CURRENT TRENDS AND STRATEGIES FOR THE MANAGEMENT OF TYPE A AORTIC DISSECTION

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CURRENT TRENDS AND STRATEGIES FOR THE MANAGEMENT OF TYPE A AORTIC DISSECTION

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Editorial: Current trends and strategies for the management of type A aortic dissection

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KEYWORDS

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Editorial on the Research Topic
Current trends and strategies for the management of type A aortic dissection

Introduction

Acute type A aortic dissection (ATAAD) is a life-threatening emergency with a mortality increasing by 1–2% per hour (1, 2). Surgical intervention aims to relieve cardiac tamponade from intra-pericardial aortic rupture, prevent myocardial ischaemia by establishing satisfactory coronary perfusion, resect the primary aortic intimal tear, reconstitute the damaged aorta, restore aortic valve competency, achieve false lumen obliteration and limit propagation of the dissection into branch vessels (3, 4). Patients presenting with ATAAD should therefore be transferred expeditiously to a dedicated aortic center, where the availability of specialist care has been demonstrated to translate into more favorable outcomes in this high-risk population (5). Interestingly, the improved outcome observed in patients with delayed ATAAD presentation who are operated at >48 h beyond symptom onset may reflect their less severe pathology and malperfusion (6).

This Research Topic explores (i) the role of novel biomarkers for prognostication of patients undergoing surgery for ATAAD, (ii) risk factors for post-operative complications and models for their prediction and (iii) current surgical management strategies.

Biomarkers in acute type A aortic dissection

The careful selection to surgery of patients presenting with ATAAD is of great importance. Biomarkers can facilitate surgical decision-making by discriminating those patients who are more likely to have a better outcome. In this Research Topic, Jiang et al. analyse the association between the pre-operative levels of the biomarker transcription regular protein 1, which linked with the development of ATAAD, and post-operative mortality. Low lymphocyte counts are commonly correlated with organ dysfunction and immunosuppression states, but their role in post-operative surgical outcomes is less well demonstrated. In their original research article, Luo et al. investigate the influence of pre-operative CD4+ lymphopenia on outcomes following ATAAD surgery. These findings will provide greater insight into the role of immunomodulation in ATAAD and by extension stimulate efforts in organ protection during complex aortic surgery. Stroke is one of the most feared neurological adverse events following ATAAD and its surgical repair. Neurofilament Light Chain (NFL) is another promising biomarker being appraised in the post-operative neurological prognosis of patients following surgery for ATAAD, as evaluated by Zhang et al. in another original study within this research theme.

Risk factors and prediction of outcomes following acute type A aortic dissection

Despite improvements in patient referral pathways, peri-operative care and surgical management, ATAAD continues to carry significant risks of in-hospital mortality. The analysis by Yuan et al. provides valuable information on pre- and intra-operative risk factors affecting mortality in ATAAD patients.

Malperfusion is perhaps the most important risk factor for adverse outcomes following ATAAD with the number of organ systems affected contributing an additive effect on mortality (6). Patients presenting with coma, cerebral or coronary ischaemia and haemodynamic instability are likewise associated with adverse outcomes (7–9). Ischaemic liver injury is prevalent in patients undergoing ATAAD repair on account of the surgical complexity and extended cardiopulmonary bypass and cross-clamp durations. Risk factors for ischaemic liver injury after ATAAD surgery are presented in the study by Liu et al., along with a model for risk calculation in individual patients.

Patients presenting with shock, pericardial tamponade and those requiring cardiopulmonary resuscitation prior to surgery are all associated with adverse outcomes (7). Post-operative bleeding following ATAAD surgery may culminate in irreversible organ dysfunction, and thereby increase mortality. Coinciding with this research theme, important risk factors for massive bleeding after ATAAD surgery, related clinical outcomes and a predictive model are described by Zhang et al. Similarly, Chen et al. report on the various predictors, identified utilizing a machine learning approach, for length of stay on the intensive care unit following surgery for ATAAD. This has important implications for resource allocation and expenditure within critical care settings.

ATAAD additionally carries a relatively high risk of post-operative renal impairment and renal failure is another important risk factor for poor outcome identified in the International Registry of Aortic Dissection database (5). Jiao et al. propose a model to determine in-hospital mortality risk in patients undergoing continuous renal replacement therapy following ATAAD.

Age has a significant bearing on outcome following surgical repair of ATAAD. While mortality in the septuagenarians has been reported to be only 16%, it increases to 35% in octogenarians (9). The incidence of obesity worldwide has increased significantly in recent decades and elevated BMI has been suggested to have a negative impact on outcomes following ATAAD surgery. Pan et al. here examine the relationship between obesity and outcome in a Chinese cohort of patients undergoing surgery for ATAAD.

Earlier studies on gender suggested it to be an important determinant of outcome (10), although more recent studies have shown that gender in the last decade has ceased to be an important risk factor (11, 12). The UK National Adult Cardiac Surgical Audit identified impaired left ventricular function, previous cardiac surgery, need for concomitant coronary artery bypass grafting and preoperative mechanical ventilation as additional risk factors for adverse outcomes (13). The German Registry for Acute Type A Aortic Dissection score in addition found usage of catecholamines at referral, and involvement of arch, head and neck vessels and descending aorta as additional risk factors (14).

Current surgical management

Surgical intervention for ATAAD involves cardiopulmonary bypass, hypothermic circulatory arrest and retrograde cerebral perfusion (15). Cerebral and myocardial protection require special consideration. Femoral, right axillary and direct aortic cannulation sites for arterial return are variably preferred. Similarly, the optimal perfusion strategy remains debated, with no general consensus regarding the depth of hypothermia for circulatory, and benefits of retrograde vs. selective antegrade cerebral perfusion (16).

The extent of aortic replacement is of paramount importance and determined by the location of intimal tear. Proximally, aortic root replacement may be accomplished using modifications of the Bentall-de Bono procedure. Alternatively, aortic valve preservation with commissural resuspension may be feasible in 60–80% of patients (17) where the valve is structurally normal, or the valve may be directly repaired (18), and combined with reconstruction of the aortic root in the absence of an aortic root aneurysm or aortopathy. In the scenario of extensive aortic root dissection, concomitant aortic valve dysfunction or coronary malperfusion, formal root replacement is mandated alongside potential coronary artery bypass grafting. Carefully selected patients without an aneurysm or tear involving the sinuses of Valsalva may benefit from a valve-sparing root replacement approach to avoid the risks of structural valve degeneration, anticoagulation and endocarditis inherent with prosthetic valve implantation.

Two schools of thought prevail for reconstruction of the aortic arch in ATAAD. Resection of the entry tear can be achieved utilizing a more conservative approach comprising ascending aortic resection with beveled replacement of the underside of the aortic arch (hemi-arch replacement) in nearly all ATAAD cases. A more aggressive operation is reasonable in patients with connective tissue disease or an aneurysmal arch and is essential for intimal tears extending onto the greater curvature of the aortic arch associated with cerebral malperfusion (17). This encompasses complete aortic arch resection with separate direct anastomosis of the supra-aortic vessels into the aortic graft in the conventional elephant trunk procedure, or their reimplantation as a patch. The more contemporary frozen elephant trunk adaptation (18, 19) permits reconstruction of the aortic arch in addition to concurrent stabilization of the descending aorta with deployment of an endovascular stent to address co-existing visceral and limb malperfusion syndromes. Proponents of aggressive arch intervention in ATAAD argue that this strategy enhances long-term survival by encouraging false lumen occlusion, thereby inhibiting descending aortic aneurysm formation and decreasing future reintervention rates on the distal aorta (20, 21). Irrespective of the strategy employed, the distal aortic anastomosis should strictly be performed under circulatory arrest to allow adequate opportunity for careful resection of the dissection aorta and meticulous re-apposition of the aortic wall, thereby preserving cerebral and distal aortic perfusion. With greater emphasis on percutaneous aortic arch intervention in ATAAD, innovative stent-graft designs are being developed. Recently, the Ascyrus Medical Dissection Stent (AMDS) has emerged as a partially uncovered stent permitting continuous arch vessel perfusion and descending aortic coverage (22, 23). In their original research article, Mehdiani et al. present their early results using this prosthesis in ATAAD.

Conclusion

ATAAD is a devastating aortic complication with high morbidity and mortality necessitating prompt cardiac surgical assessment and intervention. The underlying pathophysiological mechanisms are complex. Just as we begin to uncover and understand more about this entity, there is also great potential in applying this knowledge to improve outcomes for those patients affected by this deadly disease. This broad Research Topic examines current trends and surgical management of ATAAD from both an in-depth scientific and real-world clinical perspective. We hope that the mix of articles provides an enriching experience for the reader and enhances their understanding of this highly important aortic pathology.

Author contributions

PN and GM contributed to conception and design of the study. PN, VS, GM, and MA wrote the first draft of the manuscript and wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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TAZ Is Related to Postoperative In-Hospital Mortality of Acute Type A Aortic Dissection

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Background: Surgical repair of acute type A aortic dissection (ATAAD) has high risk and mortality, and there are few biomarkers of postoperative in-hospital mortality until now. This study investigated the association between WW domain–containing transcription regulator protein 1 (TAZ) and the postoperative in-hospital mortality of ATAAD patients.

Methods: This is a retrospective cohort study. Data and blood samples were collected from 95 consecutive patients with ATAAD who underwent surgeries in our hospital from July 1, 2016, to December 31, 2016. The data collection included all the risk factors introduced by the modified EuroSCORE (European System for Cardiac Operative Risk Evaluation). The predictors of postoperative in-hospital death were confirmed by univariate regression analysis. Multivariable logistic regressions were used to analyze the association of the preoperative plasma level of TAZ and the postoperative in-hospital mortality of ATAAD patients. In addition, we used the generalized additive model to identify non-linear relationships.

Results: Three models were used in the multivariable logistic regression analysis of the relationship between the preoperative plasma level of TAZ and postoperative in-hospital death. In the crude model, the preoperative plasma level of TAZ showed a positive correlation with postoperative in-hospital death [odds ratio (OR) = 1.33, 95% confidence interval (CI): 1.01–1.74, $P = 0.04$]. In adjusted model I and adjusted model II, similar results were found (OR = 1.35, 95% CI: 1.01–1.80, $P = 0.04$ and OR = 1.35, 95% CI: 1.01–1.81, $P = 0.04$). The risk of postoperative in-hospital death in the preoperative plasma level of the TAZ≥12.70 ng/mL group was 10.08 times (OR = 10.08, 95% CI: 1.63–62.37; $P = 0.01$) that of the preoperative plasma level of the TAZ < 12.70 ng/mL group.

Conclusions: The high preoperative plasma level of TAZ suggested poor surgical prognosis for ATAAD patients. The patients with a preoperative plasma level of TAZ ≥ 12.7 ng/ml had much higher postoperative in-hospital mortality.

Keywords: aortic dissection, heart surgery, mortality, ascending aorta and total aortic arch replacement, TAZ

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INTRODUCTION

Aortic dissection (AD), especially the acute type A aortic dissection (ATAAD) with dissected ascending aorta, is the most life-threatening vascular disease (1, 2). Based on the present guidelines, all patients with ATAAD should be transferred to the operating room if possible (3, 4). Although there has been a significant decline in the in-hospital surgical mortality rate of patients presenting with ATAAD with the advancement of related technology, surgical repair remains high risk and has a high mortality rate (3.09–30.00%), which deters most aortic surgeons (2, 5, 6). Some preoperative presentations, such as malperfusion phenomena, are considered predictive factors for postoperative mortality (2). However, there are few biomarkers of postoperative mortality until now.

WW domain–containing transcription regulator protein 1 (TAZ) is ubiquitous in the human body and mainly found downstream of the Hippo pathway, which regulates many fundamental biological processes (7). Our previous research focused on the molecular pathogenesis of ATAAD and found that altered mechanical stress induced the change of Hippo pathway, which contributes to ATAAD development (8). As TAZ play important roles in the development of ATAAD, they might also be related to postoperative mortality of ATAAD.

In this study, we investigated the preoperative plasma levels of TAZ of patients with ATAAD and studied the association between the preoperative plasma level of TAZ and the postoperative mortality of ATAAD patients.

MATERIALS AND METHODS

Patient Selection and Blood Sample Collection

The human study and the use of human blood were approved by the Ethics Committee of Beijing Anzhen Hospital (Institutional Review Board File 2014019) and were consistent with the principles outlined in the Declaration of Helsinki. All patients (104) with ATAAD who underwent surgeries in our hospital and enrolled in "*A study of the prediction and the treatment of Acute Aortic Syndrome (ChiCTR1900022637)*" from July 1, 2016, to December 31, 2016, were included for the purpose of this analysis. After excluding nine patients with genetic syndrome related to aortic disease, such as Marfan, Turner, Loeys–Dietz, or Ehlers–Danlos syndrome, 95 consecutive patients were involved in the final analysis (**Figure 1**). All the patients received the surgery in 24 h after the onset of the disease. The surgical procedures included 67 patients with Bentall [one patient with CABG (coronary artery bypass grafting), one patient with MVP (mitral valvuloplasty) ± TVP (tricuspid valvuloplasty), 57 patients with total arch replacement using a tetrafurcate graft and stented elephant trunk implantation (5), one patient with total arch replacement using a tetrafurcate graft and stented elephant trunk implantation + CABG], 22 patients with ascending aortic replacement (one patient with CABG, 19 patients with total arch replacement using a tetrafurcate graft and stented elephant trunk implantation), and six patients with redo-operation (one patient with ascending aortic replacement, one patient with ascending aortic replacement + CABG, four patients with Bentall + total arch replacement using a tetrafurcate graft and stented elephant trunk implantation). The right axillary artery was used for antegrade selective cerebral perfusion when performing total arch replacement using a tetrafurcate graft and stented elephant trunk implantation under deep hypothermia circulation arrest.

All the patients received the surgery in 24 h after the onset of aortic dissection, and blood samples were collected from these patients before the surgical intervention was initiated.

Blood Sample Assays

After collection, the blood sample was anticoagulated with sodium citrate and then centrifuged for 15 min at 3,500 rpm at 4°C. All the samples were divided into 0.5-ml per centrifuge tubes, stored at −80°C, and only used for this study. The mean sample storage duration was 84.50 days when ELISA was performed. The preoperative plasma levels of TAZ were determined by ELISA (Uscn, Wuhan, China), as previously described (9). All ELISAs were performed three times, and the mean value was used for analysis.

Data Collection

Data were assembled from the database of "*A study of the prediction and treatment of Acute Aortic Syndrome (ChiCTR1900022637)*," which was established based on standardized electronic medical records from our hospital. The data collection included all the risk factors introduced by the modified EuroSCORE (10), such as preoperative variables [age, sex, BMI (calculated based on height and weight), hypertension, diabetes status, pulmonary disease, extracardiac arteriopathy, neurological or musculoskeletal dysfunction, recent myocardial infarction, previous cardiac surgery, cardiac tamponade, left ventricular ejection fraction (LVEF), serum creatinine, critical preoperative state, unstable angina, d-dimer, platelet, fibrinogen, c-reactive protein, troponin I, ascending aorta diameter, pleural effusion, pericardial effusion, coronary arteries involved, location of intimal defect] and intraoperative variables (cardiopulmonary bypass time, aortic cross-clamp time and antegrade cerebral perfusion) and postoperative outcome variable (in-hospital death).

Statistical Analysis

Data were expressed as frequency and percentage, as mean ± standard deviation (SD), or as median and interquartile range (IQR). *T* tests and Mann–Whitney *U* tests were applied according to the different distributions of the variables. Logistic regression analysis was performed to identify the predictors of in-hospital mortality. According to the recommendation of the STROBE statement, both non-adjusted and adjusted multiple regression models were used to evaluate the effect of the predictor on mortality after surgery. We selected these confounders on the basis of their associations with the outcomes of interest or a change in effect estimate of more than 10% (11), which included BMI (as a continuous variable) and cardiac tamponade (as a categorical variables). Moreover, the decision to add each measured potential confounder in the model was based on previous scientific evidence, namely, for cardiopulmonary

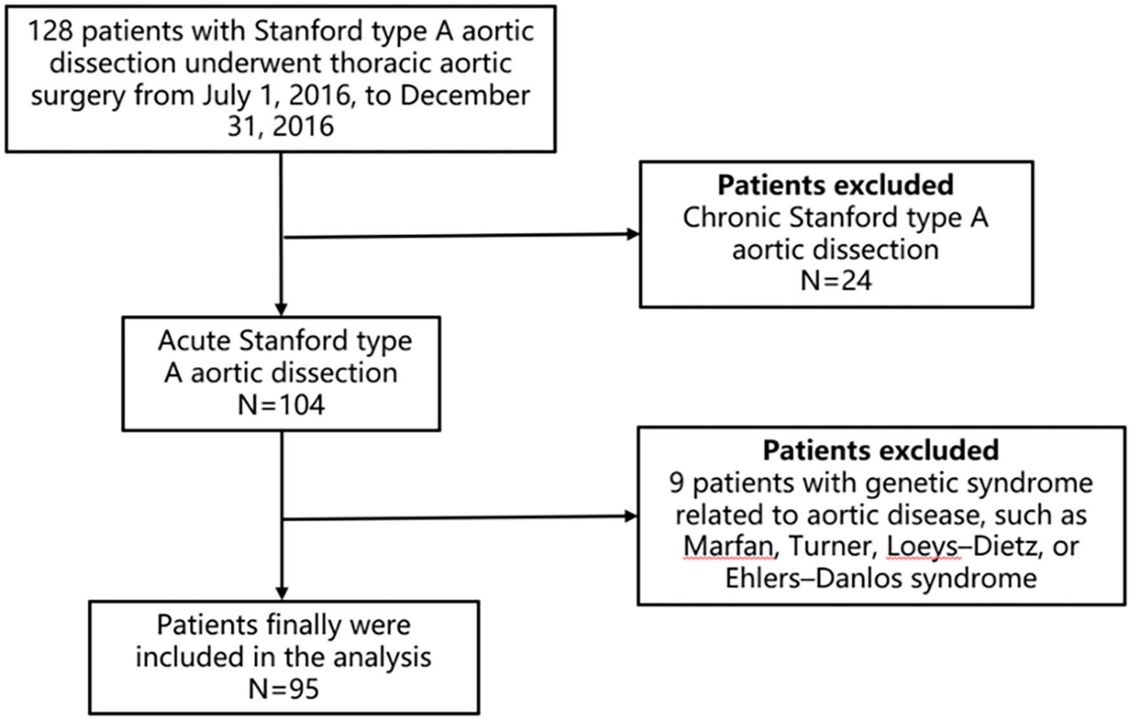

FIGURE 1 | Flowchart of the screening and enrollment of study patients.

bypass time (as a continuous variable), serum creatinine (as a continuous variable), and recent myocardial infarction (as a categorical variable). To explore multicollinearity among different covariates in the model, we excluded variables with variance inflation factor >5. In addition, the generalized additive model (GAM) was used to identify non-linear relationships. Receiver operating characteristic (ROC) curves constructed using Bootstrap resampling (times = 500) were used to find the optimal cutoff values for the preoperative plasma level of TAZ (with maximizing the sum of sensitivity and specificity) to predict in-hospital mortality. $P < 0.05$ was considered statistically significant (two-sided). All analyses were completed by the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X & Y Solutions, Inc., Boston, MA).

RESULTS

Baseline Characteristics of Participants

Table 1 lists the baseline characteristics of the 95 consecutive patients in this cohort. Nine patients (9.47%) died in the hospital [cardiogenic shock, low cardiac output syndrome ($n = 1$); septic shock ($n = 1$); lung infection, respiratory failure ($n = 1$), renal failure, paraplegia, heart failure ($n = 1$); cerebral infarction ($n = 2$); multiple-organ failure, electrolyte disorder, anemia ($n = 1$); cardiogenic shock, ventricular fibrillation ($n = 1$); distal dissection rupture, tachycardia ($n = 1$)]. The average preoperative plasma level of TAZ of these individuals was 11.76 ± 3.00 ng/ml. Compared with the surviving patients (11.55 ± 2.98 ng/ml), dead patients had a significantly higher preoperative plasma level of TAZ (13.80 ± 2.45 ng/ml) ($P = 0.03$).

Univariate Analysis of Predictors for Postoperative In-Hospital Death

The results of univariate analysis showed that the preoperative plasma level of TAZ was correlated with more postoperative in-hospital death. We also found that age, gender, BMI, systolic blood pressure, diastolic blood pressure, heart rate, hypertension, smoking history, recent myocardial infarction, previous cardiac surgery, cardiac tamponade, LVEF, serum creatinine, critical preoperative state, unstable angina, d-dimer, platelet, fibrinogen, c-reactive protein, troponin I, ascending aorta diameter, pleural effusion, pericardial effusion, coronary arteries involved, cardiopulmonary bypass time, and cross-clamp time were not associated with postoperative in-hospital death in this cohort (**Table 2**).

The Linear Relationship Between the Preoperative Plasma Level of TAZ and the Postoperative In-Hospital Death in Different Models

Univariate linear regression models were used to evaluate the associations between TAZ expression and postoperative in-hospital death after adjusting for age, sex, BMI, recent myocardial infarct, serum creatinine, cardiac tamponade, and

TABLE 1 | Baseline characteristics of participants in ATAAD.

Postoperative in-hospital death	No	Yes	*P*-value
N	86	9	
TAZ, ng/mL, mean ± SD	11.55 ± 2.98	13.80 ± 2.45	0.03*
Age, years, mean ± SD	51.42 ± 11.67	47.11± 10.68	0.36
Sex (male) *n* (%)	58 (67.44%)	8 (88.89%)	0.27
BMI, kg/cm^2, mean ± SD	25.69 ± 3.42	26.66 ± 5.51	0.69
Systolic blood pressure, mmHg, mean ± SD	126.07 ± 19.86	119.56 ± 19.12	0.28
Diastolic blood pressure, mmHg, mean ± SD	73.52 ± 11.10	73.56 ± 17.02	0.89
Heart rate, mean ± SD	81.00 ± 9.29	81.56 ± 7.32	0.46
Hypertension *n* (%)	42 (48.84%)	5 (55.56%)	0.70
Smoking history *n* (%)	25 (29.07%)	3 (33.33%)	0.72
Diabetes status *n* (%)	0 (0.00%)	0 (0.00%)	> 0.99
Pulmonary disease *n* (%)	0 (0.00%)	0 (0.00%)	> 0.99
Extracardiac arteriopathy *n* (%)	5 (5.81%)	0 (0.00%)	> 0.99
Neurological or musculoskeletal dysfunction *n* (%)	2 (2.33%)	0 (0.00%)	> 0.99
Previous cardiac surgery *n* (%)	11 (12.79%)	1 (11.1%)	> 0.99
Recent myocardial infarct *n* (%)	58 (67.44%)	6 (66.67%)	0.96
Cardiac tamponade *n* (%)	8 (9.30%)	1 (11.11%)	> 0.99
LVEF (%)	59.91 ± 7.85	62.89 ± 6.74	0.30
Serum creatinine, μmol/L, mean ± SD	84.48 ± 41.11	84.48 ± 41.11	0.53
Critical preoperative state *n* (%)	66 (76.74%)	8 (88.89%)	0.68
Unstable angina *n* (%)	3 (3.49%)	1 (11.11%)	0.28
D-dimer, median IQR, ng/mL	2051 (1006.25–3809.25)	3,341 (2,006–4,996)	0.26
Platelet, G/L, mean ± SD	154.45 ± 56.60	152.33 ± 37.92	0.91
Fibrinogen, g/L, mean ± SD	3.37 ± 1.71	3.08 ± 0.92	0.62
C-reactive protein, mg/L, mean ± SD	74.38 ± 27.66	78.24 ± 29.97	0.69
Troponin I, median IQR, ng/mL	0.08 (0.01-0.80)	0.04 (0.02–1.36)	0.51
Ascending aorta diameter, cm, mean ± SD	4.81 ± 0.73	4.81 ± 0.63	0.99
Pleural effusion *n* (%)	17 (19.77%)	2 (22.22%)	0.86
Pericardial effusion *n* (%)	21 (24.42%)	2 (22.22%)	0.88
Coronary arteries involved *n* (%)	5 (5.81%)	1 (11.11%)	0.53
Location of intimal defect *n* (%)			0.74
Ascending aorta	51 (59.30%)	6 (66.67%)	
Aorta arch	30 (34.88%)	3 (33.33%)	
Distal ascending aorta	5 (5.81%)	0 (0.00%)	
Cross-clamp time, min, mean ± SD	101.48 ± 41.54	105.22 ± 52.93	0.85
Cardiopulmonary bypass time, min, mean ± SD	187.87 ± 73.53	200.33 ± 53.94	0.29

Results are expressed as n (%) or mean ± standard deviation (SD) or median interquartile range (IQR).
BMI: body mass index; LVEF: left ventricular ejection faction; TAZ: WW domain –containing transcription regulator protein 1.
** P value indicates significance at P< 0.05.*

cardiopulmonary bypass time (**Figure 2**). The red line represents the model's fit spline, while the blue line represents the 95% confidence intervals.

Multiple Regression Analysis: The Predictive Ability of the Preoperative Plasma Level of TAZ for Postoperative In-Hospital Death

The multiple regression analysis results are shown in **Table 3**. Three models were constructed: crude model (not adjusted), adjusted model I (adjusted for age, sex, and BMI), and adjusted model II (adjusted for age, sex, BMI, recent myocardial infarct, serum creatinine, cardiac tamponade, and cardiopulmonary bypass time). In the crude model, the preoperative plasma level of TAZ showed a positive correlation with postoperative in-hospital death (OR = 1.33, 95% CI: 1.01–1.74, $P = 0.04$). In adjusted model I and adjusted model II, similar results were indicated (OR = 1.35, 95% CI: 1.01–1.80, $P = 0.04$ and OR = 1.35, 95% CI: 1.01–1.81, $P = 0.04$).

As demonstrated in **Figure 3**, the ROC curve was used to determine the best threshold of the preoperative plasma level of TAZ by using a bootstrap resampling (times = 500), which showed an area under the curve of 0.72. The best threshold

TABLE 2 | The unadjusted association of clinical characteristics with in-hospital mortality (*N* = 95).

Variables	Statistics	OR (95% CI)	*P*-value
TAZ, ng/mL, mean ± SD	11.76 ± 3.00	1.33 (1.01, 1.74)	0.04*
Age, years, mean ± SD	51.01 ± 11.59	0.97 (0.91, 1.03)	0.29
Sex (male), *n* (%)	66 (69.5%)	3.86 (0.46, 32.41)	0.21
BMI, kg/cm^2, mean ± SD	25.8 ± 3.6	1.08 (0.89, 1.29)	0.45
Systolic blood pressure, mmHg	125.5 ± 19.8	0.98 (0.95, 1.02)	0.35
Diastolic blood pressure, mmHg	73.53 ± 11.66	1.00 (0.94, 1.06)	0.99
Heart rate, mean ± SD	81.05 ± 9.09	1.01 (0.93, 1.09)	0.86
Hypertension, *n* (%)	47 (49.47%)	1.31 (0.33, 5.21)	0.70
Smoking history, *n* (%)	28 (29.47%)	1.22 (0.28, 5.26)	0.79
Recent myocardial infarction *n* (%)	64 (67.37%)	0.97 (0.22, 4.15)	0.96
Previous cardiac surgery, *n* (%)	12 (12.63%)	0.85 (0.10, 7.49)	0.89
Cardiac tamponade, *n* (%)	9 (9.47%)	1.22 (0.13, 11.03)	0.86
LVEF, %, mean ± SD	60.22 ± 7.76	1.06 (0.96, 1.17)	0.27
Serum creatinine, μmol/L, mean ± SD	85.55 ± 42.72	1.01 (0.99, 1.02)	0.46
Critical preoperative state, *n* (%)	74 (77.89%)	2.42 (0.29, 20.57)	0.42
Unstable angina, *n* (%)	4 (4.21%)	3.46 (0.32, 37.24)	0.31
D-dimer, median IQR, ng/mL	2058 (1030.5–4252)	1.00 (1.00,1.00)	0.28
Platelet, G/L, mean ± SD	154.25 ± 54.95	1.00 (0.99, 1.01)	0.91
Fibrinogen, g/L, mean ± SD	3.35 ± 1.65	0.89 (0.58, 1.38)	0.61
C-reactive protein, mg/L, mean ± SD	74.75 ± 27.74	1.01 (0.98, 1.03)	0.69
Troponin I, median IQR, ng/mL	0.08 (0.01–0.88)	1.02 (0.95, 1.10)	0.53
Ascending aorta diameter, cm, mean ± SD	4.81 ± 0.72	1.01 (0.39, 2.63)	0.99
Pleural effusion *n* (%)	19 (20.00%)	1.16 (0.22, 6.09)	0.86
Pericardial effusion *n* (%)	23 (24.21%)	0.88 (0.17, 4.59)	0.88
Coronary arteries involved n (%)	6 (6.32%)	2.02 (0.21, 19.53)	0.54
Cross-clamp time, min, mean ± SD	101.85 ± 42.46	1.00 (0.99, 1.02)	0.80
Cardiopulmonary bypass time, min, mean ± SD	189.05 ± 71.77	1.00 (0.99, 1.01)	0.62

Results are expressed as n (%) or mean ± standard deviation (SD) or median interquartile range (IQR).
BMI, body mass index; TAZ, WW domain–containing transcription regulator protein 1; CI, confidence interval; OR, odds ratio.
** P value indicates significance at P< 0.05.*

based on maximizing the sum of sensitivity and specificity was 12.70 (ng/mL) (sensitivity: 68.60%; specificity: 77.78%). Multiple regression analysis (**Table 3**) showed a significant difference between patients stratified by the preoperative plasma level of TAZ = 12.70 (ng/mL). The risk of postoperative in-hospital death in the preoperative plasma level of the TAZ ≥ 12.70 ng/mL group was 7.65 times (OR = 7.65, 95% CI: 1.49–39.28; *P* = 0.02) that of the preoperative plasma level of the TAZ < 12.70 ng/mL group **Table 4**. After adjustment, the result was still statistically significant: the risk of postoperative in-hospital death in the preoperative plasma level of the TAZ ≥ 12.70 ng/mL group was 10.08 times (OR = 10.08, 95% 1.63–62.37; *P* = 0.02) that of the preoperative plasma level of the TAZ < 12.7 ng/mL group.

DISCUSSIONS

In the history of ATAAD, the mortality of untreated patients with ATAAD is reported to be ∼1–2% per hour after occurrence, 50% at the end of the third day, and up to 90% within 30 days (12–15). Medical management for these patients was useless, the postoperative in-hospital mortality rate was over half (57%), and no improvement was observed as the medical technology developed (2). The present guidelines recommend that aortic surgeons try to operate on all patients with ATAAD because 1-month mortality declines almost 70% (3, 4). However, surgeons still need to remain calm and make appropriate, careful surgical choices, even though there has been a significant decline in the in-hospital surgical mortality rate of patients presenting with ATAAD, which has decreased from 25 to 18% in 17 years (2). Some preoperative presentations (such as malperfusion phenomena: neurological or musculoskeletal dysfunction, recent myocardial infarction, and tamponade) have been incorporated into predictive risk models (16, 17) based on the International Registry of Aortic Dissection (IRAD) and individual center data (18, 19). However, the present study reported that recent myocardial infarction, critical preoperative state (including neurological or musculoskeletal dysfunction), and tamponade were not associated with postoperative in-hospital death in this cohort. The reason to the different findings might be that all the small populations of patients received emergent surgery, and the clinical malperfusion phenomena, rather than signs of

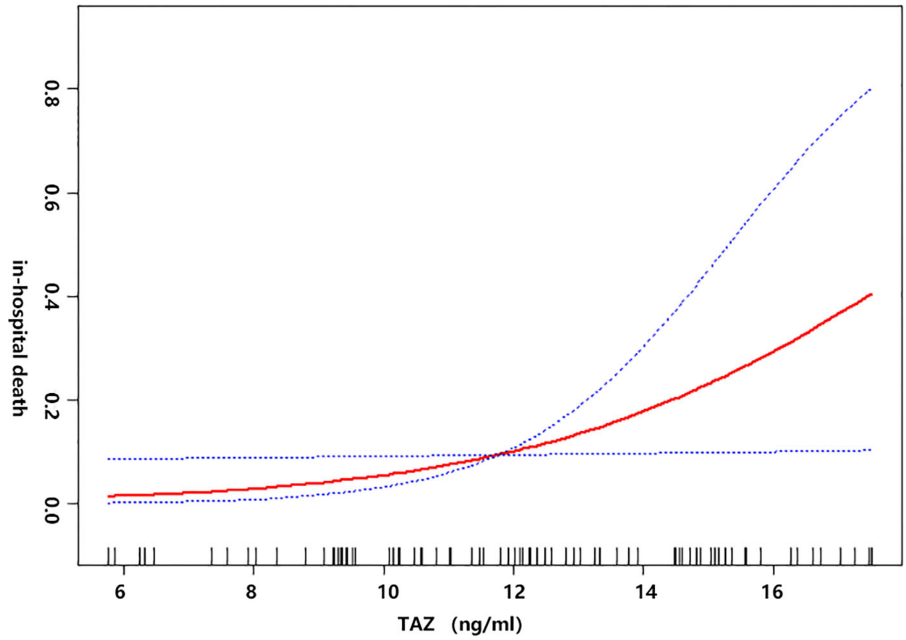

FIGURE 2 | The non-linear relationship between the preoperative plasma level of TAZ and postoperative in-hospital death after adjusting for age, sex, BMI, recent myocardial infarct, serum creatinine (μmol/L) cardiac tamponade, and cardiopulmonary bypass time (min).

TABLE 3 | Relationship between the preoperative plasma level of TAZ and Postoperative in-hospital death in different adjusted models.

Variables	Crude model		Adjusted model I		Adjusted model II	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
TAZ (ng/mL)	1.33 (1.01, 1.74)	0.04*	1.35(1.01, 1.80)	0.04*	1.35 (1.01, 1.81)	0.04*
TAZ (ng/mL)						
<12.70	1.0		1.0		1.0	
≥12.70	7.65 (1.49, 39.28)	0.02*	8.59 (1.55, 47.65)	0.01*	10.08 (1.63, 62.37)	0.01*

Crude model: adjust for none Adjusted model I: adjust for age, sex, BMI Adjusted model II: adjust for age, sex, BMI, recent myocardial infarct, serum creatinine (μmol/L), cardiac tamponade, and cardiopulmonary bypass time (min).
TAZ, WW domain–containing transcription regulator protein 1; CI, confidence interval; OR: odds ratio.
** P-value indicates significance at P< 0.05.*

malperfusion in the CT angiography, did not appear in this early stage. As a result, more easily measurable and precise biomarkers are needed for aortic surgeons to precisely evaluate the postoperative in-hospital mortality of patients and make the best choices for their patients.

TAZ exists in most human tissue, and its functional role is critical in the cardiovascular system (8, 20, 21). Our previous study found that Hippo pathway expression played a key role in hypertrophic cardiomyopathy (22). The central regulating function of the Hippo pathway was identified in a study of the phenotypic switch of vascular smooth muscle cells (VSMC) (21). We also found that clearly disrupted elastic lamellae of variable widths softened the ECM of the ascending aortic wall, possibly inducing Hippo pathway, which promoted the development ATAAD (8). The reduction of Yes-associated protein (YAP) in the middle layer of the aortic wall in ATAAD was confirmed, and its expression was negatively correlated with the ascending aorta diameter, which means that the less YAP in the tissue, the more severe the dissection is (8). It is widely known that TAZ and YAP are transcriptional co-regulators, and they are expressing and functioning similarly (23). YAP shares 45% amino acid identity

TABLE 4 | Postoperative outcome for the TAZ < 12.70 ng/ml group and TAZ ≥ 12.70 ng/ml group.

TAZ (ng/mL)	<12.70	≥12.70	*P*-value
N	61	34	
Postoperative in-hospital death n (%)	2 (3.28%)	7 (20.59%)	0.01*

TAZ, WW domain–containing transcription regulator protein 1.
** P value indicates significance at P< 0.05.*

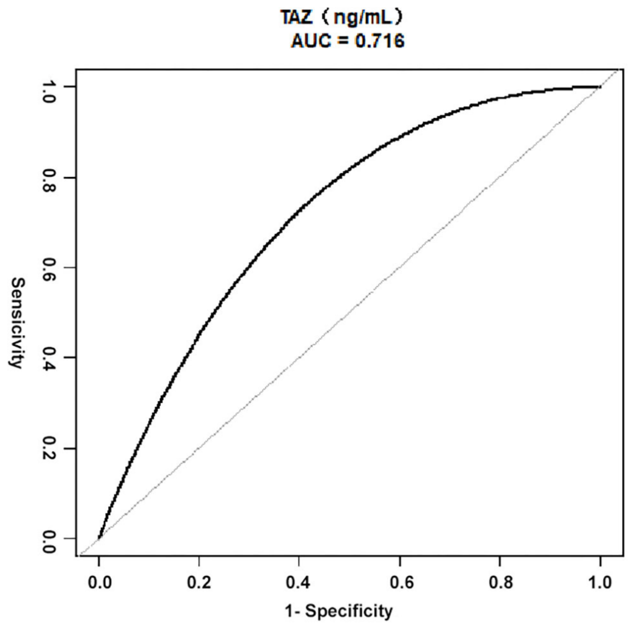

FIGURE 3 | ROC curves for the preoperative plasma level of TAZ in ATAAD, using Bootstrap resampling (times = 500) for the association of postoperative in-hospital mortality. AUC confidence interval and significance tests using Bootstrap resampling. The best threshold was based on maximizing the sum of sensitivity and specificity. The analysis reveals that 12.70 (ng/mL) was the best threshold (AUC: 0.72, 95% CI 0.53–0.86; sensitivity: 68.60%; specificity: 77.78%). ATAAD, Acute type A aortic dissection; ROC, receiver-operating characteristic; AUC, area under the curve; CI, confidence interval; TAZ, WW domain–containing transcription regulator protein 1.

with TAZ, and both of them play redundant roles in the control of cardiac growth, but the potential functional redundancy of these proteins has not been confirmed. (23). Our study provided an interesting result that TAZ was expressed at a significantly higher plasma level of ATAAD patients. Based on these findings, we propose a hypothesis that the downregulation of YAP expression in the aortic wall might lead to a compensatory increase of its transcriptional coregulator, TAZ, rather than itself, in the blood. If the hypothesis is true, the less YAP in the aortic wall would cause more severe dissection and a higher plasma level of TAZ in ATAAD patients. The increasing TAZ in blood would become a biomarker of the severity of ATAAD.

Thus, this study relied on the clinical data to determine whether there was an association between the preoperative plasma level of TAZ and the severity of ATAAD. The plasma level of TAZ in blood had a significant positive relation to postoperative in-hospital death in all the models. In the crude model, postoperative in-hospital death increased 33% as the preoperative plasma level of TAZ increased 1 ng/ml. In adjusted model I and adjusted model II, the increase in postoperative in-hospital death was 35 and 35%, respectively, when the preoperative plasma level of TAZ experienced an increase of 1 ng/ml. In adjusted model I, basic patient data, such as age, sex, and BMI, were chosen as variables. According to our clinical experience, recent myocardial infarct, serum creatinine, cardiac tamponade, and cardiopulmonary bypass time were added to adjusted model II. After that, we determined that a preoperative plasma level of TAZ = 12.70 ng/ml was a statistically significant cutoff point using the ROC curve. The postoperative in-hospital death of patients with the preoperative plasma level of TAZ ≥ 12.70 ng/ml was 10.08 times that of patients with TAZ < 12.70 ng/ml. This outcome indicates to aortic surgeons that a high preoperative plasma level of TAZ means poor surgical prognosis for ATAAD patients.

Age ≥70 years, previous cardiac surgery, cardiac tamponade, and recent myocardial infarction were reported as independent postoperative in-hospital predictors of mortality (16, 17). However, these factors played less important roles in predicting postoperative in-hospital death in the present study for the following reasons. First, the population of this study (51.01 ± 11.59 years) was younger than that in the International Registry of Acute Aortic Dissection (IRAD, population approximately 60 years old), (16, 17) so we are unable to divide the participants according to an age ≥70 years. Second, the ratio of previous cardiac surgeries in this study (12.79%) was similar to that from IRAD (13.90%) (16). Although there was a significant relationship between previous cardiac surgery and mortality reported in the literature, the results of most subgroups (aortic valve replacement, aortic aneurysm or dissection, and CABG) were not significant in our study. Finally, the predictive effect of malperfusion phenomena on postoperative in-hospital mortality is controversial. The present study reported that malperfusion phenomena, such as recent myocardial infarction, critical preoperative state (including neurological or musculoskeletal dysfunction), and cardiac tamponade, were not associated with postoperative in-hospital death in this cohort. The malperfusion phenomena might appear in the early stage, but all the patients of this study received the surgery urgently.

Several limitations exist in this study. First, this is a retrospective cohort study and provides only weak evidence between exposure and outcome, and it is difficult to distinguish between cause and effect. Second, some patients were diagnosed by the CTA from other hospitals before surgery, and it was difficult to get these CTA to do a detailed analysis, so we used data of clinical malperfusion, such as recent myocardial infarction, critical preoperative state, and cardiac tamponade. Finally, because the study population contains only 95 ATAAD patients who underwent surgery in a very short period (6 month), the results may not be generalizable to all ATAAD patients. Considering the fact that only 9 deaths occurred, the correlations and statistical analyses performed to associate the preoperative plasma level of TAZ with mortality could be improved with a larger prospective study population in the future.

CONCLUSIONS

In conclusion, this study showed for the first time that a high preoperative plasma level of TAZ suggests poor surgical prognosis in ATAAD patients and that patients with the preoperative plasma level of TAZ ≥ 12.70 ng/ml had much higher postoperative in-hospital mortality. As a result, TAZ is related to surgical mortality of patients with ATAAD and merits rigorous study in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Beijing Anzhen Hospital (Institutional Review Board File 2014019). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WJ, YZ, and HZ were expected to have made substantial contributions to the conception. YX and HL helped in sample analysis and contributed to analyzing the results. WJ, YX, and HL play major roles in writing and revising the manuscript. All authors read the manuscript and approved the final version.

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Predicting Intensive Care Unit Length of Stay After Acute Type A Aortic Dissection Surgery Using Machine Learning

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Background: Patients with acute type A aortic dissection are usually transferred to the intensive care unit (ICU) after surgery. Prolonged ICU length of stay (ICU-LOS) is associated with higher level of care and higher mortality. We aimed to develop and validate machine learning models for predicting ICU-LOS after acute type A aortic dissection surgery.

Methods: A total of 353 patients with acute type A aortic dissection transferred to ICU after surgery from September 2016 to August 2019 were included. The patients were randomly divided into the training dataset (70%) and the validation dataset (30%). Eighty-four preoperative and intraoperative factors were collected for each patient. ICU-LOS was divided into four intervals (<4, 4–7, 7–10, and >10 days) according to interquartile range. Kendall correlation coefficient was used to identify factors associated with ICU-LOS. Five classic classifiers, Naive Bayes, Linear Regression, Decision Tree, Random Forest, and Gradient Boosting Decision Tree, were developed to predict ICU-LOS. Area under the curve (AUC) was used to evaluate the models' performance.

Results: The mean age of patients was 51.0 ± 10.9 years and 307 (87.0%) were males. Twelve predictors were identified for ICU-LOS, namely, D-dimer, serum creatinine, lactate dehydrogenase, cardiopulmonary bypass time, fasting blood glucose, white blood cell count, surgical time, aortic cross-clamping time, with Marfan's syndrome, without Marfan's syndrome, without aortic aneurysm, and platelet count. Random Forest yielded the highest performance, with an AUC of 0.991 (95% confidence interval [CI]: 0.978–1.000) and 0.837 (95% CI: 0.766–0.908) in the training and validation datasets, respectively.

Conclusions: Machine learning has the potential to predict ICU-LOS for acute type A aortic dissection. This tool could improve the management of ICU resources and patient-throughput planning, and allow better communication with patients and their families.

Keywords: acute type A aortic dissection, surgery, intensive care unit, length of stay, machine learning

INTRODUCTION

Acute type A aortic dissection is one of the leading causes of mortality worldwide, with a spontaneous mortality of 1–3% per hour within the first 48 h (1). As the mortality rate is very high, immediate surgery is indicated. After surgery, medical care provided to patients in the intensive care unit (ICU) is labor intensive and costly (2). The ICU-length of stay (ICU-LOS) of patients varies substantially. Accurate prediction of ICU-LOS is of great significance in acute type A aortic dissection, especially in the context of an aging population and increasing cardiovascular surgeries. It is one of the effective solutions to tackle capacity management, recourse planning, and staffing levels (3–5).

Although there were models for predicting ICU-LOS, they had relied on conventional statistical methods, which might limit their application and performance in a larger dataset with multiple variables and samples (6–12). Recently, computational methods such as machine learning have attracted more and more attention due to their ability to predict events occurrence and aid in clinical decision-making (13). Machine learning refers to a body of methods based on computer science that use patterns in data to identify or predict an outcome. It provides a powerful set of tools to describe association between the features and outcomes of interest, particularly when they are nonlinear and complex (14–16). It is best used when there are huge number of variables, and overfitting (poor generalizability) can be a problem for traditional statistical methods. Accordingly, our aim was to design and evaluate supervised machine learning models to predict ICU-LOS based on preoperative and intraoperative data of patients after type A aortic dissection surgery.

MATERIALS AND METHODS

Patients and Data Sources

This retrospective study was approved by our institutional review board, and the informed consent from patients was waived. The entire cohort was patients who were diagnosed with acute type A aortic dissection (17) between September 2016 and August 2019 in Guangdong Provincial Cardiovascular Institute. All the patients were confirmed by computed tomography or transesophageal echocardiography. After acute type A aortic dissection surgery, the patients were transferred to ICU immediately. Patients were characterized by 84 readily available preoperative (including demographics, clinical manifestations, medication history, previous history, vital signs, laboratory findings, and auxiliary examinations) and intraoperative (including surgical types, surgical times, surgical technique, and intraoperative observation) variables. Data were input by experienced physicians and nurses and each record was audited by dedicated trained technical and medical teams. For the classification of dissection aneurysm, we used a modified version of the Stanford types proposed by Beijing Anzhen Hospital, Capital Medical University. Stanford's type A is classified as type C and type S according to the lesion of the aortic arch. Type C is defined as one of the following: (1) the primary intimal tear locates in aortic arch or distal aorta, and the dissection retrogrades to the ascending aorta or proximal aortic arch; (2) aortic aneurysm exists in aortic arch or distal aorta (diameter > 5 cm); (3) the involvement of brachiocephalic artery; and (4) caused by Marfan's syndrome. Type S is defined as follows: the location of the primary intimal tear is in the ascending aorta, without any lesions of type C.

Feature Selection for Modeling

Feature selection is an essential but important process of building a machine learning model. It implies some degree of cardinality reduction by reducing the number of features used to build a model. In this study, features with missing values more than 20% were excluded. There were a large number of variables after data cleaning, sampling, and preprocessing. Thus, we used Kendall rank correlation coefficient to select the significant features. The features with Kendall's tau ranked in the top 25% were identified.

Models' Development, Evaluation, and Validation

We divided the ICU-LOS into four intervals ($<$4, 4–7, 7–10, and $>$10 days) according to its interquartile range. Five classic machine learning models with five-fold cross-validation were developed to predict ICU-LOS, namely, Naive Bayes (NB), Linear Regression (LR), Decision Tree (DT), Random Forest (RF), and Gradient Boosting Decision Tree (GBDT). Overall, the original dataset was randomly split into a training (247 cases, 70%) dataset and a held-out validation (106 cases, 30%) dataset. Classification performance of the machine learning models was measured using the area under the curve (AUC) and the associated 95% confidence interval (CI), which was subjected by bootstrapping 100 times. Machine learning models were implemented in open-source Python 3X and Project Jupyter version 1.2.3 (Anaconda, Inc., https://jupyter.org/about). The descriptions of machine learning models were shown below.

Naive Bayes

Based on Bayes theorem, NB is a probabilistic classifier with a strong assumption of independence among variables or features. It has solid mathematical foundation and stable classification efficacy. It requires few parameters to estimate and it is not sensitive to missing data. The algorithm is relatively simple, with a small error rate. The classification principle is based on the prior probability of an object, using Bayes formula to calculate the posterior probability, that is, the probability that each object belongs to a specific class. The class with the maximum posterior probability is selected as the class that the object belongs to.

Linear Regression

LR is a kind of generalized linear regression algorithm. The independent variables of the LR model can accept a wide range of data types, including continuous and discrete variables. The LR model is easy to be trained and its parameters are easy to be explained, so it is widely used in the biomedical field, especially in epidemiology. This model uses a sigmoid function to predict the logistic transformation of the probability for each class in the dependent variable. The logged odds classify the data points in a binary fashion. The lambda parameter used for the model was a ridge value of 1.0E−8 in addition to conjugate gradient descent. Conjugate gradient descent was applied to reduce the cost function in the model. Basically, in the case of classification, the learned LR classifier is actually a set of weights θ. When there is test sample input, the weights and test data are weighted. The formula of LR is shown below.

$$P(y=1|x;\theta)=\frac{1}{1+e^{-\theta^{T}x}} \tag{1}$$

Decision Tree

There are many advantages to use the DT model in classification problems, such as low computational complexity, convenience, and efficiency. It can process data with unrelated characteristics and construct rules that are easy to be explained and understood. DT consists of nodes and directed edges. There are two types of nodes: the internal node, which represents a feature or attribute, and the leaf node, which represents a class. In general, a DT contains a root node, several internal nodes, and several leaf nodes. DT can be thought of as a collection of if–else rules. A rule is constructed from each path from root node to leaf node. The feature of inner node corresponds to the condition of the rule, and the leaf node corresponds to the decision result of the rule. The paths of DT are mutually exclusive but complete; that is, each instance is covered by only one path or one rule. The purpose of DT classifier learning is to produce a decision tree with strong generalization ability to deal with the unseen examples.

Random Forest

RF is an ensemble learning algorithm based on DT. It is very simple, is easy to implement, and has very little computing overhead, but shows amazing performance in classification and regression. Therefore, RF is praised as a method representing the technology level of ensemble learning. RF applies an ensemble of DT and bootstrapping to sample training data and split branches in each tree. The target in each split is to maximize the gained information from each random feature in each sample per tree. After evaluating the data points, the resulting class is the mode of the results of all trees. Briefly, each DT is a classifier, so for an input sample, N trees will have N classification results. The RF integrates all the classified voting results and specifies the classification with the most votes as the final output.

Gradient Boosting Decision Tree

The working mechanism of the Boosting algorithm is to train a weak learner 1 with the initial weight of the training dataset, and update the weight of the training sample according to the learning error rate of the weak learner, so that the weight of the training sample points with high learning error rate in the previous weak learner 1 becomes higher. Then, these points with high error rate get more attention in weak learner 2, and the training set with the adjusted weight is used to train weak learner 2. This is repeated until the number of weak learners reaches the pre-specified number T, and the T weak learners are integrated through the set strategy to get the final strong learner. After knowing the Boosting method, we can combine the Boosting method with the DT to get the GBDT.

Statistical Analysis

All statistical analyses were performed with Python 3.X and Project Jupyter 1.2.3 (Anaconda, Inc, https://jupyter.org/about). The packages were used as follows: "fitcnb" for NB, "glmfit" for LR, "DecisionTreeClassifier" for DT, "TreeBagger" for RF, and "GradientBoostingClassifier" for GBDT. Missing data were assumed to be missing at random and were imputed using 10-fold multiple imputation by chained equations. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as counts (percentages) of the total population. Comparisons were considered statistically significant based on a two-sided p-value of <0.05.

RESULTS

Patient Characteristics

A total of 353 patients (307 males and 46 females; mean age of 51.0 ± 10.9 years) transferred to ICU after acute type A aortic dissection surgery was included. These patients were randomly assigned to a training dataset ($n = 247$) and a validation dataset ($n = 106$). The median ICU-LOS of the patients was 7.7 days (interquartile range, 4.8–11.9 days; range, 0.2–70.5 days). Four patients died after 2.9, 5.0, 19.0, and 44.4 days after ICU admission, respectively. Two patients died of septic shock, one died of extensive bleeding due to coagulation disorders, and one died of multiple organ dysfunction syndrome. Except for aortic dissection surgery, the four patients also received hemodialysis therapy and one of them required tracheotomy.

The initial predictor variables included 84 preoperative and intraoperative features for each patient. After data cleaning, sampling, and preprocessing, 11 variables with low correlation were excluded, and 73 variables (58 preoperative features and 15 intraoperative features) were finally included in the analysis. **Supplementary Table 1** shows the comparisons of baseline characteristics between the training and validation datasets. All characteristics except respiratory frequency were not statistically different between the two groups.

Feature Selection

Fourteen features were selected by Kendall correlation coefficient. After excluding two clinically irrelevant variables (venous cannulation position: superior/inferior vena cava and venous cannulation position: right atrium/vena cava), 12 features were eventually extracted to build the models, namely, 9 preoperative and 3 intraoperative features (**Figure 1**). They were ranked as follows: D-dimer ($\tau = 0.247$), serum creatinine ($\tau = 0.209$), lactate dehydrogenase ($\tau = 0.171$), cardiopulmonary bypass time ($\tau = 0.170$), fasting blood glucose ($\tau = 0.156$), white blood cell count ($\tau = 0.154$), surgical time ($\tau = 0.150$), aortic cross-clamping time ($\tau = 0.149$), with Marfan's syndrome ($\tau = 0.133$), without Marfan's syndrome ($\tau = -0.133$), without aortic aneurysm ($\tau = -0.149$), and platelet count ($\tau = -0.214$).

Machine Learning Models' Performance for Predicting ICU-LOS

The predictive performance of different machine learning models is illustrated in **Figure 2**. The models had diverse abilities in

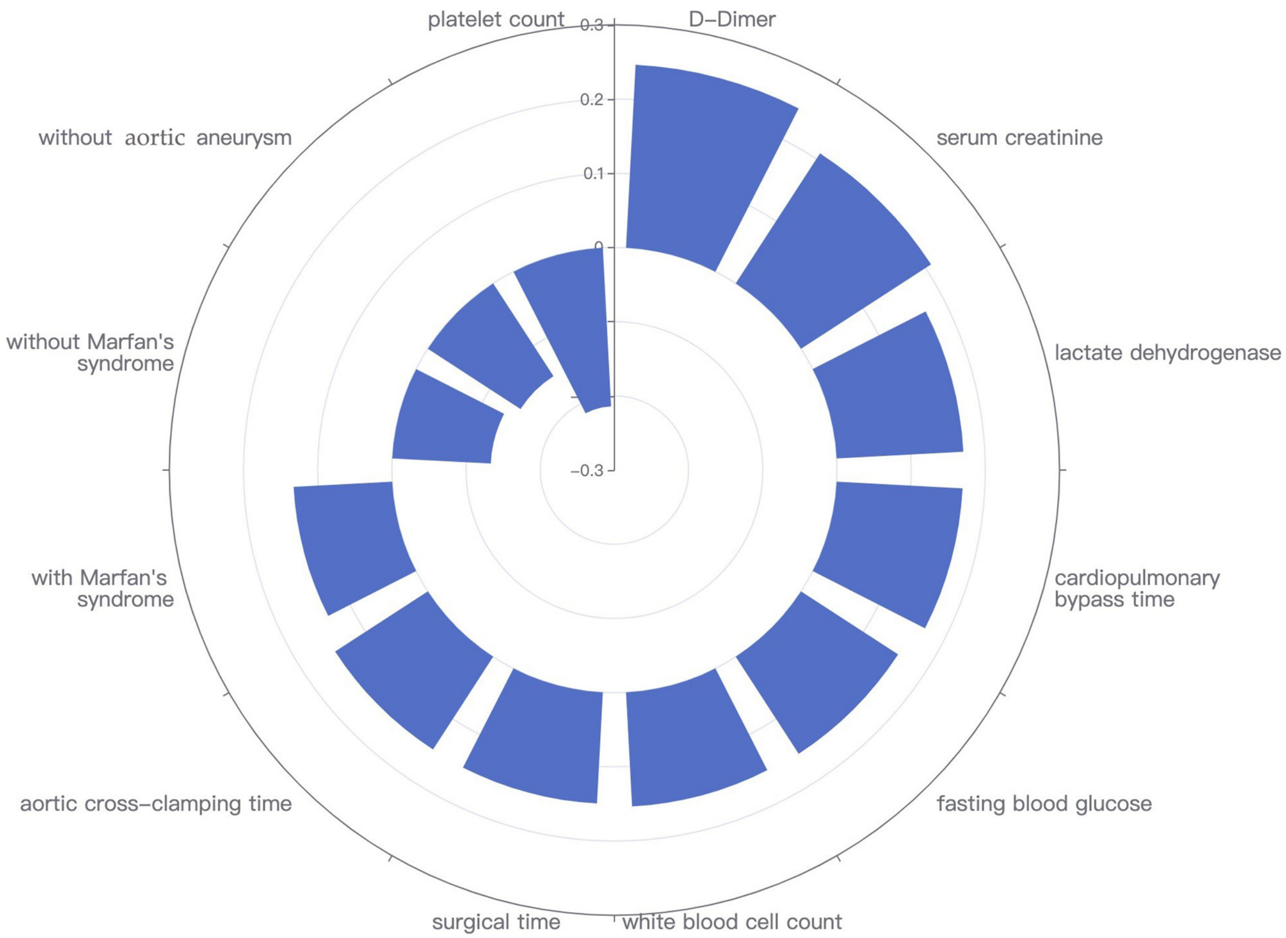

FIGURE 1 | Twelve features selected by Kendall correlation coefficient for models building.

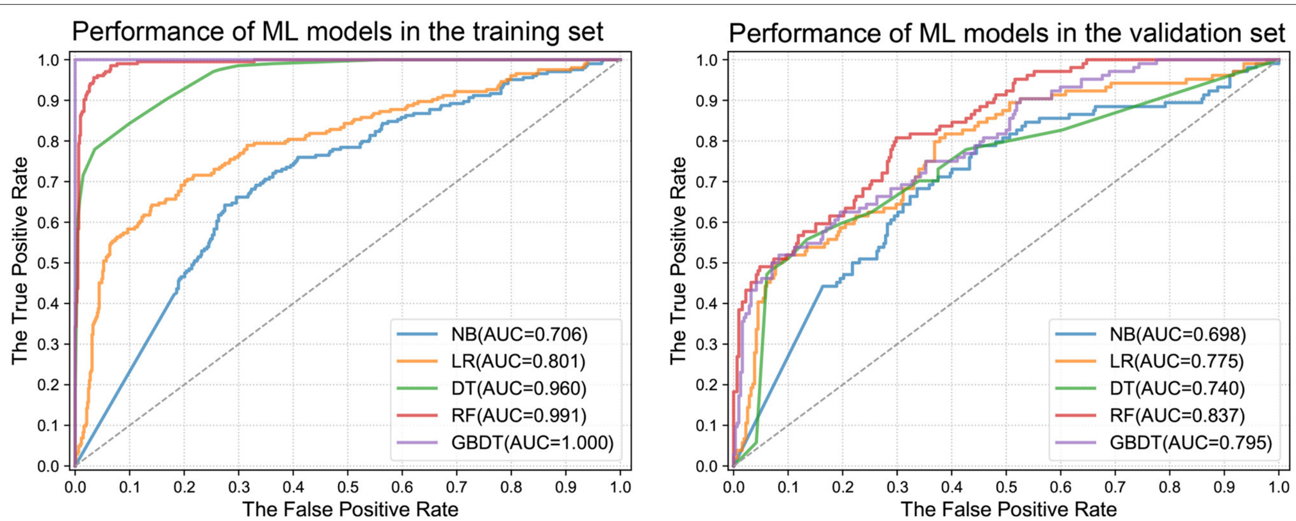

FIGURE 2 | Receiver operating characteristic area under the curves of machine learning models in the training and validation datasets. ML, machine learning; NB, Naive Bayes; LR, Linear Regression; DT, Decision Tree; RF, Random Forest; GBDT, Gradient Boosting Decision Tree; AUC, area under the curve.

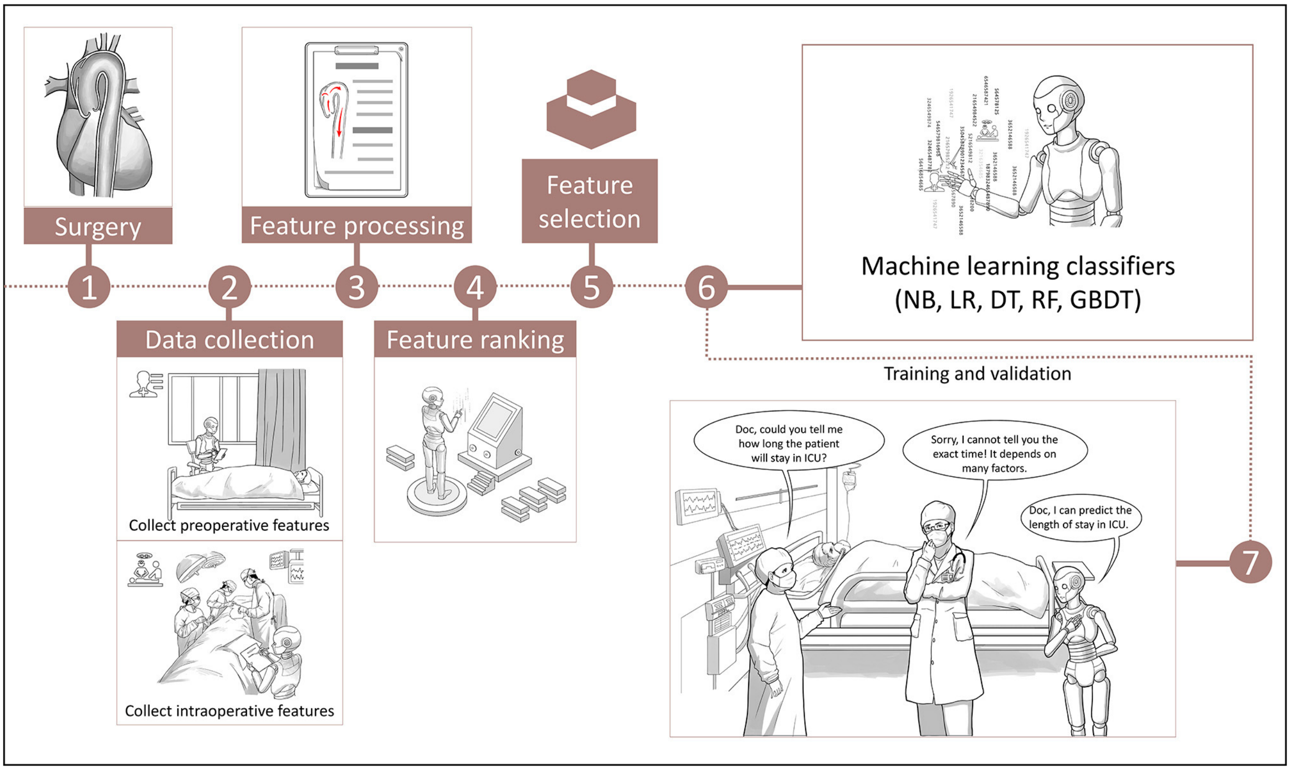

FIGURE 3 | The cartoon flow chart of machine learning models building. NB, Naive Bayes; LR, Linear Regression; DT, Decision Tree; RF, Random Forest; GBDT, Gradient Boosting Decision Tree; ICU, intensive care unit.

predicting categorical ICU-LOS. Among the five classifiers, RF achieved the highest performance, with an AUC of 0.991 (95% CI: 0.978–1.000) in the training dataset and 0.837 (95% CI: 0.766–0.908) in the validation dataset. **Figure 3** depicts the cartoon of machine learning models building.

DISCUSSION

The study showed that machine learning classifiers could accurately predict ICU-LOS in patients after acute type A aortic dissection surgery. RF had the highest performance in predicting ICU-LOS. The 12 predictors included in the models were generally readily available at the hospital. D-dimer, serum creatinine, and lactate dehydrogenase were the top three preoperative predictors, and the cardiopulmonary bypass time, surgical time, and aortic cross-clamping time were the top three intraoperative predictors.

The selection of the patients determines the applicability of the models constructed in the respective studies. Although there were models to predict ICU-LOS (6, 9, 18, 19), most of them focused on cardiac surgical patients and thus may not be suitable for aortic dissection surgical patients. The logistic regression was the most common model, with AUCs ranging from 0.60 to 0.84. The cutoff values for predicting ICU-LOS in those models differed greatly, for instance, 24, 55, and 72 h. Compared with the previous regression models, the models were built using the novel machine learning methods and included as many factors that may influence the ICU-LOS as possible. Consequently, the accuracy of the machine learning models could be up to 99%. This study may pave the way for the application of machine learning in the field of aortic dissection and promote further works on this topic.

Identifying the risk factors that significantly affect the ICU-LOS enables making more effective plan to reduce ICU duration (8, 20). Many studies (6, 8–12, 21) have evaluated the risk factors for ICU-LOS after cardiac surgeries, including type of surgery, emergent status, renal dysfunction, creatinine, sex, age, left ventricular function, myocardial infarction, cardiopulmonary bypass time, aortic cross-clamp time, and previous cardiac operation. We found that serum creatinine, lactate dehydrogenase, cardiopulmonary bypass time, and aortic cross-clamp time have been reported previously. Moreover, we identified some new factors, such as Marfan's syndrome and aortic aneurysm. It is not unexpected that Marfan's syndrome and aortic aneurysm were risk factors as both may need more extensive surgery, longer surgical time, and longer aortic cross-clamp time. However, we did not report some factors that were recognized as crucial predictors of prognosis for aortic dissection, such as concomitant malperfusion and preoperative ventilatory support, which may impair the power of prediction model.

It is important to select the final model by using different machine learning methods as each machine learning approach has its strength and weakness for different data forms. In the selection of classification models, we used NB, LR, DT, RF, and GBDT for modeling. The NB and LR models require high independence of features, but most of our features are dummy variables with a correlation with each other. Thus, the two models had poor performance in predicting ICU-LOS. The DT model has the advantages of high classification accuracy, simple mode generation, and good robustness to noisy data. RF is a supervised learning algorithm, which is an integrated learning algorithm based on the DT model. It shows excellent performance in classification and regression. The GBDT model is a result of integrated learning of DT, which incorporates the benefits of multiple machine learners. We found that these three models had satisfactory predictive performance, and RF was the best. These results confirm the explorative nature of the machine learning process that requires iterative and explorative experiments in order to discover the model design that can achieve the target accuracy for a specific problem.

However, there are some limitations that should be acknowledged. First, the data were analyzed retrospectively using electronic medical records not originally designed for the analyses performed. However, this authenticates our analysis; it confirms its utility in a real-world clinical setting. Second, this model was not externally validated, which may be not reflective and may also restrict generalizability. Further studies are warranted to address the viability of this model. Finally, the complexity and abstractness of machine learning models make it difficult to explain, which may hinder its reproducibility and clinical application. Advanced techniques are expected to be developed to make the content of machine learning easier to be understood.

Machine learning for big data analysis has revolutionized the traditional way of conducting cardiovascular disease research (22). Machine learning provides an innovative approach to data analysis and imaging interpretation beyond what is provided by conventional statistics. The ability to automatically handle large multidimensional and multivariate data could ultimately expose novel associations between specific features and outcome, and identify trends and patterns that would not be apparent to investigators. With the growing amount of patient data and the rapid implementation of automated algorithms in other fields of medicine, artificial intelligence will shortly become an indispensable part of clinical medicine (23).

CONCLUSIONS

We developed and validated machine learning models to predict the ICU-LOS in patients with acute type A aortic dissection. The performance of RF was the best with accuracy based on AUCs in the training dataset of 0.991 and the validation dataset of 0.837. The 12 predictors required for calculation of the ICU-LOS are generally readily available at the hospital. However, external validation is necessary to address the generalizability of the model.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Jinan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

QC, BZ, and JY contributed to the conception and design of the study, the analysis and interpretation of data, and the work draft. XM, LZ, FW, JF, and WH participated in the data extraction and analysis. ML and ZC designed figures and tables. RF and SZ offered guidance in study design and revised the article critically for important intellectual content. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.675431/full#supplementary-material

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ORIGINAL RESEARCH
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Development and Validation of a Diagnostic Model to Predict the Risk of Ischemic Liver Injury After Stanford A Aortic Dissection Surgery

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Objective: To define the risk factors of ischemic liver injury (ILI) following Stanford A aortic dissection surgery and to propose a diagnostic model for individual risk prediction.

Methods: We reviewed the clinical parameters of ILI patients who underwent cardiac surgery from Beijing Anzhen Hospital, Capital Medical University between January 1, 2015 and October 30, 2020. The data was analyzed by the use of univariable and multivariable logistic regression analysis. A risk prediction model was established and validated, which showed a favorable discriminating ability and might contribute to clinical decision-making for ILI after Stanford A aortic dissection (AAD) surgery. The discriminative ability and calibration of the diagnostic model to predict ILI were tested using C statistics, calibration plots, and clinical usefulness.

Results: In total, 1,343 patients who underwent AAD surgery were included in the study. After univariable and multivariable logistic regression analysis, the following variables were incorporated in the prediction of ILI: pre-operative serum creatinine, pre-operative RBC count $<$3.31 T/L, aortic cross-clamp time $>$140 min, intraoperative lactic acid level, the transfusion of WRBC, atrial fibrillation within post-operative 24 h. The risk model was validated by internal sets. The model showed a robust discrimination, with an area under the receiver operating characteristic (ROC) curve of 0.718. The calibration plots for the probability of perioperative ischemic liver injury showed coherence between the predictive probability and the actual probability (Hosmer-Lemeshow test, $P = 0.637$). In the validation cohort, the nomogram still revealed good discrimination (C statistic = 0.727) and good calibration (Hosmer-Lemeshow test, $P = 0.872$). The 10-fold cross-validation of the nomogram showed that the average misdiagnosis rate was 9.95% and the lowest misdiagnosis rate was 9.81%.

Conclusion: Our risk model can be used to predict the probability of ILI after AAD surgery and have the potential to assist clinicians in making treatment recommendations.

Keywords: ischemic liver injury, Stanford A aortic dissection, cardiac surgery, risk prediction model, intensive care unit

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INTRODUCTION

Ischemic liver injury (ILI) is a clinical syndrome characterized by acute and dramatic increases in serum aminotransferase to a level of more than 10 times the upper limit of normal, which is caused by insufficient oxygen and blood delivery to the hepatocytes (1–3). The underlying etiologies leading to ILI are cardiac, circulatory or respiratory failure (2–6). The incidence of ILI ranges between 1 and 12% in intensive care unit (ICU) (3, 6–9), and may be even higher in patients with cardiogenic shock (3, 6, 10). The all-cause mortality rate is 25 ∼ 73% (1, 2, 5–7), of which more than 50% occurred during ICU stay (2, 3, 7, 11). The surgical procedures for Stanford A aortic dissection (AAD) are complicated, and the situation is changeable during the operation. Despite improvement in perioperative management and surgical techniques, the malperfusion syndromes (i.e., ischemic liver injury) are often present as sequelae of general ischemia (12, 13).

Reliable prognostication in ILI after AAD surgery provides clinicians with helpful information about diagnosis and short-term and long-term outcomes. ILI is the most common cause of dramatic elevation of serum transaminase levels in ICU (5–7, 14, 15). Clinicians should try to recognize the incidence of ILI as early as possible to avoid complications of the hepatic injury which may trigger progression of multiorgan failure (5–7, 16–18). However, Denis et al. found that, in cardiac intensive care unit, the diagnosis of ischemic liver injury may be delayed under some circumstances (18). A delay in diagnosis may signify delayed treatment and worse outcomes. In addition, the occurrence of ILI has significantly increased in-hospital mortality of those critically ill patients (7, 11). By far, the main clinical management of ILI is the cure of the underlying diseases in the ICU (3, 4), it rarely has specific treatments to improve the liver function (7, 11). Statin treatment may be protective against the development of ischemic liver injury (1, 10, 19), but the therapeutic potential after occurrence of ILI and an overall survival benefit was not identified. Therefore, it is important to predict whether ILI occurs after AAD surgery.

Although several risk factors (20–23) have been identified are associated with the occurrence of post-operative ILI, to our knowledge, barely any study has illustrated these factors in patients with AAD surgery. Therefore, accurate prediction in patients with ILI after AAD surgery remains a challenge. The aim of the present research is to define clinical risk factors of ischemic liver injury after AAD surgery using single center cohort of patients. In particular, we hope to create and internally validate a model to predict the individual risk of ILI.

METHODS

Patients and Data Collection

Between January 1, 2015, and October 30, 2020, we retrospectively reviewed 1,513 patients who were diagnosed as Stanford A aortic dissection and underwent aortic surgery in Beijing Anzhen Hospital, Capital Medical University. The exclusion criteria (**Figure 1**) were (1) patients who were younger 18 years, (2) patients with abnormal liver function before surgery, (3) patients who died during surgery and within 24 h after surgery, (4) patients with other diseases which result in hepatocellular injury, (5) missing data. Finally, 1,343 patients were included in analytic cohort. The study was approved by the Institutional Ethics Committee of the Beijing Anzhen Hospital.

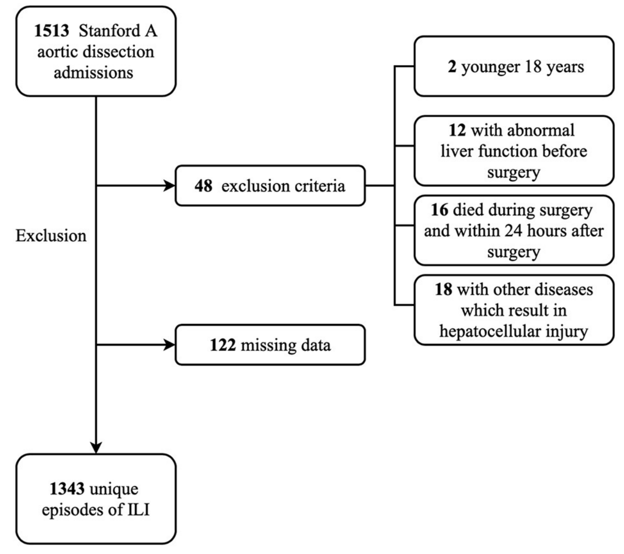


FIGURE 1 | Flow diagram of the exclusion criteria. ILI, ischemic liver injury.

Demographic and clinical data were collected, including age, sex, BMI, medical history, pre-operative alanine aminotransferase (ALT), the peak level of post-operative ALT, pre-operative serum creatinine (Cr), pre-operative red blood cell (RBC) count, coagulation function (i.e., INR, D-Dimer), cardiopulmonary bypass (CPB) time, aortic cross-clamp time (ACT), deep hypothermic circulatory arrest (DHCA) time, blood loss volume, blood transfusion volume, atrial fibrillation within 24 h after operation, ICU stay time, and all-cause mortality in hospital. The primary outcomes of interest were ischemic liver injury after cardiac surgery.

Statistical Analysis

Categorical variables were reported as whole numbers and proportions, and continuous variables were reported as medians with interquartile ranges (IQRs). Clinical variables associated with the risk factors for ILI were based on clinical importance and predictors identified in previously published articles (2, 21, 22, 24). We use the variance inflation factor (VIF) to evaluate all variables for collinearity. Continuous predictors (i.e., CPB time and Cr) were categorized after being assessed using median or mean value.

We randomly divided 1,343 patients into the training (940 cases) and internal test (403 cases) sets. The significance of each variable was assessed by univariable logistic regression analysis in the training cohort. The variables with $P < 0.1$ were entered into the multivariable logistic regression analysis to identify the risk factors. Next, a nomogram to predict the probability of ILI rates after cardiac surgery was constructed by using the rms package

TABLE 1 | Baseline characteristic of the 1,343 AAD patients.

Baseline variable	Total (n = 940)	Non-ILI (n = 847)	ILI (n = 93)	P-value
Age (years)	49.0 (41.0, 56.0)	49.0 (41.0, 56.0)	51.0 (42.0, 60.0)	0.257
BMI (Kg/m^2)	26.0 (23.6, 28.4)	26.0 (23.7, 28.5)	26.0 (23.2, 27.7)	0.290
Gender, female (%)	216 (23)	199 (23)	17 (18)	0.315
Medical history				
Cardiac surgery history (%)	52 (6)	50 (6)	2 (2)	0.206
Hypertension (%)	715 (76)	649 (77)	66 (71)	0.278
Hyperlipidemia (%)	55 (6)	50 (6)	5 (5)	1.000
Valvular disease (%)	307 (33)	279 (33)	28 (30)	0.663
Preoperative test				
LVEF (%)	62 (58, 66)	62 (58, 66)	60 (59, 66)	0.611
CT (Debakey type, %)				0.811
Debakey type I	632 (67)	571 (67)	61 (66)	
Debakey type II	308 (33)	276 (33)	32 (34)	
RBC < 3.31 (T/L, %)	474 (50)	415 (49)	59 (63)	0.011
INR	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	1.3 (1.1, 1.5)	<0.001
ALT (U/L)	19.0 (14.0, 30.0)	19.0 (13.0, 30.0)	19.0 (15.0, 33.0)	0.138
Creatinine (μmol/L)	95.4 (74.2, 129.2)	93.9 (73.1, 125.8)	120.5 (87.2, 169.1)	<0.001
D-Dimer (ng/ml)	1,751.5 (934.3, 2,733.3)	1,723.0 (909.5, 2,660.5)	2,113.0 (1231.0, 3,111.0)	0.006
Intraoperative variables				
CPB time > 199 (min)	476 (51)	418 (49)	58 (62)	0.023
DHCA time > 25.6 (min, %)	366 (39)	337 (40)	29 (31)	0.133
ACT > 140 (min)	171 (18)	147 (17)	24 (26)	0.062
Blood loss > 1,200 (ml)	447 (48)	391 (46)	56 (60)	0.014
RBCS > 2.47 (U)	262 (28)	234 (28)	28 (30)	0.701
Plasma > 213(ml)	344 (37)	303 (36)	41 (44)	0.143
WRBC (%)	468 (50)	413 (49)	55 (59)	0.073
Lactic acid level (mmol/L)				<0.001
<3	223 (24)	214 (25)	9 (10)	
≥3 and <4.5	259 (28)	233 (28)	26 (28)	
≥4.5 and < 7	241 (26)	218 (26)	23 (25)	
≥7	217 (23)	182 (21)	35 (38)	
AF (%)	125 (13)	101 (12)	24 (26)	<0.001
Death (%)	93 (10)	67 (8)	26 (28)	<0.001
ALT-max (U/L)	119.0 (53.0, 234.5)	104.0 (49.0, 176.0)	897.0 (629.0, 2195.0)	<0.001
ICU detention time (hour)	48.0 (24.0, 115.0)	46.0 (23.0, 107.5)	99.0 (40.0, 201.0)	<0.001

LVEF, left ventricular ejection fraction; CT, whether the dissection involves the abdominal aorta; RBC, red blood cell; INR, International Normalized Ratio; ALT, alanine aminotransferase; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory; ACT, aortic cross-clamp time; RBCS, the transfusion of red cells suspension; Plasma, the transfusion of plasma; WRBC, the transfusion of washed red blood cells; AF, atrial fibrillation within post-operative 24 h; Death, in-hospital all-cause die; ALT-max, the peak value of post-operative alanine aminotransferase.

*The normal ranges of diagnostic tests: RBC (4.3–5.8 * $10^{12/L}$), INR (0.8–1.2), ALT (9–50 U/L), Creatinine (57–111 μmol/L), D-Dimer (0–243 ng/ml), Lactic acid (0.5–1.6 mmol/L).*

of R, version 4.0.3 (http://www.r-project.org/). The regression coefficients in multivariate logistic regression are proportionally converted to a point scale, and the total points are transformed into predicted probabilities (25).

The performance of the nomogram was evaluated by discrimination and calibration. The discriminative ability of the model was reflected by the area under the receiver operating characteristic curve (is equivalent to the C statistics). Calibration was performed by a visual calibration plot via 1,000 bootstrap samples to decrease the overfit bias (26). An insignificant Hosmer-Lemeshow (HL) test also implies good calibration ($P >$ 0.05). In addition, we calculated the misdiagnosis rate by using 10-fold cross-validation. The statistical analysis and graphics were performed with R 4.0.3. All tests were 2-tailed, and $P < 0.05$ was considered to be statistically significant.

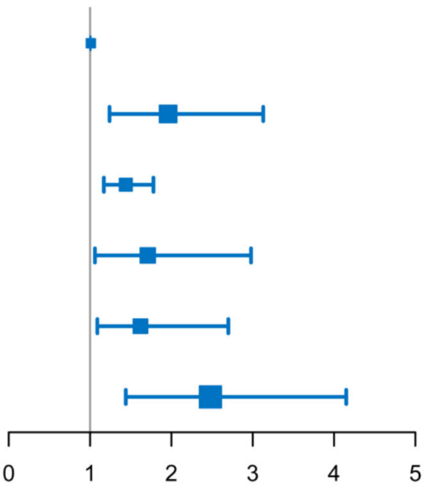
RESULTS

Demographic and Clinical Characteristics

In two groups of cases, there were 99 cases of simple aortic arch replacement, 23 cases of ascending aorta and aortic arch replacement, 898 cases of total-arch replacement and elephant

TABLE 2 | Logistic multivariable regression analysis showing the risk variables of ILI after AAD surgery.

Variable	OR (95%CI)	P.value
Creatinine (μmol/L)	1.01 (1.00 ,1.01)	0.021
RBC<3.31 (T/L, %)	1.96 (1.24 ,3.13)	0.004
Lactic acid (mmol/L)	1.44 (1.17 ,1.78)	<0.001
ACT>140 (min)	1.71 (1.06 ,2.98)	0.026
WRBC (%)	1.62 (1.09 ,2.70)	0.021
AF (%)	2.48 (1.44 ,4.15)	<0.001



OR, Odds ratio; CI, confidence interval; RBC, red blood cell; ACT, aortic cross-clamp time; WRBC, the transfusion of washed red blood cells; AF, atrial fibrillation within post-operative 24 h.

trunk surgical procedure, and concurrent operations included: 539 cases of Bentall, 4 cases of David, 3 cases of Wheat's, and 59 cases of coronary artery bypass grafting.

The median patient age was 49 years (IQR, 41–56 years), and 23% (216 of 940) of the patients were female. In total, 71% (66 of 93) of the ILI patients were complicated with hypertension, and 30% (28 of 93) of the ILI patients had valvular disease. There were 6% (52 of 940) of the patients had underwent cardiac surgery before. The pre-operative RBC count lower than 3.31T/L was observed in 49% (415 of 847) of non-ILI patients and 63% (59 of 93) of ILI patients. The pre-operative serum creatinine was 120.5 μmol/L (IQR, 87.2–169.1 μmol/L) in ILI patients, while only 93.9 μmol/L (IQR, 73.1–125.8 μmol/L) in Non-ILI patients. Compared to non-ILI patients ($n = 847$), 59% of ILI patients ($n = 93$) more blood transfused (washed red blood cells, WRBC) during operation. ILI patients had significantly higher intraoperative lactic acid level (median of 5.8 vs. 4.3 mmol/L, $P < 0.001$). They were more likely to have atrial fibrillation (26 vs. 12%, $P < 0.001$) within 24 h after surgery. The CPB time exceeded 199 min was observed in 49% (418 of 847) of Non-ILI patients and 62% (58 of 93) of ILI patients. In total, 26% (24 of 93) of the patients underwent surgery with long ACT time (>140 min) in ILI patients and 17% (147 of 847) in Non-ILI patients.

In our study cohort, 93 patients had peak ALT levels exceeding 10 times of the upper limit of normal value and were diagnosed as ILI. The median peak ALT level was 897 U/L (IQR, 629–2,195 U/L) and 104 U/L (IQR, 49–176 U/L) in the ILI and Non-ILI patients, respectively. The all-cause mortality associated with ILI was 28% (26 of 93). In addition, ILI patients had longer ICU stay time (median of 99 vs. 46 h, $P < 0.01$). More characteristics of patients are presented in **Table 1**.

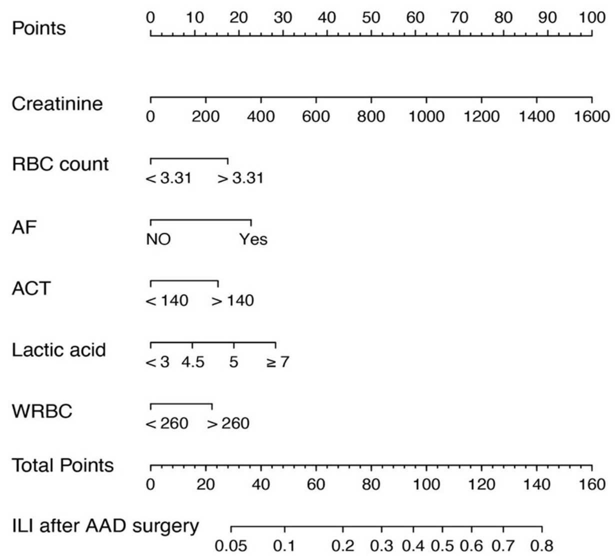


FIGURE 2 | Nomogram predicting ILI risk in patients after AAD surgery. The nomogram to predict the risk of ILI for patients after AAD surgery was created based on 6 independent prognostic factors. The value of each of variable was given a score on the point scale axis. A total score could be calculated by adding each single score, and we can estimate the probability of ILI by projecting the total score to the lower total point scale.

Selected Factors for Model

The variables used in this analysis were clinical important characteristics and proved risk factors. The results of univariable logistic regression analysis are listed in **Table 2**. On multivariable analysis, the variables of pre-operative serum creatinine (OR, 1.01; 95% CI, 1.00–1.01; $P = 0.021$), pre-operative RBC count (OR, 1.96; 95% CI, 1.24–3.13; $P = 0.004$), intraoperative lactic acid level (OR, 1.44; 95% CI, 1.17–1.78; $P < 0.001$), ACT (OR, 1.71; 95% CI, 1.06–2.98; $P = 0.026$), the transfusion of WRBC (OR, 1.62; 95% CI, 1.09–2.70; $P = 0.021$), atrial fibrillation

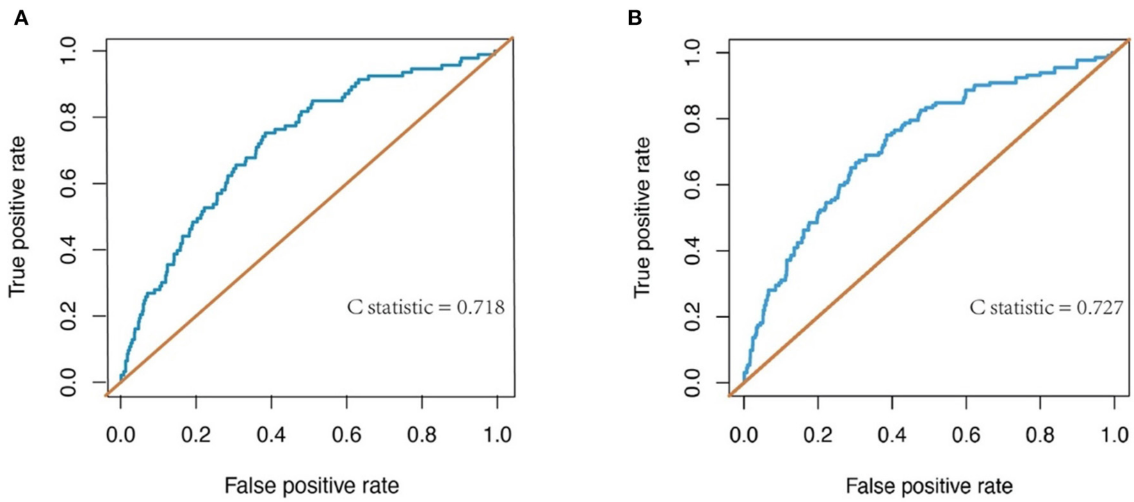


FIGURE 3 | Receiver-operating characteristic (ROC) curve for evaluating the discrimination performance of the model in both the training and validation cohorts. **(A)** ROC curve to evaluate discrimination performance in the training cohort; C-statistic was 0.718. **(B)** ROC curve for evaluating discrimination performance in the validation cohort; C-statistic was 0.727.

(OR, 2.48; 95% CI, 1.44–4.15; $P < 0.001$) were independently associated with ILI (**Table 2**).

Nomograms and Model Performance

In accordance with the multivariable logistic regression analysis, a nomogram was created to predict ILI after cardiac surgery, including 6 significant risk factors: pre-operative serum creatinine, pre-operative RBC count, intraoperative lactic acid level, ACT, the transfusion of WRBC, atrial fibrillation (**Figure 2**). A total score reached by summing up the single scores, was used to estimate the probability of ILI.

The discrimination of the predict model in the training cohort was assessed using an unadjusted C statistic of 0.718 (95% CI, 0.665–0.771) and a bootstrap-corrected C statistic of 0.701. In the validation cohort, the model represented a C statistic of 0.727 (95% CI, 0.640–0.816) for the estimation of ILI risk (**Figure 3**). The calibration plots showed that the predicted probabilities of ILI fitted well with the actual prevalence rates (**Figure 4**) and the HL test ($P = 0.637$ in the training cohort, $P = 0.872$ in the validation cohort) also demonstrated the good calibration. In addition, 10-fold cross-validation in full data set of the predict model demonstrated that the average misdiagnosis rate was 9.79% and the lowest misdiagnosis rate was 9.56%.

DISCUSSION

Previous studies have demonstrated multiple, but poorly studied risk factors for ILI, after Stanford A aortic dissection (AAD) surgery. In the present study, the formal nomogram, which demonstrated that pre-operative serum creatinine, pre-operative RBC count <3.31 T/L, aortic cross-clamp time >140 min, intraoperative lactic acid level, the transfusion of WRBC, atrial fibrillation within post-operative 24 h might increase the risk of ILI after AAD surgery. In our nomogram, the greater contributors to the risk of ILI were the intraoperative lactic acid level and atrial fibrillation.

Due to the complexity of surgery, long operation time, extracorporeal circulation (i.e., CPB), and macro trauma, post-operative ILI has higher morbidity and mortality than that reported in other types of ischemic liver injury (23, 27, 28). In this study, we found that the incidence of ILI after AAD surgery was 9.9% and the all-cause mortality was 30.8%. Additionally, researchers (6, 7, 11, 29) have shown that the severity and duration of ischemia as the primary determinants of the prognostic of ILI, and liver damage can influence the outcome of AAD surgery. Therefore, the current study is very useful clinically because the model can predict the post-operative ILI as early as possible. Among the currently available prediction tools, a nomogram is easy to quantify the risk of ILI and has good discrimination and calibration in predicting outcomes (30). As far as we know, no study before has reported the model as we did to assess the risk variables independently for their inclusion in ultimate nomogram for post-operative ILI.

Some researchers (22, 23, 31, 32) have reported that a correlation between female gender, hypertension, diabetes, lower CPB temperature, valvular disease, and ischemic liver injury. In the risk prediction model, we noted no association of these factors with ILI after AAD surgery (**Table 1**). In contrast, longer aortic cross-clamp time (28, 33), blood transfusion (22, 34) (the transfusion of WRBC), pre-operative serum creatinine (23, 27, 29) have been reported to increase the risk of ischemic liver injury. Indeed, our study suggested that these 3 variables were also significantly associated with ILI after AAD surgery.

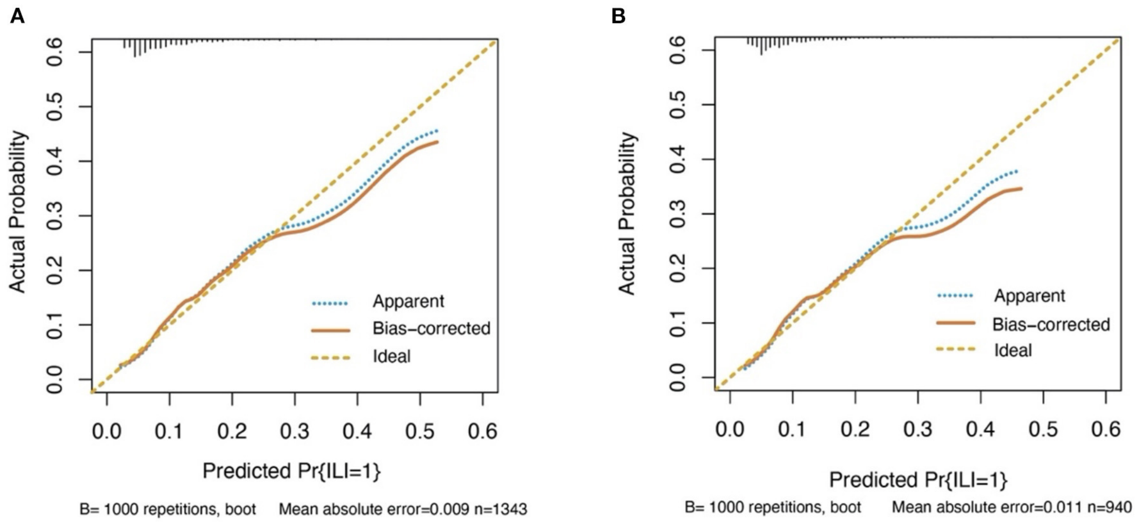


FIGURE 4 | Calibration curves for the prediction model in both cohorts. The curves describe the calibration of the nomogram in terms of agreement between predicted risks (x-axes) and actual outcomes (y-axes). The diagonal line indicates perfect prediction by an ideal model. The curve indicates the performance of the model. **(A)** Training cohort. **(B)** Validation cohort.

In addition, we demonstrated that a low pre-operative RBC count (<3.31 T/L), high intraoperative lactic acid level and atrial fibrillation were associated with an increased probability of ILI after AAD surgery.

In the current study, we found the intraoperative lactic acid level is significantly associated with post-operative ILI. Deeb et al. (13) reported that aortic dissection can result in the vital branch arterial stricture, especially the combination of celiac and mesenteric arterial stenosis (35), which may reduce the blood supply to the liver. If not treated timely, liver dysfunction and even infarction may happen caused by ischemia. Moreover, Muraki et al. (36) have reported that the serum lactate level can be a sensitive marker of the mesentery ischemia, and consequently a rapid increase in lactate level can reflect the ischemic liver injury. These studies support our clinical opinion that high intraoperative lactic acid level is an important risk factor for the ILI after AAD surgery.

Dysrhythmias occur frequently in the post-operative period of cardiac surgery, particularly atrial fibrillation, which occurs in 10 to 65% of patients requiring cardiopulmonary bypass (22, 37). During acute atrial fibrillation with rapid ventricular response, the rapid heart rate impairs the diastolic filling time and the effective atrial contraction (22, 38, 39). Additionally, Anter et al. have reported that the onset of atrial fibrillation was significantly associated with worsening of the cardiac index and the New York Heart Association (NYHA) functional class (38). As a result, the cardiac output may reduce 15 ∼ 25% (37), which decreases the hepatic blood flow and contribute to the development of ischemic liver injury.

Hepatic congestion and ischemia are common causes of ischemic liver injury. Lee et al. (40) have reported that tissue oedema in various diseases may induce hypoxia. Meanwhile, some researchers (40, 41) suggest that red blood cells have adaptive mechanisms by export of nitrate oxide bioactivity, which can support basic cellular activities in response to hypoxia. In addition, red blood cells play an important role in systemic oxygen transport and can sense the relationship between tissue oxygen demand and oxygen supply (41). Therefore, we propose that pre-operative low red blood cells count may be a risk factor of ILI after AAD surgery. Future researchers can prove this opinion by prospective studies.

The present study has several limitations. Firstly, the samples of our study were from a single institution, the proposed nomogram needs externally validation in future studies. Secondly, we constructed the prediction model retrospectively, a prospective study is required to verify the reliability of this model. Finally, the accuracy of the nomogram has not reached high reliability. If critical clinical decisions are required, there is still a misdiagnosis rate.

CONCLUSIONS

In summary, we have developed and internally validated a nomogram for predicting the risk of ischemic liver injury. The nomogram provides individual predictions of each patient, which can help improving treatment suggestions for patients with ILI after AAD surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

ML collected, analyzed the data, and wrote the manuscript. WT, WY, TW, and NL reviewed and edited it. All authors contributed to the submitted version.

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Clinical Analysis of Risk Factors for Mortality in Type A Acute Aortic Dissection: A Single Study From China

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Objective: Acute type A aortic dissection (ATAAD) is a fatal condition that requires emergency surgery. The aim of the present study was to determine pre- and intra-operative risk factors for in-hospital mortality in patients with ATAAD.

Methods: Consecutive 313 patients with ATAAD who underwent emergency surgery at our hospital from February 2012 to February 2017 were enrolled in our study. Univariate and multivariate logistic regression analysis were performed to identify the pre-operative and intra-operative risk factors for in-hospital mortality.

Results: Of the 313 patients, 32 patients (10.2%) died. Compared with survivors, non-survivors had higher heart rate, serum potassium level and EuroSCORE II, and higher incidence of moderate to severe pericardial effusion, supra-aortic vessels involvement, myocardial ischemia and lower-extremity ischemia. As for surgery-related factors, the duration of surgery and cardiopulmonary bypass time were longer in non-survivors than survivors. In addition, non-survivors were more likely to undergo coronary-artery bypass graft compared with survivors. On multivariate analysis, elevated plasma potassium level (OR: 43.0, 95% CI: 3.8–51.5, $p < 0.001$), high incidence of supra-aortic vessels involvement (OR: 4.4, 95% CI: 1.5–7.0, $p = 0.008$) and lower-extremity ischemia (OR: 4.9, 95% CI: 1.6–6.9; $p = 0.009$), and longer duration of surgery (OR 6.0, 95% CI: 1.8–18.7, $p = 0.000$) and cardiopulmonary bypass time (OR: 3.7, 95% CI: 1.3–9.3, $p = 0.001$) were independently predictive of higher mortality in patients with ATAAD.

Conclusions: Supra-aortic vessels involvement, lower-extremity ischemia and elevated plasma potassium level are independent predictors of mortality in patients with ATAAD. A significant decrease in duration of surgery and cardiopulmonary bypass time is helpful to improve survival of patients.

Keywords: acute type A aortic dissection, surgery, mortality, risk factors, retrospective

INTRODUCTION

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular condition that requires emergent surgery. In recent years, the incidence of ATAAD has been increasing significantly due to high prevalence and poor control of hypertension (1). The development of advanced imaging technology had resulted in improving the diagnosis of ATAAD. Despite the improvement in medical management and surgical technique, the hospital mortality in patients with ATAAD remains high. Previous studies reported that the mortality was 16.9–18.4% after surgical repair of ATAAD (1–3). Therefore, it is necessary to recognize pre- and intra-operative risk factors for hospital mortality in patients with ATAAD.

Therefore, the aim of our study was to identify pre- and intra-operative risk factors for in-hospital mortality in patients with ATAAD.

METHODS

Patients

Consecutive 321 patients with ATAAD who were admitted to the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from February 2012 to February 2017 were enrolled. Patients treated with endovascular repair ($n = 6$) or conservative treatment ($n = 2$) were excluded. Finally, 313 patients who underwent emergency surgery were included in our study. All patients were diagnosed by computed tomography angiography, magnetic resonance imaging or echocardiography. The study was approved by the institutional ethics board of Union Hospital Tongji Medical College, Huazhong University of Science and Technology.

Clinical Data

Patients' demographic characteristics, medical histories, comorbidities, echocardiographic data, laboratory results, vessel involvement, organ ischemia, primary tear location, surgical type, duration of surgery, and outcomes were retrieved from electronic medical records. Medical histories included hypertension, diabetes, dyslipidemia, coronary artery disease and previous heart surgery. Echocardiographic data were composed of diameter of ascending aorta, moderate to severe pericardial effusion, aortic regurgitation and left ventricular ejection fraction. The diameter of ascending aorta was measured from the parasternal long-axis view. Left ventricular ejection fraction was assessed by M-mode echocardiography. Involvement of vessel branches included ascending aorta, aortic arch and supra-aortic vessels involvements. Surgical type encompassed ascending aorta replacement, aortic valve replacement, aortic arch replacement, elephant truck procedure, Coronary Artery Bypass Graft (CABG), and aortic sinus repair. Outcomes was defined as in-hospital mortality after operation. EuroSCORE II were calculated based on the prior method (http://www.euroscore.org/calc.html).

Surgical Procedure

Operative techniques were composed of cardiopulmonary bypass (CPB), moderate hypothermia, circulatory arrest, and unilateral antegrade cerebral perfusion (u-ACP). The central venous pressure, bilateral radial artery pressure, electrocardiography, nasopharyngeal and rectal temperature and intermittent arterial blood gas analysis were monitored. Near-infrared spectroscopy (NIRS) was used to monitor cerebral saturation. When u-ACP was used, cerebral perfusion was performed through the right axillary artery. If the vessel was dissected, the true lumen of the branch vessel was cannulated. The flow rate for u-ACP was 10–15 mL/kg/min with perfusion pressure of 50–70 mmHg. After CPB was established, cooling was initiated. After clamping of the ascending aorta, cardiac arrest was accomplished with cold cardioplegic solution. Subsequently, the aortic root procedure depending on the severity and extent of the disease, including aortic root formation or Bentall procedure with or without CABG were performed.

Statistical Analysis

Categorical variables are presented as frequencies and percentages. Normally distributed continuous variables are presented as the means and standard deviations. Non-normally distributed continuous variables are presented as medians with quartiles. Continuous variables were compared using the t-test or Mann-Whitney U test. Categorical data were compared using the Fisher's exact or Chi-square tests. Receiver-operating characteristic (ROC) curves were used to obtain diagnostic cutoff values, as well as specificity and sensitivity. Estimations of the risk factors of mortality were performed using univariate and multivariate logistic regression models. To avoid the interaction between the pre-operative and intra-operative variable when the pre-operative and intra-operative variables were enrolled together in multivariate logistic regression analysis, we analyzed the pre- or intra-operative data independently. The possible pre-operative risk factors, including demographics, comorbidities, echocardiographic measurements, vessel involvement and laboratory results, were included in the pre-operative univariate logistic regression analysis. The potentially intra-operative predictors of higher mortality, including surgical type and duration of surgery, were entered into in the intra-operative univariate logistic regression analysis. Variables with p values $<$ 0.05 in univariate logistic regression analysis were entered into multivariate logistic regression models. The results of the logistic regressions are presented as odds ratio (OR) with confidence intervals (CI). The statistical analyses were performed with SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). A 2-sided p value $<$ 0.05 was considered to indicate statistical significance.

RESULTS

A total of 313 patients were included in our study. Pre-operative characteristics of patients with ATAAD are summarized in **Table 1**. The mean age of patients with ATAAD was 48 years, and 264 (84%) were men. Only unilateral antegrade cerebral perfusion was performed in every patient with supra-aortic vessels involvement. NIRS was used in the intra-operative assessment of brain perfusion. Of these patients, 32 patients (10.2%) died. Non-survivors had higher heart rate and plasma potassium level than survivors. Compared

TABLE 1 | Pre-operative characteristics of patients with ATAAD.

	Survivors (n = 281)	Non-survivors (n = 32)	*P*-value
Age (years), mean ± SD	48 ± 10	48 ± 11	0.87
Sex			
Female, *n* (%)	47 (15.0)	2 (0.6)	0.12
Male, *n* (%)	234 (85.0)	30 (99.4)	
Medical histories, n (%)			
Hypertension	168 (59.8)	20 (62.5)	0.77
Diabetes	4 (1.4)	2 (6.3)	0.23
Dyslipidemia	10 (3.6)	3 (9.4)	0.27
Coronary artery disease	30 (10.7)	6 (18.8)	0.29
Smoking history	137 (48.8)	19 (59.4)	0.26
Alcohol history	113 (40.2)	14 (43.8)	0.70
Previous heart surgery	3 (0.7)	2 (6.3)	0.08
Antihypertensive drugs			
ACEI	43 (0.36)	6 (0.4)	0.73
CCB	39 (0.32)	5 (0.33)	1.0
β-blocker	27 (0.22)	3 (0.2)	1.0
ARB	12 (0.1)	1 (0.07)	1.0
Admission vital signs			
Heart rate (beats per minute)	80 ± 15	87 ± 16	0.01
Systolic blood pressure (mm Hg)	135 ± 29	133 ± 26	0.61
Diastolic blood pressure (mm Hg)	72 ± 19	73 ± 12	0.68
Echocardiographic measurements			
DAA (mm), mean ± SD	47 ± 8	47 ± 5	0.94
Moderate to severe PE	163 (58.0)	25 (78.1)	0.03
LVEF (%), mean ± SD	62.7 ± 5.4	60.2 ± 6.1	0.12
Aortic regurgitation	155 (55.2)	15 (46.9)	0.37
Laboratory results (maximum value pre-surgery), mean ± SD			
Leukocyte (10^9)	12.0 ± 4.1	12.7 ± 4.9	0.36
Platelets (10^9)	168.0 ± 66.3	165.3 ± 65.1	0.83
Creatinine (μmol/l)	106.4 ± 79.7	125.9 ± 59.5	0.19
Neutrophil (10^3/μl)	13.5 ± 57.9	10.9±4.7	0.80
Plasma potassium (mg/dl)	3.8 ± 0.4	4.7±0.4	<0.001
Involvement of vessel branches			
Ascending aorta	280 (99.6)	32 (100.0)	0.91
Aortic arch	257 (91.5)	32 (100.0)	0.17
Supra-aortic vessels	160 (56.9)	26 (81.3)	<0.01
Organ ischemia			
Lower limb ischemia	16 (5.7)	11 (34.4)	<0.01
Myocardial ischemia	28 (10.0)	9 (28.1)	<0.01
Primary tear location, n (%)			
Ascending aorta	155 (55.2)	15 (46.9)	0.37
Aortic arch	71 (25.3)	5 (15.6)	0.23
Descending aorta	24 (8.5)	9 (28.1)	0.32
Unknown	31 (11.0)	3 (9.4)	0.78
EuroSCORE II, (%)	4.6 ± 1.5	12.1 ± 3.9	<0.001

DAA, diameter of ascending aorta; PE, pericardial effusion; ACEI, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction.

with survivors, non-survivors displayed higher prevalence of moderate to severe pericardial effusion, involvement of supra-aortic vessels, myocardial ischemia and lower limb ischemia.

TABLE 2 | Procedure characteristics of patients with ATAAD.

	Survivors (n = 281)	Non-survivors (n = 32)	*P*-value
Procedure type, n (%)			
Ascending aorta replacement	147 (52.3)	21 (65.6)	0.15
Aortic valve replacement	135 (48.0)	11 (34.4)	0.14
Aortic arch replacement	263 (93.6)	32 (100.0)	0.28
Elephant truck procedure	247 (87.9)	32 (100.0)	0.07
CABG	30 (10.7)	9 (28.1)	0.01
Aortic sinus repair	52 (18.5)	8 (25.0)	0.38
Duration of procedure, mean ± SD			
Procedure time (h)	8.3 ± 2.1	9.8 ± 1.9	<0.001
CPB time (min)	230 ± 45	293 ± 92	0.01
Cross-clamp time (min)	125 ± 26	128 ± 26	0.66
HCA time (min)	22 ± 7	26 ± 10	0.10
Lowest rectal temperature (°C)	23.7 ± 1.5	24.1 ± 1.3	0.10
Cerebral perfusion time (min)	22 ± 6	24 ± 8	0.55

CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest.

There were no significant differences in age, sex, systemic arterial pressure, comorbidities (hypertension, diabetes, dyslipidemia and coronary artery disease), antihypertensive drug use between non-survivors and survivors. With regard to echocardiographic data, the diameter of ascending aorta, left ventricular ejection fraction and the prevalence of aortic regurgitation were similar in survivors and non-survivors. In addition, leukocyte, neutrophil and platelets counts, and creatinine level did not differ between survivors and non-survivors.

Intra-operative characteristics of patients with ATAAD are presented in **Table 2**. Compared with survivors, non-survivors had longer operation time and cardiopulmonary bypass time (CPBT). Non-survivors were more likely to undergo CABG than survivors. There was no statistically significant difference in aorta occlusion time, circulatory arrest time, lowest rectal temperature and cerebral perfusion time between non-survivors and survivors. Additionally, non-survivors had a similar treatment with ascending aorta replacement, aortic valve replacement, half or whole arch replacement, elephant trunk technique and aortic sinus repair as survivors.

ROC curves were used to determine the optimal cut-off values for operation time, extracorporeal circulation time, admission heart rate and blood potassium level to identify mortality in ATAAD patients (**Table 3**; **Figure 1**). ROC analysis revealed that duration of operation > 9.5 h [area under the curve (AUC): 0.73], CPBT > 227 min (AUC: 0.72), heart rate > 82 beats/min (AUC: 0.65) and plasma potassium > 4.4 mmol/L (AUC: 0.92) were associated with in-hospital mortality in patients with ATAAD.

Univariate logistic regression analysis including pre-operative variables revealed that plasma potassium > 4.4 mmol/L, supra-aortic branch involvement, lower limb ischemia, and myocardial ischemia were predictors of higher mortality in patients with ATAAD. Multivariable logistic regression analysis demonstrated that plasma potassium > 4.4 mmol/L

(OR: 43.0, 95% CI: 3.8–51.5, $p < 0.001$), supra-aortic branch involvement (OR: 4.4; 95% CI: 1.5–7.0, $p = 0.008$), and lower limb ischemia (OR: 4.9, 95% CI: 1.6–6.9, $p = 0.009$) were independently predictive of in-hospital mortality (**Table 4**).

Univariate logistic regression analysis including intra-operative variables showed that elephant truck procedure, CABG, operation time > 9.7 h, CPBT > 227 min could predict higher mortality in patients with ATAAD. Multivariable logistic regression analysis revealed that operation time >9.7 h (OR: 6.0, 95% CI: 1.8–18.7, $p < 0.001$), CPBT > 227 min (OR: 3.7, 95% CI: 1.3–9.3, $p = 0.002$), and elephant truck procedure (OR: 4.1, 95% CI: 1.4–6.9, $p = 0.008$) were independent predictors of in-hospital mortality (**Table 5**).

TABLE 3 | ROC curves to obtain diagnostic cut-off values.

Variables	Cut-off value	Sensitivity (%)	Specificity (%)	AUC
Duration of operation (h)	9.5	58.1	78.4	0.73
CPB time (min)	227	83.3	52.7	0.72
Heart rate (beats/min)	82	53.1	72.6	0.65
Plasma potassium (mmol/l)	4.4	72.0	97.2	0.92

CPB, cardiopulmonary bypass.

DISCUSSION

In this study of 313 consecutive patients with ATAAD who underwent emergency surgery from February 2012 and February 2017, the overall hospital mortality was 10.2%. Although the hospital mortality was lower than that of previous studies (1–3), it is still unacceptable. It is necessary to summarize the risk factors for in-hospital mortality in patients with ATAAD. Our results indicated that pre- and intra-operative risk factors for in-hospital mortality in patients with ATAAD were elevated level of plasma potassium, higher incidence of supra-aortic vessels involvement and lower-extremity ischemia, and longer duration of operation and cardiopulmonary bypass time.

The present study showed that supra-aortic vessels involvement was a risk factor for hospital death. The extension of ATAAD with involvement of the supra-aortic branches largely determined the pre-operative state of the patients and influenced the post-operative outcome. Mortality may increase rapidly if the supra-aortic vessels are involved in the dissection process. Patients with ATAAD with supra-aortic vessel involvement have a higher risk of post-operative stroke. Understandably, anastomosis of branch vessels is required during surgery in these patients, which prolonged the time of extracorporeal circulation and operation, and further may lead to diminished blood supply to the brain. Thus, cerebral malperfusion further increase in-hospital mortality (1, 4). In the current study, we found that 186 patients had supra-aortic vessels involvement.

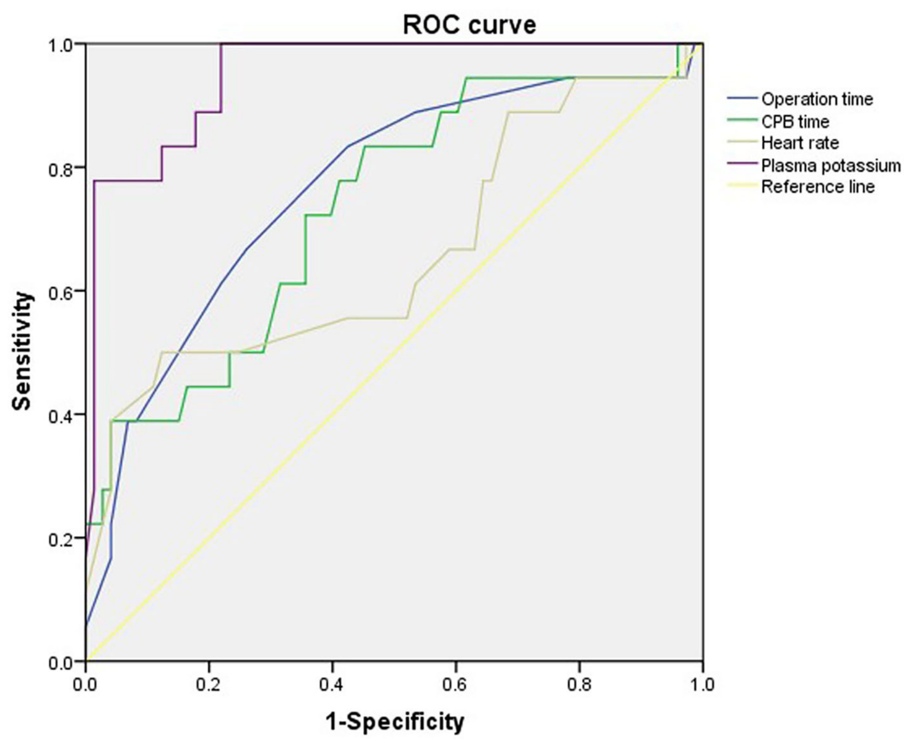

FIGURE 1 | Receiver-operating characteristic curves of operation time, extracorporeal circulation time, admission heart rate and blood potassium level to identify mortality in ATAAD patients.

TABLE 4 | Logistic analysis of pre-operative risk factors for mortality in ATAAD.

Variables	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (years)	1.0	0.003–0.03	0.87			
Sex	3.0	1.1–2.2	0.14			
Heart rate > 82 (beats/min)	1.9	0.7–3.2	0.07			
Systolic blood pressure (mmHg)	1.0	−0.03–0.27	0.61			
Diastolic blood pressure (mmHg)	1.0	0.003–0.08	0.78			
Hypertension	3.0	1.1–3.9	0.05			
Smoking history	1.5	0.4–1.1	0.29			
Dyslipidemia	2.8	1.0–2.3	0.13			
Diabetes	4.6	1.5–3.0	0.09			
Previous heart surgery	6.2	1.8–3.8	0.051			
Plasma potassium > 4.4 (mmol/l)	45.3	3.8–64.6	<0.001	43.0	3.8–51.5	<0.001
Creatinine (μmol/l)	1.0	0.002–1.6	0.20			
Neutrophil (10^3/l)	1.0	−0.002–0.06	0.81			
Platelets (10^9)	1.0	−0.001–0.05	0.83			
Moderate to severe pericardial effusion	2.4	0.9–3.8	0.051			
LVEF (%)	0.9	−0.08–1.8	0.18			
Aortic regurgitation	0.9	−0.06–0.03	0.87			
DAA (mm)	1.0	−0.002–0.01	0.94			
Supra-aortic vessels involvement	5.5	1.7–13.2	<0.001	4.4	1.5–7.0	0.008
Myocardial ischemia	3.0	1.1–5.9	0.02	2.2	0.8–1.5	0.22
Lower-extremity ischemia	5.0	1.6–15.2	<0.001	4.9	1.6–6.9	0.009

DAA, diameter of ascending aorta; LVEF, left ventricular ejection fraction.

TABLE 5 | Logistic analysis of intra-operative risk factors for mortality in ATAAD.

Variables	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95%CI	P-value
Ascending aorta replacement	1.8	0.6–2.3	0.13			
Elephant truck procedure	3.4	1.2–5.8	0.02	4.1	1.4–6.9	0.008
Aortic valve replacement	0.6	−0.57–2.1	0.15			
Aortic arch replacement	2.2	0.8–3.7	0.14			
CABG	3.3	1.2–7.3	0.007	1.9	0.6–1.5	0.23
Operation time > 9.7 (h)	5.3	1.7–18.4	<0.001	6.0	1.8–18.7	<0.001
CPB time > 227 (min)	4.4	1.5–13.0	<0.001	3.7	1.3–9.3	0.002
HCA time (min)	1.0	0.03–0.6	0.45			
Cross-clamp time (min)	1.0	0.004–0.2	0.65			
Lowest rectal temperature (°C)	1.5	0.4–3.8	0.05			
Cerebral perfusion time (min)	1.0	0.03–0.4	0.54			

CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; CABG, coronary artery bypass graft.

Twenty six of these patients (14.0%) died during hospitalization. Thereby, an appropriate protection procedure is important to prevent irreversible brain injury. The various cerebral protection (antegrade/ retrograde; monolateral/bilateral) can be used during aortic arch surgery. The unilateral antegrade cerebral perfusion was performed during aortic arch surgery in this study. The relative benefits of unilateral antegrade cerebral perfusion compared with bilateral antegrade cerebral perfusion as cerebral perfusion strategies remained undetermined. Tong et al. revealed that bilateral antegrade cerebral perfusion did not significantly reduce 30-days mortality and permanent neurologic dysfunction compared to unilateral antegrade cerebral perfusion (5). However, Misfeld et al. showed that early mortality and medium-term survival was not affected by the type of cerebral protection used (6). In addition, Zierer et al. demonstrated that unilateral antegrade cerebral perfusion had the equal brain protection compared to bilateral antegrade cerebral perfusion (7). More and more data show that unilateral cerebral perfusion in moderate hypothermia is safe when performed during NIRS monitoring and that avoiding deep hypothermia preserves cerebral autoregulation blood flow, resulting in an optimal unilateral perfusion. Only unilateral antegrade cerebral perfusion was performed in every patient with supra-aortic vessels involvement during February 2012 to February 2017 in this study. So, we did not determine the different impact of the type of cerebral protection on clinical outcomes in cases of an aortic arch surgery and involvement of supra-aortic vessels in our hospital. It deserves further investigation whether unilateral antegrade cerebral perfusion is superior to bilateral antegrade cerebral perfusion in patients with ATAAD with supra-aortic vessels involvement.

In this study, non-survivors had the higher incidence of lower limb ischemia than survivors. Moreover, multivariate logistic regression analysis showed that lower limb ischemia was a risk factor for mortality in patients with ATAAD, which was similar as previous studies (8, 9). Poor perfusion of the lower extremities can lead to serious post-operative complications (10). In our study, lower-extremity ischemia was diagnosed in 27 patients with no palpable pulses in the femoral artery before surgery. Eleven of these patients (40.7%) died during hospitalization. Uchida et al. showed that improvements of the blood supply of lower-extremity by draining the brachial arterial blood to the ischemic lower limb arteries, may significantly improve symptoms (11). Whether this strategy should be mandatory is highly controversial. Preece et al. demonstrated that inferior-limb ischemic artery reperfusion before aortic repair increased intra-operative mortality in ATAAD patients (12).

In addition to supra-aortic vessels involvement and lower limb ischemia, elevated level of plasma potassium was found to be another independent risk factor of higher in-hospital mortality in patients with ATAAD. Indeed, our study demonstrated that non-survivors had higher blood potassium level than survivors. Moreover, the current observation demonstrated that the optimal cut-off value of plasma potassium level for predicting higher mortality in patients with ATAAD was over 4.4 mmol/L. Patients who had higher level of plasma potassium above the cutoffs had increased risk of mortality. Potassium serum levels within the high normal range (>4.4 to < 5.0 mmol/L), which were frequently ignored by clinicians in the emergency department, were associated with higher in-hospital mortality. This finding is consistent with the results of Chen et al., who found that the blood potassium level other than 3.5 to 4.5 mmol/L at admission was related to higher in-hospital and long-term mortality in ATAAD patients (13). Previous studies found a U-shaped relationship between serum potassium levels at admission and in-hospital mortality, which potassium levels outside the interval of <3.5 to 4.5 mmol/L were associated with higher risk in all-cause mortality (13, 14). The risk of cardiovascular mortality increases with the elevated potassium levels, due to the fact that the heart is more susceptible to potassium fluctuation than other tissues. An increase in serum potassium level is associated with reduced ventricular excitability and has been shown to cause increased diastolic threshold of excitability in experimental animals and humans (15, 16), which would be associated with an increased prevalence of cardiac arrhythmias. A large body of evidences have demonstrated that even a mild change within the normal range is associated with higher mortality in patients with various cardiovascular diseases, such as hypertension (17), acute coronary syndrome (14, 18), and heart failure (19, 20), which reveal that the optimal blood potassium level may be different from the definite clinical normal range in diverse cardiovascular diseases. ATAAD patients with more severe circumstances (such as use of antihypertensive drugs, hemorrhage and hemolysis) may experience a serum potassium disturbance, which is similar to that in other cardiovascular diseases. However, current guidelines do not underscore potassium management in patients with aortic diseases (21, 22). Our results demonstrated that higher potassium levels at admission had an adverse effect on the in-hospital mortality of patients with ATAAD, and accordingly, more active management may be necessary.

The duration of extracorporeal circulation was significantly longer in non-survivors than survivors. Furthermore, a multivariable analysis showed that the duration of surgery and the duration of extracorporeal circulation were risk factors for in-hospital mortality. Our findings are consistent with previous studies (23). A long operation time reflects the severity of ATAAD; moreover, it had an adverse effect on organ perfusion. Therefore, these may be the reason why longer duration of operation is associated with unfavorable outcomes in patients with ATAAD.

Previous researches indicated that myocardial ischemia was a risk factor for in-hospital mortality in patients with ATAAD. In our study, univariate regression analysis demonstrated that myocardial ischemia was a predictor of mortality in patients with ATAAD. However, in multivariate logistic regression analysis, myocardial ischemia was no longer significantly predictive of in-hospital mortality. In our series, 37 patients had myocardial infarction before surgery, and 9 of them (24.3%) died during hospitalization. This may be the reason that most patients with myocardial ischemia were simultaneously treated with coronary artery bypass graft during the aortic replacement, which markedly improved myocardial ischemia and the prognosis.

In our study, 188 patients with ATAAD presented with medium to large amounts of pericardial effusion. Non-survivors had a higher incidence of medium to large amounts of pericardial effusion than survivors. However, univariate and multiple regression analysis revealed that moderate to severe pericardial effusion could not predict higher in-hospital death in patients with ATAAD. This finding was not in line with the study of Santi Trimarchi et al., which demonstrated that pericardial tamponade was an independent predictor of post-operative mortality in patients with ATAAD (8).

Our study revealed that elephant truck procedure was a risk factor of mortality in patients with ATAAD. This result was not in keeping with the observation of Goda et al., which indicated that various surgical methods did not affect the early post-operative mortality in ATAAD patients (9). However, Tan et al. found that simultaneous aortic valve replacement or Bentall surgery in ATAAD patients was a protective factor for post-operative mortality (23). Future studies are needed to confirm the effect of various surgical treatment on outcomes in patients with ATAAD.

Limitations

Our study had some limitations. First, this was a retrospectively single-center study, extrapolation of our findings could be affected by local bias. In addition, sample size of this study is relatively limited. Future multicenter studies with larger sample sizes are needed to verify our findings. Another limitation of our study is that we did not determine the different impact of the type of cerebral protection on clinical outcomes in cases of an aortic arch surgery and involvement of supra-aortic vessels, because that only unilateral antegrade cerebral perfusion was performed in every patient with supra-aortic vessels involvement in our study. The effect of cerebral protection type on outcomes in patients with supra-aortic vessels involvement is an interesting topic. Future study that investigates the different impact of cerebral protection type on clinical outcomes could be the next step. Finally, the numbers of non-survivors were small, the exiguous number of the mortality group and the great numeric difference between the two groups could represent a statistical limitation for a solid conclusion based on this study.

CONCLUSION

Supra-aortic vessels involvement, lower-extremity ischemia and elevated plasma potassium level are pre-operative risk factors for in-hospital mortality in patients with ATAAD. Among intra-operative factors, longer operation time and cardiopulmonary bypass time are associated with increased in-hospital mortality. For further improvement of outcomes, quicker diagnosis, more appropriate pre-operative management and minimizing any delay in surgery are mandatory.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of Tongji Medical College of Huazhong University of Science and Technology. Written informed consent was not required for this study, in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

MX and LZ contributed to the conception of the study. HY, ZS, and YL analyzed and interpreted the clinical data and imaging findings, and they were major contributors in writing the manuscript. YZ, WW, and ML helped perform the analysis with constructive discussions. All authors read and approved the final manuscript.

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Neurofilament Light Chain Protein Is a Predictive Biomarker for Stroke After Surgical Repair for Acute Type A Aortic Dissection

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Background: Although great progress has been made in surgery and perioperative care, stroke is still a fatal complication of acute type A aortic dissection (ATAAD). Serum biomarkers may help assess brain damage and predict patient's prognosis.

Methods: From March, 2019 to January, 2020, a total of 88 patients underwent surgical treatment at the Department of Cardiovascular Surgery of Beijing Anzhen Hospital, China, and were enrolled in this study. Patients were divided into two groups according to whether they had suffered a stroke after the operation. Blood samples were collected at 8 time points within 3 days after surgery to determine the level of S100β, neuron-specific enolase (NSE) and neurofilament light chain protein (NFL). Receiver operating characteristic curves (ROC) were established to explore the biomarker predictive value in stroke. The area under the curve (AUC) was used to quantify the ROC curve.

Results: The patient average age was 48.1 ± 11.0 years old and 70 (79.6%) patients were male. Fifteen (17.0%) patients suffered stroke after surgery. The NFL levels of patients in the stroke group at 12 and 24 h after surgery were significantly higher than those in the non-stroke group (all $P < 0.001$). However, the NSE and S100β levels did not differ significantly at any time point between the two groups. The predictive value of NFL was the highest at 12 and 24 h after surgery, and the AUC was 0.834 (95% CI, 0.723–0.951, $P < 0.001$) and 0.748 (95% CI, 0.603–0.894, $P = 0.004$), respectively. Its sensitivity and specificity at 12 h were 86.7 and 71.6%, respectively. The NFL cutoff value for the diagnosis of stroke at 12 h after surgery was 16.042 ng/ml.

Conclusions: This study suggests that NFL is an early and sensitive serum marker for predicting post-operative neurological prognosis of ATAAD patients. Further studies, including large-scale prospective clinical trials, are necessary to test whether the NFL can be used as a biomarker for clinical decision-making.

Keywords: type A aortic dissection, aortic operation, stroke, biomarker (BM), neurofilaments (NFs)

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INTRODUCTION

Acute type A aortic dissection (ATAAD) is a challenging condition that requires complex and life-saving cardiovascular surgery. Although the success rate of surgery has improved in recent years (1), post-operative neurological complications unfortunately still occur. Therefore, there is a clinical need to unravel specific biomarkers that can help identify irreversible nerve damage in the early post-operative period, so treatment strategies can be actioned in a timely manner.

Previously, serum neuron-specific enolase (NSE) and S100β protein were considered promising candidate marker proteins for predicting the neurological status of patients after cardiac surgery (2–4), however, studies on these two markers yielded conflicting results (5, 6). More importantly, these two markers are not only expressed in neurons but also in other; NSE is expressed in red blood cells and platelets, and S100β is expressed in fat and other tissues or organs (7–9). This lack of specificity makes it difficult to identify changes in serum levels that are specifically associated with brain damage.

Neurofilament light chain protein (NFL) is the main component of neurofilament core and the main intermediate filament protein of neurons and axons (10, 11). Rosén et al. (12) suggested that the NFL level in the cerebrospinal fluid has a high degree of sensitivity and specificity in predicting brain damage in patients after cardiac arrest. However, due to the various complications and contraindications of lumbar puncture, its usage has been limited. On this basis, Moseby-Knappe et al. (13) have investigated the biomarker value of NFL in blood samples and found that, similarly to the cerebrospinal fluid, the increase in NFL levels in blood samples is also associated with the poor neurological results after cardiac arrest. However, to date there are no data on serum biomarker levels in stroke patients after ATAAD. In order to find a reliable and specific biomarker that can help predict post-operative neurological results in patients who suffered stroke, we conducted a prospective observational cohort study and investigated changes in serum S100β, NSE, and NFL levels after surgery.

METHODS

Study Design

This study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, China, and complies with the requirements of the Good Clinical Practice international guidelines. All procedures are within the normal routine intensive care routine with no additional risk to the patients, therefore the institutional review board abandoned the need to obtain patient's informed consent. The research protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki. The data for this observational cohort study was collected in a prospective manner. Patients who met the inclusion criteria (see below) were admitted to the theater, blood samples were collected to determine the level of biomarkers at 8 time points: 5 min after induction of anesthesia (T0), at the beginning of selective cerebral perfusion (T1), at the time weaned from cardiopulmonary bypass (CPB) (T2), 6 h after operation (T3), 12 h after operation (T4), 24 h after operation (T5), 48 h after operation (T6), and 72 h after operation (T7). Blood samples were collected independently by two clinicians, neither of who was responsible for the treatment of the patients. In the process of treating patients, no clinicians had access to relevant information about S100β, NSE, and NFL levels. Patients were divided into groups according to whether they had suffered a stroke after the operation. Post-operative stroke was defined as the development of new global or focal neurological deficits within 30 days post-surgery, as assessed by cranial CT scan. Based on previous studies (14, 15), malperfusion syndrome is defined as compromised blood flow in 1 or more organs resulting in ischemia and organ dysfunction due to the dissection-related obstruction of the aorta and its branch vessels.

Patients

Patients with ATAAD who underwent surgery at the Department of Cardiovascular Surgery of Beijing Anzhen Hospital, China, were prospectively included in the study. Inclusion criteria were: age > 18 years old; underwent total arch replacement (TAR), and stented elephant trunk (SET) implantation. Exclusion criteria were: continuous coma before surgery, and lack of at least 4 of 8 blood samples.

Surgical Techniques

All operations were performed through a median sternum incision. Briefly, operations used the right axillary artery cannulation for cardiopulmonary bypass and selective cerebral perfusion (5–10 ml/kg·min) under hypothermic circulatory arrest (HCA). First, proximal aortic root operations, including ascending aorta replacement or Bentall procedure, were completed. If surgery was combined with concomitant operations, it was completed during the cooling period. As stated in our previous studies (16, 17), we used TAR + SET implantation to treat aortic arch, which included implanting SET in the descending aorta (Cronus, MicroPort, China), and then using four branched graft (Vascutek, Terumo, Japan) to complete TAR. After the descending aorta anastomosis was completed, the distal reperfusion was started. First, the left carotid artery was reconstructed to achieve bilateral perfusion, then the ascending aorta was reconstructed to prevent coronary ischemia, and finally the subclavian artery and the innominate artery were reconstructed.

Biomarker Measurements

All tests complied with the standard biosecurity and institutional safety procedures. At each of the blood collection time points, 2 ml of blood from the central venous tube was drawn and discarded, then 5 ml of blood was drawn and collected into a tube containing ethylenediamine tetra acetic acid, and kept refrigerated at 4°C. Then, the sample was centrifuged at 3,000 rpm for 10 min and the serum was collected and stored at −80°C. The levels of S100, NSE and NFL were analyzed by a commercial enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). Samples were run on TECAN Infinite F50 (TECAN group, Männedorf, Switzerland). The detection limit was specified by the manufacturer. All tests were carried out by laboratory technicians blind to the clinical data. All tests are performed in duplicate, and the mean was calculated and used for analysis.

Statistical Analysis

Categorical variables were expressed as numbers (percentage). Continuous variables conforming to a normal distribution were expressed as mean ± SD, or expressed as the median (interquartile range). Comparisons were performed using the Student's t-test, Mann-Whitney U-test, Chi-square-test, or Fisher's exact-test. The generalized additive mixed model was used to compare the NFL levels of the two groups at each time point. Receiver operating characteristic curves (ROC) were generated to provide data on the predictive ability of biomarkers to detect stroke. The area under the curve (AUC) was used to quantify the ROC curve. Youden's index (J = Sensitivity + Specificity-1) was used to determine the most appropriate cut-off value. All tests were two-sided, with $P < 0.05$ as the significance threshold. GraphPad Prism 8 for Windows (GraphPad software, La Jolla, CA, USA) was used for graphing. R and Empower Stats (http://www.empowerstats.com, X&Y Solutions, Inc., MA, USA) were used for all statistical analyses.

RESULTS

Pre-operative and Intraoperative Data of Patients

From 14 March, 2019 to 19 January, 2020, a total of 108 patients underwent surgical treatment in the Department of Cardiovascular Surgery of Beijing Anzhen Hospital, Beijing, China. Ninety-nine met the eligibility criteria, and nine were excluded. Eleven patients were excluded at a later stage due to poor sample quality or hemolysis, missing samples, or sample transportation problems. In total, we collected data on 88 consecutive cases, of which 15 (17.0%) suffered post-operative stroke. Three patients suffered a stroke on the second day after surgery, four patients on the third day after surgery, and two patients on the fourth day after surgery. The remaining six patients suffered a stroke on the 5th, 6th, 7th, 9th, 10th, and 11th post-operative day.

As shown in **Table 1**, the average age of the patients was 48 years old, the average BMI was 27.3, 70 cases (79.6%) were male, and emergency operations accounted for 94.3% of all operations. The most common comorbidity was hypertension in 74 cases (84.1%). Smoking history was present in 45 cases (51.1%). The average CPB time was 198.9 ± 34.8 min, the aortic cross-clamp time was 113.2 ± 25.6 min, and the HCA time was 24.2 ± 9.8 min. Among root treatment methods, Bentall procedure accounted for 25 cases (28.4%). There were 11 cases of concomitant operations, including three cases of CABG (3.4%) and eight cases of bypass (9.1%).

Compared with the non-stroke group, patients who had developed stroke after surgery had a higher pre-operative rate of moderate/severe aortic regurgitation (7/15, 46.7% vs. 16/73, 21.9%; $P < 0.05$), and malperfusion syndrome (8/15, 53.3% vs. 28/73, 38.4%; $P < 0.05$). In terms of intraoperative data, patients in the stroke group experienced significantly longer CPB time and aortic cross-clamp time (216.7 ± 25.2 vs. 195.2 ± 35.5 min, 129.9 ± 25.8 vs. 109.7 ± 24.3 min; all $P < 0.05$). Other analysis revealed no statistical difference between the two groups.

Post-operative Mortality and Morbidity

Table 2 shows the rate of post-operative complications of these patients. The overall mortality rate of the patients was 12.5% (11/88). Five of the patients who died had a stroke after surgery, accounting for 33.3% of the patients in the Stroke group ($P < 0.05$). There were 14 cases of continuous renal replacement therapy (15.9%), two cases of paraplegia (2.3%), and five cases (5.7%) of re-examination for bleeding. Although the length of hospital stay was not statistically different between groups, the ICU time of the stroke group was longer than that of the non-stroke group ($P < 0.001$).

Serum Biomarker Levels

A total of 535 samples were collected at 5 min after induction of anesthesia (T0), at the beginning of selective cerebral perfusion (T1), at the time of weaning from CPB (T2), 6 h after operation (T3), 12 h after operation (T4), 24 h after operation (T5), 48 h after operation (T6), and 72 h after operation (T7). As shown in **Supplementary Table S1** and in **Figure 1C**, the levels of NFL in patients in the stroke group were significantly higher than those in the non-stroke group at 12 and 24 h after surgery (all $P < 0.001$). However, the NSE levels did not differ significantly at any time point between the two groups (**Figure 1A**). Although the average S100β level of stroke patients was higher in patients who had a stroke than in patients who did not have a stroke at all study time points, the difference was not significant (all $P > 0.05$; **Figure 1B**).

Serum NFL Predictive Ability

We performed ROC analysis and AUC, and measured the biomarker cutoff value, sensitivity, specificity and predictive value at T4 and T5. As shown in **Figures 2A,B**, S100β and NSE did not demonstrate a good predictive ability. As shown in **Table 3**, the predictive value of NFL was the highest at 12 h (T4) and 24 h (T5) after surgery, with an AUC of 0.834 (95% CI, 0.723–0.951, $P < 0.001$) and 0.748 (95% CI, 0.603–0.894, $P = 0.004$), respectively. Its sensitivity and specificity at 12 h after surgery were 86.7 and 71.6%, respectively. The NFL cutoff value for the diagnosis of stroke at 12 h after surgery was 16.042 ng/ml. These analysis indicate the value of NFL holds as a predictor of stroke risk.

DISCUSSION

In summary, this prospective study evaluated the level changes and diagnostic accuracy of the biomarkers S100β, NSE, and NFL at 8 different time points in 3 days in ATAAD patients treated with TAR+FET in our cardiovascular surgery center. This study is one of the first and largest studies to evaluate the temporal profiles of these three biomarkers in ATAAD patients with and without stroke. The main findings of this study are:

TABLE 1 | Pre-operative and intraoperative characteristics.

Variables	Total (*n* = 88)	Non-stroke (*n* = 73)	Stroke (*n* = 15)	*P*-value
Age	48.1 ± 11.0	47.8 ± 11.5	50.0 ± 8.2	0.479
Gender				0.453
Male	70 (79.5)	57 (78.1)	13 (86.7)	
Female	18 (20.5)	16 (21.9)	2 (13.3)	0.228
BMI (kg/m^2)	27.3 ± 4.5	27.0 ± 4.6	28.6 ± 4.2	
Diabetes mellitus	1 (1.1)	0	1 (6.7)	0.170
Hypertension	74 (84.1)	61 (83.6)	13 (86.7)	0.765
Coronary artery disease	3 (3.4)	3 (4.1)	0	0.424
Prior cerebrovascular accident	5 (5.7)	3 (4.1)	2 (13.3)	0.160
Chronic renal insufficiency	2 (2.3)	2 (2.7)	0	0.517
Prior cardiovascular intervention	3 (3.4)	3 (4.1)	0	0.424
Smoking history	45 (51.1)	35 (47.9)	10 (66.7)	0.186
Drinking history	33 (37.5)	28 (38.4)	5 (33.3)	0.714
Malperfusion syndrome	26 (29.5)	18 (24.7)	8 (53.3)	0.027
Ejection fraction	63.3 ± 4.8	63.5 ± 5.0	62.0 ± 4.0	0.261
Aortic regurgitation (moderate or severe)	23 (26.2)	16 (21.9)	7 (46.7)	0.047
Emergency	83 (94.3)	68 (93.2)	15 (100.0)	0.297
Operation time (h)	7.4 ± 1.3	7.3 ± 1.4	7.8 ± 0.6	0.178
Lowest nasal temperature (°C)	25.1 ± 1.8	25.1 ± 1.9	24.8 ± 1.2	0.554
Lowest bladder temperature (°C)	26.7 ± 1.8	26.8 ± 1.9	26.2 ± 1.2	0.237
CPB time (min)	198.9 ± 34.8	195.2 ± 35.5	216.7 ± 25.2	0.028
Cross-clamp time (min)	113.2 ± 25.6	109.7 ± 24.3	129.9 ± 25.8	0.005
Lower body circulatory arrest time (min)	24.2 ± 9.8	24.2 ± 9.4	24.2 ± 12.0	0.994
Selective cerebral perfusion time (min)	34.2 ± 10.9	33.6 ± 11.0	37.5 ± 10.5	0.201
Aortic root repair				0.642
Ascending aorta replacement	63 (71.6)	53 (72.6)	10 (66.7)	
Bentall procedure	25 (28.4)	20 (27.4)	5 (33.3)	
Concomitant operation				
Extra-anatomic bypass	8 (9.1)	7 (9.6)	1 (6.7)	0.720
CABG	3 (3.4)	3 (4.1)	0	0.424
Intraoperative PLT transfusion	4 (4.5)	3 (4.1)	1 (6.7)	0.665
Intraoperative RBC transfusion	18 (20.5)	16 (21.9)	2 (13.3)	0.453
Intraoperative FFP transfusion	21 (23.9)	18 (24.7)	3 (20.0)	0.700

Data represent n (%), mean ± SD, or median (interquartile range).

TABLE 2 | Patient mortality and morbidity.

Variables	Total (*n* = 88)	Non-stroke (*n* = 73)	Stroke (*n* = 15)	*P*-value
ICU stay time (h)	60.6 (22.7–114.2)	40.5 (18.7–90.0)	180.5 (84.0–278.2)	<0.001
Hospital stay time (d)	13.0 (10.0–16.2)	10.0 (13.0–16.0)	14.0 (10.0–18.5)	0.954
Tracheostomy	7 (8.0)	4 (5.5)	3 (20.0)	0.058
Re-exploration for bleeding	5 (5.7)	4 (5.5)	1 (6.7)	0.856
CRRT	14 (15.9)	11 (15.1)	3 (20.0)	0.634
Paraplegia	2 (2.3)	2 (2.7)	0	0.517
Gastrointestinal bleeding	5 (5.7)	4 (5.5)	1 (6.7)	0.856
Mortality	11 (12.5)	6 (8.2)	5 (33.3)	0.007

Data represent n (%), mean ± SD, or median (interquartile range).

(1) After surgical repair of ATAAD, the serum NFL level of stroke patients is increased in comparison with patients with a good neurological prognosis, (2) Serum NFL level appears to hold more predictive value than the conventional biomarkers S100β and NSE, (3) Serum NFL level is a more reliable and sensitive predictor of stroke after surgical repair of ATAAD.

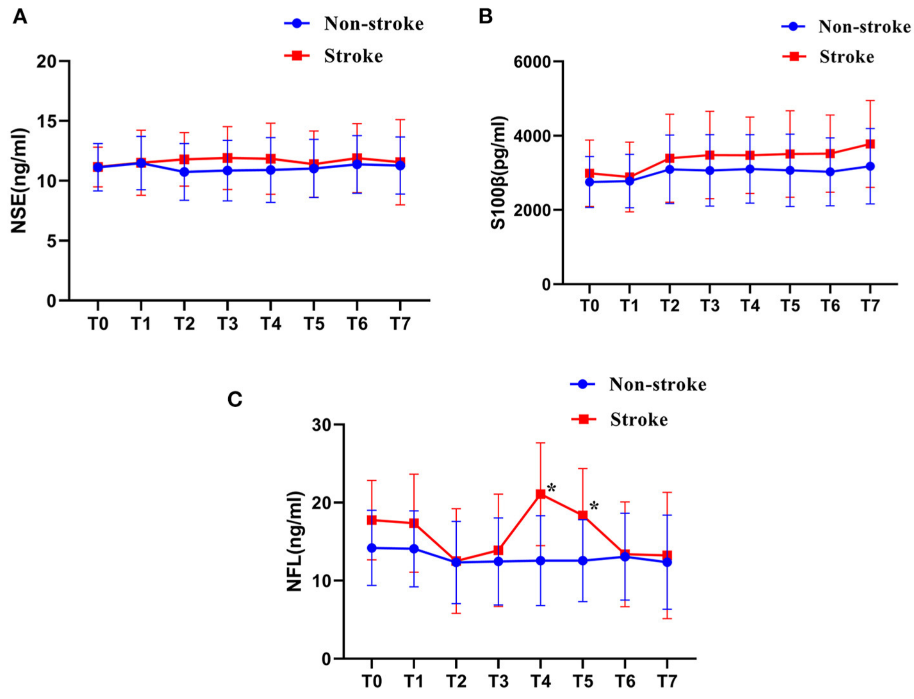

FIGURE 1 | (A–C) Biomarker comparison across groups and time points *$P < 0.001$.

NFL level at 12 h after surgical repair of ATAAD may become an important tool for detecting stroke, potentially complement existing methods neurological prognosis for assessment and help make earlier clinical predictions.

In the past, NFL was rarely used in the assessment of neurological prognosis in the field of cardiac surgery. Alifier et al. (18) found that patients who had cardiac surgery showed higher NFL levels than those underwent other operations, and patients who experienced CPB had even higher levels. In a study conducted by Saller et al. (19) patients who had undergone cardiac surgery were divided into three groups (off-pump coronary artery bypass without delirium group, CPB without delirium group and CPB with delirium group). The authors observed a sharp increase in NFL levels in patients suffering post-operative delirium after CPB, and speculated that surgery or trauma could cause systemic inflammation, inducing a neuroinflammatory response and microglia activation, eventually leading to neuronal damage (20).

Currently, little is known about the changes in serum NFL levels during the perioperative period of ATAAD, so we set out to investigate this question. In this study, the median NFL level of patients who had a stroke 12 h after ATAAD was almost double of that of patients who did not have a stroke (21.4 vs. 11.8 ng/ml), and it was still significantly higher than that of non-stroke patients at 24 h. However, it decreased rapidly at 48 h after ATAAD, a finding that appears inconsistent with the slow change of NFL reported in other studies (13, 18). For example, it may take weeks or months for NFL levels to return to normal after traumatic brain injury, as reported in a study in a population of professional boxers (21). Interestingly, although there was no statistical difference, patients in the stroke group had a higher baseline value (T0) than those in the non-stroke group.

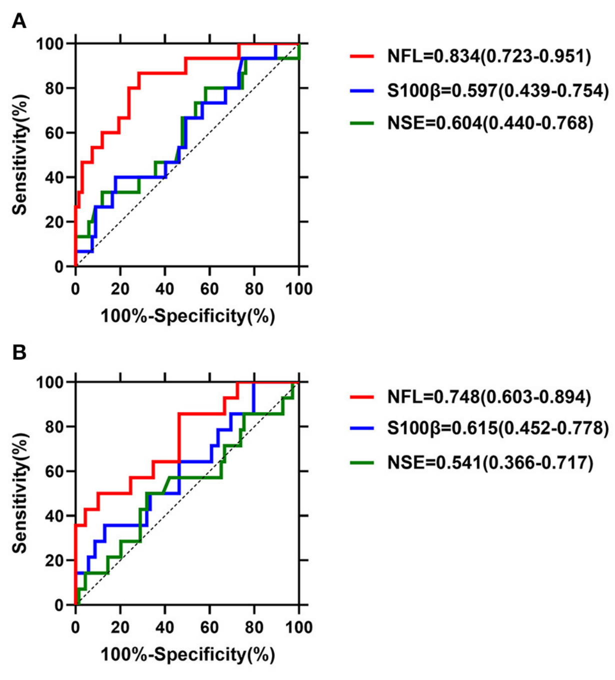

FIGURE 2 | (A,B) Biomarker accuracy for predicting post-operative stroke.

TABLE 3 | Cut-off points, sensitivities, specificities, and AUC values of NFL levels for stroke prediction by ROC analysis.

Variables	Cut-off value (ng/ml)	Specificity	Sensitivity	AUC	95% CI of AUC	*P*-value
NFL-T4	16.042	0.716	0.867	0.834	0.723–0.951	<0.001
NFL-T5	19.339	0.899	0.500	0.748	0.603–0.894	0.004

According to previous studies, diseases such as amyotrophic lateral sclerosis, multiple sclerosis, and HIV-associated dementia may significantly increase NFL serum levels and affect the predicted value of NFL (22–24). Although the patients enrolled in our study had no reported history of such medical conditions, these factors should be taken into consideration when evaluating patients. In addition, we suggest that there might be other explanations for this seemingly inconsistent finding. As a major cause of stroke, cerebral small vessel disease (CSVD) is one of the most frequent pathologic conditions neurologists can encounter. A recent study (25) reported a two-fold increase of serum NFL levels in CSVD subjects compared with healthy controls, an association was observed with both imaging and clinical features. Gattringer et al. (26) found that serum NFL levels have also been associated with the occurrence of small subcortical infarcts and with new-CSVD-related MRI lesions, suggesting NFL levels could act as a putative marker of active CSVD. Age constitutes a major risk factor for CSVD, and vascular aging is very frequently accompanied by chronic major vascular conditions for CSVD, including hypertension, diabetes, and smoking. All of these conditions and comorbidities are present in the patients included in this study and are more common in the stroke group. Since ATAAD patients often require emergency surgery and lack adequate pre-operative examination, CSVD might be related to the actual underlying conditions of these patients.

An ideal biomarker for brain injury should be both specific and sensitive. When the central nervous system (CNS) is injured, it can pass through the blood-brain barrier, leading to increased biomarker levels in the blood (27). S100β is widely expressed in various glial cells of the CNS in mammals, and previous studies have shown satisfactory sensitivity and specificity for serum S100β in the diagnosis of ischemic stroke after cardiac surgery (2). Similarly, as an enzyme of glycolysis, there are many clinical studies that support the use of NSE as a marker of brain injury after CPB (3, 4). However, in our study, when comparing NFL with NSE and S100β, NFL was the only marker that predicted stroke accurately at 12 h after surgery, with a better accuracy at 24 h than other biomarkers. The reason for this difference may be that NSE is susceptible to hemolysis (7). The application of S100β has also been questioned due to its expression in extracranial tissue sources such as fat cells and chondrocytes (8, 9).

Although surgical techniques, anesthesia and extracorporeal circulation management, post-operative monitoring and even artificial blood vessel materials have all greatly improved in the past 20 years, strokes after ATAAD are still relatively common, with an incidence of about 10–30% (28, 29). In this study, the incidence of post-operative stroke in the entire cohort was 15%. Of the 11 patients who died, five had post-operative stroke, which seriously affected their quality of life, endangered their lives, and brought great economic and spiritual burdens to their family. Prior literature has reported a variety of mechanisms involved in brain injury after ATAAD including the formation of embolus (atherosclerotic plaque, air, or blood clots) originating from the aorta or CPB circuit, brain hypoperfusion during CPB, and hypoperfusion related to systemic inflammation (30). However, it is difficult to evaluate the patient's neurological condition during surgery and during the early post-operative period for a number of reasons: due to the effects of post-operative sedation and mechanical ventilation, coupled with unstable vital signs, moving the patient may not be appropriate, and traditional "gold standard" examinations such as CT and MRI are restricted; due to the influence of drugs, EEG data may not be accurate and near infrared spectroscopy is also of limited value in continuous monitoring of brain tissue oxygen saturation (31). Peripheral blood biomarkers that reflect brain damage could provide objective quantitative measures to help guide clinical practice and management, for example by improving the assessment of damage and contributing to a timely and accurate diagnosis.

This study also has limitations. First, the sample size was relatively small, and therefore larger prospective studies with longer follow-up are needed. Second, our study was a prospective observational study, and therefore randomized controlled trials are necessary to validate the results. Before the serum NFL level can be used for clinical decision-making in ATAAD patients, it is important that the cut-off values are validated and a reliable laboratory reference range established.

CONCLUSIONS

This study suggests for the first time the value of serum NFL as an early and sensitive serum marker for predicting post-operative stroke of ATAAD patients, particularly 12 h after surgery. Our findings should be validated by large-scale prospective clinical trials to test whether serum NFL levels have a value in clinical decision-making.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KZha, XP, and QL: design the research. KZha, SD, KZhu, and LS: analyze the data. KZha, ZW, and QL: write the article. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.754801/full#supplementary-material

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ORIGINAL RESEARCH
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Association of Apoptosis-Mediated CD4$^+$ T Lymphopenia With Poor Outcome After Type A Aortic Dissection Surgery

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Background: Many patients with type A aortic dissection (AAD) show low lymphocyte counts pre-operatively. The present study investigated the prognostic values of lymphopenia and lymphocyte subsets for the postoperative major adverse events (MAEs) in AAD patients undergoing surgery, and explore mechanisms of lymphopenia.

Methods: We retrospectively analyzed pre-operative lymphocyte counts in 295 AAD patients treated at two hospitals, and evaluated their correlation with MAEs. We prospectively recruited 40 AAD patients and 20 sex- and age-matched healthy donors (HDs), and evaluated lymphocyte subsets, apoptosis, and pyroptosis by flow cytometry.

Results: Multivariable regression analysis of the retrospective cohort revealed pre-operative lymphopenia as a strong predictor of MAEs (odds ratio, 4.152; 95% CI, 2.434–7.081; $p < 0.001$). In the prospective cohort, lymphocyte depletion in the AAD group was mainly due to loss of CD4$^+$ and CD8$^+$ T cells as compared with HDs (CD4$^+$ T cells: 346.7 ± 183.6 vs. 659.0 ± 214.6 cells/µl, $p < 0.0001$; CD8$^+$ T cells: 219.5 ± 178.4 vs. 354.4 ± 121.8 cells/µl, $p = 0.0036$). The apoptosis rates of CD4$^+$ and CD8$^+$ T cells were significantly higher in AAD patients relative to HDs (both $p < 0.0001$). Furthermore, the pre-operative CD4$^+$ T cells count at a cut-off value of 357.96 cells/µl was an effective and reliable predictor of MAEs (area under ROC curve = 0.817; 95% CI, 0.684-0.950; sensitivity, 74%; specificity, 81%; $p < 0.005$). Pre-operative lymphopenia, mainly due to CD4$^+$ T cells exhaustion by apoptosis, correlates with poor prognosis in AAD patients undergoing surgery.

Conclusion: Pre-operative lymphopenia in particular CD4$^+$ T lymphopenia via apoptosis correlates with poor prognosis in AAD patients undergoing surgery.

Keywords: CD4$^+$ T lymphopenia, apoptosis, major adverse events, outcomes, aortic dissection

INTRODUCTION

Stanford type A aortic dissection (AAD) is a life-threatening cardiovascular emergency with a high risk of death if not swiftly corrected through surgery (1). Despite recent advances in surgery and organ protection, surgical intervention is associated with high mortality and morbidity (2). However, the mechanisms underlying surgical recovery remain unclear. Thus, better understanding of the mechanisms driving prognosis may help develop novel therapeutic strategies for peri-operative multiple organ protection during AAD surgery.

Mounting evidence indicates that immunomodulation of lymphocytes plays a critical role at wounds or damage at other organs (3, 4). Lymphocyte counts have been widely used as markers of systemic immune changes. Studies have revealed association between preoperative lymphopenia and heightened risk of infection after liver transplantation surgery (5), as well as myocardial injury in patients undergoing non-cardiac surgery (6). Low lymphocyte counts independently correlate with mortality and urgent need for transplantation following heart failure (7). A recent study found reduced T-cell levels and elevated B-cell counts in AAD patients (8), but the extent to which lymphocytes are involved in the prognosis after AAD surgery is not known. Particularly, low CD4 cell count has been demonstrated to be a potent marker of excessive immunosuppression in sepsis and renal transplant recipients (9, 10). Severe or transient lymphopenia in sepsis is well-known to inhibit T cell immunity (11). However, it is unknown the incidence of lymphopenia and its association with postoperative outcomes in the AAD patients undergoing aorta arch surgery, a complex surgery with cardiopulmonary bypass (CPB) and various postoperative complications.

In this study, we investigated the impact of preoperative lymphopenia on postoperative AAD outcomes. We retrospectively analyzed the association between lymphocyte count and postoperative major adverse events (MAEs). Additionally, we prospectively studied the lymphocyte subsets involved in the prognosis of postoperative adverse events, and to elucidate the potential mechanisms underlying lymphopenia in AAD patients.

MATERIALS AND METHODS

Retrospective Clinical Data Collection and Analysis (Cohort 1)

We retrospectively identified all Stanford type-A aortic dissection patients undergoing surgery between April 2017 and April 2019 at Xiangya Hospital and the Second Xiangya Hospital of Central South University, China. The dissection is considered as AAD based on the onset of symptoms <14 days prior to admission (12). Inclusion criteria: All Stanford type-A aortic dissection patients undergoing surgery. A total of 317 patients with AAD were identified. Exclusion criteria: Patients were excluded because of pregnancy, as were those with infection, immunodeficiency syndrome, cancer, sub-acute or chronic dissection and those with missing data of preoperative blood cell count. The remaining 295 patients were included in the study population (**Supplementary Figure 1**).

Prospective Lymphocyte Subset Characterization Data (Cohort 2)

A cohort of 40 consecutive AAD patients receiving total arch replacement were prospectively identified and recruited at the time of admission between June 2019 and January 2020. Inclusion criteria: All Stanford type-A aortic dissection patients undergoing surgery. Exclusion criteria: The study subjects with immunodeficiency syndrome, cancer, sub-acute or chronic dissection, coronary heart disease, diabetes, heart failure and cerebral vascular disease were excluded. And those who recently had a surgery or infectious diseases were also excluded (**Supplementary Figure 2**). Fresh blood samples for all experiments were collected within an hour before the induction of anesthesia. A control group consisted of 20 healthy age- and gender-matched subjects, each providing a single morning blood sample. Only healthy control subjects were recruited (**Supplementary Table 1**). All prospective participants provided written informed consent. Ethical approval for the study was granted by the institutional medical ethics review board of the Second Xiangya Hospital. This study was registered in Chinese Clinical Trial Registry (ChiCTR), with registration number: ChiCTR1900023815.

All of the methods were in accordance with the Declaration of Helsinki. All baseline data were done by one member in research team, and outcome documents were collected by a different team member blinded to baseline data. All documentation was analyzed by a third member in group.

Surgical Procedure

Peri-operative surgical management and clinical practices at the two centers were similar and followed the procedure previously described (13–15). In brief, arterial cannulation was done through the right axillary artery. Femoral artery cannulation was occasionally chosen in the case of dissection in the right axillary artery or high pump pressure. Antegrade cerebral perfusion was started after the arrival of target cooling temperature. After completing the anastomosis, perfusion in the lower body was resumed, the CPB flow was gradually returned to 2.0–2.4 $L/m^2/min$, and rewarming was initiated. During the rewarming phase, the branches of the aortic arch were reconstructed. After operation, the patients were transported to the intensive care unit (ICU).

End Points

The primary end point was the incidence of MAEs during hospitalization. Postoperative complications included acute kidney injury (AKI), infection, arrhythmia, myocardial infarction, cerebrovascular accident, spinal cord injury, re-intubation, re-operation. Mortality was defined as in-hospital mortality. Patients meeting at least one criterion, were classified as suffering from postoperative MAEs.

Data Collection and Definitions

The database included pre-operative demographic data, medical history, laboratory results, intraoperative surgical related factors and postoperative complications. Malperfusion was defined as occlusion of the vessels observed by contrast-enhanced CT or the symptom of ischemia or infarction. Arrhythmia is defined as any clinically apparent heart rhythm disturbance, including atrial fibrillation, supraventricular tachycardia, and sudden cardiac arrest. Infection includes one or more of the following: pneumonia, deep sternal wound infection, urinary tract infection, and septicemia. AKI is defined as a two-fold increase in baseline creatinine, or the need for renal replacement therapy (16). Cerebrovascular accident include transient ischaemic attack, stroke, or cerebral haemorrhagic events during postoperative period (17). Mechanical ventilation time is defined as the period between patient admission into ICU and extubation. Re-intubation was defined as re-intubation for any reason during hospitalization after extubation. Re-operation was defined as the need for re-operation for any reason during hospitalization after the initial cardiac procedure (18).

Leukocyte Quantification

Leukocyte analysis was done on blood collected in ethylene diaminetetra acetic acid (EDTA)-treated tubes using automatic analyzers under standard operating procedures approved for clinical use. The preoperative blood results (complete blood counts) of each patient were identified, and those closest to the time of surgery were recorded. Lymphopenia was indicated by a total lymphocyte count of <1,000/μl (19).

Enumeration of Major Leukocyte Populations

Blood was collected in 4 ml EDTA-treated tubes (BD Biosciences, California, USA). Flow cytometry was performed on whole blood within 4 h after blood collection. Absolute numbers of T and B lymphocytes were quantified using TruCount tubes (BD Biosciences, California, USA). Absolute counts of $CD45^+$ cells, $CD3^+$, $CD4^+$, $CD8^+$ T lymphocytes and $CD19^+$ B lymphocytes were analyzed on a 5-color BD TruCount flow cytometric assay, as described previously (20).

Flow Cytometry

To measure apoptosis by flow cytometry, we stained the cells with Annexin V and propidium iodide (PI) (BD Biosciences) in order to estimate the rate of early-phase apoptosis, late-phase apoptosis or necrosis in each sample. PI indicates late apoptosis or necrotic cells. Cells that are positive for Annexin V, but not for PI are considered to be in early-phase apoptosis (21). To this end, cells were washed twice with cold PBS (Gibco) and resuspended at a concentration of 1×10^6 cells/ml in Annexin V-binding buffer (BD Biosciences, San Jose, California, USA). They were then incubated for 15 min at room temperature with 5 μl Annexin V and 5 μl PI. 400 μl of Annexin V-binding buffer was then added and samples analyzed on a FACS Calibur cytometer (Cytek) using FlowJo v10 (Tree Star Corp) software. Every measurement includes 10^4 cells.

TABLE 1 | Demographic and clinical characteristics of patients with lymphopenia and non-lymphopenia.

	Lymphopenia (*n* = 167)	Non-lymphopenia (*n* = 128)	*p*- value
Demographics			
Age	52 ± 9.0	48 ± 10	0.004
Male	125 (75)	111 (87)	0.012
Debakey classification			0.015
I	167 (100)	123 (96)	
II	0 (0)	5 (4)	
Medical history			
Smoking	66 (40)	67 (52)	0.028
Hypertension	123 (74)	97 (76)	0.677
Diabetes mellitus	6 (4)	3 (2)	0.783
Marfan syndrome	3 (3)	2 (2)	1.000
Coronary heart disease	22 (13)	7 (6)	0.028
Cardiovascular surgery	4 (2)	3 (2)	1.000
Cerebral vascular disease	10 (6)	4 (3)	0.384
Organ malperfusion	73 (44)	53 (41)	0.691
Laboratory results			
WBC, 10^9/L	12.4 ± 3.5	13.2 ± 4.0	0.064
Neutrophil, 10^9/L	10.6 (8.6, 12.6)	10.5 (8.1, 13.1)	0.578
Monocyte, 10^9/L	0.6 (0.5, 0.8)	0.8 (0.7, 1.1)	<0.001
Lymphocyte, 10^9/L	0.8 (0.6, 0.9)	1.3 (1.1, 1.5)	<0.001
Creatinine, mg/dL	1.0 (0.8, 1.3)	0.9 (0.8, 1.4)	0.964
LVEF, %	66 (62, 70)	65 (61, 69)	0.833
Symptom onset to hospital presentation, h	12 (8, 24)	21 (12, 39)	<0.001
Presentation to surgery, h	22 (13, 35)	21 (14, 35)	0.580
Procedure type			
Total arch replacement	164 (98)	117 (91)	0.014
Hemiarch replacement	2 (1)	6 (5)	0.142
Bentall procedure	7 (4)	5 (4)	1.000
David procedure	7 (4)	5 (4)	1.000
CABG	22 (13)	5 (4)	0.011
Duration of procedure			
CPB, h	3.8 (2.8, 4.7)	3.4 (2.3, 4.6)	0.052
ACCT, h	1.7 (1.0, 2.5)	1.4 (0.9, 2.3)	0.098
HCA ≥ 30 min	47 (28)	29 (23)	0.285
HCA temperature, °C	25.3 (24, 28.4)	27 (24.8, 29)	0.070
Duration of surgery, h	8.5 ± 2.4	7.8 ± 2.5	0.032

Data are presented as number (%), mean (SD) or median (IQR).
Depending on the types of data, the Student t test or Mann-Whitney test or Fisher exact test was applied, and p < 0.05 was considered to indicate statistical significance.
ACCT, aortic cross clamp time; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass time; HCA, hypothermic circulatory arrest; LVEF, left ventricular ejection fraction; IQR, interquartile range; WBC, white blood cell.

To detect apoptosis, PBMCs were isolated and immediately resuspended at 1×10^6 cells/ml. Multicolor cytofluorimetric analysis was then done using CD3-PE/cy7, CD4-percp-cy5.5, CD8-BV510, CD19-APC (all from BioLegend) antibodies. This analysis was done by automatic compensation for minimized fluorescence spillover and by using fluorescence minus one (FMO) control to establish positive/negative boundaries.

To detect pyroptosis, PBMCs were stained with CD3-PE/cy7, CD4-percp-cy5.5, CD8-BV510 and CD19-APC (all from BioLegend) antibodies. They were then incubated with fluorochrome-labeled Caspase-1 Inhibitors (Immunohistochemistry Technologies), which irreversibly bind to activated caspase-1.

Statistical Analysis

Patient clinical characteristics and postoperative outcomes were presented as frequencies and percentages for categorical variables and compared using chi-square test or Fisher exact test. Normally distributed continuous variables were presented as mean and standard deviations (SD) and compared using Student *t* test while non-normally distributed variables were presented as medians and interquartile 25th and 75th percentiles (IQRs) and compared using the non-parametric Mann-Whitney U tests. Survival curves within time in ventilation, length in ICU stay and hospital stay were plotted by the Kaplan Meier (KM) method and compared by log-rank test. For the retrospective analysis, multivariable logistic regression was used to evaluate the independent predictive value of pre-absolute lymphocyte count (ALC) in primary study endpoints and to adjust for possible confounding factors. Variables with $p < 0.10$ from univariable analyses results were considered confounders in the multivariable logistic regression analysis. Results of the logistic regression model are given as odds ratio (OR) and 95% confidence interval (CI). For the prospective cohort, $CD4^+$ T cells counts as a predictor for postoperative outcomes were estimated by receiver operating characteristic (ROC) curve analysis. Youden's index was defined for all the points along the ROC curve, and the maximum value of the index was used as a criterion for selecting the optimum cut-off point. The ability of the cut-off value for $CD4^+$ T cells counts to predict postoperative outcomes were further evaluated by using multivariable logistic regression analysis. We hypothesized that the area under the curve of the MAE of $CD4^+$ T cells counts would be 0.8. We calculated the required sample size for the ROC analysis. Considering the α error of 0.05, 90% power, and sample size ratio in the negative/positive group of 1, among MAEs and No MAEs, 34 patients were needed. Considering the attrition rate of 10%, at least a total of 38 AAD patients were included in the study. Actually, 40 AAD patients were included in our study. Linear regression was used to analyze the influence of apoptosis rate of lymphocyte ($CD3^+$, $CD4^+$ and $CD8^+$ T cells) on their absolute counts. Data analysis was done using SPSS 23.0 software (SPSS, Chicago, IL, USA). All tests were two-sided and considered statistically significant at $p < 0.05$.

RESULTS

Clinical Characteristics of the Patients

Clinical baseline characteristics in AAD are shown in **Table 1**. Demographic characteristics of lymphopenia and non-lymphopenia populations were similar in terms of pre-operative ejection fraction (EF) value, serum creatinine levels, hypothermic circulatory arrest (HCA) time, HCA temperature, aortic cross clamp time (ACCT), CPB time and comorbidities. Male gender and smoking status were more frequent among the group with non-lymphopenia ($p < 0.05$). Relative to non-lymphopenia patients, lymphopenia correlated with more advanced age, longer time of operation ($p < 0.05$) and more percentage of coronary heart disease (13 vs. 6%; $p = 0.028$). The percentage of lymphopenia patients undergoing coronary artery bypass grafting (CABG) surgery (13 vs. 4%; $p = 0.011$) and total arch replacement (98 vs. 91%; $p = 0.014$) was higher than non-lymphopenia patients. Other significant differences included shorter time of symptom onset to hospital presentation (12 vs. 21 h; $p < 0.001$) and lower pre-operative monocyte count (0.6 vs. 0.8 × 10^9/L; $p < 0.001$).

TABLE 2 | Postoperative events of patients with lymphopenia and non-lymphopenia.

	Lymphopenia (*n* = 167)	Non-lymphopenia (*n* = 128)	*p*- value
AKI	61 (37)	22 (17)	<0.001
Infection	64 (38)	34 (27)	0.034
Arrhythmia	55 (33)	19 (15)	<0.001
Re-operation	11 (7)	4 (3)	0.283
Re-intubation	19 (11)	8 (6)	0.120
Spinal cord injury	20 (12)	10 (8)	0.241
Cerebrovascular accident	39 (23)	28 (22)	0.764
Postoperative myocardial infarction	14 (8)	2 (2)	0.021
Mortality	17 (10)	5 (5)	0.042
MAE	128 (77)	60 (47)	<0.001

Data are presented as number (%).
χ^2 test or Fisher exact test was applied to examine postoperative events of patients with lymphopenia and non-lymphopenia. The $p < 0.05$ was considered to indicate statistical significance.
AKI, acute kidney injury; MAE, major adverse events.

Lymphopenia Predicts Post-operative Complications

Analysis of correlation between lymphopenia and postoperative MAEs revealed significantly higher rates of AKI, infection, arrhythmia, myocardial infarction, mortality, and overall MAEs in lymphopenia patients relative to non-lymphopenia group ($p < 0.05$, **Table 2**). 37% of the lymphopenia patients developed AKI after surgery, compared to17% in controls ($p < 0.001$). Mortality rate was higher in the lymphopenia relative to non-lymphopenia group (10 vs. 5%; $p = 0.042$). No difference was observed in lymphopenia patients relative to non-lymphopenia group in terms of cerebrovascular accident, spinal cord injury, re-intubation, and re-operation (**Table 2**).

Multivariable analysis showed that pre-operative lymphopenia independently correlated with increased risk of MAE after surgery (OR, 4.152; 95% CI 2.434–7.081; $p < 0.001$) (**Tables 3**, **4**). Other predictors include organ malperfusion (OR, 2.481; 95% CI 1.432–4.298; $p = 0.001$), and CPB time

TABLE 3 | Baseline characteristics of patients with MAE and no MAE in retrospective cohort.

	MAE (n = 188)	No MAE (n = 107)	*p-value*
Demographics			
Age	51 (46, 56)	49 (42, 55)	0.009
Male	150 (80)	86 (80)	0.904
Debakey classification			0.357
I	186 (99)	104 (97)	
II	2 (1)	3 (3)	
Medical history			
Smoking	88 (47)	45 (42)	0.430
Diabetes	6 (3)	3 (3)	1.000
Marfan syndrome	3 (2)	2 (2)	1.000
Hypertension	145 (77)	75 (70)	0.182
Coronary heart disease	24 (13)	5 (5)	0.025
Cardiovascular surgery	4 (2)	3 (3)	0.707
Cerebral vascular disease	11 (6)	3 (3)	0.369
Organ malperfusion	93 (50)	33 (31)	0.002
Laboratory results			
WBC, 10^9 /L	12.4 (10, 15.3)	9.8 (12.4, 14.1)	0.413
Neutrophil, 10^9 /L	10.6 (8.5, 13.2)	10.4 (8.1, 11.9)	0.085
Monocyte, 10^9 /L	0.7 (0.5, 0.9)	0.8 (0.6, 1.0)	0.179
Lymphocyte, 10^9 /L	0.9 (0.7, 1.1)	1.1 (0.9, 1.4)	<0.001
Creatinine, mg /dL	1.0 (0.8, 1.5)	0.9(0.7, 1.2)	0.006
LVEF, %	66 (61, 70)	65 (61, 69)	0.849
Symptom onset to hospital presentation, h	13 (6, 21)	18 (7, 30)	0.075
Presentation to surgery, h	21 (11, 32)	25 (14, 36)	0.012
Involvement of vessel branches			
Coronary artery	63 (33)	30 (28)	0.331
Innominate artery	119 (63)	52 (49)	0.014
LSA	102 (54)	50 (47)	0.214
Left common carotid artery	96 (51)	49 (46)	0.384
Celiac trunk	71 (38)	34 (32)	0.302
Superior mesenteric artery	48 (26)	22 (21)	0.335
Right renal artery	56 (30)	31 (29)	0.883
Left renal artery	76 (40)	38 (36)	0.405
Procedure type			
Total arch replacement	179 (95)	102 (95)	0.965
Hemiarch replacement	7 (4)	1 (1)	0.296
Bentall procedure	9 (5)	3 (3)	0.601
David procedure	8 (4)	4 (4)	1.000
CABG	23 (12)	4 (4)	0.026
Duration of procedure			
CPB, h	3.7 (2.8, 4.9)	3.5 (2.1, 4.3)	0.001
ACCT, h	1.8 (1.0, 2.6)	1.3 (0.7, 2.2)	0.001
HCA ≥ 30 min	54 (29)	22 (21)	0.123
HCA temperature, °C	25.2 (24.3, 29)	27.6 (25, 29)	0.040
Time of surgery, h	8.7 (6.8, 10.1)	7.7 (5.5, 8.8)	<0.001

Values are expressed as number (%), mean (SD) or median (IQR).
Depending on the types of data, the Student t test or Mann-Whitney test or Fisher exact test was applied, and p < 0.05 was considered to indicate statistical significance.
ACCT, aortic cross clamp time; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass time; HCA, hypothermic circulatory arrest; LSA, left subclavian artery; LVEF, left ventricular ejection fraction; MAE, Major adverse events; IQR, interquartile range; WBC, white blood cell.

(OR, 1.285; 95% CI, 1.063–1.552; p = 0.010). As shown in **Supplementary Figure 3**, KM curves indicated patients with lymphopenia had longer time in ventilation during a 72-h followed-up periods ($p = 0.001$), more length of ICU stay ($p < 0.001$) and hospitalizations ($p = 0.005$).

$CD4^+$ T Lymphopenia Correlates With MAEs After AAD Surgery

Next, we sought to identify the lymphocyte subgroups that correlate with clinically significant outcomes. We found that lymphopenia in AAD patients is primarily due to the reduction of T cells (**Figure 1**). $CD3^+$ T cells counts, but not B cells, were significantly reduced in the AAD group compared to healthy donors (HDs) ($CD3^+$ T cells: 615.6 ± 327.3 vs. 1,175.0 ± 264.3 cells/µl, $p < 0.0001$; $CD19^+$ B cells: 177.8 ± 118.3 vs. 228.3 ± 94.5 cells/µl, $p = 0.1048$). Among $CD3^+$ T cells, reduced $CD4^+$ and $CD8^+$ T cells were observed in the AAD group as compared with HD group (CD4: 346.7 ± 183.6 vs. 659.0 ± 214.6 cells/µl, $p < 0.0001$; CD8: 219.5 ± 178.4 vs. 354.4 ± 121.8 cells/µl, $p = 0.0036$) (**Figure 1**).

When stratified according to MAEs incidence, lymphocyte subset analysis showed that patients who developed complications had lower preoperative $CD3^+$ and $CD4^+$ T cells levels relative to those with an uneventful recovery ($CD3^+$ T cells: 768.9 ± 302.4 vs. 476.9 ± 289.9 cells/µl, $p = 0.0035$; $CD4^+$ T cells: 447.6 ± 179.0 vs. 255.4 ± 135.8 cells/µl, $p = 0.004$, No MAE group vs. MAE group) (**Figures 2A,B**). In contrast, $CD8^+$ T cells and B cells did not differ between no MAE group and MAE group ($CD8^+$ T cells: 264.3 ± 187.3 vs. 178.9 ± 163.9 cells/µl, $p = 0.1326$; $CD19^+$ B cells: 188.3 ± 122.1 vs. 171 ± 116.2 cells/µl, $p = 0.6505$) (**Figures 2C,D**). Similar observations show $CD4^+$ T cells levels relative to those with AKI and infection (**Figures 2E–L**). In addition, we found that the pre-operative $CD4^+$ T cells counts at a cut-off value of 357.96 cells/µl is an effective and reliable predictor of MAEs (area under ROC curve 0.817; 95% CI, 0.684-0.950; $p < 0.005$). This cut-off achieves a 74% sensitivity and 81% specificity, supporting the hypothesis that $CD4^+$ T lymphopenia may predispose to poor AAD surgical outcomes (**Supplementary Figure 4**). After adjustment for age, organ malperfusion, symptom onset to surgery, multivariate analysis revealed $CD4^+$ T cells count as being independently correlated with elevated MAEs (HR, 9.384; 95% CI 1.85–47.59; $p = 0.009$) (**Table 5**; **Supplementary Table 2**).

Apoptosis, but Not Pyroptosis Contributes to $CD4^+$ T Lymphopenia in AAD

We assessed the spontaneous cell death in AAD patients. Pyroptosis and apoptosis are two major types of active cell death. This analysis did not reveal differences between AAD patients and healthy subjects in terms of lymphocyte pyroptosis (**Figure 3A**). Of note, lymphocytes undergoing apoptosis were markedly elevated in AAD patients relative to those in healthy subjects (**Figure 3B**). The apoptosis rate of AAD T lymphocytes was significantly higher relative to that of healthy subjects (8.100 ± 3.958 vs. 22.12 ± 9.512%, $p < 0.0001$). Separate analysis of changes in T cells subsets, revealed that AAD patients exhibited significantly higher $CD4^+$ (6.243 ± 3.168 vs. 20.010 ± 9.054%, $p < 0.0001$) and $CD8^+$ T cells (8.003 ± 5.963 vs.

TABLE 4 | Univariable and multivariable logistic regression analysis of possible predictors of MAE.

Predictors	Univariable		Multivariable	
	OR (95% CI)	***p-value***	**OR (95% CI)**	***p-value***
Age, years	1.028 (1.003–1.054)	0.027		
Coronary heart disease	2.985 (1.204–8.072)	0.031		
Innominate artery injury	1.824 (1.127–2.952)	0.014		
Organ malperfusion	2.195 (1.331–3.620)	0.002	2.481 (1.432–4.298)	0.001
CABG surgery	3.589 (1.207–10.675)	0.022		
Symptom onset to hospital presentation, hour	0.993 (0.986–1.000)	0.047		
Creatinine, mg/dL	1.581 (0.989–2.529)	0.056		
Neutrophil count, 10^9 /L	1.071 (0.998–1.149)	0.057		
Lymphopenia	3.970 (2.404–6.556)	<0.001	4.152 (2.434–7.081)	<0.001
CPB, h	1.384 (1.155–1.659)	<0.001	1.285 (1.063–1.552)	0.010
ACCT, h	1.579 (1.199–2.080)	0.001		
HCA temperature, °C	0.930 (0.859–1.007)	0.074		

Binary logistic regression analysis was applied to examine factors associated with the MAE (dependent variable) in the retrospective cohort (n = 295). The p < 0.05 was considered to indicate statistical significance.

ACCT, aortic cross clamp time; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass time; CI, confidence interval; HCA, hypothermic circulatory arrest; MAE, major adverse events; OR, odds ratio.

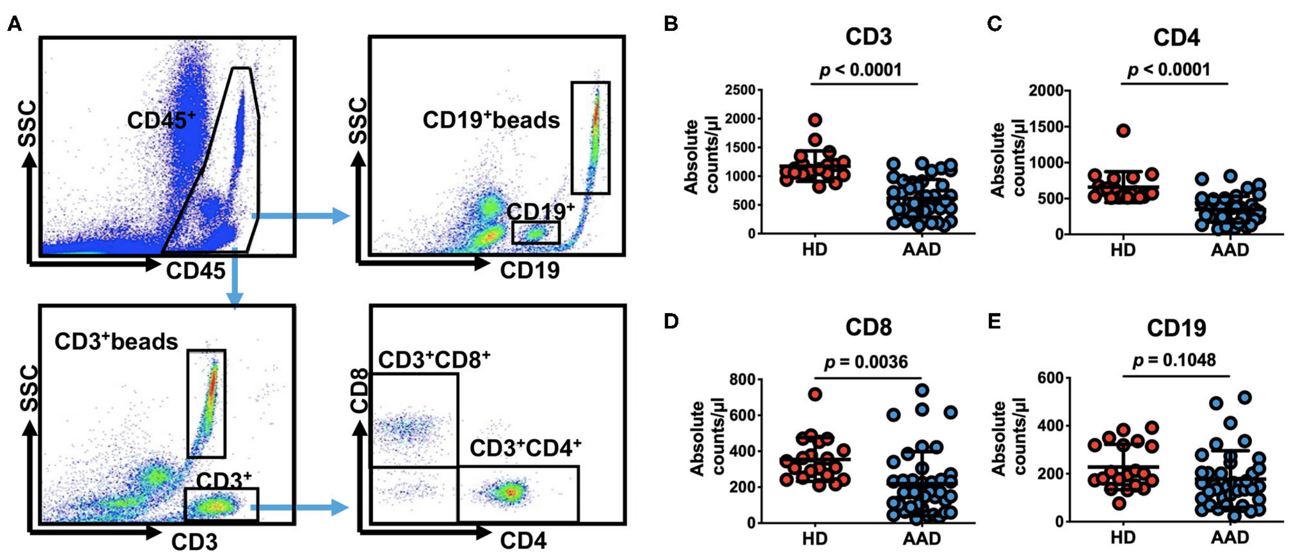

FIGURE 1 | Pre-operative peripheral blood lymphocyte subsets count in 40 patients undergoing surgical repair of type A aortic dissection and 20 healthy donors. **(A)** Quantitation of numbers in a lysed whole-blood, that is, all lymphocytes presented in the lymphocyte gate identified by CD45 fluorescence and side scatter on flow cytometry and consisting mainly of CD3$^+$, CD4$^+$, CD8$^+$, CD19$^+$ cells and their corresponding beads are examined. **(B–E)** Comparison of pre-operative peripheral blood lymphocyte subsets counts between AAD patients and HDs (data shown as means ± SD). CD3$^+$ beads, the beads corresponding CD3$^+$ cells, CD19$^+$ beads, the beads corresponding CD19$^+$ cells.

23.720 ± 12.920%, $p < 0.0001$) apoptosis relative to healthy subjects. Correlation analysis showed that CD4$^+$ and CD8$^+$ T lymphocytes apoptotic rates were inversely correlated to their absolute counts (**Figure 3C**).

DISCUSSION

There is a high incidence of postoperative complications in AAD patients undergoing surgery (22). In the present study, we have shown that pre-operative lymphopenia is predictive of poor outcome after AAD surgery. Lymphopenia is primarily driven by loss of CD4$^+$ and CD8$^+$ T cells subsets, which result from spontaneous apoptosis but not pyroptosis. Furthermore, we have identified an association between CD4$^+$ T cells population and development of MAEs, with the AUC of ROC analyses for distinguishing between MAE and no MAE subjects to be 0.8. This provides what we believe to be the first evidence of a role for these cells in AAD prognosis after surgery.

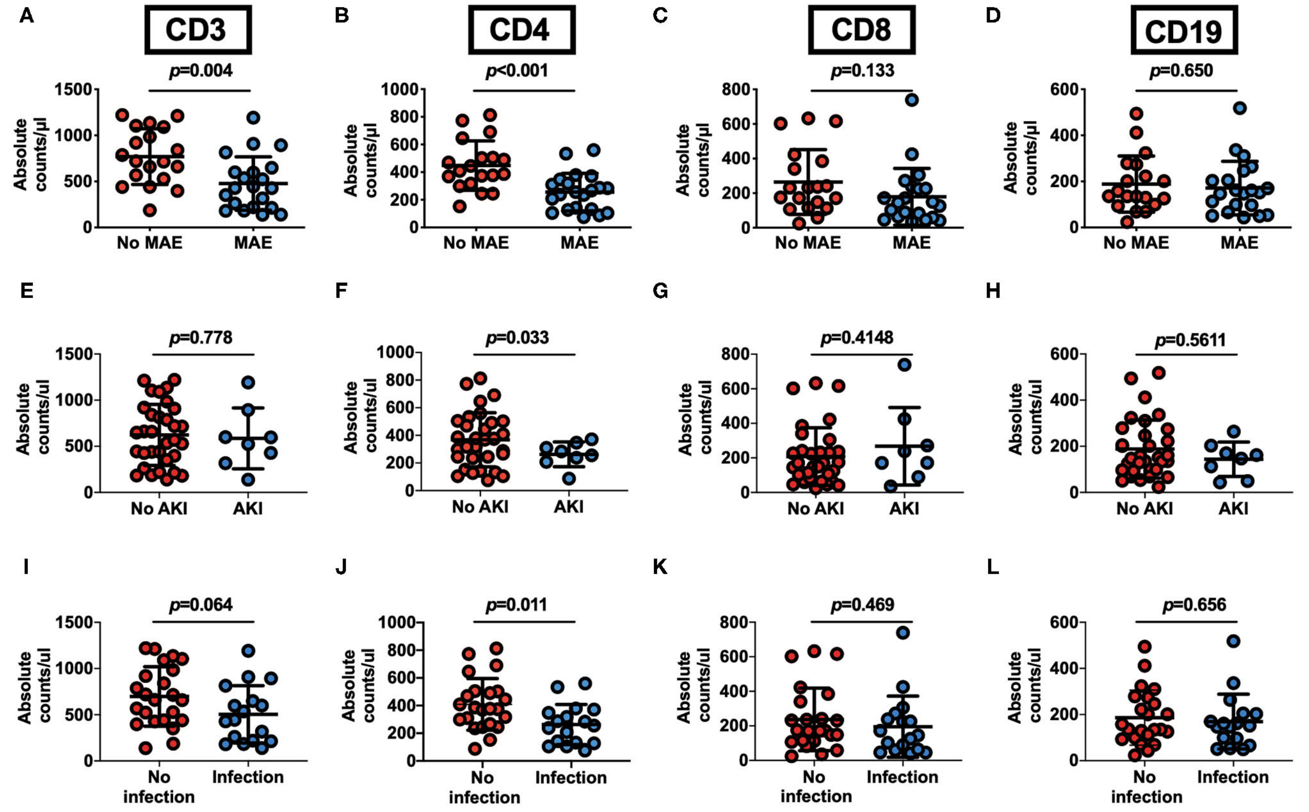

FIGURE 2 | Pre-operative peripheral blood CD4+ T lymphocyte count as an outcome predictor following surgery for acute Type A aortic dissection. **(A–D)** Pre-operative peripheral blood lymphocyte subsets counts in 40 patients undergoing surgical repair of type A aortic dissection with respect to postoperative occurrence of MAEs. AAD patients with MAE ($n = 21$) or no MAE ($n = 19$). **(E–H)** Preoperative peripheral blood lymphocyte subsets counts in AAD patients with or without postoperative AKI. Patients with AKI ($n = 8$) and No AKI ($n = 32$). **(I–L)** Pre-operative peripheral blood cells lymphocyte subsets counts in AAD patients with or without postoperative infection. Patients with infection ($n = 17$) and No infection ($n = 23$). Plots indicate means ± SD.

TABLE 5 | Univariable and multivariable logistic regression analysis of possible predictors of MAE in prospective cohort.

Predictors	Univariable		Multivariable	
	OR (95% CI)	*p-value*	OR (95% CI)	*p-value*
Age, years	1.028 (0.969–1.096)	0.337		
$CD4^+$ T cells lymphopenia	11.90 (2.674–52.96)	0.001	9.384 (1.850– 47.59)	0.009
Organ malperfusion	16.36 (1.835–150.0)	0.012	11.90 (1.123–126.2)	0.040
Symptom onset to surgery, h	0.993 (0.986–1.001)	0.091		

Binary logistic regression analysis was applied to examine factors associated with the MAE (dependent variable) in the prospective cohort ($n = 40$). The $p < 0.05$ was considered to indicate statistical significance.

CI, confidence interval; MAE, major adverse events; OR, odds ratio.

Inflammatory response has been known as key mechanism underlying aortic dissection. The upregulation of cytokines, endothelial adhesion molecules or chemokines are found to play a role in multiple organ injury, including myocardial ischemic injury, acute kidney injury and gastrointestinal disorders (23–28). These data led us to speculate that immune cells are important to the postoperative organ injury in AAD patients. However, current risk assessment indices for AAD outcomes do not incorporate leukocyte subsets despite their close correlation with infection and heart failure (29, 30). The present study is the first, to our knowledge, to directly assess the prognostic significance of lymphocyte counts alone in AAD patients after surgery. The overall prevalence of lymphopenia observed in our study was markedly high (56.6%). Our data implicate that decreased lymphocytes, but not altered monocytes or neutrophils, are closely associated with postoperative MAEs, including acute renal injury, infection, myocardial infarction, arrhythmia, and death during hospitalization.

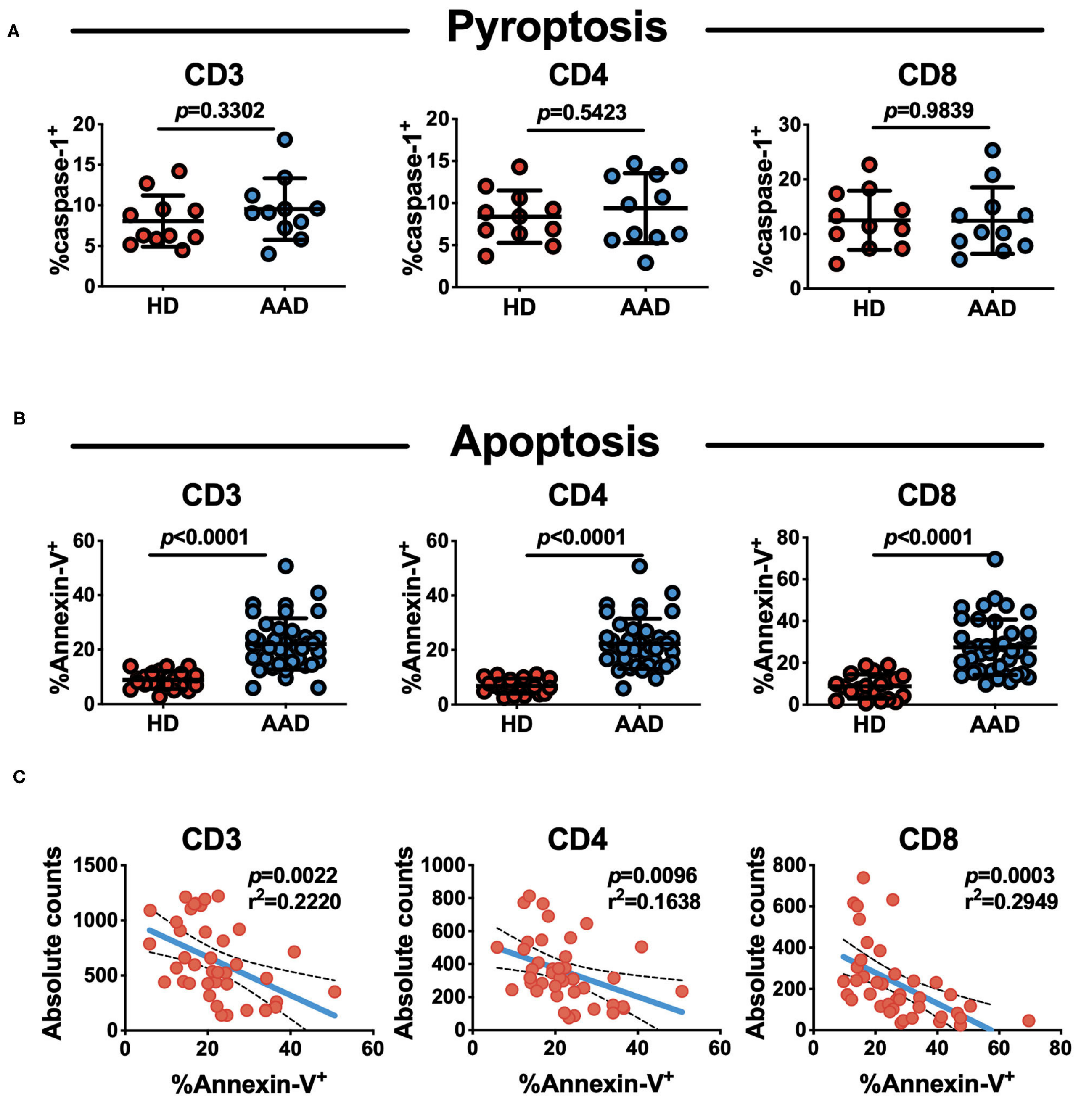

FIGURE 3 | Increased spontaneous apoptosis, not pyroptosis of T lymphocytes in AAD patients. **(A)** Analysis of pyroptosis status of lymphocyte subsets with flow cytometry ($n = 11$). **(B)** Analysis of apoptosis status of lymphocyte subsets with flow cytometry. Mean ± SD comparing their rates on AAD patients ($n = 40$) and HDs ($n = 20$). **(C)** Correlation of absolute lymphocyte ($CD3^+$, $CD4^+$ and $CD8^+$) counts and apoptosis rate in AAD patients ($n = 40$).

Our data also show that lymphocyte loss is primarily due to the reduced $CD4^+$ and $CD8^+$ T cells, but not $CD19^+$ B cells. The decrease of $CD4^+$ T cells in AAD patients is consistent with Porto's report (23). But a reduction of $CD8^+$ T cells and no significant change of B cells were found in the present study, in contrast to Porto' report delineating an increase in B cells and unchanged $CD8^+$ T cells in AAD patients. This discrepancy may be due to the different detection methods. Porto' study used the percentage of $CD8^+$ T cells or B cells against total lymphocytes, unlike absolute numbers of T and B lymphocytes quantified using TruCount tubes in the present study. Given the dramatic reduction of total lymphocytes counts in most of AAD patients, the fact that unchanged B cells absolute number divided by decreased total lymphocytes counts makes the percentage of B cells higher than healthy controls, so did $CD8^+$ T cells. Together with Porto's study, our observations suggest a more profound reduction of $CD4^+$ T cells than that of $CD8^+$ T cells.

Lymphocytes pyroptosis and apoptosis are widely reported in various diseases (31–33). However, we observed that lymphocyte pyroptosis in AAD patients was comparable to that of healthy subjects, whereas lymphocyte apoptosis was dramatically increased in AAD patients. These findings indicate that apoptosis, but not pyroptosis, may at least in part, account for lymphocyte loss. Indeed, the apoptotic rate of $CD4^+$ T cells was inversely related with absolute lymphocyte counts. Apoptosis may be triggered during early AAD stages, when intense inflammation causes severe tear of the aortic intima or when ischemia reperfusion of multi-organs stimulates release of pro-apoptotic substances, such as TNF-α and nitric oxide. Supporting this assumption, our recent study showed the serum derived from AAD patients activated gene expression of the pro-inflammatory cytokines in the cultured peripheral blood mononuclear cells from HDs (34).

Importantly, $CD4^+$ T lymphopenia is correlated with postoperative MAEs in the present study. It is interesting to note the dramatic exhaustion of lymphocytes caused by apoptosis. The apoptosis of T lymphocytes, in turn, may contribute to immunosuppression through the effects of apoptotic cells. In fact, except for lymphocyte apoptosis, decreased HLA-DR expression was also reported in AAD patients after surgery (35). These findings suggest that intense and constant tear of aortic wall in AAD may cause an immunosuppressive state like sepsis, which substantially contributes to morbidity and mortality. Indeed, sepsis induced immunosuppression is well-known characterized by lymphocyte exhaustion and the reprogramming of antigen-presenting cells (36). In addition, acute loss of lymphocytes from circulating blood also occurs following ischemia-reperfusion in STEMI patients receiving PPCI, and the lymphopenia after PPCI predicts long-term mortality in STEMI patients (37). $CD4^+$ T cells depletion may promote poor outcomes via multiple mechanisms, including weakened immunity, disruption of the balance between anti-inflammatory and pro-inflammatory mediators, and exacerbation of myocardial damage. Despite the unclear mechanism, it is possible that T cell lymphopenia disrupts helper T cell (Th) 1/Th2 imbalance and reduces the population of regulatory T cells, which may accelerate recovery (38, 39).

LIMITATIONS

A limitation of this study is difficulty in establishing causality in human subjects. Causality may be addressed by blocking and reconstituting effects in animal models, or through restoring the lymphocyte counts in randomized trials. Thus, our study only provides informative evidence and advances our understanding of the human immune system in clinical AAD surgery settings. Further investigations are needed to establish how specific $CD4^+$ T cells subsets contribute to MAEs in AAD.

CONCLUSION

In summary, our results highlight the prognostic value of preoperative lymphocyte counts in AAD patients undergoing surgery. In particular, the loss of $CD4^+$ T cells via apoptosis may influence development of postoperative MAEs in AAD patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Medical Ethics Review Board of the Second Xiangya Hospital, Changsha, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL and R-PD: concept, design, and critical revision of the manuscript for important intellectual content. DF, W-JL, and H-YZ: acquisition and analysis of data. J-JS, WL, and HL: conducting all the experiments, and drafting of the manuscript. J-JS, Z-LH, and HL: statistical analysis. HL, J-MX, and R-PD: administrative, technical, or material support. HL, R-PD, J-MX, and HT: supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.747467/full#supplementary-material

Supplementary Figure 1 | Flow chart for retrospective cohort.

Supplementary Figure 2 | Flow chart for prospective cohort.

Supplementary Figure 3 | Kaplan–Meier analysis of the difference in the postoperative outcomes between lymphopenia and non-lymphopenia. Patients with lymphopenia had longer time in ventilation and more length of ICU stay and hospitalizations. We excluded the patients who died during the intensive care unit or hospitalization. **(A)** Mechanical ventilation for $\geq$ 72 h; **(B)** length of ICU stay for $\geq$14 days; **(C)** hospital stay $\geq$ 30 days. *P* values were generated by log-rank test.

Supplementary Figure 4 | Receiver-operating characteristic curves displaying the ability of the lymphocyte count and $CD4^+$ T cells count to predict postoperative outcomes in AAD patients in the prospective cohorts. AUC, the area under the curve; CI, confidence interval.

Supplementary Table 1 | Baseline data of the enrolled AAD patients and control donors.

Supplementary Table 2 | Baseline characteristics of patients with MAE and No MAE in prospective cohort.

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Development and Validation of a Prognostic Model to Predict the Risk of In-hospital Death in Patients With Acute Kidney Injury Undergoing Continuous Renal Replacement Therapy After Acute Type a Aortic Dissection

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Background: This study aimed to construct a model to predict the risk of in-hospital death in patients with acute renal injury (AKI) receiving continuous renal replacement therapy (CRRT) after acute type A aortic dissection (ATAAD) surgery.

Methods: We reviewed the data of patients with AKI undergoing CRRT after ATAAD surgery. The patients were divided into survival and nonsurvival groups based on their vital status at hospital discharge. The data were analyzed using univariate and multivariate logistic regression analyses. Establish a risk prediction model using a nomogram and its discriminative ability was validated using C statistic and the receiver operating characteristic (ROC) curve. Its calibration ability was tested using a calibration curve, 10-fold cross-validation and Hosmer–Lemeshow test.

Results: Among 175 patients, in-hospital death occurred in 61 (34.9%) patients. The following variables were incorporated in predicting in-hospital death: age > 65 years, lactic acid 12 h after CRRT, liver dysfunction, and permanent neurological dysfunction. The risk model revealed good discrimination (C statistic = 0.868, 95% CI: 0.806–0.930; a bootstrap-corrected C statistic of 0.859, the area under the ROC = 0.868). The calibration curve showed good consistency between predicted and actual probabilities (*via* 1,000 bootstrap samples, mean absolute error = 2.2%; Hosmer–Lemeshow test, $P = 0.846$). The 10-fold cross validation of the nomogram showed that the average misdiagnosis rate was 16.64%.

Conclusion: The proposed model could be used to predict the probability of in-hospital death in patients undergoing CRRT for AKI after ATAAD surgery. It had the potential to assist doctors to identify the gravity of the situation and make the targeted therapeutic measures.

Keywords: acute kidney injury, acute type A aortic dissection, continuous renal replacement, in-hospital death, nomogram

BACKGROUND

Acute type A aortic dissection (ATAAD) has a high incidence of postoperative acute kidney injury (AKI) due to its special pathophysiological changes and the surgical procedure, which seriously affects the patient's prognosis. AKI has a reported incidence ranging from 20 to 67%, according to the differences in the definition of AKI (1, 2). Some studies showed that the mortality due to postoperative AKI was 10–20 times higher than that without AKI in patients after ATAAD surgery (3, 4). In addition, the mortality for those in need of renal replacement therapy (RRT) was higher. The high risk of short-term mortality in patients undergoing RRT affects the prognosis of patients, making it necessary to identify prognostic factors and perform targeted interventions. Therefore, an effective model needed to be constructed for predicting the risk of in-hospital death in patients with AKI undergoing continuous renal replacement therapy (CRRT) after ATAAD surgery (in this study, all patients treated with RRT undergoing CRRT).

The nomogram has been considered as an effective way to create a straightforward visual graph of a numerical predictive model that quantifies the risk of a clinical outcome. This study aimed to identify the clinical risk factors for in-hospital death in patients with AKI undergoing CRRT after ATAAD surgery, and establish and validate a predictive model.

METHODS

Patients

From June 1, 2015, to February 28, 2019, we retrospectively examined 175 patients with postoperative AKI who underwent ATAAD surgery and received CRRT in Beijing Anzhen Hospital, Capital Medical University (**Figure 1**). The inclusion criteria were as follows: (1) age $\geq$ 18 years, (2) undergoing ATAAD surgery with moderate hypothermia circulation arrest (MHCA) process, (3) CRRT due to postoperative AKI, (4) needing intensive care unit (ICU) treatment for at least 3 days. The exclusion criteria were as follows: (1) previous RRT or kidney transplant, (2) pregnant women, (3) moribund with expected death within 24 h, (4) patients who survived <12 h after CRRT, (5) previous chronic renal insufficiency (met any of the following criteria for more than 3 months: proteinuria $\geq$ 30 mg/24 h, urine albumin to creatinine ratio $\geq$ 3 mg/mmol, abnormal urine routine, electrolyte disorder caused by renal tubular damage, abnormal renal pathology, abnormal renal imaging, renal transplantation, and estimated glomerular filtration rate < 30 ml/min).

AKI was diagnosed based on changes in the urine output, serum creatinine, or both, according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification. Every patient had a urinary catheter to measure urine output every hour, and serum creatinine measurements were performed at least once daily.

Abbreviations: ATAAD, Acute Type A Aortic Dissection; AKI, Acute Kidney Injury; CRRT, Continuous Renal Replacement Therapy; BMI, Body Mass Index; CAD, Coronary Atherosclerotic Disease; CABG, Coronary Artery Bypass Grafting; CPB, Cardiopulmonary Bypass; MHCA, Moderate Hypothermic Circulatory Arrest; BUN, Blood Urea Nitrogen; RBC, Red Blood Cell; ICU, Intensive Care Unit; ILI, Ischemic Liver Injury; PND, Permanent Neurological Dysfunction.

Data Collection

Relevant data related to the surgery were recorded. (1) The preoperative general data included age, gender, weight, height, time from the occurrence of dissection to the surgery, history of hypertension, type of dissection, maximum diameter of the aorta, cardiac function grade, myocardial ischemia, aortic regurgitation, renal insufficiency, pleural effusion, pericardial tamponade, aortic rupture, shock, smoking history, diabetes, oral administration of β-receptor blockers, and calcium antagonists. (2) The intraoperative data included operative time, cardiopulmonary bypass (CPB) time, circulatory arrest time, minimum temperature, crystal colloid input, and blood transfusion. (3) The postoperative data included blood pressure, central venous pressure, mechanical ventilation time, ICU stay, blood transfusion volume, and so forth. The complications included lung infection, respiratory failure, other organ dysfunction [Liver dysfunction is defined as serum alanine aminotransferase or aspartate aminotransferase that are at least 10 times the upper limit of normal value. Permanent neurological dysfunction (PND) is defined as a stroke due to embolism or hemorrhage, it is confirmed by consultation with a neurologist and by imaging (CT/MRI)], hemodynamic instability, arrhythmia, CRRT catheterization or anticoagulation-related bleeding, and electrolyte and acid–base imbalance. The urine volume per hour, daily intake and output, blood creatinine level, urea nitrogen, electrolyte, pH, and internal environment (whether acid–base balance) were recorded postoperatively. The patient treatment measures were recorded, including mechanical ventilation, vasoactive drug use, and fluid therapy.

The timing of most patients undergoing CRRT initiated within 8 h of AKI stage 3 using the KDIGO classification or if any of the following absolute indications for RRT were present: serum urea level > 40 mmol/L; Serum potassium concentration of >6 mmol/L despite medical treatment (bicarbonate and/or glucose-insulin infusion); pH < 7.15 in a context of pure metabolic acidosis (PaCO2 below 35 mmHg) or in a context of mixed acidosis with PaCO2 $\geq$ 50 mmHg without the possibility of increasing alveolar ventilation.

Grouping: The patients were divided into survival and nonsurvival groups based on the vital status at hospital discharge.

Statistical Analysis

Patients' baseline characteristics were expressed as frequency and percentage for categorical variables, and as mean ± standard deviation or median and interquartile range (IQR) for continuous variables, as appropriate. Indicators with missing values warranted interpolation by multiple imputations using the MICE package (5). We assumed that the data were missing at random (6); therefore, we performed predictive mean matching (7) to generate five complete imputed data sets that fit the logistic models. The binary data were tested using the χ^2 test or Fisher exact test. Normally distributed data were compared for significance using t-tests. The Mann–Whitney U-test was applied for data with nonnormal distribution. The significance

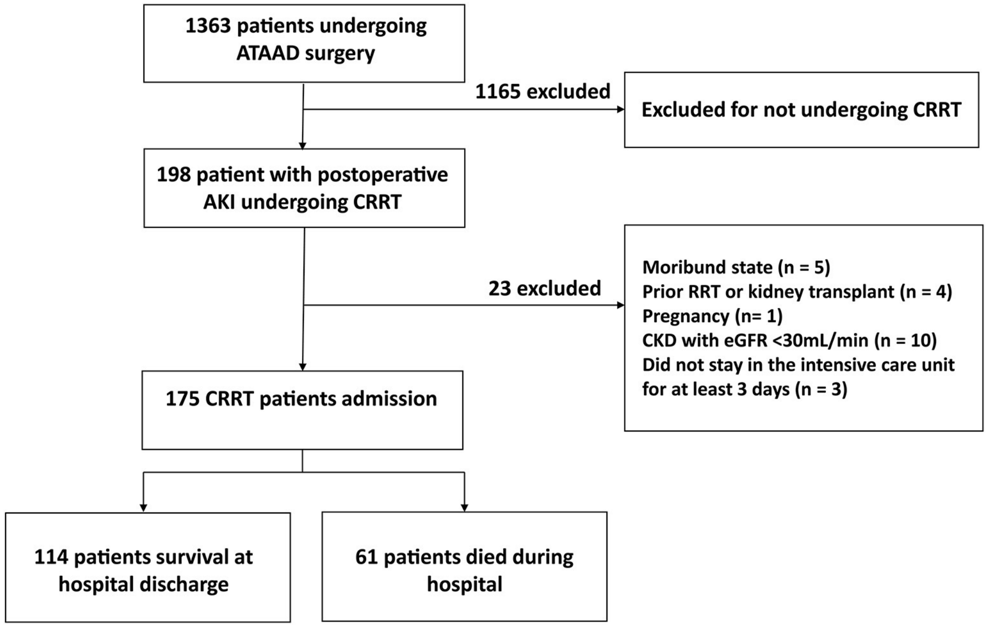

FIGURE 1 | Study flowchart. OR, Odds ratio; CI, confidence interval; PND, permanent neurological dysfunction.

of each variable was assessed by univariate logistic regression analysis. The variables with *P*-value < 0.1 were entered into the multivariate logistic regression analysis to identify the independent risk factors. Based on the results of the final regression analysis, a nomogram to predict the risk of in-hospital death in patients with postoperative AKI undergoing CRRT after ATAAD surgery was constructed using the R software (R software, version 4.1.2). The regression coefficients in multivariate logistic regression were proportionally transformed into a point scale, and the total points were converted into predicted probabilities (8).

The sample size calculation showed that a sample of 32 from the positive group and 60 from the negative group achieve 80% power to detect a difference of 0.15 between the area under the receiver operating characteristic (ROC) curve (AUC) under the null hypothesis of 0.85 and an AUC under the alternative hypothesis of 0.7000 using a two-sided z-test at a significance level of 0.05.

The performance of the nomogram was valuated by discrimination and calibration. The discrimination was demonstrated by the area under the ROC curve (equivalent to the C statistics). The calibration was performed using a visual calibration plot comparing the predicted and actual probabilities of in-hospital death. Furthermore, the calibration was performed using a visual calibration plot *via* 1,000 bootstrap resamples for internal validation to evaluate their predictive accuracies (9). The Hosmer–Lemeshow test was also recommended to assess calibration. Furthermore, we used 10-fold cross-validation to calculate the misdiagnosis rate. The statistical analysis and graphics were implemented by using R 4.1.2. All tests were two tailed, and a *P*-value < 0.05 indicated a statistically significant difference.

RESULTS

A total of 175 patients with postoperative AKI undergoing CRRT after ATAAD were included in this study. The in-hospital death occurred in 61 (34.9%) patients. The comparison of the baseline data showed that the proportion of age > 65 years in the nonsurvival group was significantly higher than that in the survival group [age > 65 years: 18 cases (29.5%) in the nonsurvival group vs. 7 cases (6.1%) in the survival group, *P* < 0.001]. Therefore, the age > 65 years was included in multiple logistic regression analyses. No significant differences were found in other baseline data between the two groups (**Table 1**).

The comparison of intraoperative data between the two groups revealed that the CPB time in the nonsurvival group was longer than that in the survival group (CPB time: nonsurvival group 235.6 ± 64.8 min vs. survival group: 219.6 ± 48.9 min, *P* = 0.04). Other intraoperative data, including the type of surgery, operative time, aortic cross-clamp time, MHCA time, and intraoperative blood transfusion volume, showed no statistical difference (**Table 2**). Therefore, CPB time was included in multivariate logistic regression analysis.

The comparison of the clinical and laboratory data during CRRT between the two groups revealed that the lactic acid 6 h after CRRT, 12 h after CRRT, and 24 h after CRRT in the nonsurvival group was higher than that in the survival group (lactic acid 6 h after CRRT: 6.5 ± 4.9 mmol/L in the nonsurvival group vs. 3.7 ± 2.7 mmol/L in the survival group,

TABLE 1 | Baseline characteristics in the survival and nonsurvival groups.

Variables	Survival group	Nonsurvival group	P
Sex (male/female)	73/41	31/12	0.34
Age > 65 (%)	7 (6.1)	18 (29.5)	**<0.001**
BMI (kg/m^2)	25.1 ± 3.5	25.7 ± 4.2	0.44
Hypertension (%)	82 (71.9)	49 (80.3)	0.22
CAD (%)	8 (7.0)	5 (8.2)	0.78
Diabetes (%)	9 (7.9)	6 (9.8)	0.66
Preoperative EF (%)	63.9 ± 6.1	61.0 ± 6.9	0.48
Creatinine (μmol/L, x ± S)	115.8 ± 84.2	117.9 ± 75.6	0.90
Urea nitrogen (mmol/L, x ± S)	8.9 ± 5.5	9.7 ± 5.9	0.55
Albumin (g/L, x ± S)	38.8 ± 7.7	36.9 ± 7.3	0.53
Myohemoglobin (μg/L, x ± S)	329.7 ± 197.6	285.7 ± 190.3	0.41
Leukocytes (10^9/L, x ± S)	11.8 ± 4.4	12.6 ± 3.9	0.33
Hemoglobin (g/L, x ± S)	130.4 ± 20.6	131.4 ± 20.6	0.80

BMI, Body Mass Index; CAD, Coronary atherosclerotic heart disease. Bold vaue indicates P < 0.05.

TABLE 2 | Intraoperative variables in the survival and nonsurvival groups.

Variables	Survival group	Nonsurvival group	P
Surgery type			
Bentall replacement (%)	54 (47.4)	32 (52.5)	0.52
Total aortic arch replacement (%)	108 (94.7)	58 (95.1)	0.92
Partial aortic arch replacement (%)	6 (5.3)	3 (4.9)	0.89
Combined CABG (%)	10 (8.8)	1 (1.6)	0.07
Operative time (min, *x* ± *S*)	406.6 ± 185.6	442.6 ± 237.6	0.32
CPB time (min, *x* ± *S*)	219.6 ± 48.9	235.6 ± 64.8	**0.04**
Aortic cross-clamp time (min, *x* ± *S*)	120.6 ± 29.7	128.2 ± 37.6	0.11
MHCA time (min, *x* ± *S*)	22.8 ± 9.5	22.9 ± 9.2	0.97
Intraoperative infusion of RBC (u, Q1, Q3)	4.0 (2.0, 6.0)	4.0 (0.0, 10.0)	0.61
Intraoperative infusion of platelets (u, Q1, Q3)	0 (0, 0)	0 (0, 0)	0.87
Intraoperative infusion of plasma (u, Q1, Q3)	400.0 (0, 400.0)	400.0 (0, 800.0)	0.08

CABG, Coronary artery bypass grafting; CPB, cardiopulmonary bypass; MHCA, moderate and hypothermia circulation arrest; RBC, red blood cell. Bold vaue indicates P < 0.05.

$P < 0.001$; lactic acid 12 h after CRRT: 7.1 ± 5.2 mmol/L in the nonsurvival group vs. 3.1 ± 1.8 mmol/L in the survival group, $P < 0.001$; lactic acid 24 h after CRRT: 7.8 ± 5.9 mmol/L in the nonsurvival group vs. 2.7 ± 1.6 mmol/L in the survival group, $P < 0.001$). However, the OR of lactic acid 12 h after CRRT was the highest among them (lactic acid 6 h after CRRT: OR, 1.24; 95% CI, 1.10–1.40; lactic acid 12 h after CRRT: OR, 1.59; 95% CI, 1.34–1.89; lactic acid 24 h after CRRT: OR, 1.38; 95% CI, 1.18–1.60). Other CRRT data, including the duration of CRRT and laboratory indicators at the beginning of CRRT showed no statistical difference (**Table 3**). Therefore, lactic acid 12 h after CRRT was included in multivariate logistic regression analysis.

The comparison of postoperative complications and transfusion data during the ICU stay between the two groups: the proportion of liver dysfunction and PND in the nonsurvival group was significantly higher than those in the survival group [liver dysfunction: 24 cases in the nonsurvival group (39.3%) vs. 7 cases in the survival group (6.1%), $P < 0.001$; PND: 27 cases in the nonsurvival group (44.3%) vs. 12 cases in the survival group (10.5%), $P < 0.001$]. No significant differences were observed in other complications and the volume of blood transfusion during the ICU stay between the two groups (**Table 4**). Therefore, liver dysfunction and PND were included in multivariate logistic regression analysis.

Factors Selected for the Model

Our study showed that the variables, including age > 65 years, lactic acid after 12 h of CRRT, liver dysfunction, PND and CPB time, had significant differences in the univariate logistic regression analysis ($P < 0.1$) and were included in multivariate logistic regression analysis. The result showed that age > 65 years (OR, 6.78; 95% CI, 2.12–23.18; $P = 0.002$), lactic acid 12 h after CRRT (OR, 1.48; 95% CI, 1.25–1.79; $P < 0.001$), liver dysfunction (OR, 5.25; 95% CI, 1.71–17.48; $P = 0.005$), and PND (OR, 4.81; 95% CI, 1.85–12.97; $P = 0.001$) were independent risk factors for in-hospital death in patients with AKI undergoing CRRT after ATAAD (**Figure 2**).

Nomograms and Model Performance

A nomogram was constructed to predict in-hospital death, including four significant independent risk factors: age > 65 years, lactic acid 12 h after CRRT, liver dysfunction, and PND (**Figure 3**). The total score was obtained by summing up the single scores used to estimate the probability of in-hospital mortality. The discrimination of the predictive model was estimated using a C statistic of 0.868 (95% CI, 0.806–0.930) and a bootstrap-corrected C statistic of 0.859; the area under the ROC curve was 0.868 (**Figure 4**). The calibration curve showed that the predicted probabilities of in-hospital death fitted well with the actual prevalence rates (calibration curve: *via* 1,000 bootstrap samples, mean absolute error = 0.022 (2.2%)) (**Figure 5**). The Hosmer–Lemeshow test ($P = 0.846$) also demonstrated good calibration. The 10-fold cross-validation of the nomogram showed that the average misdiagnosis rate was 16.64%.

DISCUSSION

Several factors have been reported to be associated with high mortality during CRRT (10–12). Researchers have been striving to develop prediction models for patients with AKI. However, These models have limited applicability to patients undergoing CRRT (13–15). For example, in a previous study, one model, HELENICC score, was suggested for patients undergoing CRRT (16). However, this study included only patients with septic AKI. Patients with postoperative AKI undergoing CRRT after ATAAD surgery that have higher in-hospital mortality and worse

TABLE 3 | Laboratory indicators during CRRT in the survival and nonsurvival groups.

Variables	Survival group	Nonsurvival group	*P*
Albumin upon initiation of CRRT (g/L, $x \pm S$)	31.2 ± 13.2	28.8 ± 7.0	0.27
Leukocytes upon initiation of CRRT (G/L, $x \pm S$)	24.1 ± 17.1	15.0 ± 6.9	0.28
BUN upon initiation of CRRT (ummol/L, $x \pm S$)	20.9 ± 11.4	20.1 ± 12.3	0.67
Creatinine upon initiation of CRRT (mmol/L, $x \pm S$)	289.9 ± 164.8	256.7 ± 123.3	0.23
Hemoglobin upon initiation of CRRT (g/L, $x \pm S$)	94.1 ± 20.3	89.7 ± 18.5	0.11
Lactic acid upon initiation of CRRT (mmol/L, $x \pm S$)	5.2 ± 4.7	6.4 ± 5.2	0.12
Lactic acid 6 h after CRRT (mmol/L, $x \pm S$)	3.7 ± 2.7	6.5 ± 4.9	**<0.001**
Lactic acid 12 h after CRRT (mmol/L, $x \pm S$)	3.1 ± 1.8	7.1 ± 5.2	**<0.001**
Lactic acid 24 h after CRRT (mmol/L, $x \pm S$)	2.7 ± 1.6	7.8 ± 5.9	**<0.001**
Serum upon initiation of CRRT (mmol/L, $x \pm S$)	5.6 ± 4.9	4.5 ± 2.7	0.32
Bicarbonate upon initiation of CRRT (mmol/L, $x \pm S$)	24.0 ± 5.5	24.7 ± 4.2	0.50

BUN, Blood urea nitrogen. Bold values indicates P < 0.05.

TABLE 4 | Postoperative complications and transfusion data during the ICU stay in the survival and nonsurvival groups.

Variables	Survival group	Nonsurvival group	*P*
Liver dysfunction (%)	7 (6.1)	24 (39.3)	**<0.001**
PND (%)	12 (10.5)	27 (44.3)	**<0.001**
Paraplegia inferior (%)	12 (10.5)	7 (11.5)	0.85
Catheter-related bloodstream infection (%)	2 (1.8)	3 (4.9)	0.23
Lung infection (%)	14 (12.3)	14 (23.0)	0.07
Gastrointestinal bleeding (%)	7 (6.1)	8 (13.1)	0.12
Infusion of RBC during the ICU stay (u, Q1, Q3)	12.0 (6.0, 18.0)	14.0 (5.5, 22.5)	0.52
Infusion of plasma during the ICU stay (ml, Q1, Q3)	400.0 (0, 600.0)	400.0 (0, 600.0)	0.99
Infusion of platelet during the ICU stay (u, Q1, Q3)	3.0 (1.0, 5.0)	2.5 (0.0, 4.0)	0.44

PND, permanent neurological dysfunction. Bold values indicates P < 0.05.

prognosis, making it necessary to screen for prognostic factors and perform targeted interventions. In this study, a nomogram was developed and validated for predicting the risk of in-hospital death in these patients. In additional, this nomogram had excellent discriminative performance and calibration, which provided individual predictions for each patient.

The present study created an uncomplicated intuitive graph of a statistical predictive model that quantified the risk of in-hospital death in patients with AKI undergoing CRRT after ATAAD surgery. In the proposed nomogram, age > 65 years was the greatest contributor to the risk of in-hospital death, followed by liver dysfunction and PND; lactic acid after 12 h of CRRT showed the smallest effect on the probability of in-hospital death.

This study showed that the in-hospital mortality rate was higher in patients aged more than 65 years and undergoing CRRT because of the decreased immune function of elderly patients, the physiological function of their organs degenerated, and the renal blood flow and glomerular filtration rate decreased every year with age, accompanied by hypertension, hyperlipidemia, diabetes, and other diseases. Therefore, they were more likely to have a poorer prognosis after CRRT for postoperative AKI. Commereuc and his colleagues (17) showed that the mortality of patients with AKI, who were older than 65 years and required CRRT in the ICU, was more than 70%, which was up to 76% in patients aged more than 80 years, with a significantly higher risk of death compared with patients aged < 50 years. The prognosis of patients requiring CRRT was worse with increasing age. The aforementioned results also supported the conclusions of this study.

This study showed that high lactic acid values 12 h after CRRT was an independent prognostic factor for in-hospital death in patients undergoing CRRT for AKI after ATAAD. Blood lactic acid is an important indicator of systemic perfusion and oxygen metabolism; it reflects increased anaerobic metabolism in the presence of hypoperfusion (18). Elevated blood lactate levels have been shown to be a sensitive, early biochemical indicator of tissue hypoperfusion and oxygen insufficiency and can be used to assess disease severity and prognosis (19, 20). If patients do not get effective clearance of blood lactate in a short time, no improvement is seen in histiocyte hypoperfusion and oxygenation disorders, the progression of the disease worsens, shock and respiratory failure occur, and case fatality rate

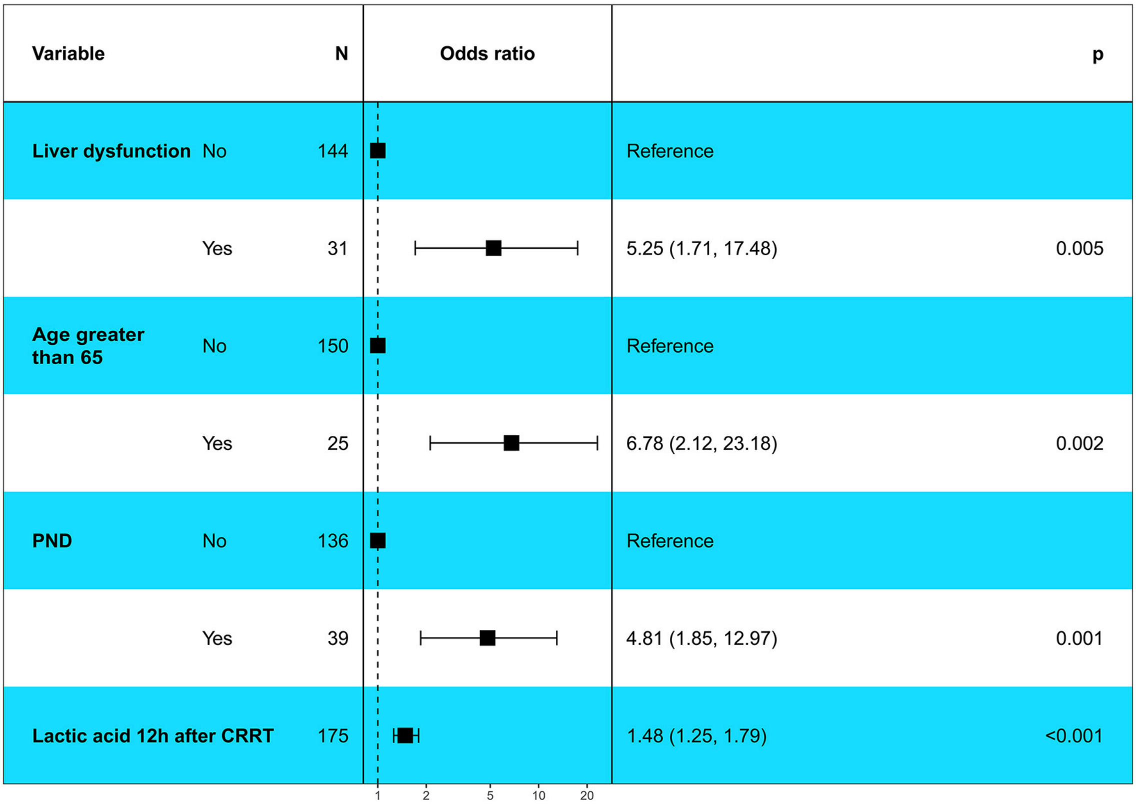

FIGURE 2 | Multivariable logistic regression analysis showed the independent risk factors of in-hospital death in patients with postoperative AKI undergoing CRRT after ATAAD surgery. PND, Permanent neurological dysfunction.

increases. If the clinical rescue treatment is appropriate, the tissue perfusion and oxygenation improve, the concentration of lactate in tissue cells decreases quickly, and the condition improves until recovery (21). Lactic acid remains high 12 h after CRRT, suggesting that the ischemic and hypoxic states of the tissues are still severe after CRRT, and the prognosis of such patients is poor.

In this study, liver dysfunction was a predictive factor for in-hospital death, which was defined as ischemic liver injury (ILI). A practical clinical definition of liver dysfunction is as follows: a syndrome with rapid and short-term increases in either AST or ALT levels to a level of more than 10 times the upper limit of normal, which is most usually occurred in critically ill patients. It is characterized by a predominant hepatocellular structure of damage, which is caused by insufficient blood and oxygen delivery to the liver cells. The latent etiologies often resulted in ILI are circulatory, cardiac or respiratory failure (22–24). Most specialists come to an agreement that outright conspicuous falls in systemic blood pressure are a typical predisposing characteristic of ILI. The incidence of ILI in the ICU (22, 25–28) was 1-12% and might be even higher in patients with cardiogenic shock (23, 25, 29). The surgical procedure for ATAAD is difficult, and the situation is full of challenges during the surgery. Malperfusion syndromes, such as liver dysfunction, can be present. If patients with AKI also have liver dysfunction, their in-hospital mortality increases significantly.

PND manifested mainly as stroke due to embolism or hemorrhage, which was diagnosed by a neurologist and confirmed by imaging (CT/MRI). Brain injury was one of the most important factors, other than cardiac insufficiency, leading to poor prognosis after cardiac surgery. Studies showed (30, 31) that the incidence of perioperative stroke was significantly higher in cardiac surgery than in noncardiac and non-neurosurgery. The incidence of perioperative stroke after cardiac surgery in patients with ATAAD was higher than that after other types of cardiac surgery (32). A deep hypothermic circulatory arrest (DHCA) has been shown to be one of the most risk factors for neurological complications after CPB. The incidence of stroke increased by 1.8–13.6%, and early mortality increased by 6.1–15% in adults after DHCA (33, 34). With the application of multiple brain protection strategies in patients with ATAAD, the incidence of neurological injury after ATAAD surgery is lower than before, but it is still an important factor affecting the prognosis of patients. The present study showed that patients requiring CRRT with PND had significantly increased in-hospital mortality. Multimodal brain

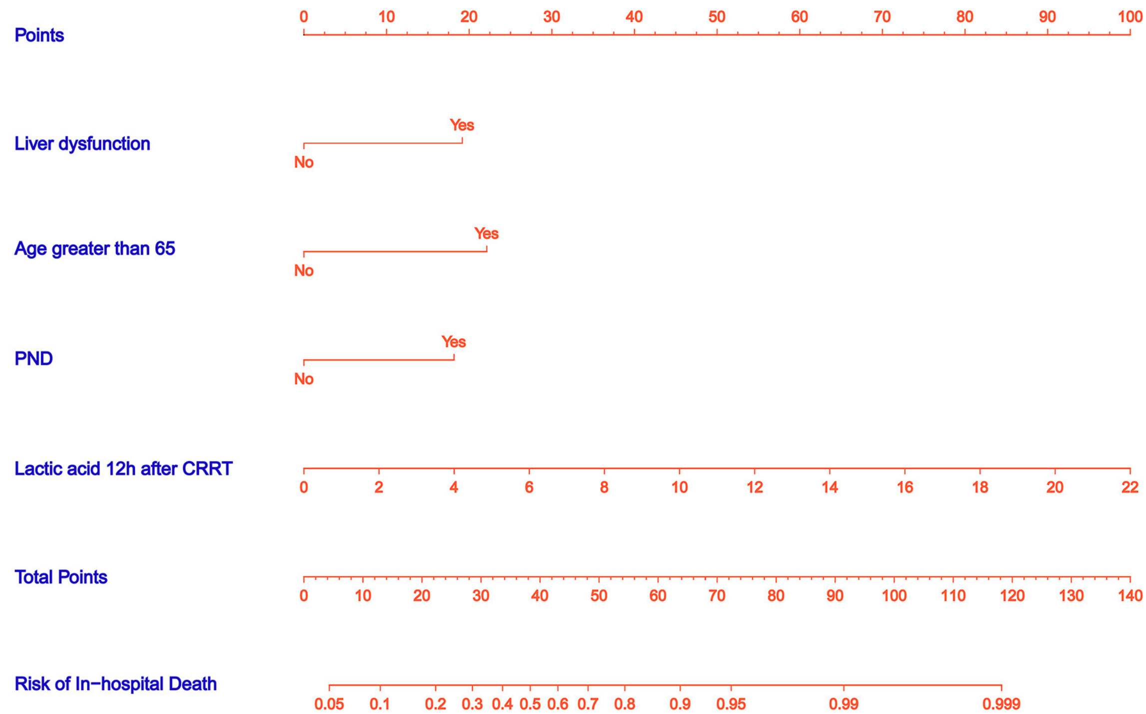

FIGURE 3 | Nomogram predicts in-hospital death risk in patients with postoperative AKI undergoing CRRT after ATAAD surgery. The nomogram was established to predict the risk of in-hospital death based on four independent prognostic factors. The total score can be calculated by summation of single scores. We can estimate the probability of in-hospital death by projecting the total score to the lower total point scale.

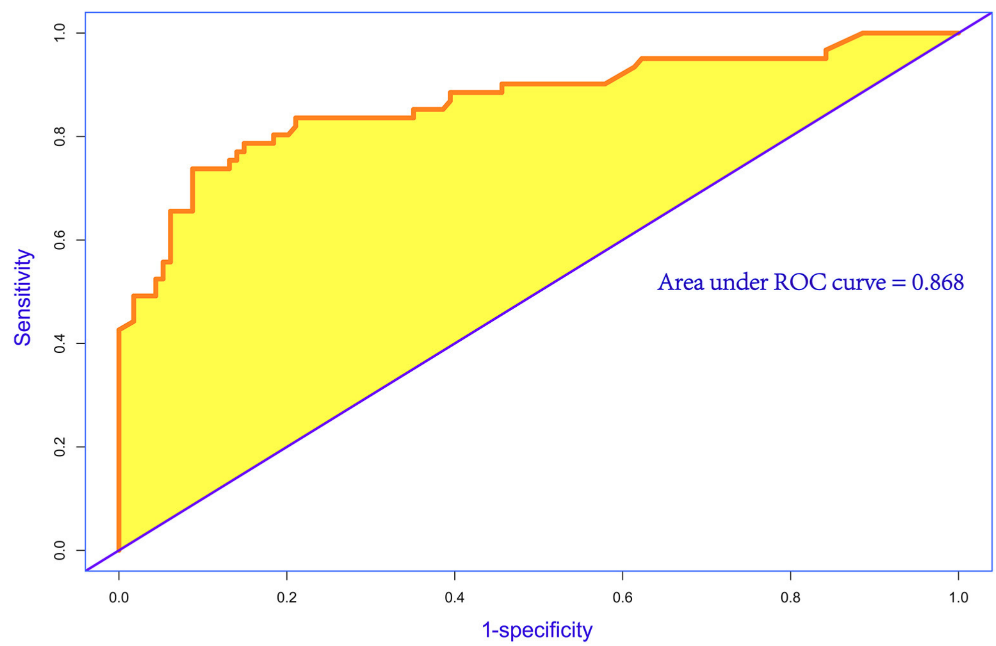

FIGURE 4 | Receiver operating characteristic (ROC) curve for evaluating the discrimination performance of the model. The area under the ROC curve was 0.868 and C statistic was also 0.868.

function monitoring and the active use of multiple perioperative brain protection strategies during the perioperative period may improve patients' outcomes.

This study had a few limitations. First, although the internal validation of the model produced excellent discrimination and fabulous calibration, the generalizability of this nomogram

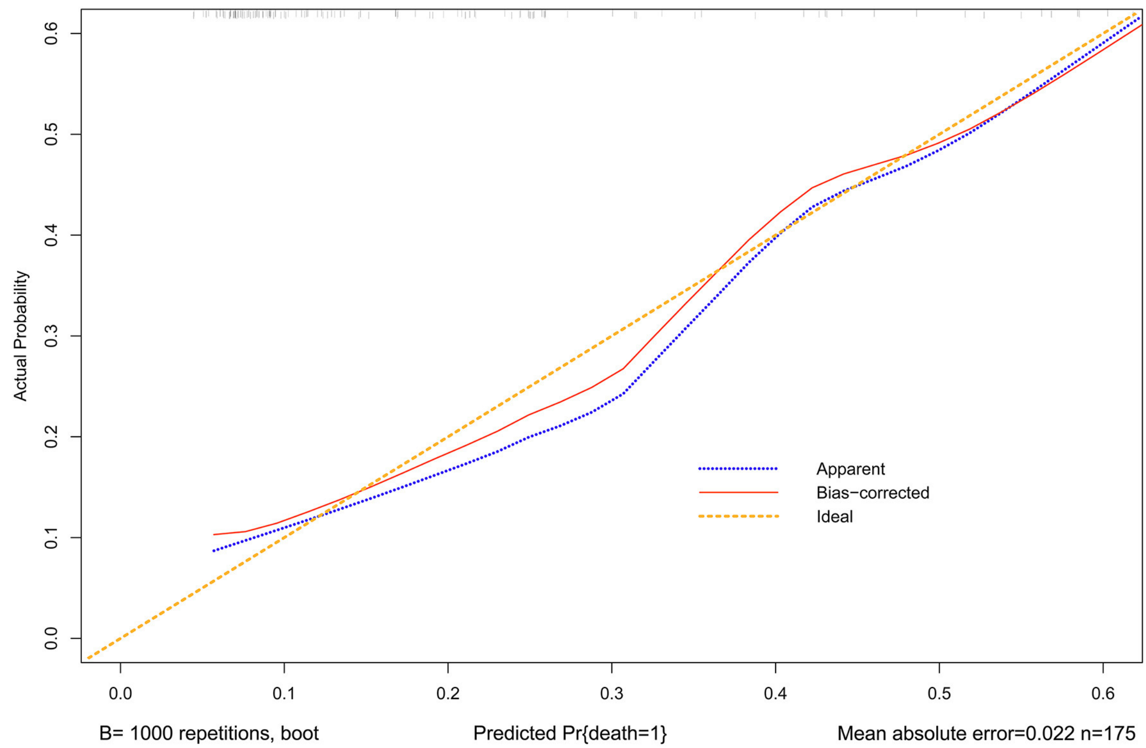

FIGURE 5 | Calibration curves for the nomogram. The *x*-axis represents the nomogram-predicted probability, and the *y*-axis represents the actual probability of the nomogram. A perfect prediction would correspond to the 45° yellow dashed line. The blue dotted line represents the entire cohort ($n = 175$), and the red solid line is bias-corrected by bootstrapping (B = 1,000 repetitions), indicating observed nomogram performance. The mean absolute error = 0.022 (2.2%).

still required external validation, especially from other countries, taking the differences in clinical behavior and epidemiology. Second, the prediction model was constructed retrospectively, and a retrospective research had its own limitations. It is necessary to carry out a prospective study to test the model. Third, the misdiagnosis rate of this model was still exists, and doctors used it should get noticed.

CONCLUSIONS

In summary, a nomogram was developed and validated for predicting the risk of in-hospital death in patients with postoperative AKI undergoing CRRT after ATAAD surgery. The nomogram could help identify the gravity of the situation and provide treatment recommendations for these patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee of the Beijing Anzhen Hospital (No. KS2019034-3). All patients gave their written informed consent.

AUTHOR CONTRIBUTIONS

RJ carried out the studies, participated in collecting data, and drafted the manuscript. XL and ML participated in acquisition, analysis, or interpretation of data. NL, LS, and JZ reviewed and edited it. All authors contributed to the interpretation of the data and the completion of figures and tables and have read and approved the final manuscript.

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ORIGINAL RESEARCH
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Massive Bleeding After Surgical Repair in Acute Type A Aortic Dissection Patients: Risk Factors, Outcomes, and the Predicting Model

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Background: Massive bleeding throughout aortic repair in acute type A aortic dissection (ATAAD) patients is a common but severe condition that can cause multiple serious clinical problems. Here, we report our findings regarding risk factors, short-term outcomes, and predicting model for massive bleeding in ATAAD patients who underwent emergent aortic repair.

Methods: A universal definition of perioperative bleeding (UDPB) class 3 and 4 were used to define massive bleeding and comprehensively evaluate patients. A total of 402 consecutive patients were enrolled in this retrospective study during 2019. Surgical strategies used to perform aortic arch procedures included total arch and hemiarch replacements. In each criterion, patients with massive bleeding were compared with remaining patients. Multivariable regression analyses were used to identify independent risk factors for massive bleeding. Logistic regression was used to build the model, and the model was evaluated with its discrimination and calibration.

Results: Independent risk factors for massive bleeding included male sex (OR = 6.493, $P < 0.001$), elder patients (OR = 1.029, $P = 0.05$), low body mass index (BMI) (OR = 0.879, $P = 0.003$), emergent surgery (OR = 3.112, $P = 0.016$), prolonged cardiopulmonary bypass time (OR = 1.012, $P = 0.002$), lower hemoglobin levels (OR = 0.976, $P = 0.002$), increased D-dimer levels (OR = 1.000, $P = 0.037$), increased fibrin degradation products (OR = 1.019, $P = 0.008$), hemiarch replacement (OR = 5.045, $P = 0.037$), total arch replacement (OR = 14.405, $P = 0.004$). The early-stage mortality was higher in massive bleeding group (15.9 vs. 3.9%, $P = 0.001$). The predicting model showed a well discrimination (AUC = 0.817) and calibration ($\chi^2 = 5.281$, $P = 0.727 > 0.05$).

Conclusion: Massive bleeding in ATAAD patients who underwent emergent aortic repair is highly associated with gender, emergent surgery, increased D-dimer levels, longer CPB time, anemia, and use of a complex surgical strategy. Since massive bleeding may lead to worse outcomes, surgeons should choose suitable surgical strategies in patients who are at a high risk of massive bleeding.

Keywords: aortic (rupture) dissection, bleeding, perioperative management, surgery strategy, clinical research

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INTRODUCTION

Acute type A aortic dissection (ATAAD) is one of the most complex and life-threatening disorders and can lead to catastrophic results, such as aortic rupture or even death (1). Medically managed ATAAD patients are at risk of poor outcomes, and mortality rates in these patients reach 20, 30, and 50% in the first 24 h after acute presentation, after 48 h, and after 1 month, respectively (2). Therefore, emergent aortic repair is the best treatment option for ATAAD and is potentially life-saving. Despite improvements in patient diagnosis and surgical techniques, aortic repair is still associated with high morbidity and mortality rates compared with other cardiac procedures (3, 4). Among all possible complications of aortic surgery, postoperative bleeding is one of the most prevalent and intractable. In particular, when the hemorrhage is massive, failed or delayed treatment may cause irreversible organ dysfunction, such as renal failure, cardiovascular events including myocardial injury, or even death (5). Therefore, a full understanding of ATAAD risk factors can significantly benefit clinical practice. Many factors may be related to postoperative hemorrhage, including surgical damage to blood vessels and hemostatic function disorders (6, 7). However, specific risk factors, and their incidence differ based on the institution as well as the country from which the data are collected (8). The present study aimed to analyze possible risk factors and short-term outcomes for massive postoperative bleeding in patients with ATAAD who underwent aortic repair emergently, we also made a predictive model which could provide details needed for clinical practitioners to avoid or minimize poor outcomes of the procedure.

MATERIALS AND METHODS

Patient Enrollment

This was a single-center, retrospective study, and data were collected from the electronic medical record database of Beijing Anzhen Hospital. A total of 402 consecutive patients who underwent emergent surgery for ATAAD repair during 2019 were enrolled in this study. Patients younger than 18 years old or diagnosed with hereditary connective tissue diseases before were excluded from the study. Each patient was counted only once in the analysis. The Institutional Review Board of Beijing Anzhen Hospital of Capital Medical University approved this retrospective study and waived the need for informed patient consent. The institutional approval number is 202075X.

Definition of the Massive Bleeding

In this study, the universal definition of perioperative bleeding (UDPB) was used to define massive bleeding (9, 10). The UDPB defines perioperative bleeding by nine clinical events during the surgery or within the first postoperative day. In UDPB, class 3 and 4 bleeding often requires or has already been performed aggressive medical interventions, otherwise, it may lead to extremely serious adverse consequences. Therefore, in this study, class 3 and 4 bleeding was defined as perioperative massive bleeding. Kidney disease: improving global outcomes (KDIGO) grade 3 was used to define the acute kidney injury in this study, and the fraction of inspired oxygen less than 300 was defined as respiratory failure.

Operative Management

All surgeries were performed *via* median sternotomy under moderate hypothermic circulatory arrest. A dual-stage atriocaval cannula was inserted into the right atrium, and the right axillary artery was isolated routinely for CPB and selected cerebral perfusion. The ascending aorta was clamped at the distal end, and then the patients' nasopharyngeal temperature was reduced to approximately 25°C. During the cooling, proximal manipulations, such as aortic valve repair, sinus of Valsalva reconstruction, and composite valved graft replacement, would be commenced if necessary. CPB was discontinued when the nasopharyngeal temperature was lower than 25°C, while the selected cerebral perfusion was continued at a rate of approximately 5 to 10 $mL \times kg^{-1} \times min^{-1}$ toward the right axial artery.

Methods of aortic arc surgery include hemiarch replacement and total arc replacement + frozen elephant trunk (FET); decision-making depends on the general condition of the patient, location of the entry tear, the distal extent of dissection, the occurrence of malperfusion, and intraoperative findings. The hemiarch replacement included arc repair of the distal anastomosis located at the proximal end of the aortic arch or part of the small curvature. In total arc replacement + FET, a stent is inserted as the FET into the descending aorta, and the remaining aortic arch is replaced by the four-branch artificial vessel. More details regarding the surgical procedure have been discussed in our previous studies (11–13).

Statistical Analysis

Continuous data were presented as means ± standard deviation (SD) with a normal distribution and median (lower quartile, upper quartile) with a non-normal distribution, the categorical variables were described as percentages. For performing comparisons, a Student's *t*-test or Mann–Whitney *U* test was used for continuous variables, and the Chi-square test or Fisher's exact test was used for categorical variables. Multivariable regression analyses were conducted to explore relationships between perioperative parameters and severe bleeding using binary logistic modeling techniques. The risk predicting model was built using logistic regression. The area under the receiver operating characteristic curve (AUC) and 95% confidence intervals (CIs) were used to assess a model's ability to discriminate between high- and low-risk patients. Hosmer–Lemeshow good of fit test was used to evaluate the calibration of the model. *P*-values determined using two-tailed distributions <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 25.0 (IBM SPSS, Armonk, NY, United States) and GraphPad Prism 8.

RESULTS

Baseline Characteristics

In this study, 402 patients were enrolled, 69 of them presented with massive postoperative bleeding (17.2%), the detailed

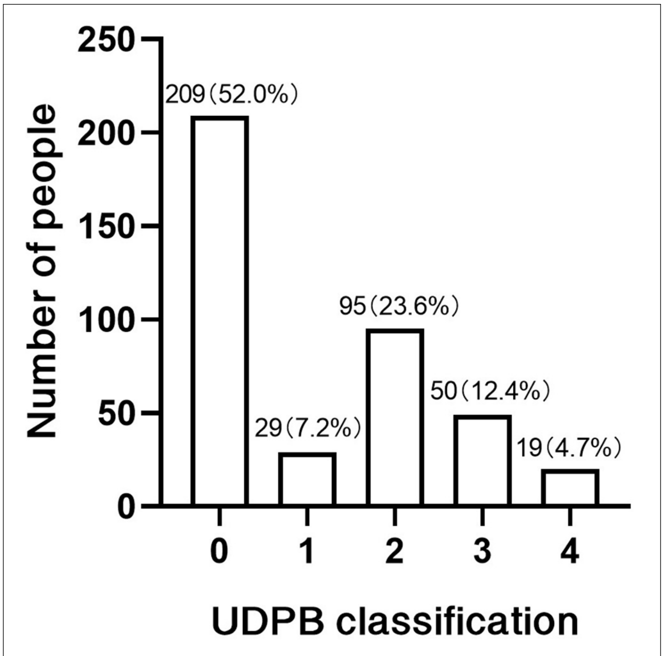

FIGURE 1 | Bleeding classification according to the UDPB.

classification of massive bleeding was shown in **Figure 1**. The basic characteristics of patients were summarized in **Table 1**. The mean age was 52.13 ± 11.96 and 48.73 ± 11.63 years (P = 0.029), the mean body mass index (BMI) was 24.99 ± 3.99 in the massive bleeding group and 26.72 ± 7.86 in the non-massive bleeding group (P = 0.029), the mean hemoglobin and platelet count in two groups were 129.34 ± 22.26 g, 134.78 ± 18.41 g (P = 0.036), 180.72 ± 53.28 109/L, and 198.26 ± 75.57 109/L (P = 0.024), separately.

All the details of operation data were summarized in **Table 2**. A total of 298 patients underwent emergent aortic repairs within 24 h of onset (74.1%). In the management of the proximal aorta, 172 patients underwent aortic root replacement (Bentall procedure) (42.8%), 230 patients underwent ascending aorta replacement (58.2%). The management of the aortic arch consists of 2 procedures, 315 patients underwent total arch replacement (78.4%), 60 patients underwent hemiarch replacement (14.9%).

Risk Factors of the Massive Bleeding

Based on the definition of the UDPB bleeding classification, a univariate analysis of the patient's perioperative condition revealed that risk factors associated with massive bleeding after the surgery included aged patients (P = 0.029), male patients (P = 0.050), emergent surgery (P = 0.044), preoperative renal dysfunction (P = 0.013), low hemoglobin level (P = 0.036), low platelet count (P = 0.024), elevated D-dimer level (P = 0.045), increased fibrin degradation products (P = 0.002), prolonged cardiopulmonary bypass time (P < 0.001), prolonged aortic cross-clamp time (P = 0.01), and total arch replacement (P = 0.012). In a multivariate regression analysis, this study set massive bleeding as the study endpoint and obtained independent risk factors associated with it including male sex (OR = 6.493, P < 0.001, 95% CI = 2.429–17.360), elder patients (OR = 1.029, P = 0.05, 95% CI = 1.000–1.059), low BMI (OR = 0.879, 95% CI: 0.806–0.957, P = 0.003), emergent surgery (OR = 3.112, 95% CI: 1.235–7.843, P = 0.016), prolonged cardiopulmonary bypass time (OR = 1.012, 95% CI: 1.004–1.021, P = 0.002), lower hemoglobin levels (OR = 0.976, 95% CI: 0.959–0.993, P = 0.002), increased D-dimer levels (OR = 1.000, P = 0.037), increased fibrin degradation products (OR = 1.019, 95% CI: 1.005–1.033, P = 0.008), hemiarch replacement (OR = 5.045, 95% CI: 1.098–23.173, P = 0.037), total arch replacement (OR = 14.405, 95% CI: 2.046–101.404, P = 0.004) (**Table 3**).

Perioperative Outcomes

In terms of prognosis, 24 patients died in the early stage after surgery, with a mortality rate of 15.9% in the massive bleeding group (11 patients) and 3.9% in the non-massive bleeding group (13 patients, P = 0.001), the in-hospital survivorship curve was shown in **Figure 2**. The average hospitalization time was 17.79 ± 12.73 and 14.54 ± 8.49 days, the average length of stay in the intensive care unit was 4 (2, 8) and 2 (1, 4) days, and the average duration of tracheal intubation was 41 (17.75, 96) and 16 (12, 36) h, respectively. More details were summarized in **Table 4**.

The Predicting Model

A logistic regression analysis was performed to develop a predicting model in this study, the R^2 was 0.31 and the standardized beta coefficients for the included variables were male sex (1.871), age (0.029), emergent surgery (1.135), hemoglobin level (−0.024), CPB time (0.012), BMI (−0.129), fibrin degradation products (0.019), hemiarch replacement (1.618), and total arch replacement (2.668). The resulting regression equation to predict the mean ascending aorta length was:

Logit(P) = −3.226 + sex [m = 1, f = 0] × 1.871 + age (years) × 0.029 + emergent surgery [y = 1, n = 0] × 1.135 – hemoglobin level (g/L) × 0.024 + CPB time (min) × 0.012 – BMI × 0.129 + fibrin degradation products (μg/mL) × 0.019 + hemiarch replacement [y = 1, n = 0] × 1.618 + total arch replacement [y = 1, n = 0] × 2.668 (14). In terms of evaluating the discrimination of the model, the area under the curve (AUC) was 0.817 (95% CI: 0.760–0.873, P < 0.001, **Figure 3**). In the Hosmer–Lemeshow goodness-of-fit test, the model demonstrated good calibration, the Hosmer–Lemeshow χ^2 was 5.281, P = 0.727 > 0.05, and the calibration plot was shown in **Figure 4**.

DISCUSSION

Postoperative bleeding and the need for blood product transfusion are quite common after aortic surgery (3). At the same time, massive bleeding may lead to numerous complications such as re-exploration, which is associated with increased mortality (15). In previous studies, the definition of

TABLE 1 | Preoperative characteristics of the study population.

Variables	Massive bleeding group (*n* = 69)	Non-massive bleeding group (*n* = 333)	*P*-value
Male sex	59 (86.8%)	234 (70.3%)	0.005
Age (years)	52.13 ± 11.96	48.73 ± 11.63	0.029
Body mass index	24.99 ± 3.99	26.72 ± 7.86	0.010
Hypertension	57 (82.6%)	277 (83.2%)	0.269
Diabetes mellitus	1 (1.4%)	12 (3.6%)	0.365
Past cerebral infarction	1 (1.4%)	9 (2.7%)	0.553
Preoperative anticoagulant	5 (7.4%)	13 (3.9%)	0.211
Acute cardiac tamponade	1 (1.4%)	6 (1.8%)	0.839
Acute myocardial infarction	1 (1.4%)	6 (1.8%)	0.839
Renal failure	1 (1.4%)	5 (1.5%)	0.974
Malperfusion syndrome	6 (8.7%)	31 (9.3%)	0.872
White blood cell count ($\times 10^9$/L)	12.11 ± 4.36	11.65 ± 4.12	0.404
Red blood cell count ($\times 10^9$/L)	4.38 ± 0.55	4.40 ± 0.74	0.815
Platelet count ($\times 10^9$/L)	180.72 ± 53.28	198.26 ± 75.57	0.024
Mean platelet volume (fL)	10.56 ± 0.90	10.51 ± 1.14	0.053
Hemoglobin (g/L)	129.34 ± 22.26	134.78 ± 18.41	0.036
Prothrombin time (s)	13.62 ± 4.91	12.91 ± 3.16	0.713
International normalized ratio	1.13 (1.04, 1.17)	1.11 (1.04, 1.77)	0.673
D-dimer (ng/mL)	3036.5 (1630, 11970.5)	2040 (790.5, 3229.5)	0.007
Fibrin degradation products (μg/mL)	46.76 (14.68, 95.11)	18.76 (7.33, 37.56)	0.001
Aspartate transaminase level (U/L)	22 (17, 29.5)	23 (17, 35)	0.355
Alanine transaminase level (U/L)	20 (14, 28.5)	22 (15, 38)	0.067
γ-GT (U/L)	24 (14, 35.5)	31 (19, 65.75)	0.058
Serum creatinine (μmol/L)	88.2 (69.72, 129)	84.3 (68.32, 106.22)	0.251
Blood urea nitrogen (mg/dL)	7.83 ± 3.25	7.19 ± 4.39	0.268
Serum lipase (U/L)	12.1 (7.75, 24.1)	12.6 (8.2, 20.65)	0.853
Serum amylase (U/L)	44.45 (36.92, 65.25)	46.1 (35.3, 59.5)	0.735
CK-MB (ng/mL)	1.65 (1.1, 6.67)	1.3 (0.8, 2.97)	0.01
Cardiac troponin I (ng/mL)	0.01 (0, 0.15)	0.01 (0, 0.06)	0.464
Myoglobin (ng/mL)	40.25 (25.72, 96.32)	29.5 (19.82, 49.4)	0.004

Values are expressed as number (%), median (lower quartile, upper quartile), or mean ± SD.

TABLE 2 | Surgical data of study population.

Variables	Massive bleeding group (*n* = 69)	Non-massive bleeding group (*n* = 333)	*P*-value
Emergent surgery	58 (84.1%)	240 (80.8%)	0.044
Aortic root replacement	32 (46.4%)	140 (42.0%)	0.590
Hemiarch replacement	2 (2.9%)	58 (17.4%)	0.002
Total arch replacement	62 (89.9%)	253 (76.0%)	0.012
Concomitant CABG	6 (8.7%)	25 (7.5%)	0.736
Concomitant vascular bypass	4 (5.8%)	18 (5.4%)	0.896
Concomitant aortic valvuloplasty	1 (1.4%)	10 (3.0%)	0.472
Concomitant mitral valve replacement	1 (1.4%)	1 (0.3%)	0.217
Concomitant abdominal aortic replacement	1 (1.4%)	0 (0)	0.028
Cardiopulmonary bypass time (min)	209.60 ± 43.55	187.83 ± 42.09	<0.001
Aortic cross-clamp time (min)	118.09 ± 26.97	108.44 ± 28.25	0.01
Circulatory arrest time (min)	23.59 ± 11.35	22.94 ± 12.25	0.651

Values are expressed as number (%) or mean ± SD. CABG, coronary artery bypass graft surgery.

massive bleeding has varied depending on the countries and centers, and is less often measured by a uniform standard. In this study, the UDPB bleeding classification was used to measure postoperative bleeding in patients with ATAAD, with class 3–4 bleeding requiring aggressive clinical intervention and therefore defined as massive bleeding by this study. The proportion of bleeding at all levels in our center is generally consistent with previous studies.

TABLE 3 | Risk factors of postoperative massive bleeding.

Variables	OR	*P*-value	95% CI
Male sex	6.493	0.001	2.429–17.360
Elder patients	1.029	0.05	1.000–1.059
BMI	0.879	0.003	0.806–0.957
Emergent surgery	3.112	0.016	1.235–7.843
Prolonged cardiopulmonary bypass time	1.012	0.002	1.004–1.021
Hemoglobin levels	0.976	0.002	0.959–0.993
D-dimer levels	1.000	0.037	1.000–1.002
Fibrin degradation products levels	1.019	0.008	1.005–1.033
Hemiarch replacement	5.045	0.037	1.098–23.173
Total arch replacement	14.405	0.004	2.046–101.404

Gender was considered an independent risk factor for massive postoperative bleeding in patients with aortic type A coarctation, along with low body mass index. In general, low weight patients are associated with female patients, but the present study concluded the opposite, that male patients are more likely to have massive postoperative bleeding after aortic repair surgery, which is consistent with the results of many previous trials (16–18). The possible reason for this is that in our study, most male patients were in middle age, with poorly controlled hypertension, which may lead to difficulty in intraoperative hemostasis, another reason might be the rate of fibrin production as well as the intensity of thrombosis is higher in healthy adult females than in healthy males (19). At the same time, elderly patients have a higher risk of massive postoperative bleeding compared to younger patients, probably because the vascular condition is worse in elderly patients, which makes the operation more difficult. The coagulation mechanism of elderly patients is not as well developed as that of younger patients, which makes them more prone to massive postoperative bleeding, and therefore the prognosis of elderly patients needs to be considered more comprehensively before and during the surgery.

In this study, elevated D-dimer and preoperative low hemoglobin status were both strongly associated with postoperative bleeding, suggesting that preoperative assessment of coagulation mechanisms is particularly important, and that D-dimer, as a degradation product of fibrinolysis of blood clots, is often indicative of fibrin production and lysis, commonly in response to inflammation, trauma, tumor, recent surgery, and acute aortic syndrome or pulmonary embolism (20, 21). Previous studies have shown that elevated D-dimer is significantly and positively associated with the severity of the tear in aortic dissection, and it has therefore been mentioned in several studies that patients with significantly elevated D-dimer tend to undergo more complex procedures, but this is accompanied by difficulties in intraoperative hemostasis and heavy bleeding in the early postoperative period, which in turn affects the early prognosis of the patient (22, 23). Itagaki et al. found that an increase in D-dimer was accompanied by a decrease in platelet count, further demonstrating the value of D-dimer as a predictor of bleeding risk in the early stages of the disease (24). Our study did not find a significant effect of preoperative anticoagulant use on postoperative massive bleeding, probably due to the young age of the patients with type A aortic dissection seen at our center and the very limited number of patients with coronary artery disease on antiplatelet agents. Most of the patients on anticoagulants were misdiagnosed at other hospitals and underwent coronary angiography or were treated as myocardial infarctions; the number of such patients was so small that it did not significantly affect the statistical results.

Although it was shown in this study that emergent surgery raises the risk of massive postoperative bleeding, and similar results were obtained in other studies such as Zindovic et al. Emergent surgical treatment to save the patient's life is still the first choice compared to the risk of death from a ruptured aortic coarctation aneurysm that the patient is waiting to face (25). With regard to the choice of procedure, a single-center retrospective study by Xue et al. covering 958 patients suggested that differences in arch procedure alone did not result in

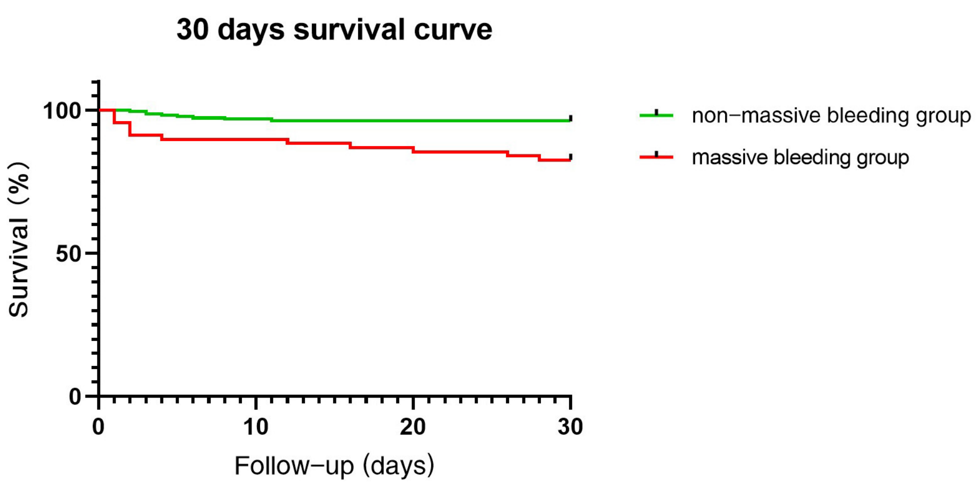

FIGURE 2 | Survival in patients with and without massive bleeding.

TABLE 4 | Short-term outcomes of study population.

Variables	Massive bleeding group (*n* = 69)	Non-massive bleeding group (*n* = 333)	*P*-value
Mortality	11 (15.9%)	13 (3.9%)	0.001
Respiratory failure	28 (41.2%)	70 (21.0%)	0.001
Acute kidney injury	18 (26.5%)	32 (9.6%)	0.001
Endotracheal intubation time (h)	41 (17.75, 96)	16 (12, 36)	0.001
ICU stay (days)	4 (2, 8)	2 (1, 4)	0.001
Cerebrovascular event	7 (10.3%)	30 (9.0%)	0.739
Paraplegia	4 (5.9%)	15 (4.5%)	0.626
Reintubation	9 (13.2%)	31 (9.3%)	0.325
Re-exploration for bleeding	19 (27.5%)	0 (0)	0.001

Values are expressed as number (%), median (lower quartile, upper quartile), or mean ± SD.

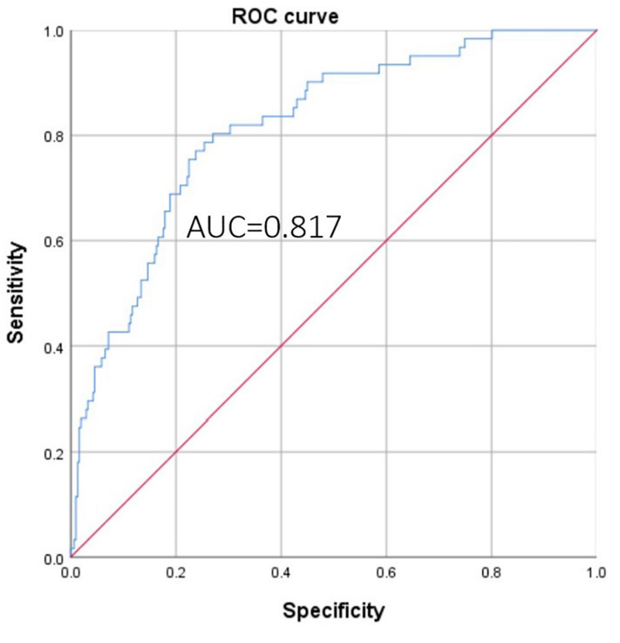

FIGURE 3 | ROC curve of the model for predicting massive bleeding.

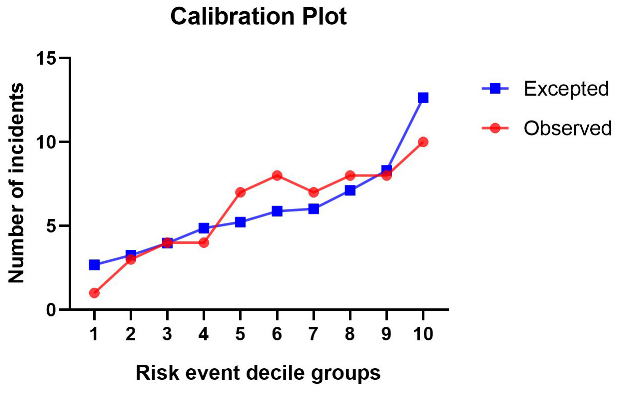

FIGURE 4 | Calibration plot of the model for predicting massive bleeding.

significant mortality differences and that it was the preoperative status that really affected the prognosis of patients with type A dissection, which is generally consistent with the results of the present study (26). Our study suggests that either hemiarch replacement or total arch replacement increases the likelihood of massive postoperative bleeding compared to ascending aortic surgery alone, but the surgical approach still needs to be tailored to the patient.

The results of this study showed a significant difference in the short-term prognosis of patients undergoing aortic repair with the presence or absence of massive bleeding, with patients who had massive bleeding in the study having a worse prognosis than those in the non-massive bleeding group. Our results showed that there was a statistical difference in mortality between the two groups, and the main causes of death in the massive bleeding group included cerebrovascular accident and postoperative multiorgan failure, of which multiorgan failure was more closely related to massive bleeding, blood volume deficiency, and ischemia-reperfusion injury.

This study found that among patients who presented with massive postoperative bleeding, there was a significant increase in the need for continuous renal replacement therapy due to impaired renal function. Inadequate preoperative as well as intraoperative renal perfusion, activation of the inflammatory response triggered by postoperative bleeding, postoperative low cardiac output and hemodynamic changes are all possible predisposing factors for the occurrence of postoperative acute kidney injury (27, 28).

In terms of the respiratory system, this study suggests that the duration of tracheal intubation was significantly longer in patients who presented with massive postoperative bleeding and required longer periods of ventilator assistance. The possible causes include prolonged CPB time, endotoxemia due to poor visceral perfusion, ischemia-reperfusion injury to the lungs, surgical trauma, or the use of protamine, an inflammatory response that can cause damage to the lungs, and inappropriate postoperative ventilatory parameters and fluid management may exacerbate this damage (29). The amount of blood product infusion associated with massive bleeding can also be significantly elevated, and some studies have shown that blood product infusion significantly increases the incidence of respiratory distress after cardiac surgery. Moreover, the low blood pressure caused by massive bleeding can also make postoperative fluid management very difficult, and excessive fluid rehydration may cause pulmonary edema further aggravating the blow to the lungs (30).

Several previous studies have discussed predicting the risk of bleeding after cardiac surgery, but most of these studies were limited to coronary surgery (14, 31, 32). In this study, we used a logistic regression model to predict the risk of massive bleeding after aortic repair in ATAAD patients, the model was performed well and showed good discrimination

(AUC = 0.817) and calibration. Since multiple adverse prognoses are associated with massive bleeding, patients at high risk should be more carefully assessed preoperatively and treated with a reasonable treatment plan.

The limitation of this study was the retrospective nature of the analysis. Despite the use of multivariable analyses to limit the effects of confounding variables, the effects of baseline differences as confounders could not be ruled out. Postoperative bleeding may also be related to many surgical factors such as different surgical strategies, insufficient anastomosis, improper surgical manipulation, and suture lines. Further studies investigating mechanisms underlying these risk factors for massive bleeding are required. Risk factors for each set of criteria were not completely the same, and more clinical trials are needed to identify which criteria are more favorable in clinical use. At the same time, although the predicting model showed good discrimination and calibration in our study, more data from multiple centers may validate the model in further studies.

CONCLUSION

The present study reported several risk factors for massive bleeding in patients with ATAAD who underwent emergent aortic repair, including gender, emergent surgery, increased D-dimer level, increased CPB time, and use of a complex surgical strategy. Massive bleeding may lead to higher mortality, longer stay in the intensive unit, and longer hospitalization. Our predicting model showed good discrimination and calibration, for patients who were evaluated as having a high risk of massive bleeding, surgeons should choose a suitable surgical strategy to prevent bleeding complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The Institutional Review Board of Beijing Anzhen Hospital of Capital Medical University approved this retrospective study and waived the need for informed patient consent. The institutional approval number is 202075X.

AUTHOR CONTRIBUTIONS

C-HZ was responsible for the conceptualization, data collection, statistical analysis, and writing the draft. Y-LZ and Y-PG were responsible for the statistical analysis. J-MZ was responsible for the conceptualization, methodology, and investigation. H-OH, Z-YQ, C-NL, and Y-PG were responsible for the investigation. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Obesity Increases In-Hospital Mortality of Acute Type A Aortic Dissection Patients Undergoing Open Surgical Repair: A Retrospective Study in the Chinese Population

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Objective: The prevalence of obesity is increasing worldwide, and the role of the obesity paradox in cardiovascular surgery remains controversial. In this study, we redefined obesity according to the Chinese criteria and examined the relationship between obesity and in-hospital mortality in patients with acute type A aortic dissection (AAD) undergoing open surgical repair.

Materials and Methods: A total of 289 patients with AAD (between 2014 and 2016) were divided into the non-obese group and obese group for correlation analysis, general information, demographic factors, blood biochemistry, surgical details, and complications, which were used as covariates. Survival was estimated by the Kaplan–Meier method, and any differences in survival were evaluated with a stratified log-rank test. Least Absolute Shrinkage and Selection Operator (LASSO) regression and logistic regression were used to evaluate the effect and interaction of obesity on surgical mortality.

Results: All the 289 patients had a mean age of 48.64 (IQR 44.00–55.00) and 74.39% were men. Of the 289 patients, 228 were non-obese (78.89%) and 61 were obese (21.11%). Patients with obesity were younger and more prone to unstable blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)], preoperative hypoxemia and delirium, prolonged operative time, and surgical wound deep infection ($p < 0.05$). In the fully adjusted model, we observed an increased risk of in-hospital mortality in patients with obesity after fine-tuning other covariates including age and sex (HR = 2.65; 95% CI = 1.03 to 6.80; $p = 0.042$). The interaction suggested

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that obesity was more likely to cause death in elderly patients (age ≥ 60), although it was more common in younger patients (test for interaction, $p = 0.012$).

Conclusion: Obesity, interacting with age, increases the risk of in-hospital mortality in patients with AAD undergoing open surgical repair. Although more verification is needed, we believe these findings provide further evidence for the treatment of AAD.

Keywords: obesity, body mass index, aortic dissection, open surgical repair, in-hospital mortality

INTRODUCTION

Over the past three decades, China has experienced rapid economic development and nutrition transition, and the prevalence of overweight and obesity in China has increased 2 to 3 times since the 1980s (1). The pandemic of obesity is rising worldwide, affecting individuals of all ages, involving various diseases, and increasing the economic burden. More than two-thirds of deaths related to high body mass index (BMI) were due to cardiovascular disease (2). However, the existence of a protective obesity paradox makes the role of obesity in cardiovascular surgeries uncertain (3), as is the case in open surgical repair of acute Stanford type A aortic dissection (AAD).

In recent years, increasing efforts have been made to assess the trends and effects of BMI within and across nations (4). Other studies have attempted to compare the potential effects of high BMI on a variety of aortic surgery outcomes. These efforts, while useful, appeared to deviate from daily clinical practice. In these studies, patients with obesity appeared to have a higher risk of acute kidney injury (AKI) (5), hypoxemia (6), acute lung injury (7), and prolonged intubation (8, 9) in the perioperative period of AAD, who also have a higher prevalence of several risk factors for AAD according to previous researches (10, 11), such as hypertension, hyperlipidemia, and stroke. However, what is puzzling is that the results of these studies all showed that obesity was not related to AAD mortality. Are we omitting the role of the perioperative "obesity paradox"? Or did the obesity interaction mask a single effect?

On the one hand, most of the patients in the study Kreibich et al. (9) underwent hemiarch replacement surgery (9), which was different from the current mainstream total arch replacement (12, 13). On the other hand, the unified international BMI classification is not applicable to the Chinese population due to differences in ethnicity and living habits, and the overall proportion of BMI ≥ 30 kg/m^2 may be about 3% in China (14, 15), while it may exceed 10% in other regions (2). Based on these findings, World Health Organization (WHO), the International Association for the Study of Obesity, and the International Obesity Task Force have suggested lower BMI cutoffs for overweight and obesity in Asian populations (16). Thus, the use of the international BMI classification for comparisons might confound any association between body weight and mortality of AAD. The influence of obesity on perioperative or open surgical repair AAD remains unclear in the Chinese population based on Chinese standards. This study aims to evaluate the effect and interaction of obesity with gender, age, and blood pressure on in-hospital mortality.

MATERIALS AND METHODS

Patients

This was a retrospective, observational research consisting of 289 in-patients operated at the hospital from January 2014 to December 2016. All patients presented with AAD and were treated by open surgical repair. We non-selectively and consecutively collected data for all participants at the Second Xiangya Hospital of Central South University, Changsha, Hunan, China. Anonymous data were compiled from the electronic hospital medical record system. Ethical approval for the study was provided by the hospital's institutional review board. Informed consent was waived because the study was retrospective.

Inclusion/Exclusion

The inclusion criteria were hospital admission for patients with acute type AAD within ≤14 days after symptoms onset. The following were used as exclusion criteria: (1) unfinished height or weight test; (2) non-surgically managed condition; and (3) endovascular aortic repair (**Figure 1**).

Standard Measures

The diagnosis was mainly based on 2014 ESC guidelines on the treatment and diagnosis of aortic ailments (17). Any dissection that involved the ascending aorta with presentation within 14 days of symptom onset was defined as AAD. The diagnosis of AAD was confirmed by imaging like computed tomography (CT) or magnetic resonance imaging (MRI). Admission BMI (kg/m^2) measured at baseline was calculated as weight in kilograms divided by the square of height in meters (1). For correlation analysis between obesity and mortality, patients were divided into two groups according to the Chinese criterion (WS/T 428–2013) (10): non-obese (BMI: < 28 kg/m^2) and obese (BMI: ≥ 28 kg/m^2). Overall survival was defined as the time from surgery until death from any cause. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured half an hour after pharmacotherapy. Pre-operative and post-operative complications were diagnosed by clinical examination and confirmed by CT angiography. Other covariates involving general information, demographic data, blood biochemistry, medical imaging examination, and treatment variables that can affect in-hospital mortality were confirmed based on clinical characteristics.

Surgical Procedure

The detailed surgical procedures have been previously described in the literature (18, 19). To summarize in brief, cardiopulmonary

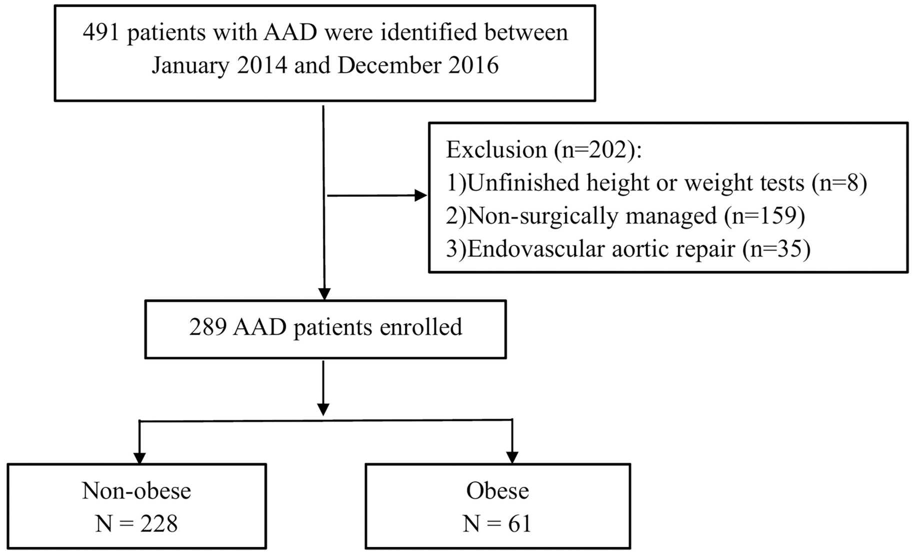

FIGURE 1 | A flowchart of patient enrollment.

bypass (CPB) was instituted through the right atrial graft to the right axillary artery by cannulation. Femoral artery cannulation was used if the dissection involved the right axillary artery or if the pumping pressure was too high. The aortic repair included replacing the entire ascending aorta, when the aortic root or valve was also involved, while the Bentall procedure, the Wheat procedure, or the Valsalva sinuplasty, among others, was performed simultaneously. Coronary artery bypass grafting was performed in patients with dissection involving the coronary artery or in patients with pre-operative severe coronary heart disease (20).

Missing Data Addressing

We performed multiple multivariable imputations to address missing data in order to maximize statistical power and minimize bias. Five imputed datasets with chained equations were created using R-package mice (21). Our multiple imputations of the dataset were mainly based on the following principles: (1) there were no missing data for the primary outcome; (2) replacement of categorical variables was not advisable, as the plausibility is still debated; and (3) 5% missingness is suggested as a maximum upper threshold below which multiple imputations provides benefit. Sensitivity analysis found no significant differences between the generated complete data and raw data. Thus, all multivariable analysis results based on the imputed datasets were combined with Rubin's rules (22, 23).

Statistical Analysis

Continuous variables were expressed as median (interquartile range, IQR). A *t*-test and the Mann–Whitney *U*-test were used for parametric and non-parametric data, respectively. Categorical variables were expressed as frequencies and compared using Fisher's precision probability test or Chi-square analysis. Survival was estimated by the Kaplan–Meier method, and any differences in survival were evaluated with a stratified log-rank test. Least Absolute Shrinkage and Selection Operator (LASSO) regression was applied to minimize the potential collinearity of variables measured from the same patient and over-fitting of variables (24). Multivariable analyses with the Cox proportional hazards model were used to estimate the simultaneous effects of prognostic factors on survival. Interactions with prognostic factors were also examined with the Cox proportional-hazards model. EmpowerStats (X&Y Inc Solutions, Boston, MA, United States)[1] and R version 4.0.5[2] were used for statistical analyses. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Characteristics of Baseline

The 289 patients had a mean age of 48.64 and 74.39% of them were men. Of the 289 patients, 228 were non-obese (78.89%) and 61 were obese (21.11%). The differences in baseline characteristics are presented in **Table 1**. Compared with non-obese patients, patients with obesity on admission appeared to be younger, had lower DBP, had a higher probability of hypertension, and were more difficult to obtain expected blood pressure (100∼120 mmHg) from half an hour after pharmacotherapy. A total of eight patients with Marfan syndrome were all non-obese, but the difference between the two groups was not statistically significant (Fisher's precision probability test, $p = 0.138$). There was also no significant difference between the two groups in terms of gender, diabetes mellitus, stroke, and bicuspid aortic valve ($p > 0.05$).

[1]http://www.empowerstats.com
[2]http://www.r-project.org

TABLE 1 | Baseline characteristics of the patients.

Characteristic	Overall (*n* = 289)	Non-obese (*n* = 228)	Obese (*n* = 61)	*p*-Value
Age, year	48.64 (44.00–55.00)	49.30 (44.75–55.00)	46.18 (39.00–53.00)	0.015
Age ≥ 60.00	38 (13.15)	31 (13.60)	7 (11.48)	0.663
Gender				0.838
Men	215 (74.39)	169 (74.12)	46 (75.41)	
Women	74 (25.61)	59 (25.88)	15 (24.59)	
SBP, mmHg	133.27 (114.00–154.00)	131.75 (114.00–148.25)	138.97 (115.00–162.00)	0.074
<100.00	30 (10.38)	20 (8.77)	10 (16.39)	0.083
100.00–120.00	74 (25.61)	66 (28.95)	8 (13.11)	0.012
>120.00	185 (64.01)	142 (62.28)	43 (70.49)	0.235
DBP, mmHg	75.73 (66.00–84.00)	76.74 (69.75–86.00)	71.98 (57.00–80.00)	0.034
<60.00	40 (13.84)	23 (10.09)	17 (27.87)	<0.001
60.00–90.00	195 (67.47)	158 (69.30)	37 (60.66)	0.201
>90.00	54 (18.69)	47 (20.61)	7 (11.48)	0.104
Heart rate/min	80.83 (70.00–90.00)	80.81 (71.00–90.00)	80.90 (65.00–91.00)	0.849
<60.00	21 (7.27)	20 (8.77)	1 (1.64)	0.057
History of				
Hypertension	133 (46.02)	115 (50.44)	41 (67.21)	0.020
Diabetes mellitus	156 (53.98)	8 (3.51)	4 (6.56)	0.289
Marfan	8 (2.77)	8 (3.51)	0 (0.00)	0.138
Stroke	20 (6.92)	14 (6.14)	6 (9.84)	0.312
Bicuspid aortic valve	6 (2.08)	5 (2.19)	1 (1.64)	0.788

Data are presented as n (%) or mean (IQR).
SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 2 | Clinical pre-operative data.

Variable	Overall (*n* = 289)	Non-obese (*n* = 228)	Obese (*n* = 61)	*P*-Value
Pre-operative blood test				
CRP, mg/L	59.12 (17.30–92.10)	57.39 (17.30–86.20)	65.31 (15.93–106.33)	0.393
Creatinine, umol/L	100.51 (71.30–110.10)	98.54 (70.60–108.68)	107.61 (83.80–112.30)	0.370
RDW	14.02 (13.67–16.00)	13.44 (12.70–14.00)	14.80 (13.40–15.40)	0.019
PLR	167.15 (89.92–210.31)	169.63 (89.70–216.16)	157.25 (95.24–207.41)	0.375
NLR	11.10 (6.52–14.90)	10.83 (6.34–14.13)	12.19 (7.41–17.99)	0.022
Transthoracic echocardiography				
Aortic regurgitation				0.812
None	106 (36.68)	82 (35.96)	24 (39.34)	
Mild	145 (50.17)	116 (50.88)	29 (47.54)	
Medium	29 (10.03)	22 (9.65)	7 (11.48)	
Severe	9 (3.11)	8 (3.51)	1 (1.64)	
Left ventricular ejection fraction	66.36 (62.00–70.00)	66.66 (63.00–70.25)	65.21 (62.00–69.00)	0.110
20.00–40.00	2 (0.69)	0 (0.00)	2 (3.28)	0.044
40.00–60.00	38 (13.15)	28 (12.28)	10 (16.39)	0.399
>60.00	251 (86.85)	200 (87.72)	51 (83.61)	0.399
Pericardial effusion	77 (26.64)	58 (25.44)	19 (31.15)	0.370
Ascending aortic diameter, mm	46.13 (41.00–50.00)	46.09 (40.00–50.00)	46.28 (41.00–49.00)	0.868
Pre-operative complications				
Hypoxemia	25 (8.65)	15 (6.58)	10 (16.39)	0.015
Delirium	8 (2.77)	4 (1.75)	4 (6.56)	0.043

Data are presented as n (%) or mean (IQR).
CRP, C-reactive protein; RDW, red cell volume distribution width; PLR, platelet lymphocyte ratio; NLR, neutrocyte lymphocyte ratio.

Clinical Pre-operative Data

Obese patients have higher red cell volume distribution width (RDW) and neutrocyte lymphocyte ratio (NLR). Two patients with left ventricular ejection fraction (LEVF) <20% were obese, and the difference was statistically significant (Fisher's precision probability test, $p = 0.044$). The obese group also appeared to be more susceptible to hypoxemia (6.58 vs. 16.39%, $p = 0.015$) and delirium (1.75 vs. 6.56%, $p = 0.043$). Patients presented

TABLE 3 | Intraoperative details.

Variable	Overall (n = 289)	Non-obese (n = 228)	Obese (n = 61)	p-Value
Root procedure				
Bentall	255 (88.23)	206 (90.00)	49 (80.00)	0.063
David	26 (9.00)	21 (9.21)	5 (8.20)	0.102
Wheat	8 (2.77)	6 (2.63)	2 (3.29)	0.086
Aortic arch procedure				
Total arch replacement	270 (93.43)	210 (92.11%)	60 (98.36)	0.080
Hemiarch replacement	9 (3.11)	8 (3.51%)	1 (1.64)	0.690
Elephant trunk procedure	271 (93.77)	211 (92.54)	60 (98.36)	0.095
Concomitant procedure				
Aortic valve replacement	7 (2.42)	5 (2.19)	2 (3.28)	0.624
CABG	30 (10.38)	22 (9.65)	8 (13.11)	0.431
Time of operation				
Total operation, min	538 (450–650)	528 (430–645)	574 (485–660)	0.012
Aortic cross-clamp, min	124 (84–153)	122 (83–148)	128 (101–159)	0.376
Cardiopulmonary bypass, min	262 (197–318)	255 (192–311)	289 (255–329)	0.004
Hypothermic circulatory arrest, min	32 (0–54)	30 (0–52)	39 (0–60)	0.028
Ventricular fibrillation, seconds	36 (15–54)	37 (17–55)	33 (0–54)	0.255

Data are presented as n (%) or mean (IQR).
CABG, coronary artery bypass graft.

TABLE 4 | Post-operative Characteristics.

Variables	Overall (n = 289)	Non-obese (n = 228)	Obese (n = 61)	p-Value
Post-operative blood test				
RDW	14.97 (13.67–16.00)	15.06 (13.70–16.00)	14.63 (13.50–15.60)	0.172
PLR	153.63 (86.44–201.61)	156.52 (91.27–213.25)	141.26 (85.71–189.90)	0.244
NLR	11.78 (8.84–14.15)	11.75 (8.93–14.30)	11.89 (8.71–14.03)	0.844
Complications				
Respiratory infection	36 (12.77)	29 (12.89)	7 (12.28)	0.902
Surgical wound deep infection	10 (3.53)	5 (2.22)	5 (8.62)	0.019
Renal replacement therapy	53 (18.79)	40 (17.78)	13 (22.81)	0.385
Paraplegia	8 (2.82)	6 (2.64)	2 (3.51)	0.663
Temporary neurological dysfunction	12 (4.26)	8 (3.56)	4 (7.02)	0.247
Stroke	13 (4.58)	10 (4.41)	3 (5.26)	0.782
Hospital stay, day	19.96 (14.00–23.00)	20.50 (15.00–23.00)	17.95 (12.00–21.00)	0.066
ICU stay rate	0.42 (0.27–0.53)	0.37 (0.25–0.47)	0.59 (0.50–0.68)	<0.001
In-hospital mortality	39 (13.49)	26 (11.40)	13 (21.31)	0.043

Data are presented as n (%) or mean (IQR).
RDW, red cell volume distribution width; PLR, platelet lymphocyte ratio; NLR, neutrocyte lymphocyte ratio; ICU, intensive care unit.

with similar rates of pre-operative C-reactive protein (CRP), creatinine, platelet lymphocyte ratio (PLR), aortic regurgitation, LEVF, pericardial effusion, ascending aortic diameter ($p > 0.05$) (**Table 2**).

Intraoperative Details

Operative details are shown in **Table 3**. Overall, Bentall procedure (88.23%), total arch replacement (93.43%), and elephant trunk procedure (93.77%) were the main surgical procedures. There were seven (2.42%) patients who underwent aortic valve replacement and thirty (10.38%) patients who underwent coronary artery bypass graft (CABG). Patients with obesity required a longer duration of surgical procedure, CPB, and hypothermic circulatory arrest. No statistical difference was found between the different groups in root and aortic arch procedure, elephant trunk procedure, concomitant procedure, time of aortic cross-clamp, and ventricular fibrillation ($p > 0.05$).

Post-operative Characteristics

The outcome characteristics are summarized in **Table 4**. There was no statistical difference between the two groups in RDW, PLR, NLR, respiratory infection, renal replacement therapy, paraplegia, temporary neurological dysfunction, stroke, and hospital stay. However, it seemed that patients with obesity were more likely to develop surgical wound deep infection (2.22 vs. 8.62%, $p = 0.019$), higher intensive care unit (ICU) stay rate (0.37

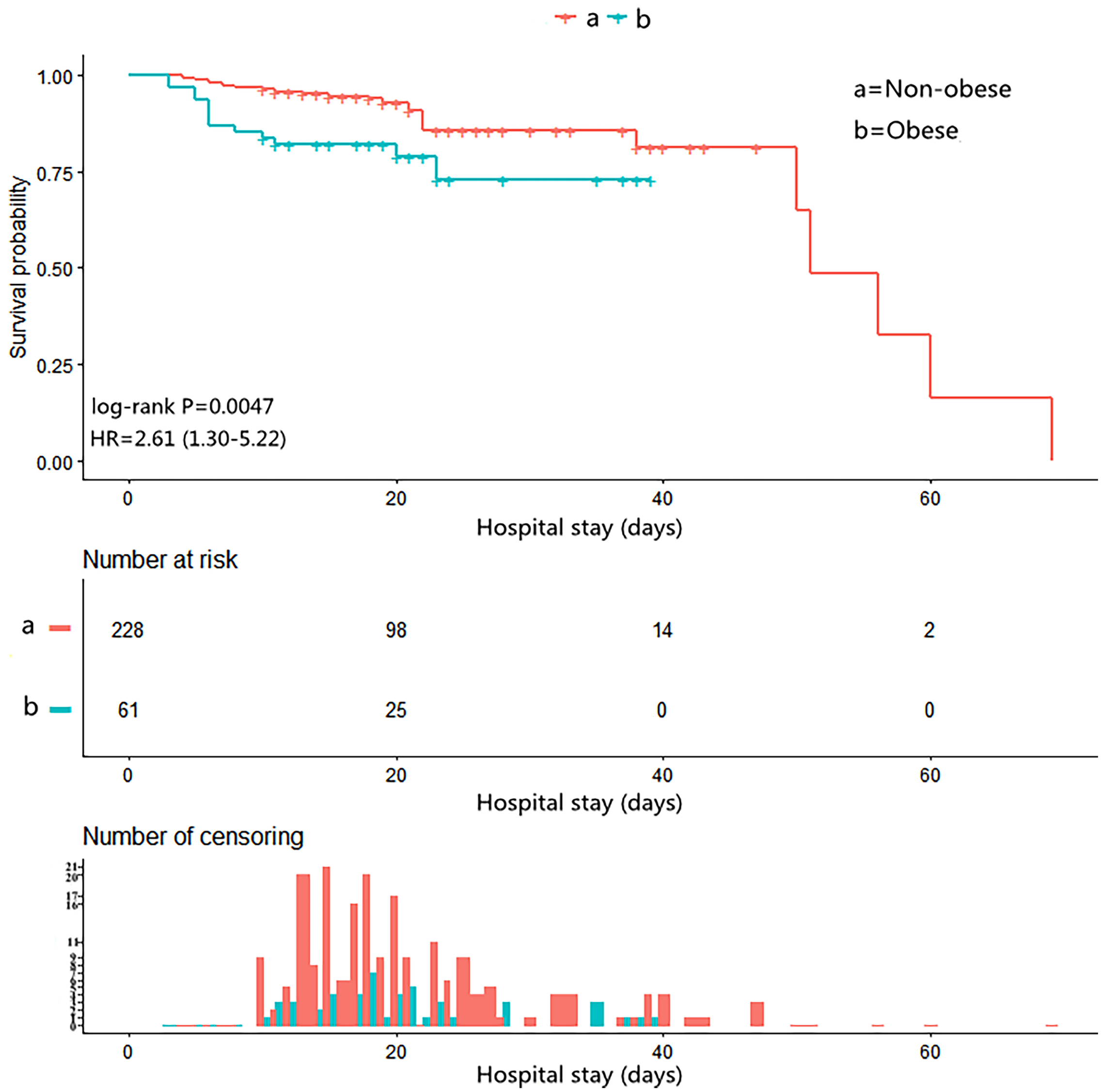

FIGURE 2 | The Kaplan–Meier curves for in-hospital survival in the chronological trend after open surgical repair in AAD.

vs. 0.59, $p < 0.001$), and in-hospital mortality (11.4 vs. 21.31%, $p = 0.043$, **Supplementary Figure 1**).

Kaplan–Meier Analysis in Different Groups

Follow-up data were available for 289 patients. The Kaplan–Meier analysis showed that the cumulative survival rate of patients with obesity in the hospital was significantly reduced (log-rank test $p = 0.0047$, **Figure 2**).

Adjusted and Unadjusted Models for Obesity and In-Hospital Mortality

A total of 59 variables measured at the hospital (**Tables 1–4**) were included in the LASSO regression. After LASSO regression selection (**Supplementary Figure 2**), 13 variables remained significant predictors of in-hospital mortality, including clinical features and test results: obesity, gender, age $\geq$ 60, SBP, DBP, heart rate, pre-operative delirium, LEVF (20–40,%), time of ventricular fibrillation during surgery, post-operative NLR, post-operative PLR, renal replacement therapy, and stroke.

We defined the above 12 variables other than obesity as covariates affecting in-hospital mortality in patients with AAD. We constructed three models to analyze the independent effects of obesity on in-hospital mortality (univariate and multivariate) based on the proportional hazards model. The hazard ratio (HR) and 95% confidence intervals (CI) were listed in **Figure 3**. In the full model (model II), after adjusting for all covariates, patients with obesity had a higher risk of in-hospital mortality during hospitalization compared to non-obese patients (HR = 2.65; 95% CI = 1.03 to 6.80; $p = 0.042$) (**Figure 3**).

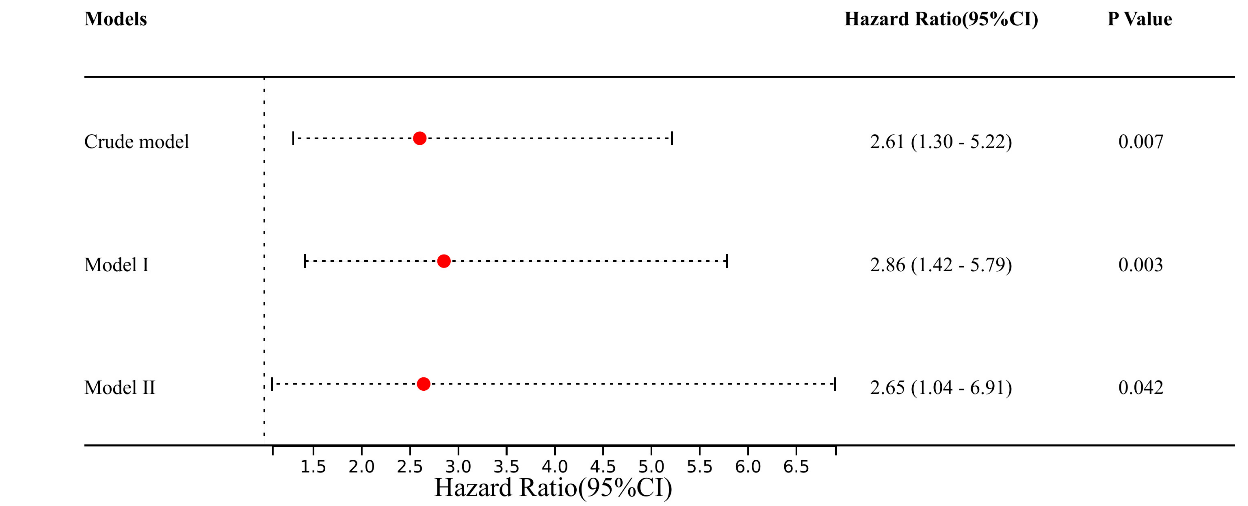

FIGURE 3 | The effect of obesity on outcomes following multivariable analysis based on the Cox proportional-hazard model. Crude model: adjusted for none. Model I: adjusted for: gender and age. Model II: adjusted for gender, age, SBP, DBP, heart rate, pre-operative delirium, LEVF 20–40%, time of ventricular fibrillation during surgery, aortic valve replacement, CABG, post-operative PLR, post-operative NLR, renal replacement therapy, and stroke. SBP, systolic blood pressure; DBP, diastolic blood pressure; LEVF, left ventricular ejection fraction; CABG, coronary artery bypass graft; PLR, platelet lymphocyte ratio; NLR, neutrocyte lymphocyte ratio.

Interaction Between Obesity and Covariates

The predetermined covariates were gender (men vs. women), age (<60 years vs. ≥ 60 years), SBP (<100 vs. 100–120 vs. > 120), and DBP (<60 vs. 60–90 vs. > 90) according to clinical guidelines and previous studies (17.25). We evaluated interactions between the four prognostic factors (gender, age, SBP, and DBP) (**Figure 4**) and obesity with a stepwise procedure for multivariate analysis. **Figure 4** shows that there are significant interactions between age and obesity on in-hospital mortality (test for interaction, $p = 0.012$). **Supplementary Tables 1**, **2** present the subgroup analysis by age to analyze the effects of obesity and its effect on in-hospital mortality at different ages. We found that obesity was associated with an increased risk of in-hospital mortality in elderly patients (adjusted HR 5.06, 95% CI 2.12–8.69), while no obesity in younger patients protected them (adjusted HR 0.83, 95% CI 0.61–0.95).

DISCUSSION

This study results, comparing the role of obesity in open surgical repair of patients with AAD, are summarized as follows: (1) patients with obesity were younger and more prone to unstable blood pressure (SBP and DBP), pre-operative hypoxemia and delirium, prolonged operative time, and surgical wound deep infection; (2) in the fully adjusted model, we observed an increased risk of in-hospital mortality in patients with obesity after fine-tuning other covariates including age and sex; and (3) the interaction suggested that obesity was more likely to cause death in elderly patients (age ≥ 60), although it was more common in younger patients.

The prevalence of obesity is gradually getting younger as may be expected (2). We found that obesity was associated with a higher prevalence of hypertension and instability of blood pressure (extremely high or low), which may be mostly explained by the consequence of compromised aortic physiologic microregulation (25, 26). These clinical features may exacerbate aortic intima tear or rupture and may also reveal cardiac tamponade that inhibits cardiac pumping, which may partly account for poorer outcomes in patients with obesity. Hypoxemia, delirium, and wound infection may be associated with obesity-induced decreased lung compliance, obstructive sleep apnea, cervical or cerebral atherosclerosis, and fat liquefaction (27–29), while the long-term surgical procedure may increase the risk factors for death, such as inflammation, thrombosis, infection, etc. (30). We noticed that the obese group had longer operative time, CPB time, and hypothermic circulatory arrest time, which was consistent with previous reports (8, 31). On the one hand, the anatomical variation of obesity is more likely to increase the difficulty of intraoperative operations, such as anesthesia, thoracotomy, hemostasis, and suturing (32). On the other hand, the physiological abnormalities of obesity can easily break the intraoperative homeostasis of patients, such as unstable blood pressure, obesity-hypoventilation syndrome, and microcirculatory perfusion disorders (33, 34). All of these factors may lead to poorer surgical outcomes in patients with obesity. Consequently, surgeons need to pay more attention to the patient's respiratory or airway status, mental state, inflammation, and change of dressing on the wound compared to non-obese patients. In this study, we also observed that patients with obesity had higher pre-operative RDW and NLR, which are risk factors for cardiovascular mortality described in previous studies (35–37). Their elevation may be associated with obesity-related lower-grade chronic inflammation and inflammatory

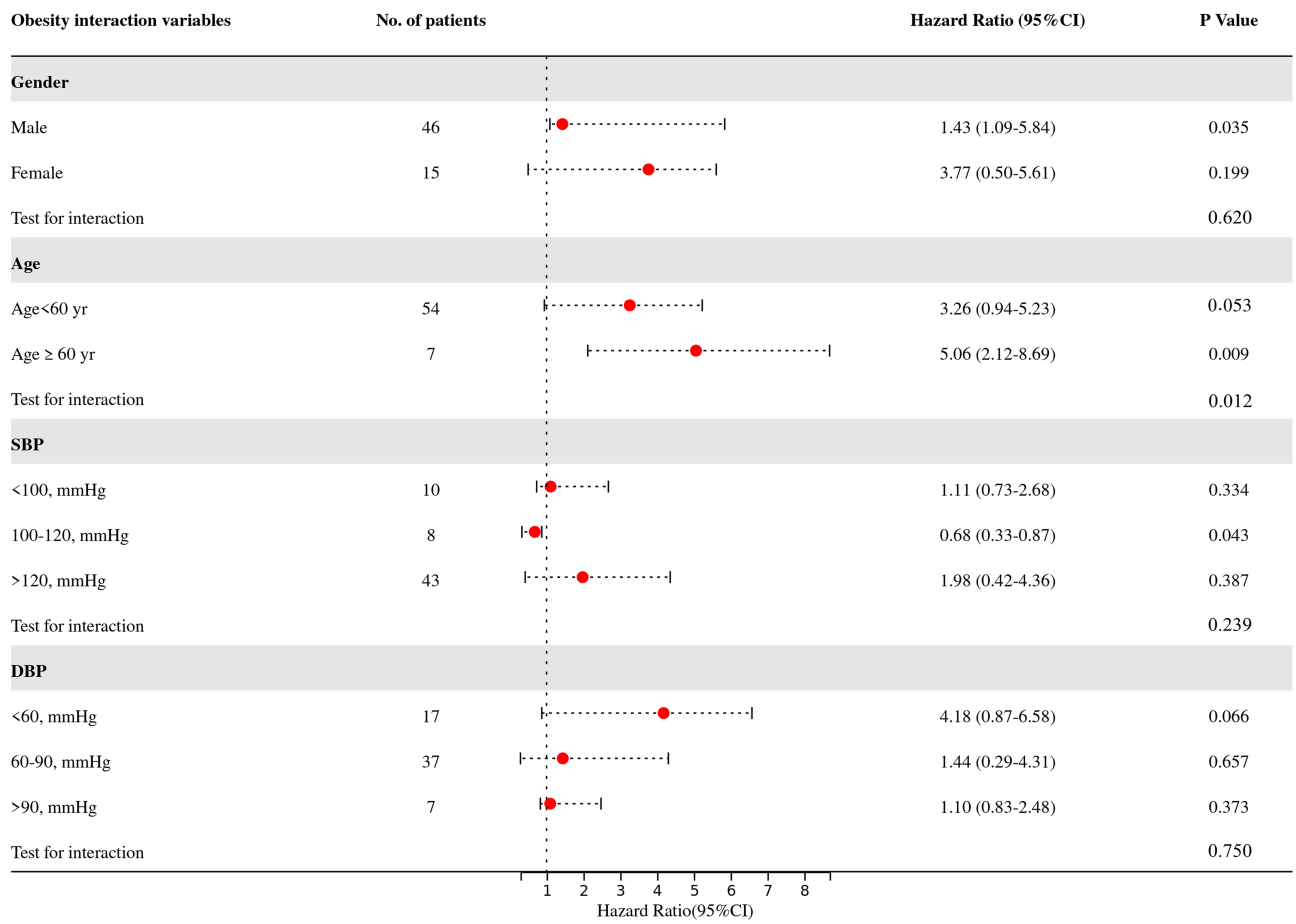

FIGURE 4 | Multivariate-adjusted hazard ratios for death in patients in the obese group as compared with the non-obese group, according to four prognostic factors. Adjust variables: gender, age, SBP, DBP, heart rate, pre-operative delirium, LEVF 20–40%, time of ventricular fibrillation during surgery, aortic valve replacement, CABG, post-operative PLR, post-operative NLR, renal replacement therapy, and stroke. SBP, systolic blood pressure; DBP, diastolic blood pressure; LEVF, left ventricular ejection fraction; CABG, coronary artery bypass graft; PLR, platelet lymphocyte ratio; NLR, neutrocyte lymphocyte ratio.

mechanisms of aortic dissection (38–40). Of note, despite the differences in baseline characteristics being unavoidable, gender, past medical history besides hypertension, surgical details, and treatment management did not differ between the two groups.

The role of obesity in aortic disease has been controversial. Several previous studies have shown that obesity was not significantly associated with mortality through aortic dissection but only increases perioperative complications and ventilation time (7, 41, 42). The BMI of patients also had no effect on the early major adverse outcomes and mid-term survival by continuous grouping (8, 9). Whereas, BMI has also been reported to be a risk factor affecting the hospital mortality rate of aortic dissection undergoing Sun's operation (43). Other studies suggested that morbid obesity significantly increased the mortality in open abdominal aortic surgery (41, 44, 45), which prompted the controversy still unresolved. On the one hand, BMI in patients with aortic dissection may present a non-linear relationship with adverse outcomes, which may be irregular and different from the U-shaped curve of the "obesity paradox" in cardiac surgery (3). This seems to explain why the effect of BMI on major adverse outcomes from aortic dissection varies among reports. On the other hand, these studies may have omitted the difference in obesity in the Chinese population. As mentioned earlier, the unified international BMI classification is not applicable to the Chinese population due to differences in ethnicity and living habits, which confound the association between BMI and AAD mortality. The previous reports may also have tended to associate obesity with better outcomes, such as hemiarch replacement and non-emergency surgery. In fact, due to anatomical lesions and high mortality rate, the current surgical procedure for patients with AAD is still emergency total arch replacement in order to prevent dissection extending, replace damaged aorta, and restore blood supply to vital organs as soon as possible (46).

The characteristics of such patients were reflected in our study. Although multiple risk factors for in-hospital mortality in patients with AAD were identified by LASSO regression, we still observed that obesity increased in-hospital mortality after full adjustment for confounders. When the study sample is less than 10 times the number of variables, the application of LASSO regression can mainly avoid overfitting and multicollinearity by using the tuning parameter (λ) for dimensionality reduction. The strong predictors screened by LASSO regression were substituted into the Cox proportional-hazard model to assess risks, which may also be closer to clinical practice (47–49). We found obesity to be a risk factor for in-hospital mortality in patients with AAD undergoing open surgical repair (HR = 2.65; 95% CI = 1.03 to 6.80; $p = 0.042$) and also unexpectedly found a significant interaction between obesity and age in in-hospital mortality effect (test for interaction, $p = 0.012$). Our results, if confirmed, suggest that elderly patients with AAD may be more susceptible to poor prognosis due to obesity, which may be omitted in previous studies leading to an unclear role of obesity. The elderly, with multiple comorbidities such as hypertension, diabetes, and arteriosclerosis, are prone to poor basic organ function and are inherently at higher risk of surgery. On this basis, the presence of obesity is likely to accelerate the deterioration of elderly patients due to complications. Of course, further design and verification will be necessary.

Obesity is a multifactorial disease that results from interactions between genetics and lifestyle. The heritability for obesity is known to be around 40%, while the remainder can be explained by lifestyle factors, which suggests that obesity is a modifiable risk factor (26, 50). Healthy living and weight management recommended by WHO are necessary for patients, because obesity may increase mortality at admission compared with the patient without obesity, despite unifying the surgical procedures. Compared to surgical options, the degree of patient obesity may also be a focus for surgeons, as obesity may upset the balance from onset to post-operative management, especially in elderly patients with obesity. In these patients, the surgeon may need to pay more attention to blood pressure stability, respiratory or airway status, mental status, inflammation, and change of dressing on the wound (51).

The study still has some limitations. First, as mentioned in the Methods, our study was based on the Chinese population, reducing the generalizability of the findings, and it is unclear whether it is applicable to other ethnicities. Second, survivorship bias may be unavoidable due to the high mortality of AAD. Third, our findings are derived from single-center observational data, and further multi-center studies and a high-quality meta-analysis should be carried out to provide more evidence. Simultaneously, limited by the sample size, we were unable to assess the interaction of stratified root procedure and concomitant surgery with multivariate adjustment, which will be addressed in our future studies. Finally, this study did not explore the effect of obesity degree and BMI on in-hospital mortality, as the Chinese criteria do not subdivide the obesity degree. The continuous grouping of BMI, linear or non-linear relationships, and optimal cutoff values for prediction were also not further explored, which may be addressed in our future studies.

CONCLUSION

Obesity, interacting with age, increases the risk of in-hospital mortality in patients with AAD undergoing open surgical repair. Although more verification is needed, we believe that these findings provide further evidence for the treatment of AAD.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hospital Institutional Review Board of the Second Xiangya Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XP and XC drafted, revised, and reviewed the manuscript. XP, ZX, and GY conducted the statistical analysis and reviewed and revised the manuscript. ND and YZ organized the database. All authors significantly contributed to the conception, study design, execution, data acquisition, analysis, interpretation, approved the final version, and agreed on the journal and are responsible for this study.

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SUPPLEMENTARY MATERIAL

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Early Results of a Novel Hybrid Prosthesis for Treatment of Acute Aortic Dissection Type A With Distal Anastomosis Line Beyond Aortic Arch Zone Zero

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Introduction: Acute aortic dissection type A (AADA) is associated with high perioperative morbidity and mortality. A novel non-covered hybrid prosthesis (Ascyrus Medical Dissection Stent (AMDS) Hybrid Prosthesis, Cryolife/Jotec, Hechingen, Germany) can be easily implanted to stabilize the true lumen (TL), improve remodeling, and preserve organ perfusion. Although developed for implantation in aortic zone 0, occasionally, partial replacement of the aortic arch and further distal implantation of AMDS may appear favorable. Implantation of AMDS with anastomosis line beyond zone 0 has not been described yet.

Materials and Methods: Between 08/2019 and 12/2020, a total of $n = 97$ patients were treated due to AADA at a single University hospital. Of those, $n = 28$ received an AMDS hybrid prosthesis, of whom in eight patients, due to intraoperative finding the distal anastomosis line was placed distal to the brachiocephalic trunk. Three patients had AMDS implantation in zone I and four were treated by implantation of the prostheses in zone II, and one patient had the implantation performed in zone III. Clinical outcome and the development of a proportional area of TL and false lumen (FL) at defined levels of the thoracic aorta were analyzed.

Results: None of the surviving patients (87.5%) showed signs of clinical malperfusion (i.e., stroke, spinal cord injury, and need for dialysis). A postoperative CT scan showed an open TL in all patients. The proportion of TL with respect to total aortic diameter (TL+FL) was postoperatively significantly higher in zone III ($p = 0.016$) and at the level of T11 ($p = 0.009$). The mean area of TL+FL was comparable between pre- and postoperative CT-scan ($p =$ n.s.). One patient with preoperative resuscitation died of multiple organ failure on extracorporeal life support on postoperative day 3.

Conclusion: Implantation of AMDS can be safely performed in patients who need partial replacement of the aortic arch beyond zone 0. The advantages of the AMDS can be

combined with those of the total arch repair (remodeling of the arch and prevention of TL collapse) without the possible disadvantages (risk of spinal cord injury).

Keywords: acute aortic dissection type A (AADA), hemiarch and aortic arch replacement, aortic remodeling, *frozen elephant trunk*, AMDS

INTRODUCTION

Acute aortic dissection type A (AADA) remains a life-threatening condition despite the continuous improvement of operative technique and perioperative care for decades (1). Emergency surgery represents the first-line therapy and aims at replacement of the ascending aorta and removal of the primary entry tear (2). An extension of surgery to the aortic arch is preferred when an intimal tear is localized in this region (3–5). In the extreme, total aortic arch replacement (TAR) with concomitant implantation of a stent-graft prosthesis in the descending thoracic aorta (referred to as *frozen elephant trunk*) may be performed, which is currently regarded as the ultimate solution at the technical level to promote favorable aortic remodeling (6, 7). However, real-world data demonstrate a significant increase in 30-day mortality with TAR when compared with the technically more simple replacement for the ascending aorta with an open distal anastomosis, the so-called hemiarch replacement (HAR) (8), while HAR has been associated with an increased risk for aortic re-intervention in the follow-up (9). To simplify the therapy of AADA and make the operation performable for most surgeons irrespective of their specific experience profile, HAR has become a commonly applied technique. Furthermore, according to previous reports, TAR can be performed by nearly all surgeons due to the simplification of the implantation technique, however, an increased risk of stroke remains (10, 11). The Ascyrus Medical Dissection Stent (AMDS Hybrid Prosthesis, Cryolife/Jotec, Hechingen, Germany) has been designed to simplify surgical treatment of the downstream thoracic aorta by implantation line located proximal to the brachiocephalic trunk (zone 0), in addition to the standard replacement of the ascending aorta. Initial short-term results from a multicenter study suggest that the use of AMDS may have a positive impact by (1) sealing the distal anastomotic line to avoid distal anastomotic line new entry (DANE), (2) further supporting positive aortic remodeling by avoiding true lumen (TL) collapse, and (3) also reducing malperfusion associated with AADA (12). However, DANE is only one of several factors contributing to adverse remodeling of the aortic arch and the downstream thoracic aorta. The presence of intimal tear in the aortic arch and a retrograde perfusion of the supra-aortic vessels due to a re-entry further distally in the supra-aortic vessels have been reported as relevant factors requiring an extension of aortic replacement beyond zone 0 (13). Until now, there are reports on the outcome and prognostic value of AMDS implantation distal to the brachiocephalic trunk, i.e., beyond zone 0. It may be hypothesized that such an approach preserves the beneficial impact of AMDS on remodeling of the distal thoracic aorta while reducing the impact of retrograde supra-aortic perfusion of false lumen (FL) and also reducing the proportion of dissected aortic wall in the arch region. This report summarizes our experience with a consecutive series of patients undergoing emergency aortic surgery for AADA involving AMDS implantation in the aortic arch zone I–III.

TABLE 1 | Reasons for deviation from zone 0.

Reason for deviation	*n* (8)
Exclusion of intimal tear (re-entry)	7
Dissection of the supra-aortic vessel	7
Ascending proximal aneurysm extending to the arch	2
Circumferential tear of supra-aortic vessel	2
True lumen collapse of the thoracic aorta	3

There are multiple reasons for deviation. The zone for implantation is chosen by the most distal problem (dissection of supra-aortic vessel or intimal tear in the arch).

PATIENTS AND METHODS

Patient's Population and Data Collection

In this study, 97 consecutive patients undergoing cardiac surgery due to AADA at a single university hospital between 08/2019 and 12/2020 were reviewed. Of these, 28 patients (28.9%) received an AMDS hybrid prosthesis at the decision of the attending surgeon. This report analyses the in-hospital course and outcome of those patients in whom AMDS was implanted with the anastomosis line beyond zone 0: three in zone I (between the brachiocephalic trunk and the left common carotid artery, LCCA), four in zone II [between LCCA and left subclavian artery (LSA)], and one in zone III (distal to the LSA) (**Table 1**).

Demographic data, comorbidities, intraoperative procedures, and postoperative variables of outcome were collected systematically and entered prospectively into a standardized institutional database. Expected mortality was determined using prognostic models from the literature [EuroScore II, Penn, and German Registry for Acute Aortic Dissection Type A (GERAADA) models (14)]. These data were analyzed retrospectively in this study.

ASCYRUS MEDICAL DISSECTION STENT

The AMDS consists of an uncovered stent part and a proximal felt neck. Both elements intend to readapt the intima against the media and the adventitia and thereby reduce the force of separation between these layers, especially in the area of the anastomosis. This reduces the incidence of DANE and leads to remodeling of the aorta. Due to the fact that the stent is not covered, an occlusion of vertebral vessels is impossible.

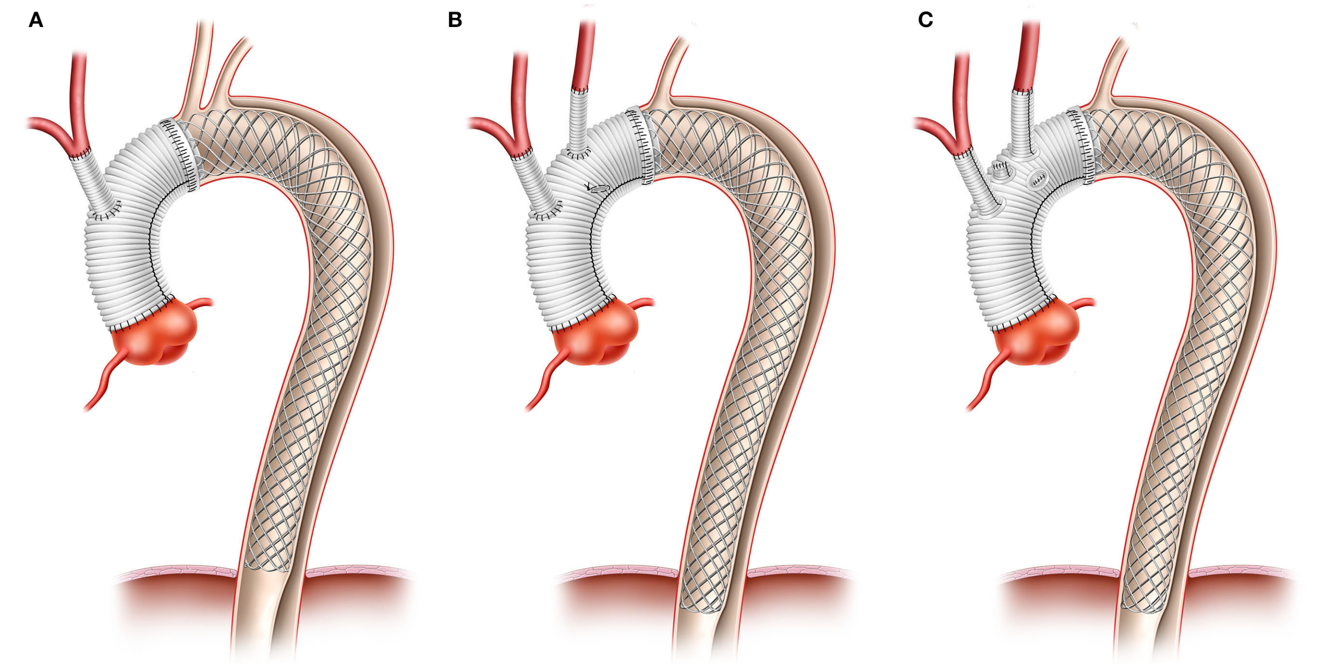

FIGURE 1 | Morphology of different surgical procedure. Anastomosis was ether performed in zone I using a single tube graft for INA **(A)**, or more distally using single tubes for the anastomosis of supra aortic vessels **(B)** or a branched prosthesis **(C)**.

CT Scan

Operative diagnosis was confirmed in all patients based on preoperative contrast-enhanced CT scans covering at least the thoracic cavity. Measurement of the aortic diameter was performed as described before (15) and suggested by STORAGE guidelines (16). Regardless of the localization of intimal tear (entry), the total diameter of the aorta including the aortic wall (such as TL and FL) at the level of zone I and at the level of pulmonary bifurcation was documented. All patients received at least one postoperative CT scan. In all in-hospital survivors, pre-discharge CT scans were performed.

Arch growth was determined in centerline measurement on the planes perpendicular to the aorta using multiplanar CT reformation at the level of zone III. The diameter and the area of TL and FL were measured at the level zone III and at the level of the 11th thoracic vertebrae (T11). For comparison, CT scan images obtained prior to the operation and prior to discharge were analyzed. For a standardized comparison, the ratio of TL area to FL area was calculated and analyzed.

Surgical Procedure

All patients underwent emergency surgery with cardiopulmonary bypass (CPB) initiated with arterial cannulation *via* the right axillary artery and venous cannulation of the right atrium or the right femoral vein. By clamping the innominate artery, lower body circulatory arrest was initiated at a body core temperature of 26–28°C measured in the bladder, while unilateral antegrade cerebral perfusion was achieved with continued perfusion of the right axillary artery. After transecting the ascending aorta, a balloon-inflatable perfusion catheter was endoluminally introduced, and perfusion of the LCCA was achieved for bilateral antegrade cerebral perfusion as the standard technique. Intraoperative near-infrared spectroscopy (NIRS) was used to monitor cerebral oxygenation, particularly during CPB time and hypothermic lower body circulatory arrest (HCA). Further aortic transection was performed up to the intended anastomosis line. AMDS was then implanted using a Teflon stripe on the adventitial aortic side to re-enforce the anastomosis line. Either a branched prosthesis ($n = 3$) or a tube graft ($n = 5$) was used for partial arch replacement. During reperfusion time, supra-aortic vessels were anastomosed to side branches where a branched prosthesis was used, or a small-diameter single tube graft (10 or 12 mm) was employed as an interposition graft for anastomosis of the supra-aortic vessels (**Figure 1**).

Ethics Committee Approval

This study was approved by the Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (Ref. 2016116135).

Statistical Analysis

Statistical analyses were performed with the Statistical Package for Social Sciences® (SPSS) 25.0 (IBM, Chicago, USA). Using this program, descriptive statistics and statistical comparisons between CT measurements were performed using the Wilcoxon matched-pairs signed rank test. A p-value of < 0.05 was considered statistically significant. Data are presented as mean ± standard error of mean (SEM).

TABLE 2 | Baseline characteristics.

Characteristics Mean (SD), *N* (%)	Total number of patients *N*= 8
Age (years)	63.63 ± 14.98
Gender (female)	3 (37.5)
BMI (kg/m²)	29.45 ± 5.23
BSA (m²)	2.0 ± 0.3
Hypertension	5 (52.5)
Diabetes	0 (0)
Smoke	4 (50)
Chronic obstructive pulmonary disease	1 (12.5)
Chronic kidney disease	1 (12.5)
Coronary artery disease	2 (25)
Previous aortic pathology	0 (0)
Intubation	2 (25)
Acute shock	1 (12.5)
Preoperative CPR	1 (12.5)
Need of catecholamine	1 (12.5)
Malperfusion	
- CT morphologically	8 (100)
Symptomatically/clinical	
- Coronary	2
- Neurological	2
- Mesenteric/renal	0
- Extremity	1
PENN Classification	
PENN class Aa	2
PENN class Ab	2
PENN class Ac	2
PENN class Ab&c	1
Acute neurological deficit	2 (25)
GERAADA score (%)	35.16 ± 18.33
EuroScore (%)	35.74 ± 19.31
Aortic regurgitation ≥ I°	4 (50)
Left ventricular ejection fraction (LVEF) (%)	44 ± 12
Pericardial effusion	2 (25)

Baseline characteristics, GERAADA, EuroScore, and the PENN Classification are presented. The PENN Classification refers to a previously described classification of ischemic presentation (17).

TABLE 3 | Surgical and perioperative data.

Characteristics Mean (SD), *N*(%)	Total number of patients *N* = 8
Total operation time	435.9 ± 140.2
CPB time	285.3 ± 61.7
X-clamp time	169.4 ± 60.3
Lower body HCA time	65.0 ± 12.6
Selective antegrade cerebral perfusion time	158.8 ± 63.2
Lowest body core temperature	26.2 ± 1.18
Cardioplegic solution	
- cold blood	7 (87.5)
- crystalloid	1 (12.5)
Root surgery	
- Aortic valve reimplantation (David)	3 (37.5)
- Root repair	5 (62.5)
Level of AMDS implantation	
- Zone I	3 (37.5)
- Zone II	4 (50)
- Zone III	1 (12.5)
AMDS prosthesis size	
- 40 tubular	1 (12.5)
- 40–30 tapered	0 (0)
- 55 tubular	3 (37.5)
- 55–40 tapered	4 (50)

CPB, cardio-pulmonary bypass; X-clamp, cross-clamp; HCA, hypothermic circulatory arrest.

RESULTS

Baseline Characteristics

Baseline characteristics are presented in **Table 2**. While the mean age was 63 ± 15 years, three patients were women (37.5%). No patient had previous cardiac surgery. Furthermore, two patients (25%) presented with prior intubation, of whom one patient was intubated in the setting of cardio-pulmonary resuscitation, while another patient was intubated due to neurological deterioration. Another patient presented with isolated left leg paresis. In addition, two patients were admitted to the hospital due to angina symptoms and ST elevation. The mean predicted 30-day mortality by the GERAADA score was 35.16 ± 18.33%. In the preoperative CT scan, two patients showed pericardial effusion. Angiographic signs of malperfusion were found in all patients.

Operative Data

Surgical and perioperative data are presented in **Table 3**. The mean CPB time was 285.25 ± 61.67 min. The lowest body core temperature was 26.2 ± 1.2°C. While lower body HCA time was 65.0 ± 12.6 min and cerebral perfusion time was 158.8 ± 63.2 min. Myocardial protection was achieved with the crystalloid cardioplegic solution in one patient, whereas a cold blood cardioplegic solution was used in the remaining seven patients.

Implantation of the AMDS was performed at the level of aortic arch zone III ($n = 1$), zone II ($n = 4$), or zone I ($n = 3$).

Postoperative Outcome

Measures of the postoperative outcome are summarized in **Table 4**. One patient with preoperative shock and cardiopulmonary resuscitation (CPR) needed postoperative extracorporeal life support (ECLS) with a consecutive bleeding disorder and the need for re-thoracotomy. This patient experienced therapy-refractory multiple organ failure and died on postoperative day 3. In-hospital and 30-day mortality were 12.5%. The mean duration of ICU stay was 4.72 ± 2.55 days, patients were discharged from the hospital after an average of 14.86 days. One patient underwent re-intubation due to CO_2-retention and showed prolonged weaning from ventilator,

TABLE 4 | Postoperative outcome.

Characteristics Mean (SD), *N* (%)	Total number of patients *N* = 8
Ventilation time ($n = 7$) (h; days)	53.9 ± 21.1 (2.2 ± 0.9)
Duration in ICU (h; days)	113.3 ± 61.3 (4.7 ± 2.6)
Duration on IMC (h; days)	84.3 ± 80.5 (3.5 ± 3.4)
Total hospital stay (days)	14.9 ± 6.8
Need of mechanical circulatory support (central ECLS)	1 (12.5)
Major bleeding	1 (12.5)
Tracheotomy	1 (12.5)
Acute kidney injury with need for hemodialysis	3 (37.5)
Stroke	0 (0)
Spinal cord injury	0 (0)
Postoperative clinical malperfusion	0 (0)
Postoperative still existing dissection of supra-aortic branches	3 (37.5) (patients 3 + 5 + 8)
Perfusion of the false lumen in the arch	2 (25) (patients 5 + 8)
Postoperative true lumen collapse	0 (0)
Postoperative infection	0 (0)
In-hospital death	1 (12.5)
30-day mortality	1 (12.5)

ECLS, extracorporeal-life support.

underwent tracheotomy, and was transferred to respiratory weaning center on postoperative day 13. The mean ventilation time was 2.24 ± 0.88 days. Among surviving patients (7/8), no patient showed relevant postoperative neurological deficit (e.g., stroke and spinal cord injury). All survivors had a Glasgow Coma Scale (GCS) of 15 and a Richmond Agitation Sedation Scale (RASS) of 0 at the time point of discharge.

Postoperative CT scans demonstrated that no patient suffered from TL collapse. At the level of the aortic arch, perfusion of the FL was detected in only two patients (arch remodeling). No patients experienced postoperative clinical malperfusion whereby in three patients, a dissection of supra-aortic vessels was detected even after the operation.

Comparison of CT-Measurements

Table 5 shows the CT measurements. Area analyses demonstrated a significant enlargement of the TL in zone III and further distally (T11) when assessing postoperative images as compared with the preoperative status. A decrease in mean cross-sectional area of FL in the latter aortic segments was observed. The ratio between cross-sectional areas of TL and FL, respectively, was significantly higher postoperatively with more than doubled values at the level of zone III. The total diameter increased slightly at both analyzed levels of the thoracic aorta (**Figure 2**).

DISCUSSION

In this study, we demonstrate that implantation of an AMDS hybrid prosthesis beyond aortic arch zone 0 is feasible, reproducible, and safe. No patient suffered from postoperative spinal cord injury or malperfusion syndrome. A significant increase in perfused TL could be observed at different segments of the aorta, while a significant reduction of FL cross-sectional area was observed.

Obviously, a shorter operation time can be life-rescuing in the particular emergency settings of surgery for AADA (18). The primary aim of surgery in those patients with significantly impaired outcomes is early survival. Furthermore, the freedom of re-intervention should be aimed for as surgery and interventional procedures are associated with further risk of mortality and morbidity.

Hemiarch repair is associated with a shorter CPB time and operation time. However, the need for a second operation can be possible (9, 19–21). While total arch replacement with *the frozen elephant trunk* allows for the distal extension of the stent and allows sealing of potential distal intima tears. At the same time, covered stents can lead to spinal artery occlusion and spinal cord injury (22). In addition, neurological complications, e.g., stroke and TIA, can be higher in patients treated with TAR (7, 23). However, few AADA centers describe the feasibility of TAR due to a simplified operation technique with a proximalized distal anastomose line, in the acute setting of aortic dissection. Still, many centers prefer HAR over more complex surgery involving extended aortic arch replacement with or without stent graft implantation (TAR).

The AMDS hybrid prosthesis consists of an uncovered stent part and a proximal felt neck located at the level of the anastomotic line. Therefore, this device represents a hybrid solution intended for implantation at aortic zone 0 with technical complexity compared to that of the hemiarch replacement. However, the first clinical results suggest that an additional benefit of aortic remodeling with reduced malperfusion and a lower rate of DANE speak in favor of the implementation of AMDS (12, 24).

A few scenarios can make the use of the AMDS in the first moment impossible (**Table 1**). However, by shifting the distal anastomosis line more distally, AMDS could also be implanted in cases with focal re-entry in the aortic arch region. By careful preoperative assessment of the CT scan, preoperative determination of surgical strategy and location of the anastomotic line may be possible in the majority of patients presenting with AADA. The results presented herein show that this technique is a safe and reproducible alternative to TAR, combining the benefits from simple hemiarch with some benefits otherwise observed with the more complex total arch replacement. Intimal tears in the arch region could be resected, dissected supra-aortic vessels could be repaired in most patients, TL collapse could be prevented in all patients, and the risk of spinal cord injury was virtually omitted. We could also confirm the results of Bozso et al. (24), that by using the ADMS, DANE could be prevented and no antegrade perfusion was performed, which also led to the remodeling of the aorta.

The CT analysis showed a significant increase in the TL at the level of zone III and T11 in our cohort. No TL collapse was observed in any part of the aorta. The area of FL was reduced in six patients in zone III and seven patients in T11, leading to

TABLE 5 | CT measurements.

	Pre	Post	*p*	Median change (%)
Area of TL at zone III (mm²)	412.61 ± 201.99	558.12 ± 1,419.60	**0.0078**	**58.32**
Area of FL at zone III (mm²)	528.04 ± 104.18	402.38 ± 243.73	0.1953	−34.03
Area of TL + FL at zone III (mm²)	940.65+193.75	960.50+276.26	0.9453	−1.81
TL/TL + FL ratio at zone III	0.42+0.14	0.60+0.15	**0.0313**	
Average diameter at zone III (mm)	34.90 ± 4.53	37.10 ± 6.10	0.5156	4.57
Area of TL at T11 (mm²)	240.83 ± 150.67	463.81 ± 88.99	**0.0078**	**105.29**
Area of FL at T11 (mm²)	484.10 ± 196.58	262.36 ± 69.14	**0.0234**	**–48.46**
Area of TL + FL at zone III (mm²)	724.93+101.52	726.17+125.81	0.7422	−3.89
TL/TL + FL ratio at T11	0.34+0.24	0.64+0.07	**0.0234**	
Average diameter at T11 (mm)	31.24 ± 3.06	32.91 ± 3.87	0.1094	4.97

TL, true-lumen; FL, false-lumen. Bold indicates statistical significant differences.

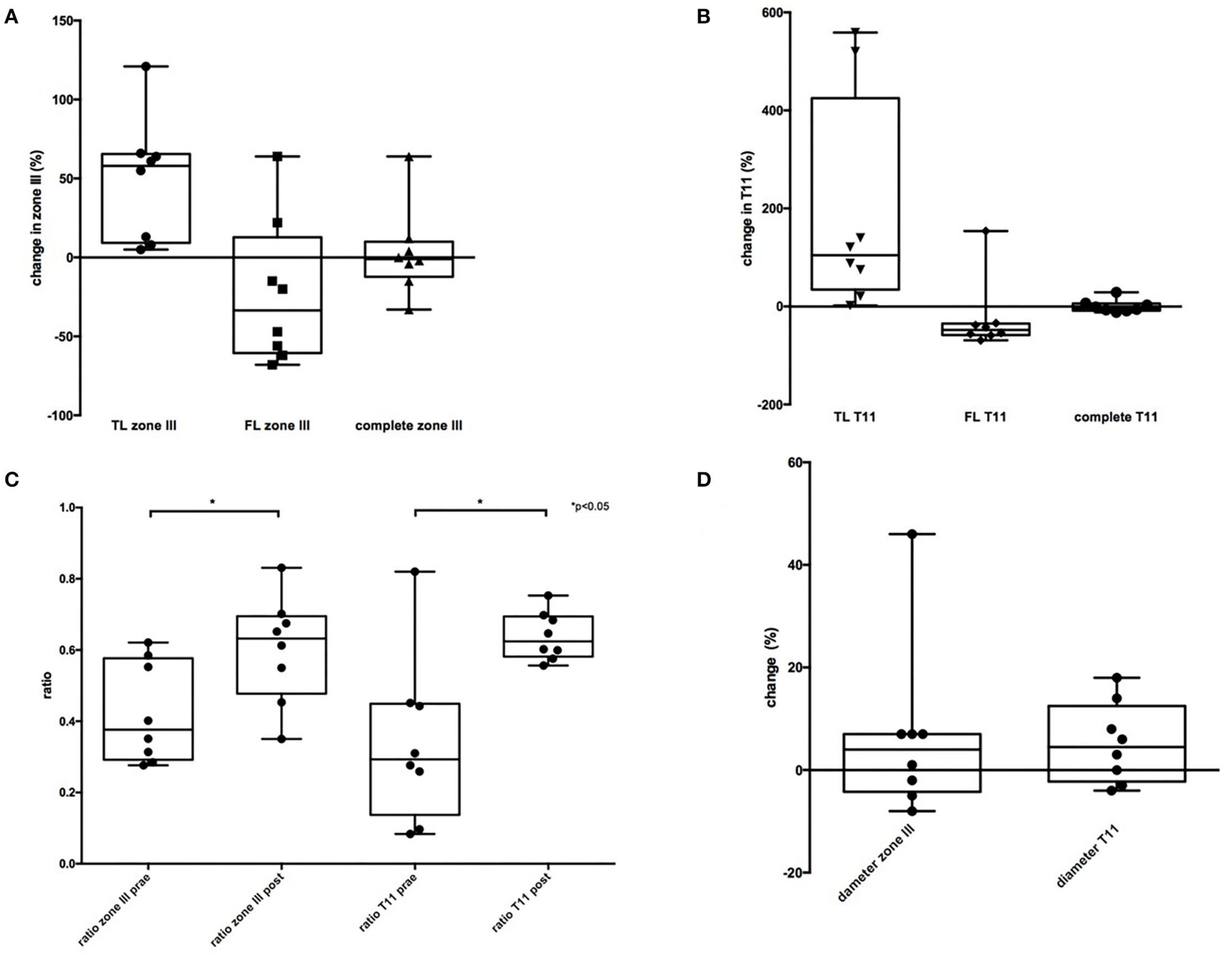

FIGURE 2 | Comparison of CT-measurement. **(A)** Showing an enlargement of the true lumen (TL) and a decrease of the false lumen (FL) in zone III. Area of TL + FL did not changed. **(B)** TL showed a significantly bigger increase in T11 and a significant decrease of the FL. Area of TL + FL did not changed. **(C)** ratio of TL/TL + FL was postoperatively significant higher in both zones compared to preoperative CT. **(D)** total diameter showed no significant difference.

a relatively stable total area in both zones, indicating remodeling of the arch and the descending aorta. The ratios of TL/TL+FL were significantly higher in both zones, which may be regarded as evidence of favorable remodeling. While the ratio in preoperative CT scans is below 0.5 (meaning the proportion of TL compared with the entire aortic cross-sectional area is $<50\%$), the TL proportion was increased in postoperative CT scans (ratio > 0.5).

In two patients, an increased aortic diameter on postoperative CT with growth of FL area at the level of aortic zone III and T11 was observed. In these patients, a persistent dissection of supra-aortic vessels (in particular of the LSA) was noted. We speculate that a suspected entry/re-entry in that vessel may cause a retrograde flow into the FL and thus may prevent a positive remodeling of the downstream thoracic aorta.

Preoperative CT scans are often not sensitive enough for identifying additional intima tears in the supra-aortic vessels. Recognized dissected supra-aortic vessels should be anastomosed separately to further enforce favorable arch remodeling. However, the associated increase in technical complexity may have a negative impact on the overall outcome, which will have to be addressed in future studies.

The purpose of this study was not to compare TAR with AMDS due to different patient selection criteria. The aim of the study was rather to show that in patients where a standard implantation of AMDS at the level of aortic zone 0 is not favored, a movement of the implantation site distally may be a solution to preserve the advantages associated with the implantation of the hybrid stent. For the first time, we could show that intimal tears in the arch region or circular re-entry sites at supra-aortic vessels can be treated using this strategy. However, a meticulous study of the preoperative CT scan is of paramount value for accurate strategy planning as well as to identify possible reentries in supra-aortic vessels, which may cause postoperative growth of FL and may lead to further need for intervention.

LIMITATION

This study has several limitations. First, this is a retrospective observational study with a small number of patients. In addition, only immediate results are demonstrated; follow-up and long-term results are needed to evaluate the role of the presented approach for sustainable positive arch remodeling, especially in those two patients with the growth of the FL in the early period. As a standard, follow-up visits at 3, 6, and 12 months were presumed but could not be realized in all patients due to incompliance. Furthermore, longitudinal observation of a larger cohort is necessary.

CONCLUSION

The implantation of the novel hybrid prosthesis can be performed safely and reproducibly at the aortic arch levels beyond zone 0 in patients with AADA. Applying this approach, an early remodeling of the aortic arch and the prevention of TL collapse with no risk of spinal cord injury can be achieved.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (Ref. 2016116135). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AM and PA conceived the concept of the present study and drafted the paper. LW, SB, and YS contributed with data collection. MI and GA supported CT-data acquisition and data processing. MW, AL, and HS contributed to study design. All authors took part in both data interpretation and critical revision of the manuscript.

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