Characteristics and outcomes of Stanford type A aortic dissection patients with post-operation severe hyperbilirubinemia: a retrospective cohort study

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Research

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Abstract

Objective

Hyperbilirubinemia is one of the common complications after cardiac surgery and is associated with increased mortality. However, to the best of our knowledge, the report on clinical significance of postoperative severe hyperbilirubinemia in Stanford type A aortic dissection (AAD) patients is limited. Therefore, the purpose of our present study is to assess the characteristics and outcomes of AAD patients with post-operation severe hyperbilirubinemia.

Methods

Patients who underwent surgical treatment for AAD in our center between January 2015 and December 2018 were retrospectively screened. In-hospital mortality, long-term mortality, acute kidney injury (AKI), and the requirement of continuous renal replacement therapy (CRRT) were assessed as endpoints. Univariate and multivariate regression models were employed to identify the risk factors of these endpoints.

Results

Of the 2210 screened patients, 271 (12.3%) were included. Of the included patients, 222 (81.9%) experienced postoperative AKI, and 50 (18.5%) received CRRT. In-hospital mortality was 30.3%. The 1-year, 2-year, and 3-year cumulative mortality were 32.9%, 33.9%, and 35.3%, respectively. Multivariate Logistic regression analysis indicated that age ($P < 0.033$), AKI stage 3 ($P < 0.001$), the total amount of blood transfusion after surgery ($P = 0.019$), mean arterial pressure (MAP) in the first postoperative day ($P = 0.012$), the use of extracorporeal membrane oxygenation (ECMO) after surgery ($P = 0.02$), and the peak total bilirubin (TB) concentration ($P = 0.023$) were independent risk factors of in-hospital mortality. The optimal cut-off value of peak TB on predicting in-hospital mortality was 121.2 μmol/l. Older age, high preoperative serum creatinine (SCr) concentration, and prolonged cardiopulmonary bypass (CPB) time were identified as the independent risk factors of AKI. High preoperative SCr concentration was identified as the only independent risk factor of the requirement of CRRT.

Conclusions

Post-operation severe hyperbilirubinemia is a common clinical presentation in AAD surgery patients. Post-operation severe hyperbilirubinemia AAD patients with older age, lower MAP, increased blood transfusion, stage 3 AKI, the use of ECMO, and the increased peak TB had higher risk of in-hospital mortality.

1. Introduction

Aortic dissection (AD) is an acute life-threatening condition with a prevalence of about 3/100,000 per year. The International Registry of AD revealed that 67% of AD patients presented with Stanford type A aortic dissection (AAD), which was characteristic as the involvement of the ascending aorta. And,

approximately 86% of AAD patients required swift open cardiac surgery to avoid fatal complications such as aortic rupture and cardiac tamponade.[1–3] In spite of the improvement in medical management and surgical technique, AAD surgery was associated with early mortality as high as 20%.[4–8]

Hyperbilirubinemia is a common severe complication after cardiac operation. The reported incidence of post-operation hyperbilirubinemia varied widely (10–57%) and related to the severity of cardiac diseases and the type of cardiac surgery. Although hyperbilirubinemia was reported to be associated with in-hospital mortality and mortality after discharge, the effects of hyperbilirubinemia on patient prognosis were heterogeneous.[9–14] For patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), recent studies suggested that severe hyperbilirubinemia (5 times the normal upper limit) instead of mild bilirubin significantly increased patient mortality.[15] Additionally, the occurrence of acute kidney injury (AKI) and the acceptance of continuous renal replacement therapy (CRRT) after cardiac surgery were suggested to be associated with the decrease of patient survival proportion. As we know, the pathogenesis, disease severity classification, prognosis, and operation method are different between different cardiac diseases. The inclusion of all kinds of cardiac surgery in one study most likely would reduce the specificity and repeatability of the conclusions. Up to now, the reports on the characteristics and outcomes of AAD surgery patients who had post-operation severe hyperbilirubinemia are limited.

Therefore, the purpose of our present study is to describe the clinical characteristics and to investigate the risk factors of AKI, the requirement of CRRT, in-hospital mortality, and long-term mortality in AAD surgery patients who had post-operation severe hyperbilirubinemia. The results of our present study might be useful for decision makers regarding their treatment strategy and for patients and their families regarding the expected progression.

2. Patients And Method

2.1. Study design and patients selection

Our present study was retrospectively designed. Consecutive patients who underwent surgery for AD in our center between January 2015 and December 2018 were screened. AD was proven by enhanced computed tomography and defined as type A or type B according to the Stanford classification. Patients with post-operation severe hyperbilirubinemia were considered for inclusion. Postoperative severe hyperbilirubinemia was defined as occurrence of a serum TB concentration of more than 85.5 μmol/l (5 times the normal upper limit) in any measurement during the hospital staying after AAD surgery. Patients were excluded if they had any of the following conditions: (1) age < 18 years; (2) Stanford type B aortic dissection; (3) the occurrence of severe hyperbilirubinemia before surgery; (4) severe hyperbilirubinemia caused by the reoperation during this hospitalization. The local Institutional Review Board of the hospital approved this retrospective study and waived the requirement of informed consent for the use of patients' medical data.

2.2. Surgical procedure

The primary surgical strategy for open-heart surgery at our institution is a sternotomy procedure from right midclavicular line with moderate hypothermic cardiopulmonary bypass (CPB). Vasoactive drugs were administered at the discretion of the attending anesthesiologist on the basis of hemodynamics. In general, dopamine, epinephrine, and norepinephrine were administrated to achieve better renal perfusion during and after the operation.

2.3. Data collection

Demographic data, comorbidities, and operation details were retrieved from our hospital's electronic medical record system. All the routine laboratory data was recorded before operation (the nearest to the time of surgery) and in the post-operation period. The severity of illness before and after surgery was assessed by using the acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA) score, and model for end-stage liver disease (MELD) score. Urine output was recorded every day after the surgery.

2.4. Outcomes and definition

Post-operation outcomes including the amount of blood transfusion, mechanical ventilation time, the use of extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), AKI, the usage of CRRT, bilirubin adsorption (BA) or plasma exchange (PE), and vasoactive agent, the duration of hospitalization, ICU stay time, and in-hospital mortality. For those patients who were alive on discharge, telephone survey was performed to obtain the patients long-term outcome.

Kidney Disease Improving Global Outcomes (KDIGO) criteria[16] based on SCr or urine output was employed to diagnose and grade AKI. The latest SCr concentration before surgery was defined as preoperative SCr concentration. The decision to start CRRT was made at the discretion of the attending nephrologist. Main indications for starting CRRT were progressive AKI, fluid overload, hyperkalemia, and severe metabolic acidosis.[16]

2.5. Statistical analysis

Data were analyzed using SPSS version 22.0 software (SPSS, Inc, Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as frequencies with percentages. To evaluate the differences between groups, the independent sample t-test was used for continuous variables, whereas the chi-square test or Fisher's exact test was used for categorical variables. Factors significantly associated with these endpoints in univariate analysis were included in the multivariate logistic regression analysis or Cox proportional hazard analysis to identify the independent risk factors. Accumulated survival proportion was estimated with the Kaplan-Meier method, and the between-group differences of survival proportion were assessed using the log-rank test. Area under the receiver operating characteristic curve (AUC-ROC) was calculated to assess peak TB concentration on the ability to detect in-hospital mortality. Youden index was used for assessment of optimal cut-off values. For all analyses, all statistical tests were 2-sided, and a P-value < 0.05 was considered as statistically significant.

3. Result

3.1. Patient characteristics

Of the 2210 screened patients, 279 were considered as candidates for inclusion (Fig. 1). Of these patients, 2, 3, and 3 were excluded because of Stanford type B aortic dissection, preoperative TB ≥ 85.5 μmol/l, and post-operation severe hyperbilirubinemia caused by reoperation during this hospitalization, respectively. Ultimately, 271 AAD surgery patients with post-operation severe hyperbilirubinemia were included in our present study.

The baseline characteristics of the included patients were summarized in Table 1. There were 223 male and 48 female, and the mean age of the patients was 49.1 ± 11.0 years. AAD surgery involved the aortic valve in 83.8% patients, aortic arch in 86% patients, and coronary artery in 17% patients. Preoperative TB concentration was 25.0 ± 15.0 μmol/l. The mean onset time of severe hyperbilirubinemia was 2.8 ± 1.3 days after AAD surgery. The mean peak serum TB concentration was 150.9 ± 93.0 μmol/l and the averaged time to peak TB concentration was 3.8 ± 3.0 days after AAD surgery. The change of TB concentration during the seven days after surgery was showed in Fig. 2. The median follow-up time was 18.63 (0.5–55.9) months. And, 3 patients were lost to follow-up. The time of lost to follow-up was 16-, 95-, and 365-day after the surgery, respectively.

Table 1. Baseline characteristics of the included patients	
Variables	**Value**
Preoperative	
Age, mean ± SD (years)	49.1 ± 11.0
Male, n (%)	223 (82.3%)
Co-morbidity	
Hypertension, n (%)	158 (58.3%)
Diabetes, n (%)	3 (1.1%)
Cerebrovascular disease, n (%)	16 (5.9%)
Previous cardiac surgery, n (%)	8 (2.9%)
APECHEII score, mean ± SD	9.2 ± 3.2
MELD score, mean ± SD	9.2 ± 4.1
SOFA score, mean ± SD	2.1 ± 1.5
MAP, mean ± SD (mm/Hg)	90.5 ± 12.9
TB, mean ± SD (μmol/l)	25.0 ± 15.0
CB, mean ± SD (μmol/l)	7.8 ± 8.1
WBC, mean ± SD (10^9/l)	11.7 ± 5.0
Hb, mean ± SD (g/l)	136.1 ± 19.9
PLT, mean ± SD (10^9 /l)	157.2 ± 68.5
SCr, mean ± SD (μmol/l)	111.1 ± 38.3
PT, mean ± SD (s)	12.0 ± 2.2
Intraoperative	
Type of operation	
Aortic valve, n (%)	227 (83.8%)
Aortic arch, n (%)	233 (86%)
Coronary artery, n (%)	46 (17%)
Operation duration, mean ± SD (h)	6.8 ± 1.6
CPB time, mean ± SD (min)	226.5 ± 60.9
ACC time, mean ± SD (min)	102.2 ± 28.0

The amount of blood transfusion (U)	18.8 ± 10.6
Postoperative	
APECHE II score	16.9±2.5
SOFA score	12.1±2.6
Meld score	18.6±4.4
AST, mean ± SD (U /L)	347.6±1387.2
ALT, mean ± SD (U/L)	164.4±526.6
TB, mean ± SD (μmol /l)	189.1±74.6
CB, mean ± SD (μmol /l)	110.7±37.9
WBC, mean ± SD (10^9/l)	12.9±4.8
Hb, mean ± SD (g/l)	112.9±16.6
PLT, mean ±SD (10^9 /l)	99.8±49.5
SCr, mean± SD (μmol/l)	162.8±71.8
PT, mean± SD (s)	13.6±2.9
Peak TB level, mean ± SD (μmol/l)	150.9 ± 93.0
Peak TB level > 171μmol/l, n (%)	55 (20.4%)
Peak TB level > 340μmol/l, n (%)	12 (4.4%)
Time to peak TB level, mean ± SD (d)	3.8 ± 3.0
Time to peak TB level > 5 d, n (%)	47 (17.4%)

ACC, Aortic cross clamp; APECHEII, acute physiology and chronic health evaluation II; CB, conjugated bilirubin; CPB, cardiopulmonary bypass; Hb, hemoglobin; MAP, mean arterial pressure; MELD, model for end-stage liver disease; min, minute; PLT, platelet; PT, prothrombin time; SCr, serum creatinine; SD, standard deviation; SOFA, sequential organ failure assessment; TB, total bilirubin; WBC, white blood cell.

3.2. Postoperative AKI

Of the 271 included patients, 222 patients (82.1%) had AKI after AAD surgery, of which 102 (40.2%), 34 (12.5%), and 84 (29.2%) were stage 1, stage 2, and stage 3 AKI (Table 2), respectively. The results of univariate and multivariate logistic regression are presented in Table 3. In the univariate analysis, age, hypertension, preoperative SCr concentration, APECHE Ⅱ score, and MELD score, operation time, and CPB time were associated with the occurrence of postoperative AKI. Multivariate analysis indicated that increased age (OR 1.056, 95%CI 1.026–1.088, P < 0.001), higher preoperative SCr concentration (OR

1.026, 95%CI 1.010–1.043, P = 0.002), and prolonged CPB time (OR 1.007, 95%CI 1.000–1.013, P = 0.042) were identified as independent risk factors of AKI in AAD surgery patients with post-operation severe hyperbilirubinemia.

Table 2
The major outcomes of the included patients

Variables	Value
In-hospital mortality, n (%)	82 (30.3%)
Reoperation, n (%)	17 (6.3%)
AKI, n (%)	222 (81.9%)
Stage of AKI	
Stage 1, n (%)	102 (40.2%)
Stage 2, n (%)	34 (12.5%)
Stage 3, n (%)	84 (29.2%)
Use of CRRT, n (%)	50 (18.5%)
Use of PE/BA, n (%)	11 (14.1%)
Use of IABP, n (%)	1 (0.4%)
Use of ECMO, n (%)	7 (2.6%)
Use of vasoactive agent, n (%)	173 (63.8%)
Mechanical ventilation time, mean ± SD (days)	3.3 ± 5.7
The amount of blood transfusion, mean ± SD (U)	34.8 ± 43.3
In hospital time, mean ± SD (days)	19.8 ± 10.7
ICU stay time, mean ± SD (days)	6.6 ± 6.3
Onset of severe hyperbilirubinemia, mean ± SD (days)	2.8 ± 1.3

AKI, acute kidney injury; BA, bilirubin adsorption; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICU, intensive care unit; PE, plasma exchange.

Table 3
Logistic regression analysis for postoperative AKI and CRRT

Characteristic	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	P value	OR (95%CI)	P value
Postoperative AKI				
Age	1.061 (1.032–1.092)	< 0.001	1.056 (1.026–1.088)	< 0.001
Hypertension (yes/no)	2.766 (1.469–5.208)	0.002		
Preoperative				
SCr	1.030 (1.014–1.047)	< 0.001	1.026 (1.010–1.043)	0.002
APECHE II score	1.399 (1.213–1.615)	< 0.001		
MELD score	1.130 (1.035–1.233)	0.007		
Operation duration	1.346 (1.089–1.633)	0.006		
CPB time	1.008 (1.001–1.014)	0.015	1.007 (1.000–1.013)	0.042
Postoperative CRRT				
Male (yes/no)	4.006 (1.192–13.462)	0.025		
Preoperative				
SCr	1.011 (1.003–1.018)	0.004	1.009 (1.002–1016)	0.017
APECHE II score	1.333 (1.033–1.244)	0.008		
MELD score	1.083 (1.007–1.164)	0.032		
ACC time	1.011 (1.000–1.022)	0.049		

ACC, aortic cross clamp; AKI, acute kidney injury; APECHEII, acute physiology and chronic health evaluation II; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; MELD, model for end-stage liver disease; SCr, serum creatinine

3.3. Postoperative CRRT

Of the included patients, 50 (18.5%) patients received CRRT after AAD surgery. Univariate analysis indicated that male, preoperative SCr concentration, APECHE Ⅱ score, MELD score, and aortic cross-clamp (ACC) time were associated with the need for CRRT. In the multivariate logistic regression analysis, only preoperative SCr concentration (OR 1.011, 95%CI 1.002–1016, P = 0.003) was identified as an independent predictor of the acceptance of CRRT (Table 3).

3.4. In-hospital mortality

There were 82 (30.3%) in-hospital deaths. Univariate analysis revealed that 20 pre-operation, intra-operation, and post-operation factors were associated with in-hospital mortality. After the adjustment of the important clinical parameters, independent risk factors of in-hospital mortality identified by multivariate logistic analysis included age (OR 1.005, 95%CI 1.004–1.099, P = 0.033), the amount of blood transfusion (OR 1.018, 95%CI 1.003–1.033, P = 0.019), stage 3 AKI (OR 46.134, 95%CI 5.436–391.525, P < 0.001), the use of ECMO (OR 20.795, 95%CI 1.620–266.917, P = 0.02), and the peak TB concentration (OR 1.017, 95%CI 1.002–1.032, P = 0.023). Postoperative MAP tended to be a protective factor (OR 0.955, 95%CI 0.922–0.990, P = 0.012, Table 4, model 1).

Table 4

Logistic regression analysis for in-hospital mortality

In-hospital mortality	Univariate logistic regression		Multivariate logistic regression (model 1)		Multivariate logistic regression (model 2)	
Characteristic	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Age (yes/no)	1.035 (1.009–1.062)	0.008	1.005 (1.004–1.099)	0.033	1.046 (1.002–1.093)	0.040
Male (yes/no)	2.483 (1.106–5.575)	0.027				
Preoperative						
SCr	1.009 (1.002–1.016)	0.008				
APECHE II score	1.178 (1.082–1.282)	< 0.001				
Intraoperative						
CPB time	1.007 (1.003–1.011)	0.002				
ACC time	1.012 (1.002–1.021)	0.014				
Postoperative						
MAP	0.948 (0.926–0.971)	< 0.001	0.955 (0.922–0.990)	0.012	0.963 (0.930–0.977)	0.031
Re-operation (yes/no)	3.611 (1.324–9.852)	0.012				
The total amount of blood transfusion	1.046 (1.032–1.060)	< 0.001	1.018 (1.003–1.033)	0.019	1.020 (1.005–1.034)	0.007
Mechanical ventilation time	1.533 (1.341–1.798)	< 0.001				

Model 1 was established by analysis of peak TB concentration; Model 2 was established by subgroup analysis of peak bilirubin concentration greater or less than 121.2 μmol/l

ACC, aortic cross clamp; AKI, acute kidney injury; APECHEII, acute physiology and chronic health evaluation II; BA, bilirubin adsorption; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MAP, mean arterial pressure; PE, plasma exchange; SCr, serum creatinine; TB, total bilirubin

In-hospital mortality	Univariate logistic regression		Multivariate logistic regression (model 1)		Multivariate logistic regression (model 2)	
AKI (yes/no)	28.350 (3.842–209.203)	0.001				
Stage of AKI		< 0.001		< 0.001		< 0.001
Stage 1	5.859 (0.735–46.720)	0.095	2.424 (0.267–21.990)	0.431	2.218 (0.253–19.426)	0.472
Stage 2	10.138 (1.162–88.457)	0.036	4.560 (0.478–43.545)	0.187	3.698 (0.385–35.548)	0.257
Stage 3	165.053 (21.354–1275.729)	< 0.001	46.134 (5.436–391.525)	< 0.001	46.318 (5.666–378.663)	46.318
Use of CRRT (yes/no)	23.756 (10.359–54.481)	0.001				
Use of PE/BA (yes/no)	11.527 (2.432–54.631)	0.002				
Use of ECMO (yes/no)	14.842 (1.757–125.357)	0.013	20.795 (1.620–266.917)	0.02	10.130 (0.900–113.958)	0.061
Peak TB concentration	1.009 (1.005–1.012)	< 0.001	1.017 (1.002–1.032)	0.023		
Peak TB ≥ 121 μmol/l, (yes/no)	3.899 (2.220–6.847)	< 0.001			2.681 (1.119–6.425)	0.027
Peak TB > 171 μmol/l, (yes/no)	3.785 (2.045–7.005)	< 0.001				
Time to peak TB concentration	1.441 (1.277–1.626)	< 0.001				
ICU stay time	1.268 (1.172–1.371)	< 0.001				

Model 1 was established by analysis of peak TB concentration; Model 2 was established by subgroup analysis of peak bilirubin concentration greater or less than 121.2 μmol/l

ACC, aortic cross clamp; AKI, acute kidney injury; APECHEII, acute physiology and chronic health evaluation II; BA, bilirubin adsorption; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MAP, mean arterial pressure; PE, plasma exchange; SCr, serum creatinine; TB, total bilirubin

ROC analysis (Fig. 4) identified that peak TB concentration was associated with increased mortality, and the optimal cut-off value identified by the Youden index was 121.2 μmol/l (sensitivity: 72%, specificity: 60%). And, the multivariate analysis revealed that patients with peak TB concentration ≥ 121.2 μmol/l had a significantly higher risk of in-hospital mortality (OR = 2.681, 95%CI 1.119–6.425, P = 0.027, Table 3, model 2), compared with the patients with peak TB concentration < 121.2 μmol/l.

3.5. Long-term mortality

Of the 12 patients who died after discharge, 4 had non-AKI, 3 had stage 1 AKI, 3 had stage 2 AKI, and 2 had stage 3 AKI during their hospital stay, respectively. The accumulated 1-year, 2-year, and 3-year mortality proportions were 32.9%, 33.9%, and 35.3%, respectively (Fig. 4A). The risk factors of long-term mortality were presented in Table 5. Univariate analysis revealed 20 factors, including the post-operation AKI, the acceptance of CRRT and ECMO, and the peak TB concentration ≥ 121.2 μmol/l (Fig. 4B-E), were significantly related to patient long-term mortality. Multivariate COX regression analysis revealed that stage 3 AKI (HR 12.604, 95%CI 5.002–31.762, P < 0.001) significantly increased long-term mortality, compared with patients without AKI. The use of ECMO (HR 12.167, 95%CI 4.588–32.264, P < 0.001) was identified as an independent predictor of long-term mortality as well. In contrast, postoperative MAP (HR 0.979, 95%CI 0.962–0.995, P = 0.012) was identified as an independent protective factor of long-term mortality.

Table 5

COX regression analysis for long-term mortality

Follow-up mortality	Univariate COX regression		Multivariate COX regression	
Characteristic	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.023 (1.003–1.043)	0.026		
Preoperative				
SCr	1.006 (1.002–1.010)	< 0.001		
APECHE II score	1.122 (1.060–1.188)	< 0.001		
MELD score	1.052 (1.003–1.105)	0.039		
Intraoperative				
Operation duration	1.248 (1.098–1.414)	0.001		
CPB time	1.005 (1.002–1.008)	0.001		
Postoperative				
MAP	0.971 (0.957–0.985)	< 0.001	0.979 (0.962–0.995)	0.012
The total amount of blood transfusion	1.009 (1.007–1.011)	< 0.001		
Mechanical ventilation time	1.035 (1.020–1.051)	< 0.001		
AKI (yes/no)	6.25 (2.295–17.024)	< 0.001		
Stage of AKI		< 0.001		< 0.001
Stage 1	1.404 (0.506–3.901)	0.515	1.037 (0.365–2.946)	0.946

ACC, aortic cross clamp; AKI, acute kidney injury; APECHEII, acute physiology and chronic health evaluation II; BA, bilirubin adsorption; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MAP, mean arterial pressure; MELD, model for end-stage liver disease; PE, plasma exchange; SCr, serum creatinine; TB, total bilirubin

Follow-up mortality	Univariate COX regression		Multivariate COX regression	
Stage 2	2.772 (0.929–8.271)	0.068	2.236 (0.774–6.990)	0.133
Stage 3	15.071 (6.043–37.587)	< 0.001	12.604 (5.002–31.762)	< 0.001
Use of CRRT (yes/no)	6.368 (4.174–9.709)	< 0.001		
Use of PE/BA (yes/no)	3.184 (1.596–6.351)	0.001		
Use of ECMO (yes/no)	6.108 (2.638–14.139)	< 0.001	12.167 (4.588–32.264)	< 0.001
Onset of hyperbilirubinemia	1.217 (1.044–1.418)	0.012		
Peak TB concentration	1.004 (1.003–1.006)	< 0.001		
Peak TB > 121 μmol/l (yes/no)	2.595 (1.679–4.001)	< 0.001		
Peak TB > 171 μmol/l (yes/no)	2.292 (1.488–3.530)	< 0.001		
Time to peak TB concentration	1.156 (1.107–1.208)	< 0.001		
ICU stay time	1.037 (1.022–1.053)	< 0.001		

ACC, aortic cross clamp; AKI, acute kidney injury; APECHEII, acute physiology and chronic health evaluation II; BA, bilirubin adsorption; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MAP, mean arterial pressure; MELD, model for end-stage liver disease; PE, plasma exchange; SCr, serum creatinine; TB, total bilirubin

4. Discussion

It has been reported that severe hyperbilirubinemia was associated with increased mortality in patients underwent cardiac surgery.[10, 15, 17] Up to now, limited information was available on the risk factors associated with in-hospital and long-term mortality in AAD patients with post-operation severe hyperbilirubinemia. Our presented study had several findings. Firstly, the occurrence of AKI, the requirement for CRRT, and the in-hospital mortality were higher than previous studies of patients undergoing AAD surgery without severe hyperbilirubinemia. Secondly, age, preoperative SCr concentration, and CPB time were independent risk factors for postoperative AKI, and preoperative SCr concentration was an independent risk factor for post-operation CRRT as well. Finally, the peak TB

concentration, post-operation stage 3 AKI, the total amount of blood transfusion after AAD surgery, the use of ECMO, and low MAP after surgery were significantly associated with mortality.

4.1. AAD patients with severe hyperbilirubinemia were associated with worse prognosis

The analysis of our present cohort of AAD patients with post-operation severe hyperbilirubinemia showed an overall incidence of post-operation AKI of 81.9%, a requirement for CRRT of 18.5%, and the in-hospital mortality rate of 30.3%. In previous studies of AAD patients underwent surgical treatment without post-operation severe hyperbilirubinemia, the reported AKI incidences were ranged from 40–78%,[5–7, 18–23] the reported incidences of requirement for CRRT were ranged from 3% to 8%,[5, 7] and the reported in-hospital mortalities were ranged from 15–26%.[4, 5, 7, 19, 24] The discrepancy most likely attributed to the fact that all of the included AAD patients in our study developed severe hyperbilirubinemia. The development of severe hyperbilirubinemia after AAD surgery related to the severity of the AAD and the severity of injury during AAD operation. In animal model, hyperbilirubinemia was proved to have pro-apoptotic effects and aggravate renal ischemia-reperfusion injury.[25] Additionally, high concentration of bilirubin could lead to inflammatory response and cell apoptosis of the brain,[26] which might be one of the potential mechanism of the high mortality of our present cohort.

4.2. Risk factors of postoperative AKI and CRRT

In our present cohort, older age and high preoperative SCr concentration were identified as independent risk factors for AKI. Meanwhile, preoperative SCr concentration was also associated with the requirement of CRRT after AAD surgery. A recent meta-analysis of patients underwent AAD surgery[18] showed that older age was identified as an independent risk factor of AKI as well. Older age might deteriorate renal function by causing the adverse structural and functional changes of kidney, such as multiple abnormalities in water homeostasis, tubulopathy, interstitial fibrosis, progressive glomerulosclerosis, and afferent-efferent arteriolar shunts.[27] Therefore, older age-mediated adverse renal structural and functional changes might contribute to the high development of postoperative AKI after AAD surgery in older patients. The aforementioned meta-analysis showed that preoperative SCr concentration did not correlate with postoperative AKI with significant heterogeneity (I^2 = 72.8%). In our opinion, pre-operation elevated SCr concentration might indicate structural kidney damage or hemodynamic derangements in AAD patients, which further aggravated the development of post-operation AKI and the requirement of CRRT. Additionally, our result indicated pronged CPB time was a risk factor of postoperative AKI for AAD patients with post-operation severe hyperbilirubinemia as well, which was consistent with previous study.[7, 23] During CPB surgery, the high occurrence of intravascular hemolysis leaded to an acute rise of free hemoglobin, which could lead to increased intravascular nitric oxide consumption. And, the decrease of nitric oxide could cause kidney vascular constriction and renal perfusion reduction, and then caused tubular epithelial cell injury. Additionally, the increased renal perfusion after CPB might contribute to cell injury or cell death by the increase open of the mitochondrial permeability transition pores (mPTPs). Moreover, the increased production of reactive oxygen species was identified as another mechanism of

AKI after CPB.[28] Therefore, surgeons most likely could reduce the AKI risk of AAD patients by the improvement of their operation strategies and the reduction of CPB time.

4.3. Risk factors of in-hospital and long-term mortality

In previous studies, older age had been identified as an independent risk factor of mortality for patients with hyperbilirubinemia after cardiac surgery.[29] In our present study, older age was established a risk factor for in-hospital mortality for patients with hyperbilirubinemia after AAD surgery as well. Aging indicated diminished functional capacity of the liver and added to the cumulative burden in the case of developed hyperbilirubinemia. Additionally, different from the a recent study outlining the increased risk of mortality for patients with hyperbilirubinemia after cardiac surgery associated with time to peak bilirubin,[29] our study indicated that peak TB concentration was an independent driver of in-hospital mortality for patients with severe hyperbilirubinemia after AAD surgery. And, we found out that the optimal cut-off value of peak TB on predicting in-hospital mortality was 121.2 μmol/l. This difference might be attributed to the existence of severe hyperbilirubinemia after AAD surgery and the limitation of small sample size. In a study for patients with jaundice after open heart surgery, Chu et al.[30] reported patients with more severe hyperbilirubinemia or delayed serum peak TB concentration might be significantly associated with more transfused blood and hypotension. Increased amount of blood transfusions contributed to hemolysis, and hypotension would reduce hepatic perfusion[31], which both caused an increased bilirubin load. This might be one of the potential mechanisms that the number of transfused blood units and lower MAP increased mortality in our present study. Previous studies suggested that mechanisms underlying the development of post-operation late peak TB concentration differed from those of the early peak bilirubin concentration. The immediate development of post-operation peak TB concentration and rapid decline thereafter reflected the transient damaging effects by CPB surgery, whereas late development of post-operation peak TB concentration was a consequence of hepatic dysfunction caused by persistent cardiac failure or sepsis.[12, 32] Therefore, attention should be paid to the monitoring of heart failure and optimizing hemodynamics after AAD surgery to prevent further deterioration. Furthermore, identifying and implementing effective risk reduction strategies is needed. Molecular adsorbent recirculation system, prometheus therapy, fractionated plasma separation and adsorption have shown promise in reducing bilirubin concentration,[33, 34] but further study in this area is needed.

AKI had been incorporated into a risk tool to predict early mortality for patients underwent AAD surgery.[18] Our results added to these findings and demonstrated stage 3 AKI markedly increased both in-hospital and long-term mortality. A previous meta-analysis of cohort studies found that patients with AKI had higher risk of chronic kidney disease (CKD) and end-stage renal disease (ESRD), and the risk increased with the severity of AKI.[35] Although renal function following hospital discharge was not evaluated in our present study, it was possible that patients with AKI were more likely to have CKD or ESRD, subsequently with a higher probability of long-term mortality. Additionally, our study also showed in-hospital and long-term mortality was independently predicted by the use of ECMO. ECMO mainly applied to offer a temporary hemodynamic support for refractory cardiogenic shock, while patients

received ECMO most likely occurred irreversible myocardial injury and increased the risk of mortality during ECMO or after weaning from ECMO.[36, 37] Therefore, more careful postoperative management is needed to improve prognosis.

4.4. Study limitation

Our present study was a retrospective clinical research from a single institution and had some limitations. First, SCr concentration on admission was regard as preoperative renal function. However, some patients might already have AKI on admission. As a result, the number of patients with AKI may be underestimated. Second, the number of major adverse events including the use of ECMO, plasma exchange and bilirubin adsorption was small, which will be likely to reduce the statistical power for risk factor analysis. Finally, the renal prognosis was not regular followed up after the hospital discharge, which is important for the evaluation of the renal outcome. Therefore, further prospective multicenter studies with larger samples are needed to obtain stronger evidences.

5. Conclusion

Post-operation severe hyperbilirubinemia is a common clinical presentation in AAD surgery patients. Post-operation severe hyperbilirubinemia AAD patients with older age, lower MAP, increased blood transfusion, stage 3 AKI, the use of ECMO, and the increased peak TB had higher risk of in-hospital mortality. These patients most likely need more intensive monitoring.

Abbreivations

AAD	Stanford type A aortic dissection
AD	Aortic dissection
ACC	Aortic cross clamp
AKI	Acute kidney injury
APECHEII	Acute physiology and chronic health evaluation II
AUC-ROC	Area under the receiver operating characteristic curve
BA	Bilirubin adsorption
CI	confidence interval
CKD	Chronic kidney disease
CPB	Cardiopulmonary bypass
CRRT	Continuous renal replacement therapy
ECMO	Extracorporeal membrane oxygenation
ESRD	End-stage renal disease
IABP	Intra-aortic balloon pump
ICU	Intensive care unit;
KIDGO	Kidney Disease Improving Global Outcomes
MAP	Mean arterial pressure
MELD	Model for end-stage liver disease
mPTPs	Mitochondrial permeability transition pores
OR	Odds ratio
PE	Plasma exchange
SCr	Serum creatinine
SOFA	Sequential organ failure assessment
TB	Total bilirubin

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Declarations

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Declarations

Ethics approval and consent to participate

The local Institutional Review Board of the hospital approved this retrospective study and waived the requirement of informed consent for the use of patients' medical data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XC, MB, and LZ contributed equally to this work. XC, MB, SS, and XC conceived the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. LZ, LL, YL, and LZ performed statistical analyses and helped to draft the manuscript. WZ, LW, YW, MZ, and JH collected the data and revised the manuscript critically for important intellectual content. XC collected the data, performed statistical analyses and helped to revise the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Figures

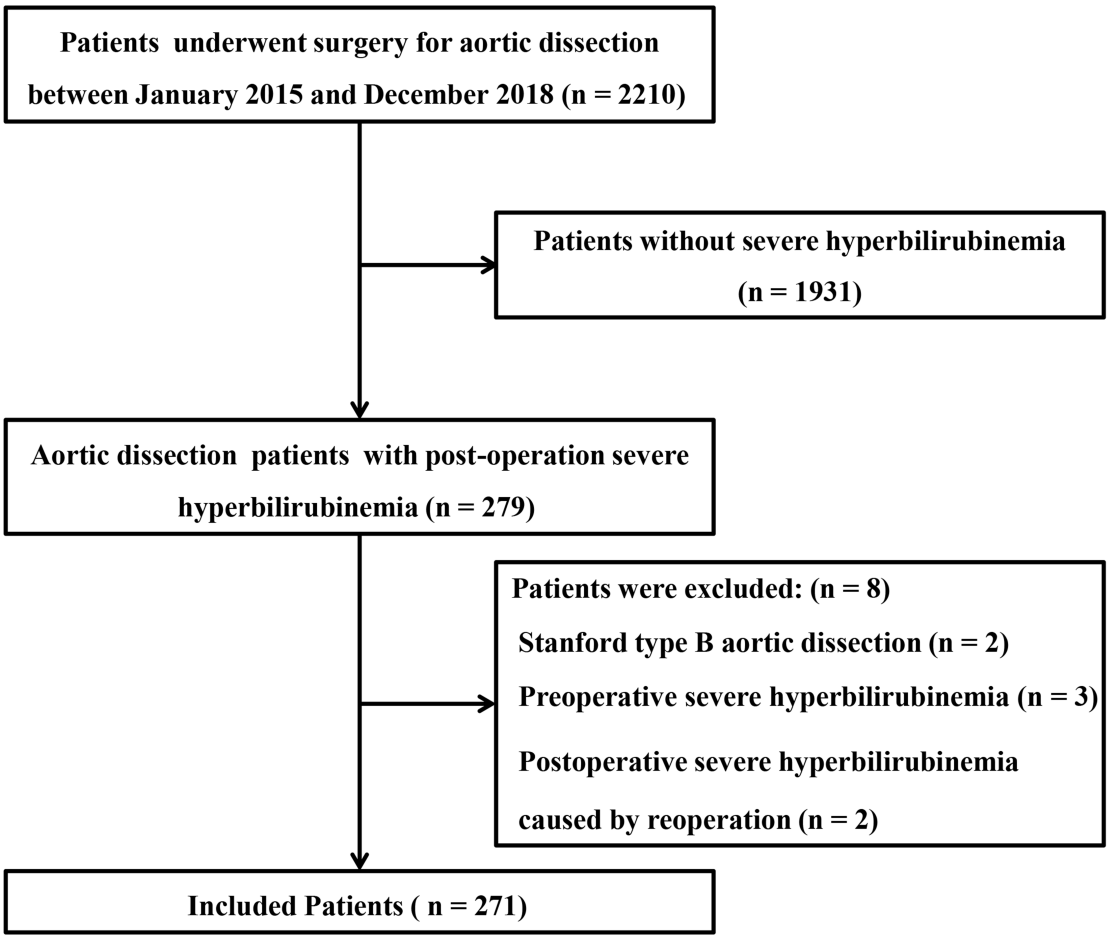

Figure 1

Patient inclusion flow chart

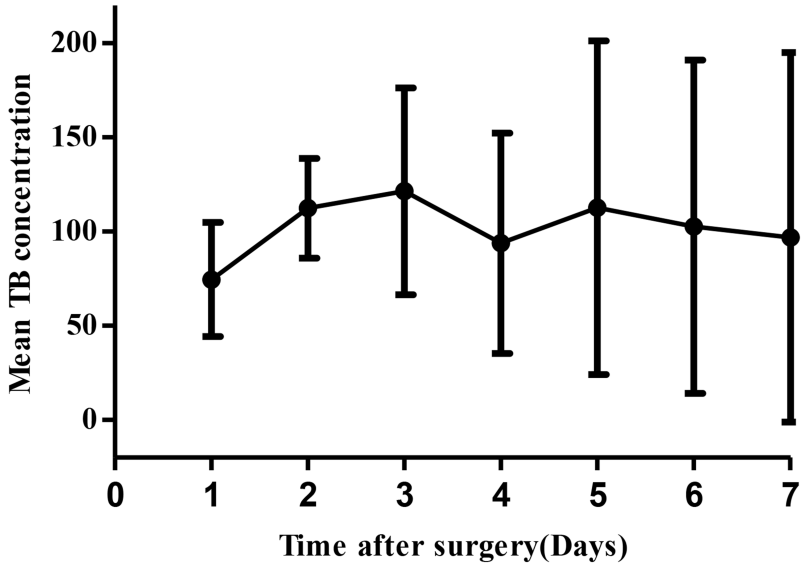

Figure 2

The averaged serum total bilirubin concentration during the postoperative seven days

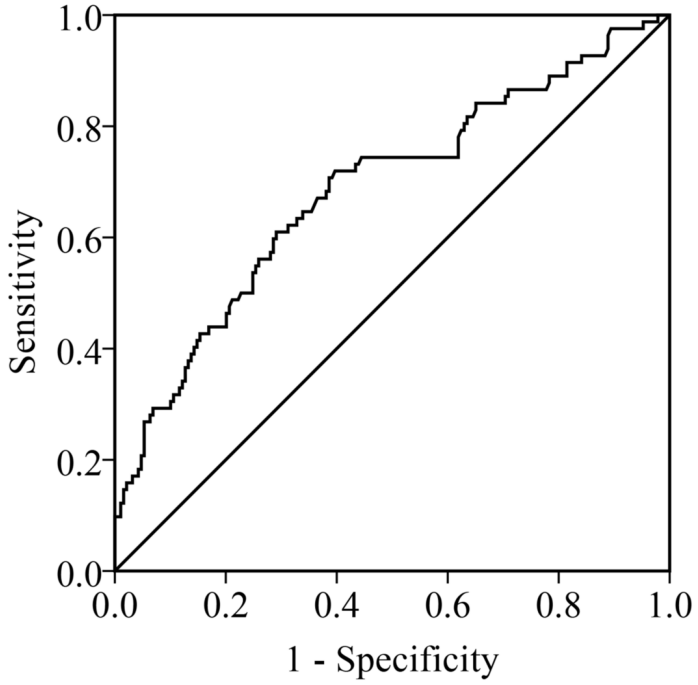

Figure 3

Receiver operator curve (ROC) of peak TB concentration predicting in-hospital mortality (area under the curve: 0.68, 95% CI: 0.614 - 0.758)

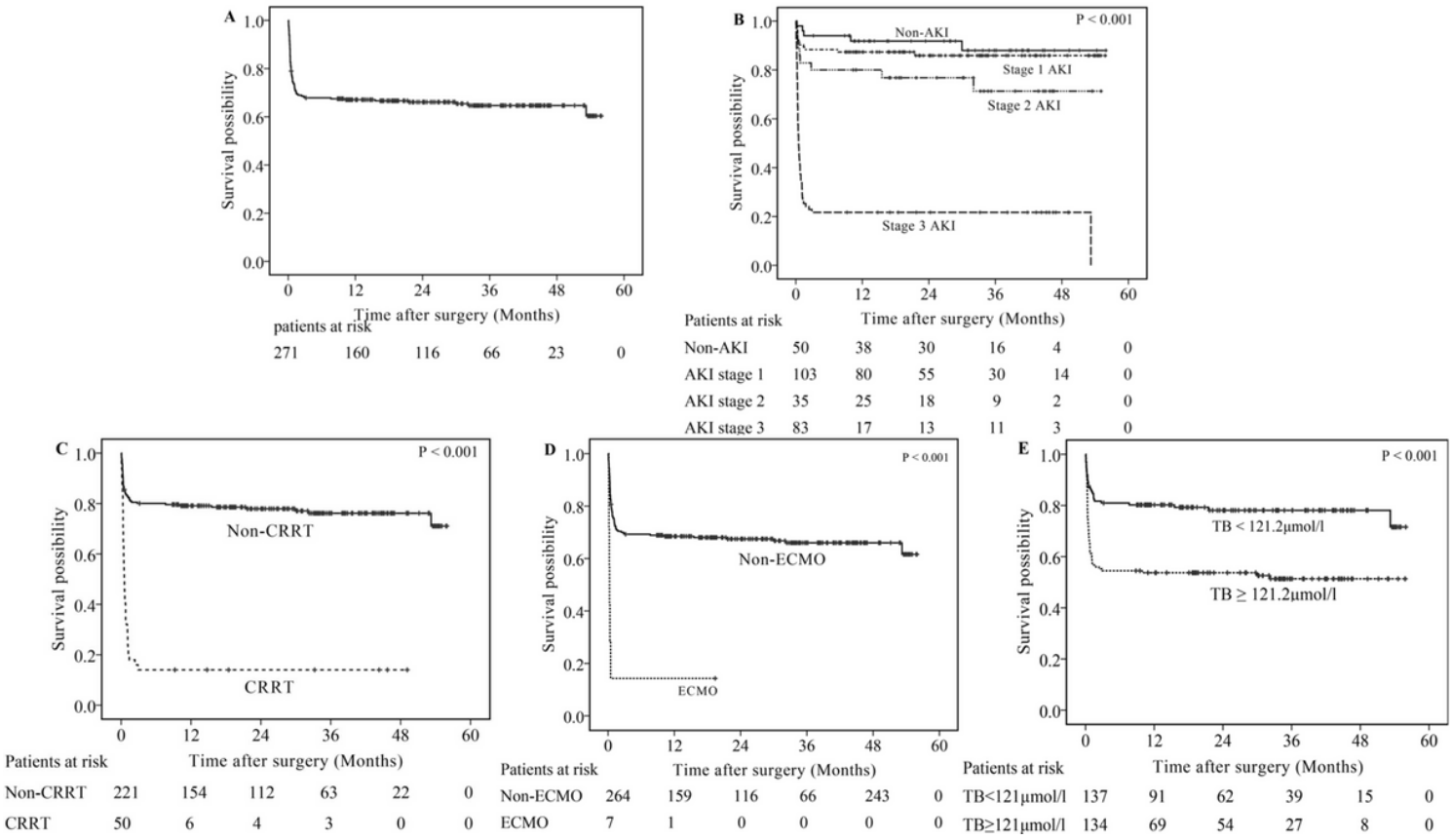

Figure 4

Long-term survival results of (A) all patients, (B) patients without AKI and those with stage 1, 2, or 3 AKI, (C) patients without the use of CRRT and those with CRRT, (D) patients without the use of ECMO and those with ECMO, (E) patients with post-operation peak TB ≥ 121.2 μmol/l and those with post-operation peak TB < 121.2 μmol/l.