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**ORIGINAL ARTICLE**



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# Laboratory signatures differentiate the tolerance to hypothermic circulatory arrest in acute type A aortic dissection surgery

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**Key question**

Can a combination of laboratory signatures predict mortality in acute type A aortic dissection (ATAAD) surgery?

**Key finding(s)**

Inflammatory, immune, coagulation, and metabolic signatures identifies risk stratifications for in-hospital mortality.

**Take-home message**

The 5A lab-based risk tool using readily available laboratory signatures on admission robustly predicted in-hospital mortality in ATAAD patients.

**5A Lab-based Risk Score**

| Indicator | Point | | | |
|---|---|---|---|---|
| *Age (year)* | >60 | +2.0 | | |
| *Body mass index (kg/m2)* | >28 | +1.5 | | |
| *Platelet-neutrophil ratio* | 10-20 | +2.0 | <10 | +3.0 |
| *Estimated glomerular filtration rate (ml/min/1.73²)* | 30-90 | +1.5 | <30 | +2.0 |
| *D-dimer (mg/l)* | 5-25 | +3.0 | >25 | +4.0 |
| *Fibrinogen (g/l)* | <1.5 | +2.0 | | |
| *Lymphocyte-monocyte ratio* | 1.0-2.0 | +1.5 | >2.0 | +2.0 |

## Abstract

**OBJECTIVES:** Our goal was to investigate whether laboratory signatures on admission could be used to identify risk stratification and different tolerance to hypothermic circulatory arrest in acute type A aortic dissection surgery.

**METHODS:** Patients from 10 Chinese hospitals participating in the Additive Anti-inflammatory Action for Aortopathy & Arteriopathy (5A) study were randomly divided into derivation and validation cohorts at a ratio of 7:3 to develop and validate a simple risk score model using preoperative variables associated with in-hospital mortality using multivariable logistic regression. The performance of the model was

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assessed using the area under the receiver operating characteristic curve. Subgroup analyses were performed to investigate whether the laboratory signature-based risk stratification could differentiate the tolerance to hypothermic circulatory arrest.

**RESULTS:** There were 1443 patients and 954 patients in the derivation and validation cohorts, respectively. Multivariable analysis showed the associations of older age, larger body mass index, lower platelet–neutrophile ratio, higher lymphocyte–monocyte ratio, higher D-dimer, lower fibrinogen and lower estimated glomerular filtration rate with in-hospital death, incorporated to develop a simple risk model (5A laboratory risk score), with an area under the receiver operating characteristic of 0.736 (95% confidence interval 0.700–0.771) and 0.715 (95% CI 0.681–0.750) in the derivation and validation cohorts, respectively. Patients at low risk were more tolerant to hypothermic circulatory arrest than those at middle to high risk in terms of in-hospital mortality [odds ratio 1.814 (0.222–14.846); odds ratio 1.824 (1.137–2.926) ($P = 0.996$)].

**CONCLUSIONS:** The 5A laboratory-based risk score model reflecting inflammatory, immune, coagulation and metabolic pathways provided adequate discrimination performances in in-hospital mortality prediction, which contributed to differentiating the tolerance to hypothermic circulatory arrest in acute type A aortic dissection surgery.

Clinical Trials. gov number NCT04918108

**Keywords:** Mortality • Aortic dissection • Risk model • Hypothermia • Circulatory arrest

**ABBREVIATIONS**

| | |
|---|---|
| ATAAD | acute type A aortic dissection |
| 5A | Additive Anti-inflammatory Action for Aortopathy & Arteriopathy |
| eGFR | estimated glomerular filtration rate |
| GERAADA | German Registry for Acute Aortic Dissection Type A |
| IRAD | International Registry of Acute Aortic Dissections |

## INTRODUCTION

Acute type A aortic dissection (ATAAD) is a major cardiovascular catastrophe that is associated with a high risk of death [1–3]. Malperfusion is the dominant determinant of death following surgical repair [4, 5]. Key pathogenetic factors from systemic changes secondary to aortic dissection further aggravate and exacerbate the progress of the disease [6, 7]. Importantly, bursts of excess inflammatory, coagulation and metabolic activations are likely the potential causes of further injury [8], which greatly contributed to the poor outcomes.

Several risk models have been developed to predict mortality [9–14], such as the International Registry of Acute Aortic Dissections (IRAD) and the German Registry for Acute Aortic Dissection Type A (GERAADA) score [15, 16]; however, most models require more variables and complicated calculations to assess the risk of mortality. Given that these biomarkers may reflect different aspects of pathophysiological responses to this acute catastrophe, we hypothesized that a combination of routine laboratory signatures on admission might provide useful information for a rapid initial risk stratification [17, 18].

Hypothermic circulatory arrest facilitates emergency treatment of ATAAD, especially for the repair of aortic arch pathologies [19]. However, despite its widespread use, hypothermic circulatory arrest is associated with significantly increased risks of morbidity and mortality [20]. So, it is of great importance to identify patients who are more or less tolerant to this hypothermic circulatory arrest technique, thereby helping us to provide individual treatment strategies and reduce postoperative complications.

Our goal was to develop a laboratory-based simple risk model based on a combination of routine laboratory signatures at admission and to investigate whether the signature-based risk stratification could differentiate tolerance to hypothermic circulatory arrest in patients with ATAAD who underwent emergency surgical repair.

## METHODS

### Study design and population

This was a multicentre, retrospective study based on the investigator-initiated Additive Anti-inflammatory Action for Aortopathy & Arteriopathy (5A) III project. We identified patients with ATAAD who underwent surgical repair at 10 Chinese cardiovascular centres between January 2016 and January 2021 (Supplemental Materials). Patients aged 18 years or older were included in this study provided that they underwent primary surgical repair within 24 h after admission. Exclusion criteria were (i) not receiving surgical repair; (ii) time from onset to admission > 14 days; and (iii) patients with haematological diseases (Supplemental Fig. 1). We retrospectively analysed patients with ATAAD from the 5A cohort, in which patients were randomly divided into a training set (70% of patients) and a testing set (30%). The 5A study was approved by the research ethics committees of all collaborating hospitals (2021-SR-381). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was registered with Clinical Trials.gov number NCT04918108. Informed consent was waived for this retrospective observational study.

### Data collection

The following data profiles were collected: demographic characteristics, medical history, laboratory profiles, procedural variables and in-hospital outcomes. The absolute count of leucocytes, platelets, neutrophils, monocyte and lymphocytes and the respective levels of haemoglobin, creatinine, urea nitrogen, fibrinogen, albumin, D-dimer, B-type natriuretic peptide, aspartate aminotransferase and alanine aminotransferase were measured in blood specimens obtained immediately upon admission. The estimated glomerular filtration rate (eGFR) was calculated using serum creatinine levels in the Chronic Kidney Disease Epidemiology Collaboration equations [21]. Drinking alcohol was

defined as the consumption of at least 30 g alcohol per week for 1 year or more. Stroke was defined as any permanent (manifest stroke) or temporary neurologic deficit or deterioration (transient ischaemic attack or prolonged reversible ischaemic neurologic deficit before the latest month of admission).

## Outcome

The primary outcome was in-hospital mortality, defined as any death, regardless of cause, occurring during the hospitalization subsequent to the operation according to the Society of Thoracic Surgeons criteria [22]. Secondary outcomes included 30-day mortality, intensive care unit mortality, mechanical ventilation duration, intensive care unit length of stay and hospital length of stay.

## Statistical analyses

Continuous variables are reported as the mean (standard deviation) for normally distributed values and as the median (interquartile range) for non-normal values. Categorical variables are expressed as number and percentage. Comparisons of continuous variables between groups were performed with the Student *t*-test or the Mann–Whitney U-test, as appropriate. Comparisons of categorical variables were assessed with the $\chi^2$ or the Fisher exact test, as appropriate.

Model derivation and validation were performed according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement [23].

Demographic characteristics, medical history and laboratory profiles were initially included in the multivariable logistic regression as candidate predictors. We selected the best possible final model based on Akaike's information criterion in multivariable logistic regression. We also tested the collinearity between variables to be included in the model by assessing the variance inflation factor for each covariate. A variance inflation factor value <10 was considered to indicate no statistically significant collinearity.

Binary logistic regressions with restricted cubic spline functions were used to model the relationship between each candidate variable selected and the probability of death [24]. For ease of use, the continuous variables selected were categorized based on clinically useful cutoff values or statistically relevant inflection points or thresholds in the restricted cubic splines. Risk scoring points were allocated for each independent predictor with simple weighting guided by beta-coefficients to develop a laboratory-based risk scoring system. Subsequently, we fitted both the dose–response relationship between laboratory-based risk scores and the in-hospital mortality on a continuous scale [24].

To assess the external validity of performance of the model, using an independent, external data set of 954 patients, we examined the discrimination performance via the area under the receiver operating characteristic curve (AUC) with the 95% confidence interval (CI) and the calibration performance via calibration plots and the Hosmer-Lemeshow goodness-of-fit test and the Brier score [25–27]. We also plotted decision curves to assess the net benefit of decisions [28].

We further calculated the AUC of the IRAD and the GERAADA risk score models and compared the 2 results with that of the laboratory-based risk score model according to the method of DeLong *et al.* [29].

## Subgroup analysis

Based on the tertiles of predicted risk probability, patients were classed as being at low (bottom tertile), middle (middle tertile) and high risk (top tertile) in the total cohort, respectively. The probability of death was calculated in each risk category, and odd ratios (OR) with 95% confidence intervals (CI) were assessed by logistic regression. Subgroup analyses were performed to investigate whether the risk stratifications (low vs middle–high risk) could differentiate the tolerance to hypothermic circulatory arrest (with or without).

## Power and sample size calculations

For binary outcome measures, we hypothesized that a minimum of 10 events (i.e. patients with the defined outcome) per variable would be required to prevent overfitting. In the derivation cohort, the effective sample size in the model was attained (163 events for 7 variables).

All statistical analyses were performed using Stata version 14 (Stata Corp, College Station, TX, USA) and R software, version 3.2.0 (R Foundation for Statistical Computing, Institute for Statistics and Mathematics, Vienna, Austria). A two-sided *P* value of <0.05 was considered to indicate statistical significance.

# RESULTS

## Patient characteristics

A total of 1433 patients in the derivation cohort and 954 in the validation cohort were analysed. Table 1 shows the patient characteristics as stratified by study cohort. There were 163 (11.4%) in-hospital deaths in the derivation cohort and 114 in-hospital deaths (11.9%) in the validation cohort. The other baseline, clinical and procedural characteristics as well as hospital outcomes were similar between the derivation and validation cohorts (Table 1).

## Factors associated with mortality

All 22 candidate laboratory indicators from the derivation cohort were associated with in-hospital death on univariable analysis (Supplemental Table 1). Further multivariable logistic regression identified 7 covariates (older age, larger body mass index, lower platelet–neutrophile ratio, higher lymphocyte–monocyte ratio, higher D-dimer, lower fibrinogen and lower eGFR) that were independently associated with in-hospital death (Fig. 1; Supplemental Fig. 2). The collinearity and model assessment are displayed in Supplemental Tables 2 and 3. Categorical modelling of each risk indicator revealed a significant relationship with death and guided point allocation for the development of a 5A laboratory-based risk score (Fig. 2).

## 5A Laboratory-based risk score

In the derivation cohort, a dose dependency of the in-hospital mortality risk was identified for increasing 5A laboratory-based risk scores as a continuous variable [OR 1.345 (95% CI, 1.253–1.444), $P < 0.0001$; Fig. 3A]. This risk score identified an

**Table 1:** Baseline, clinical and procedural characteristics and hospital outcomes between the derivation and the validation cohorts

| | Derivation cohort (N = 1 433) | Validation cohort (N = 954) | *P*-value |
|---|---|---|---|
| **Demographic variables** | | | |
| Age (year) | 54.0 (44.0-62.2) | 54.0 (46.0-62.0) | 0.320 |
| Sex (male) | 1025 (71.6%) | 679 (71.1%) | 0.800 |
| Height, cm | 170 (165-175) | 170 (165-175) | 0.782 |
| Weight, kg | 73.0 (64.0-81.0) | 73.0 (63.9-82.0) | 0.926 |
| Body mass index (kg/m$^2$) | 25.4 (22.9-27.8) | 25.5 (22.9-28.0) | 0.923 |
| Body surface area (m$^2$) | 1.9 (1.8-2.1) | 1.9 (1.8-2.1) | 0.763 |
| **Medical history** | | | |
| Smoking (%) | 643 (44.9%) | 442 (46.3%) | 0.507 |
| Drinking alcohol (%) | 449 (31.4%) | 321 (33.6%) | 0.241 |
| Hypertension (%) | 1115 (78.1%) | 739 (77.5%) | 0.757 |
| Diabetes mellitus | 90 (6.3%) | 49 (5.1%) | 0.235 |
| Hyperlipidaemia (%) | 136 (9.5%) | 80 (8.4%) | 0.351 |
| Stroke (%) | 89 (6.2%) | 54 (5.7%) | 0.572 |
| Chronic lung diseases (%) | 39 (2.7%) | 26 (2.7%) | 0.997 |
| Coronary heart disease (%) | 146 (10.2%) | 95 (10.0%) | 0.464 |
| Arrhythmia (%) | 105 (7.3%) | 64 (6.7%) | 0.556 |
| Malperfusion (%) | 444 (31.0%) | 307 (32.2%) | 0.537 |
| Renal | 193 (13.5%) | 131 (13.7%) | |
| Intestinal | 44 (3.1%) | 32 (3.4%) | |
| Cerebral | 144 (10.1%) | 91 (9.6%) | |
| Coronary | 216 (15.1%) | 155 (16.2%) | |
| **Laboratory signatures** | | | |
| Haemoglobin (g/l) | 123 (105-139) | 125 (106-139) | 0.809 |
| Leucocyte count (10*9/l) | 11.4 (8.5-14.4) | 11.5 (8.8-14.7) | 0.519 |
| Platelet count (10*9/l) | 165 (126-210) | 160 (125-207) | 0.092 |
| Monocyte count (10*9/l) | 0.68 (0.47-0.97) | 0.67 (0.46-0.93) | 0.404 |
| Lymphocyte count (10*9/l) | 1.01 (0.66-1.44) | 0.99 (0.66-1.41) | 0.668 |
| Neutrophil count (10*9/l) | 9.7 (6.8-12.3) | 9.8 (7.0-12.7) | 0.428 |
| Fibrinogen (g/l) | 2.8 (2.1-4.0) | 2.7 (2.0-3.7) | 0.643 |
| D-dimer (mg/l) | 8.7 (3.2-15.2) | 8.4 (2.9-18.5) | 0.169 |
| eGFR (ml/min/1.73m2) | 72.2 (51.3-96.8) | 70.4 (49.1-95.9) | 0.541 |
| NT-proBNP (pg/ml) | 276.4 (110.4-621.9) | 330.0 (134.0-773.0) | 0.113 |
| Aspartate aminotransferase (u/l) | 26.6 (19.0-47.0) | 26.9 (18.9-46.9) | 0.989 |
| Alanine aminotransferase (u/l) | 26.0 (15.8-43.9) | 23.7 (15.0-41.1) | 0.778 |
| Blood urea nitrogen (mmol/l) | 7.2 (5.4-9.5) | 7.2 (5.6-9.4) | 0.469 |
| Creatinine (umol/l) | 86.7 (67.5-119.0) | 87.6 (69.0-119.2) | 0.929 |
| Lymphocyte–monocyte ratio | 1.4 (0.9-2.3) | 1.4 (0.9-2.3) | 0.806 |
| Neutrophil–lymphocyte ratio | 10.2 (5.5-16.7) | 10.6 (5.8-16.7) | 0.599 |
| Platelet–lymphocyte ratio | 162.2 (113.3-250.0) | 164.0 (109.7-248.5) | 0.452 |
| Platelet–neutrophils ratio | 16.9 (11.8-26.5) | 16.2 (11.3-25.0) | 0.583 |
| Systemic immune-inflammation index | 1586 (700-3411) | 1638 (697-3369) | 0.908 |
| Systemic inflammatory response index | 6.9 (3.4-11.9) | 6.7 (3.5-11.5) | 0.992 |
| Prognostic nutritional index | 43.4 (39.9-47.1) | 43.4 (40.0-47.8) | 0.814 |
| **Procedural variables (%)** | | | |
| **Root procedures** | | | 0.636 |
| Aortic valve replacement (%) | 81 (5.7%) | 51 (5.3%) | |
| Bentall procedure (%) | 290 (20.3%) | 211 (22.1%) | |
| David procedure (%) | 11 (0.8%) | 7 (0.7%) | |
| **Arch procedures** | | | 0.111 |
| Hemi-arch replacement (%) | 95 (6.6%) | 70 (7.3%) | |
| Total arch replacement (%) | 1114 (77.8%) | 765 (80.1%) | |
| Total arch replacement plus FET implant (%) | 1094 (76.4%) | 754 (79.0%) | 0.143 |
| Inclusion technique (%) | 337 (23.5%) | 231 (24.2%) | 0.713 |
| Hypothermic circulatory arrest (%) | 1199 (83.7%) | 827 (86.6%) | 0.055 |
| Concomitant CABG (%) | | | |
| Concomitant valve surgery (%) | 36 (2.5%) | 18 (1.9%) | 0.311 |
| **Hospital outcomes** | | | |
| In-hospital mortality (%) | 163 (11.4%) | 114 (11.9%) | 0.679 |
| 30-day mortality (%) | 145 (10.1%) | 100 (10.5%) | 0.785 |
| ICU mortality (%) | 146 (10.2%) | 108 (11.3%) | 0.387 |
| ICU stay (days) | 5.0 (2.0-9.0) | 5.0 (3.0-10.0) | 0.171 |
| Hospital stay (days) | 18.0 (12.0-25.0) | 18.0 (12.0-26.0) | 0.381 |
| Mechanical ventilation time (h) | 38.0 (17.5-100.0) | 41.0 (18.0-105.9) | 0.915 |

Continuous data are presented as median (interquartile range), and dichotomous data are presented as n (%).

CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; FET: frozen elephant trunk; ICU: intensive care unit; NT-proBNP: N-terminal probrain natriuretic peptide.

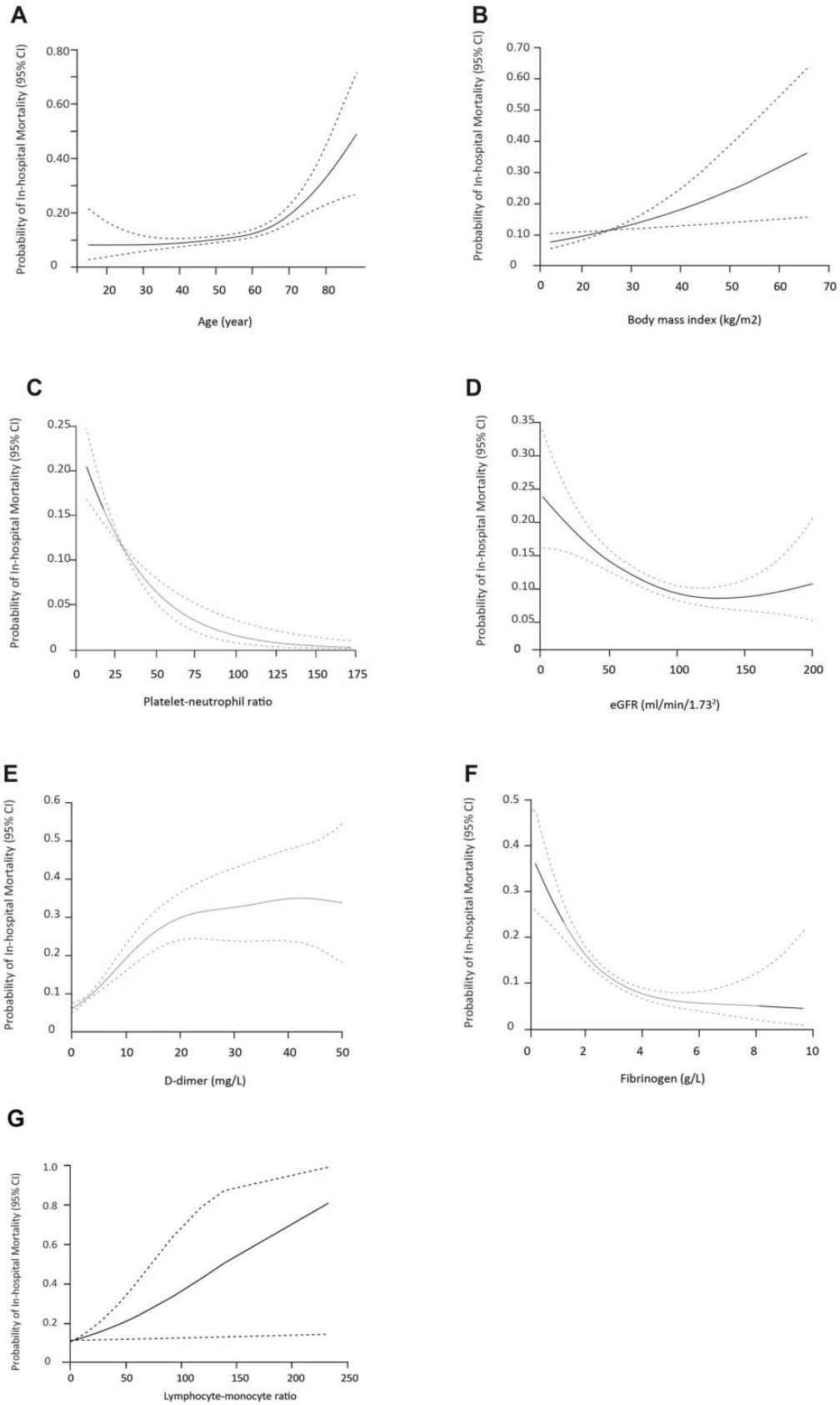


**Figure 1:** Restricted cubic splines of in-hospital deaths by selected variables. (**A**–**G**) Univariable analysis splines of in-hospital mortality by age, body mass index, platelet-neutrophil ratio, eGFR, D-dimer, fibrinogen and lymphocyte–monocyte ratio. eGFR: estimated glomerular filtration rate.

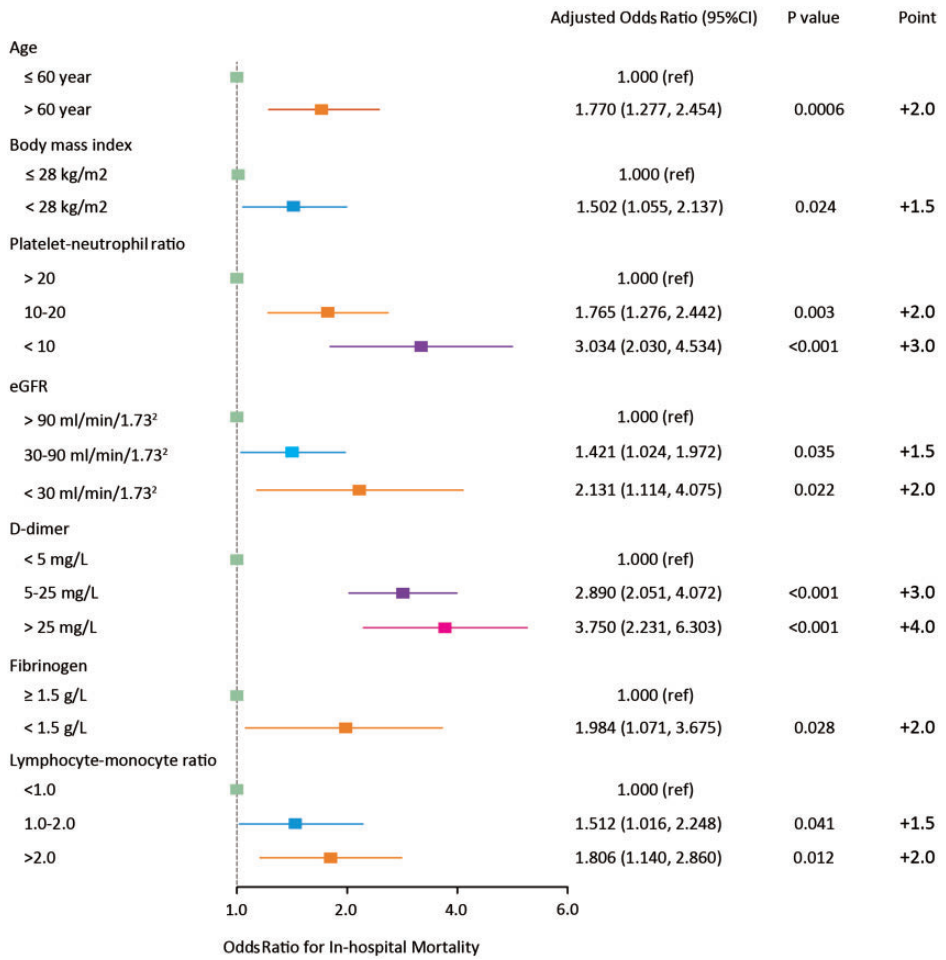


**Figure 2:** Adjusted odds ratios of in-hospital deaths by selected variables. eGFR: estimated glomerular filtration rate.

approximate 15-fold gradient in mortality risk with good discrimination [AUC 0.736 (95% CI 0.700–0.771)] for in-hospital mortality in the derivation cohort (Fig. 4A). The calibration curve revealed good qualitative agreement between the predicted risk and the observed mortality rates (Fig. 4C), with a goodness-of-fit (*P*-value for Hosmer-Lemeshow test = 0.138) and a Brier score of 0.040. The decision curves for mortality probability suggested relatively good performance in terms of clinical application (Fig. 4E).

## Validation

The 5A laboratory-based risk score demonstrated an adequate discrimination performance in predicting in-hospital mortality [0.715 (95% CI 0.681–0.750)] (Fig. 4B). Validation also confirmed good calibration ability, with a goodness-of-fit (*P*-value for the Hosmer-Lemeshow test = 0.107) and a Brier score of 0.058 in the validation set (Fig. 2D). The decision curve analysis also displayed adequate yield (Fig. 4F).

## Comparison with current risk scores

The 2 currently existing risk scores showed similarly adequate discrimination performances [GERAADA risk score: AUC 0.725 (95% CI 0.689, 0.760); IRAD risk score: AUC 0.729 (95% CI 0.695, 0.764) in total cohort (each vs 5A laboratory-based risk score, $P > 0.05$)] (Fig. 5A, B). Calibration and decision curve analyses are shown in Fig. 5C–F.

## Subgroup analyses

According to the tertiles of the predicted risk probability of in-hospital death, 795 patients and 1592 patients were classed as a low-risk group and a middle- to high-risk group, respectively. There was a significantly increased trend in mortality across the low-, middle- and high-risk groups [OR 5.487 (95% CI 2.559, 11.764); OR 39.177 (95% CI 19.199, 79.947); (*P* for trend < 0.0001; Fig. 3B)]. There was a higher rate of hypothermic circulatory arrest in the middle- to high-risk group than in the low-risk group [632/795 (79.5%) vs 1394/1592 (87.6%); $P < 0.0001$]. Patients at low risk were more tolerant to hypothermic circulatory arrest than those at middle to high risk in terms of in-hospital death [7/632 (1.1%) vs 1/163 (0.6%), OR 1.814 (0.222–14.8460), $P = 0.579$ among the low-risk group; 248/1394 (17.8%) vs 21/198 (10.65), OR 1.824 (1.137–2.926), $P = 0.013$] among the middle- to high-risk groups) ($P = 0.996$).

## Discussion

Key findings of the present study in Chinese patients with ATAAD who underwent emergency surgical repair are as follows: (i) Each

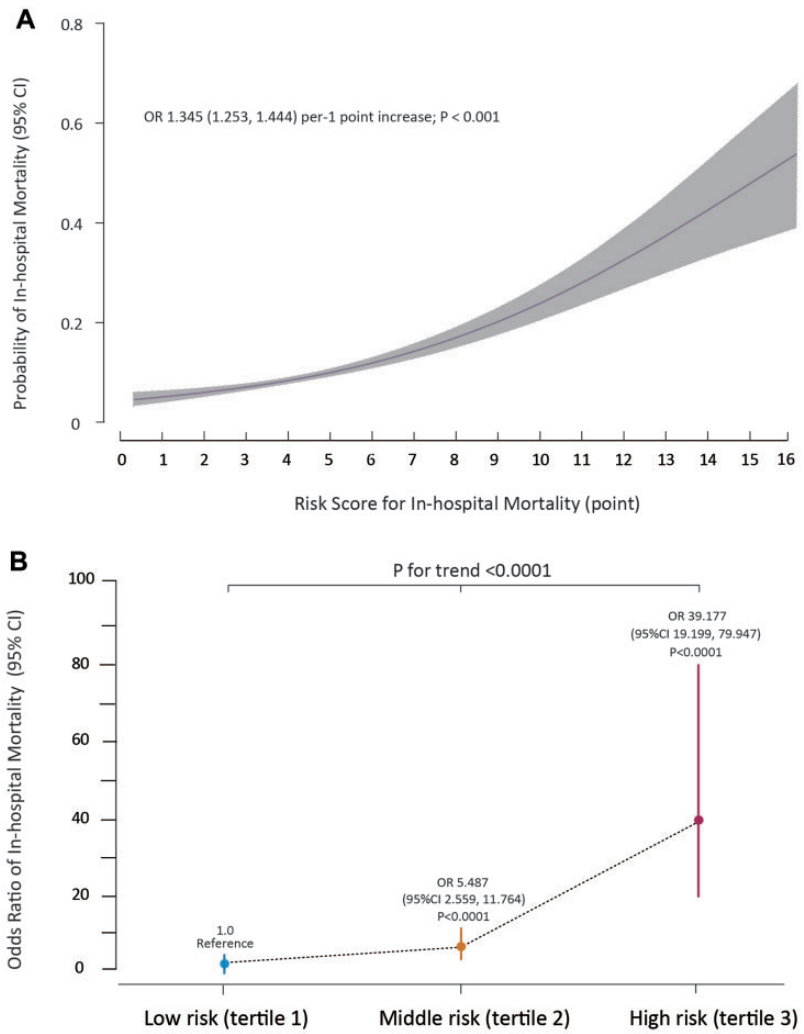


**Figure 3:** 5A laboratory-based risk score and in-hospital mortality in derivation cohort. (**A**) Functional relationship between risk score and in-hospital mortality. (**B**) Association between risk classifications and in-hospital mortality. OR: odds ratio; CI: confidence interval.

of 7 predictors quantified on admission (older age, larger body mass index, lower platelet–neutrophile ratio, higher lymphocyte–monocyte ratio, higher D-dimer, lower fibrinogen and lower eGFR) were independently associated with an increased risk of in-hospital death; (ii) the predictive value of the 5A laboratory-based risk score for mortality was comparable to those of the previous models (GERAADA and IRAD risk scores); and (iii) patients at low risk were more tolerant to hypothermic circulatory arrest than those at middle to high risk in terms of in-hospital mortality. Summarily, our findings suggest that a specific combination of inflammatory, immune, coagulation and metabolic signatures provided adequate discrimination performances in in-hospital mortality prediction, which contributed to differentiating the tolerance to hypothermic circulatory arrest in ATAAD surgery.

Death remains a major concern in patients with aortic dissection at present, and a prompt risk assessment of death is of great significance for clinical management. Several risk models have been developed and used for predicting the number of deaths in clinical practice [5, 9, 15, 16, 30, 31]. However, some clinical concerns can make early evaluation difficult due to the need for complex risk calculations and statistical knowledge. We therefore focused on preoperative routine clinical and laboratory variables to develop a simplified risk score model (5A laboratory-based risk score) for predicting death following ATAAD surgery.

Several biomarkers related to immune responses, inflammation and coagulation have been reported to be independent predictors of mortality in patients with ATAAD [32–34]. Acute aortic syndrome is generally associated with a burst of inflammatory and coagulation responses. Our findings showed that a lower platelet–neutrophile ratio, a higher lymphocyte–monocyte ratio, higher D-dimer, lower fibrinogen and lower eGFR in addition to older age and larger body mass index were independent risk factors for in-hospital mortality in patients treated for ATAAD [35, 36].

To the best of our knowledge, this was the first study with such a large sample size to investigate the tolerance to hypothermic circulatory arrest during surgical repair of ATAAD in a multicentre study of the Asian population with ATAAD. We observed that more patients in the middle- to high-risk group experienced concomitant hypothermic circulatory arrest than those in the low-risk group. Also, we found that hypothermic circulatory

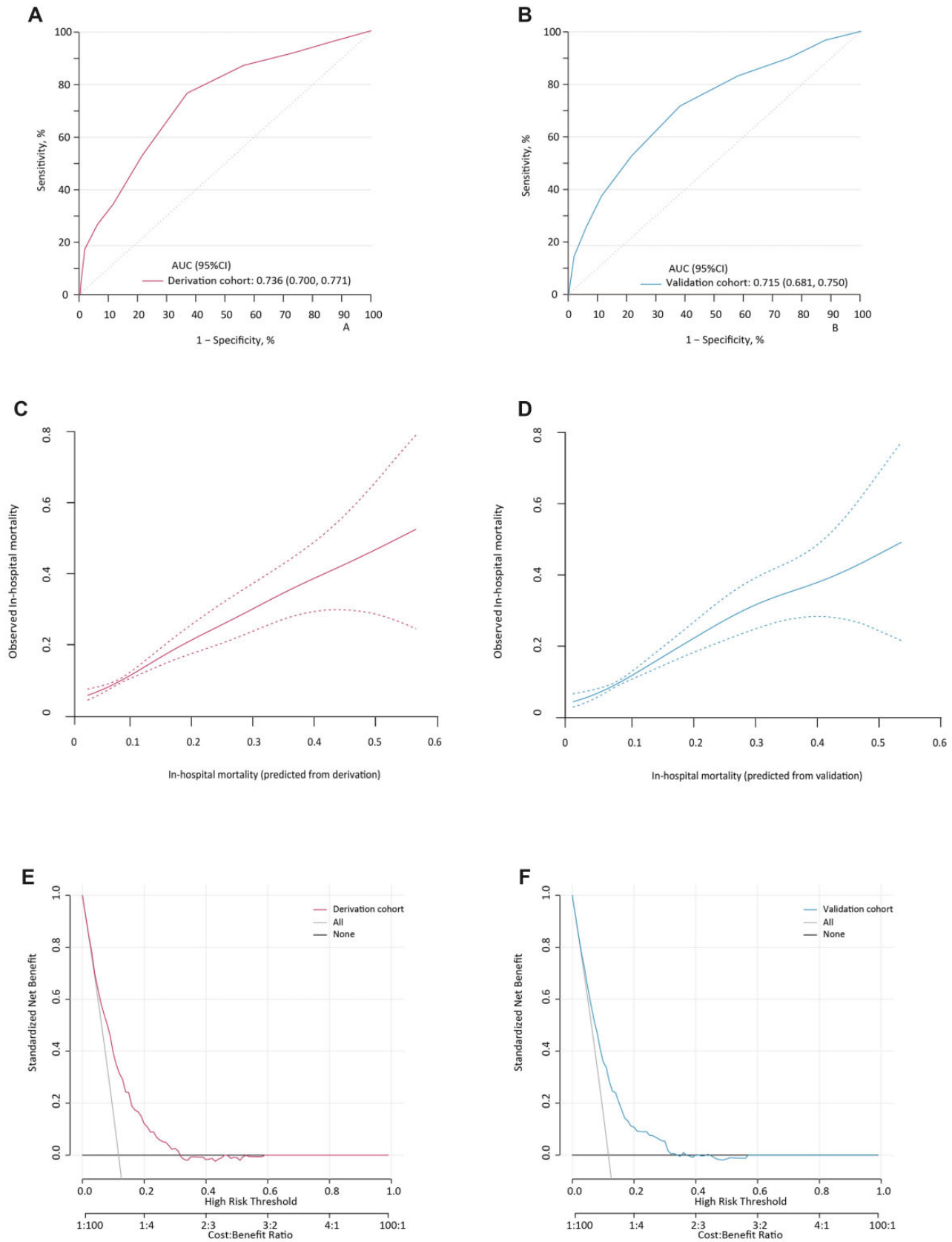


**Figure 4:** Prediction performances of 5A laboratory-based risk score in the derivation and validation cohorts. (**A, B**) ROC curve in the derivation and validation cohort. (**C, D**) Calibration curve of this risk model in the derivation and validation cohort. (**E, F**) Decision curve analysis of this risk model in the derivation and validation cohort. ROC: receiver operating characteristic curve; AUC: the area under the receiver operating characteristic curve; CI: confidence interval.

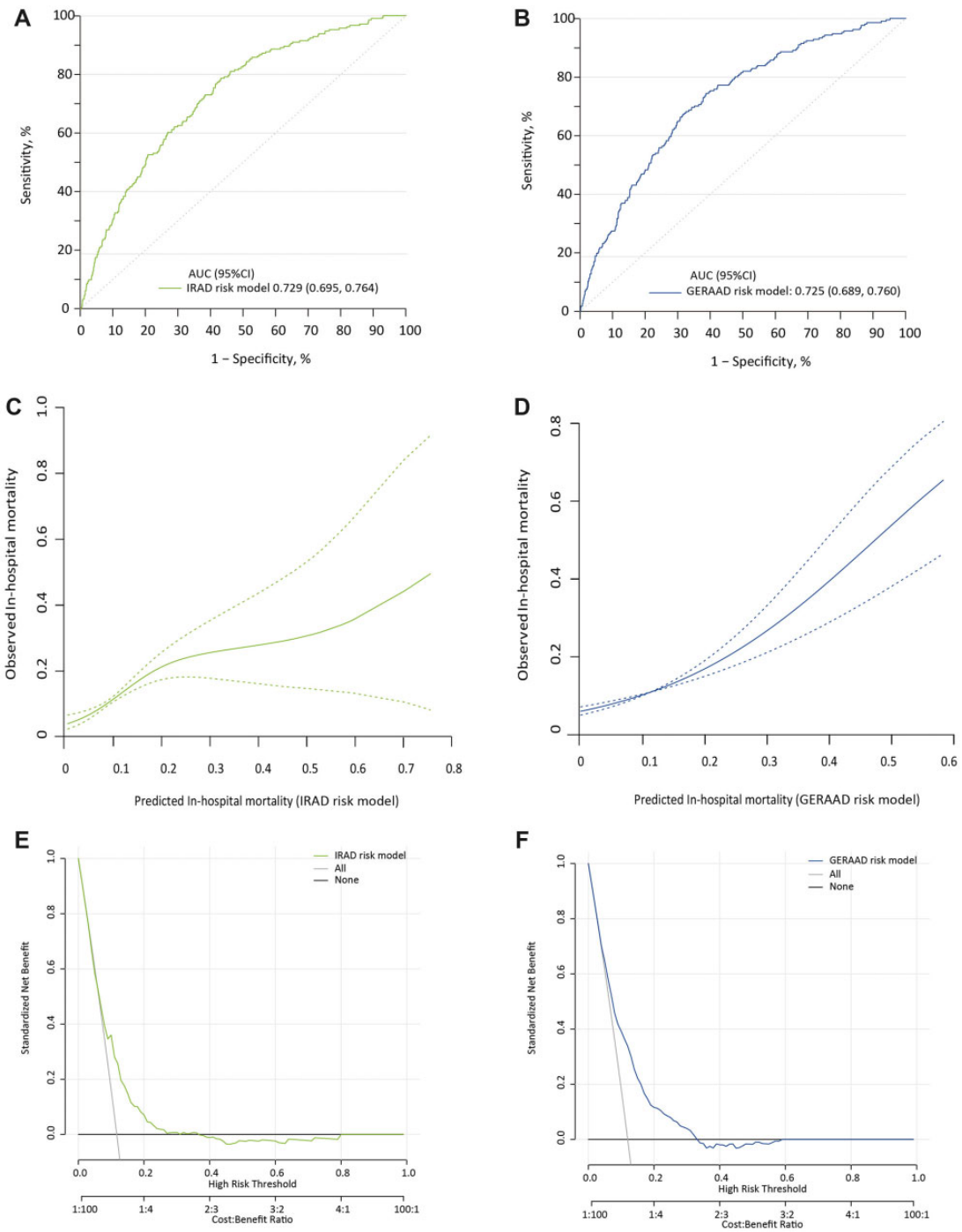


**Figure 5:** Prediction performances of currently existing models in the total cohort. (**A, B**) ROC curve of IRAD and GERAADA risk score. (**C, D**) Calibration curve of IRAD and GERAADA risk score. (**E, F**) Decision curve analysis of IRAD and GERAADA risk score. AUC: area under the receiver operating characteristic curve; CI: confidence interval; GERAAD: German Registry for Acute Aortic Dissection Type A; IRAD: International Registry of Acute Aortic Dissection; ROC: receiver operating characteristic curve.

arrest in patients at low risk was associated with a similar risk of in-hospital death ($P = 0.579$); however, hypothermic circulatory arrest in patients at middle to high risk was associated with a higher risk of in-hospital death ($P = 0.013$). Our study results suggested that low-risk patients were more tolerant to hypothermic circulatory arrest than middle to high-risk patients when we considered in-hospital deaths. These findings reinforced the fact that, for the predicted middle- to high-risk patients, a less aggressive arch repair strategy is warranted with no need for hypothermic circulatory arrest. However, a more aggressive strategy may be recommended for patients with the predicted low risk of death against the risk of future aortic events associated with less invasive aortic treatment even if hypothermic circulatory arrest is needed [37]. Studies designed to mitigate its occurrence would be of significant merit. Besides, patients who experienced hypothermic circulatory arrest had a significantly longer cardiopulmonary bypass duration than those who did not experience hypothermic circulatory arrest as a result of repairing

concomitant lesions, which could lead to increased operating time and a prolonged period of cooling or rewarming, resulting in a higher risk of operative death [19, 38, 39].

## Limitations

First, the cohort we analysed was predominantly from Chinese aortic centres; calibration may be different when applied to other environments. Second, performance was compared only with the IRAD and the GERAADA risk score and merits comparison with other risk models that were unable to be tested using our data set. Third, our 5A laboratory-based risk score model was developed retrospectively, so it is necessary to conduct a prospective study to validate the risk model. Moreover, our model involves hypothermic circulatory arrest, but we failed to collect data regarding hypothermic circulatory arrest time and temperature, which appear to be significant enhancers of postoperative adverse outcomes.

## CONCLUSION

We developed and validated a pragmatic laboratory-based model (5A laboratory-based risk score) in a large, well-characterized cohort of patients with ATAAD. Our simple integer laboratory-based risk score model utilizing variables readily available at admission might be helpful for robustly early prediction of the risk of in-hospital death in patients having ATAAD surgery. In addition, patients at low risk were more tolerant of hypothermic circulatory arrest than those at middle to high risk in terms of in-hospital death. Our findings suggest that a specific combination of inflammatory, immune, coagulation and metabolic risk stratifications provided adequate discrimination ability in predicting in-hospital death, which differentiated the tolerance to hypothermic circulatory arrest in patients with ATAAD. However, more external validation is necessary to address the generalizability of the model.

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## Data availability

All relevant data are within the manuscript and its supporting information files.

## Author contributions

**Hong Liu:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Supervision; Writing–original draft; Writing–review & editing; **Si-Chong Qian:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Supervision; Writing–original draft; Writing–review & editing; **Lu Han:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing; **Zhi-Qiang Dong:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing; **Yong-Feng Shao:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing; **Hai-Yang Li:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Supervision; Writing–original draft; Writing–review & editing; **Wei Zhang:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Supervision; Writing–original draft; Writing–review & editing; **Hong-Jia Zhang:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing.

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