients confirmed through CAG or CCTA. Some studies have validated the utility of specific pretest indicators, such as age, sex, and traditional cardiovascular disease risk factors(e.g., hypertension), to identify low-risk ANOCA patients [18]. However, several investigations have shown that specific blood biomarkers, including high-sensitivity troponin and lower HDL-C levels, operate as independent predictive factors for poor prognosis in ANOCA patients, adding prognostic value[19]. To date, comprehensive studies that screen noninvasive indicators and develop a prognostic model are lacking, and most previous studies are reliant on data derived from the Women's Ischemia Syndrome Evaluation (WISE) study[19–21],

which exclusively includes female participants. One study also used WISE data to validate the effectiveness of some risk scores originally designed for other populations, such as the ASCVD score, in predicting adverse outcomes in ANOCA patients, but the results showed suboptimal performance [22]. Therefore, it is necessary to develop a predictive model based on non-invasive indicators to forecast adverse outcomes in ANOCA patients of both sexes. This study aims to bridge this gap to optimize clinical decision-making and patient management.

Method

Study Population

This is a retrospective cohort study that consecutively enrolled patients who presented with suspected symptoms of CAD and underwent coronary angiography at the Department of Cardiology or Emergency Department of the Second Hospital of Tianjin Medical University between January 2019 and June 2023. The Second Hospital of Tianjin Medical University is a cardiac center serving the northern Chinese city of Tianjin and its surrounding regions. This study adheres to the principles outlined in the TRIPOD statement [23].

Patients meeting the following criteria were excluded from the study: (1) patients with acute coronary syndrome or obstructive coronary arteries (defined as a luminal stenosis of ≥50% in a major epicardial coronary artery); (2) patients with a prior diagnosis of CAD, history of percutaneous coronary

intervention (PCI), or coronary artery bypass grafting (CABG); (3) individuals with severe liver or kidney dysfunction, malignancies, or other conditions significantly affecting life expectancy; (4) those with substantial missing baseline data; and (5) patients lost to follow-up. This study received approval from the Ethics Committee of the Second Hospital of Tianjin Medical University, and the requirement for written informed consent from patients was waived.

Clinical Data Collection

Patient data were retrospectively obtained from electronic medical records, including demographic information, medical history, vital sign data, laboratory parameters, echocardiographic data, coronary angiography findings and other relevant details.

Follow-Up and Endpoints

Trained follow-up team members conducted regular patient follow-up after discharge at 30 days, 3 months, 6 months, and annually thereafter. Follow-up was performed using the hospital information system, telephone, or email. The follow-up data for this study were collected up to August 1, 2023.

The primary endpoint was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or coronary-artery bypass grafting (CABG) during follow-up. The secondary endpoint was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat

PCI, and CABG during follow-up.

Statistical Analysis

For the small amount of missing data in smoking and alcohol consumption history, multiple imputation was performed using the MICE package (Multiple Imputation by Chained Equations package). To establish a reliable model, the entire study cohort was randomly stratified into two subsets, a training set and a validation set, with a ratio of 0.75 to 0.25, respectively. The training set was used to generate the predictive model, while the validation set was utilized for model internal validation.

Categorical variables were described as frequencies and percentages, with group differences assessed using the chi-square test or Fisher's exact test as applicable. Continuous variables were expressed as either the mean ± standard deviation (SD) or median [interquartile range, IQR], and group comparisons were conducted using the t test or Kruskal–Wallis test as appropriate. The variables selected through LASSO regression were incorporated into the Cox proportional hazards regression model, and a nomogram was generated based on the Cox regression analysis model. The discriminative ability of the predictive model was evaluated using AUC. The model's calibration was assessed through the calibration curve. Additionally, decision curve analysis was employed to evaluate the clinical utility of the nomogram.

The total score for each patient was calculated based on the nomogram, and the study population was

stratified into high-risk and low-risk groups according to the score corresponding to the 3-year 95% event-free survival probability. Event-free survival for the high- and low-risk groups in the training and validation sets was estimated by Kaplan–Meier method and compared with the log-rank test. All statistical analyses were performed with R software version 4.3.1 (R Foundation for Statistical Computing). All statistical tests were two- tailed, with a significance level set at P<0.05.

Result

Study Population and Patient Characteristics

Out of a consecutive cohort of 17,816 patients who underwent coronary angiography for suspected coronary artery disease, 9,883 individuals with significant coronary artery stenosis and 1,816 patients with a documented history of coronary heart disease were excluded. An additional 131 individuals were excluded due to missing baseline or follow-up data, and 52 patients with severe conditions such as malignant tumors were also excluded. of the final analysis included 5,934 patients with negative coronary angiography results (**Figure 1**).

The mean age of the overall cohort was 43.6 ± 10.8 years, with 58.3% being female, and the median follow-up time was 631 [270, 972] days. Detailed baseline data are provided in **Supplementary Table 1**. During the follow-up period, 145 (2.44%) patients had primary endpoint events, 82 (1.38%) had MACE, 106 (1.79%) had all-cause death, 33 (0.56%) had MI, and 11 (0.19%) had a stroke. The

Kaplan-Meier method was employed to estimate the survival without various adverse events for the total study population (**Supplementary Figure 1**).

Nomogram built based on LASSO-COX regression

The entire cohort was randomly divided into a training cohort consisting of 4,452 patients and a validation cohort comprising 1,482 patients. There were no statistically significant differences in the collected variables between these two groups (**Supplementary Table 1**). LASSO regression was employed to select variables with the strongest correlation to the primary endpoint. As the regularization parameter (λ) increased, certain coefficients were reduced to zero, effectively eliminating those variables from the model (**Figure 2A**). We used a tenfold cross-validation approach to identify the optimal model. Due to the relatively limited number of cases undergoing primary endpoint events in the validation cohort (145), we employed the one standard error (1-se) rule, resulting in eight selected variables (**Figure 2B**). These variables were incorporated into a Cox proportional hazards regression model, with results presented in **Table 2**. A nomogram was developed based on the Cox regression model, with the regression coefficients of these factors amalgamated into a scoring system, ranging from 0 to 100(**Figure 3**). For example, an 81-year-old male patient with a hemoglobin level of 92 g/L, serum urea of 14.1 mmol/L, serum sodium of 145.6 mmol/L, an ALT/AST ratio of 1.68, NT-proBNP at 272 ng/L, left atrial diameter of 38.83 millimeters, and an LVEF of 62% received a total score of 115. The 1-year, 2-year and 3-year event-free survival rates were 99.5%, 96.2% and 89.0%, respectively.

Table 2. Prediction of event-free survival probability using the Cox proportional hazards regression model based on LASSO regression.

Variable	coefficients	z score	HR	95%CI	p value
Age	0.043	4.167	1.044	0.023, 0.063	<0.001
Hemoglobin	-0.015	-2.871	0.985	-0.026, -0.005	0.004
Urea	0.074	3.947	1.077	0.037, 0.111	<0.001
Serum sodium	-0.074	-5.694	0.929	-0.1, -0.049	<0.001
ALT/AST ratio	0.444	2.439	1.559	0.087, 0.8	0.015
NT-proBNP	0	2.094	1	0, 0	0.036
Left atrial diameter	0.076	5.959	1.079	0.051, 0.8	<0.001
LVEF	-0.022	-2.289	0.979	-0.04, -0.003	0.022

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase; LVEF, left ventricular ejection fraction.

Discrimination and calibration of the nomogram

The discriminative ability of the model was assessed by plotting receiver operating characteristic curves. In the training set, the AUC for 1-, 2-, and 3-year predictions was 0.82, 0.90, and 0.89, respectively. In the validation set, the corresponding AUC for 1-, 2-, and 3-year predictions were 0.75, 0.77, and 0.78, respectively (**figure 4**).

Figure 5 illustrates calibration plots for the models predicting 1-, 2-, and 3-year survival in both the training and validation datasets. In well-calibrated models, the points closely align with the ideal 45-degree line, indicating that predicted survival closely matches observed survival and demonstrating

good model calibration.

Decision Curve

Decision curve analysis was employed to evaluate the potential improvement in clinical outcomes through nomogram-assisted decision-making for patients. As illustrated in **Figure 6**, the results reveal that across a broad spectrum of threshold probabilities in both the training and testing cohorts, utilizing the nomogram for predicting the 2-year or 3-year event-free survival probability offers a more significant net benefit when compared to strategies of 'treat all' or 'treat none.' These findings underscore the clinical utility of the nomogram.

Risk stratification

Considering that the study population consists of low-risk patients with non-obstructive coronary artery stenosis, the threshold for further risk stratification was set at a higher event-free survival probability, specifically a score of 104 points corresponding to the 95% 3-year event-free survival probability as determined by the nomogram. Individuals scoring below this threshold were categorized as low-risk, while those scoring equal to or above it were classified as high-risk. Kaplan-Meier curves depicting event-free survival were created for the two risk groups in the training and validation sets (**Figure 7**). Furthermore, MACE-event free survival of these groups is shown in **Supplementary Figure 2**. These results consistently demonstrated the model's efficacy in patient risk stratification.

Discussion

This study focused on patients initially suspected of having CAD but who were found to have nonobstructive coronary arteries following coronary angiography. A wide range of variables, including demographic infomation, vital signs, laboratory parameters, and echocardiographic measurements, were meticulously examined. Ultimately, 8 key variables, namely age, hemoglobin levels, serum urea, serum sodium levels, ALT/AST ratio, NT-proBNP levels, left atrial diameter, and LVEF, were identified. The study successfully developed a nomogram to predict the probability of event-free survival for these patients, demonstrating excellent discriminatory and calibration abilities in both the training and validation sets. The utilization of this predictive model in clinical practice empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes.

In clinical practice, a substantial number of patients with potential cardiac issues, such as chest pain, actively seek medical attention in both outpatient and emergency department settings. In the United Kingdom, for instance, approximately 1-2% of adults consult primary care facilities when experiencing chest pain for the first time [15]. Similarly, millions of individuals in the United States undergo stress tests in outpatient clinics each year for undiagnosed heart conditions [24]. However, research has

consistently shown that following diagnostic assessments like coronary angiography, approximately 50% of patients do not exhibit obstructive coronary artery stenosis [5,16,25,26]. Traditionally, such patients were often considered to have a favorable prognosis and no significant cardiac conditions , potentially resulting in the omission of further diagnostic measures and therapeutic interventions [27–29]. However, recent research has indicated that these patients face a significantly elevated risk of adverse outcomes compared to the general population. The WISE study revealed that at over a 10-year follow-up, patients without obstructive coronary stenosis on coronary angiography had rates of cardiovascular death and MI of 6.7% and 12.8%, respectively, underscoring the heightened risk among female ANOCA patients [21,30,31]. Other studies have also demonstrated that ANOCA patients, regardless of their gender, face an increased risk of experiencing CAD-related outcomes compared to the general population[16,26,32].

Our findings from this study indicate that ANOCA patients tend to be younger, with an average age of 43.6 years, and a higher proportion of them are female (58.3%) [7]. During a median follow-up period of 2 years, the rates of all-cause death, MI, and stroke were 1.79%, 0.56%, and 0.19%, respectively. These findings align with a previous study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3% [26]. Our research further supports the characterization of ANOCA patients and provides additional evidence of their elevated risk for adverse outcomes across diverse populations.

While clinical guidelines suggest risk stratification of chest pain patients and deferring testing for those

with a low likelihood of CAD, this strategy may inadvertently exclude high-risk ANOCA patients who require further assessment and appropriate therapeutic interventions [13,14]. As highlighted in a recent review, a significant proportion of ANOCA patients (ranging from 75% to 90%) exhibit various underlying causes, such as coronary microvascular dysfunction (CMD), microvascular spasm, endothelial dysfunction, epicardial coronary spasm, and/or myocardial bridging [7,33], emphasizing the critical importance of identifying high-risk ANOCA patients to optimize their further management.

Current research on factors related to adverse outcomes in the ANOCA population is limited. One study attempted to develop a risk tool for chest pain patients with normal coronary arteries to predict favorable outcomes. This tool comprised 10 variables, including age, gender, and the presence of conditions like hypertension, diabetes, or dyslipidemia. However, it is important to note that this study solely relied solely on pretest clinical data and accessed coronary arteries through coronary CTA [18]. In contrast, our predictive model incorporated pre-test indicators, including demographic variables and medical history, with age being one of the key factors. Age is a variable included in many traditional CAD prediction models because it is easily obtainable and reflects the aging of the entire cardiovascular system, including increased arterial stiffness and decreased vascular endothelial function [22,34].

Previous studies have also indicated that several blood biomarkers are associated with unfavorable outcomes in ANOCA patients, including lower levels of HDL-C, elevated levels of soluble urokinase-type plasminogen activator receptor, and high-sensitivity troponin [19,20]. However, none of these

studies conducted comprehensive screening of clinical variables or developed a predictive model. After a thorough screening of blood biomarkers, our predictive model incorporated hemoglobin, serum urea, serum sodium and NT-proBNP, which are rarely reported to be associated with adverse outcomes in ANOCA patients. Anemia, for example, is a common pathological condition involved in the occurrence and development of CAD and heart failure through various mechanisms [35]. It significantly increases the risk of developing CAD and heart failure and is associated with adverse outcomes in these patients [36,37]. Serum urea reflects renal function, which is a crucial factor influencing the cardiovascular system [38]. Previous research has shown that an elevated serum urea levels increase the risk of CAD and serve as a predictive factors for adverse outcomes in CAD and heart failure patients [39,40]. The role of serum sodium in cardiovascular disease is still not fully understood, but several studies have indicated that even mild reductions in serum sodium, even within the normal range, are associated with higher all-cause mortality and cardiovascular mortality in elderly individuals or the general population [41–44]. The underlying mechanisms behind this association require further research. NT-proBNP is a widely recognized marker for heart failure and exhibits strong predictive capabilities for the prognosis of heart failure patients [45]. Previous studies have also demonstrated its ability to predict cardiovascular events and mortality even in community-dwelling or elderly populations without heart failure [46–49].

Our predictive model also considered echocardiographic parameters. Echocardiography is a noninvasive, easily performed, and cost-effective imaging technique that provides comprehensive insights into cardiac structure and function. In our model, left atrial diameter and LVEF were included.

Left atrial enlargement is closely associated with conditions like atrial fibrillation and heart failure, and factors such as hypertension and mitral valve diseases can also lead to left atrial enlargement. It is commonly regarded as a biomarker for adverse cardiovascular outcomes [50–53]. The LVEF serves as one of the diagnostic and classificatory criteria for heart failure, with the latter often signifying the advanced stage of diverse cardiac ailments and indicates an unfavorable prognosis [54,55].

Strengths and limitations

This study has several limitations. First, it is a retrospective study conducted at a single medical center, which may introduce some potential biases. Second, the study population consisted entirely of individuals from northern China, so caution should be exercised when generalizing the findings of this study to other populations. Third, due to the limitations of retrospective research, we were unable to further subdivide nonobstructive coronary stenosis into "normal coronary" (without significant coronary atherosclerosis) and "nonobstructive CAD" (stenosis <50%), although these two groups may have similar subsequent management. Finally, the predictive model lacks validation in an external population, but internal validation was performed, and it demonstrated good discrimination and calibration.

Conclusion

In summary, we conducted a comprehensive evaluation of clinically accessible variables and

successfully developed a predictive model for assessing adverse outcomes in patients with suspected CAD who do not exhibit obstructive coronary artery stenosis. This nomogram equips clinicians with a valuable tool for risk stratification in ANOCA patients, allowing for optimized management and treatment strategies aimed at improving patient outcomes.

List of abbreviations

ANOCA, angina with nonobstructive coronary arteries

ACU, areas under the curve

ALT, alanine transaminase

AST, aspartate transaminase

LVEF, left ventricular ejection fraction

CAD, coronary artery disease

MI, myocardial infarction

CAG, coronary angiography

CCTA, coronary computed tomography angiography

HDL-C, high-density lipoprotein cholesterol

PCI, percutaneous coronary intervention

CABG, coronary-artery bypass grafting

MACE, major adverse cardiovascular events

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Availability of data and materials

The original data supporting the findings of this study can be obtained from the corresponding author upon request.

Author contributions

ZL and CKY conceived and designed the protocol; ZL, XZK, HST, ZYK, and GTS collected the data; ZL analyzed the data; ZL wrote the manuscript; CKY, RHW, LT, ZJK, XZK, HST, ZYK, GTS and WX critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Disclosures

The authors do not have any associations that are pertinent to the subject matter of this paper to disclose.

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Figure and table

Figure 1. Flowchart of study participation. CAD, coronary artery disease.

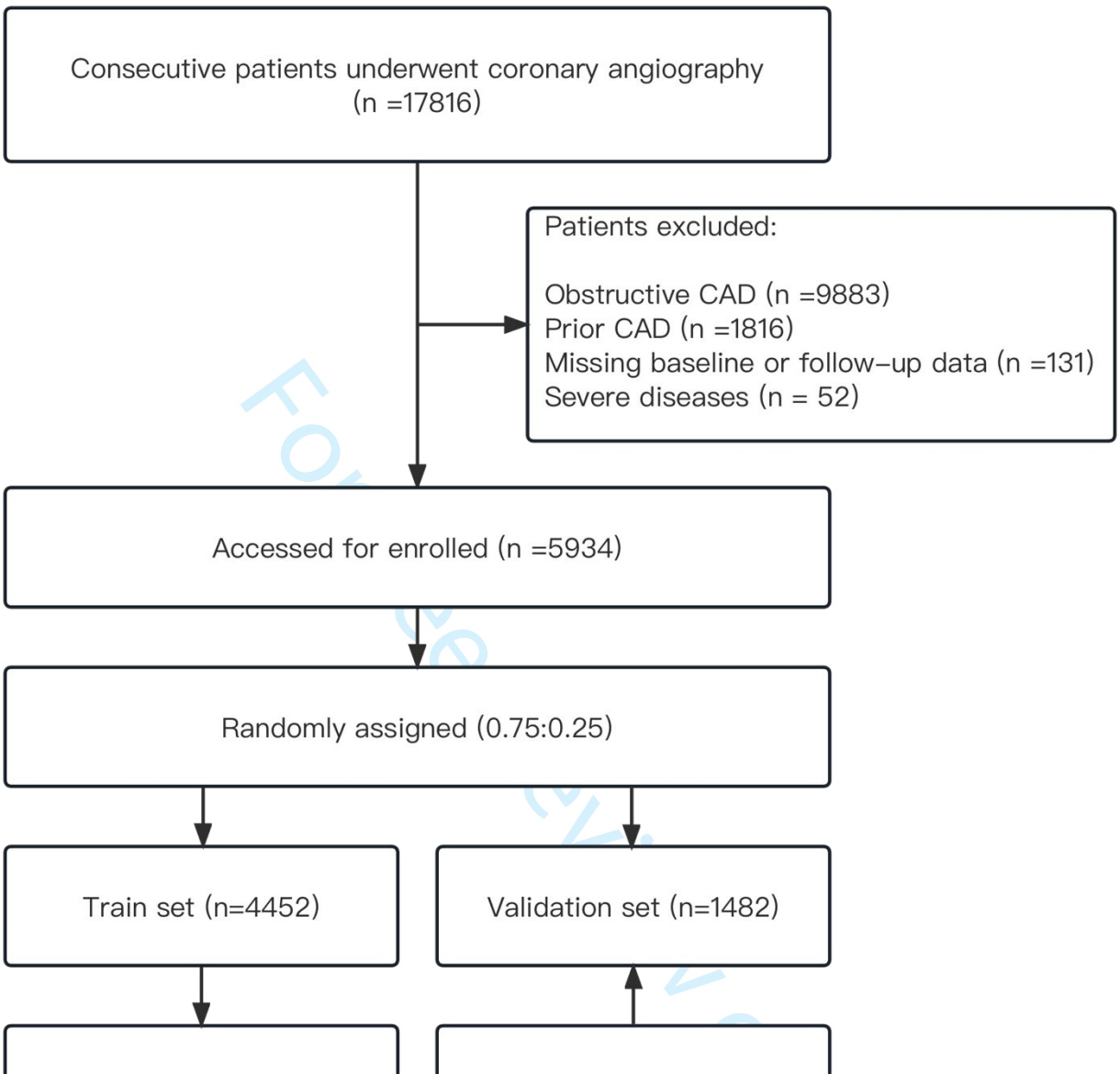


Figure 2. Variable Selection Based on LASSO Regression. (A) Variation Characteristics of Variable Coefficients; (B) Selection Process of Optimal λ Value in LASSO Regression Model Using Cross-

Validation.

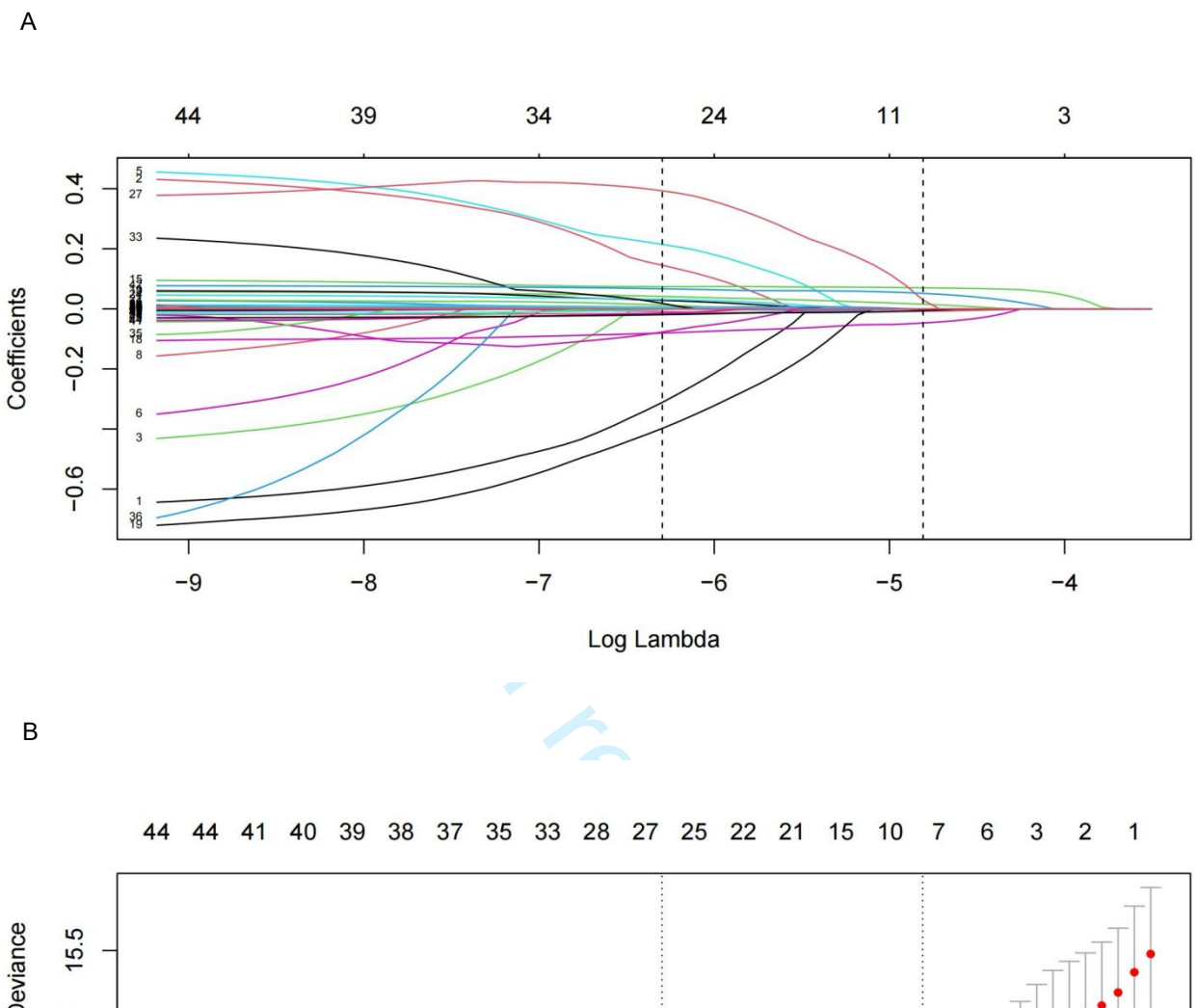


Figure 3. Nomogram for predicting the probability of 1-, 2-, and 3-year event-free survival of ANOCA patients as assessed by coronary angiography. ALT, alanine transaminase; AST, aspartate

transaminase; LVEF, left ventricular ejection fraction.

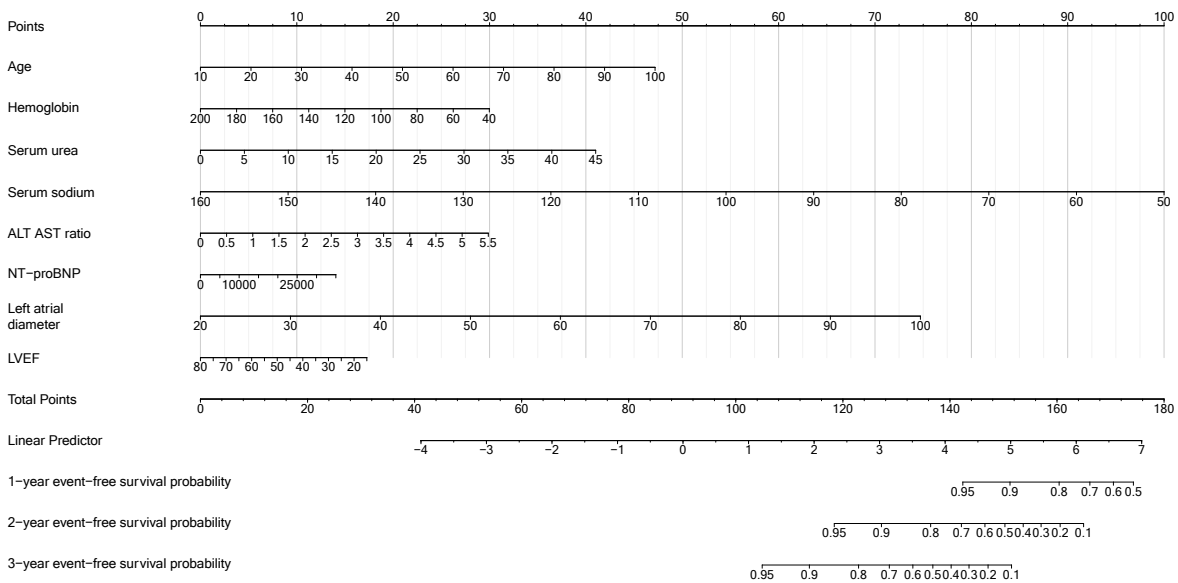


Figure 4. Receiver operating characteristic curve for the 1-, 2-, and 3-year primary endpoints of the nomogram in the training set (A) and validation set (B). AUC, area under receiver operating characteristic curve.

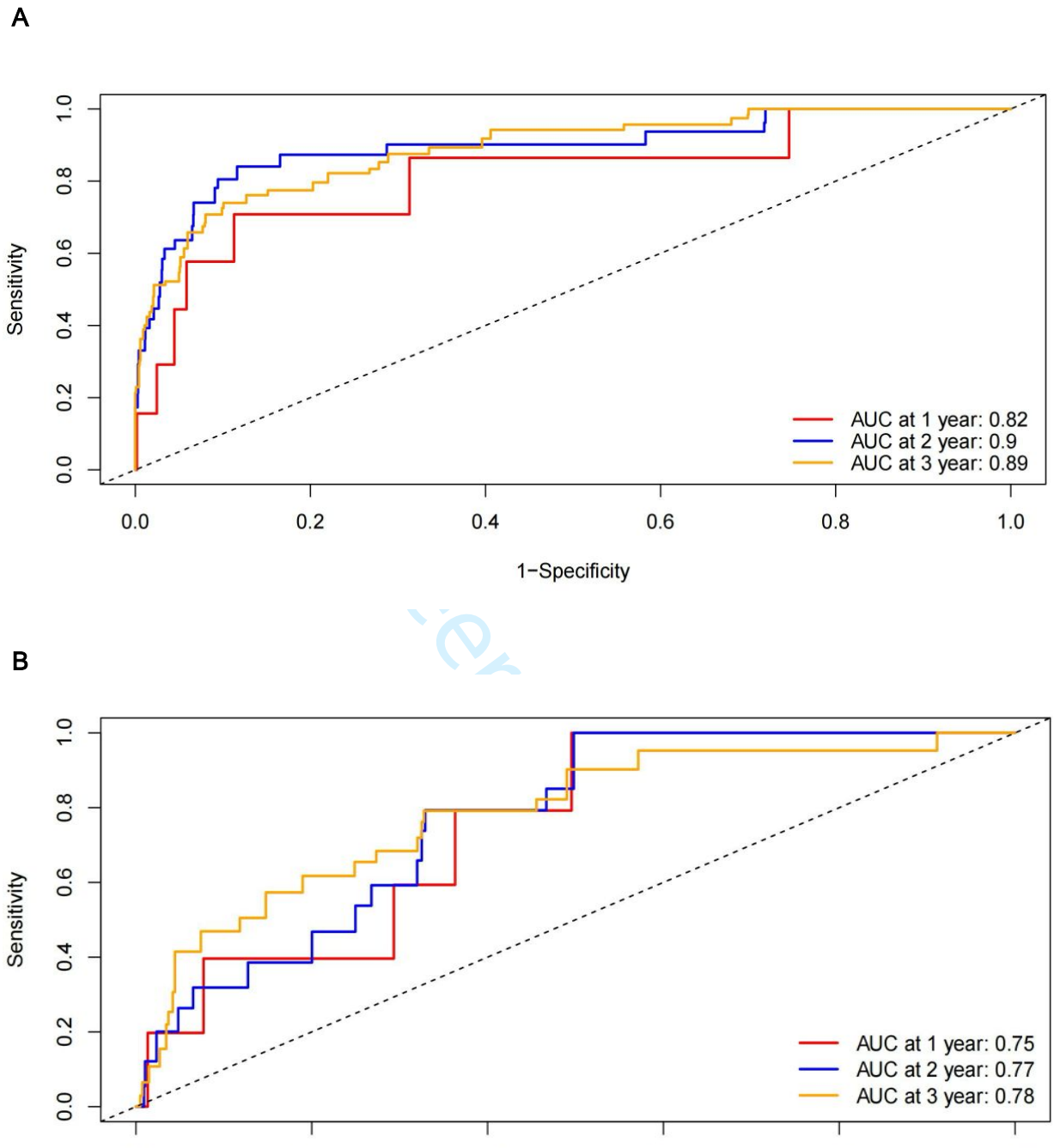


Figure 5. Calibration plot of predicted 1-, 2-, and 3-year event-free survival based on the nomogram in the training set and validation set. (A–C) Training set; (D–F) Validation set.

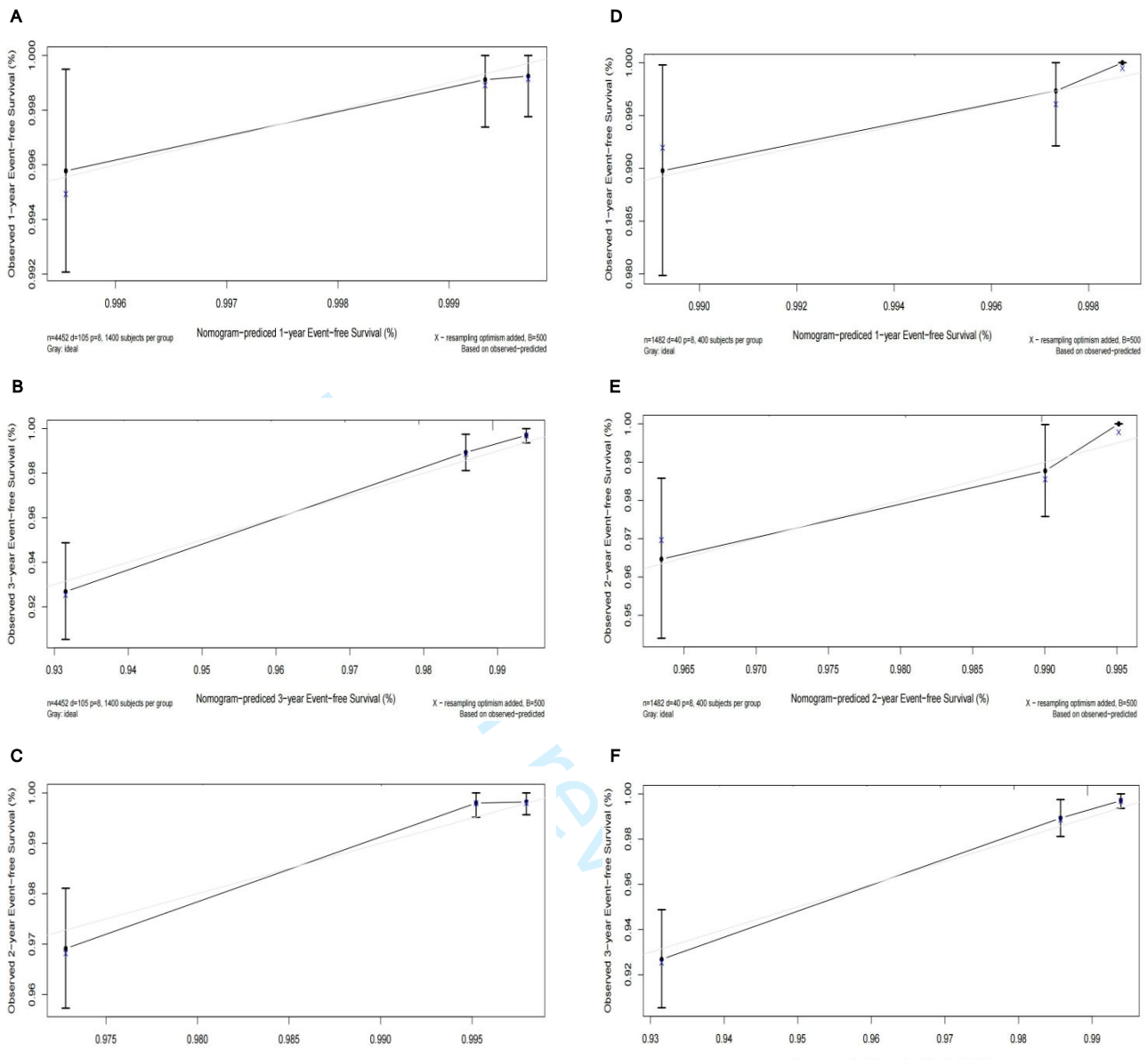


Figure 6. Decision curve analysis of the nomogram in the training cohort (A) and validation cohort (B). The x-axis represents the threshold probability, and the y-axis measures the net benefit. The left-slanting straight line shows the net benefit of treating all patients. The bottom horizontal gray line represents the net benefit of not treating any patients. The curve in the middle represents the nomogram.

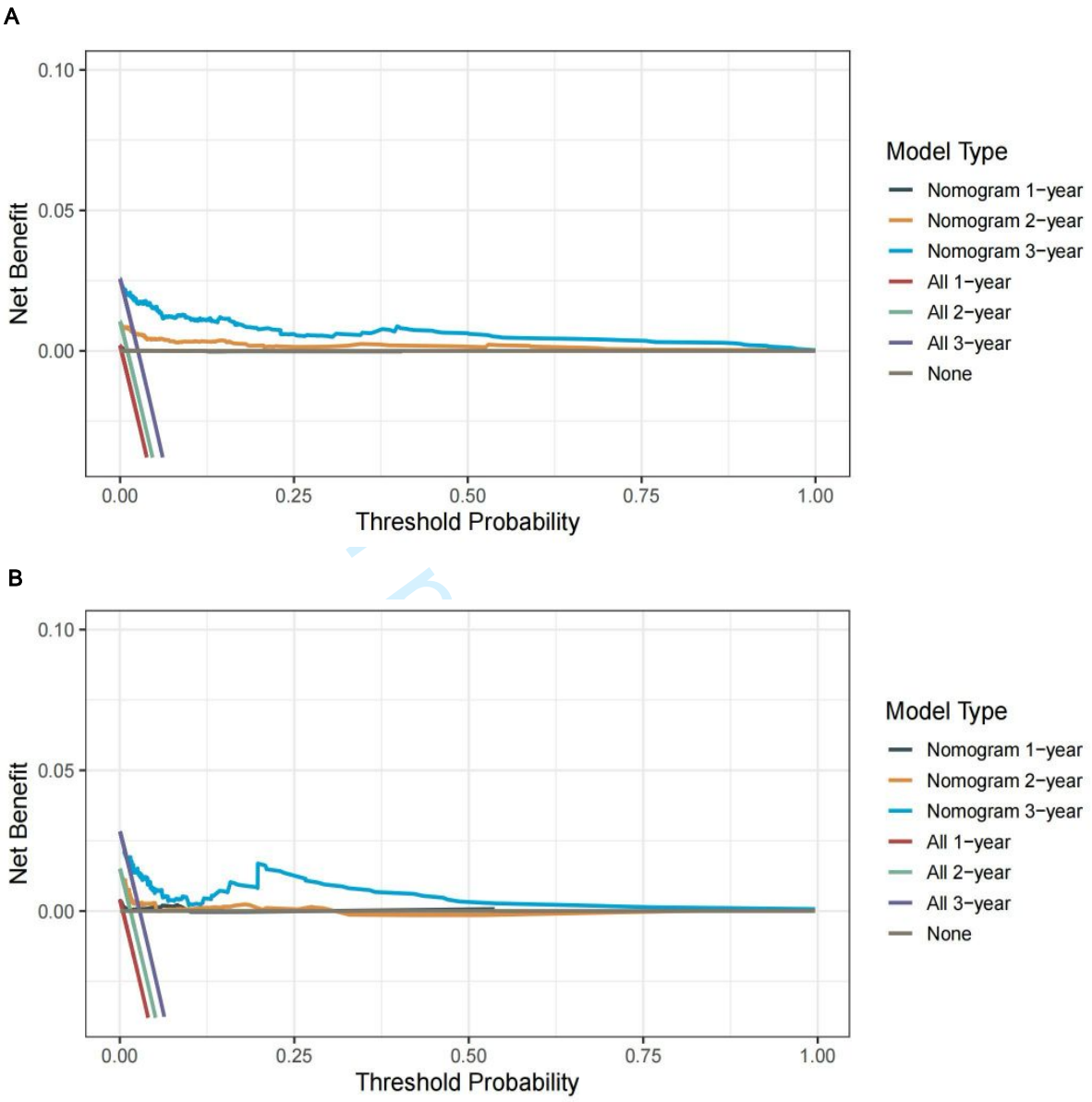
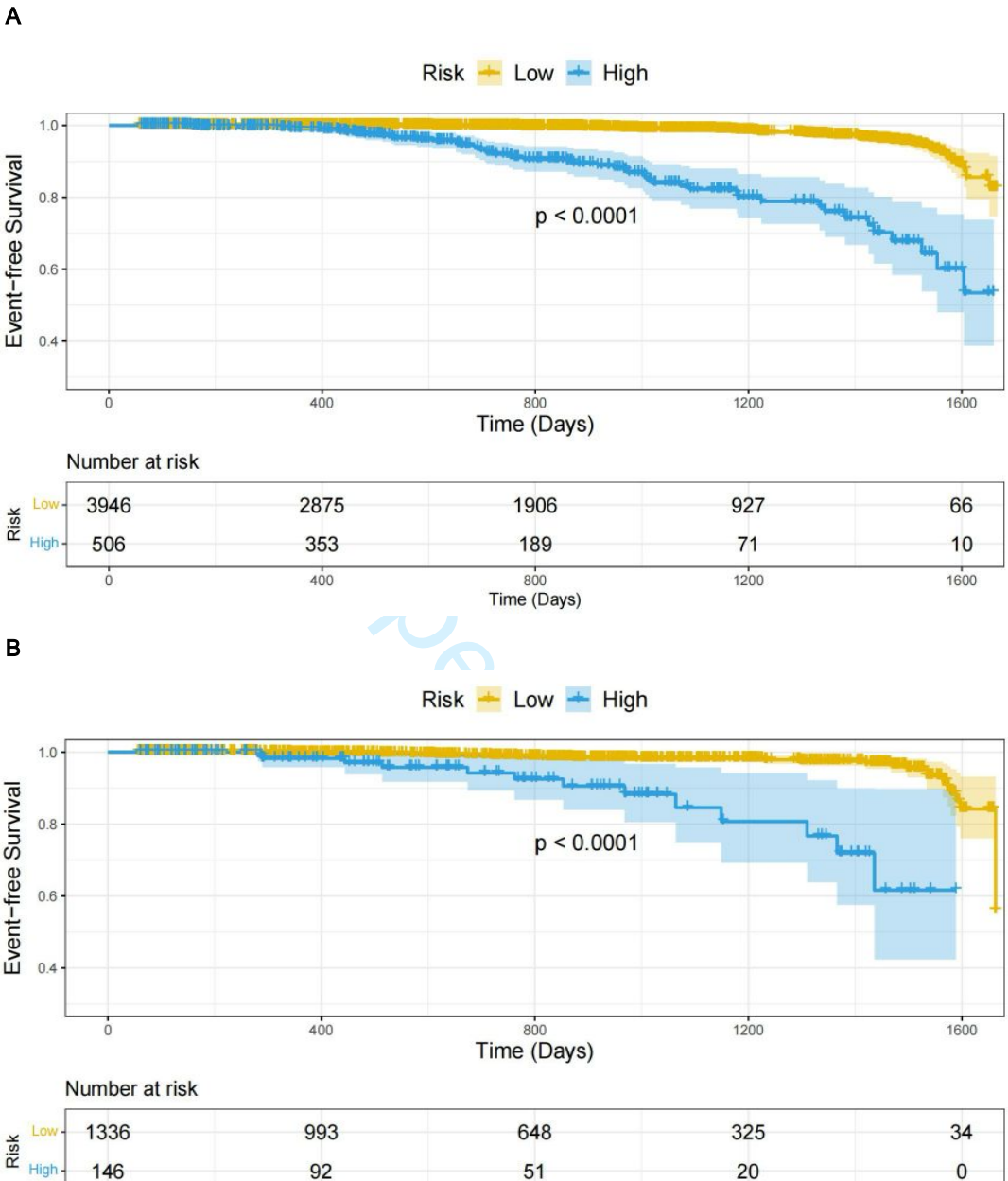


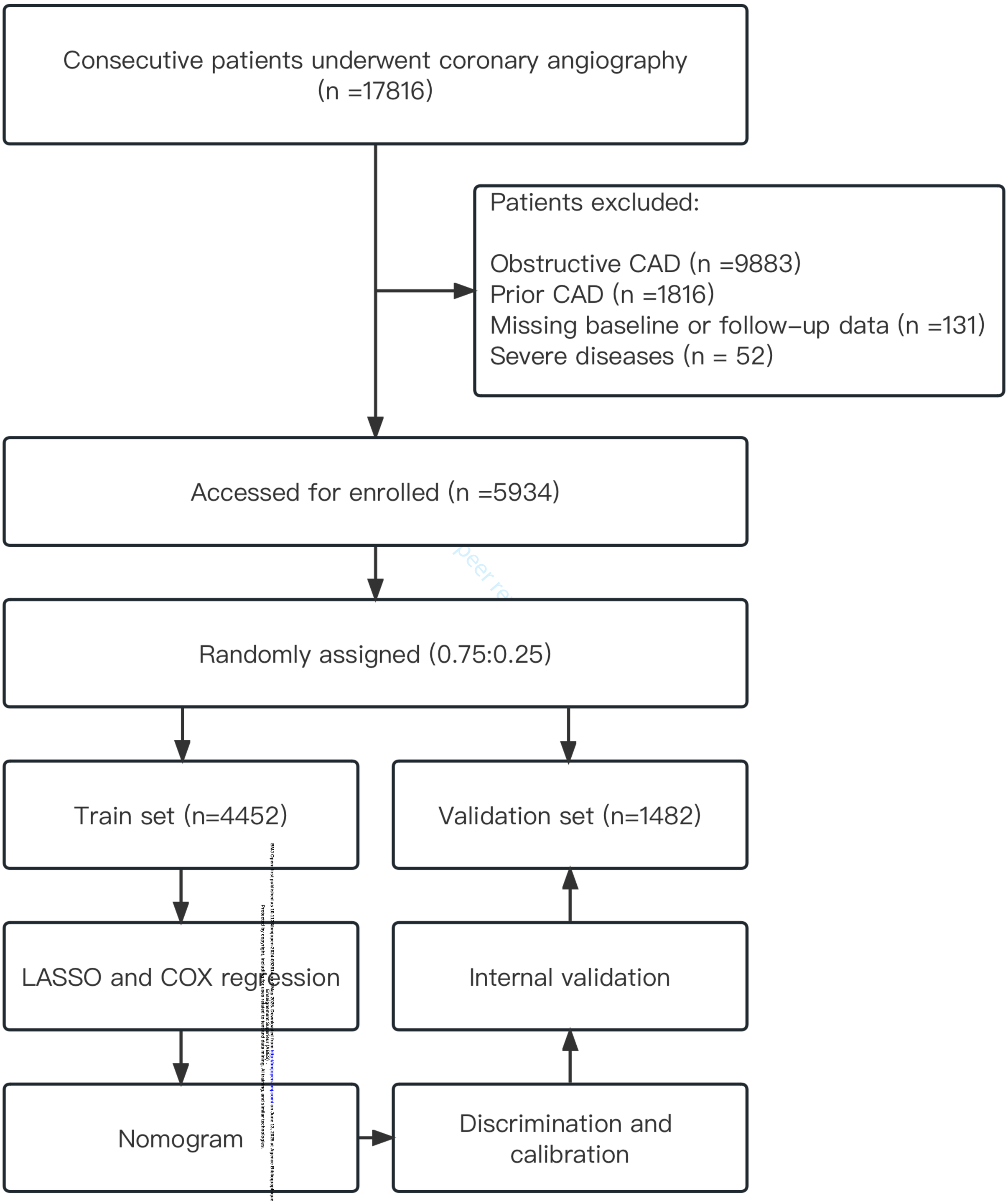
Figure 7. Kaplan-Meier curves for 1-year, 2-year, and 3-year event-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).



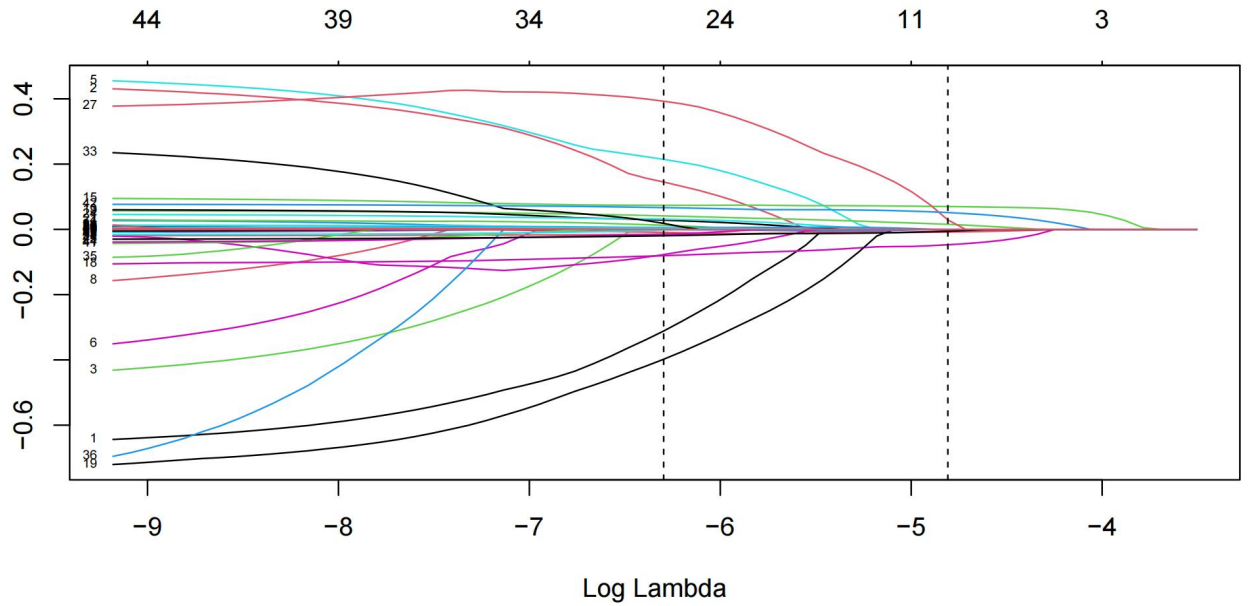
Supplementary Table 1. Clinical data of the total population, training set and validation set.

Supplementary Figure 1. Event-free survival probability of different adverse events in the total population.

Supplementary Figure 2. Kaplan-Meier curves for 1-year, 2-year, and 3-year MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).



A



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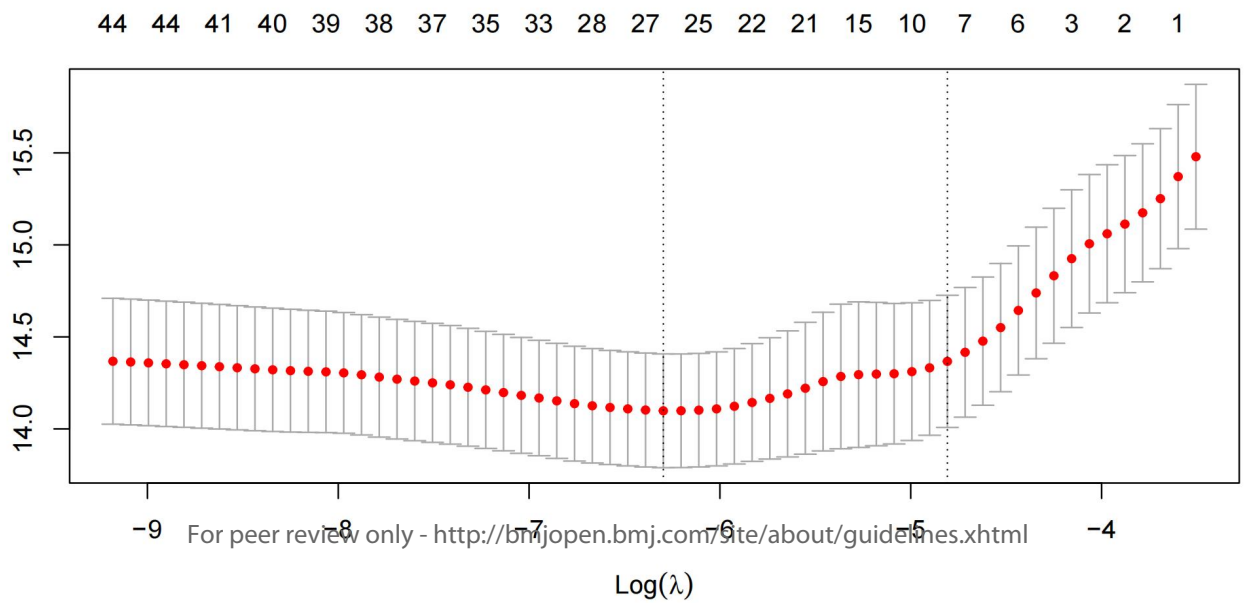

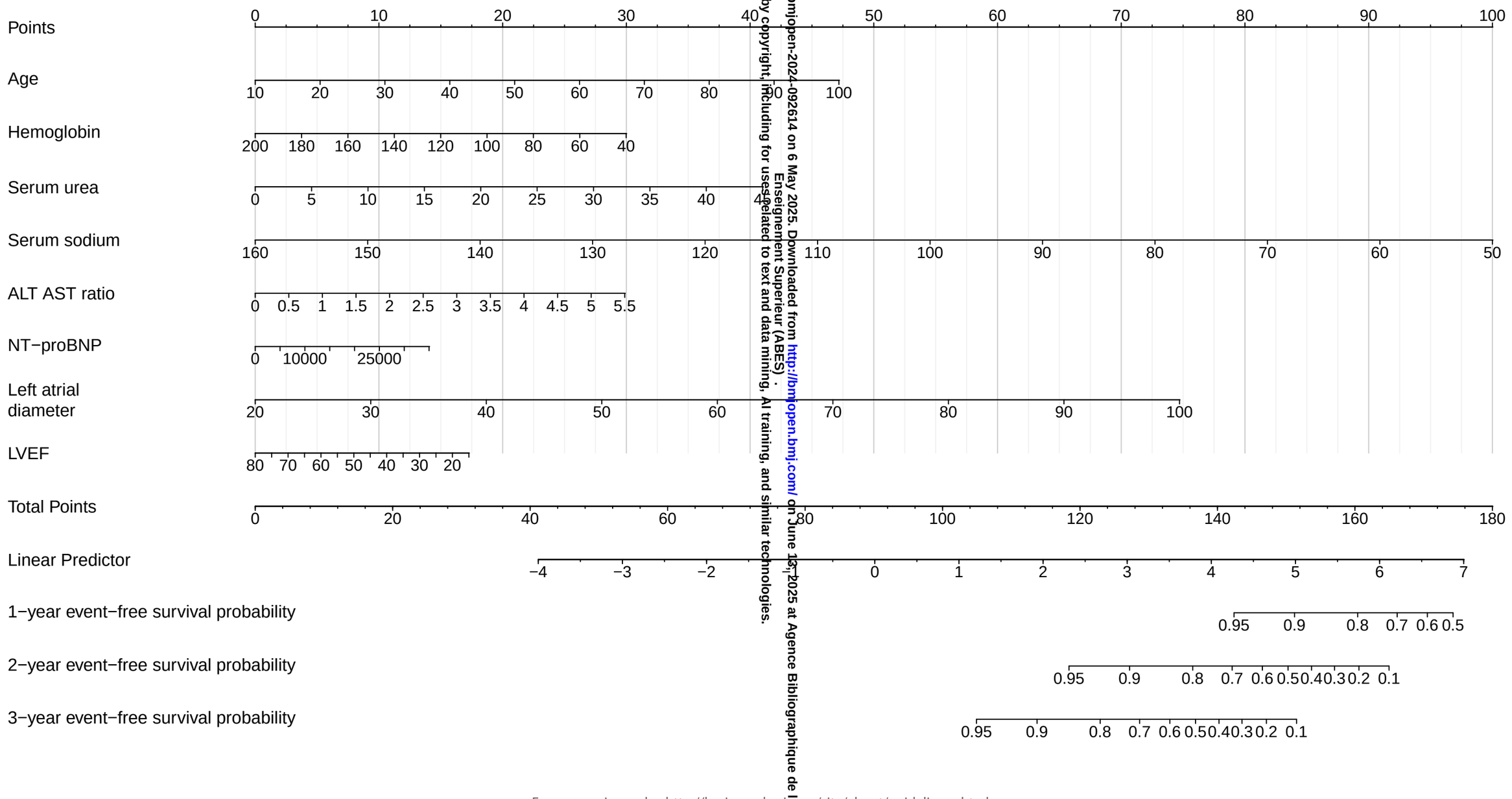

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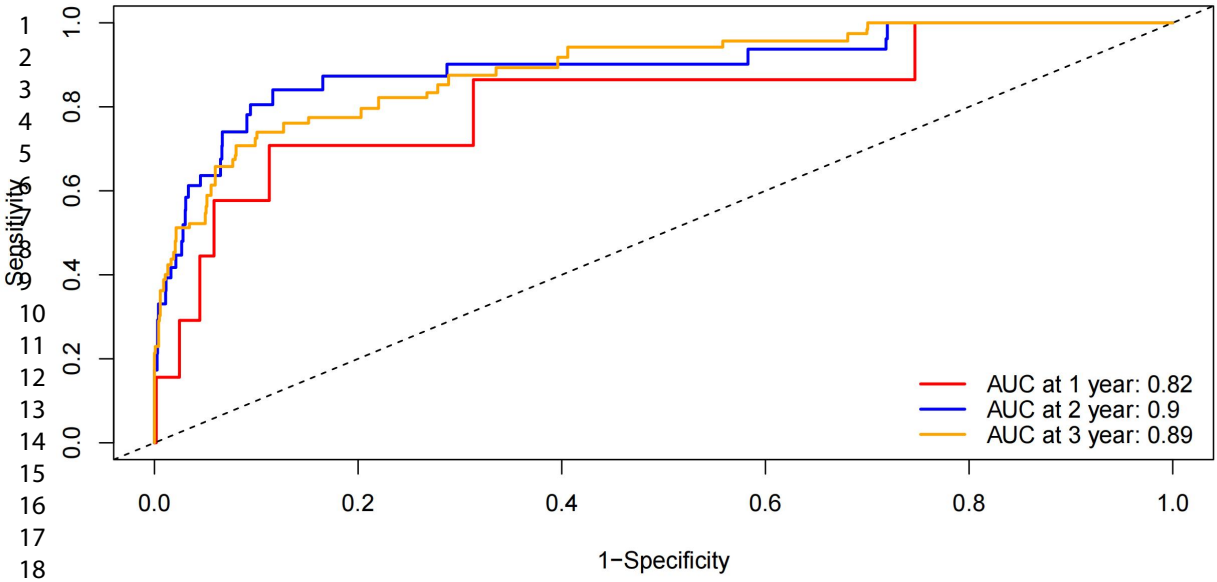

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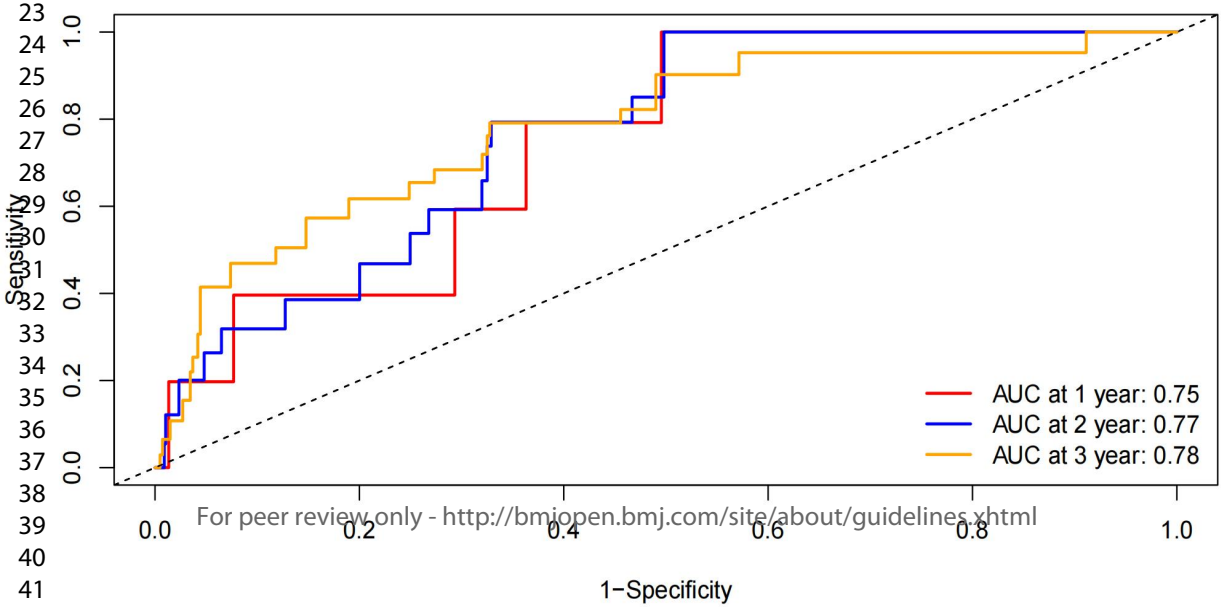

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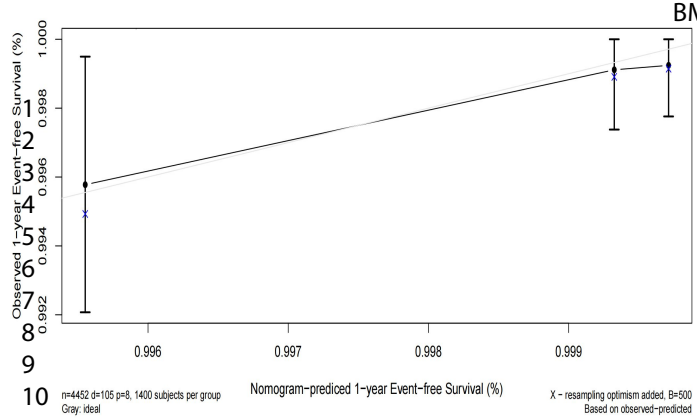

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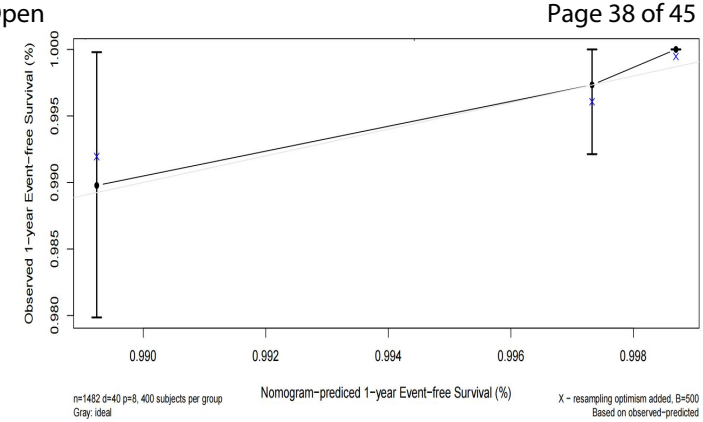

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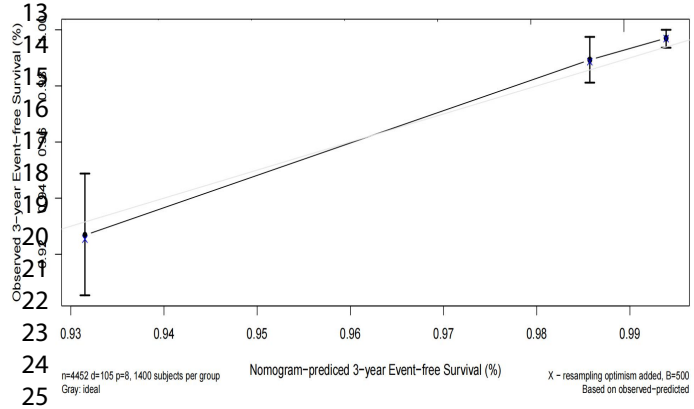

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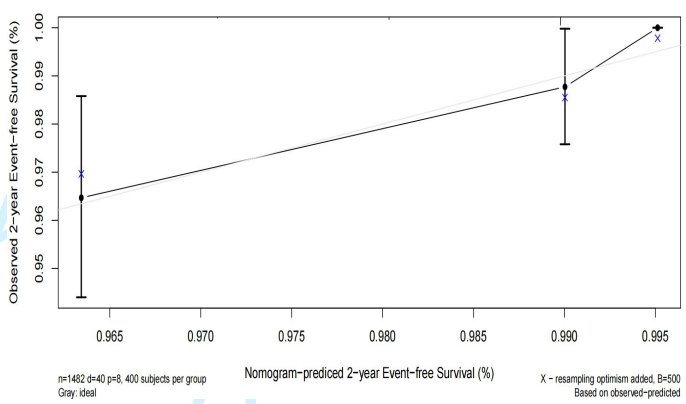

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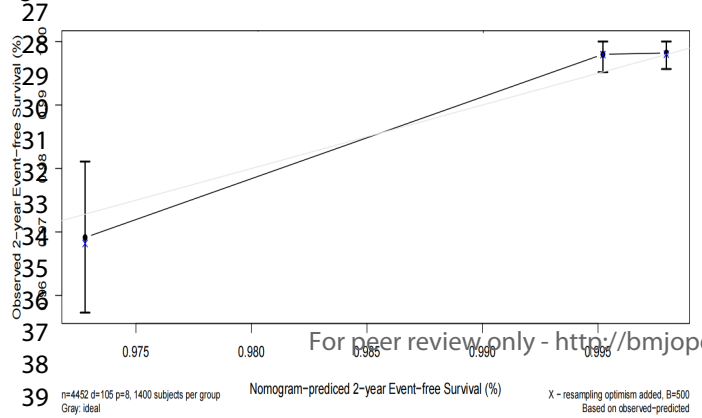

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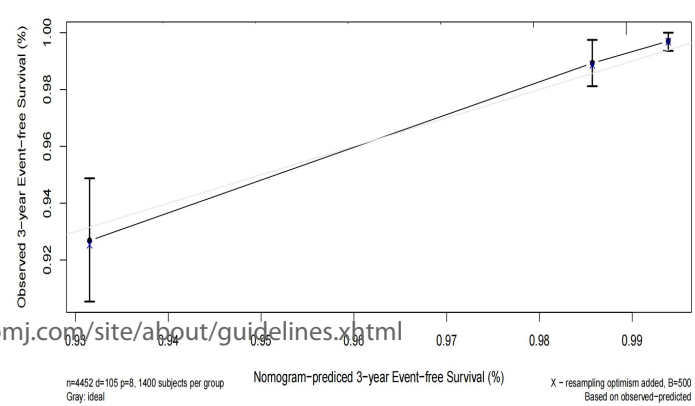
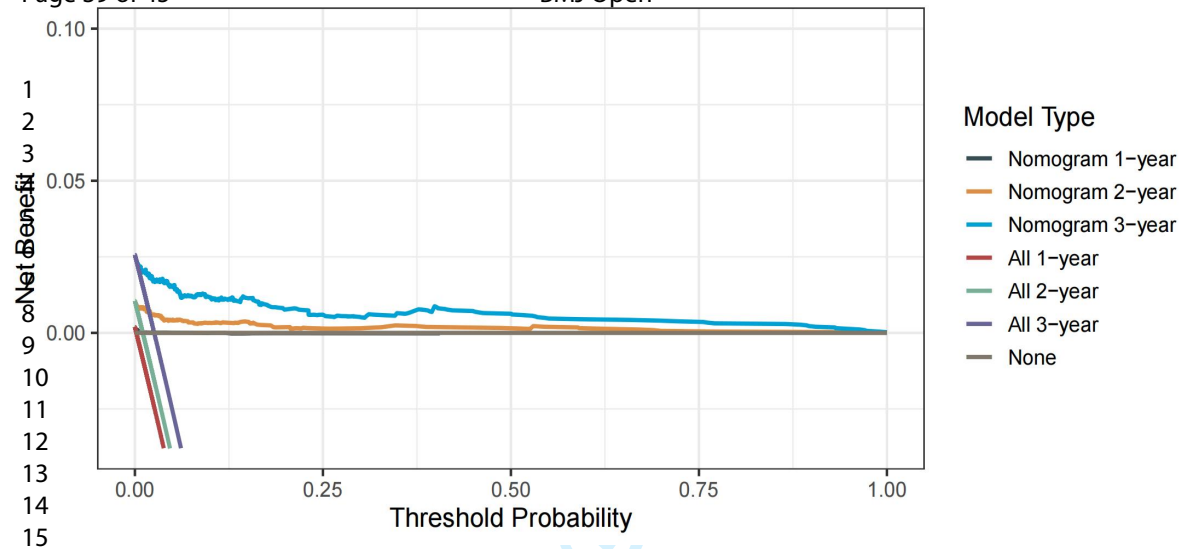


A



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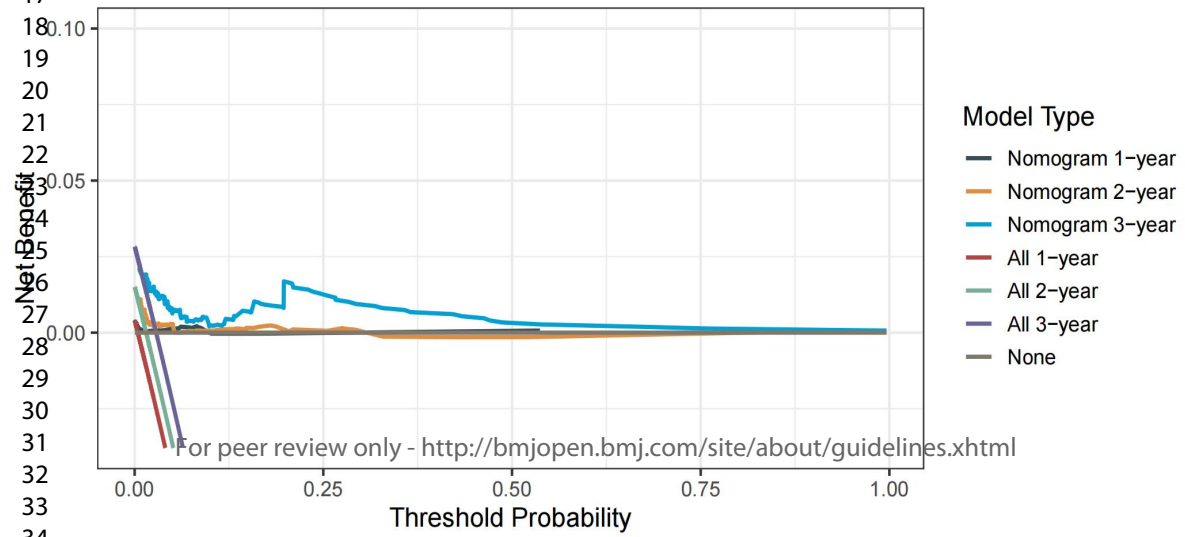

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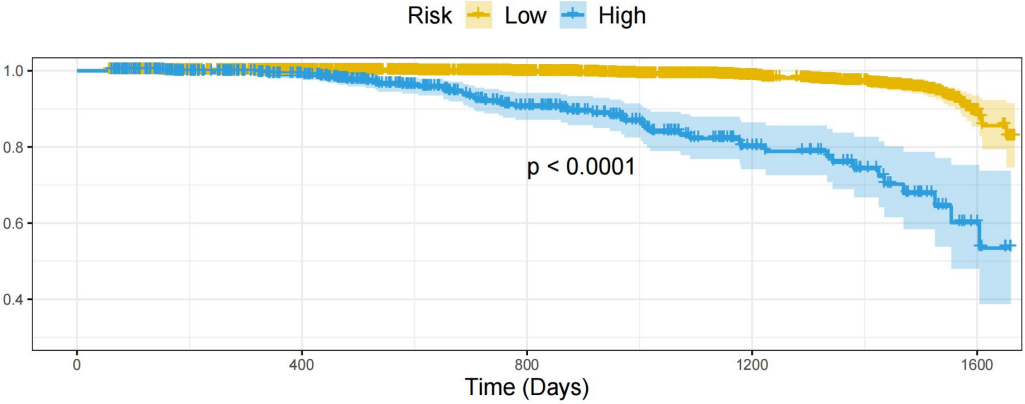
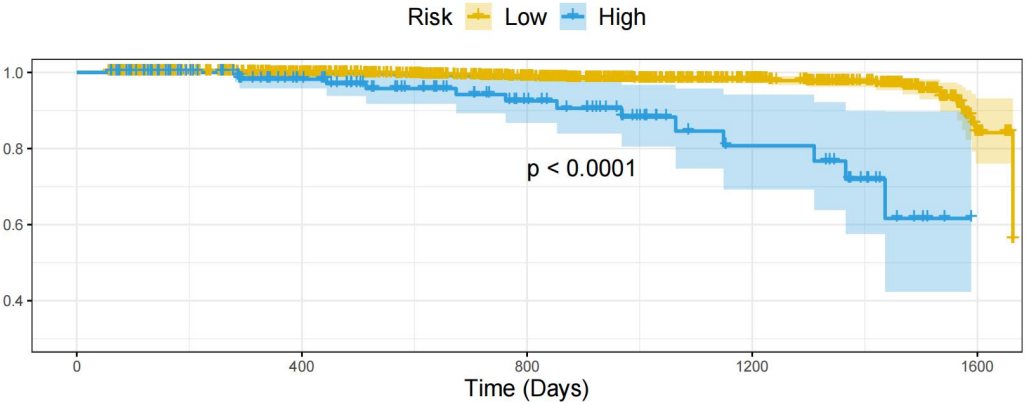


Number at risk

Risk					
Low	3946	2875	1906	927	66
High	506	353	189	71	10

Time (Days): 0, 400, 800, 1200, 1600

B



Number at risk

Risk					
Low	1336	993	648	325	34
High	146	92	51	20	0

Time (Days): 0, 400, 800, 1200, 1600

Supplement

Supplementary Table 1. Clinical data of the total population, training set and validation set.

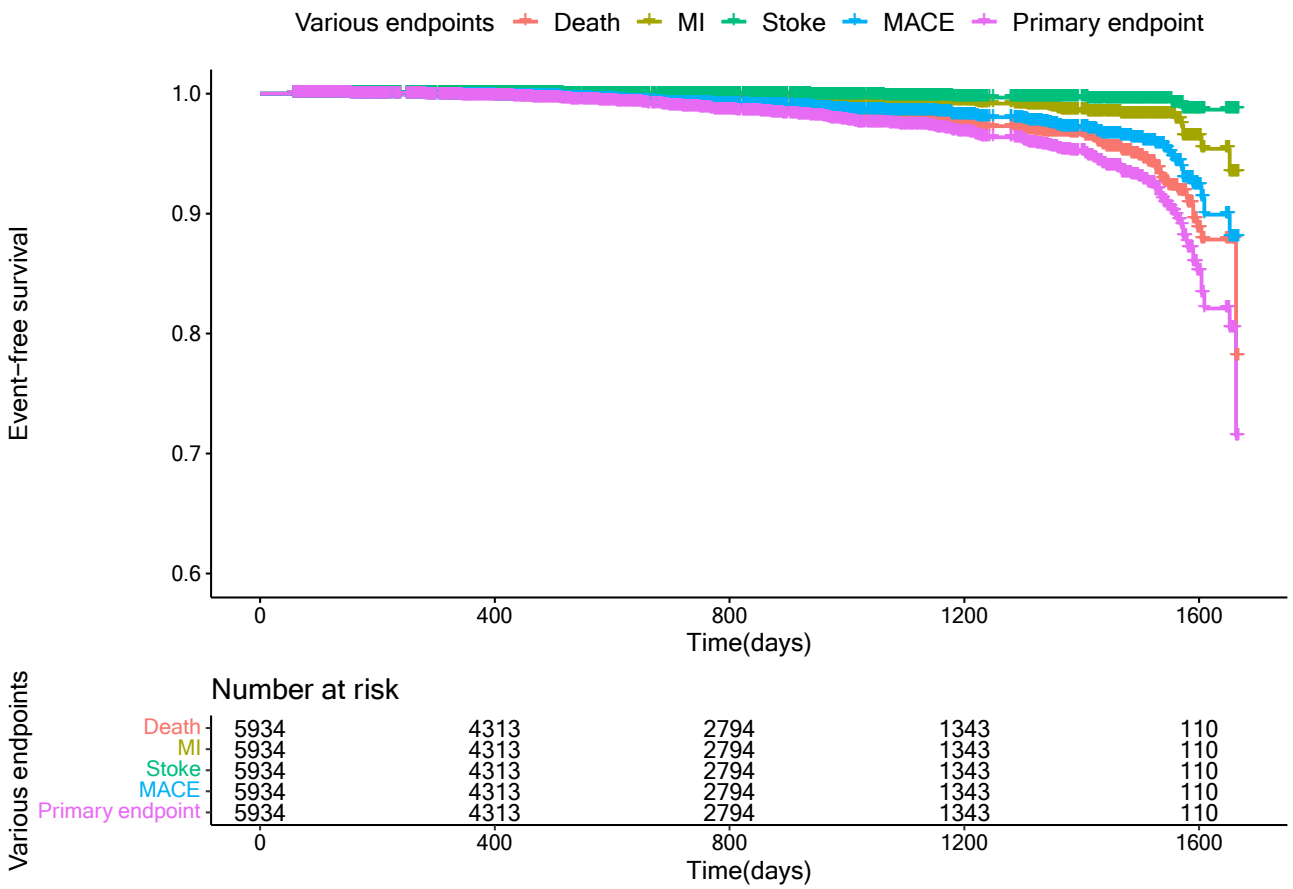
Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
Female, n (%)	3462 (58.3%)	2609 (58.6%)	853 (57.6%)	0.499
Age, years	43.6 (10.8)	43.7 (10.9)	43.5 (10.6)	0.563
Smoking, n (%)	1509 (25.4%)	1126 (25.3%)	383 (25.8%)	0.698
Drinking, n (%)	1883 (31.7%)	1415 (31.8%)	468 (31.6%)	0.909
Hypertension, n (%)	3698 (62.3%)	2802 (62.9%)	896 (60.5%)	0.094
Diabetes mellitus, n (%)	1123 (18.9%)	846 (19.0%)	277 (18.7%)	0.820
Diabetic complications, n (%)	19 (0.32%)	13 (0.29%)	6 (0.40%)	0.595
Dyslipidemia, n (%)	582 (9.81%)	423 (9.50%)	159 (10.7%)	0.185
CKD, n (%)	202 (3.40%)	151 (3.39%)	51 (3.44%)	0.993
SBP, mmHg	136 (19.8)	136 (19.9)	136 (19.7)	0.340
DBP, mmHg	81.9 (12.3)	81.9 (12.4)	81.8 (11.9)	0.757
Heart rate, beats/min	73.8 (15.2)	73.8 (13.9)	73.9 (18.5)	0.798
WBC, 10^9/L	6.67 (2.03)	6.68 (2.01)	6.67 (2.11)	0.969
Hemoglobin, g/L	136 (16.6)	136 (16.6)	136 (16.4)	0.881
Urea, mmol/L	6.09 (2.68)	6.09 (2.72)	6.08 (2.57)	0.831
Serum creatinine, μmol/L	65.9 [55.7; 79.8]	66.2 [55.7; 79.7]	65.4 [55.5; 80.0]	0.748
Uric acid, μmol/L	335 (100)	335 (101)	335 (99.0)	0.889
Serum sodium, mmol/L	142 (3.51)	142 (3.32)	142 (4.01)	0.829
Serum potassium, mmol/L	4.12 (0.56)	4.12 (0.47)	4.13 (0.76)	0.649
Serum chloride, mmol/L	106 (3.37)	106 (3.42)	106 (3.21)	0.515
Anion gap, mmol/L	14.0 (2.40)	13.9 (2.40)	14.0 (2.42)	0.844

Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
Total protein, g/L	68.2 (6.41)	68.2 (6.37)	68.2 (6.54)	0.968
Albumin, g/L	42.4 (3.88)	42.4 (3.87)	42.3 (3.91)	0.406
Globulin, g/L	25.9 (4.19)	25.8 (4.16)	25.9 (4.30)	0.353
ALT, U/L	17.7 [13.0; 24.7]	17.8 [13.1; 24.8]	17.6 [12.6; 24.5]	0.169
AST, U/L	17.7 [14.6; 21.6]	17.8 [14.6; 21.6]	17.5 [14.6; 21.5]	0.341
ALT/AST ratio	1.06 (0.41)	1.05 (0.41)	1.07 (0.42)	0.157
Total bilirubin, μmol/L	13.6 (6.67)	13.6 (6.81)	13.4 (6.23)	0.257
Indirect Bilirubin, μmol/L	9.63 (4.69)	9.67 (4.75)	9.51 (4.53)	0.242
Direct Bilirubin, μmol/L	3.40 [2.30; 4.60]	3.40 [2.30; 4.60]	3.40 [2.40; 4.60]	0.611
Alkaline phosphatase, U/L	76.5 (23.6)	76.5 (23.6)	76.6 (23.7)	0.820
Total cholesterol, mmol/L	4.75 (1.12)	4.75 (1.13)	4.74 (1.08)	0.919
Triglycerides, mmol/L	1.63 (1.11)	1.62 (1.11)	1.65 (1.10)	0.485
HDL-C, mmol/L	1.22 (0.31)	1.22 (0.32)	1.20 (0.30)	0.083
LDL-C, mmol/L	2.97 (0.88)	2.97 (0.88)	2.98 (0.87)	0.498
VLDL-C, mmol/L	0.56 (0.37)	0.56 (0.39)	0.56 (0.30)	0.627
Troponin I, ng/ml	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.536
NT-proBNP, ng/L	83.7 [35.1; 266]	83.0 [34.3; 265]	86.7 [38.0; 269]	0.415
CKMB, U/L	12.1 [9.30; 14.7]	12.0 [9.24; 14.7]	12.3 [9.30; 14.7]	0.529
D-Dimer, μg/L	276 [2.34; 434]	274 [1.78; 427]	282 [4.65; 457]	0.110
Glucose, mmol/L	6.81 (2.48)	6.82 (2.45)	6.78 (2.56)	0.579
Left atrial diameter, mm	38.7 (5.24)	38.7 (5.28)	38.6 (5.11)	0.331

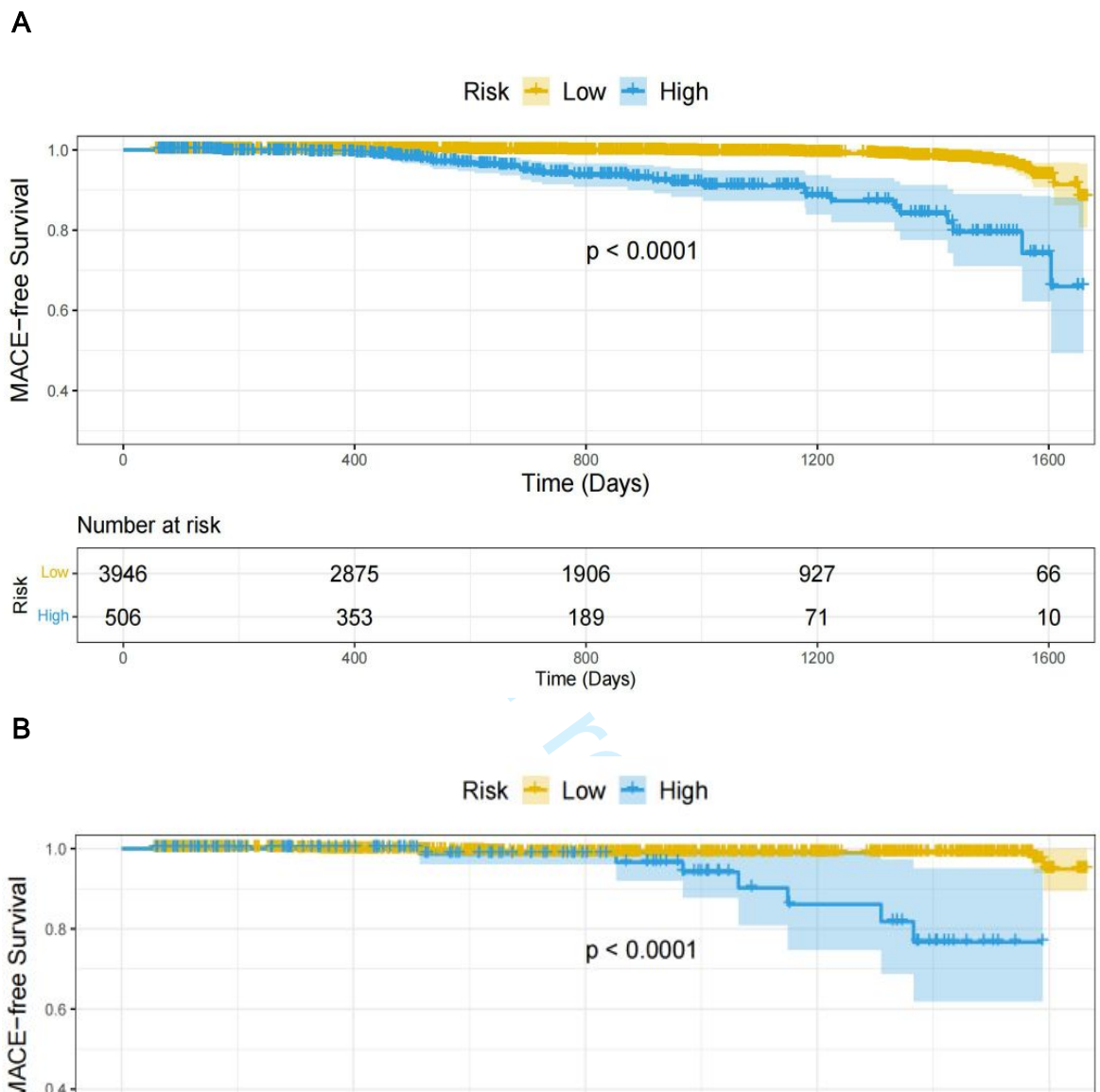
Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
LVEDD, mm	47.4 (4.46)	47.4 (4.51)	47.3 (4.28)	0.373
LVESD, mm	26.9 (5.62)	26.9 (5.65)	27.0 (5.52)	0.737
RVEDD, mm	20.8 (3.37)	20.7 (3.61)	20.8 (2.53)	0.623
LVEF, %	61.7 (6.75)	61.7 (6.77)	61.6 (6.70)	0.486
Event-free survival time, days	635 (403)	633 (402)	641 (406)	0.512
Death, n (%)	106 (1.79%)	78 (1.75%)	28 (1.89%)	0.816
MI endpoint, n (%)	33 (0.56%)	21 (0.47%)	12 (0.81%)	0.189
Stroke endpoint, n (%)	11 (0.19%)	6 (0.13%)	5 (0.34%)	0.156
MACE, n (%)	82 (1.38%)	64 (1.44%)	18 (1.21%)	0.611
Primary endpoint, n (%)	145 (2.44%)	105 (2.36%)	40 (2.70%)	0.523

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; CKMB, creatine kinase-MB; LVEDD, left ventricular-end-diastolic diameter; LVESD, left ventricular-end-systolic diameter; RVEDD, right ventricular-end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MACE, major adverse cardiovascular events.

Supplementary Figure 1. Event-free survival probability of different adverse events in the total population



Supplementary Figure 2. Kaplan-Meier curves for 1-year, 2-year, and 3-year MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).



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Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study

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Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study

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Abstract

Objectives

To develop and validate a risk prediction model for adverse outcomes in patients with angina with nonobstructive coronary arteries (ANOCA) confirmed by invasive coronary angiography.

Design

Retrospective cohort study.

Setting

A tertiary cardiovascular care center in East Asia.

Participants

From 17,816 consecutive patients undergoing coronary angiography for suspected coronary artery disease, 5,934 met ANOCA criteria after rigorous exclusion: (1) significant stenosis (≥50% luminal narrowing), (2) established coronary artery disease history, (3) incomplete baseline/follow-up data, (4) non-cardiovascular life-limiting conditions.

primary and secondary outcome measures

The primary outcome was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or coronary-artery bypass grafting (CABG). The secondary outcome was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat PCI, and CABG.

Results

The derivation cohort (n=4,452) and validation cohort (n=1,482) demonstrated comparable baseline

characteristics. The nomogram incorporated eight prognosticators: age, hemoglobin, serum urea, serum sodium, ALT/AST ratio, NT-proBNP, left atrial diameter, and LVEF. The prediction model showed robust discrimination for primary endpoint (derivation AUC: 0.82 [1-year], 0.90 [2-year], 0.89 [3-year]; validation AUC: 0.75, 0.77, 0.78). Calibration plots revealed close alignment between predicted and actual event-free survival probabilities in both cohorts. Risk stratification identified two distinct prognostic groups with significant survival differences (log-rank $p < 0.0001$).

Conclusions

This predictive model integrates routinely available clinical parameters to accurately stratify mortality and cardiovascular risk in ANOCA patients, providing a potential valuable decision-support tool for personalized therapeutic strategies.

Strengths and limitations of this study

- This study utilized a large sample size (n=5934) with rigorous internal validation through training and testing cohorts.
- Leveraged LASSO-penalized Cox regression with 10-fold cross-validation to optimize model generalizability.
- The nomogram integrates routinely available clinical variables, enhancing clinical applicability.
- Limitations include the retrospective design, which may introduce selection bias.
- Data were derived from a single center, potentially limiting generalizability.

Key word

Angina, coronary artery disease, MINOCA, prognosis, nomogram.

Backgrounds

Chest pain is a common symptom among patients seeking medical services, often raising concerns about potentially life-threatening conditions such as coronary artery disease (CAD) [1,2]. Timely and accurate diagnostic assessments, including electrocardiography, coronary computed tomography angiography, and coronary angiography, are frequently recommended for individuals presenting with chest pain to rule out severe conditions such as myocardial infarction (MI) [3,4]. However, in the cohort of patients undergoing diagnostic workup, approximately half exhibit nonobstructive coronary arteries (stenosis less than 50%)[5,6], a condition known as angina with nonobstructive coronary arteries (ANOCA) [7].

ANOCA patients often seek medical care due to symptoms and undergo repetitive invasive examinations, leading to significant healthcare resource utilization and imposing individual burdens and additional risks [8–10]. In a randomized controlled trial involving over 10,000 patients suspected of CAD with intermediate pretest likelihood, only approximately 12% of them yielded a positive result in the final coronary artery functional tests [11]. Patients with a low pretest probability exhibit an exceedingly low positivity rate in diagnostic workup and experience fewer adverse outcomes [12]. Therefore, clinical guidelines recommend delaying diagnostic testing for patients at low risk for CAD[13,14]. However, patients without obstructive coronary arteries confirmed by coronary angiography (CAG) or coronary computed tomography angiography (CCTA) have been observed to experience more adverse outcomes compared to the general population[15–17]. Identifying high-risk individuals in ANOCA patients remains a challenge.

There is limited research on predicting adverse outcomes in ANOCA patients confirmed through CAG or CCTA. Some studies have validated the utility of specific pretest indicators, such as age, sex, and traditional cardiovascular disease risk factors(e.g., hypertension), to identify low-risk ANOCA patients [18]. However, several investigations have shown that specific blood biomarkers, including high-sensitivity troponin and lower HDL-C levels, operate as independent predictive factors for poor prognosis in ANOCA patients, adding prognostic value[19]. To date, comprehensive studies that screen noninvasive indicators and develop a prognostic model are lacking, and most previous studies are reliant on data derived from the Women's Ischemia Syndrome Evaluation (WISE) study[19–21], which exclusively includes female participants. One study also used WISE data to validate the effectiveness of some risk scores originally designed for other populations, such as the ASCVD score, in predicting adverse outcomes in ANOCA patients, but the results showed suboptimal performance[22]. Therefore, it is necessary to develop a predictive model based on non-invasive indicators to forecast adverse outcomes in ANOCA patients of both sexes. This study aims to bridge this gap to optimize clinical decision-making and patient management.

Method

Study Population

This is a retrospective cohort study that consecutively enrolled patients who presented with suspected

symptoms of CAD and underwent coronary angiography at the Department of Cardiology or Emergency Department of the Second Hospital of Tianjin Medical University between January 2019 and June 2023. The Second Hospital of Tianjin Medical University is a cardiac center serving the northern Chinese city of Tianjin and its surrounding regions. This study adheres to the principles outlined in the TRIPOD statement [23].

ANOCA patients were defined as angina with nonobstructive epicardial coronary arteries (stenosis <50%), adhering to current expert consensus[7]. Patients meeting the following criteria were excluded from the study: (1) patients with acute coronary syndrome or obstructive coronary arteries (defined as a luminal stenosis of ≥50% in a major epicardial coronary artery[7,24]); (2) patients with a prior diagnosis of CAD, history of percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG); (3) individuals with severe liver or kidney dysfunction, malignancies, or other non-cardiovascular conditions significantly affecting life expectancy; (4) those with substantial missing baseline data; and (5) patients lost to follow-up. This study received approval from the Ethics Committee of the Second Hospital of Tianjin Medical University, with a waiver for written informed consent granted for the retrospective use of fully anonymized clinical data (No. KY2025K008).

Clinical Data Collection

Patient data were retrospectively obtained from electronic medical records, including demographic information, medical history, vital sign data, laboratory parameters, echocardiographic data, coronary

angiography findings and other relevant details.

Follow-Up and Endpoints

A dedicated follow-up team conducted systematic post-discharge surveillance through a standardized protocol, with scheduled assessments at 30 days, 3 months, 6 months, and annually thereafter. Data collection employed a multimodal approach: (1) comprehensive electronic health record review, (2) cross-referencing with regional death registries, (3) and telephone or email interviews. The observational window for this analysis was finalized on August 1, 2023. Two board-certified cardiologists (L.Z. and Z.K.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria[25,26]. For discrepancies in event classification, an adjudication committee comprising two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience) conducted final arbitration through consensus review.

The primary endpoint was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or coronary-artery bypass grafting (CABG) during follow-up. The secondary endpoint was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat PCI, and CABG during follow-up. The composite endpoint was selected based on its established utility in prognostic studies of ANOCA [22,27–29].

Statistical Analysis

For the small amount of missing data in smoking and alcohol consumption history, multiple imputation was performed using the MICE package (Multiple Imputation by Chained Equations package). To establish a reliable model, the entire study cohort was randomly stratified into two subsets, a training set and a validation set, with a ratio of 0.75 to 0.25, respectively. The training set was used to generate the predictive model, while the validation set was utilized for model internal validation.

Categorical variables were described as frequencies and percentages, with group differences assessed using the chi-square test or Fisher's exact test as applicable. Continuous variables were expressed as either the mean ± standard deviation (SD) or median [interquartile range, IQR], and group comparisons were conducted using the t test or Kruskal–Wallis test as appropriate. Variables with VIF ≥5 were excluded prior to LASSO regression to mitigate multicollinearity. The variables selected through LASSO regression were incorporated into the Cox proportional hazards regression model, and a nomogram was generated based on the Cox regression analysis model. The discriminative ability of the predictive model was evaluated using AUC. The model's calibration was assessed through the calibration curve. Additionally, decision curve analysis was employed to evaluate the clinical utility of the nomogram.

The total score for each patient was calculated based on the nomogram, and the study population was stratified into high-risk and low-risk groups according to the score corresponding to the 3-year 95% event-free survival probability. Event-free survival for the high- and low-risk groups in the training

and validation sets was estimated by Kaplan–Meier method and compared with the log-rank test. All statistical analyses were performed with R software version 4.3.1 (R Foundation for Statistical Computing). All statistical tests were two- tailed, with a significance level set at P<0.05.

Patient and public involvement

None.

Result

Study Population and Patient Characteristics

Out of a consecutive cohort of 17,816 patients who underwent coronary angiography for suspected coronary artery disease, 9,883 individuals with significant coronary artery stenosis and 1,816 patients with a documented history of coronary heart disease were excluded. An additional 131 individuals were excluded due to missing baseline or follow-up data, and 52 patients with severe conditions such as malignant tumors were also excluded. of the final analysis included 5,934 patients with negative coronary angiography results (**Figure 1**).

The mean age of the overall cohort was 43.6 ± 10.8 years, with 58.3% being female, and the median follow-up time was 631 [270, 972] days. Detailed baseline data are provided in **Supplementary Table 1**. During the follow-up period, 145 (2.44%) patients had primary endpoint events, 82 (1.38%) had MACE, 106 (1.79%) had all-cause death, 33 (0.56%) had MI, and 11 (0.19%) had a stroke. The

Kaplan-Meier method was employed to estimate the survival without various adverse events for the total study population (**Supplementary Figure 1**).

Nomogram built based on LASSO-COX regression

The entire cohort was randomly divided into a training cohort consisting of 4,452 patients and a validation cohort comprising 1,482 patients. There were no statistically significant differences in the collected variables between these two groups (**Supplementary Table 1**). LASSO regression was employed to select variables with the strongest correlation to the primary endpoint. As the regularization parameter (λ) increased, certain coefficients were reduced to zero, effectively eliminating those variables from the model (**Figure 2A**). We used a tenfold cross-validation approach to identify the optimal model. Due to the relatively limited number of cases undergoing primary endpoint events in the validation cohort (145), we employed the one standard error (1-se) rule, resulting in eight selected variables (**Figure 2B**). These variables were incorporated into a Cox proportional hazards regression model, with results presented in **Table 1**. All models satisfied proportional hazards assumptions (global test p=0.057). A nomogram was developed based on the Cox regression model, with the regression coefficients of these factors amalgamated into a scoring system, ranging from 0 to 100(**Figure 3**). For example, an 81-year-old male patient with a hemoglobin level of 92 g/L, serum urea of 14.1 mmol/L, serum sodium of 145.6 mmol/L, an ALT/AST ratio of 1.68, NT-proBNP at 272 ng/L, left atrial diameter of 38.83 millimeters, and an LVEF of 62% received a total score of 115. The 1-year, 2-year and 3-year event-free survival rates were 99.5%, 96.2% and 89.0%, respectively.

Table 1. Prediction of event-free survival probability using the Cox proportional hazards regression model based on LASSO regression.

Variable	coefficients	z score	HR	95%CI	p value
Age	0.043	4.167	1.044	0.023, 0.063	<0.001
Hemoglobin	-0.015	-2.871	0.985	-0.026, -0.005	0.004
Urea	0.074	3.947	1.077	0.037, 0.111	<0.001
Serum sodium	-0.074	-5.694	0.929	-0.1, -0.049	<0.001
ALT/AST ratio	0.444	2.439	1.559	0.087, 0.8	0.015
NT-proBNP	0	2.094	1	0, 0	0.036
Left atrial diameter	0.076	5.959	1.079	0.051, 0.8	<0.001
LVEF	-0.022	-2.289	0.979	-0.04, -0.003	0.022

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase; LVEF, left ventricular ejection fraction.

Discrimination and calibration of the nomogram

The discriminative ability of the model was assessed by plotting receiver operating characteristic curves. In the training set, the AUC for 1-, 2-, and 3-year predictions was 0.82, 0.90, and 0.89, respectively. In the validation set, the corresponding AUC for 1-, 2-, and 3-year predictions were 0.75, 0.77, and 0.78, respectively (**figure 4**).

Figure 5 illustrates calibration plots for the models predicting 1-, 2-, and 3-year survival in both the training and validation datasets. In well-calibrated models, the points closely align with the ideal 45-degree line, indicating that predicted survival closely matches observed survival and demonstrating

good model calibration.

Decision Curve

Decision curve analysis was employed to evaluate the potential improvement in clinical outcomes through nomogram-assisted decision-making for patients. As illustrated in **Figure 6**, the results reveal that across a broad spectrum of threshold probabilities in both the training and testing cohorts, utilizing the nomogram for predicting the 2-year or 3-year event-free survival probability offers a more significant net benefit when compared to strategies of 'treat all' or 'treat none.' These findings underscore the clinical utility of the nomogram.

Risk stratification

Considering that the study population consists of low-risk patients with non-obstructive coronary artery stenosis, the threshold for further risk stratification was set at a higher event-free survival probability, specifically a score of 104 points corresponding to the 95% 3-year event-free survival probability as determined by the nomogram. Individuals scoring below this threshold were categorized as low-risk, while those scoring equal to or above it were classified as high-risk. Kaplan-Meier curves depicting event-free survival were created for the two risk groups in the training and validation sets (**Figure 7**). Furthermore, MACE-event free survival of these groups is shown in **Supplementary Figure 2**. These results consistently demonstrated the model's efficacy in patient risk stratification.

Discussion

This study focused on patients initially suspected of having CAD but who were found to have nonobstructive coronary arteries following coronary angiography. A wide range of variables, including demographic information, vital signs, laboratory parameters, and echocardiographic measurements, were meticulously examined. Ultimately, 8 key variables, namely age, hemoglobin levels, serum urea, serum sodium levels, ALT/AST ratio, NT-proBNP levels, left atrial diameter, and LVEF, were identified. The study successfully developed a nomogram to predict the probability of event-free survival for these patients, demonstrating excellent discriminatory and calibration abilities in both the training and validation sets. The utilization of this predictive model in clinical practice empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes.

In clinical practice, a substantial number of patients with potential cardiac issues, such as chest pain, actively seek medical attention in both outpatient and emergency department settings. In the United Kingdom, for instance, approximately 1-2% of adults consult primary care facilities when experiencing chest pain for the first time [15]. Similarly, millions of individuals in the United States undergo stress tests in outpatient clinics each year for undiagnosed heart conditions [30]. However, research has

consistently shown that following diagnostic assessments like coronary angiography, approximately 50% of patients do not exhibit obstructive coronary artery stenosis [5,16,24,31]. Traditionally, such patients were often considered to have a favorable prognosis and no significant cardiac conditions , potentially resulting in the omission of further diagnostic measures and therapeutic interventions [32–34]. However, recent research has indicated that these patients face a significantly elevated risk of adverse outcomes compared to the general population. The WISE study revealed that at over a 10-year follow-up, patients without obstructive coronary stenosis on coronary angiography had rates of cardiovascular death and MI of 6.7% and 12.8%, respectively, underscoring the heightened risk among female ANOCA patients [21,35,36]. Other studies have also demonstrated that ANOCA patients, regardless of their gender, face an increased risk of experiencing CAD-related outcomes compared to the general population[16,31,37].

Our findings from this study indicate that ANOCA patients tend to be younger, with an average age of 43.6 years, and a higher proportion of them are female (58.3%) [7]. During a median follow-up period of 2 years, the rates of all-cause death, MI, and stroke were 1.79%, 0.56%, and 0.19%, respectively. These findings align with a previous study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3% [31]. Our research further supports the characterization of ANOCA patients and provides additional evidence of their elevated risk for adverse outcomes across diverse populations.

While clinical guidelines suggest risk stratification of chest pain patients and deferring testing for those

with a low likelihood of CAD, this strategy may inadvertently exclude high-risk ANOCA patients who require further assessment and appropriate therapeutic interventions [13,14]. As highlighted in a recent review, a significant proportion of ANOCA patients (ranging from 75% to 90%) exhibit various underlying causes, such as coronary microvascular dysfunction (CMD), microvascular spasm, endothelial dysfunction, epicardial coronary spasm, and/or myocardial bridging [7,38], emphasizing the critical importance of identifying high-risk ANOCA patients to optimize their further management.

Current research on factors related to adverse outcomes in the ANOCA population is limited. One study attempted to develop a risk tool for chest pain patients with normal coronary arteries to predict favorable outcomes. This tool comprised 10 variables, including age, gender, and the presence of conditions like hypertension, diabetes, or dyslipidemia. However, it is important to note that this study solely relied solely on pretest clinical data and accessed coronary arteries through coronary CTA [18]. In contrast, our predictive model incorporated pre-test indicators, including demographic variables and medical history, with age being one of the key factors. Age is a variable included in many traditional CAD prediction models because it is easily obtainable and reflects the aging of the entire cardiovascular system, including increased arterial stiffness and decreased vascular endothelial function [39,40].

Previous studies have also indicated that several blood biomarkers are associated with unfavorable outcomes in ANOCA patients, including lower levels of HDL-C, elevated levels of soluble urokinase-type plasminogen activator receptor, and high-sensitivity troponin [19,20]. However, none of these

studies conducted comprehensive screening of clinical variables or developed a predictive model. After a thorough screening of blood biomarkers, our predictive model incorporated hemoglobin, serum urea, serum sodium and NT-proBNP, which are rarely reported to be associated with adverse outcomes in ANOCA patients. Anemia, for example, is a common pathological condition involved in the occurrence and development of CAD and heart failure through various mechanisms [41]. It significantly increases the risk of developing CAD and heart failure and is associated with adverse outcomes in these patients [42,43]. Serum urea reflects renal function, which is a crucial factor influencing the cardiovascular system [44]. Previous research has shown that an elevated serum urea levels increase the risk of CAD and serve as a predictive factors for adverse outcomes in CAD and heart failure patients [45,46]. The role of serum sodium in cardiovascular disease is still not fully understood, but several studies have indicated that even mild reductions in serum sodium, even within the normal range, are associated with higher all-cause mortality and cardiovascular mortality in elderly individuals or the general population [47–50]. The underlying mechanisms behind this association require further research. NT-proBNP is a widely recognized marker for heart failure and exhibits strong predictive capabilities for the prognosis of heart failure patients [51]. Previous studies have also demonstrated its ability to predict cardiovascular events and mortality even in community-dwelling or elderly populations without heart failure [52–55].

Our predictive model also considered echocardiographic parameters. Echocardiography is a noninvasive, easily performed, and cost-effective imaging technique that provides comprehensive insights into cardiac structure and function. In our model, left atrial diameter and LVEF were included.

Left atrial enlargement is closely associated with conditions like atrial fibrillation and heart failure, and factors such as hypertension and mitral valve diseases can also lead to left atrial enlargement. It is commonly regarded as a biomarker for adverse cardiovascular outcomes [56–59]. The LVEF serves as one of the diagnostic and classificatory criteria for heart failure, with the latter often signifying the advanced stage of diverse cardiac ailments and indicates an unfavorable prognosis [60,61].

Limitations

This study has several limitations. First, the retrospective design precludes control of treatment strategies and introduces potential selection bias. Second, the study population consisted entirely of individuals from northern China, so caution should be exercised when generalizing the findings of this study to other populations. Third, the inability to subclassify ANOCA patients into those with versus without atherosclerosis represents an important limitation, as pathophysiological differences between these cohorts may contribute to population heterogeneity. However, this aligns with current guideline definitions， and future studies incorporating intracoronary imaging could refine risk stratification. Finally, while the predictive model developed from single-center data has not yet undergone external validation, internal validation confirmed its robust discrimination and calibration, indicating strong performance within the original cohort.

Conclusion

In summary, we conducted a comprehensive evaluation of clinically accessible variables and successfully developed a predictive model for assessing adverse outcomes in angina patients with suspected CAD who do not exhibit obstructive coronary artery stenosis. This nomogram equips clinicians with a valuable tool for risk stratification in ANOCA patients, allowing for optimized management and treatment strategies aimed at improving patient outcomes.

List of abbreviations

ANOCA, angina with nonobstructive coronary arteries

ACU, areas under the curve

ALT, alanine transaminase

AST, aspartate transaminase

LVEF, left ventricular ejection fraction

CAD, coronary artery disease

MI, myocardial infarction

CAG, coronary angiography

CCTA, coronary computed tomography angiography

HDL-C, high-density lipoprotein cholesterol

PCI, percutaneous coronary intervention

CABG, coronary-artery bypass grafting

MACE, major adverse cardiovascular events

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Data availability statement

The original data supporting the findings of this study can be obtained from the corresponding author upon reasonable request.

Contributors

L.Z. Conceptualization, Investigation, Methodology, Data curation, Software, Formal analysis, Visualization, Writing – original draft. Z.K.X. Investigation, Data curation, Formal analysis, Writing – review and editing. X.W. Methodology, Writing – review and editing. J.K.Z. Methodology, Writing

– review and editing. S.T.H. Data curation, Writing – review and editing. Y.K.Z. Data curation, Writing – review and editing. T.S.G. Data curation, Writing – review and editing. T.L. Supervision, Validation, Writing – review and editing. S.W.R. Supervision, Validation, Funding acquisition, Writing – review and editing. K.Y.C. Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review and editing. All authors approved the final manuscript. K.Y.C. is responsible for the overall content as guarantor.

Competing interests

This study received infrastructure support from Tianjin Medical University. The funding organization played no role in study design, data collection, analysis, interpretation, manuscript preparation, or publication decisions. All authors declare no additional competing interests.

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Figure and table

Figure 1. Flowchart of study participation. CAD, coronary artery disease.

Figure 2. Variable Selection Based on LASSO Regression. (A) Variation Characteristics of Variable Coefficients; (B) Selection Process of Optimal λ Value in LASSO Regression Model Using Cross-Validation.

Figure 3. Nomogram for predicting the probability of 1-, 2-, and 3-year event-free survival of ANOCA patients as assessed by coronary angiography. ALT, alanine transaminase; AST, aspartate transaminase; LVEF, left ventricular ejection fraction.

Figure 4. Receiver operating characteristic curve for the 1-, 2-, and 3-year primary endpoints of the nomogram in the training set (A) and validation set (B). AUC, area under receiver operating characteristic curve.

Figure 5. Calibration plot of predicted 1-, 2-, and 3-year event-free survival based on the nomogram in the training set and validation set. (A–C) Training set; (D–F) Validation set.

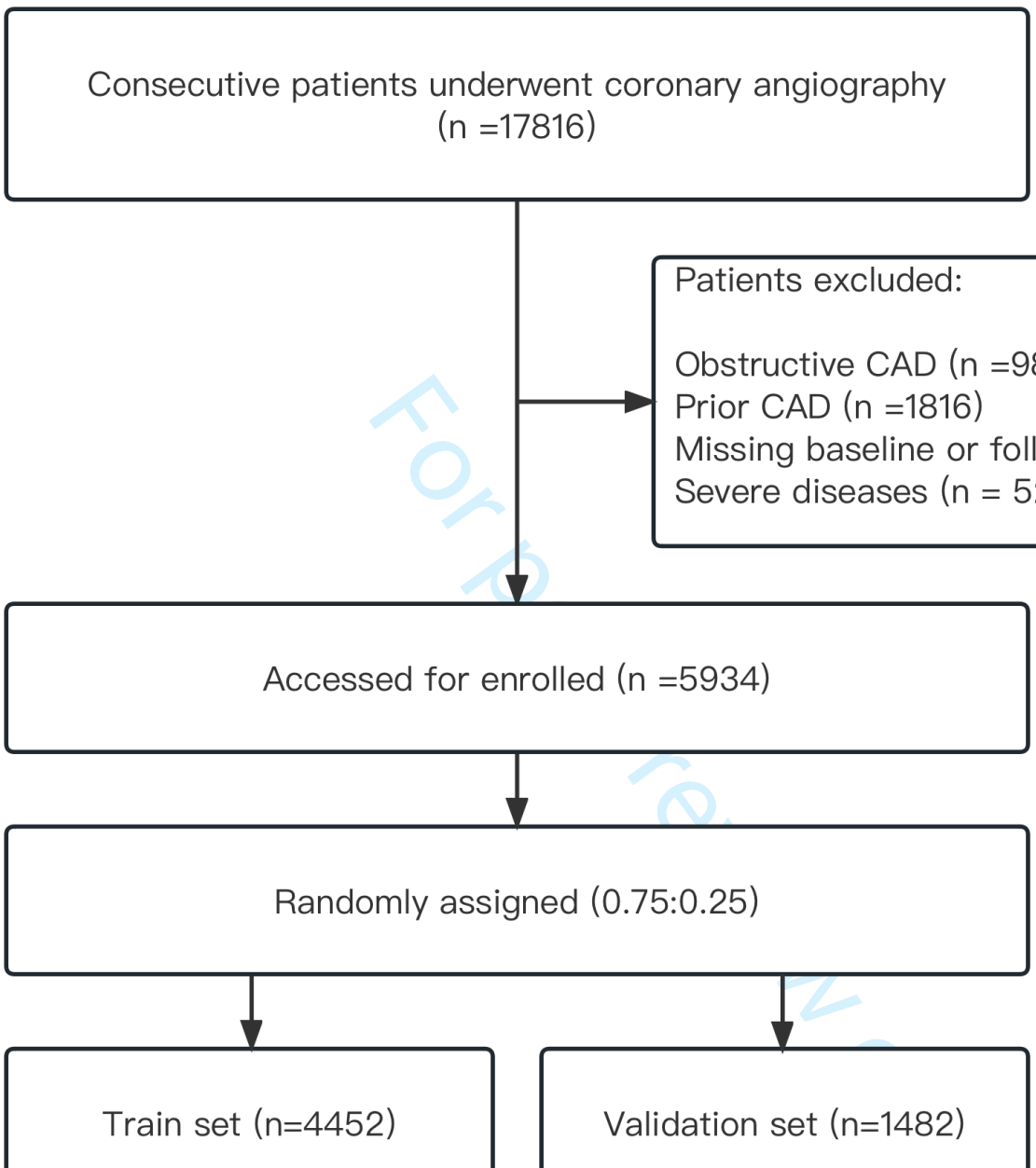
Figure 6. Decision curve analysis of the nomogram in the training cohort (A) and validation cohort (B). The x-axis represents the threshold probability, and the y-axis measures the net benefit. The left-slanting straight line shows the net benefit of treating all patients. The bottom horizontal gray line represents the net benefit of not treating any patients. The curve in the middle represents the nomogram.

Figure 7. Kaplan-Meier curves for primary endpoint event-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).

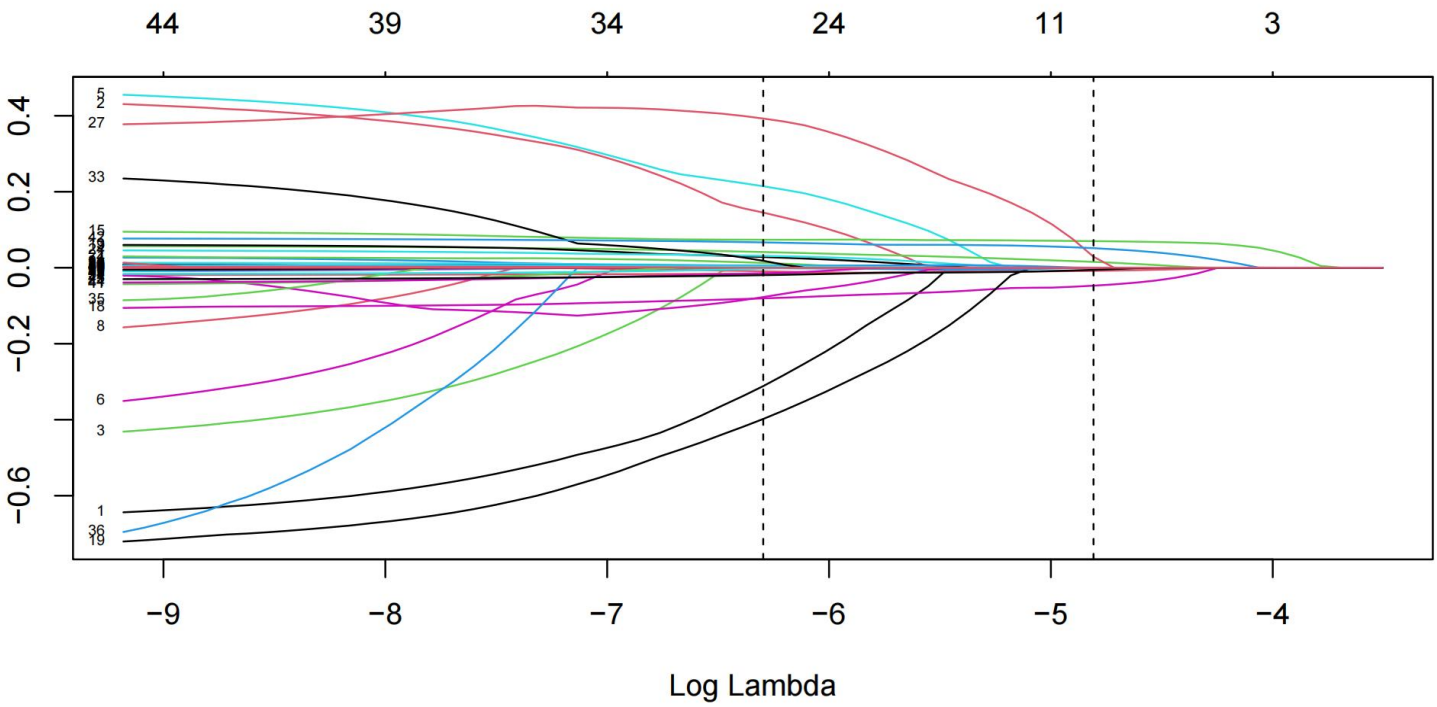
Supplementary Table 1. Clinical data of the total population, training set and validation set.

Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the total population.

Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).



A



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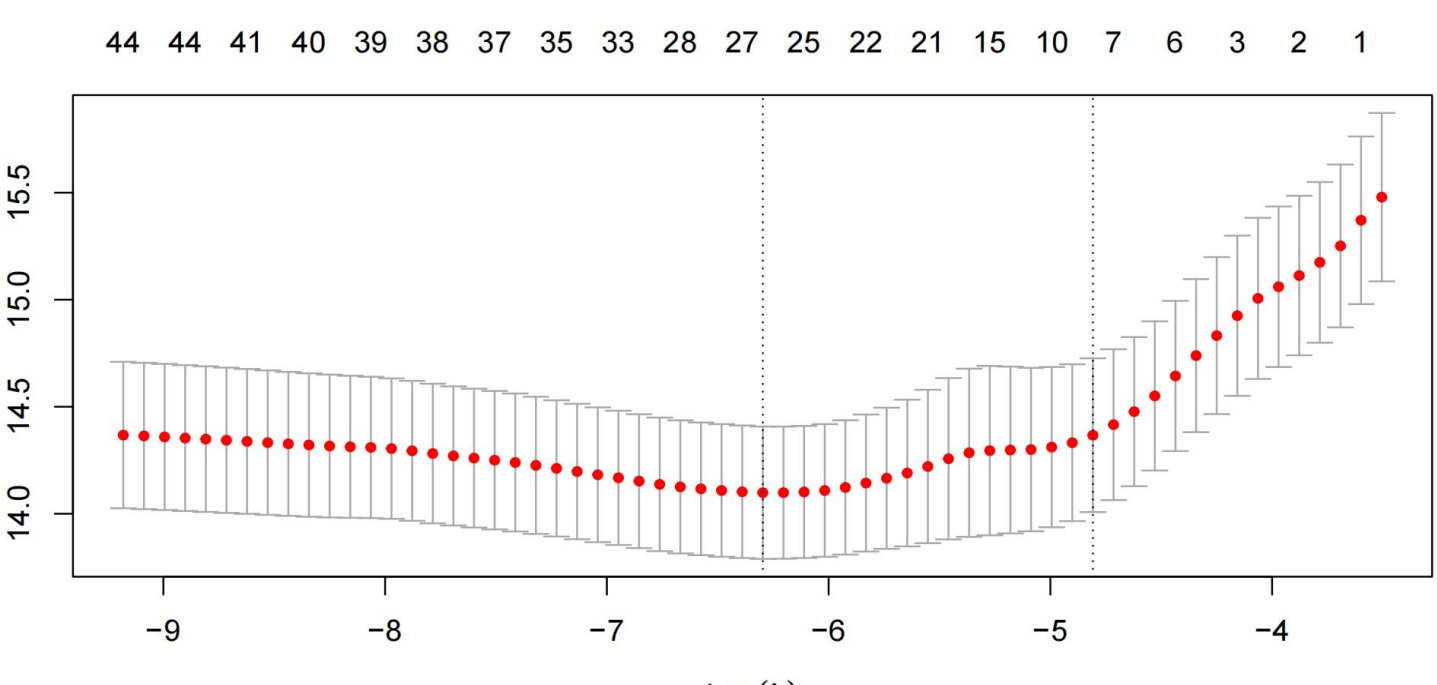

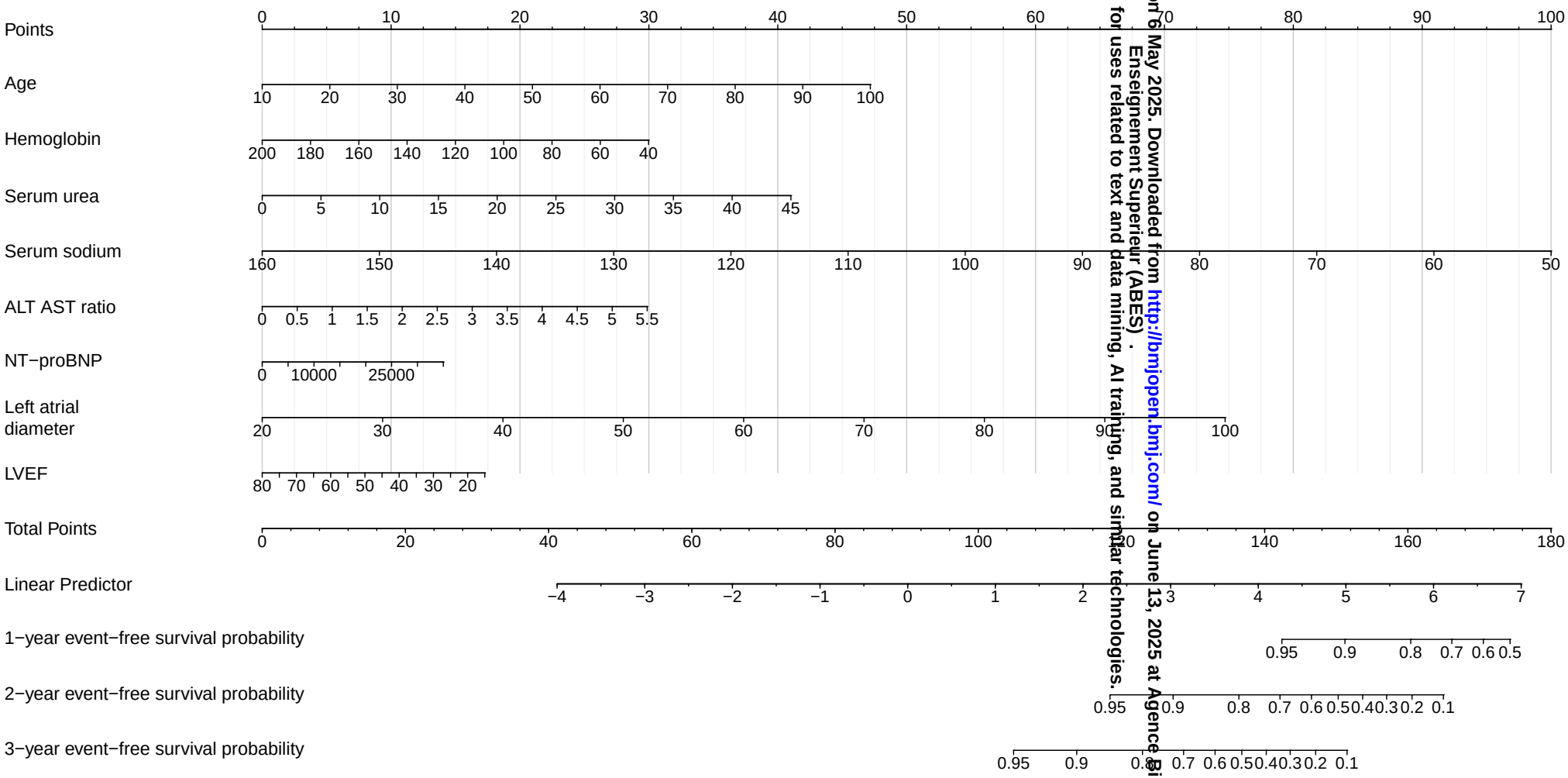

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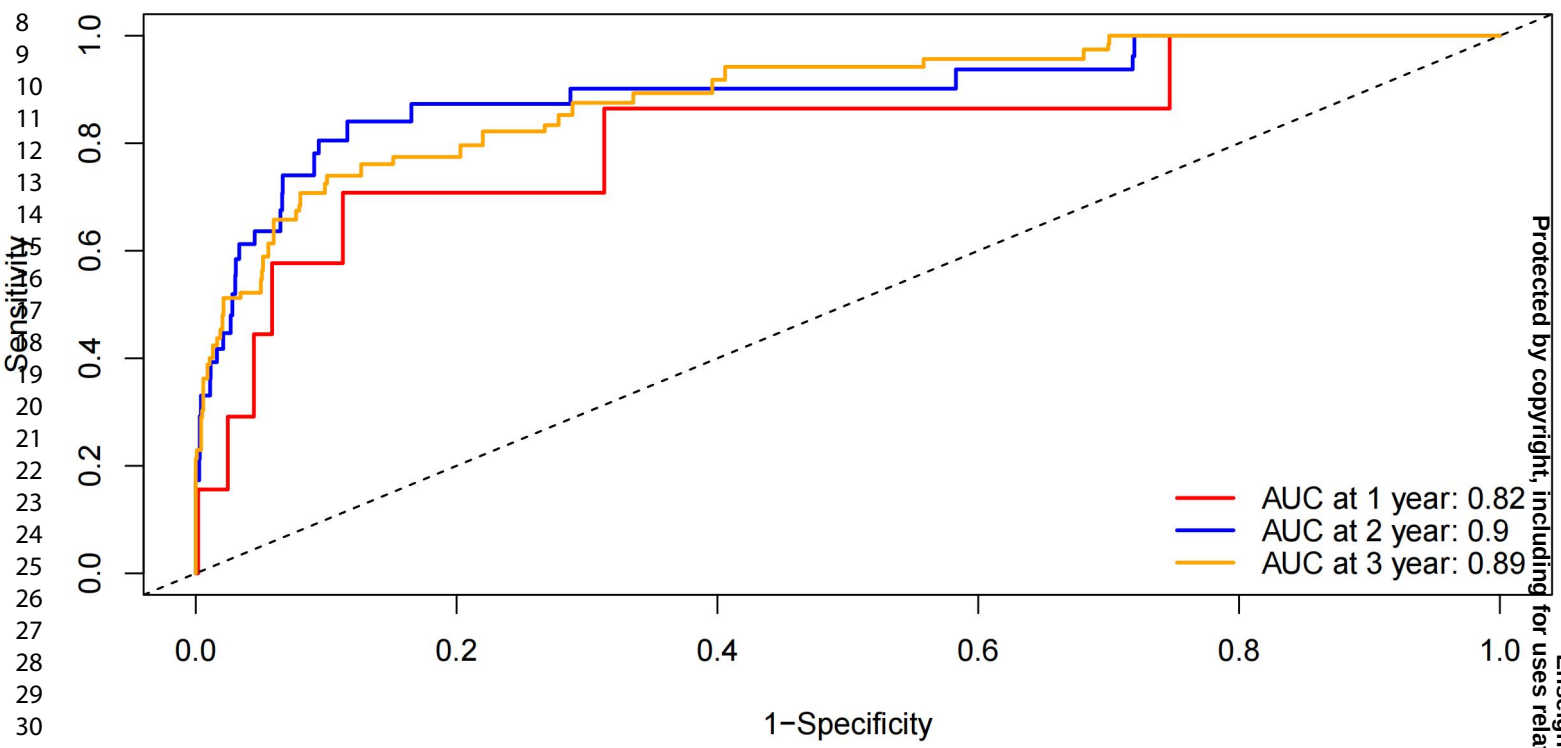

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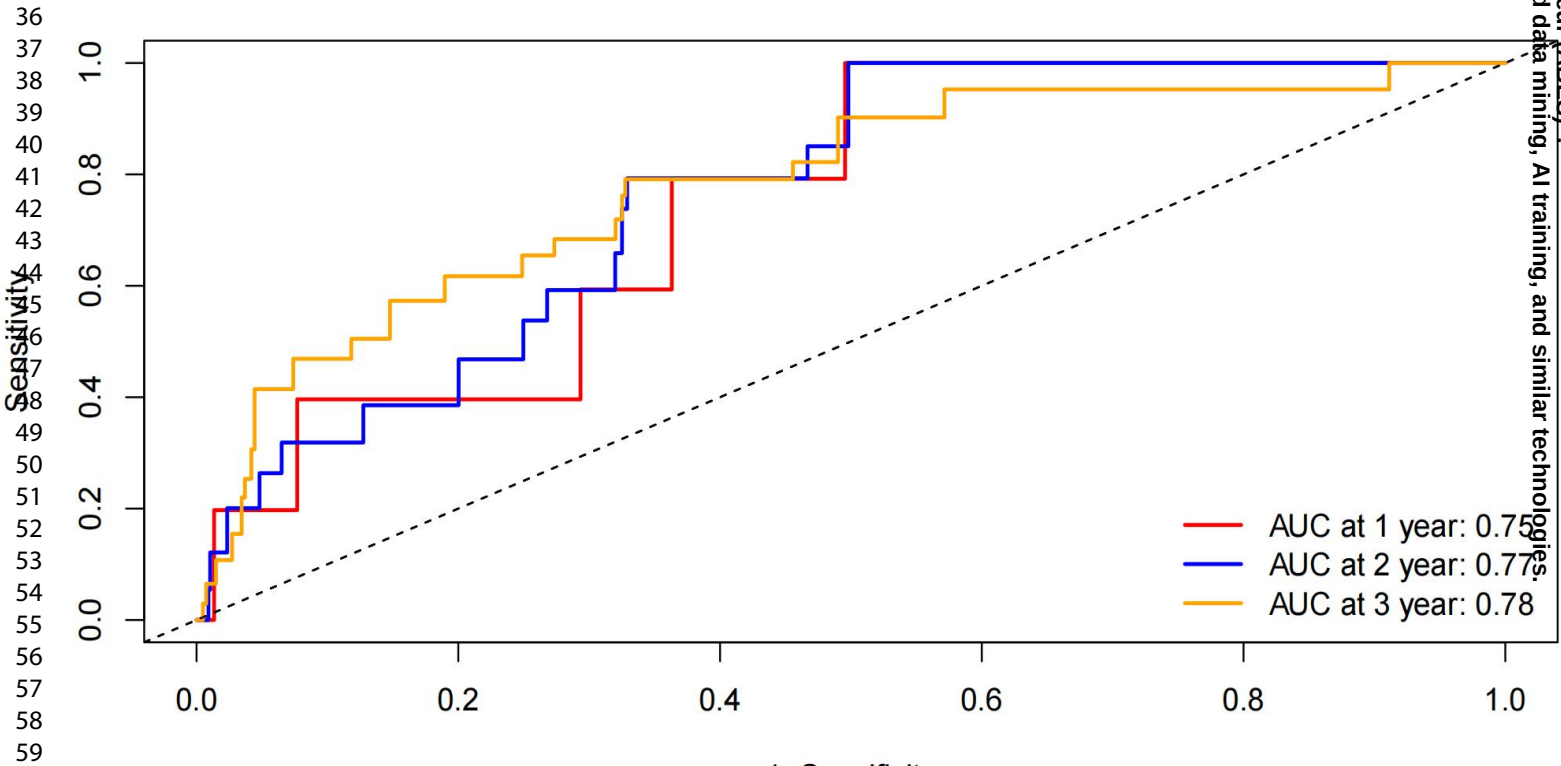

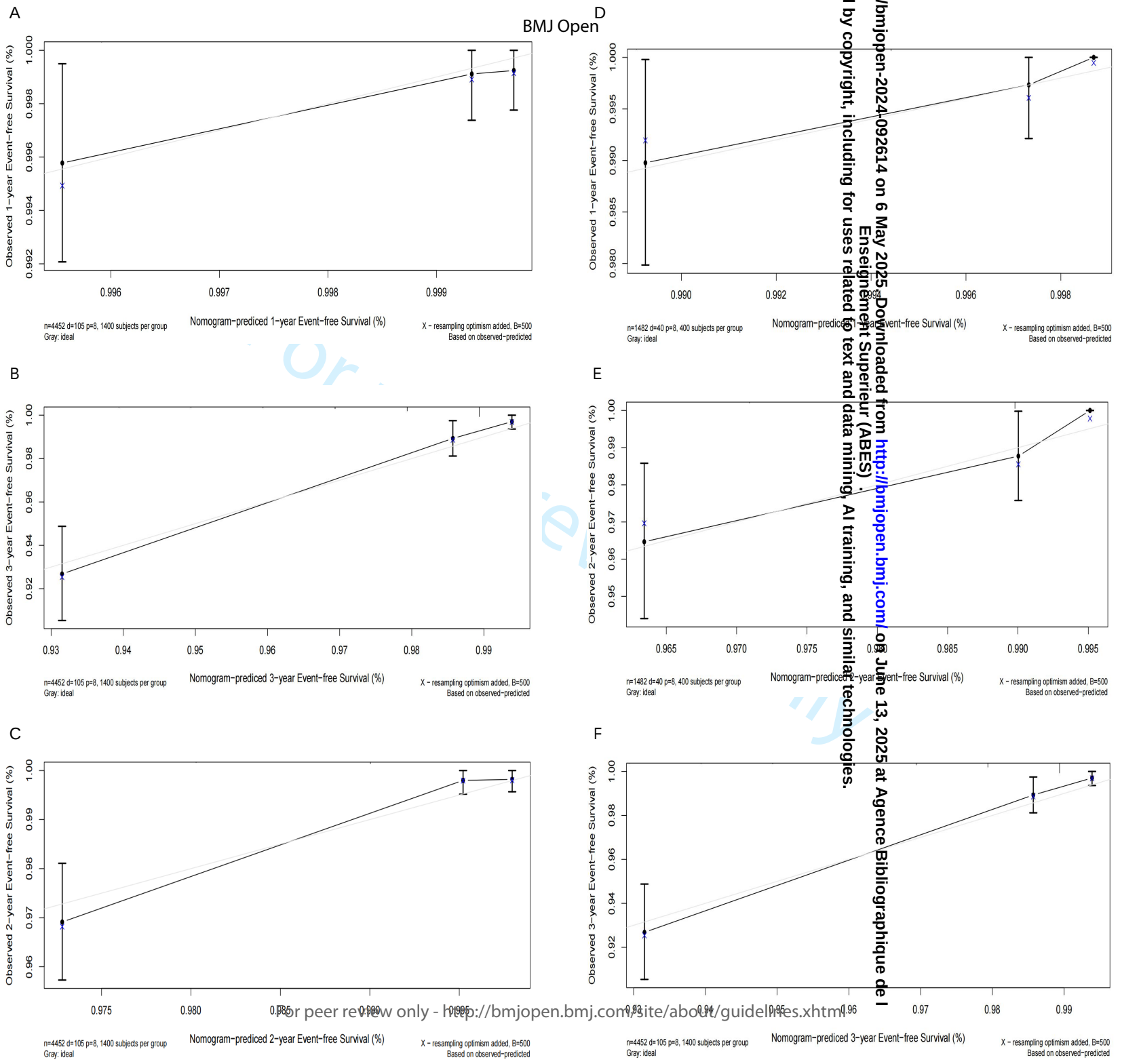

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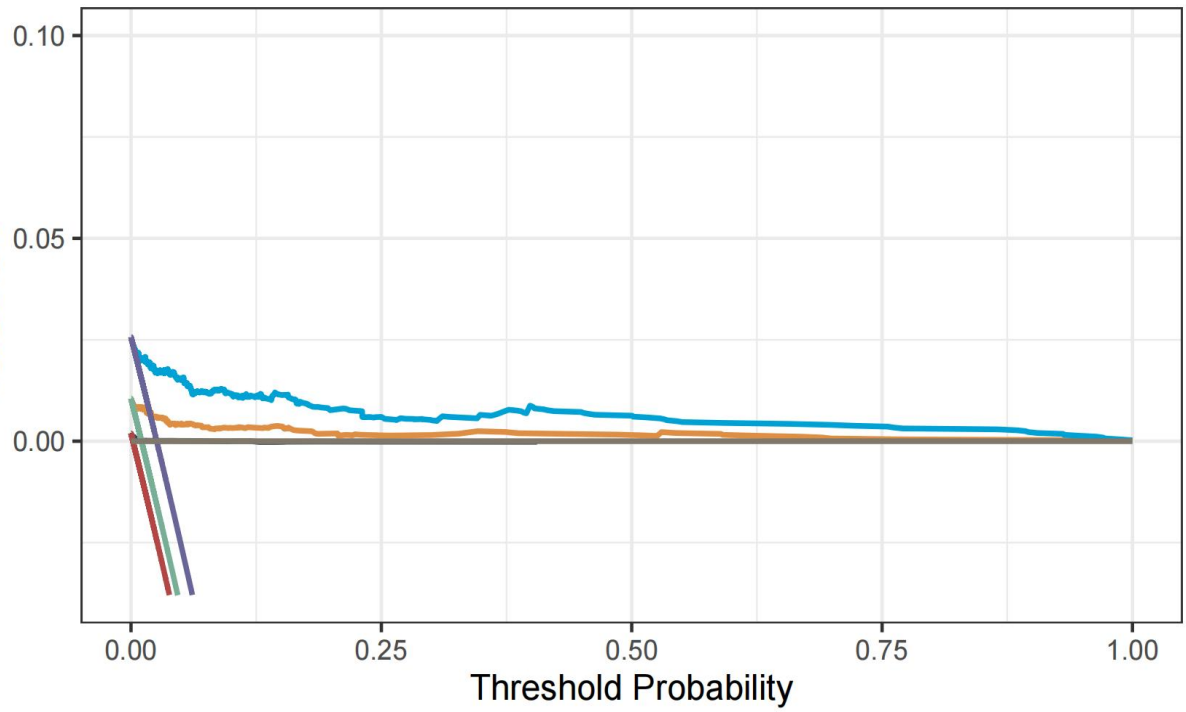

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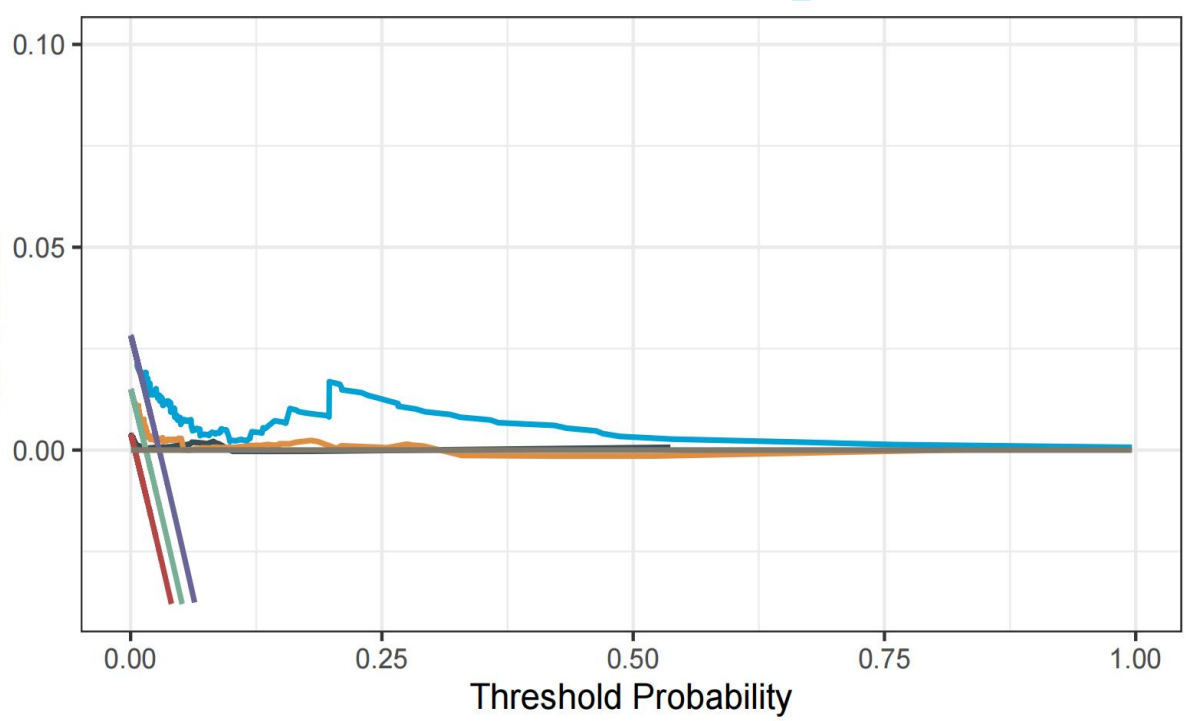

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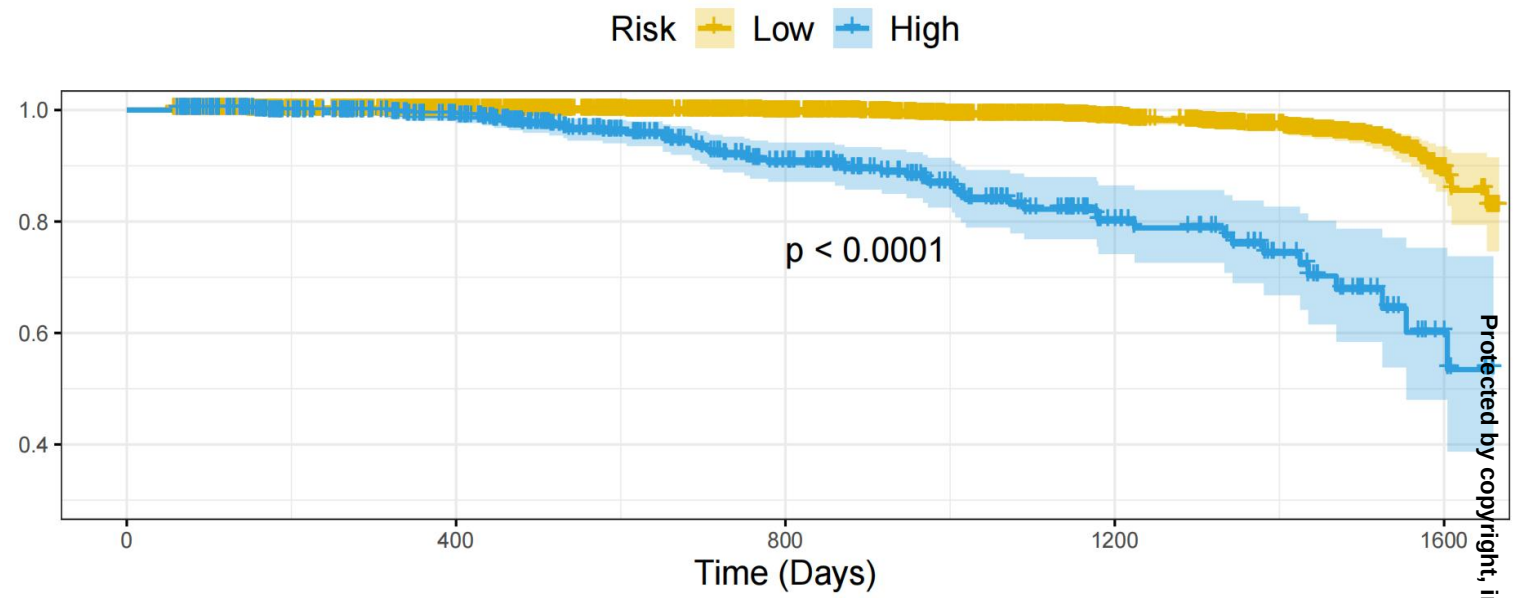
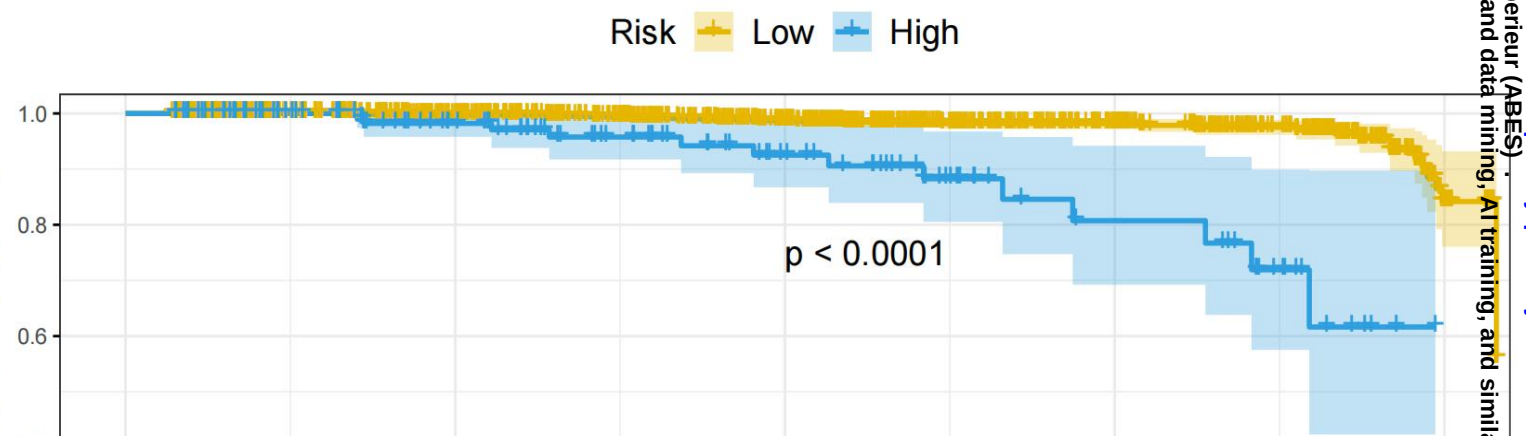


Number at risk

Low	3946	2875	1906	927	66
High	506	353	189	71	10

0 400 800 1200 1600

Time (Days)



Number at risk

Low	1336	993	648	325	34
High	146	92	51	20	0

0 400 800 1200 1600

Time (Days)

Supplement

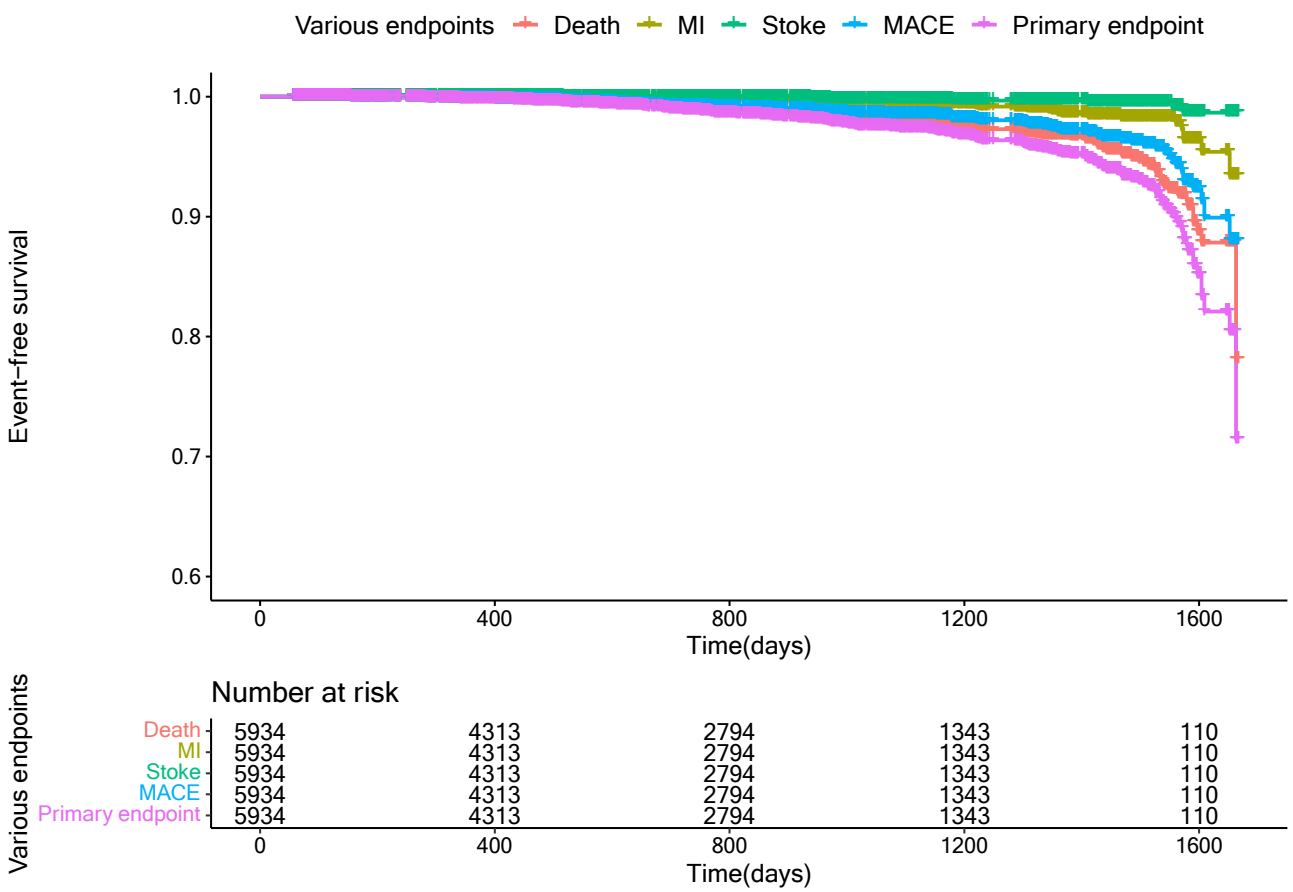
Supplementary Table 1. Clinical data of the total population, training set and validation set.

Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
Female, n (%)	3462 (58.3%)	2609 (58.6%)	853 (57.6%)	0.499
Age, years	43.6 (10.8)	43.7 (10.9)	43.5 (10.6)	0.563
Smoking, n (%)	1509 (25.4%)	1126 (25.3%)	383 (25.8%)	0.698
Drinking, n (%)	1883 (31.7%)	1415 (31.8%)	468 (31.6%)	0.909
Hypertension, n (%)	3698 (62.3%)	2802 (62.9%)	896 (60.5%)	0.094
Diabetes mellitus, n (%)	1123 (18.9%)	846 (19.0%)	277 (18.7%)	0.820
Diabetic complications, n (%)	19 (0.32%)	13 (0.29%)	6 (0.40%)	0.595
Dyslipidemia, n (%)	582 (9.81%)	423 (9.50%)	159 (10.7%)	0.185
CKD, n (%)	202 (3.40%)	151 (3.39%)	51 (3.44%)	0.993
SBP, mmHg	136 (19.8)	136 (19.9)	136 (19.7)	0.340
DBP, mmHg	81.9 (12.3)	81.9 (12.4)	81.8 (11.9)	0.757
Heart rate, beats/min	73.8 (15.2)	73.8 (13.9)	73.9 (18.5)	0.798
WBC, 10^9/L	6.67 (2.03)	6.68 (2.01)	6.67 (2.11)	0.969
Hemoglobin, g/L	136 (16.6)	136 (16.6)	136 (16.4)	0.881
Urea, mmol/L	6.09 (2.68)	6.09 (2.72)	6.08 (2.57)	0.831
Serum creatinine, μmol/L	65.9 [55.7; 79.8]	66.2 [55.7; 79.7]	65.4 [55.5; 80.0]	0.748
Uric acid, μmol/L	335 (100)	335 (101)	335 (99.0)	0.889
Serum sodium, mmol/L	142 (3.51)	142 (3.32)	142 (4.01)	0.829
Serum potassium, mmol/L	4.12 (0.56)	4.12 (0.47)	4.13 (0.76)	0.649
Serum chloride, mmol/L	106 (3.37)	106 (3.42)	106 (3.21)	0.515
Anion gap, mmol/L	14.0 (2.40)	13.9 (2.40)	14.0 (2.42)	0.844

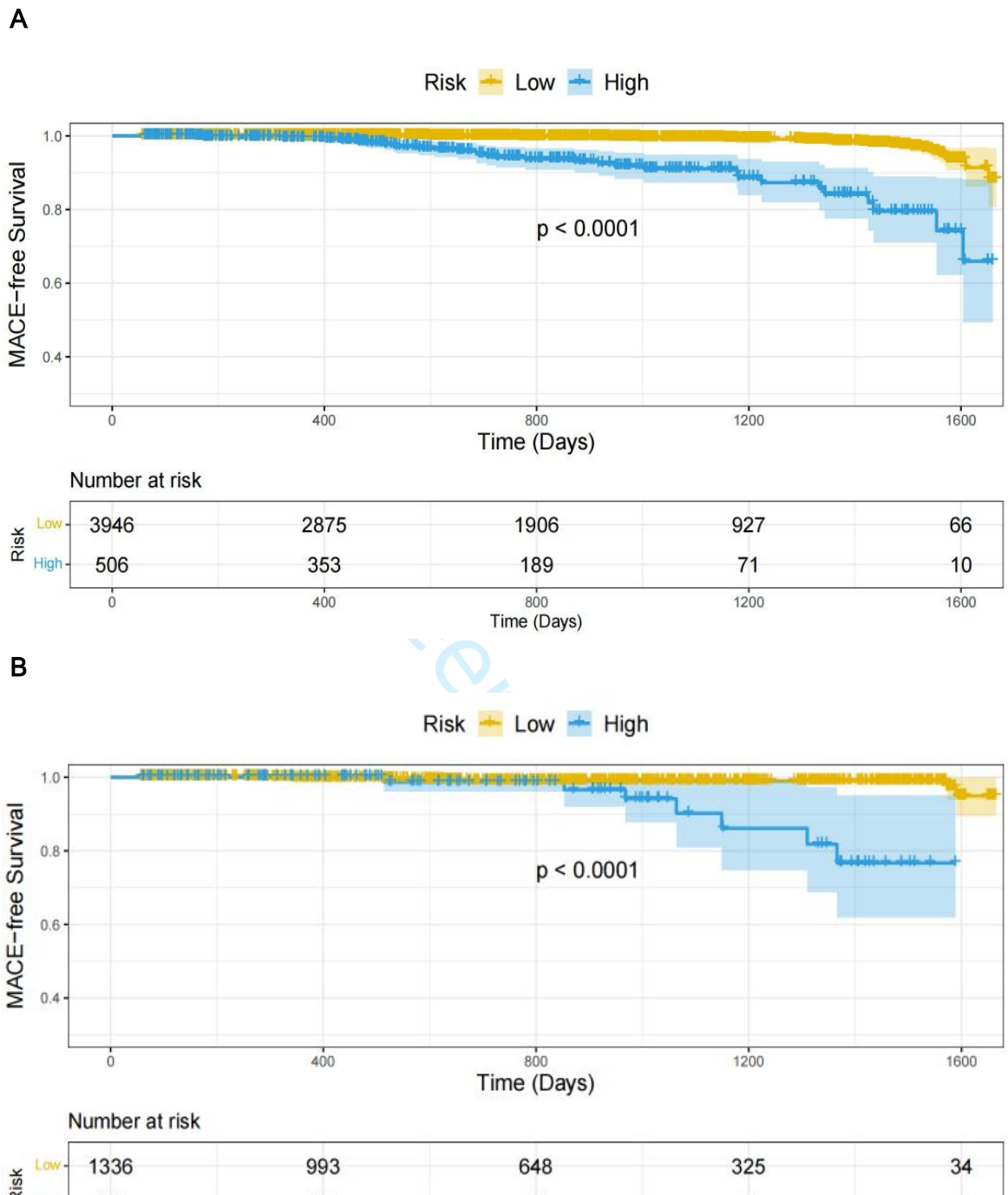
Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
Total protein, g/L	68.2 (6.41)	68.2 (6.37)	68.2 (6.54)	0.968
Albumin, g/L	42.4 (3.88)	42.4 (3.87)	42.3 (3.91)	0.406
Globulin, g/L	25.9 (4.19)	25.8 (4.16)	25.9 (4.30)	0.353
ALT, U/L	17.7 [13.0; 24.7]	17.8 [13.1; 24.8]	17.6 [12.6; 24.5]	0.169
AST, U/L	17.7 [14.6; 21.6]	17.8 [14.6; 21.6]	17.5 [14.6; 21.5]	0.341
ALT/AST ratio	1.06 (0.41)	1.05 (0.41)	1.07 (0.42)	0.157
Total bilirubin, μmol/L	13.6 (6.67)	13.6 (6.81)	13.4 (6.23)	0.257
Indirect Bilirubin, μmol/L	9.63 (4.69)	9.67 (4.75)	9.51 (4.53)	0.242
Direct Bilirubin, μmol/L	3.40 [2.30; 4.60]	3.40 [2.30; 4.60]	3.40 [2.40; 4.60]	0.611
Alkaline phosphatase, U/L	76.5 (23.6)	76.5 (23.6)	76.6 (23.7)	0.820
Total cholesterol, mmol/L	4.75 (1.12)	4.75 (1.13)	4.74 (1.08)	0.919
Triglycerides, mmol/L	1.63 (1.11)	1.62 (1.11)	1.65 (1.10)	0.485
HDL-C, mmol/L	1.22 (0.31)	1.22 (0.32)	1.20 (0.30)	0.083
LDL-C, mmol/L	2.97 (0.88)	2.97 (0.88)	2.98 (0.87)	0.498
VLDL-C, mmol/L	0.56 (0.37)	0.56 (0.39)	0.56 (0.30)	0.627
Troponin I, ng/ml	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.536
NT-proBNP, ng/L	83.7 [35.1; 266]	83.0 [34.3; 265]	86.7 [38.0; 269]	0.415
CKMB, U/L	12.1 [9.30; 14.7]	12.0 [9.24; 14.7]	12.3 [9.30; 14.7]	0.529
D-Dimer, μg/L	276 [2.34; 434]	274 [1.78; 427]	282 [4.65; 457]	0.110
Glucose, mmol/L	6.81 (2.48)	6.82 (2.45)	6.78 (2.56)	0.579
Left atrial diameter, mm	38.7 (5.24)	38.7 (5.28)	38.6 (5.11)	0.331

Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
LVEDD, mm	47.4 (4.46)	47.4 (4.51)	47.3 (4.28)	0.373
LVESD, mm	26.9 (5.62)	26.9 (5.65)	27.0 (5.52)	0.737
RVEDD, mm	20.8 (3.37)	20.7 (3.61)	20.8 (2.53)	0.623
LVEF, %	61.7 (6.75)	61.7 (6.77)	61.6 (6.70)	0.486
Event-free survival time, days	635 (403)	633 (402)	641 (406)	0.512
Death, n (%)	106 (1.79%)	78 (1.75%)	28 (1.89%)	0.816
MI endpoint, n (%)	33 (0.56%)	21 (0.47%)	12 (0.81%)	0.189
Stroke endpoint, n (%)	11 (0.19%)	6 (0.13%)	5 (0.34%)	0.156
MACE, n (%)	82 (1.38%)	64 (1.44%)	18 (1.21%)	0.611
Primary endpoint, n (%)	145 (2.44%)	105 (2.36%)	40 (2.70%)	0.523

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; CKMB, creatine kinase-MB; LVEDD, left ventricular-end-diastolic diameter; LVESD, left ventricular-end-systolic diameter; RVEDD, right ventricular-end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MACE, major adverse cardiovascular events.



Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the total population



Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).

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Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study

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Development and validation of a risk prediction model for adverse outcomes in patients with suspected coronary artery disease and no significant stenosis on angiography: a retrospective cohort study

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Abstract

Objectives

To develop and validate a risk prediction model for adverse outcomes in patients with angina with nonobstructive coronary arteries (ANOCA) confirmed by invasive coronary angiography.

Design

Retrospective cohort study.

Setting

A tertiary cardiovascular care center in China.

Participants

From 17,816 consecutive patients undergoing coronary angiography for suspected coronary artery disease, 5,934 met ANOCA criteria after rigorous exclusion: (1) significant stenosis (≥50% luminal narrowing), (2) established coronary artery disease history, (3) incomplete baseline/follow-up data, (4) non-cardiovascular life-limiting conditions.

primary and secondary outcome measures

The primary outcome was a composite of all-cause death, nonfatal myocardial infarction (MI), stroke, and repeat percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG). The secondary outcome was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat PCI, and CABG.

Results

The derivation cohort (n=4,452) and validation cohort (n=1,482) demonstrated comparable baseline characteristics. The nomogram incorporated eight prognosticators: age, hemoglobin, serum urea, serum sodium, alanine aminotransferase (ALT) / aspartate aminotransferase (AST) ratio, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left atrial diameter, and left ventricular ejection fraction (LVEF). The prediction model showed robust discrimination for primary endpoint, achieving area under the curve (AUC) values of 0.82 (1-year), 0.90 (2-year), and 0.89 (3-year) in the derivation cohort, with corresponding validation cohort AUCs of 0.75, 0.77, and 0.78. Calibration plots revealed close alignment between predicted and actual event-free survival probabilities in both cohorts. Risk stratification identified two distinct prognostic groups with significant survival differences (log-rank $p < 0.0001$).

Conclusions

This predictive model integrates routinely available clinical parameters to accurately stratify mortality and cardiovascular risk in ANOCA patients, providing a potential valuable decision-support tool for personalized therapeutic strategies.

Strengths and limitations of this study

- This study utilized a large sample size (n=5934) with rigorous internal validation through training and testing cohorts.
- Leveraged LASSO-penalized Cox regression with 10-fold cross-validation to optimize model

generalizability.

- The nomogram integrates routinely available clinical variables, enhancing clinical applicability.
- Limitations include the retrospective design, which may introduce selection bias.
- Data were derived from a single center, potentially limiting generalizability.

Key word

Angina, coronary artery disease, MINOCA, prognosis, nomogram.

Backgrounds

Chest pain is a common symptom among patients seeking medical services, often raising concerns about potentially life-threatening conditions such as coronary artery disease (CAD) [1,2]. Timely and accurate diagnostic assessments, including electrocardiography, coronary computed tomography angiography (CCTA), and coronary angiography (CAG), are frequently recommended for individuals presenting with chest pain to rule out severe conditions such as myocardial infarction (MI) [3,4]. However, in the cohort of patients undergoing diagnostic workup, approximately half exhibit nonobstructive coronary arteries (stenosis less than 50%)[5,6], a condition known as angina with nonobstructive coronary arteries (ANOCA) [7].

ANOCA patients often seek medical care due to symptoms and undergo repetitive invasive examinations, leading to significant healthcare resource utilization and imposing individual burdens and additional risks [8–10]. In a randomized controlled trial involving over 10,000 patients suspected of CAD with intermediate pretest likelihood, only approximately 12% of them yielded a positive result in the final coronary artery functional tests [11]. Patients with a low pretest probability exhibit an exceedingly low positivity rate in diagnostic workup and experience fewer adverse outcomes [12]. Therefore, clinical guidelines recommend delaying diagnostic testing for patients at low risk for CAD[13,14]. However, patients without obstructive coronary arteries confirmed by CAG or CCTA have been observed to experience more adverse outcomes compared to the general population[15–17]. Identifying high-risk individuals in ANOCA patients remains a challenge.

There is limited research on predicting adverse outcomes in ANOCA patients confirmed through CAG or CCTA. Some studies have validated the utility of specific pretest indicators, such as age, sex, and traditional cardiovascular disease risk factors(e.g., hypertension), to identify low-risk ANOCA patients [18]. However, several investigations have shown that specific blood biomarkers, including high-sensitivity troponin and lower high-density lipoprotein cholesterol (HDL-C) levels, operate as independent predictive factors for poor prognosis in ANOCA patients, adding prognostic value[19]. To date, comprehensive studies that screen noninvasive indicators and develop a prognostic model are lacking, and most previous studies are reliant on data derived from the Women's Ischemia Syndrome Evaluation (WISE) study[19–21], which exclusively includes female participants. One study also used WISE data to validate the effectiveness of some risk scores originally designed for other populations, such as the Atherosclerotic Cardiovascular Disease (ASCVD) score, in predicting adverse outcomes in ANOCA patients, but the results showed suboptimal performance[22]. Therefore, it is necessary to develop a predictive model based on non-invasive indicators to forecast adverse outcomes in ANOCA patients of both sexes. This study aims to bridge this gap to optimize clinical decision-making and patient management.

Method

Study Population

This is a retrospective cohort study that consecutively enrolled patients who presented with suspected

symptoms of CAD and underwent coronary angiography at the department of cardiology or emergency department of the Second Hospital of Tianjin Medical University between January 2019 and June 2023. The Second Hospital of Tianjin Medical University is a cardiac center serving the northern Chinese city of Tianjin and its surrounding regions. This study adheres to the principles outlined in the TRIPOD statement [23].

ANOCA patients were defined as angina with nonobstructive epicardial coronary arteries (stenosis <50%), adhering to current expert consensus[7]. Patients meeting the following criteria were excluded from the study: (1) patients with acute coronary syndrome or obstructive coronary arteries (defined as a luminal stenosis of ≥50% in a major epicardial coronary artery[7,24]); (2) patients with a prior diagnosis of CAD, history of percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG); (3) individuals with severe liver or kidney dysfunction, malignancies, or other non-cardiovascular conditions significantly affecting life expectancy; (4) those with substantial missing baseline data; and (5) patients lost to follow-up. This study received approval from the Ethics Committee of the Second Hospital of Tianjin Medical University, with a waiver for written informed consent granted for the retrospective use of fully anonymized clinical data (No. KY2025K008).

Clinical Data Collection

Patient data were retrospectively obtained from electronic medical records, including demographic information, medical history, vital sign data, laboratory parameters, echocardiographic data, coronary

angiography findings and other relevant details.

Follow-Up and Endpoints

A dedicated follow-up team conducted systematic post-discharge surveillance through a standardized protocol, with scheduled assessments at 30 days, 3 months, 6 months, and annually thereafter. Data collection employed a multimodal approach: (1) comprehensive electronic health record review, (2) cross-referencing with regional death registries, (3) and telephone or email interviews. The observational window for this analysis was finalized on August 1, 2023. Two board-certified cardiologists (L.Z. and Z.K.X., each with >5 years clinical experience) independently evaluated all events using standardized diagnostic criteria[25,26]. For discrepancies in event classification, an adjudication committee comprising two senior interventional cardiologists (T.L. and K.Y.C., both with >20 years catheterization laboratory experience) conducted final arbitration through consensus review.

The primary endpoint was a composite of all-cause death, nonfatal MI, stroke, and repeat PCI or CABG during follow-up. The secondary endpoint was major adverse cardiovascular events (MACE), defined as cardiac-related death, nonfatal MI, nonfatal stroke, repeat PCI, and CABG during follow-up. The composite endpoint was selected based on its established utility in prognostic studies of ANOCA [22,27–29].

Statistical Analysis

For the small amount of missing data in smoking and alcohol consumption history, multiple imputation was performed using the MICE package (Multiple Imputation by Chained Equations package). To establish a reliable model, the entire study cohort was randomly stratified into two subsets, a training set and a validation set, with a ratio of 0.75 to 0.25, respectively. The training set was used to generate the predictive model, while the validation set was utilized for model internal validation.

Categorical variables were described as frequencies and percentages, with group differences assessed using the chi-square test or Fisher's exact test as applicable. Continuous variables were expressed as either the mean ± standard deviation (SD) or median [interquartile range, IQR], and group comparisons were conducted using the t test or Kruskal–Wallis test as appropriate. Variables with variance inflation factor (VIF) ≥5 were excluded prior to LASSO regression to mitigate multicollinearity. The variables selected through LASSO regression were incorporated into the Cox proportional hazards regression model, and a nomogram was generated based on the Cox regression analysis model. The discriminative ability of the predictive model was evaluated using area under the curve (AUC). The model's calibration was assessed through the calibration curve. Additionally, decision curve analysis was employed to evaluate the clinical utility of the nomogram.

The total score for each patient was calculated based on the nomogram, and the study population was stratified into high-risk and low-risk groups according to the score corresponding to the 3-year 95% event-free survival probability. Event-free survival for the high- and low-risk groups in the training

and validation sets was estimated by Kaplan–Meier method and compared with the log-rank test. All statistical analyses were performed with R software version 4.3.1 (R Foundation for Statistical Computing). All statistical tests were two- tailed, with a significance level set at P<0.05.

Patient and public involvement

None.

Result

Study Population and Patient Characteristics

Out of a consecutive cohort of 17,816 patients who underwent coronary angiography for suspected coronary artery disease, 9,883 individuals with significant coronary artery stenosis and 1,816 patients with a documented history of coronary heart disease were excluded. An additional 131 individuals were excluded due to missing baseline or follow-up data, and 52 patients with severe conditions such as malignant tumors were also excluded. of the final analysis included 5,934 patients with negative coronary angiography results (**Figure 1**).

The mean age of the overall cohort was 43.6 ± 10.8 years, with 58.3% being female, and the median follow-up time was 631 [270, 972] days. Detailed baseline data are provided in **Supplementary Table 1**. During the follow-up period, 145 (2.44%) patients had primary endpoint events, 82 (1.38%) had MACE, 106 (1.79%) had all-cause death, 33 (0.56%) had MI, and 11 (0.19%) had a stroke. The

Kaplan-Meier method was employed to estimate the survival without various adverse events for the total study population (**Supplementary Figure 1**).

Nomogram built based on LASSO-COX regression

The entire cohort was randomly divided into a training cohort consisting of 4,452 patients and a validation cohort comprising 1,482 patients. There were no statistically significant differences in the collected variables between these two groups (**Supplementary Table 1**). LASSO regression was employed to select variables with the strongest correlation to the primary endpoint. As the regularization parameter (λ) increased, certain coefficients were reduced to zero, effectively eliminating those variables from the model (**Figure 2A**). We used a tenfold cross-validation approach to identify the optimal model. Due to the relatively limited number of cases undergoing primary endpoint events in the validation cohort (145), we employed the one standard error (1-se) rule, resulting in eight selected variables (**Figure 2B**). These variables were incorporated into a Cox proportional hazards regression model, with results presented in **Table 1**. All models satisfied proportional hazards assumptions (global test p=0.057). A nomogram was developed based on the Cox regression model, with the regression coefficients of these factors amalgamated into a scoring system, ranging from 0 to 100(**Figure 3**). For example, an 81-year-old male patient with a hemoglobin level of 92 g/L, serum urea of 14.1 mmol/L, serum sodium of 145.6 mmol/L, an ALT/AST ratio of 1.68, NT-proBNP at 272 ng/L, left atrial diameter of 38.83 millimeters, and an LVEF of 62% received a total score of 115. The 1-year, 2-year and 3-year event-free survival rates were 99.5%, 96.2% and 89.0%, respectively.

Table 1. Prediction of event-free survival probability using the Cox proportional hazards regression model based on LASSO regression.

Variable	coefficients	z score	HR	95%CI	p value
Age	0.043	4.167	1.044	0.023, 0.063	<0.001
Hemoglobin	-0.015	-2.871	0.985	-0.026, -0.005	0.004
Urea	0.074	3.947	1.077	0.037, 0.111	<0.001
Serum sodium	-0.074	-5.694	0.929	-0.1, -0.049	<0.001
ALT/AST ratio	0.444	2.439	1.559	0.087, 0.8	0.015
NT-proBNP	0	2.094	1	0, 0	0.036
Left atrial diameter	0.076	5.959	1.079	0.051, 0.8	<0.001
LVEF	-0.022	-2.289	0.979	-0.04, -0.003	0.022

HR, hazard ratio; CI, confidence interval; ALT, alanine transaminase; AST, aspartate transaminase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

Discrimination and calibration of the nomogram

The discriminative ability of the model was assessed by plotting receiver operating characteristic curves. In the training set, the AUC for 1-, 2-, and 3-year predictions was 0.82, 0.90, and 0.89, respectively. In the validation set, the corresponding AUC for 1-, 2-, and 3-year predictions were 0.75, 0.77, and 0.78, respectively (**figure 4**).

Figure 5 illustrates calibration plots for the models predicting 1-, 2-, and 3-year survival in both the training and validation datasets. In well-calibrated models, the points closely align with the ideal 45-degree line, indicating that predicted survival closely matches observed survival and demonstrating

good model calibration.

Decision Curve

Decision curve analysis was employed to evaluate the potential improvement in clinical outcomes through nomogram-assisted decision-making for patients. As illustrated in **Figure 6**, the results reveal that across a broad spectrum of threshold probabilities in both the training and testing cohorts, utilizing the nomogram for predicting the 2-year or 3-year event-free survival probability offers a more significant net benefit when compared to strategies of 'treat all' or 'treat none.' These findings underscore the clinical utility of the nomogram.

Risk stratification

Considering that the study population consists of low-risk patients with non-obstructive coronary artery stenosis, the threshold for further risk stratification was set at a higher event-free survival probability, specifically a score of 104 points corresponding to the 95% 3-year event-free survival probability as determined by the nomogram. Individuals scoring below this threshold were categorized as low-risk, while those scoring equal to or above it were classified as high-risk. Kaplan-Meier curves depicting event-free survival were created for the two risk groups in the training and validation sets (**Figure 7**). Furthermore, MACE-event free survival of these groups is shown in **Supplementary Figure 2**. These results consistently demonstrated the model's efficacy in patient risk stratification.

Discussion

This study focused on patients initially suspected of having CAD but who were found to have nonobstructive coronary arteries following coronary angiography. A wide range of variables, including demographic information, vital signs, laboratory parameters, and echocardiographic measurements, were meticulously examined. Ultimately, 8 key variables, namely age, hemoglobin levels, serum urea, serum sodium levels, ALT/AST ratio, NT-proBNP levels, left atrial diameter, and LVEF, were identified. The study successfully developed a nomogram to predict the probability of event-free survival for these patients, demonstrating excellent discriminatory and calibration abilities in both the training and validation sets. The utilization of this predictive model in clinical practice empowers healthcare providers to conduct more precise risk stratification, particularly for individuals initially classified as low-risk, thereby improving diagnostic, management, and treatment strategies and ultimately enhancing patient outcomes.

In clinical practice, a substantial number of patients with potential cardiac issues, such as chest pain, actively seek medical attention in both outpatient and emergency department settings. In the United Kingdom, for instance, approximately 1-2% of adults consult primary care facilities when experiencing chest pain for the first time [15]. Similarly, millions of individuals in the United States undergo stress tests in outpatient clinics each year for undiagnosed heart conditions [30]. However, research has

consistently shown that following diagnostic assessments like coronary angiography, approximately 50% of patients do not exhibit obstructive coronary artery stenosis [5,16,24,31]. Traditionally, such patients were often considered to have a favorable prognosis and no significant cardiac conditions , potentially resulting in the omission of further diagnostic measures and therapeutic interventions [32–34]. However, recent research has indicated that these patients face a significantly elevated risk of adverse outcomes compared to the general population. The WISE study revealed that at over a 10-year follow-up, patients without obstructive coronary stenosis on coronary angiography had rates of cardiovascular death and MI of 6.7% and 12.8%, respectively, underscoring the heightened risk among female ANOCA patients [21,35,36]. Other studies have also demonstrated that ANOCA patients, regardless of their gender, face an increased risk of experiencing CAD-related outcomes compared to the general population[16,31,37].

Our findings from this study indicate that ANOCA patients tend to be younger, with an average age of 43.6 years, and a higher proportion of them are female (58.3%) [7]. During a median follow-up period of 2 years, the rates of all-cause death, MI, and stroke were 1.79%, 0.56%, and 0.19%, respectively. These findings align with a previous study reporting 1-year MI rates ranging from 0.11% to 0.59% and 1-year mortality rates ranging from 1.38% to 2.3% [31]. Our research further supports the characterization of ANOCA patients and provides additional evidence of their elevated risk for adverse outcomes across diverse populations.

While clinical guidelines suggest risk stratification of chest pain patients and deferring testing for those

with a low likelihood of CAD, this strategy may inadvertently exclude high-risk ANOCA patients who require further assessment and appropriate therapeutic interventions [13,14]. As highlighted in a recent review, a significant proportion of ANOCA patients (ranging from 75% to 90%) exhibit various underlying causes, such as coronary microvascular dysfunction, microvascular spasm, endothelial dysfunction, epicardial coronary spasm, and/or myocardial bridging [7,38], emphasizing the critical importance of identifying high-risk ANOCA patients to optimize their further management.

Current research on factors related to adverse outcomes in the ANOCA population is limited. One study attempted to develop a risk tool for chest pain patients with normal coronary arteries to predict favorable outcomes. This tool comprised 10 variables, including age, gender, and the presence of conditions like hypertension, diabetes, or dyslipidemia. However, it is important to note that this study solely relied solely on pretest clinical data and accessed coronary arteries through CCTA [18]. In contrast, our predictive model incorporated pre-test indicators, including demographic variables and medical history, with age being one of the key factors. Age is a variable included in many traditional CAD prediction models because it is easily obtainable and reflects the aging of the entire cardiovascular system, including increased arterial stiffness and decreased vascular endothelial function [39,40].

Previous studies have also indicated that several blood biomarkers are associated with unfavorable outcomes in ANOCA patients, including lower levels of HDL-C, elevated levels of soluble urokinase-type plasminogen activator receptor, and high-sensitivity troponin [19,20]. However, none of these

studies conducted comprehensive screening of clinical variables or developed a predictive model. After a thorough screening of blood biomarkers, our predictive model incorporated hemoglobin, serum urea, serum sodium and NT-proBNP, which are rarely reported to be associated with adverse outcomes in ANOCA patients. Anemia, for example, is a common pathological condition involved in the occurrence and development of CAD and heart failure through various mechanisms [41]. It significantly increases the risk of developing CAD and heart failure and is associated with adverse outcomes in these patients [42,43]. Serum urea reflects renal function, which is a crucial factor influencing the cardiovascular system [44]. Previous research has shown that an elevated serum urea levels increase the risk of CAD and serve as a predictive factors for adverse outcomes in CAD and heart failure patients [45,46]. The role of serum sodium in cardiovascular disease is still not fully understood, but several studies have indicated that even mild reductions in serum sodium, even within the normal range, are associated with higher all-cause mortality and cardiovascular mortality in elderly individuals or the general population [47–50]. The underlying mechanisms behind this association require further research. NT-proBNP is a widely recognized marker for heart failure and exhibits strong predictive capabilities for the prognosis of heart failure patients [51]. Previous studies have also demonstrated its ability to predict cardiovascular events and mortality even in community-dwelling or elderly populations without heart failure [52–55].

Our predictive model also considered echocardiographic parameters. Echocardiography is a noninvasive, easily performed, and cost-effective imaging technique that provides comprehensive insights into cardiac structure and function. In our model, left atrial diameter and LVEF were included.

Left atrial enlargement is closely associated with conditions like atrial fibrillation and heart failure, and factors such as hypertension and mitral valve diseases can also lead to left atrial enlargement. It is commonly regarded as a biomarker for adverse cardiovascular outcomes [56–59]. The LVEF serves as one of the diagnostic and classificatory criteria for heart failure, with the latter often signifying the advanced stage of diverse cardiac ailments and indicates an unfavorable prognosis [60,61].

Limitations

This study has several limitations. First, the retrospective design precludes control of treatment strategies and introduces potential selection bias. Second, the study population consisted entirely of individuals from northern China, so caution should be exercised when generalizing the findings of this study to other populations. Third, the inability to subclassify ANOCA patients into those with versus without atherosclerosis represents an important limitation, as pathophysiological differences between these cohorts may contribute to population heterogeneity. However, this aligns with current guideline definitions， and future studies incorporating intracoronary imaging could refine risk stratification. Finally, while the predictive model developed from single-center data has not yet undergone external validation, internal validation confirmed its robust discrimination and calibration, indicating strong performance within the original cohort.

Conclusion

In summary, we conducted a comprehensive evaluation of clinically accessible variables and successfully developed a predictive model for assessing adverse outcomes in angina patients with suspected CAD who do not exhibit obstructive coronary artery stenosis. This nomogram equips clinicians with a valuable tool for risk stratification in ANOCA patients, allowing for optimized management and treatment strategies aimed at improving patient outcomes.

List of abbreviations

ANOCA, angina with nonobstructive coronary arteries

MI, myocardial infarction

PCI, percutaneous coronary intervention

CABG, coronary-artery bypass grafting

MACE, major adverse cardiovascular events

ALT, alanine transaminase

AST, aspartate transaminase

NT-proBNP, N-terminal pro-B-type natriuretic peptide

LVEF, left ventricular ejection fraction

AUC, area under the curve

CAD, coronary artery disease

CAG, coronary angiography

CCTA, coronary computed tomography angiography

HDL-C, high-density lipoprotein cholesterol

SD, standard deviation

IQR, interquartile range

VIF, variance inflation factor

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Data availability statement

The original data supporting the findings of this study can be obtained from the corresponding author upon reasonable request.

Contributors

L.Z. Conceptualization, Investigation, Methodology, Data curation, Software, Formal analysis,

Visualization, Writing – original draft. Z.K.X. Investigation, Data curation, Formal analysis, Writing – review and editing. X.W. Methodology, Writing – review and editing. J.K.Z. Methodology, Writing – review and editing. S.T.H. Data curation, Writing – review and editing. Y.K.Z. Data curation, Writing – review and editing. T.S.G. Data curation, Writing – review and editing. T.L. Supervision, Validation, Writing – review and editing. S.W.R. Supervision, Validation, Funding acquisition, Writing – review and editing. K.Y.C. Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review and editing. All authors approved the final manuscript. K.Y.C. is responsible for the overall content as guarantor.

Competing interests

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Figure and table

Figure 1. Flowchart of study participation. CAD, coronary artery disease.

Figure 2. Variable Selection Based on LASSO Regression. (A) Variation Characteristics of Variable Coefficients; (B) Selection Process of Optimal λ Value in LASSO Regression Model Using Cross-Validation.

Figure 3. Nomogram for predicting the probability of 1-, 2-, and 3-year event-free survival of ANOCA patients as assessed by coronary angiography. ALT, alanine transaminase; AST, aspartate

transaminase; LVEF, left ventricular ejection fraction.

Figure 4. Receiver operating characteristic curve for the 1-, 2-, and 3-year primary endpoints of the nomogram in the training set (A) and validation set (B). AUC, area under the curve.

Figure 5. Calibration plot of predicted 1-, 2-, and 3-year event-free survival based on the nomogram in the training set and validation set. (A–C) Training set; (D–F) Validation set.

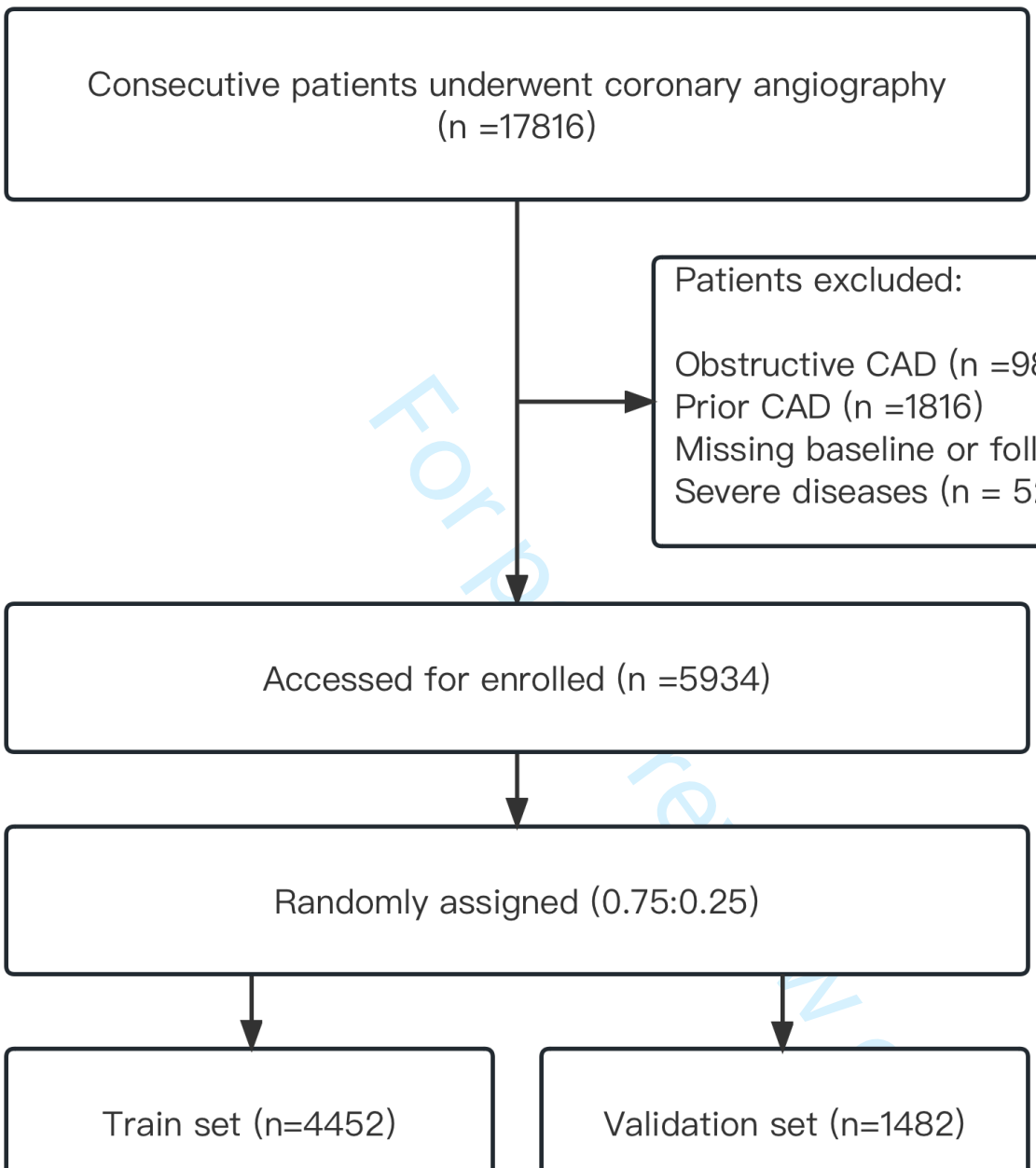
Figure 6. Decision curve analysis of the nomogram in the training cohort (A) and validation cohort (B). The x-axis represents the threshold probability, and the y-axis measures the net benefit. The left-slanting straight line shows the net benefit of treating all patients. The bottom horizontal gray line represents the net benefit of not treating any patients. The curve in the middle represents the nomogram.

Figure 7. Kaplan-Meier curves for primary endpoint event-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).

Supplementary Table 1. Clinical data of the total population, training set and validation set.

Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the total population.

Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).



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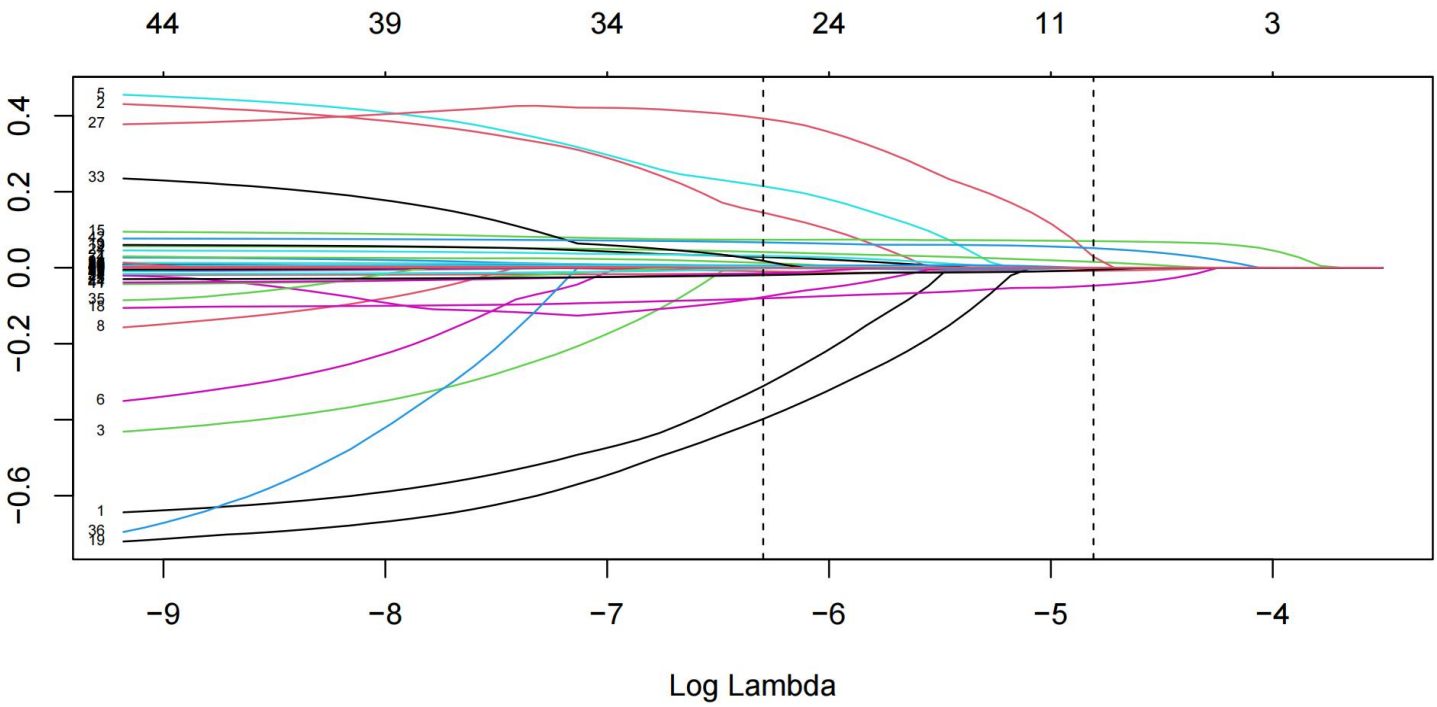

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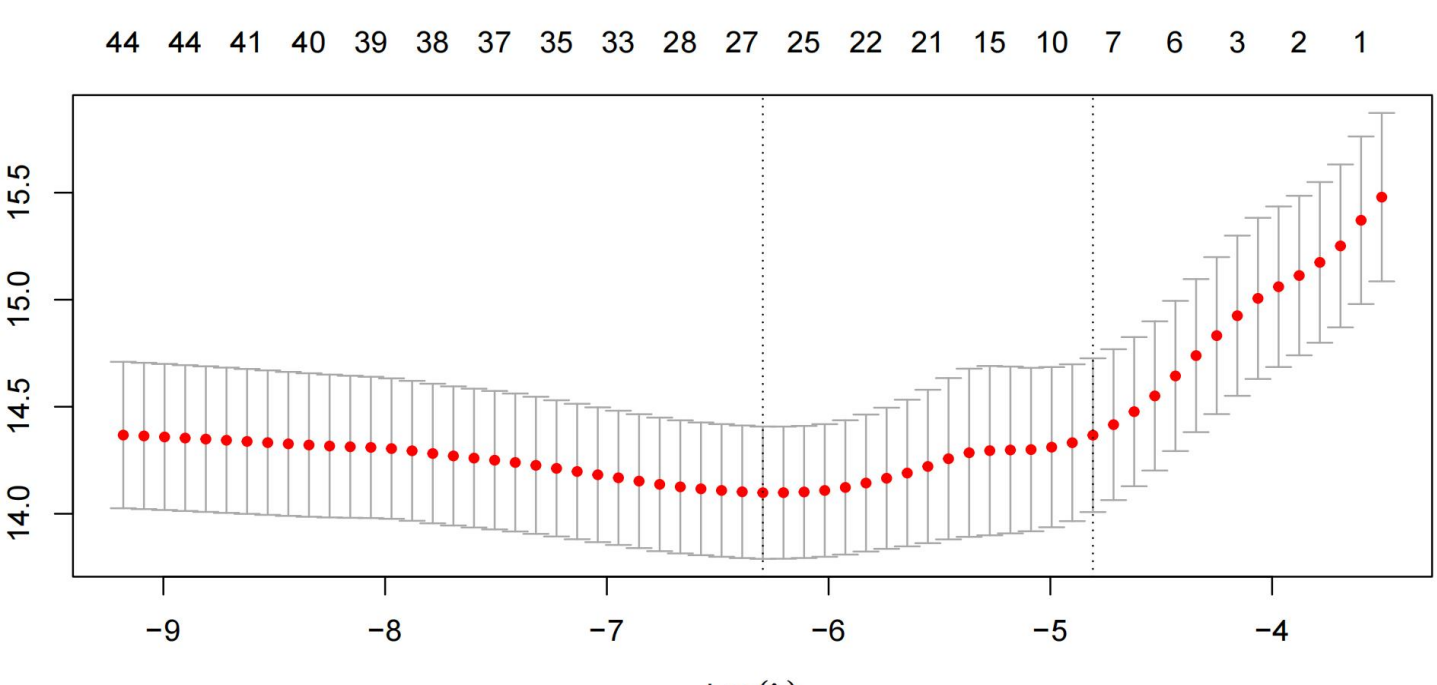

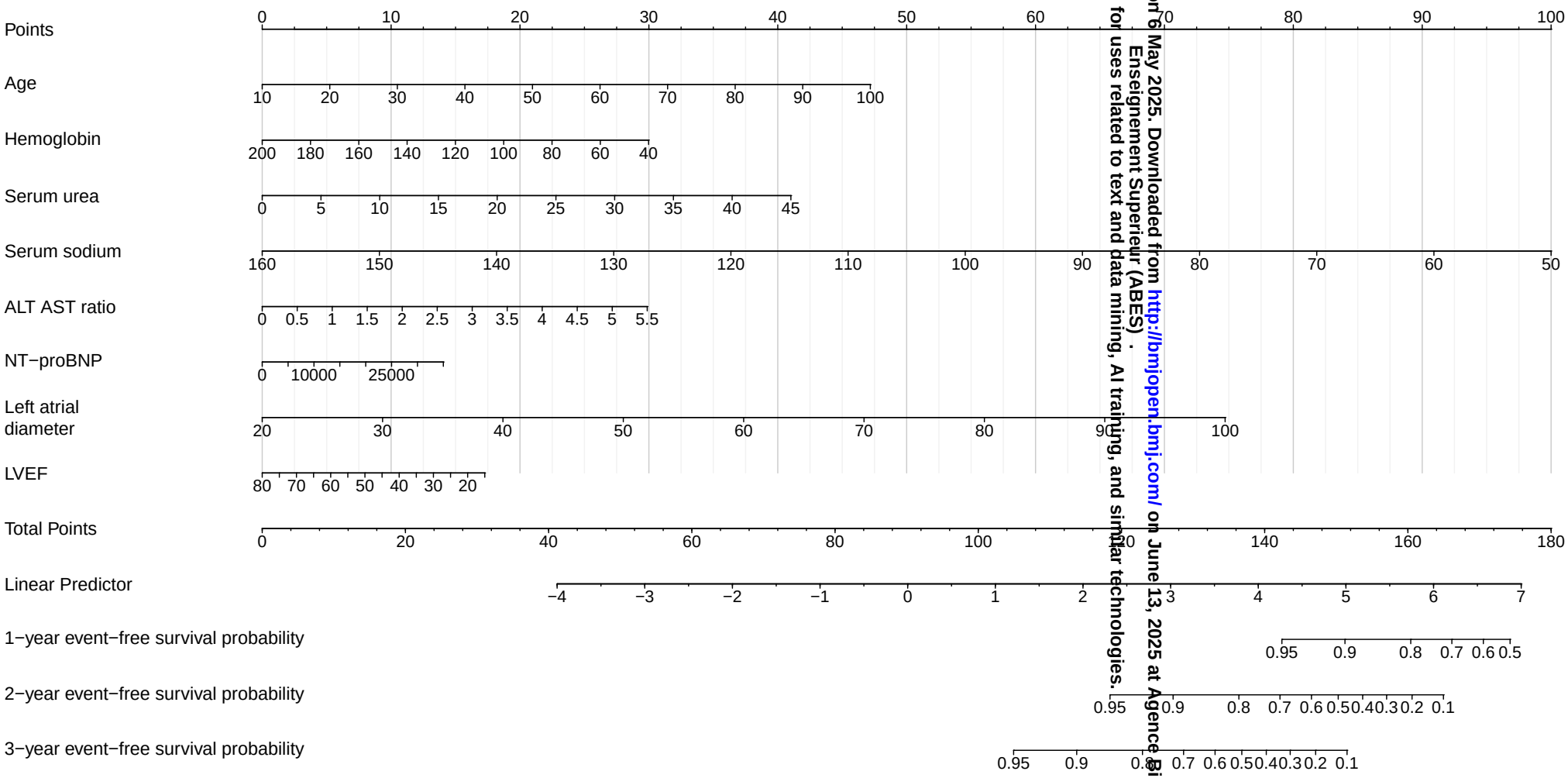

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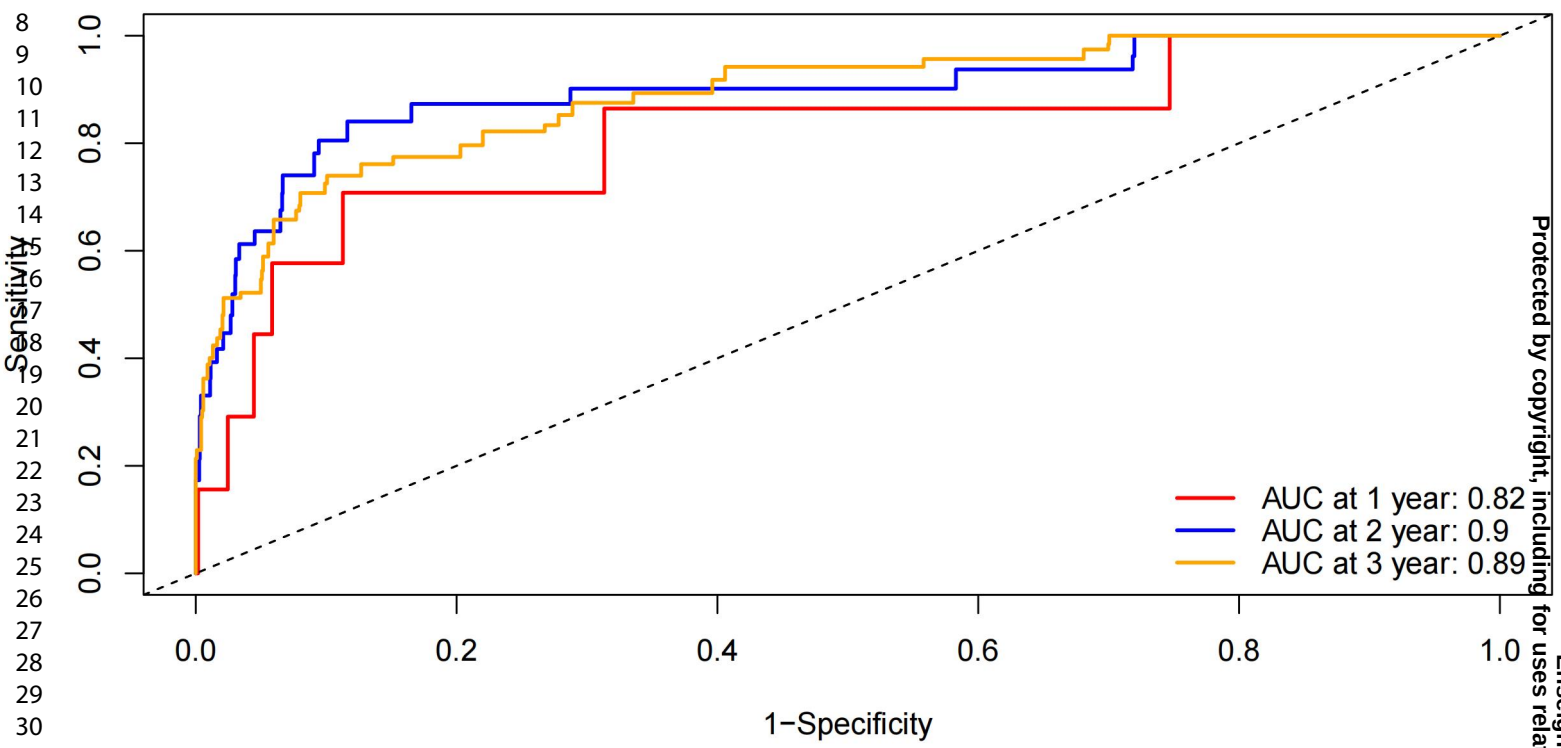

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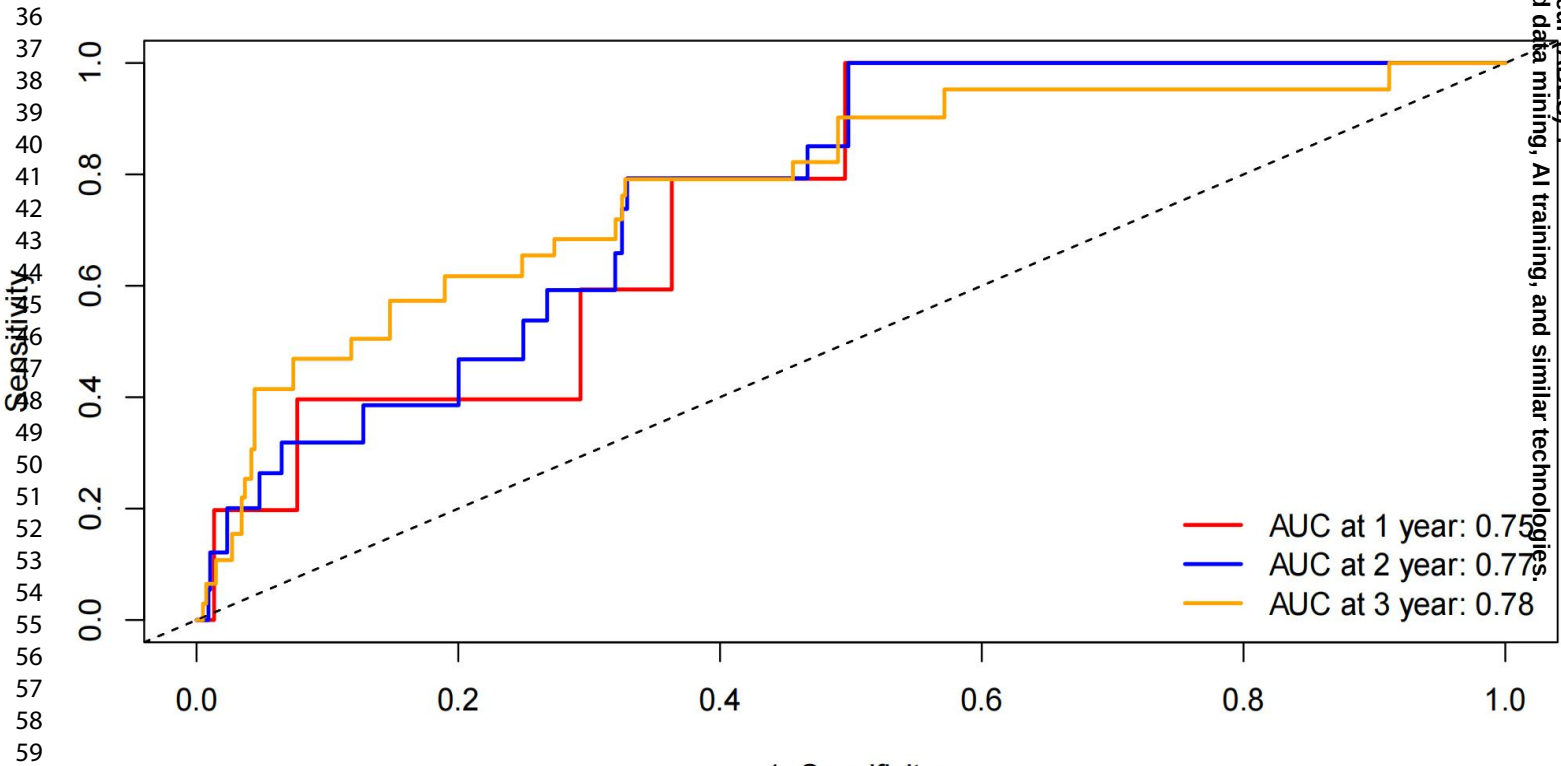

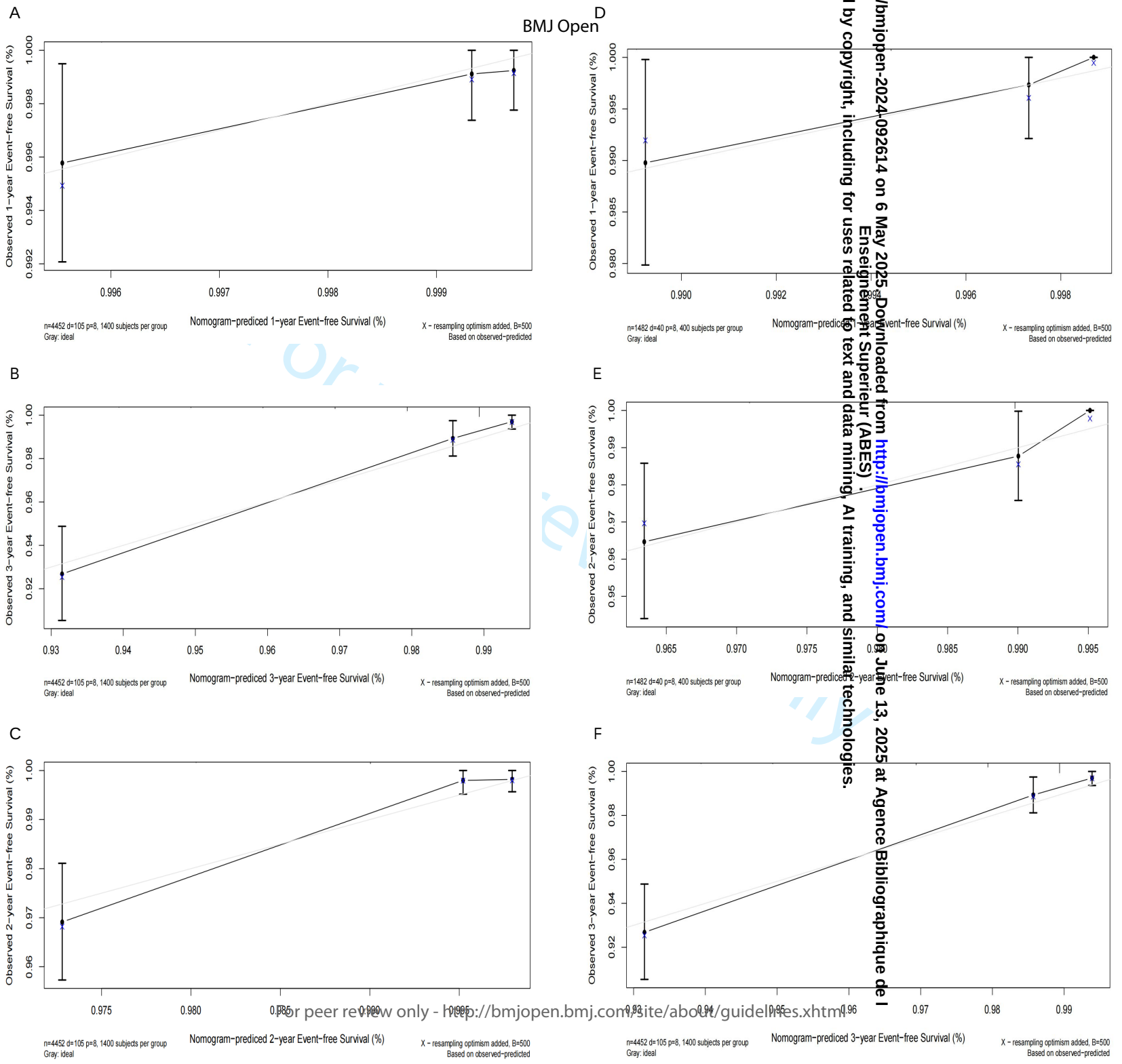

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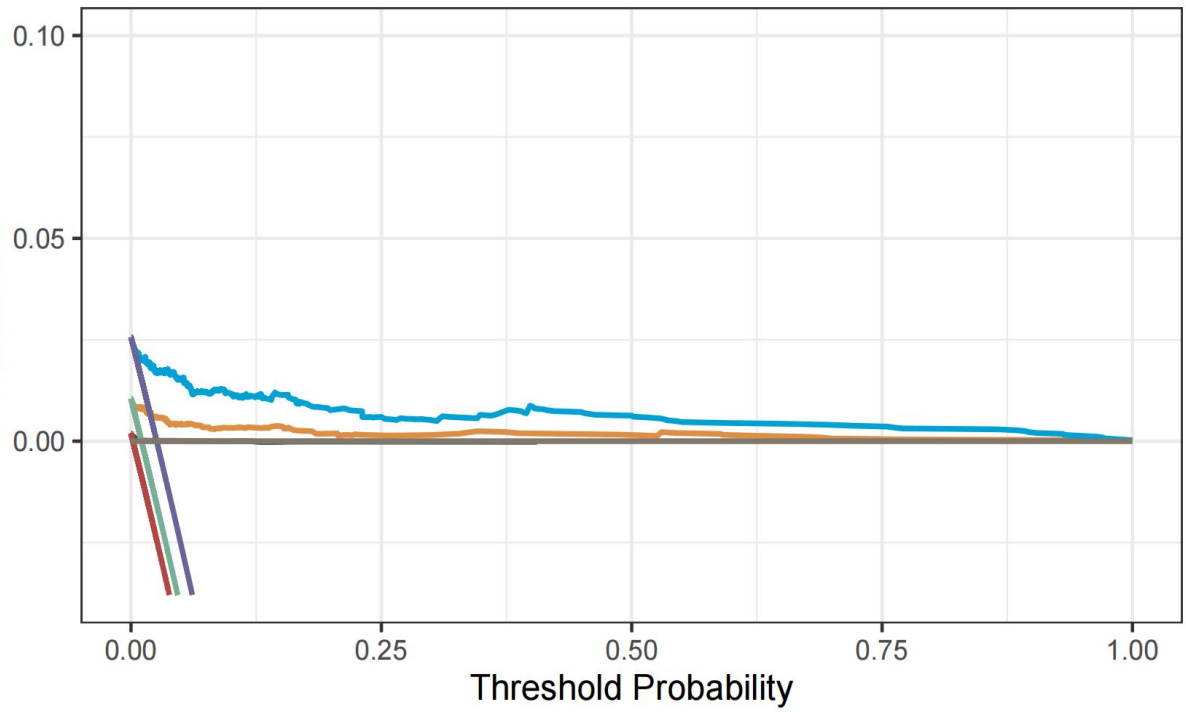

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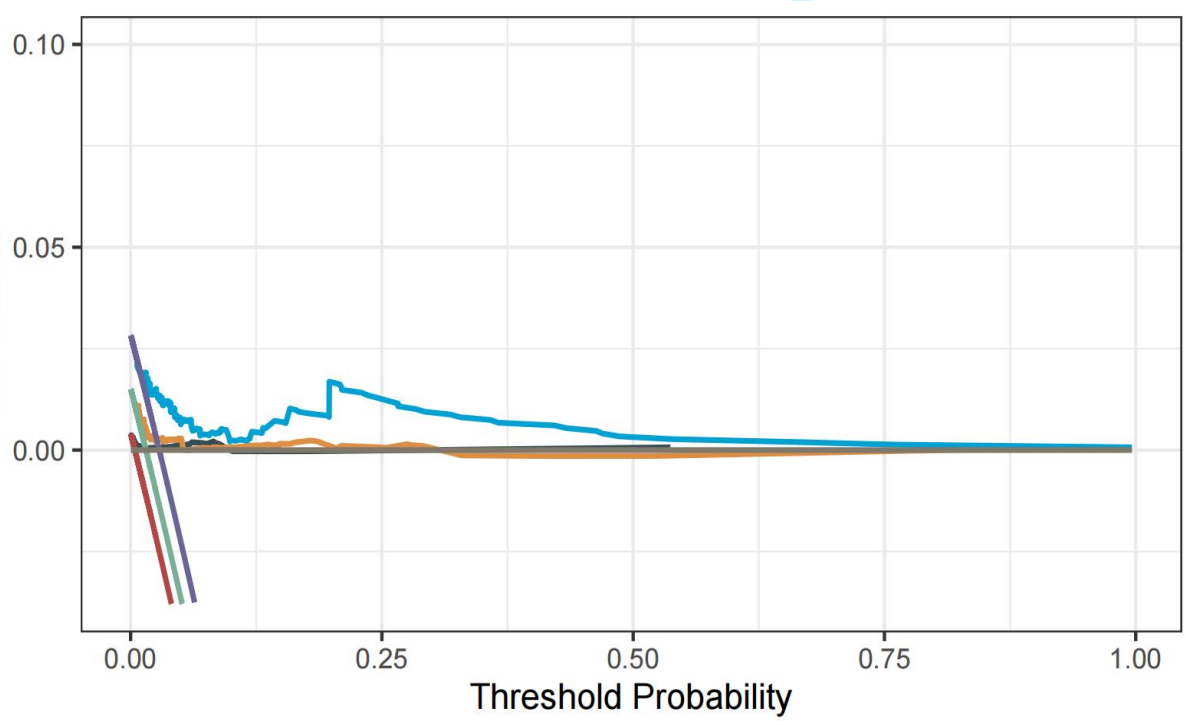

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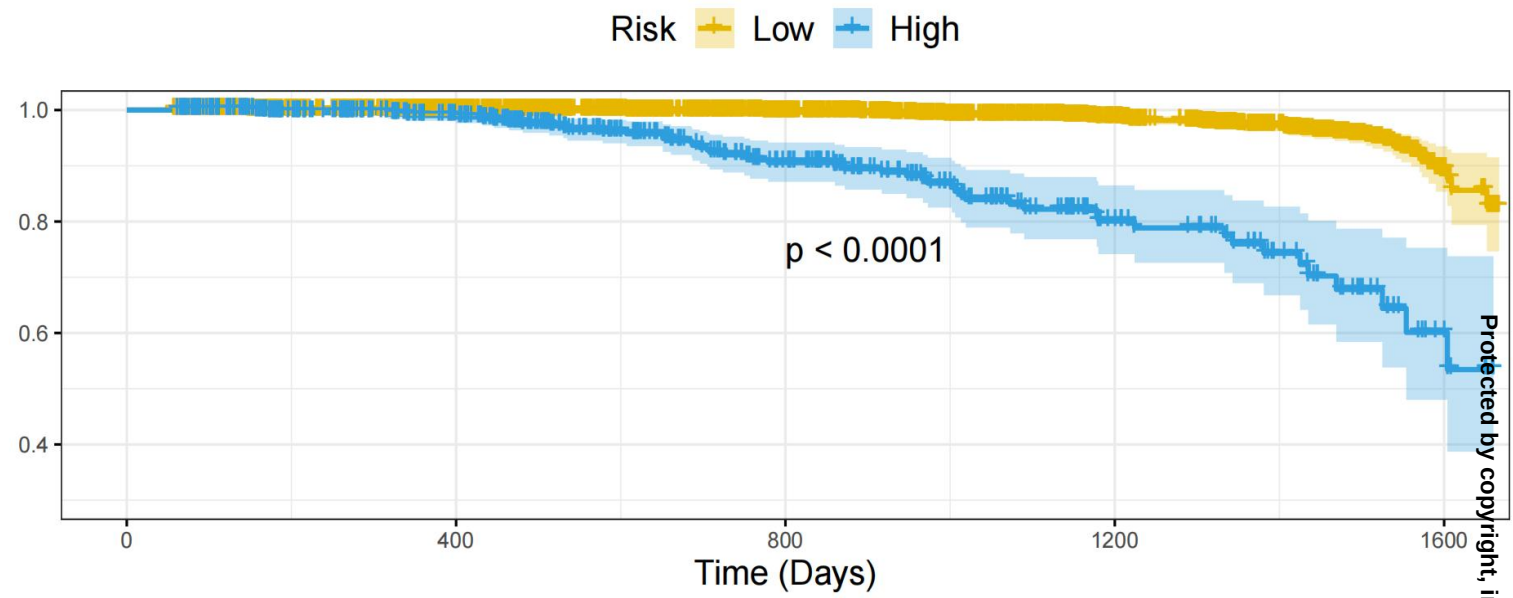
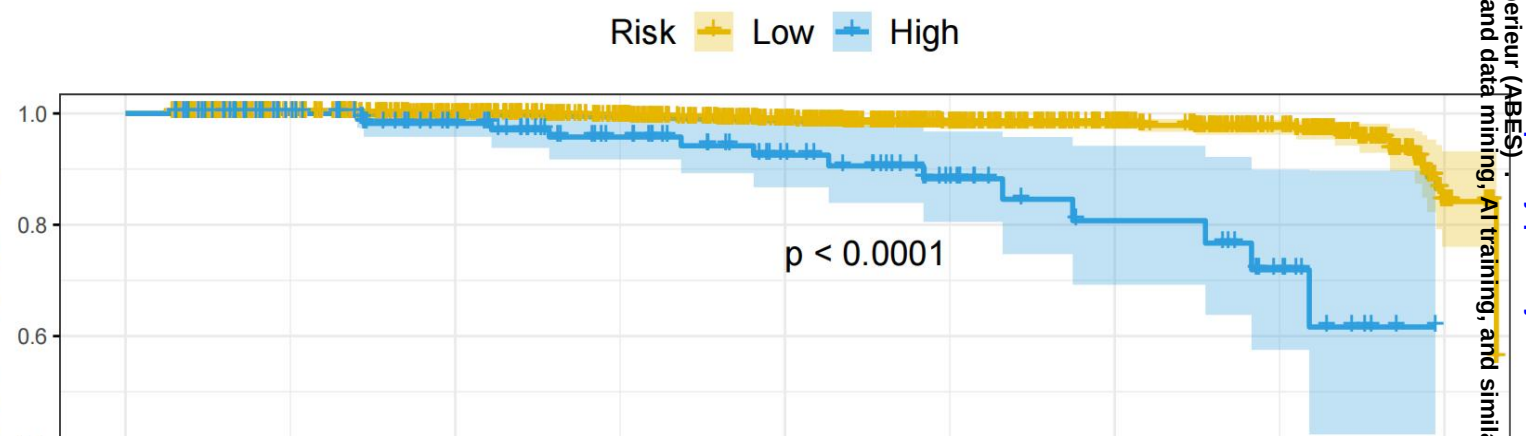


Number at risk

Low	3946	2875	1906	927	66
High	506	353	189	71	10

0 400 800 1200 1600

Time (Days)



Number at risk

Low	1336	993	648	325	34
High	146	92	51	20	0

0 400 800 1200 1600

Time (Days)

Supplement

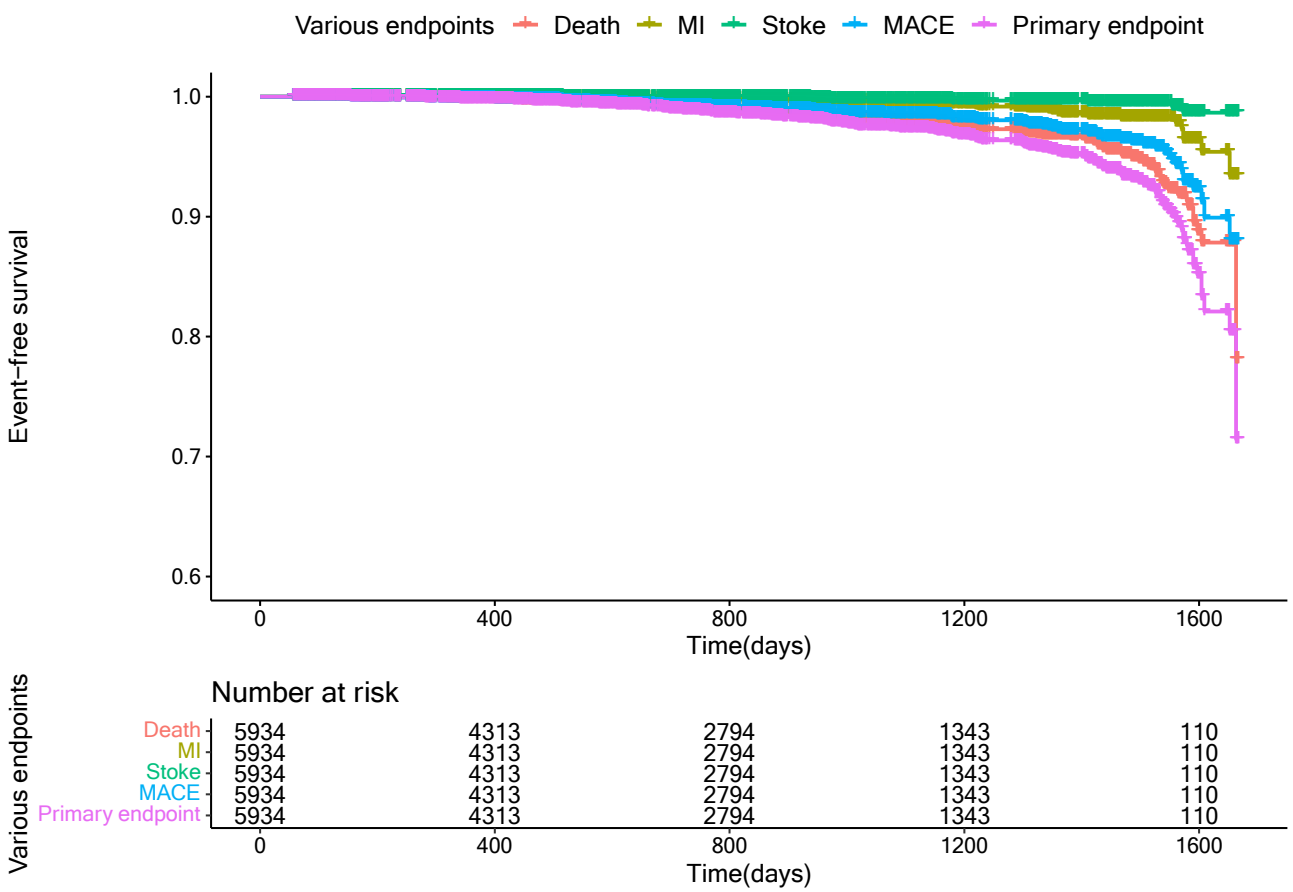
Supplementary Table 1. Clinical data of the total population, training set and validation set.

Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
Female, n (%)	3462 (58.3%)	2609 (58.6%)	853 (57.6%)	0.499
Age, years	43.6 (10.8)	43.7 (10.9)	43.5 (10.6)	0.563
Smoking, n (%)	1509 (25.4%)	1126 (25.3%)	383 (25.8%)	0.698
Drinking, n (%)	1883 (31.7%)	1415 (31.8%)	468 (31.6%)	0.909
Hypertension, n (%)	3698 (62.3%)	2802 (62.9%)	896 (60.5%)	0.094
Diabetes mellitus, n (%)	1123 (18.9%)	846 (19.0%)	277 (18.7%)	0.820
Diabetic complications, n (%)	19 (0.32%)	13 (0.29%)	6 (0.40%)	0.595
Dyslipidemia, n (%)	582 (9.81%)	423 (9.50%)	159 (10.7%)	0.185
CKD, n (%)	202 (3.40%)	151 (3.39%)	51 (3.44%)	0.993
SBP, mmHg	136 (19.8)	136 (19.9)	136 (19.7)	0.340
DBP, mmHg	81.9 (12.3)	81.9 (12.4)	81.8 (11.9)	0.757
Heart rate, beats/min	73.8 (15.2)	73.8 (13.9)	73.9 (18.5)	0.798
WBC, 10^9/L	6.67 (2.03)	6.68 (2.01)	6.67 (2.11)	0.969
Hemoglobin, g/L	136 (16.6)	136 (16.6)	136 (16.4)	0.881
Urea, mmol/L	6.09 (2.68)	6.09 (2.72)	6.08 (2.57)	0.831
Serum creatinine, μmol/L	65.9 [55.7; 79.8]	66.2 [55.7; 79.7]	65.4 [55.5; 80.0]	0.748
Uric acid, μmol/L	335 (100)	335 (101)	335 (99.0)	0.889
Serum sodium, mmol/L	142 (3.51)	142 (3.32)	142 (4.01)	0.829
Serum potassium, mmol/L	4.12 (0.56)	4.12 (0.47)	4.13 (0.76)	0.649
Serum chloride, mmol/L	106 (3.37)	106 (3.42)	106 (3.21)	0.515
Anion gap, mmol/L	14.0 (2.40)	13.9 (2.40)	14.0 (2.42)	0.844

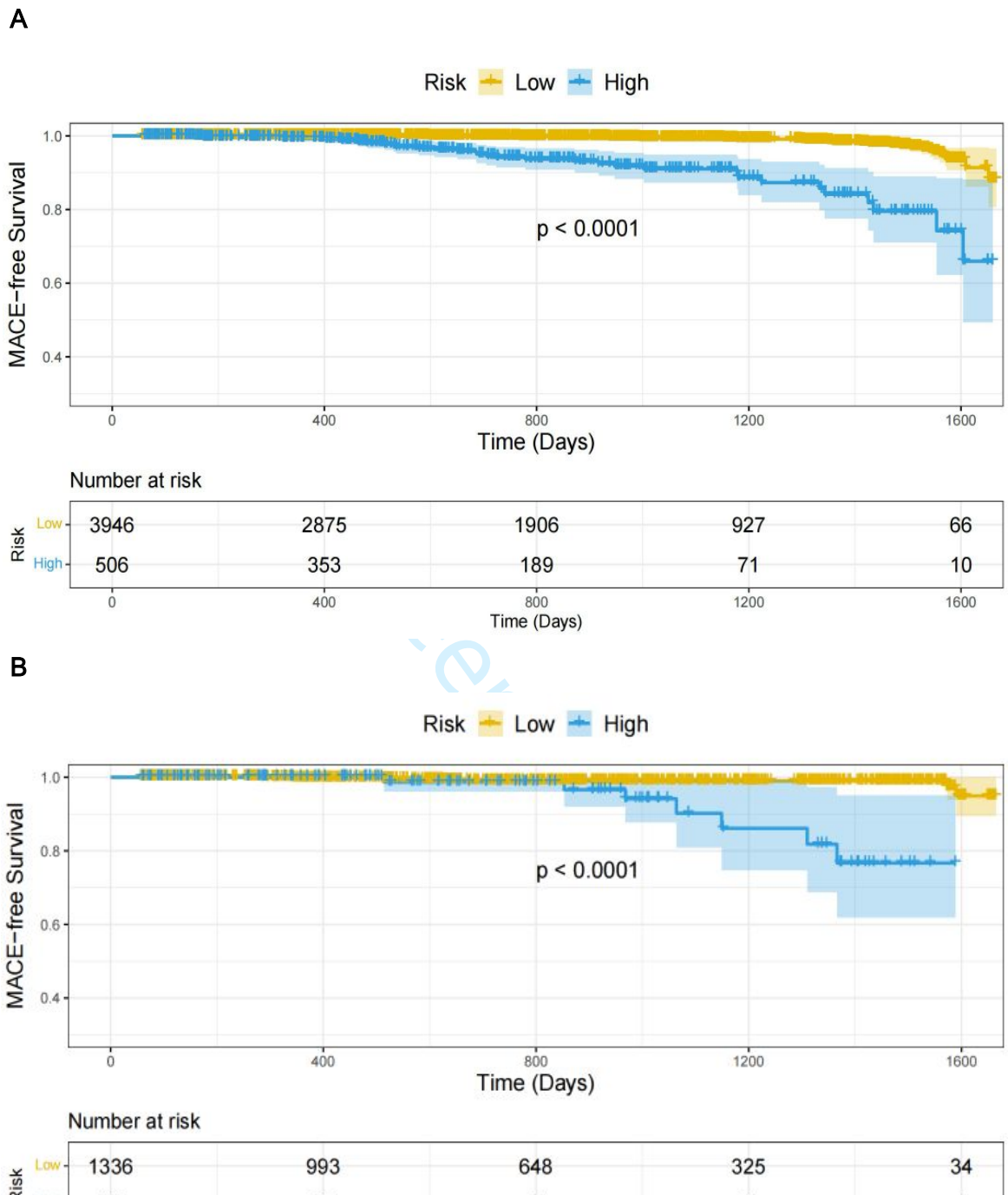
Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
Total protein, g/L	68.2 (6.41)	68.2 (6.37)	68.2 (6.54)	0.968
Albumin, g/L	42.4 (3.88)	42.4 (3.87)	42.3 (3.91)	0.406
Globulin, g/L	25.9 (4.19)	25.8 (4.16)	25.9 (4.30)	0.353
ALT, U/L	17.7 [13.0; 24.7]	17.8 [13.1; 24.8]	17.6 [12.6; 24.5]	0.169
AST, U/L	17.7 [14.6; 21.6]	17.8 [14.6; 21.6]	17.5 [14.6; 21.5]	0.341
ALT/AST ratio	1.06 (0.41)	1.05 (0.41)	1.07 (0.42)	0.157
Total bilirubin, μmol/L	13.6 (6.67)	13.6 (6.81)	13.4 (6.23)	0.257
Indirect Bilirubin, μmol/L	9.63 (4.69)	9.67 (4.75)	9.51 (4.53)	0.242
Direct Bilirubin, μmol/L	3.40 [2.30; 4.60]	3.40 [2.30; 4.60]	3.40 [2.40; 4.60]	0.611
Alkaline phosphatase, U/L	76.5 (23.6)	76.5 (23.6)	76.6 (23.7)	0.820
Total cholesterol, mmol/L	4.75 (1.12)	4.75 (1.13)	4.74 (1.08)	0.919
Triglycerides, mmol/L	1.63 (1.11)	1.62 (1.11)	1.65 (1.10)	0.485
HDL-C, mmol/L	1.22 (0.31)	1.22 (0.32)	1.20 (0.30)	0.083
LDL-C, mmol/L	2.97 (0.88)	2.97 (0.88)	2.98 (0.87)	0.498
VLDL-C, mmol/L	0.56 (0.37)	0.56 (0.39)	0.56 (0.30)	0.627
Troponin I, ng/ml	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.01 [0.01; 0.03]	0.536
NT-proBNP, ng/L	83.7 [35.1; 266]	83.0 [34.3; 265]	86.7 [38.0; 269]	0.415
CKMB, U/L	12.1 [9.30; 14.7]	12.0 [9.24; 14.7]	12.3 [9.30; 14.7]	0.529
D-Dimer, μg/L	276 [2.34; 434]	274 [1.78; 427]	282 [4.65; 457]	0.110
Glucose, mmol/L	6.81 (2.48)	6.82 (2.45)	6.78 (2.56)	0.579
Left atrial diameter, mm	38.7 (5.24)	38.7 (5.28)	38.6 (5.11)	0.331

Variable	Total N=5934	Train set N=4452	Validation set N=1482	p value
LVEDD, mm	47.4 (4.46)	47.4 (4.51)	47.3 (4.28)	0.373
LVESD, mm	26.9 (5.62)	26.9 (5.65)	27.0 (5.52)	0.737
RVEDD, mm	20.8 (3.37)	20.7 (3.61)	20.8 (2.53)	0.623
LVEF, %	61.7 (6.75)	61.7 (6.77)	61.6 (6.70)	0.486
Event-free survival time, days	635 (403)	633 (402)	641 (406)	0.512
Death, n (%)	106 (1.79%)	78 (1.75%)	28 (1.89%)	0.816
MI endpoint, n (%)	33 (0.56%)	21 (0.47%)	12 (0.81%)	0.189
Stroke endpoint, n (%)	11 (0.19%)	6 (0.13%)	5 (0.34%)	0.156
MACE, n (%)	82 (1.38%)	64 (1.44%)	18 (1.21%)	0.611
Primary endpoint, n (%)	145 (2.44%)	105 (2.36%)	40 (2.70%)	0.523

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CKMB, creatine kinase-MB; LVEDD, left ventricular-end-diastolic diameter; LVESD, left ventricular-end-systolic diameter; RVEDD, right ventricular-end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MACE, major adverse cardiovascular events.



Supplementary Figure 1. Event-free survival probability of different adverse outcomes in the total population



Supplementary Figure 2. Kaplan-Meier curves for MACE-free survival in the low-risk and high-risk groups in the training set (A) and validation set (B).