REPORT

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Inflammatory risk stratification individualizes anti-inflammatory pharmacotherapy for acute type A aortic dissection

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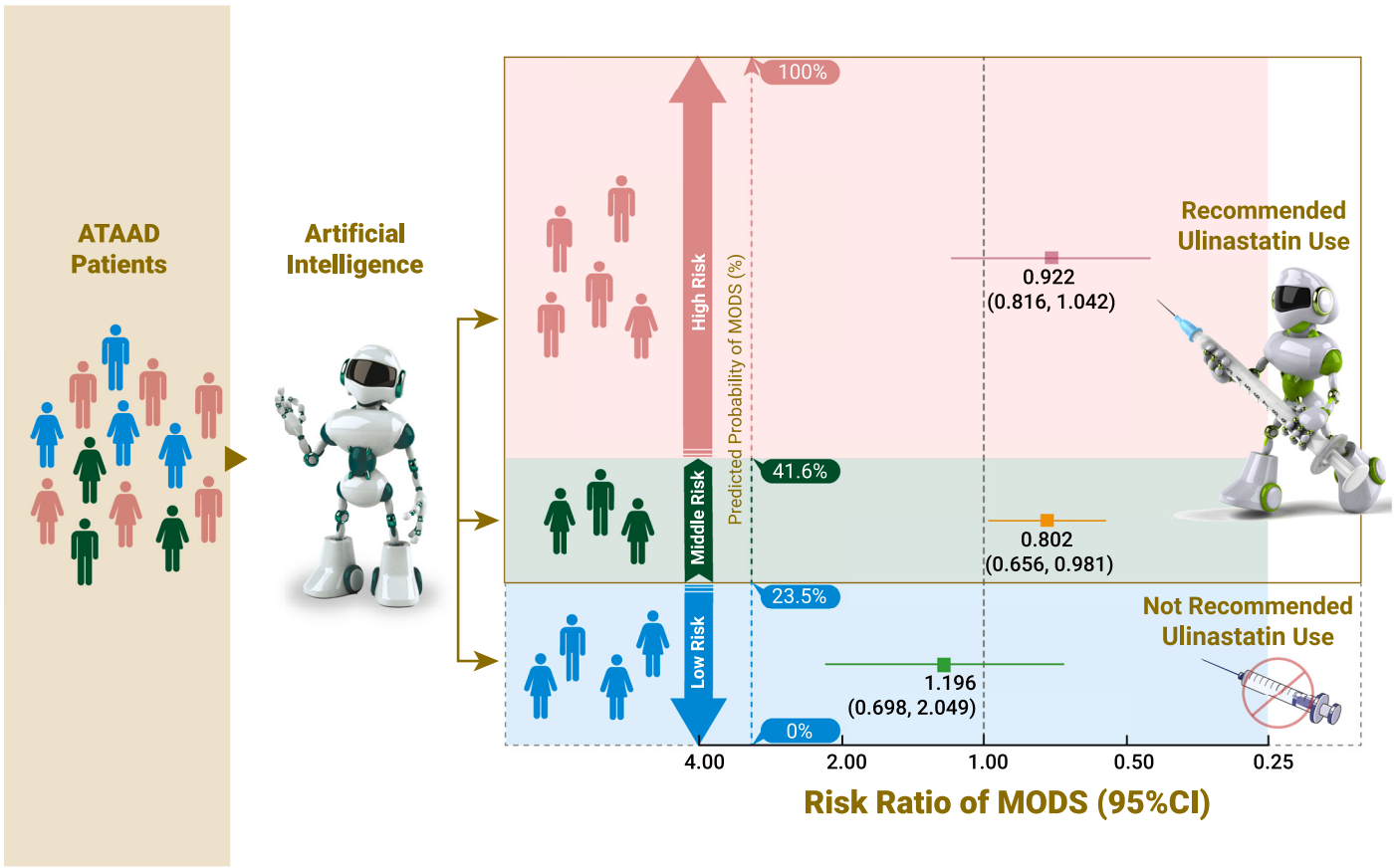
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- An inflammatory risk model is developed to predict multiple organ dysfunction syndrome (MODS) after acute type A aortic dissection (ATAAD) surgery
- The differences in inflammatory risk probabilities likely modify the association between ulinastatin use and MODS after ATAAD surgery
- Inflammatory risk stratification can help individualize anti-inflammatory pharmacotherapy, highlighting the need for precision theranostics in ATAAD surgery

REPORT

Inflammatory risk stratification individualizes anti-inflammatory pharmacotherapy for acute type A aortic dissection

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The systemic benefits of anti-inflammatory pharmacotherapy vary across cardiovascular diseases in clinical practice. We aimed to evaluate the application of artificial intelligence to acute type A aortic dissection (ATAAD) patients to determine the optimal target population who would benefit from urinary trypsin inhibitor use (ulinastatin). Patient characteristics at admission in the Chinese multicenter 5A study database (2016–2022) were used to develop an inflammatory risk model to predict multiple organ dysfunction syndrome (MODS). The population (5,126 patients from 15 hospitals) was divided into a 60% sample for model derivation, with the remaining 40% used for model validation. Next, we trained an extreme gradient-boosting algorithm (XGBoost) to develop a parsimonious patient-level inflammatory risk model for predicting MODS. Finally, a top-six-feature tool consisting of estimated glomerular filtration rate, leukocyte count, platelet count, De Ritis ratio, hemoglobin, and albumin was built and showed adequate predictive performance regarding its discrimination, calibration, and clinical utility in derivation and validation cohorts. By individual risk probability and treatment effect, our analysis identified individuals with differential benefit from ulinastatin use (risk ratio [RR] for MODS of RR 0.802 [95% confidence interval (CI) 0.656, 0.981] for the predicted risk of 23.5%–41.6%; RR 1.196 [0.698–2.049] for the predicted risk of <23.5%; RR 0.922 [95% CI 0.816–1.042] for the predicted risk of >41.6%). By using artificial intelligence to define an individual's benefit based on the risk probability and treatment effect prediction, we found that individual differences in risk probability likely have important effects on ulinastatin treatment and outcome, which highlights the need for individualizing the selection of optimal anti-inflammatory treatment goals for ATAAD patients.

INTRODUCTION

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular disease with high mortality rates.[1,2] In addition, aortic dissection itself usually triggers a potentially lethal inflammatory response, and use of cardiopulmonary bypass (CPB) as well as surgical procedures and anesthetization further provoke activation and release of proinflammatory cytokines and then exacerbate the systemic inflammatory response, leading to systemic inflammatory response syndrome (SIRS) and subsequent multiple organ dysfunction syndrome (MODS).[3,4] Inflammation runs through the onset, development, and progression of aortic dissection, which provides us with new insights into inflammatory risk stratification and anti-inflammatory pharmacotherapy.[2,5]

Ulinastatin, a glycoprotein acting as a urinary trypsin inhibitor, has been proven to have anti-inflammatory activity by inhibiting the release of pro-inflammatory cytokines and elastase from macrophages and neutrophils to suppress the systemic inflammatory response, resulting in attenuation of postoperative organ dysfunction.[6–8] However, its protective effects in cardiac surgery with CPB are still controversial. These discordant findings might suggest that the benefits of ulinastatin use depend on the differing risk profile of each patient.[8–11]

In this Chinese multicenter 5A study, we aimed to test our hypothesis that ATAAD patients who receive surgical repair receive differential systemic benefits from anti-inflammatory treatment depending on risk stratification before surgery. Using participant-level data, we applied extreme gradient boosting (XGBoost) to develop and validate an inflammatory risk model to stratify ATAAD patients at varying risk of MODS and then to evaluate its ability to identify ATAAD patients who benefitted from anti-inflammatory treatment.

METHODS

Study design and ethical approval

The Chinese Additive Anti-inflammatory Action for Aortopathy & Arteriopathy (5A) registry study is an ongoing prospective, multicenter cohort registry (15 hospitals in the regions of China) designed to collect data on the clinical backgrounds and outcomes of patients hospitalized for aortic dissection since January 2016. This study was conducted in accordance with the Declaration of Helsinki and registered in ClinicalTrials.Gov: NCT04398992. The institutional review board of each institution approved this study (2021-SR-381). Patient written consent for publication of the study data was waived because it is a retrospective observational study. Patient selection, data collection, and data analysis were performed in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[12,13]

Patient selection

From January 2016 to May 2022, consecutive patients with ATAAD hospitalized through the emergency department at participating hospitals were retrospectively identified from the

Table 1. Patient characteristics, procedural data, and outcomes in the derivation and validation cohorts

	Derivation (N = 3067)	Validation (N = 2059)	p Value
Demography			
Age (year)	52 (42–60)	52 (43–61)	0.133
Sex male (%)	2,264 (73.8%)	1,490 (72.4%)	0.269
Height (cm)	170 (165–175)	170 (165–175)	0.448
Weight (kg)	75 (65–84)	74 (65–82)	0.228
BMI, kg/m2	25.5 (22.9–28.0)	25.4 (22.9–27.8)	0.631
Medical history			
Current smoking (%)	1,316 (43.4%)	844 (41.41%)	0.160
Current alcohol drinking (%)	758 (25.3%)	482 (24.0%)	0.280
Hypertension (%)	2,249 (73.3)	1,517 (73.7%)	0.732
Diabetes mellitus (%)	161 (5.3%)	120 (5.8%)	0.366
Arrhythmia (%)	118 (3.9%)	107 (5.2%)	0.021
Stroke (%)	171 (5.6%)	112 (5.4%)	0.828
Chronic lung diseases (%)	88 (2.9%)	64 (3.1%)	0.622
Coronary heart disease (%)	287 (9.3%)	204 (9.9%)	0.699
Malperfusion[a] (%)	905 (29.5%)	647 (31.4%)	0.149
Laboratory profiles			
Hemoglobin (g/L)	134 (119–146)	135 (119–147)	0.493
Leukocyte ($\times 10^9$/L)	9.87 (6.97–13.29)	9.68 (6.83–12.93)	0.204
Platelet ($\times 10^9$/L)	183 (145–226)	181 (142–228)	0.700
Aspartate aminotransferase (U/L)	22.0 (17.0–34.0)	21.3 (17.0–31.8)	0.013
Alanine aminotransferase (U/L)	22.0 (14.4–36.0)	20.8 (14.0–33.0)	0.082
De Ritis ratio	1.06 (0.79–1.44)	1.07 (0.81–1.44)	0.252
Albumin (g/L)	39.9 (36.6–42.7)	40.0 (36.8–43.0)	0.158
Creatinine (μmol/L)	78.3 (64.7–100.9)	77.5 (63.7–98.0)	0.077
Blood urea nitrogen (mmol/L)	6.3 (4.9–8.2)	6.2 (4.9–8.0)	0.143
eGFR (mL/min/1.73 m^2)	102.1 (75.6–130.6)	101.5 (76.7–129.8)	0.745
Procedural variables			
Root procedures (%)			0.556
Root repair	308 (10.0%)	208 (10.1%)	
Aortic valve replacement only	120 (3.9%)	84 (4.1%)	
Root replacement	1015 (33.1%)	642 (31.2%)	
Bentall	935 (30.5%)	612 (29.7%)	
David	42 (1.4%)	26 (1.3%)	
Arch procedure			0.467
Hemi-arch replacement	293 (9.6%)	207 (10.1%)	
Total arch replacement	1,895 (61.8%)	1,236 (60.1%)	
Total arch replacement and FET implantation (%)	1,860 (60.6%)	1,216 (59.1%)	0.270
Concomitant CABG (%)	231 (7.5%)	129 (6.3%)	0.083
Concomitant valve surgery (%)	107 (3.5%)	83 (4.0%)	0.311
Inclusion technique (%)	1,550 (50.5%)	1,013 (49.2%)	0.362
Outcomes			

(*Continued on next page*)

Table 1. *Continued*

	Derivation (N = 3067)	Validation (N = 2059)	p Value
MODS (%)	850 (27.7%)	617 (29.9%)	0.077
In-hospital mortality (%)	262 (8.5%)	178 (8.7%)	0.891
30-day mortality (%)	237 (7.7%)	154 (7.5%)	0.749
ICU stay (days)	2.0 (1–6.0)	2.0 (1–6.0)	0.955
Mechanical ventilation time (h)	21.0 (15.0–59.0)	21.0 (15.0–60.7)	0.825
Hospital stay (days)	16.0 (12.0–23.0)	17.0 (12.0–23.0)	0.093

Data are n (%) or median (IQR). eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting; FET, frozen elephant trunk; MODS, multiple organ dysfunction syndrome; ICU, intensive care unit.
[a]Defined as one of the following conditions: coronary, renal, cerebral, spinal, intestinal, and limb malperfusion.

Chinese 5A study at their first admission and then followed after discharge. The diagnosis of aortic dissection (AD) was made by aortic computed tomography (CT) angiography at the initial presentation. Patients 18 years of age or older were included if they underwent aortic surgery within 14 days from symptom onset to hospital arrival. Key criteria for exclusion included type B AD, recurrent AD, traumatic AD, iatrogenic AD, and chronic aortic aneurysm.

Surgical procedure

Usually, total arch replacement was indicated in 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. If the dissection extended beyond the distal arch to close the false lumen, then the intimal tear was located in the proximal descending aorta to cover the intimal tear, or a very narrow true lumen was found in the distal thoracic or abdominal aorta to prevent lower-body malperfusion.[14] However, the choice of which technique is ultimately used is primarily based on comprehensive consideration of the surgeon's preference and experience, the patient's condition, and the characteristics of the dissected aorta.

Data collection

Patient information obtained included demographic data, medical history and risk factors, baseline characteristics, surgical procedures, pharmacotherapeutics, critical care, and discharge (Table S1). Cigarette smoking was defined as 1 cigarette or more per day in the last 6 months, the habits of which were categorized into current smoker versus noncurrent smoker. Alcohol consumption was defined as at least once per week, the habits of which were classified as current drinker versus noncurrent drinker. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as resting systolic blood pressure (SBP) of 140 mm Hg or greater and/or diastolic blood pressure (DBP) of 90 mm Hg or greater or defined by use of antihypertensive drugs, according to the JNC-7 guidelines. Diabetes mellitus was defined as fasting plasma glucose of 7.0 mmol/L or greater or defined by taking hypoglycemic medications. Arrhythmia was identified for those with a history of persistent arrhythmia or defined based on past electrocardiogram (ECG) or ECG examination findings on this hospital admission. Renal function was estimated by the estimated glomerular filtration rate (eGFR), calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The De Ritis ratio was calculated by dividing the serum aspartate transaminase (AST) level by the serum alanine transaminase (ALT) level. Malperfusion was evaluated based on clinical manifestations, physical examination, laboratory tests, and imaging examination, defined as one of the following conditions: coronary, renal, cerebral, spinal, intestinal, and limb malperfusion. We calculated the annual and total number of cases (volume) performed by the responsible cardiovascular center. All central laboratories at participating sites have been recognized and certified by the China National Accreditation Service for Conformity Assessment of Laboratory. Ulinastatin (TECHPOOL Biopharma, Guangzhou, China) was injected intravenously with 100,000 U once every 8 h until ICU discharge. Because this is a retrospective study, the actual ulinastatin usage and dosage mainly depended on the individual physician's preference and experience, each institute's practices and conventions, and/or resource availability in each setting.

Clinical outcomes

The primary outcome was MODS as a binary variable, defined as dysfunction of two or more organs (involving the respiratory, cardiovascular, renal, hepatic, gastrointestinal, hematological, and central nervous system) following surgical repair, measured within

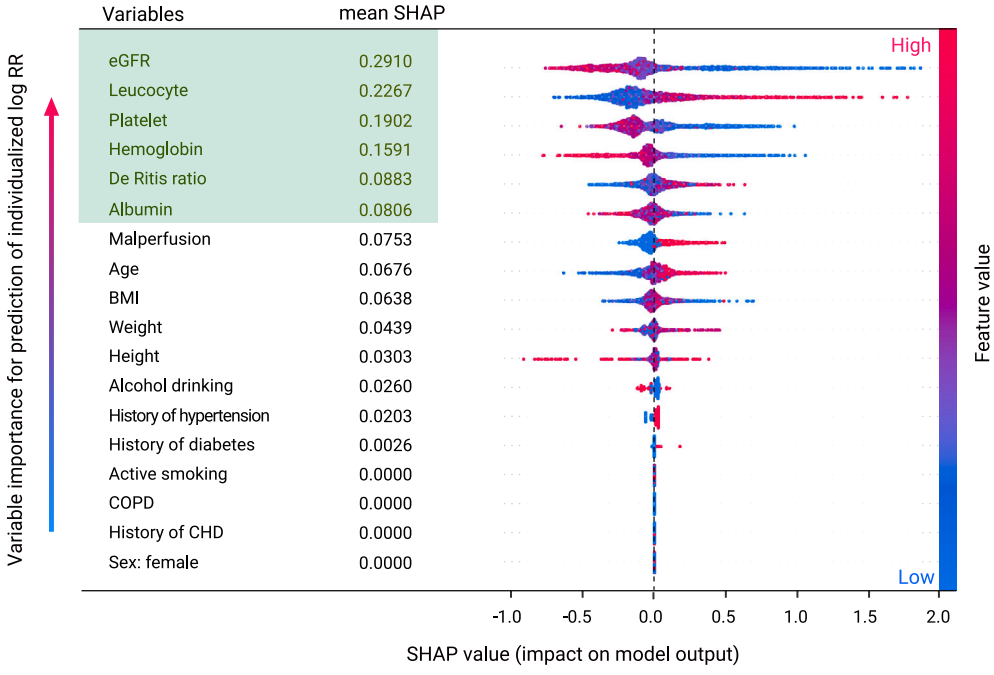

Figure 1. SHAP summary plot of the risk model
SHAP values above 0 indicate that the outcome is made more likely because of the predictor value, and SHAP values below 0 indicate that the outcome is made less likely because of the predictor value. The y axis represents the features included in model development (in descending order of importance), and the x axis indicates the change in prediction. The gradient color denotes the original value for that variable, with each point representing an individual participant. eGFR, estimated glomerular filtration rate; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; RR, risk ratio; MODS, multiple organ dysfunction syndrome; SHAP, Shapley additive explanation.

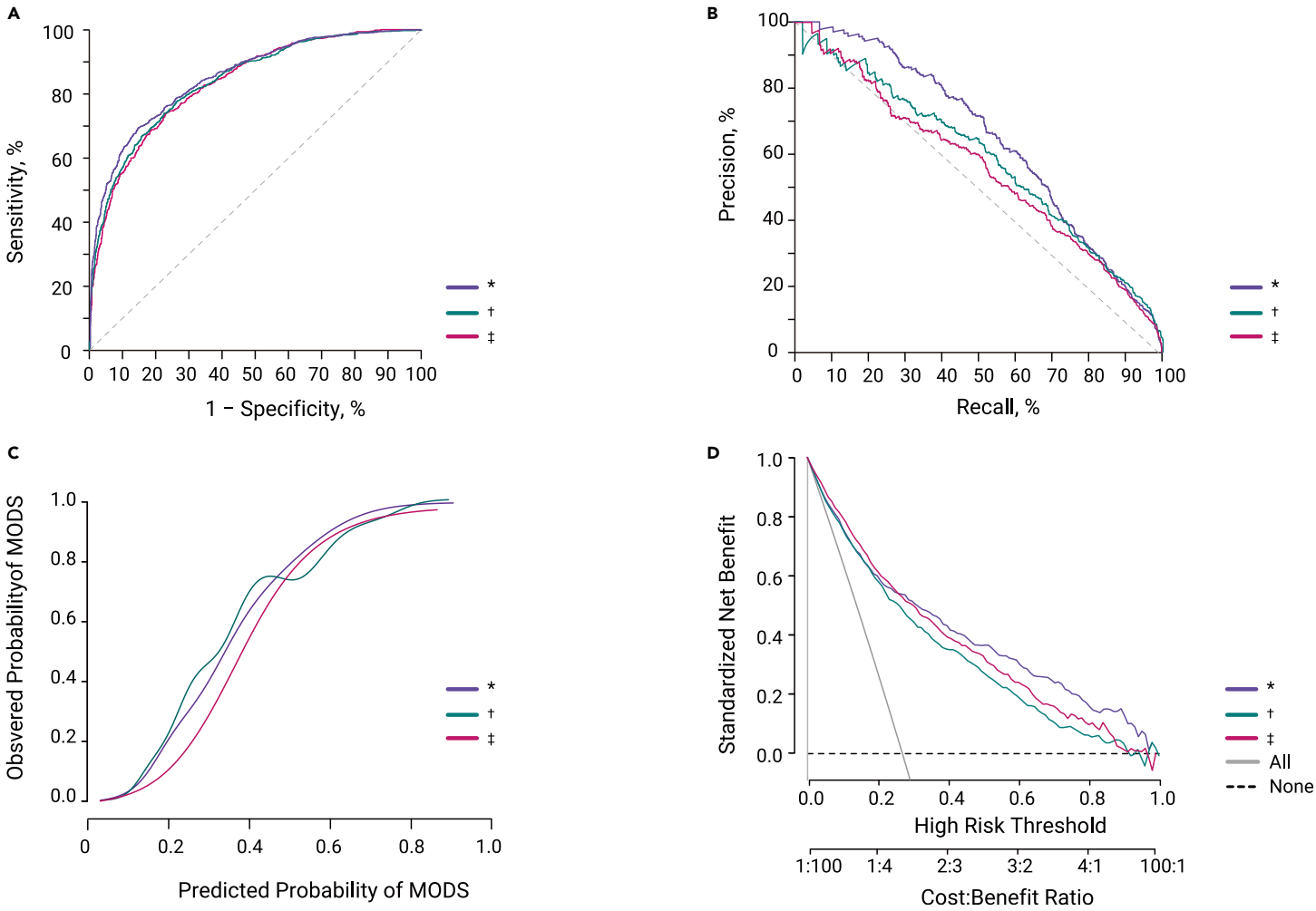

Figure 2. Performance of risk models in the derivation and validation cohorts (A) AUROC of risk models. (B) AUPRC of risk models. (C) Calibration plots of risk models. (D) Decision curves of risk models. *, Full risk model in the derivation cohort; †, inflammatory risk model in the derivation cohort; ‡, inflammatory risk model in the validation cohorts. AUROC, area under the receiver operating characteristic curve; AUPRC, area under the precision recall curve.

postoperative days or hospital discharge.[15,16] Secondary outcomes were 30-day mortality, in-hospital mortality, mechanical ventilation time, intensive care unit stay duration, and hospital stay duration.

Model derivation and validation

The final cohort was randomly divided into a derivation cohort (60%) and a validation cohort (40%). The XGBoost algorithm is a high-performance machine learning gradient-boosting ensemble of decision trees[17] with advantages of requiring the least data preprocessing and feature engineering and many tuning hyperparameters for optimization.[18] In consideration of the availability and consistent definitions, the commonly objective candidate variables among these cardiovascular centers were selected for model derivation. Then, we trained an XGBoost algorithm with these patient data to generate a risk-predictive model using this artificial intelligence (AI) algorithm. To allow interpretation of our model's predictions, we used Shapley additive explanation (SHAP) to evaluate key feature importance with identification of a predictor's relative contribution for each observation and averaged across observations to the final prediction.[19] Discrimination performance was assessed via the area under the receiver operating characteristic curve (AUROC) and area under the precision recall curve (AUPRC).[20] Calibration ability was assessed via a calibration plot, calibration plot with slope and intercept, and Brier score. Clinical utility was assessed using decision curve analysis.[21] Two AUROCs were compared according to DeLong's method and the noninferiority margin.[22]

Subgroup analysis

Patients were stratified according to the presence or absence of ulinastatin use. Cubic spline curve analysis was applied to fit the functional relationship of the predicted risk probability as a continuous variable with the primary outcome.[23] Subsequently, we divided patients into three subgroups on the basis of their risk probability (<23.5%, 23.5–41.6%, and >41.6%) and further tested whether there were interactions between anti-inflammatory pharmacotherapy (ulinastatin) and operative mortality across subgroups of these risk differences. The delta method was used to calculate the relative risk ratio (RR) and 95% confidence intervals (CI) with and without adjustment for demographic, clinical, and procedural profiles (Table S1). We further calculated the number needed to treat (NNT) or the number needed to harm (NNH) with 95% CI.[24] In addition, three propensity score methods were employed to control the imbalance from nonrandomized use of ulinastatin and to alleviate the effects of confounding factors. In brief, we used inverse probability weighting analysis, where the predicted probabilities from the propensity score model were used to calculate the stabilized inverse-probability-weighting weight, propensity score matching analysis, where the nearest-neighbor method was applied to create a matched control sample, and the propensity score as an additional covariate.[25]

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 the derivation cohort (850 events for 6 variables) and validation cohort (617 events for 6 variables).

Continuous data are presented as the mean (standard deviation [SD]) or median (interquartile range [IQR]) compared by t test or Mann-Whitney test, and categorical data are reported as percentages compared by χ^2 test or Fisher's exact test. The Kolmogorov-Smirnov test for normality was used to check data distribution. The p values were 2 tailed, and $p < 0.05$ was considered statistically significant unless otherwise stated. Statistical analysis was performed using R software, STATA statistical software, and Python programming software.

Table 2. Comparison of outcome of interest between ulinastatin use or no use in the validation cohort

	No ulinastatin use (N = 1,199)	Ulinastatin use (N = 860)	p Value
MODS			
Overall (n = 2,059)	381 (31.8%)	236 (27.4%)	0.034
Low risk (n1 = 734)	28 (6.3%)	22 (7.6%)	0.514
Middle risk (n2 = 952)	171 (32.6%)	112 (26.2%)	0.030
High risk (n3 = 373)	182 (78.4%)	102 (72.3%)	0.180
30-day mortality			
Overall (n = 2,059)	136 (11.3%)	99 (11.5%)	0.905
Low risk (n1 = 734)	5 (1.1%)	8 (2.7%)	0.103
Middle risk (n2 = 952)	53 (10.1%)	42 (9.8%)	0.877
High risk (n3 = 373)	78 (33.6%)	49 (34.8%)	0.823
In-hospital mortality			
Overall (n = 2,059)	152 (12.7%)	112 (13.0%)	0.817
Low risk (n1 = 734)	7 (1.6%)	10 (3.4%)	0.102
Middle risk (n2 = 952)	60 (11.5%)	50 (11.7%)	0.911
High risk (n3 = 373)	85 (36.6%)	52 (36.9%)	0.963

MODS, multiple organ dysfunction syndrome; ICU, intensive care unit.

RESULTS

Patient characteristics and outcomes

The flowchart for study participants is detailed in Figure S1. The final cohort consisted of 5,126 ATAAD patients who were randomly divided into a derivation cohort (60%, N = 3,067) and a validation cohort (40%, N = 2,059), with no important differences in baseline and clinical features between the two groups (Table 1). Baseline, demographic, clinical, and laboratory parameters and procedural characteristics are summarized in Table 1. The crude MODS rate was 27.7% (850 of 3,067 patients) in the derivation cohort and 29.9% (617 of 2,059 patients). Secondary outcomes of 30-day and hospital mortality as well as ventilation, ICU, and hospital stay durations are shown in Table 1. These patient data had a skewed distribution and nonlinear, sparse, and imbalanced classification data (Tables S2 and S3). We also investigated the impact of center volume on preoperative outcomes in Table S4.

Model characteristics: Discrimination, calibration, and clinical use

The SHAP analysis showed the candidate predictor's relative contribution, either positive or negative, to prediction of MODS (Figure 1), which we used to develop a full model to predict MODS, with an AUROC of 0.853 and AUPRC of 0.740 as well as good calibration (Brier scores of 0.134) and clinical utility (Figure 2). To improve the model's practical application, we selected features that were most strongly associated with the systemic effects of the anti-inflammatory strategy based on a SHAP feature importance of 0.80 or higher, which identified the top six features: renal function (eGFR), leukocytes, platelets, De Ritis ratio, hemoglobin, and albumin (Figures 1 and S2). We retrained an XGBoost tree algorithm on the subset of these six most important features and generated a parsimonious tool to predict the personalized risk of developing MODS. The final tool was named the inflammatory risk model, with an online browser-accessible version of this risk model available for external use (http://www.empowerstats.net/pmodel/?m=7473_MODSriskpredictionmodel; Figure S3). In the comparison of the two risk models, there was a strong correlation between the predictions of the parsimonious inflammatory model (six variables) and the full model (R = 0.94, 95% CI 0.91–0.97). Additionally, the discrimination of the inflammatory model was noninferior to that of the full model (AUROC 0.837 [95% CI 0.823–0.851] versus 0.853 [95% CI 0.837–0.869]) in the derivation cohort.

The final inflammatory risk model had high discrimination in validation populations, with AUROCs of 0.834 (Figure 2A). This inflammatory risk model had adequate accuracy in the derivation and validation populations, with AUPRC values of 0.708 and 0.676, respectively (Figure 2B). There was good calibration of this model with Brier scores of 0.144 and 0.157 in the derivation and validation cohort, respectively (Figure 2C). The heterogeneous profile of ATAAD individuals renders a uniform treatment strategy (treat all or no patients) inferior to this strategy informed by the inflammatory risk model. The gain from the inflammatory risk model was excellent, with threshold probabilities of risk from 0.2–0.6 (Figure 2D). The specificity, sensitivity, positive and negative likelihood ratios, positive and negative predictive values, and accuracy are shown in Table S5.

Association between ulinastatin use and MODS

Among the 2,059 patients in the validation cohort, patients with ulinastatin use were less likely to develop MODS than patients without ulinastatin use (236/860 vs. 381/1,199; RR, 0.863; 95% CI, 0.753–0.990; p = 0.035) (Table 2). The multivariable analysis also confirmed the significant association between ulinastatin use and MODS (adjusted risk ratio [RR], 0.795; 95% CI, 0.649–0.973; p = 0.026). Additional multivariable propensity score analysis yielded similar results (Figure 3). However, there was no significant difference between the two subgroups in 30-day mortality and in-hospital mortality (Table 2).

Subgroup analysis

The risk model was then used to predict MODS risk for the validation cohort and plotted against observed risk (Figure 4A). The 95% CI of spline curves for ulinastatin use versus no use across 23.5% and 41.6% showed that patients with a predicted MODS risk of less than 23.5% or greater than 41.6% will not benefit from ulinastatin use (RR 1.196 [95% CI 0.698–2.049], p = 0.514; RR 0.922 [95% CI 0.816–1.042], p = 0.194), while patients with a predicted MODS risk of 23.5%–41.6% will benefit from ulinastatin use (RR 0.802 [95% CI 0.656, 0.981], p = 0.031), which indicates that the benefit from ulinastatin use is different depending on the predicted MODS risk (Figure 4A). There was no significant interaction between the treatment effect and risk probability of less than 23.5%, 23.5%–41.6%, and greater than 41.6% ($p_{interaction}$ = 0.288). No significant difference was found in the treatment effect between the subgroups of greater than 41.6% and 23.5%–41.6% ($p_{interaction}$ = 0.949). In particular, a marginal interaction was observed between the treatment effect and risk probability of less than 23.5% and 23.5% or greater ($p_{interaction}$ = 0.077). After additional adjustment for multivariable and propensity score analysis, the results were still similar (Figure 3).

The observed MODS rates varied substantially across risk groups: 7.5% (95% CI 5.3–11.2) in the low-risk group and 26.2% (22.2–30.1) and 72.3% (64.4–79.1) in the high-risk group (Figure S4). With reference to the low-risk group, the middle- and high-risk groups conferred a significant gradient risk of MODS (RR 4.364 [95% CI 3.282–5.802], RR 11.177 [95% CI 8.502–14.694], respectively; p for trend < 0.0001) (Figure S5). The estimated NNT was 16 (95% CI 8–158), which could be interpreted as one patient being prevented from developing MODS in every 16 patients who have been treated with ulinastatin among patients with a predicted risk of 23.5%–41.6% (Figure 4B).

DISCUSSION

In this large, real-world cohort of Chinese ATAAD patients, we trained and validated an inflammatory risk model to predict MODS following surgical repair of AD. This risk model displayed adequate predictive performance with respect to discrimination, calibration, and clinical utility in derivation and validation cohorts. In patients with a risk probability of 23.5%–41.6%, ulinastatin use was associated with a lower risk of MODS. In patients with a risk probability of less than 23.5% or greater than 41.6%, ulinastatin use was not associated with the risk of MODS. However, these findings must be interpreted in the context of no significant interaction between the three risk categories and the ulinastatin treatment effect. This AI-driven model (available as a web-based tool) may provide precise risk stratification for MODS and important decision-making information for clinical anti-inflammatory pharmacotherapeutics.

There have been few clinical trials of ulinastatin use in the treatment of ATAAD. A previous report showed that ulinastatin contributes to the improvement in pulmonary function, as evidenced by the shorter mechanical ventilation time in

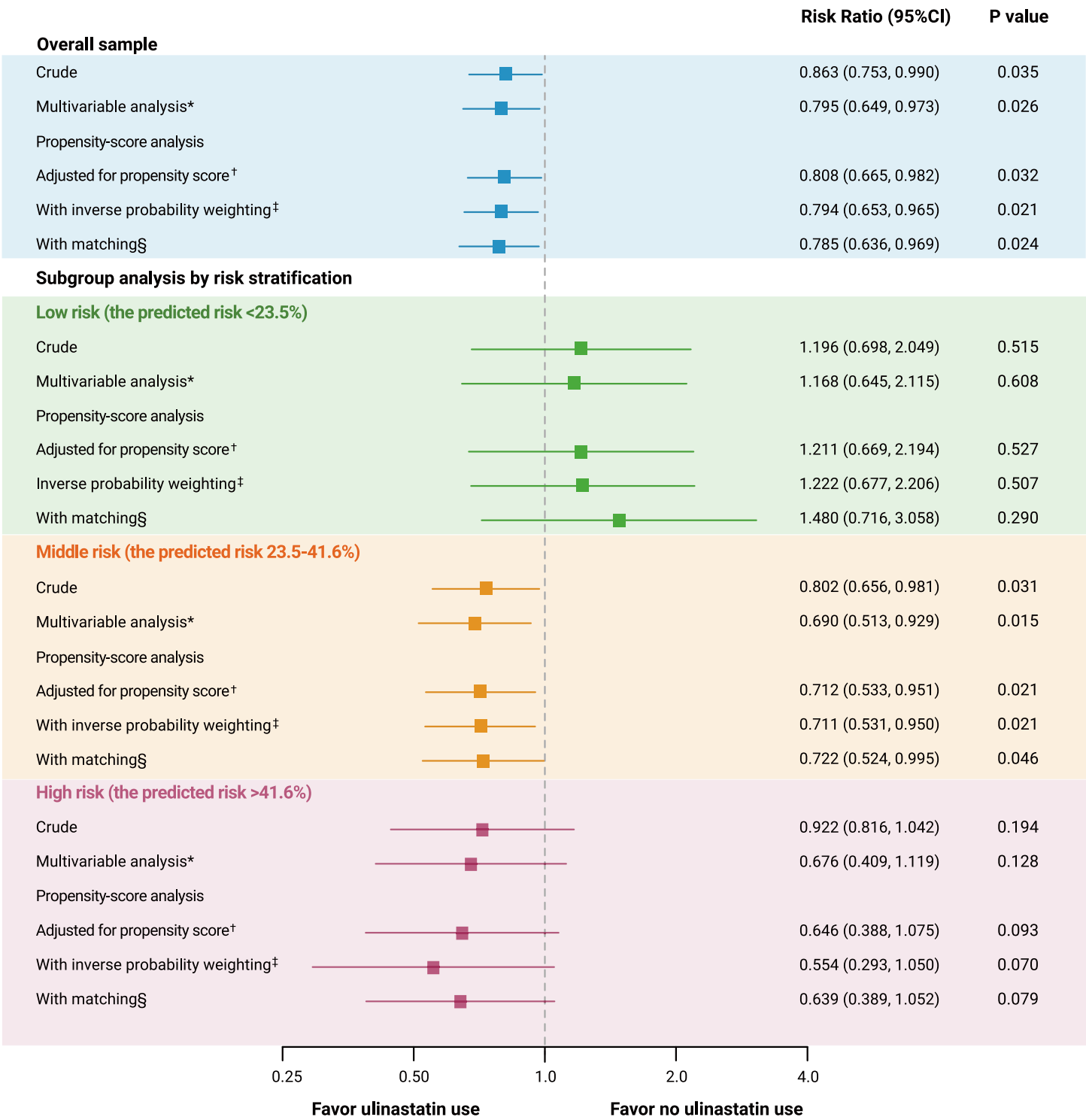

Figure 3. Association between ulinastatin use and primary outcome in the validation cohort *, Multivariable logistic model with adjustment for baseline and clinical characteristics, laboratory profiles, and procedural factors; †, multivariable logistic model with the same covariates with additional adjustment for the propensity score; ‡, multivariable logistic model with the same covariates with inverse probability weighting according to the propensity score; §, multivariable logistic model with the same strata and covariates with matching according to the propensity score. CI, confidence interval.

ATAAD patients.[26] Similarly, our recent study demonstrated that a significant interaction exists between ulinastatin use and inflammatory phenotypes (ie, ulinastatin associated with shorter ventilator time in hyperinflammatory ATAAD patients).[27] Although many additional studies have investigated the therapeutic effects of ulinastatin in cardiovascular surgery,[27–29] there is still a degree of controversy about the anti-inflammatory roles of ulinastatin.[9,30,31] Available evidence mainly shows that ulinastatin significantly reduces ventilator use time;[32,33] however, whether ulinastatin has a beneficial effect on cardiac function and coagulation needs to be clarified.

Our current report adds valuable information to the previous literature. Specifically, we address the role of ulinastatin as an anti-inflammatory treatment for ATAAD across all ages. Previous reports were largely limited to small sample sizes or single-center studies and failed to address the impact of this anti-inflammatory therapy in the ATAAD population.[26] Likewise, previous evidence focused on postoperative mortality or one single-organ adverse event as the primary endpoint, which lacked systemic comorbidity data and could not determine the impact of ulinastatin use on multiple-organ comorbidity status.[9,27–32] Conversely, our present study included assessments of multiple-organ

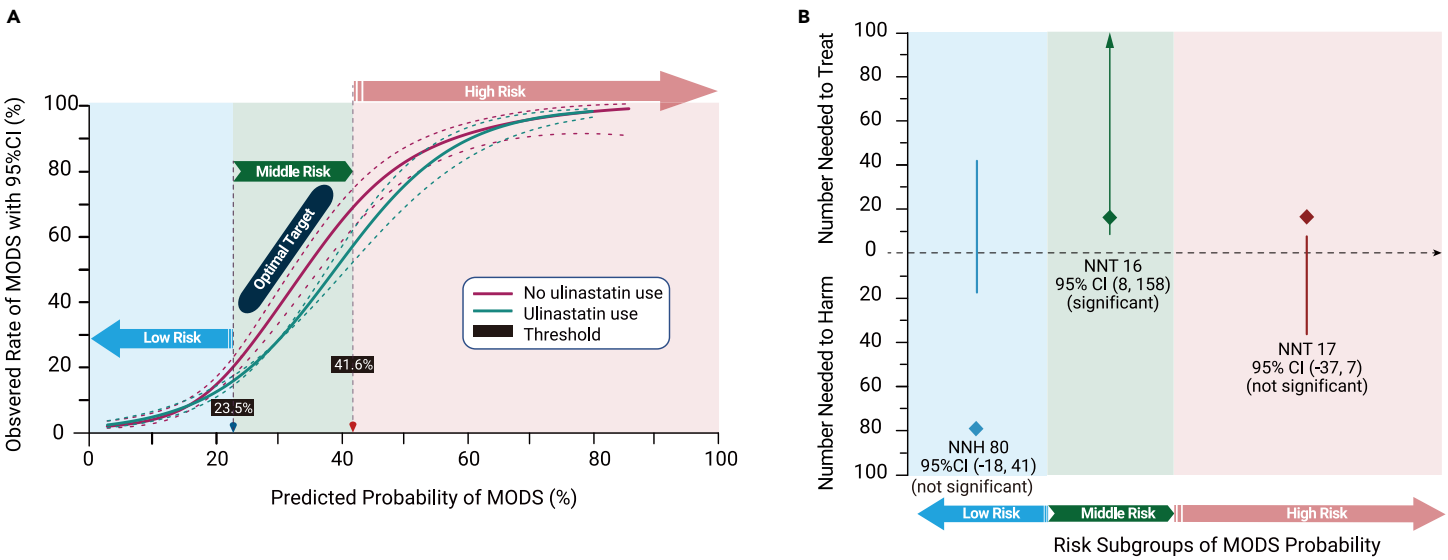

Figure 4. Association of ulinastatin use with risk of MODS (A) Relationship between predicted and observed risk of MODS by absence vs. presence of ulinastatin. (B) Number needed to treat (NNT) or harm (NNH) of ulinastatin use among low-, middle-, and high-risk subgroups.

comorbidity status along with all age categories. Moreover, our study captures the largest sample size of patients across China, which improves the generalizability of our findings.

Our study showed that, in patients with a moderate risk of MODS (risk probability of 23.5%–41.6%), ulinastatin administration was associated with a lower risk of MODS, and in patients with low or high risk (risk probability of <23.5% or >41.6%, respectively), ulinastatin administration was not associated with the risk of MODS. However, our findings must be interpreted in the context of no significant interaction between risk probabilities of less than 23.5%, 23.5%–41.6%, or greater than 41.6% and ulinastatin treatment effects. In addition, the present study provided multivariable and propensity score analysis for controlling confounding factors and minimizing the selection bias associated with treatment assignment, which makes our results more robust.

Our study has important clinical implications. Despite including these relatively simple variables, the risk model driven by the AI algorithm exhibited favorable predictive accuracy, discrimination, and clinical utility compared with traditional methods among AD patients, such as the German Registry for Acute Type A Aortic Dissection (GERAADA) score, Additive EuroSCORE, Logistic EuroSCORE, Parsonnet score, Provincial Adult Cardiac Care Network of Ontario score, Cleveland score, and SinoSCORE.[34,35] However, it is of great importance to weigh the potential benefit of ulinastatin administration against the possible unfavorable effects or risks of this treatment at the patient level in future studies. It is likely that individuals with differing risk probabilities responded differently to anti-inflammatory treatment, which might reflect the potential differences in patient characteristic-based risk profiles and therefore supports the systemic benefits of anti-inflammatory treatment despite no substantial benefits for 30-day and hospital mortality.

Strengths and limitations

From methodological and clinical perspectives, our work has important implications. Our study treats a risk probability as a continuum for assessment of individualized treatment effect, which advanced our previous findings by integrating the patient-level risk prediction and treatment effect estimates,[36,37] which provides insights into the focus shift from applying average observed effects of anti-inflammatory pharmacotherapy to risk reduction for individuals based on individualized treatment effect prediction.[38] However, several limitations might warrant concern. Given the potential differences in patients and procedural characteristics compared with populations from other regions, further validation of the present findings is needed before its clinical implementation as a decision-making apparatus. The socioeconomic and biological elements as well as other clinical variables that underly the heterogeneity in treatment effects need to be further explicated in addition to the key determinants identified in our risk model.

Conclusion

In this large, multicenter cohort of Chinese ATAAD patients, we developed an AI-driven risk calculator to assess the treatment effects for personalized consideration of anti-inflammatory treatment goals partly depending on the individual characteristics among this ATAAD population. Our findings provide insights into the potential systemic benefits from anti-inflammatory treatment, which is likely to be a valuable asset to shared decision-making in management of AD. Our findings must be interpreted, however, in the context of relevant limitations, especially the lack of a significant interaction between ulinastatin treatment and MODS risk across three risk subgroups. Future studies should highlight an individualized decision support tool-directed pathway rather than traditional pathways for appropriate inflammation-lowering therapy in patients with ATAAD.

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AUTHOR CONTRIBUTIONS

Hong Liu and H.Z. contributed to the collection, assembly, and quality control of the data. Hong Liu and Haiyang Li were responsible for the conception and design of the study. Hong Liu, S.Q., and Haiyang Li designed the strategies of data analysis and conducted the statistical analysis. All authors interpreted the data. Hong Liu and S.Q. drafted the report. All authors revised it critically for important intellectual content and agreed to submit the report for publication.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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