IJC Heart & Vasculature 50 (2024) 101341

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Anti-inflammatory response-based risk assessment in acute type A aortic dissection: A national multicenter cohort study

Hong Liu [a,1], Bing-qi Sun [b,1], Zhi-wei Tang [a,1], Si-chong Qian [c,1], Si-qiang Zheng [d], Qing-yuan Wang [a], Yong-feng Shao [a], Jun-quan Chen [e], Ji-nong Yang [f], Yi Ding [a,*], Hong-jia Zhang [c], on the behalf of the China Additive Anti-inflammatory Action for Aortopathy & Arteriopathy (5A) Investigators

[a] Department of Cardiovascular Surgery, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, PR China
[b] Department of Cardiovascular Surgery, Teda International Cardiovascular Hospital, Tianjin 300457 PR China
[c] Department of Cardiovascular Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, PR China
[d] Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, PR China
[e] Department of Cardiovascular Surgery, Tianjin Chest Hospital, Tianjin Medical University, Tianjin 300222, PR China
[f] Department of Cardiovascular Surgery, Affiliated Hospital of Qingdao University, Qingdao 266003, PR China

ARTICLE INFO

Keywords:
Extreme gradient boosting
Type A aortic dissection
Machine learning
Operative mortality

ABSTRACT

Background: Early identification of patients at high risk of operative mortality is important for acute type A aortic dissection (TAAD). We aimed to investigate whether patients with distinct risk stratifications respond differently to anti-inflammatory pharmacotherapy.

Methods: From 13 cardiovascular hospitals, 3110 surgically repaired TAAD patients were randomly divided into a training set (70%) and a test set (30%) to develop and validate a risk model to predict operative mortality using extreme gradient boosting. Performance was measured by the area under the receiver operating characteristic curve (AUC). Subgroup analyses were performed by risk stratifications (low versus middle-high risk) and anti-inflammatory pharmacotherapy (absence versus presence of ulinastatin use).

Results: A simplified risk model was developed for predicting operative mortality, consisting of the top ten features of importance: platelet-leukocyte ratio, D-dimer, activated partial thromboplastin time, urea nitrogen, glucose, lactate, base excess, hemoglobin, albumin, and creatine kinase-MB, which displayed a superior discrimination ability (AUC: 0.943, 95 % CI 0.928–0.958 and 0.884, 95 % CI 0.836–0.932) in the derivation and validation cohorts, respectively. Ulinastatin use was not associated with decreased risk of operative mortality among each risk stratification, however, ulinastatin use was associated with a shorter mechanical ventilation duration among patients with middle-high risk (defined as risk probability >5.0 %) (β −1.6 h, 95 % CI [−3.1, −0.1] hours; P = 0.048).

Conclusion: This risk model reflecting inflammatory, coagulation, and metabolic pathways achieved acceptable predictive performances of operative mortality following TAAD surgery, which will contribute to individualized anti-inflammatory pharmacotherapy.

1. Introduction

Acute type A aortic dissection (TAAD) is a severe cardiovascular disease associated with major morbidity and mortality [1]. TAAD is characterized by damage and remodeling of the aortic media and associated with secondary inflammation, immune activation, thrombosis, and metabolic disorders, and in these patients, circulating biomarkers that reflect these pathways have been associated with future risk of mortality independent of demographics and clinical comorbidities [2]. TAAD patients routinely undergo blood tests in the Emergency Department and typically remain under clinical observation for a time that is fully compatible with biochemical assays on blood samples. Biomarkers

* Corresponding author at: Department of Cardiovascular Surgery, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, PR China.
E-mail address: yidingjph@sina.com (Y. Ding).
[1] Dr. Hong Liu, Bing-qi Sun, Zhi-wei Tang, and Si-chong Qian equally contributed to this work.

https://doi.org/10.1016/j.ijcha.2024.101341
Received 16 November 2023; Received in revised form 3 January 2024; Accepted 10 January 2024

related to TAAD might be used to predict patients with compatible symptoms to obtain prognostic risk stratification of affected patients [3,4].

Considering that these pathophysiological changes persist after treatment initiation, circulating biomarkers involving pathophysiology may be a highly beneficial tool to assist physicians in therapeutic decision-making in the complex and highly challenging scenario of TAAD [5–7]. Building a risk score based on biomarkers associated with mortality is essential for identification of risk stratification of differing responses to treatment [8,9]. Furthermore, it might provide important information for future interventions for TAAD, particularly timely initiation of anti-inflammatory pharmacotherapy in individuals with a hyperinflammatory response at surgical initiation or during the early postoperative period in addition to standardized medical care [10].

Accordingly, we developed and validated a risk model by incorporating biomarkers reflecting inflammatory, coagulopathy, and metabolic pathways to predict operative mortality of TAAD and investigated whether distinct risk stratification groups respond differently to anti-inflammatory pharmacotherapy with regard to respiratory function, as evidenced by mechanical ventilation time, in a large-scale cohort of the Chinese TAAD population.

2. Methods

2.1. Study population

The multicenter 5A cohort study (Additive Anti-inflammatory Action for Aortopathy & Arteriopathy) is an ongoing national prospective cohort study of eligible patients with aortic dissection who were consecutively enrolled at 13 Chinese cardiovascular centers (Supplement). Consecutive TAAD patients who underwent surgical repair between Jan 1, 2017, and Oct 31, 2021, with documented biomarkers of interest within six hours of hospital admission were retrospectively identified from the 5A database. This study was conducted in accordance with the Declaration of Helsinki. This study was registered with Clinical Trials. gov number NCT04398992. The Institutional Review Board (IRB) of the Aortic Collaborative Institutions involved approved the study protocol and publication of data (2021-SR-381). Patient written consent for the publication of the study data was waived by the IRB due to this retrospectively observational study.

The included patients were randomly divided into a training set (70 %) and a test set (30 %). Patient selection, data collection, and data analysis were performed in accordance with Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [11]. The work is reported in line with STROCSS criteria [12].

2.2. Data collection

Biomarkers from routine laboratory tests reflecting inflammation (leukocyte, lymphocyte), coagulopathy (platelet, D-dimer, activated partial thromboplastin time [APTT], international normalized ratio [INR]), metabolic disorders (arterial PH, PaCO2, base excess, glucose, and lactate), and organ malperfusion and/or injury (alanine transaminase, aspartate aminotransferase, albumin, urea nitrogen, creatinine, creatine kinase-MB [CK-MB] and lactic dehydrogenase [LDH]) were collected within the first 6 h of emergency admission before surgery. We also derived a novel hematological parameter, the systemic thrombo-inflammatory index (STI), which was calculated as the ratio of platelet count to leukocyte count. The central laboratories of the participating institutions were all certified by the China National Accreditation Service for Conformity Assessment of Laboratory, which allows for the accuracy and standardization of all laboratory test data for each measurement. A dedicated data coordinating center performed all data management. Prespecified clinical and laboratory demographic information was obtained from hospital charts that were reviewed by independent research personnel who were unaware of the objectives of the study.

The surgery performed for TAAD patients mainly included proximal aortic repair and extensive aortic repair. The choice of technique is primarily determined by comprehensive consideration of the condition of the individual, characteristics of the dissected aorta, and the surgeon's preferences and experiences. Total arch replacement was indicated for any of the following pathologic conditions: primary intimal tear in the arch or the descending aorta; severe arch branch vessel lesions with malperfusion; known connective tissue disorders, including Marfan syndrome; and aneurysm formation in the aortic arch (aneurysm size $>$ 40 mm). A frozen elephant trunk was implanted into the true lumen of the descending thoracic aorta distal to the left subclavian artery to prevent lower body malperfusion, and the stent and technique choice were based on aortic characteristics and operator preferences.

2.3. Outcomes

The primary outcome was operative mortality, as defined as any death, regardless of cause, occurring within 30 days after surgery in or out of the hospital and after 30 days during the same hospitalization subsequent to the operation, according to Society of Thoracic Surgeons criteria [13]. Secondary outcomes included 30-day mortality, mechanical ventilation duration, intensive care unit (ICU) length of stay, and hospital length of stay.

2.4. Strategies for model development

We used either a conventional logistic regression model or an extreme gradient boosting algorithm to develop risk models based on preoperative laboratory biomarkers and clinical characteristics for operative mortality prediction following TAAD surgery. In the logistic regression model, features with p values less than 0.15 in univariate analysis were chosen as candidate variables for multivariable logistic regression analyses to delineate the factors significantly associated with operative mortality. A p value of $<$ 0.05 was considered to be statistically significant [14].

Risk models were developed using the current state-of-the-art boosting algorithm utilized for gradient boosted decision trees (XGBoost) [15,16]. An extreme gradient boosting algorithm (XGBoost) was employed for a binary classification task based on the presence or absence of operative mortality [17]. Shapley Additive Explanation (SHAP) values are a novel way of describing the contribution of a predictor's value to an individual's overall prediction in the XGBoost model. SHAP provides a powerful method to measure the importance of features and is introduced to solve the inexplicability bug of machine-learning models. SHAP calculates each variable's contribution value to the XGBoost model. The SHAP value corresponds to the measure of additive feature attributions [18–20]. Therefore, the XGBoost model can be visually interpreted globally and locally using SHAP, thus solving the artificial intelligence "black-box" problem [15].

2.5. Model assessment and validation

We evaluated the models' discrimination ability with receiver operating characteristic (ROC) curves and calculated the area under the ROC curve (AUC) of the logistic and XGBoost models. Comparison of AUCs between them followed the method of DeLong et al. [21]. Model accuracy was evaluated using the integrated Brier score, which is the mean squared difference between the predicted probability and the actual outcome. Calibration was evaluated using a calibration curve plotting the predicted probability against the observed proportion of the outcome variable [22]. To characterize the clinical significance of these models, we also calculated the model specificity, positive predictive value (PPV), negative predictive value (NPV), and classification accuracy. In addition, we performed decision curve analysis by estimating

the net benefit of the final risk model to stratify patients relative to assuming that no patient will have an event according to a continuum of decision thresholds of risk for mortality [23,24]. We used 935 independent patients to validate the selected risk model regarding discrimination, calibration and clinical decision curve analysis estimated from the same dataset used to derive the model.

In addition, we compared the selected risk model with existing risk scores (i.e., additive and logistic EuroSCORE, Parsonnet Score, Cleveland Score, Ontario Province Risk [OPR] Score, SinoSCORE, International Registry of Acute Aortic Dissection [IRAD] score, and German Registry for Acute Type A Aortic Dissection [GERAADA] score) [25–32] in terms of discrimination.

2.6. Additional analysis

Patients with predicted risk thresholds of < 5 %, 5–10 %, and > 10 % were grouped into low, middle, or high risk, respectively, in the derivation cohort. The probability of operative mortality was calculated for each risk category, and odds ratios (ORs) were assessed by logistic regression. Subgroup analyses were performed by risk stratifications (low versus middle-high risk) and anti-inflammatory pharmacotherapy (absence versus presence of ulinastatin use after surgery).

2.7. Statistical analysis

For binary outcome measures, we hypothesized that a minimum of 10 events (i.e., patients with the defined outcome) per variable is required to prevent overfitting. The effective sample size was attained in both the derivation cohort (120 events for 10 variables) and validation cohort (60 events for 10 variables).

Continuous data are presented as medians (interquartile ranges [IQRs]) depending on the nature of the variable, and categorical data are reported as percentages (%). Logistic regression was used to evaluate ORs, with 95 % confidence intervals (CIs). In this study, features with more than 20 % missing values were excluded. Missing data were handled using multiple imputation with chained equations. We fitted the functional relationship between the STI index and operative mortality using generalized additive models and further found the optimal cutoff point, which was used to classify patients into two distinct risk probabilities defined as the point that gave the largest log-likelihood value in a 2-piecewise regression model [33]. All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing) and Python programming software (version 3.6).

3. Results

3.1. ***Patient*** *characteristics*

A total of 2175 TAAD patients were included in the derivation cohort, and 935 TAAD patients formed the validation cohort (Supplemental Fig. 1). Among 3110 patients, the median age was 50 (IQR 41–59) years, 2335 (75.1 %) were male, and the median body mass index was 25.4 (IQR 23.0–27.8) kg/m^2. Of these patients, 936 (35.1 %) presented with one of the following conditions: coronary malperfusion, renal malperfusion, cerebral malperfusion, intestinal malperfusion, or any pulse deficit/limb ischemia. Baseline, clinical, laboratory, and procedural features are reported in Table 1. In particular, a higher STI index was associated with lower risk of operative mortality (OR 0.957 [95 % CI 0.941, 0.974], P < 0.001) (Supplemental Fig. 2), with a significant threshold effect at the inflection point of 17.7 (Supplemental Table 1).

3.2. Primary and secondary outcomes

The crude incidence of operative mortality was 5.8 %, 5.5 % and 6.4 % in the overall, derivation, and validation cohorts, respectively. The crude incidence of 30-day mortality was 5.1 %, 4.8 % and 6.0 % in the overall, derivation, and validation cohorts, respectively. Among the overall cohort, the median mechanical ventilation time, ICU length of stay, and hospital length of stay were 18 (IQR 14–38) h, 30 (IQR 19–64) h, and 16 (IQR 11–21) days, respectively. The primary and secondary outcomes of the derivation and validation cohorts are shown in Table 2.

3.3. Model characteristics: discrimination, calibration, and accuracy

Based on the full clinical variables alone, we developed a clinical risk model using logistic regression and the XGBoost algorithm, which achieved AUCs of 0.634 (95 % CI 0.579, 0.693) and 0.845 (95 % CI 0.804–0.886), respectively (Fig. 1). Based on the full laboratory biomarkers alone, we developed a laboratory risk model using logistic regression and the XGBoost algorithm, which achieved AUCs of 0.700 (0.652–0.749) and 0.963 (0.945–0.980), respectively (Fig. 1). Based on the combination of the full clinical variables and laboratory biomarkers, we developed a comprehensive risk model using logistic regression and the XGBoost algorithm, which achieved AUCs of 0.725 (0.676–0.774) and 0.955 (0.931–0.979), respectively (Fig. 1). Specificity, PPV, NPV, and classification accuracy values were calculated for each model (Supplemental Tables 2, 3).

Of these six risk models, the risk model based on the laboratory biomarkers alone using the XGBoost algorithm that yielded optimal discrimination was selected as the candidate risk model. Then, we trained this final XGBoost model, named the simplified Bio-XGBoost model, with the top ten features of importance among the laboratory biomarkers, including STI index, D-dimer, APTT, urea nitrogen, glucose, lactate, base excess, hemoglobin, albumin, and CK-MB. This simplified risk model showed adequate discrimination ability, with an AUC of 0.943 (95 % CI 0.928–0.958) (Fig. 3).

We constructed a SHAP summary plot (Fig. 2, Supplemental Table 4), which plots the values of each predictor in the dataset and the corresponding SHAP value. As shown, increasing D-dimer, APTT, urea nitrogen, glucose, lactate, and CK-MB were associated with increasing SHAP values. Increasing STI index, base excess, hemoglobin, and albumin were associated with decreased risk of operative mortality. Then, a user-friendly online calculator for mortality risk prediction was generated to allow providers to estimate risk of operative mortality based on the XGBoost model. The model can be accessed at https://www.empowerstats.net/pmodel/?m=7473_RiskpredictioninATAADsurgery. A screenshot of the app is shown in Supplemental Fig. 3. The distribution characteristics of the top ten features are provided in Supplemental Fig. 4.

In the validation cohort, this simplified Bio-Xgboost risk model also achieved adequate discrimination performance, with an AUC of 0.884 (95 % CI 0.836–0.932) (Fig. 3). In the derivation and validation cohorts, the simplified Bio-Xgboost model showed adequate calibration with comparable observed and predicted mortality risk (Fig. 3). In clinical decision curve analysis, the simplified Bio-Xgboost model provided a larger net benefit across the range of mortality risks (Fig. 3).

3.4. Comparison with existing risk models

In comparison, the simplified Bio-Xgboost risk model demonstrated better discrimination for predicting operative mortality than existing risk scores (additive and logistic EuroSCORE, Parsonnet score, Cleveland score, OPR score, SinoSCORE, IRAD score, and GERRAAD score in the derivation cohort) (Fig. 4).

3.5. Subgroup analysis

With reference to the low-risk group, the middle- and high-risk groups had a significantly gradient risk of operative mortality (OR 5.676 [95 % CI 3.254, 9.900]; OR 60.575 [36.164, 101.466]; P for trend < 0.0001). In the derivation cohort, 742 (34.11 %) patients received ulinastatin as anti-inflammatory pharmacotherapy. There was similar

Table 1
Baseline and clinical characteristics and perioperative outcomes of two cohorts.

	Derivation cohort (N1 = 2175)		Validation cohort (N2 = 935)		P value
	Available data	Missing data	Available data	Missing data	
Demographic characteristics					
Age (year)	50 (41–59)	10(0.45 %)	50 (40–59)	3(0.13 %)	0.323
Sex (male)	1623 (74.6 %)	0(0 %)	712 (76.1 %)	0(0 %)	0.366
Height (cm)	172 (166–176)	40(1.83 %)	172 (165–177)	18(0.82 %)	0.581
Weight (kg)	75 (65–85)	18(0.82 %)	75 (65–83)	8(0.36 %)	0.561
Body mass index (kg/m2)	25.5 (23.0–27.8)	40(1.83 %)	25.3 (23.0–27.8)	18(0.82 %)	0.535
Clinical characteristics					
Time onset to operation (day)	1 (1–2)	0(0 %)	1 (1–2)	0(0 %)	0.521
Heart rate (bpm)	80 (76–86)	4(0.18 %)	80 (76–88)	3(0.13 %)	0.346
Mean blood pressure (mmHg)	93 (85–100)	4(0.18 %)	92 (85–98)	3(0.13 %)	0.143
Smoking n (%)	940 (44.1 %)	42(1.93 %)	385 (41.8 %)	13(0.59 %)	0.236
Drinking n (%)	467 (22.3 %)	85(3.90 %)	177 (19.6 %)	30(1.37 %)	0.088
Chronic lung disease n (%)	54 (2.5 %)	7(0.32 %)	23 (2.5 %)	1(0.04 %)	0.963
Coronary heart disease n (%)	218 (10.0 %)	1(0.04 %)	80 (8.6 %)	1(0.04 %)	0.204
Hypertension n (%)	1561 (72.2 %)	12(0.55 %)	665 (71.9 %)	11(0.50 %)	0.714
Diabetes n (%)	110 (5.1 %)	0(0 %)	55 (5.9 %)	0(0 %)	0.347
Arrhythmias n (%)	62 (2.9 %)	6(0.27 %)	23 (2.5 %)	4(0.18 %)	0.541
Congestive heart failure n (%)	13 (0.6 %)	8(0.36 %)	3 (0.3 %)	3(0.13 %)	0.322
Marfan syndrome n (%)	27 (1.2 %)	1(0.04 %)	12 (1.3 %)	0(0 %)	0.924
Previous cardiac surgery n (%)	304 (14.0 %)	0(0 %)	111 (11.9 %)	0(0 %)	0.270
Dissection characteristics					
Malperfusion[#] n (%)	626 (31.8 %)	207 (9.52 %)	257 (30.4 %)	85 (9.09 %)	0.427
Intestinal	51 (2.6 %)		25(2.9 %)		
Limb	165 (8.4 %)		61 (7.2 %)		
Cerebral	194 (9.9 %)		86 (10.2 %)		
Coronary	342 (17.4 %)		140 (16.6 %)		
Renal	272 (13.8 %)		138 (16.3 %)		
Circulation characteristics					
Aortic regurgitation n (%)		133(6.11 %)		52(2.39 %)	0.661
None	669 (32.8 %)		288 (32.6 %)		
Mild	681 (33.3 %)		278 (31.5 %)		
Moderate	269 (13.2 %)		128 (14.5 %)		
Severe	423 (20.7 %)		189 (21.4 %)		
Pericardial effusion n (%)		15(0.68 %)		5(0.22 %)	0.554
None	1914 (88.6 %)		811 (87.2 %)		
Mild	188 (8.7 %)		88 (9.5 %)		
Moderate	40 (1.9 %)		19 (2.0 %)		
Severe	18 (0.8 %)		12 (1.3 %)		
Pleural effusion n (%)		9(0.41 %)		2(0.09 %)	0.473
None	2057 (95.0 %)		876 (93.9 %)		
Minor	76 (3.5 %)		40 (4.3 %)		
Major	33 (1.5 %)		17 (1.8 %)		
LVEF (%)	62 (59–66)	156(7.17 %)	62 (59–66)	60(2.75 %)	0.547
LVEDD (mm)	50 (46–55)	156(7.17 %)	50 (46–55)	60(2.75 %)	0.775
Hypotension or shock n (%)	28 (1.3 %)	0(0 %)	14 (1.5 %)	0(0 %)	0.642
Biomarkers					
Leukocyte (×109/L)	8.5 (6.2–12.0)	(0 %)	8.5 (6.3–12.0)	0(0 %)	0.599
Platelet (×109/L)	195 (158–238)	(0 %)	190.5 (155–232)	0(0 %)	0.163
Hemoglobin (g/L)	138 (126–149)	15(0.68 %)	139 (126–150)	8(0.36 %)	0.344
Creatine kinase-MB (ng/ml)	1.3 (0.8–2.3)	42(1.93 %)	1.2 (0.8–2.3)	16(0.73 %)	0.603
Lactic dehydrogenase (u/L)	194 (163–240)	568(26.11 %)	194 (164–236)	240(11.03 %)	0.841
Lactate (mmol/L)	1.4 (1.0–1.9)	235(10.80 %)	1.3 (1.0–1.9)	111(5.10 %)	0.909
Alanine transaminase (u/L)	19 (14–31)	26(1.19 %)	19 (14–29)	7(0.32 %)	0.644
Aspartate aminotransferase (u/L)	20 (16–27)	26(1.19 %)	20 (16–26)	7(0.32 %)	0.677
Albumin (g/L)	40.3 (37.2–43.1)	66(3.03 %)	40.3 (37.1–43.3)	23(1.05 %)	0.843
Blood urea nitrogen (mmol/L)	5.9 (4.7–7.4)	33(1.51 %)	5.9 (4.8–7.5)	14(0.64 %)	0.632
Creatinine (μmoI/L)	75 (63–91)	21(0.96 %)	76 (63–91.	9(0.41 %)	0.228
STI index	23.5 (14.6–34.2)	0(0 %)	22.5 (14.1–34.2)	0(0 %)	0.401
Lymphocyte (×109/L)	1.00 (0.63–1.42)	30 (1.38 %)	1.03 (0.69–1.47)	18 (1.93 %)	0.655
Platelet-lymphocyte ratio	159 (109–250)	30 (1.38 %)	165 (115–249)	18 (1.93 %)	0.268
SII index	1582 (660–3602)	86 (3.95 %)	1550 (732–306)	37 (3.96 %)	0.546
APPT (s)	30.6 (28.3–33.2)	50(2.29 %)	30.4 (28.2–32.7)	25(1.14 %)	0.293
PH	7.42 (7.40–7.44)	201(9.24 %)	7.42 (7.40–7.44)	93(4.27 %)	0.536
INR	1.07 (1.01–1.16)	29(1.33 %)	1.06 (1.01–1.14)	14(0.64 %)	0.073
$PaCO_2$ (mmHg)	35 (32–38)	201(9.24 %)	35 (32–38)	94(4.32 %)	0.811
Base excess (mmol/l)	−0.7 (-2.1–0.9)	203(9.33 %)	−0.8 (-2.0–0.7)	93(4.27 %)	0.699
Glucose (mmol/l)	6.0 (5.0–7.5)	43(1.97 %)	6.0 (5.0–7.4)	15(0.68 %)	0.610
D-Dimer (μg/ml)	7.1 (1.9–21.2)	66(3.03 %)	6.8 (1.8.5–23.6)	25(1.14 %)	0.602

Data are n (%) or median (IQR), unless otherwise specified.
APTT: activated partial thromboplastin time; LVEDV: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; INR: international normalized ratio; APTT: activated partial prothrombin time.
STI index: systemic thrombo-inflammatory index, which was calculated via platelet count / leukocyte count in peripheral blood.
SII index: Systemic inflammatory-immune index, which was calculated via neutrophil count × platelet count/ lymphocyte count in peripheral blood.

[#] Defined as one of the following conditions: coronary malperfusion, renal malperfusion, cerebral perfusion, spinal/lumbar, intestinal and limb ischemia.

Table 2
Procedural characteristics and perioperative outcomes of derivation and validation cohorts.

	Derivation cohort	Validation cohort
Procedural variables		
Aortic valve replacement (%)	67 (3.1 %)	39 (4.2 %)
Bentall (%)	786 (36.1 %)	356 (38.1 %)
David (%)	34 (1.6 %)	12 (1.3 %)
Total arch replacement + FET implantation (%)	1057 (48.6 %)	445 (47.6 %)
Hemi-arch replacement (%)	881 (40.5 %)	379 (40.5 %)
Total arch replacement (%)	1294 (59.5 %)	556 (59.5 %)
Inclusion technique (%)	1541 (70.9 %)	652 (69.7 %)
Concomitant CABG (%)	189 (8.7 %)	66 (7.1 %)
Concomitant valve surgery (%)	97 (4.5 %)	47 (5.0 %)
Cardiopulmonary bypass time (min)	171 (136–206)	172 (137–205)
Aortic cross-clamp time (min)	99 (76–125)	98 (78–119)
Circulatory arrest of lower body (%)	1410 (65.0 %)	611 (65.4 %)
Circulatory arrest time (min)	23 (18–30)	22 (17–29)
Perioperative outcomes		
Operative mortality (%)	120 (5.5 %)	60 (6.4 %)
30-day mortality (%)	104 (4.8 %)	56 (6.0 %)
Mechanical ventilation time (hrs)	18 (14–38)	18 (14–37)
ICU stay (hrs)	29 (19–63)	31 (19–67)
Hospital stay (days)	16 (11.0–22.0)	15 (11–21)

Data are n (%) or median (IQR), unless otherwise specified.
FET = frozen elephant trunk; CABG = coronary artery bypass grafting; ICU: intensive care unit.

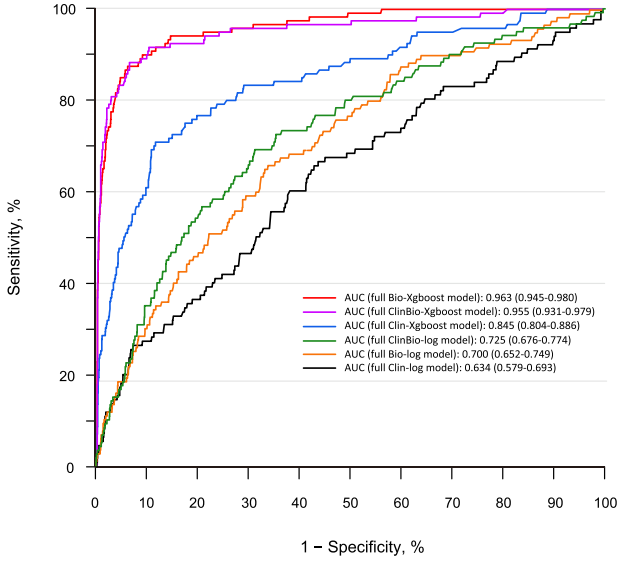

Fig. 1. Performance of the risk models in the derivation cohort AUC: area under the receiver operating characteristic curve.

operative mortality between the absence and presence of ulinastatin use both in patients at low risk (OR 1.038 [95 % CI 0.774, 1.392]; p = 0.803) and at middle-high risk (OR 0.971 [95 % CI 0.568, 1.660]; P = 0.914). However, ulinastatin use was not associated with shorter mechanical ventilation duration in the low-risk subgroup (β −2.8 h, 95 % CI [-28.9, 23.2] h; P = 0.828) but was significantly associated with shorter ventilation duration in the middle-high risk subgroups (β −1.6 h, 95 % CI [-3.1, −0.1] h; P = 0.048).

4. Discussion

In the present study, we developed and validated a risk model to predict operative mortality risk in a large, real-world cohort of TAAD patients from China. In brief, the simplified Bio-Xgboost risk model, specifically integrating inflammatory, coagulation, and metabolic biomarkers, demonstrated adequate performance. In addition, our simplified Bio-Xgboost model significantly outperformed existing risk scores. Patients with different risk probabilities of operative mortality responded differently to anti-inflammatory pharmacotherapy, with evidence of shorter mechanical ventilation duration uniquely among those at middle-high risk rather than those at low risk. This novel risk model (available as a web-based tool) will be useful for stratifying TAAD patients according to individual risk probability of operative mortality and will advance knowledge of targeted anti-inflammatory pharmacotherapy.

Independent of the dissected aorta, pathophysiological catastrophe involving inflammation, immunity, coagulation, and metabolism is a major cause of adverse outcomes at surgical initiation and during postoperative care in TAAD patients [34–36]. Biomarkers reflecting the aforementioned pathways are significantly associated with risk of early mortality following TAAD surgery [3–6]. By integrating these biomarkers, we developed and initially validated a biomarker-based risk model for operative mortality prediction in a large-scale Chinese cohort. Our data suggest that there is a critical need for novel approaches in TAAD patients, particularly with respect to initiating targeting inflammation action for patients at high risk, in addition to universal treatment guidelines.

Specifically, we found that a panel of laboratory biomarkers alone displayed better discrimination ability than the combination of biomarkers and clinical characteristics. This is not entirely unexpected. In clinical practice, biomarkers have been used to indicate the presence of complications and the severity of pathophysiology [37,38], with potential usefulness for early prognosis of severe and fatal TAAD and improving management of severe cases. However, the clinical variables included in the model are vulnerable to variations between practicing physicians. Measurement of the biomarkers reported herein may help to identify persons at high risk of operative mortality following TAAD surgery. Identifying inflammatory, thromboplastic, and metabolic processes that are associated with operative mortality risk in treated TAAD patients may help in the development of more effective therapeutic schedules [39,40].

Previous studies have revealed that TAAD is usually complicated with acute lung injury (ALI), which is a pivotal driver and risk factor for early mortality [41,42]. The inflammatory response plays an important role in the pathogenesis of ALI in TAAD patients. Therefore, taking anti-inflammatory action likely contributes to attenuating ALI and improving pulmonary function. A recent randomized controlled trial found that ulinastatin use significantly reduces ALI after surgical repair [43]. Our subgroup analysis showed that patients at middle-high risk are more likely to benefit from ulinastatin use, as evidenced by shorter mechanical ventilation support duration. However, prevention and management of inflammatory injury during TAAD remains a great challenge. The definite pathogenesis should be clearly clarified, and further investigations should be performed to identify more potential therapeutic approaches for early intervention to prevent inflammation-related damage [44,45].

4.1. Strengths and limitations

The large sample size and multicenter nature of the cohort studied and the careful clinical, radiologic, functional, and biologic characterizations are clear strengths of this study. However, several potential

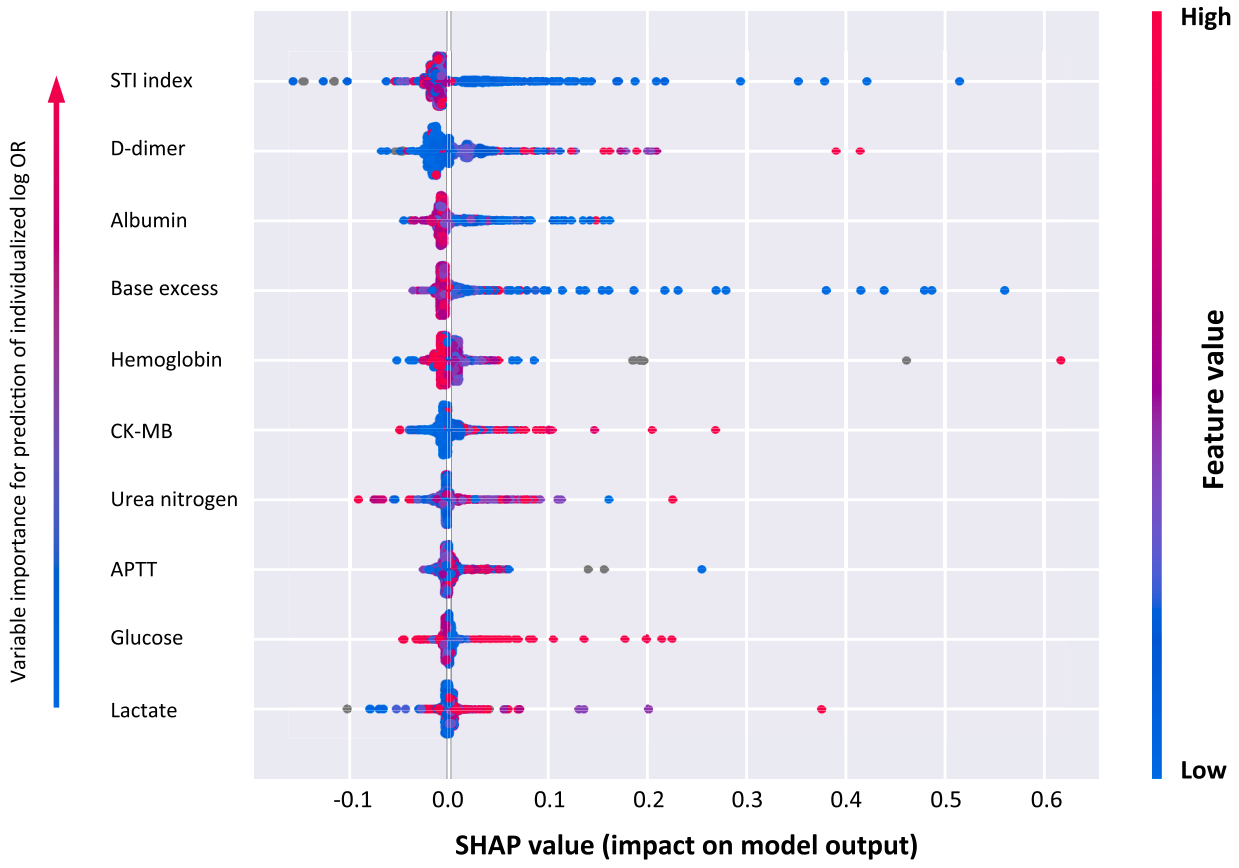

Fig. 2. SHAP summary plot of the Bio-Xgboost risk model This is a plot of the values for each predictor and the corresponding SHAP value for each predictor. The main motivation for this plot is to provide an intuitive display for how increasing predictor values can influence the Bio-Xgboost model's prediction. SHAP values above 0 indicate that the outcome is more likely because of the predictor value, and SHAP values below 0 indicate that the outcome is less likely because of the predictor value. Overlapping points are jittered in the y-axis direction to indicate the distribution of values in that area. STI: systemic thrombo-inflammatory index, APTT: activated partial thromboplastin time; CK-MB: creatine kinase-MB, SHAP: Shapley Additive Explanation.

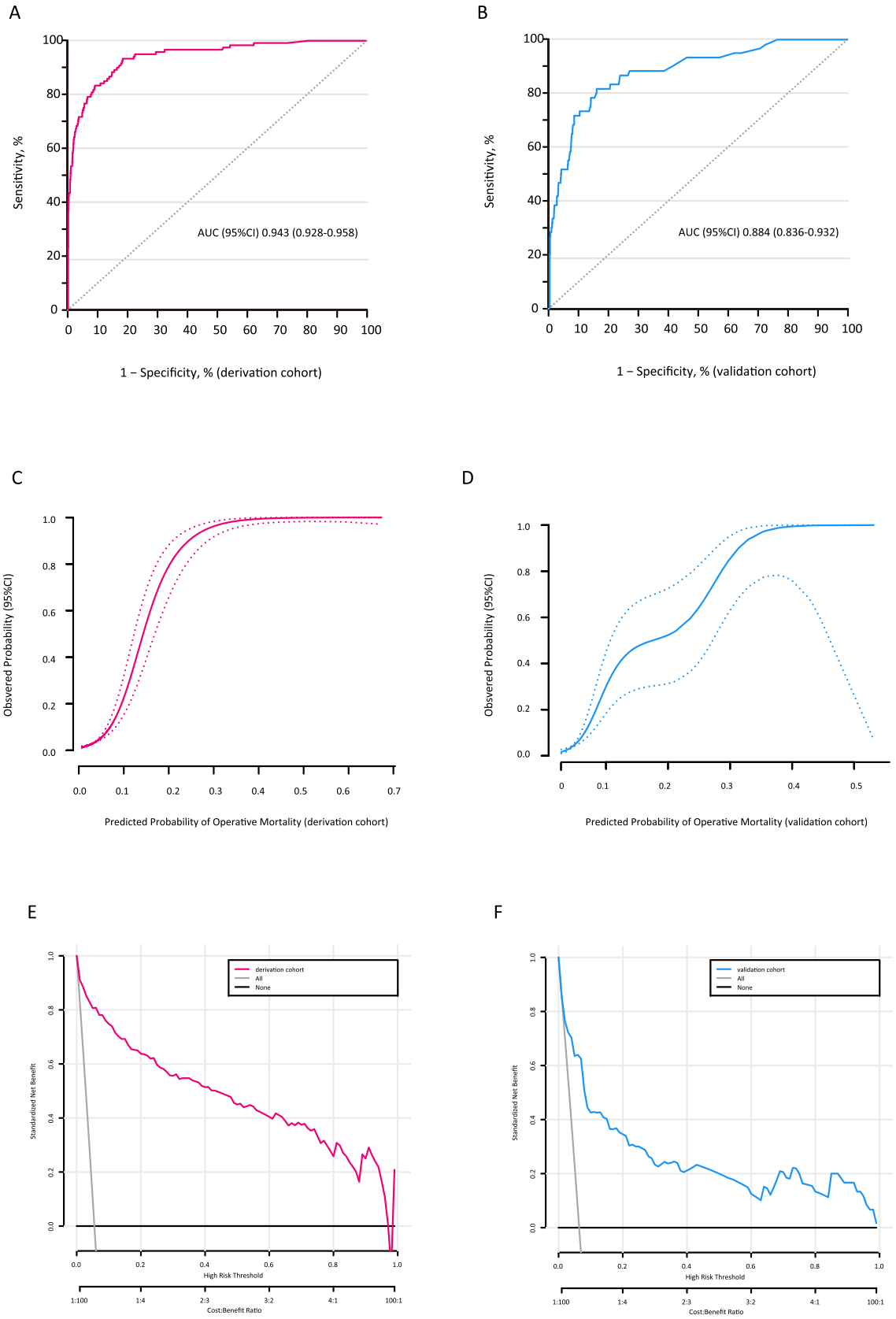

Fig. 3. Performances of the Bio-Xgboost risk model in the derivation and validation cohorts A, AUC of the Bio-Xgboost model in the derivation cohort; B, AUC of the Bio-Xgboost model in the validation cohort; C, calibration curve of the Bio-Xgboost model in the derivation cohort; D, calibration curve of the Bio-Xgboost model in the validation cohort; E, decision curves of the Bio-Xgboost model in the derivation cohort; F, decision curves of the Bio-Xgboost model in the validation cohort. AUC: area under the receiver operating characteristic curve.

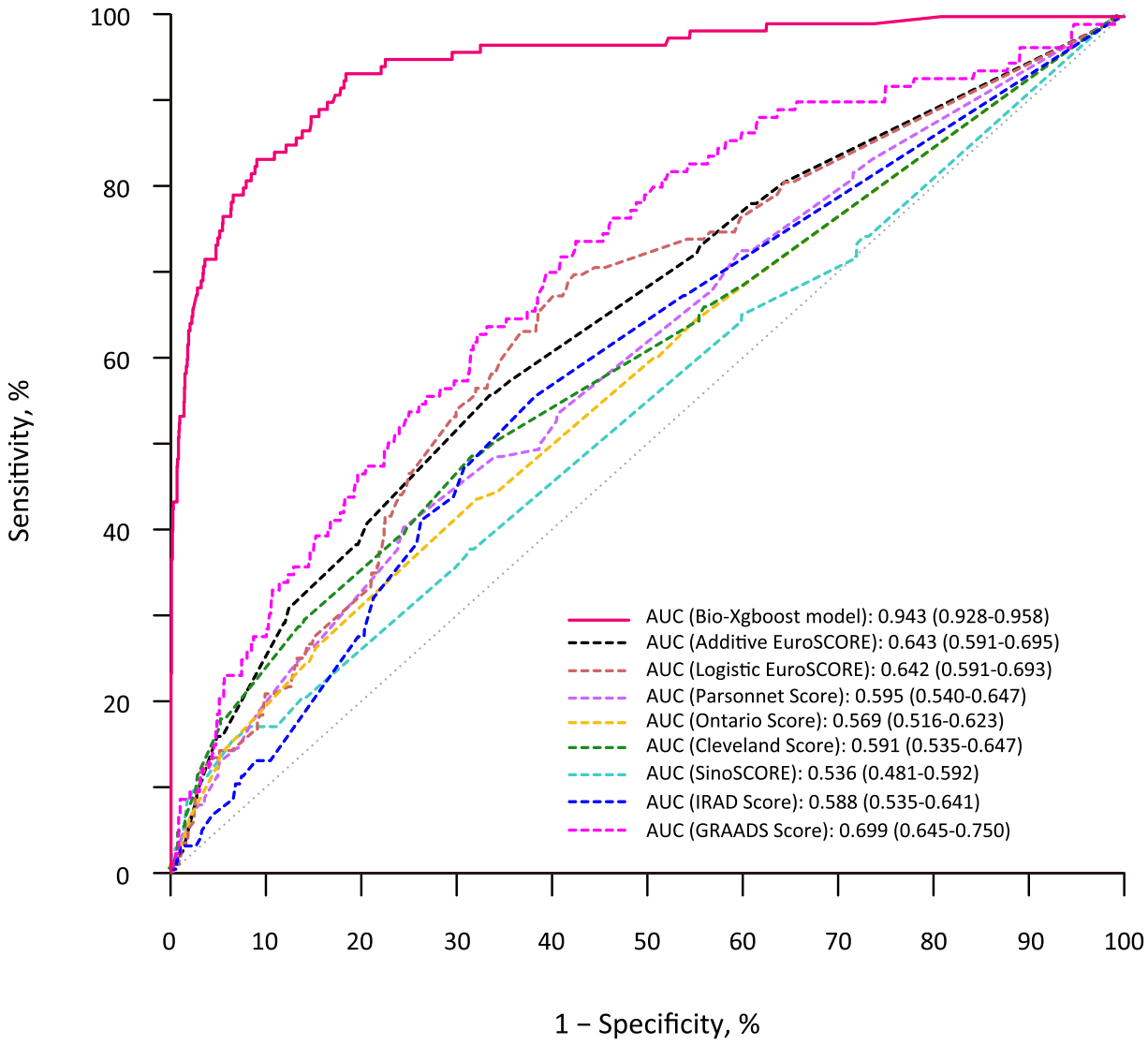

Fig. 4. Performance of the currently existing clinical risk scores in the validation cohort AUC: area under the receiver operating characteristic curve.

limitations deserve comment. One limitation of our study is the incompleteness of datasets based on clinical practice. While we obtained a large dataset for each patient, it is important to note that the data were not always complete or ideal. The panel of clinical predictors studied includes baseline demographic, clinical and echocardiographic, and imaging parameters. These variables cover most but not all clinical risk factors identified thus far. For instance, we did not include coronary angiography or cerebral perfusion imaging in the analysis because they are not routinely examined in clinical emergency settings; it is possible that other factors that were not tested would have provided additional prognostic information. In addition, specific mortality, such as cardiac, pulmonary, and renal death other than all-cause mortality, was not collected and requires future investigation. There are differences in the definition of endpoints and follow-up durations between the additive and logistic EuroSCORE, Parsonnet Score, Cleveland Score, OPR Score, SinoSCORE, IRAD score, and GERRAAD Score and our risk model, which must be interpreted in the context of the observed difference in prediction performances. Last, because our study population was very homogenous and may differ from those of other countries and regions, potentially limiting the generalizability of these results to other institutions, our findings need to be confirmed in a different population in the future.

5. Conclusion

In this study, we developed a contemporary risk model based on specific combinations of inflammatory, coagulation, and metabolic biomarkers through the machine learning algorithm XGBoost that accurately discriminated risk of operative mortality for TAAD patients. Importantly, TAAD patients at middle-high risk appear to benefit more from anti-inflammatory pharmacotherapy than those at low risk, as evidenced by shorter mechanical ventilation time following surgery, suggesting that preoperative risk stratifications may contribute to targeted inflammation treatment. Further research is needed to confirm our findings.

Funding

This work was supported by Jiangsu Province Capability Improvement Project through Science, Technology and Education (ZDXK202230), National Natural Science Foundation of China (82000305), and Public Welfare Project of Nanjing Medical University Alliance for Specific Diseases (JZ23349020230306).

Author Contributions

HL and YD had the idea of the study, conceptualized the research aims, HL, SCQ and YD design the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the acquisition of data, HL YD, and SCQ doing the statistical analysis, HL wrote the first draft of the paper, and other authors provided comments and approved the final manuscript.

Registration number Clinical Trials. gov number NCT04398992.

Availability of Data and Material

Not applicable.

Code Availability

Not applicable.

IRB Information

This study was registered with Clinical Trials. gov number NCT04398992. The Institutional Review Board (IRB) of the Aortic Collaborative Institutions involved approved the study protocol and publication of data (2021-SR-381).

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

CRediT authorship contribution statement

Hong Liu: Validation, Supervision, Software, Resources, Investigation, Data curation, Conceptualization. **Bing-qi Sun:** Project administration, Methodology, Data curation. **Zhi-wei Tang:** Writing – review & editing, Software. **Si-chong Qian:** Methodology, Investigation, Formal analysis. **Si-qiang Zheng:** Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation. **Qing-yuan Wang:** Software. **Yong-feng Shao:** Methodology. **Jun-quan Chen:** Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Ji-nong Yang:** Validation, Writing – review & editing. **Yi Ding:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology. **Hong-jia Zhang:** Validation, Resources, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101341.

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