

Nomogram to Predict Delayed Complications in Patients with Uncomplicated Acute Type B Aortic Dissection

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Abstract

Background

Delayed complications within the first 2 weeks in initially uncomplicated acute type B aortic dissection (uATBAD) are not scarce, which needs special attention to prevent potentially fatal complications. This study aims to develop a nomogram for estimating the probability of patients with uATBAD developing delayed complications.

Methods

The nomogram was derived from a retrospectively study of 135 patients with uATBAD from 2011 to 2021 at a single medical center. The performance of the nomogram was evaluated from discrimination, calibration, and clinical usefulness. The results were internally validated by bootstrapping.

Results

In the multivariate analysis, the independent predictors of delayed complications identified were age ≥ 65 years (OR, 0.320; 95%CI, 0.108-0.831; $P = 0.027$), C-reactive protein (OR, 1.017; 95%CI, 1.006-1.029; $P = 0.003$), and maximum diameter of primary entry tear (OR, 1.089; 95%CI, 1.025-1.162; $P = 0.007$). The prediction model was internally validated by bootstrapping and revealed good discrimination (optimism-corrected C statistic, 0.706) and good calibration (Hosmer–Lemeshow test, $P = 0.6468$). Decision curve analysis demonstrated that the prediction nomogram was clinically useful.

Conclusions

This study presents a nomogram based on independent predictors of clinical and morphological parameters that could help identify patients with uATBAD who might occur delayed complications and thus improve the prognosis of patients.

Background

Aortic dissection (AD) can categorize as complicated or uncomplicated based on presentation (such as rupture and organ malperfusion)^[1]. Uncomplicated acute type B aortic dissection (uATBAD) has commonly been managed by optimal medical therapy, with acceptable in-hospital mortality from 1–10% [2, 3]. However, 20%-50% of these patients required invasive treatment in the chronic phase as a result of aneurysmal degeneration or the occurrence of complications^[4–6]. Furthermore, about 30%-40% of initially uATBAD will occur delayed complications (within two weeks after the onset of symptoms), which require

intervention to prevent potentially fatal outcomes^[7, 8]. Therefore, recognition of high-risk patients in patients who might develop delayed complications and benefit from early intervention is significant.

Several predictors including demographic, clinical, pharmacologic, and morphologic variables for disease progression with uATBAD have been proposed^[9, 10]. However, many of them revealed weak evidence based on a systematic review^[10]. Although one prior study^[8] found that dynamic parameters from retrospective cardiac gating computed tomographic angiogram could help recognize high-risk patients with uATBAD, their measurements might be time-consuming and clinical applicability remains to be determined.

Few studies have concentrated on delayed complications or developed a practical predictive model that incorporates factors associated with delayed complications in patients with uATBAD. Nomograms frequently used in clinical practice were user-friendly and can promote decision-making. Therefore, we established a nomogram for predicting delayed complications in patients with uATBAD aimed to improve the prognosis.

Methods

Data source and study population

A retrospective cohort study was conducted from an established big-data intelligence database platform at the Zhejiang Provincial People's Hospital, China. 483 patients with type B aortic dissection (TBAD) were identified between January 2011 and July 2021 based on the Stanford classification^[11]. Exclusion criteria included: (1) subacute or chronic TBAD (more than two weeks after symptom onset); (2) complicated AD (within two days after symptom onset); (3) traumatic dissection; (4) patients who had infectious diseases.

The diagnosis of TBAD was confirmed by computed tomography angiography and visualization at the surgery. A dissection was considered as an acute AD when the time from symptom onset within 14 days^[1, 12]. TBAD patients presented with at least 1 of the following: aortic rupture, organ malperfusion, early expansion, refractory pain, or uncontrollable hypertension were categorized as complicated TBAD, otherwise categorized as uncomplicated TBAD^[7]. Finally, 135 uncomplicated acute TBAD were included for analysis.

Outcome

The primary outcome of the study was the incidence of delayed complications (between days 3 and 14 after symptom onset). Delayed complications encompassed organ malperfusion, early expansion^[13], aortic rupture, recurrent pain^[14], or uncontrollable hypertension^[15]. Patients were divided into the delayed complicated group (Group A) and the remaining uncomplicated group (Group B) according to whether delayed complications occurred.

Candidate predictors

Two patient demographics (age and gender), medical history, clinical presentations, four physical examinations (body mass index (BMI), heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP)), three laboratory test items (Neutrophil percentage, D-dimer, and C-reactive protein (CRP)), lipid profiles measurements (total cholesterol (TC), triglyceride(TG)), four morphological parameters(Maximum diameter of descending aorta, False lumen patency (FLP), Maximum diameter of primary entry tear (MDPET), and True lumen collapse), adverse events, management (medical or surgical), and in-hospital outcomes were identified. The morphological parameters were measured referring to the current literature^[16-18].

Statistical Analysis

Baseline characteristics of the study population were provided. All continuous variables were presented with mean±standard deviation or median (interquartile range) analyzed by Student's *t*-test if they obey a normal distribution. Otherwise, analysis was performed by the Wilcoxon rank sum test. Categorical variables were presented with frequencies and percentages analyzed with χ^2 or Fisher exact test.

Multivariate binary logistic regression analyses were carried out to identify the predictors of the incidence of delayed complications. The non-linear relationships of the continuous predictors with the incidence of delayed complications were assessed by restricted cubic splines (RCS). To derive the risk prediction model, we initially included all candidate predictors (Age ≥ 65 years, Female sex, BMI ≥ 25 kg/m², Hypertension, Smoking, Diabetes mellitus, chronic obstructive pulmonary disease (COPD), coronary artery disease, Marfan's syndrome, Chest pain, Back pain, Abdominal pain, Heart rate ≥ 100 bpm, SBP, DBP, TC, TG, Neutrophil percentage $\geq 80\%$, D-dimer ≥ 2.5 mg/L, CRP, Maximum diameter of descending aorta, FLP, MDPET, and True lumen collapse) in a multivariable logistic regression model. Then the final selection of predictors was executed by the method of backward stepwise elimination. Multicollinearity was estimated by the variance inflation factor (VIF) method, which indicates the presence of several multicollinearities if VIF ≥ 10 . Eventually, 3 parameters from 24 predictors remained in the final model.

A nomogram was established based on the 3 predictors from multivariate logistic regression analysis. We used the concordance statistic (C statistic), calibration plot, and Hosmer-Lemeshow test to assess the predictive performance of the model. The C statistic was used to discriminate between patients who will arise delayed complications and those who will not arise. The calibration of the prediction model was evaluated by the method of calibration plot and Hosmer-Lemeshow test. Internal validation was used to decrease the overfit bias by bootstrapping with 1000 samples^[19]. The clinical usefulness was evaluated by the decision curve analysis (DCA), which compares with default strategies of treating all or no patients via calculating a clinical "net benefit".^[19,20]

Data were conducted using the R statistical software package (version 4.1.0, the R Foundation for Statistical Computing) and $P < 0.05$ indicated statistical significance. This study was conducted and

reported following the Transparent Reporting of a multivariate prediction model for Individual Prediction Diagnosis guidelines^[21].

Results

Patient Characteristics

Among the 135 patients with uATBAD (16.3% female; age, 56.0 [47.0, 66.5] years), 43 patients (31.9%) were included in the delayed complicated group, while 92 patients (68.1%) were assigned into the remaining uncomplicated group. Among the 43 patients who developed delayed complications, 2 (4.65%) had aortic expansion, 10 (23.26%) developed malperfusion, 27 (62.79%) had recurrent pain, 1 (2.33%) appeared refractory hypertension, and 3 (6.98%) developed aortic rupture. Among 10 patients with malperfusion, 6 patients had renal ischemia, 1 patient had limb ischemia, and 3 patients had bowel ischemia.

In the delayed complicated group, 2 patients (two of the three patients who developed aortic rupture) died before surgery or thoracic endovascular aortic repair (TEVAR); 40 patients (93%) chose active intervention after detection of delayed complications. However, there is no death happened in the remaining uncomplicated group and 83 patients (90.2%) chose active intervention (Table 1).

Model development, performance measure, and validation

Of the 24 candidate predictors, 3 predictors (Age ≥ 65 years, CRP, and MDPET) were statistically significantly associated with delayed complications in patients with uATBAD of the final multivariate logistic regression model (Table 2).

The RCS regression showed no non-linear associations between predictors and the risk of delayed complications. The C statistic of the prediction model was 72.7% (95% CI: 0.823-1.015). The consistency between the observed and predicted proportion of the incidence of delayed complications showed good apparent calibration (Figure 1). The calibration test indicated that the S:P ratio of the predictive model was 0.976. The Brier score is 0.183. Besides, the Hosmer-Lemeshow tests proved the good predictive performance of the model ($\chi^2=6.0042$; $P=0.6468$).

The model was internally validated by bootstrapping (1000 iterations). The optimism-corrected C statistic, which is an estimate of the C statistic of the model when applied to future patients, was 70.6%. In conclusion, the current study shows that the risk prediction model has a good predictive performance for delayed complications.

Besides, DCA was carried out to assess the clinical usefulness of the predictive model. With a threshold probability $> 20\%$, using the predictive model to identify patients who might occur delayed complications would be advantageous over the schemes of “treat-all-patients” or “treat-none” schemes (Figure 3).

Development of delayed complications-predicting Nomogram

Based on the multivariable regression result, a novel nomogram was developed (Figure 2). Each selected variable received a point derived from the value and the scale at the top of the figure. To add up total points, the probability of delayed complications occurrence was matched.

Discussion

In a retrospective cohort of 135 Chinese patients with uATBAD, three risk factors for the occurrence of delayed complications were identified from the multivariate logistic regression analysis: Age ≥ 65 years (OR, 0.320; 95% CI, 0.108-0.831; $P=0.027$), CRP (OR, 1.017; 95% CI, 1.006-1.029; $P=0.003$), and MDPET (OR, 1.089; 95% CI, 1.025-1.162; $P=0.007$). A nomogram derived from accessibly clinical and morphological variables was established for a particular individual and showed a good capacity of discrimination, calibration, and clinical effectiveness. For a patient with uATBAD, it is possible to quickly and easily assess the possibility of arising delayed complications at admission using the novel prediction model. As for individuals with a high prediction probability, close monitoring and early intervention should be considered to prevent potentially fatal outcomes.

Prior researches^[7, 8] indicated that about 30~40% of delayed complications occur in patients with uATBAD. In our study, the prevalence of delayed complications and mortality before any intervention in patients with uATBAD was 31.9% and 4.7% respectively, which is comparable to the results in other relevant researches.

In this study, age ≥ 65 years was identified as a risk predictor. Research indicated that compared with Western populations, Chinese patients were significantly younger (52.7 ± 11.1 VS 64.2 ± 13.5 , $P < 0.01$)^[22]. The mean age of the derivation cohort was 56 years. Increasing age was thought to be associated with a decreased aortic growth rate^[17, 23], which might be due to the structure of the aortic wall degenerating with increasing age^[24]. Furthermore, age was found as an independent risk factor of all-cause mortality in uATBAD^[25].

CRP was recognized as a risk factor for delayed complications, which is an acute-phase inflammatory protein that represents elevated expression during inflammatory conditions^[26]. Prior study^[27] indicated that in the general population, CRP could independently predict the risk of all-cause and cardiovascular mortality. In addition, CRP was confirmed that have an association with acute aortic dissection, as an inflammatory marker^[28-30]. Several studies revealed that CRP level is a predictor for prognosis in patients with TBAD^[31, 32].

Besides, MDPET was identified as the last risk predictor for delayed complications. Evangelista et al.^[33] described the size of primary entry tear as an independent predictor of dissection-related adverse events and mortality. As Tsai et al. reported^[34], increasing size of the primary entry was associated with an increase in SBP in the false lumen, which leads to the exaggeration of the wall stress and risk of dilatation of the aorta.

The risk prediction model demonstrated good discrimination and calibration through the analysis of C statistic and calibration plots. Besides, the optimism-corrected C statistic of the model was 70.6%. Identification of high-risk patients with uATBAD who might develop delayed complications would be clinically significant since those patients might benefit most from a preemptive TEVAR.

Objectively, some limitations in this current study should be indicated. Firstly, this retrospective study was performed at a single center, thus inevitably having patient selection bias. Secondly, the number of patients in this study was relatively insufficient. Thirdly, the candidate predictors included in our study were relatively small. Finally, the model has not yet been externally validated. In the future, more centers and samples should be incorporated to verify our results.

Conclusions

In conclusion, based on the demographic, biochemical, and morphological parameters including age \geq 65 years, CRP, and the maximum diameter of primary entry tear, a predictive model of delayed complications in patients with uATBAD was established. Furthermore, we developed a novel nomogram, which could help physicians identify high-risk patients and take individual strategies to prevent potentially fatal outcomes.

Abbreviations

uATBAD: Uncomplicated acute type B aortic dissection; TBAD: Type B aortic dissection; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglyceride; CRP: C-reactive protein; RCS: Restricted cubic splines; VIF: Variance inflation factor; C statistic: Concordance statistic; DCA: Decision curve analysis; PET: Primary entry tear; TEVAR: Thoracic endovascular aortic repair.

Declarations

Ethics approval and consent to participate

The name of the ethical committee is the Human Research Ethics Committee of the Zhejiang Provincial People's Hospital. This study was performed in compliance with the Declaration of Helsinki, approved by the Human Research Ethics Committee of the Zhejiang Provincial People's Hospital (No. 2021QT358), and the need for informed consent was waived because of the retrospective nature of the analysis.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

H.B.L., J.F.L., and J.C. conceptualized the study outline, drafted and revised the manuscript; H.B.L. and Y.L. performed statistics analysis; W.B.F., R.F., and M.D. collected data. All authors reviewed the manuscript.

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Tables

Table 1. Baseline characteristics of study cohorts

Variable	Overall	Group B (Remaining uncomplicated)	Group A (Delayed complicated)	P value
No. (%)	135 (100)	92 (68.1)	43(31.9)	
Age (median [IQR]) (years)	56.0 [47.0, 66.5]	56.0 [47.8, 69.0]	56.0 [47.0, 60.5]	0.1398
Age ≥65 years	38 (28.1)	31 (33.7)	7 (16.3)	0.0586
Female sex	22 (16.3)	16 (17.4)	6 (14.0)	0.7997
BMI≥25 kg/m ²	63 (46.7)	40 (43.5)	23 (53.5)	0.3676
Hypertension	126 (93.3)	85 (92.4)	41 (95.3)	0.7184
Smoking	61 (45.2)	43 (46.7)	18 (41.9)	0.73
Diabetes mellitus	6 (4.4)	5 (5.4)	1 (2.3)	0.6641
COPD	1 (0.7)	1 (1.1)	0 (0.0)	1
CAD	3 (2.2)	3 (3.3)	0 (0.0)	0.5511
Marfan's syndrome	1 (0.7)	1 (1.1)	0 (0.0)	1
Chest pain	100 (74.1)	68 (73.9)	32 (74.4)	1
Back pain	83 (61.5)	55 (59.8)	28 (65.1)	0.6866
Abdominal pain	19 (14.1)	11 (12.0)	8 (18.6)	0.4417
Heart rate ≥100 bpm	16 (11.9)	10 (10.9)	6 (14.0)	0.8175
Systolic blood pressure (mmHg)	143.5 (19.9)	142.6 (19.5)	145.6 (20.6)	0.4151
Diastolic blood pressure (median [IQR]) (mmHg)	80.0 [71.0, 90.0]	78.5 [70.0, 87.5]	85.0 [71.5, 93.0]	0.2469
TC (median [IQR]) (mmol/L)	4.1 [3.6, 4.8]	4.1 [3.6, 4.8]	4.2 [3.8, 5.0]	0.2742
TG (median [IQR]) (mmol/L)	1.2 [0.9, 1.6]	1.2 [0.8, 1.6]	1.3 [0.9, 1.6]	0.3054
Neutrophil percentage≥80%	59 (43.7)	40 (43.5)	19 (44.2)	1
D-dimer≥2.5 mg/L	66 (48.9)	41 (44.6)	25 (58.1)	0.1987
C-reactive protein (median [IQR])	53.4	41.9 [12.0, 77.7]	66.7 [44.2, 85.3]	0.0044

(mg/L)	[21.2, 78.4]			
Maximum diameter of descending aorta (median [IQR]) (mm)	37.0 [33.0, 41.5]	37.0 [33.0, 40.0]	40.0 [33.0, 45.0]	0.0674
FL patency				0.9465
Patent	83(61.5)	57 (62.0)	26 (60.5)	
Partially thrombosed	47(34.8)	31(33.7)	16 (37.2)	
Complete thrombosed	5 (3.7)	4 (4.3)	1 (2.3)	
Maximum diameter of primary entry tear (median [IQR]) (mm)	10.0 [8.0, 16.0]	10.0 [7.0, 14.0]	13.0 [8.0, 19.0]	0.0178
True lumen collapse	37 (27.4)	19 (20.7)	18 (41.9)	0.0179
Treat				0.6784
Conservative treatment	12 (8.9)	9 (9.8)	3 (7.0)	
Open surgery	1 (0.7)	1 (1.1)	0 (0.0)	
TEVAR	122 (90.4)	82 (89.1)	40 (93.0)	
Death	2 (1.5)	0 (0.0)	2 (4.7)	0.0998

Categorical variables are presented as number (%).

Continuous variables are presented as mean \pm standard deviation unless otherwise indicated.

IQR, inter-quartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; TC, total cholesterol; TG, triglyceride; FL, false lumen; TEVAR, thoracic endovascular aortic repair.

Table2. Multivariate logistic regression analysis for prediction of the incidence of delayed complications

Variable	β	Wald	OR[95%CI]	Pvalue
Age \geq 65 years	-1.140	4.921	0.320(0.108~0.831)	0.027
C-reactive protein	0.017	9.119	1.017(1.006~1.029)	0.003
Maximum diameter of primary entry tear	0.085	7.167	1.089(1.025~1.162)	0.007

OR, odds ratio; CI, confidence interval.

Figures

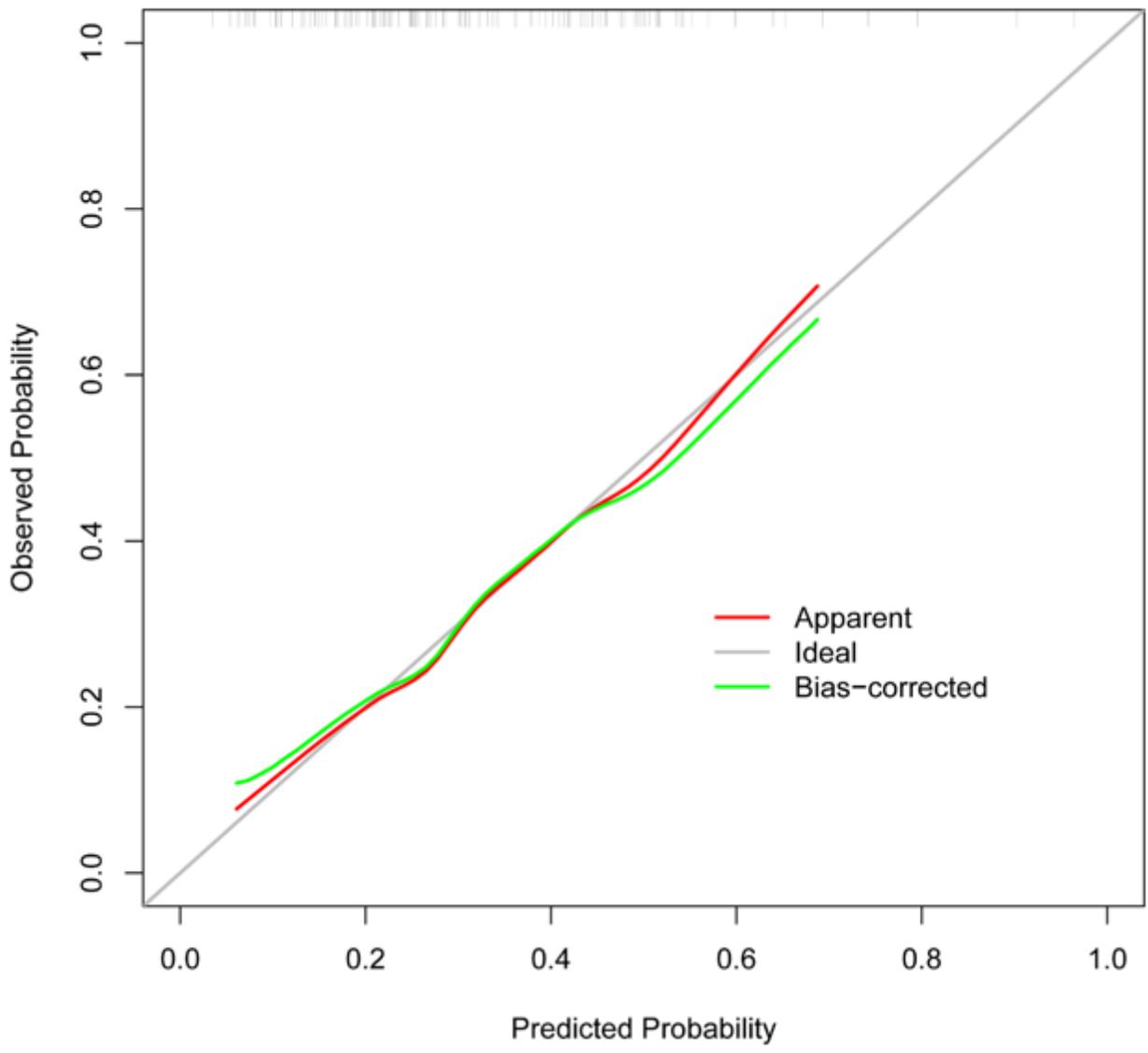


Figure 1

Calibration curves for the prediction model. The x-axis represents the predicted incidence risk. The y-axis represents the actual incidence risk. The curves show the calibration of the nomogram between predicted risks and actual outcomes of delayed complications in patients with uATBAD.

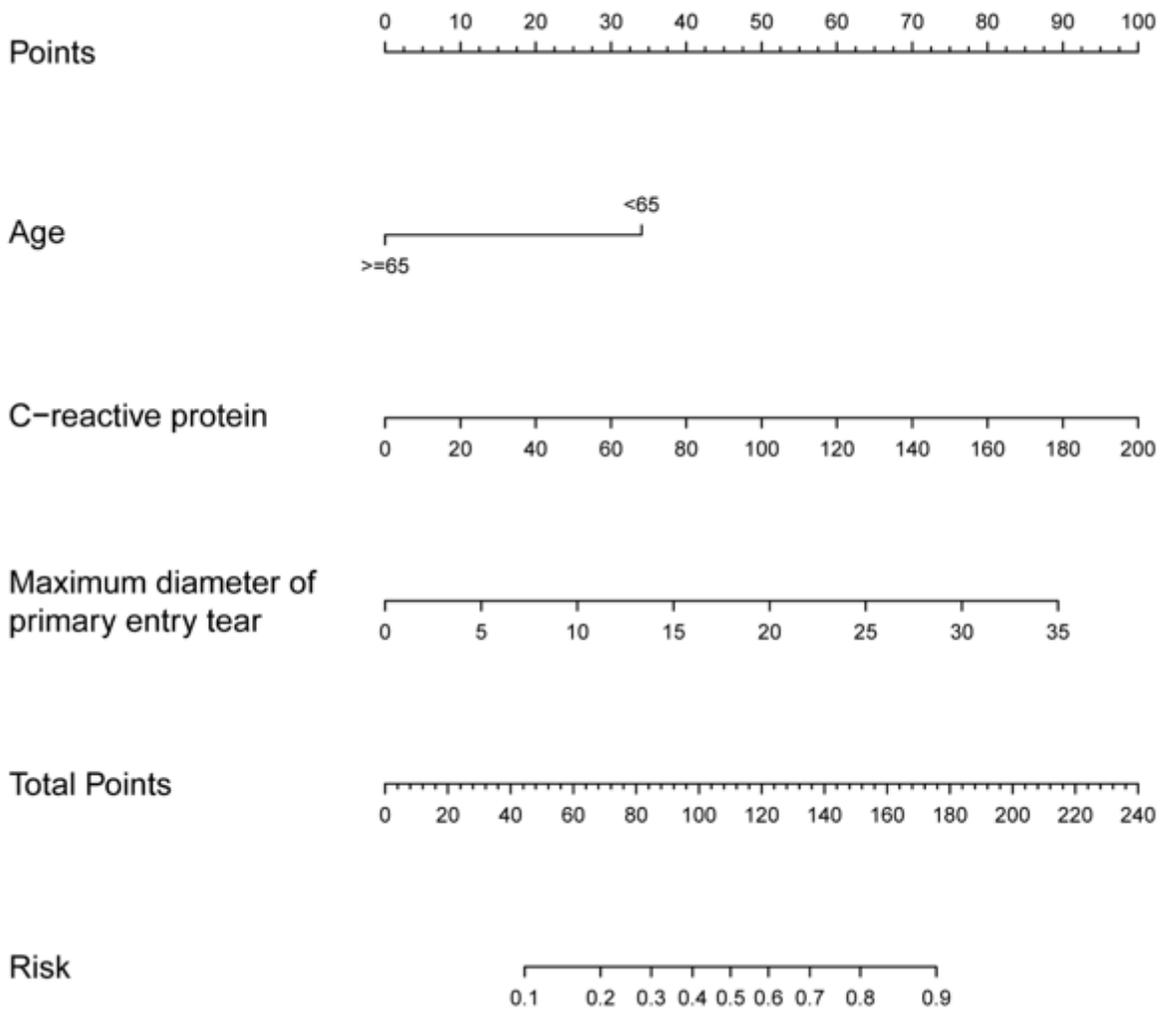


Figure 2

The nomogram for assessing the risk of delayed complications in patients with uATBAD. Each variable is represented by a scale line. To estimate the risk of the occurrence of delayed complications for a given patient, add up the points identified on the scale for each variable.

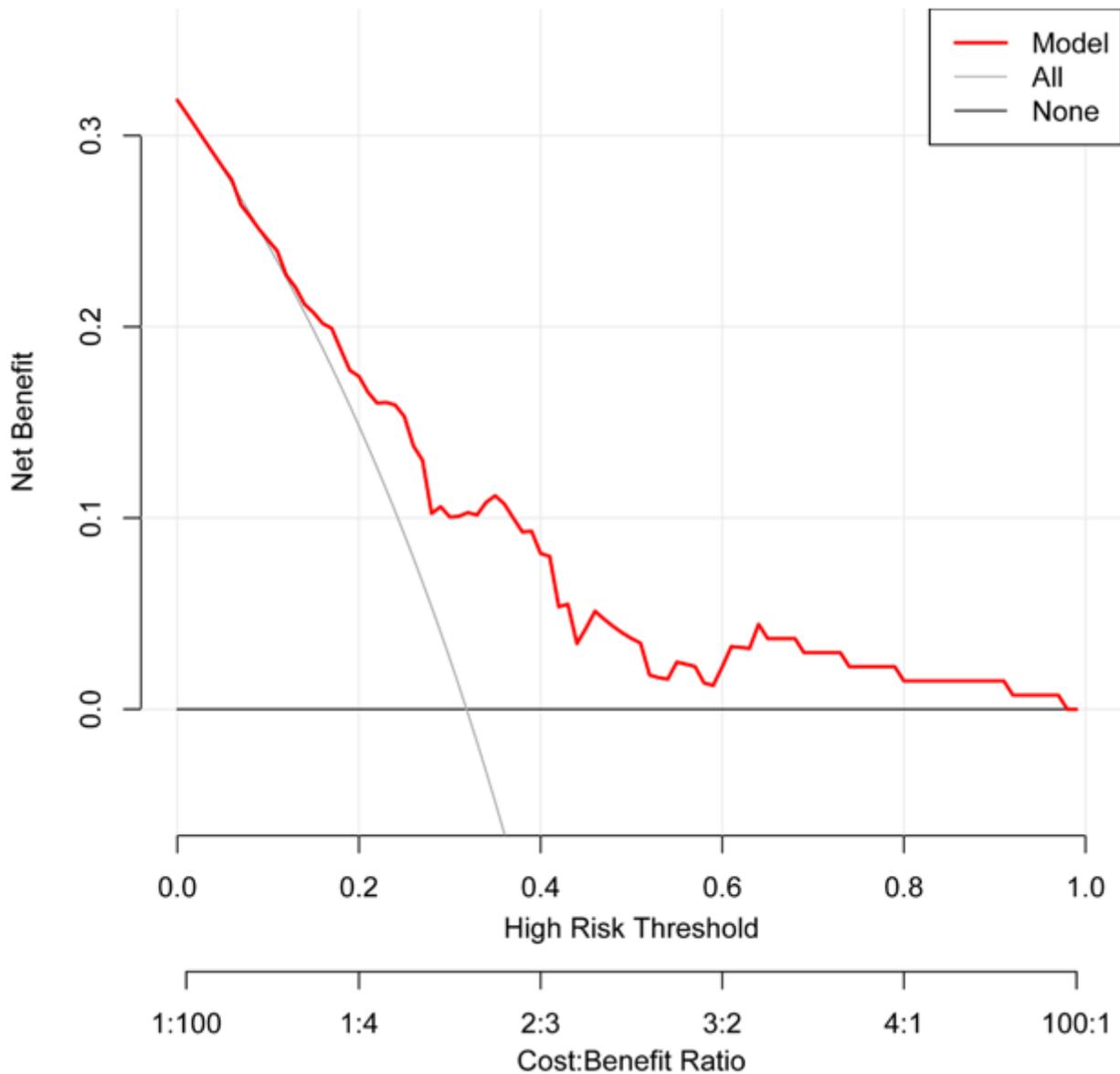


Figure 3

Decision curve analysis for the prediction model. The y-axis represents the net benefit. The red line: patients are treated if predictions exceed a threshold. The grey line: assume all patients are treated. The black line: assume no patients are treated, net benefit is zero. The decision curve showed that if the threshold probability is > 20%, using the model in the current study to predict delayed complications has more benefit than treat-all patients or treat-none scheme.