

Development and Validation of a Nomogram to Predict the Mortality Risk in Elderly Patients With ARF: A Retrospective Study in the Mimic-III Database

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Abstract

Background: To explore the risk factors of prognosis in elderly patients with acute respiratory failure (ARF), and to develop a nomogram model to predict the short-term mortality risk of ARF.

Methods: A total of 1432 patients were included in this study from MIMIC-III database. 759 patients were categorized into the training set and 673 patients were categorized into the validation set. Demographical, laboratory variables, SOFA score and APS-III score were collected within the first 24 h after the ICU admission. The univariate and multivariate logistic regression were used to identify risk factors from the training data set. A nomogram model was developed to predict the mortality risk of ARF patients within 30 days according to the risk factors.

Results: Multivariate logistic regression analysis showed that the heart rate, respiratory rate, systolic pressure, SPO₂, albumin and 24 h urine output were independent prognostic factors for 30-day mortality in ARF patients. A nomogram was established based on above independent prognostic factors. This nomogram had C-index of 0.741 (95% CI: 0.7058–0.7766), and the C-index was 0.687 (95%CI: 0.6458-0.7272) in the validation set. The calibration curves both in training and validation set were close to the ideal model. The SOFA had a C-index of 0.653 and the APS-III had a C-index of 0.707 in predicting 30-day mortality. The predictive performance of our nomogram is better than the SOFA score and APS-III score.

Conclusions: Our nomogram performed better than APS-III and SOFA scores and should be useful as decision support on the prediction of mortality risk in elderly patients with ARF.

Background

Acute respiratory failure (ARF) is a common complication of critically ill patients. With an ageing population there is a growing prevalence of ARF. The incidence of ARF in the 65–84 age group was approximately twice that of the 55–64 age group, and more than three times that of the young age group [1]. In addition, ARF in elderly patients is associated with a high mortality rate [2]. The reasons included the heterogeneity and complexity of the elderly patient condition. Therefore, accurate assessment of the severity of ARF in the elderly patients is the key to reduce its mortality.

Academic research shows that clinical signs of ARF, hypercapnia > 45 mmHg, clearance of creatinine < 50 ml minute⁻¹, elevated NT-pro-B-type natriuretic peptide or B-type natriuretic peptide were predictive of death [3]. Although the risk factors are clear, there is still no consensus about the prognostic factors and evaluation system.

Some study reported that Simplified Acute Physiology Score-II [4] could identify patients at high risk of death, and SOFA score was also as reliable as the early warning score [5] for mortality prediction in patients with ARF. However, the sensitivity and specificity of these tools prediction are Unsatisfactory. Moreover, it includes multiple indicators which are cumbersome to calculate, cannot be completed in a short time. At present, there is a lack of clinical prediction tools of death for ARF in the elderly. It is urgent

to find a risk stratification tool to predict mortality in elderly patients with ARF. The nomogram model can quantify, graph, and visualize Logistic regression results to achieve individualized prediction of disease risk. It has been successfully used in clinical diagnosis and prognostic assessment of various diseases[6, 7].

In this study, we analyze the prognostic factors of elderly ARF patients and construct a Nomogram model to predict its survival, and evaluate the risk of death of elderly patients, and then provide clinical help for early identification and intervention of high-risk patients to improve their prognosis.

Methods

Database and subjects

Subject data were retrieved from Medical Information Mart for Intensive Care III database version 1.4 (MIMIC-III v1.4). The MIMIC-III is a clinical database comprising the information of 46,520 patients who were admitted to the ICU of Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA, from 2001 to 2012[8]. MIMIC-III is a large, freely accessible database for international researchers upon a use agreement (Our certification number: 31355221). The database was approved by the institutional review boards (IRB) of the Massachusetts Institute of Technology (MIT) and BIDMC; therefore, the informed consent was waived in our study.

Participants

ARF was identified from ICD-9 code in the MIMIC-III database. For patients with multiple ICU admissions, we included only the first ICU admission. The primary outcome in this study was patients' 30-day mortality.

Data extraction

Demographical and laboratory variables were extracted from MIMIC-III database by Structure Query Language (SQL) at the first 24 h of ICU admission. We collected the following data: age, gender, vital signs, mechanical ventilation, Percutaneous oxygen saturation (SpO₂), white blood cell (WBC), hemoglobin, platelet, albumin, bilirubin, blood urea nitrogen (BUN), lactate, activated partial thromboplastin time (APTT), prothrombin time (PT), 24 hours urine output, sequential organ failure assessment (SOFA) score and Acute Physiology Score III (APS-III). If the laboratory variables were examined more than once, the most severity value associated with the illness was used in our study. SOFA and APS-III score was calculated within the first 24 h after the ICU admission. Patients with missing data and who were younger than 60 years-old were excluded from this study. Finally, 1432 ARF patients were included in our cohort. All the scripts used to calculate the SOFA and APS-III score were available from GitHub website (<https://github.com/MIT-LCP/mimic-code/tree/master/concepts>).

Statistics analysis Continuous data are presented as mean \pm standard deviation (SD) or median (IQR) according to the normal or non-normality distribution. Kolmogorov-Smirnov test was performed to

determine normal distribution. The frequency (proportion) for categorical variables. The Student t-test, Mann-Whitney U test, chi-squared test, or Fisher's exact test was performed where appropriate. For the development of the nomograms, the univariate and multivariate logistic regression were used to identify prognosis factors from the training data set. Prognosis variables that were considered clinically relevant and that showed statistics relationship in multivariate logistic regression were used to established the nomogram. The 'rms' package was used for nomogram and calibration curve. The accuracy of the nomogram to predict the 30-day mortality of ARF were quantified using C-index, the calibration of the model is assessed by the calibration curves in the training set and validation set. Moreover, we performed decision curve analysis (DCA) by quantifying the net benefits to assess the clinical value of the model. We did the statistics analyses and figures production using R software (version 3.6.1). All statistics tests were two-sided, and P values < 0.05 were considered significant.

Results

Patient characteristics

A total of 1432 patients were included in this study. Patients admitted between 2001 and 2008 (759 cases) were categorized into the training set, the 30-day mortality in the training set were 38.6%. The remaining 673 patients admitted after 2008 were categorized into the validation set, the 30-day mortality was 40.5%. The patient characteristics and laboratory findings of the training and validation sets were show in Table 1. There were no significant differences between the training and validation set.

Table 1
Patient characteristics in training and validation set.

Variables	Training set (n = 759)	Validation set (n = 673)
Age, median (IQR)	76 (68, 83)	74 (66, 82)
Gender, male, n (%)	395 (52.0)	384 (57.1)
Vital signs		
Temperature, Median (IQR) (°C)	37.6 (37.08, 38.25)	37.44 (36.89, 38.06)
Heart rate, Median (IQR) (bpm)	109 (95, 124.5)	107 (92, 122)
Systolic pressure, Median (IQR) (mmHg)	82 (72, 92)	84 (73, 95)
Respiratory rate, Median (IQR) (per minute)	28 (24, 33)	28 (24, 33)
SPO ₂ , Median (IQR) (%)	92 (88, 95)	92 (88, 95)
Laboratory findings		
WBC, Median (IQR) (10 ⁹ /L)	15.5 (10.6, 21.4)	14 (10, 19.7)
Hemoglobin, Median (IQR) (10 ⁹ /L)	9.6 (8.4, 11)	9.8 (8.5, 11.1)
Platelet, Median (IQR) (10 ⁹ /L)	181 (114.5, 250.5)	178 (115, 250)
Albumin, Median (IQR) (g/dL)	2.9 (2.4, 3.4)	3 (2.5, 3.4)
Bilirubin, Median (IQR) (mg/dL)	0.7 (0.4, 1.35)	0.7 (0.4, 1.4)
Creatinine, Median (IQR) (mg/dL)	1.5 (1, 2.4)	1.5 (1, 2.6)
Glucose, Median (IQR) (mg/dL)	107 (88, 133)	109 (90, 133)
BUN, Median (IQR) (mg/dL)	35 (23, 55)	35 (22, 56)
APTT, Median (IQR) (s)	36.3 (29, 54.95)	35.7 (28.6, 54.6)
PT, Median (IQR) (s)	15.4 (13.8, 18.5)	15.6 (13.8, 20.3)
Lactate, Median (IQR) (mmol/L)	2.7 (1.6, 5.15)	2.3 (1.5, 4.1)
Severity score		
SOFA, Median (IQR)	6 (4, 9)	7 (4, 10)
APS-III, Median (IQR)	58 (45, 76)	60 (46, 81)

SpO₂, percutaneous oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; APTT, activated partial thromboplastin time; PT, prothrombine time; SOFA, sequential organ failure assessment, APS-III, Acute Physiology Score III.

Variables	Training set (n = 759)	Validation set (n = 673)
24 h Urine output, Median (IQR) (ml)	1242 (676.5, 2112.5)	1195 (625, 1950)
Mechanical ventilation, n (%)	619 (81.6)	545 (81.0)
Length of stay, Median (IQR)	5.07 (2.59, 11.59)	5.18 (2.55, 10.09)
30-day mortality, n (%)	293 (38.6)	273 (40.6)
SpO ₂ , percutaneous oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; APTT, activated partial thromboplastin time; PT, prothrombin time; SOFA, sequential organ failure assessment, APS-III, Acute Physiology Score III.		

Prognostic factors in the nomogram

Baseline demographic, laboratory variables, including SOFA and APS-III score for the prediction of 30-day mortality were determined using univariate logistic regression firstly. The heart rate, respiratory rate, systolic pressure, spo₂, bilirubin, albumin, lactate, APTT, PT, BUN and 24 h urine output were prognostic factors of 30-day mortality in univariate logistic regression analysis. All above significant prognostic factors were entered into the multivariate logistic regression for adjusting the confounding factors for 30-day mortality. The heart rate, respiratory rate, systolic pressure, SPO₂, albumin and 24 h urine output were independent prognostic factors for 30-day mortality (Table 2).

Table 2

The prognostic factors of 30-day mortality in univariate and multivariate logistic analysis

Variables	univariate			multivariate		
	OR	95%CI	P-value	OR	95%CI	P-value
Heart rate						
≤100	reference	-	-	reference	-	-
100 ~ ≤ 120	1.53	1.07–2.21	0.0218	1.25	0.84–1.89	0.269
120	2.12	1.47–3.05	< 0.001	1.53	1.01–2.33	0.046
Systolic pressure						
≥90	reference	-	-	reference	-	-
≥ 70 ~ 90	1.65	1.15–2.37	0.007	1.10	0.74–1.63	0.629
≥60 ~ 70	3.54	2.194–5.88	< 0.001	1.77	1.01–3.13	0.048
60	7.84	4.42–14.38	< 0.001	3.68	1.91–7.28	< 0.001
Respiratory rate						
≤20	reference	-	-	reference	-	-
20 ~ ≤ 25	1.18	0.61–2.41	0.619	1.31	0.64–2.79	0.475
25	2.29	1.25–4.46	0.01	2.1	1.13–3.34	0.036
SPO ₂	0.96	0.94–0.97	< 0.001	0.97	0.96–0.99	0.005
Albumin	0.45	0.35–0.58	< 0.001	0.61	0.45–0.81	< 0.001
Bilirubin	1.12	1.05–1.21	0.001	1.03	0.95–1.13	0.451
BUN	1.01	1.00-1.02	< 0.001	1.01	0.99–1.01	0.122
Lactate	1.01	1.00-1.02	< 0.001	1.02	0.95–1.09	0.641
APTT	0.004	0.00-0.01	0.036	0.99	0.99-1.00	0.678
PT	1.02	1.00-1.03	0.012	1.01	0.99–1.02	0.349
Urine output						
≥1000	reference	-	-	reference	-	-
≥ 400 ~ 1000	2.52	1.78–3.58	< 0.001	2.11	1.44–3.09	< 0.001
400	5.20-	3.32–8.27	< 0.001	2.56	1.51–4.38	< 0.001
SpO ₂ , percutaneous oxygen saturation; BUN, blood urea nitrogen; APTT, activated partial thromboplastin time; PT, prothrombine time.						

Prognostic nomogram for 30-day mortality We established this nomogram that incorporated the significant prognostic factors from the multivariate analysis (Fig. 1). This nomogram had a C-index of 0.741 (95% confidence interval [CI], 0.7058–0.7766) for predicting the 30-day mortality in ARF patients. Meanwhile, we developed another two nomograms according to SOFA and APS-III score. The SOFA nomogram had a C-index of 0.653 (95% CI: 0.6133–0.6933) and the APS-III nomogram had a C-index of 0.707 (95% CI: 0.6697–0.7444) (supplementary materials). Our nomogram performed a better predictive power than SOFA and APS-III score. Good calibration curve for nomogram predicted 30-day mortality were observed for in ARF patients in the training set and it was better than the calibration curves for SOFA and APS-III (Fig. 2).

External validation of the nomogram The C-index of established nomogram was 0.687 (95%CI: 0.6458–0.7272) for predicting 30-day mortality in the validation set. The C-index of APS-III and SOFA were 0.677 (95%CI: 0.6351–0.7186) and 0.613 (95%CI: 0.5694–0.6565) respectively. The calibration curves revealed adequate fit of the nomogram and APS-III predicting the 30-day mortality in the validation set, which significantly better than the calibration curve for SOFA (Fig. 3).

Decision Curve Analysis of the nomogram

The decision curve analysis (DCA) showed that this nomogram had a large threshold probability range than the SOFA and APS-III score. The DCA implicated that the net benefits gained from the application of our nomogram were higher than SOFA and APS-III score. It unveiled the clinical utility of proposed nomogram. (Fig. 4).

Discussion

Nomogram is a visualization of regression analysis, which is widely used in clinical disease diagnosis and prognosis evaluation [9–12]. In this study, we developed and validated a novel nomogram to predict the mortality risk among elderly patients with ARF. Our results show that this nomogram mainly based on vital signs and laboratory examination. The initial vital signs include heart rate, respiratory rate, systolic blood pressure and SpO₂ were identified as an independent predictor of mortality in elderly patients with ARF. With the increase of heart rate and respiratory rate, the risk of death increases. Furthermore, the decrease of systolic blood pressure and blood oxygen saturation will also increase the risk of death, both of which have a greater weight in the evaluation of short-term prognosis. It can be seen that both maintaining circulation stability and increasing blood oxygen were helpful to reduce the mortality of ARF in the elderly.

Currently, urinary output and serum creatinine are used to evaluate kidney function.

However, a study has shown that serum creatinine was an unreliable indicator of acute changes in renal function[13]. Our study also showed that urinary output was superior to serum creatinine in predicting short-term mortality of elderly patients with ARF. Although, the assessment of AKI stage is not necessarily based on urine volume, the initial postoperative urine volume was considered an accurate predictor of

delayed graft function[14]. The reduction of urinary output can be attributed to insufficient blood flow to the kidneys, due to reduced blood volume and systolic pressure. Albumin, synthesized by the liver, are considered important factors associated with malnutrition among patients. It tends to improve the microcirculatory performance which supports the maintenance of major organ functions[15]. Thus, albumin was regarded as an important biomarker to evaluate the poor prognosis of hospitalized patients[16]. Our research also showed that the risk of death increased gradually with the decrease of plasma albumin. Therefore, plasma albumin may play an important role in predicting the mortality of elderly patients with ARF.

Finally, the nomogram incorporates 6 items of heart rate, respiratory rate, systolic blood pressure, SpO₂, urinary output and plasma albumin. In order to prove the calibration of the nomogram, clinical data was collected from different institutions. As is well known, the internal validity associated with the explanation of the results, and the external validity related to the generalizability of the results [17, 18]. Through the internal and external validation data set analysis, the calibration of our nomogram has been proved to be highly consistent, which was more accurate than APS-III (B) and SOFA scores. At present, SOFA score has been widely used in assessment of critical diseases[19, 20], especially in the prognosis of multiple organ failure. Compare our nomogram with these scores, it has fewer indicators, but better discrimination and calibration. This means that our nomogram may be popularized to predict the outcome of elderly patients with ARF.

However, to evaluate its clinical usefulness, it depends on how much it benefits the patient, not just its popularization[21]. DCA is a novel method which has been widely used in the evaluation of clinical research effectiveness[22–24]. It offers insight into clinical consequences on the basis of threshold probability, from which the net benefit could be derived[25]. According to the DCA results, the application value of our nomogram is better than that of APS-III (B) and SOFA scores.

Our study has several limitations. First, this study was a single center study, and the validation set was from the same hospital. We need validate our nomogram in broad external population. Second, our nomogram is only applicable to the elderly ARF patients. Third, we reported 30-day all-cause mortality instead of ARF specific decease cause.

Conclusions

In conclusion, this study presents a novel nomogram that incorporates heart rate, respiratory rate, systolic blood pressure, SpO₂, urinary output and plasma albumin. It performed better than APS-III (B) and SOFA scores and should be useful as decision support on the prediction of mortality risk in elderly patients with ARF.

Abbreviations

ARF

acute respiratory failure; MIMIC-III v1.4: Intensive Care III database version 1.4; SpO₂: Percutaneous oxygen saturation; WBC: white blood cell; BUN: blood urea nitrogen; APTT: activated partial thromboplastin time; PT: prothrombin time; SOFA: sequential organ failure assessment score; APS-III: Acute Physiology Score III.

Declarations

Ethics approval and consent to participate:

The database was approved by the institutional review boards (IRB) of the Massachusetts Institute of Technology (MIT) and BIDMC; therefore, the informed consent was waived in our study.

Consent for publication:

Not applicable.

Availability of data and materials:

All data generated or analyzed in this study are published in this article (and its additional information files).

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

HR, ZX, ZZ, CY, WL analyzed and interpreted the patient data. CQ, WJ, WZ, XJ was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

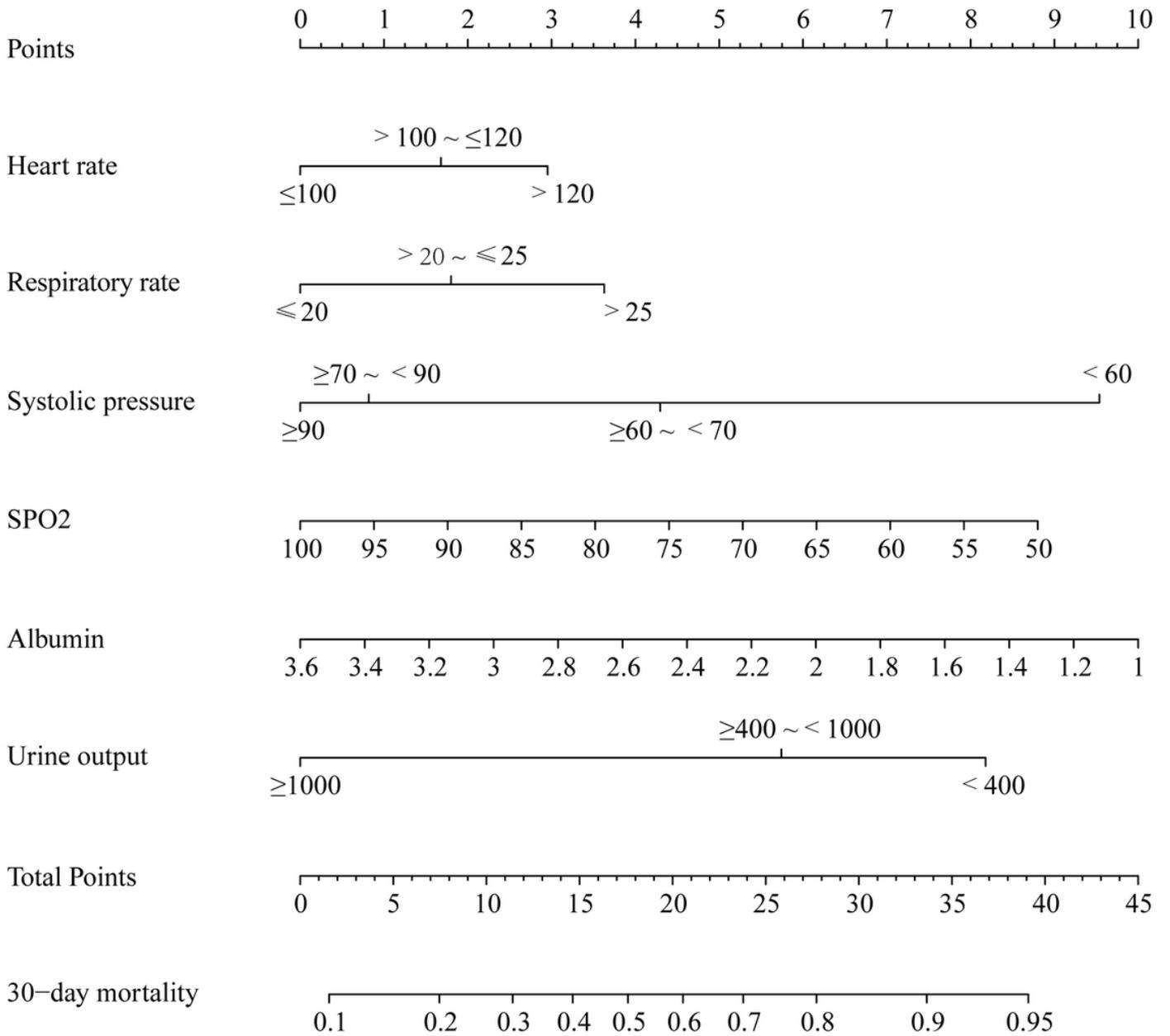


Figure 1

Nomogram to predicted 30-day mortality in ARF patients. The nomogram was developed in the training set, with the heart rate, respiratory rate, systolic pressure, SPO2, albumin, and 24 h urine output incorporated.

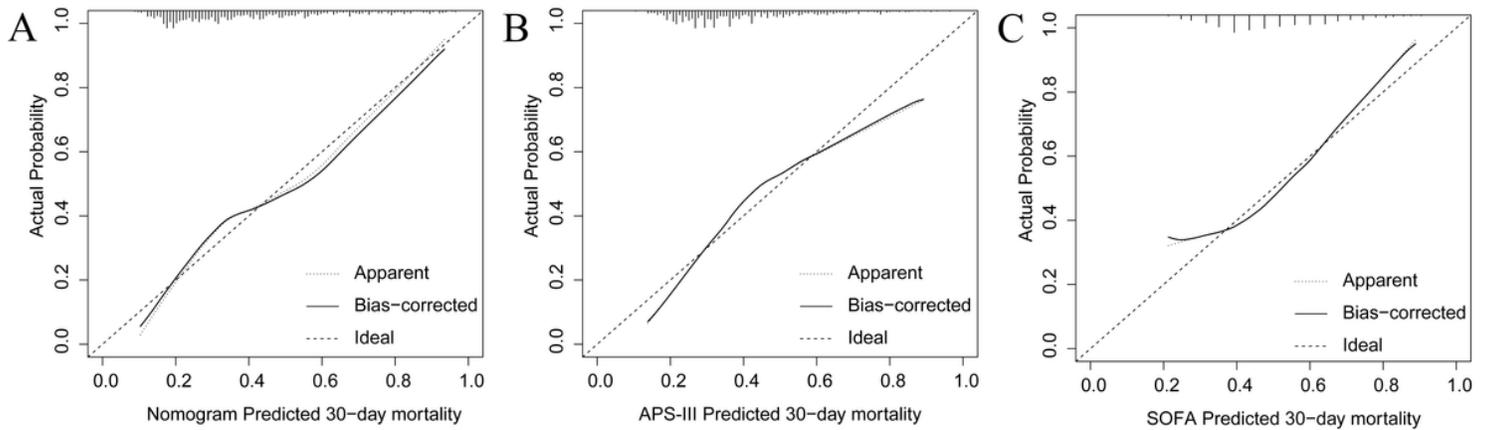


Figure 2

Calibration curves of the nomogram (A), APS-III (B) and SOFA (C) predicted 30-day mortality in training set. Calibration curve represents the calibration of the nomogram, which shows the consistency between the predicted 30-day mortality and actual 30-day mortality of ARF patients. Y-axis represents the actual 30-day mortality, X-axis represents the predicted 30-day mortality. The diagonal line represents a perfect prediction by an ideal model, and black solid line represents the prediction performance of the nomogram, of which a closer fit to the diagonal line means a better prediction.

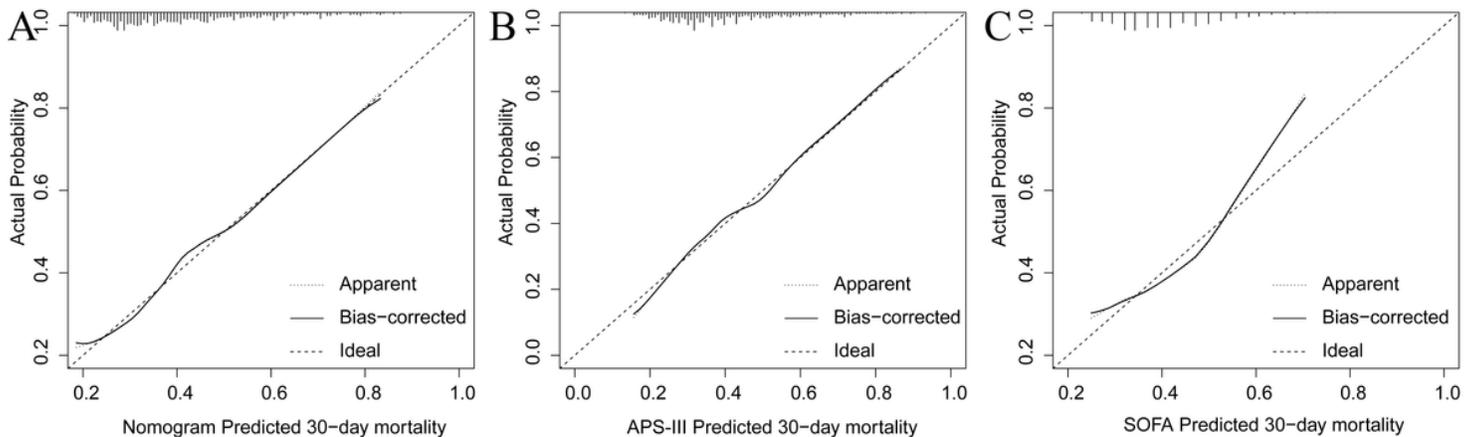


Figure 3

Calibration curves of the nomogram (A), APS-III (B) and SOFA (C) predicted 30-day mortality in validation set. Y-axis represents the actual 30-day mortality, X-axis represents the predicted 30-day mortality. Black solid line represents the prediction performance of the nomogram, the diagonal line represents an ideal nomogram model. The diagonal line represents a perfect prediction by an ideal model, and black solid line represents the prediction performance of the nomogram, of which a closer fit to the diagonal line means a better prediction.

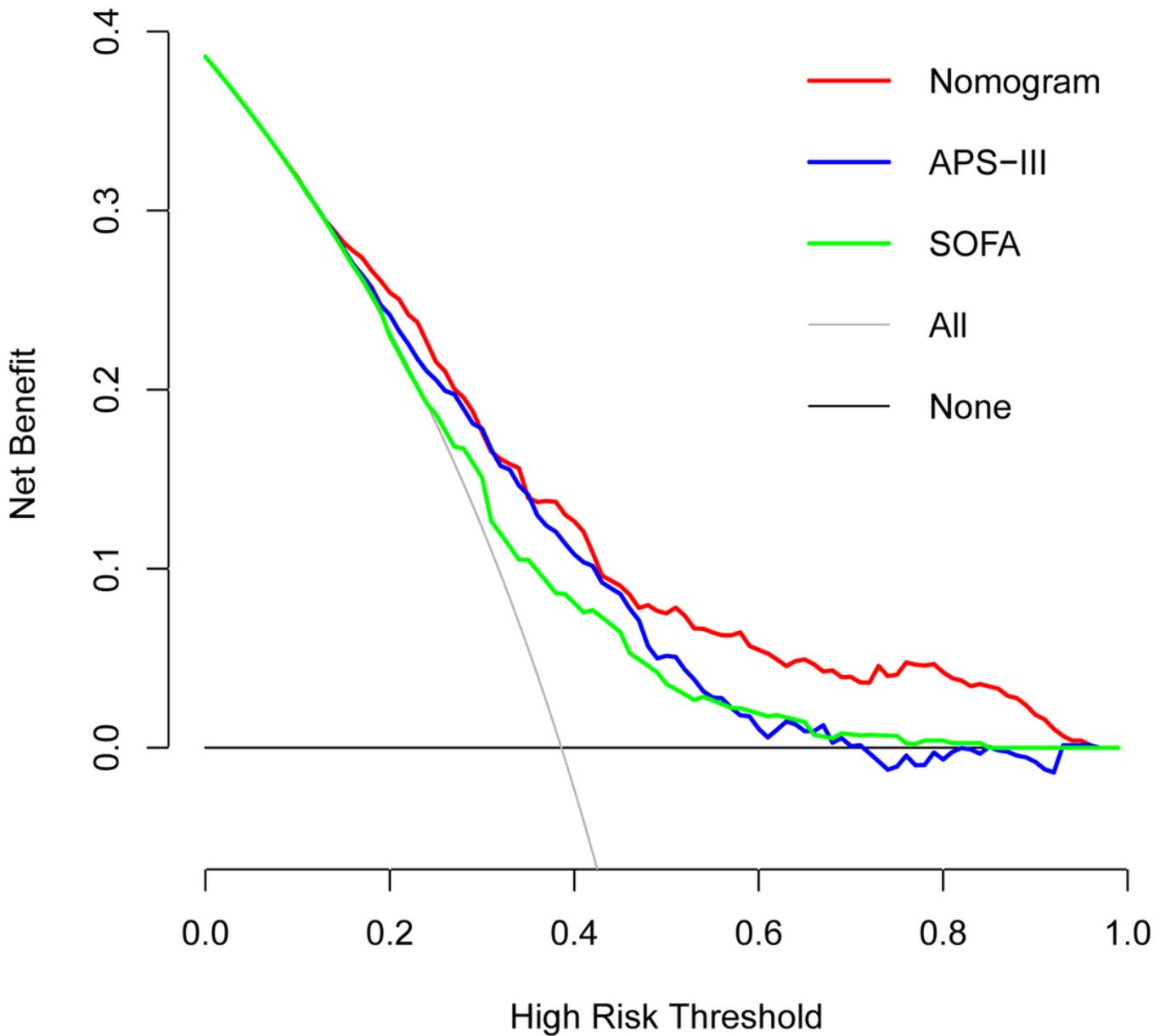


Figure 4

Decision curve for the training set cohort implicating the net benefit with respect to the use of the nomogram, APS-III, and SOFA score for predicting 30-day in ARF patients. The Y-axis represents the net benefit. The X-axis represents the threshold value. The red line represents the nomogram model, blue line represents the APS-III score and green line represents the SOFA score. The light grey line represents the assumption that all patients have the outcome (dead). Thin black line represents the assumption that no patients have the outcome (dead).

Supplementary Files

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