

Article

Risk Factors of Hyperbilirubinemia after Acute Type A Aortic Dissection

Wenbo Yu¹, Yuan Liang¹, Junjian Yu², Jianfeng Gao¹, Wentong Li², Chennan Tian², Xuehong Zhong², Peijun Li², Ziyou Liu^{2,*}, Jianxian Xiong^{2,*}

¹First Clinical Medical College of Gannan Medical University, 341000 Ganzhou, Jiangxi, China

²Department of Cardiovascular Surgery, The First Affiliated Hospital of Gannan Medical University, 341000 Ganzhou, Jiangxi, China

*Correspondence: xiongjianxian@126.com (Jianxian Xiong); ziyoudoc@126.com (Ziyou Liu)

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Abstract

Objective: To explore the risk factors of hyperbilirubinemia after acute type A aortic dissection (ATAAD). **Methods:** Retrospective analysis of the data of 150 patients with ATAAD surgery in the First Affiliated Hospital of Gannan Medical University from 2021 to 2023. There were 117 males and 33 females. They were divided into patients according to the highest postoperative plasma total bilirubin level. Two groups, 85 cases in the hyperbilirubinemia group (HB group) total bilirubin (TBIL) $>51.3 \mu\text{mol/L}$; 65 cases in the non-hyperbilirubinemia group (NHB group) (TBIL $<51.3 \mu\text{mol/L}$). Two independent samples *t*-test was used to compare the two groups of samples, binary logistic regression analyzed the risk factors leading to postoperative HB, and the receiver operating characteristic (ROC) curve analyzed the critical values of the risk factors. **Result:** The incidence of postoperative HB was 56.7%. The preoperative plasma TBIL had an odds ratio (OR) of 1.213 (95% confidence interval (CI): 1.044–1.410, $p = 0.012$). The operation time had an OR of 1.019 (95% CI: 1.008–1.030, $p = 0.001$). The cardiopulmonary bypass (CPB) time had an OR of 1.053 (95% CI: 1.019–1.087, $p = 0.022$). The aortic cross-clamp time had an OR of 1.030 (95% CI: 1.006–1.055, $p = 0.015$). ROC curve analysis revealed critical values for preoperative plasma TBIL, operation time, CPB time, and aortic cross-clamp time as 12.95 $\mu\text{mol/L}$, 387.5 min, 190.5 min, and 117.5 min, respectively. **Conclusion:** HB is a frequently observed complication after surgery in patients with ATAAD, and it is associated with a poor prognosis. Several risk factors contribute to the increased occurrence of HB, including preoperative serum TBIL levels, operation time, CPB time, and aortic cross-clamp time.

Keywords

acute type A aortic dissection; hyperbilirubinemia; risk factors

Introduction

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular disease characterized by rapid onset and high mortality [1]. The mortality rate increases by 1% within 1 hour after onset, and without timely medical intervention, the mortality rate can reach as high as 30%–50% within 48 hours [2]. Sun's surgery [3], which involves total aortic arch artificial vascular replacement and stent-elephant trunk surgery, is currently considered the standard surgical procedure for treating ATAAD. However, this surgery is challenging, time-consuming, highly complex, and traumatic. Even with timely surgery, postoperative complications remain a significant factor affecting patient prognosis.

Hyperbilirubinemia (HB) is a common complication after cardiac surgery, particularly after ATAAD surgery, which involves a lengthy and challenging procedure with prolonged cardiopulmonary bypass (CPB) time. Bilirubin, a metabolite of heme, is normally excreted by the liver. However, during surgery, red blood cells are destroyed and hemolyzed, and there may be liver dysfunction, leading to excessive bilirubin production and abnormal excretion, resulting in its accumulation in the plasma. HB occurs when the concentration of total plasma bilirubin is too high. Since bilirubin itself is toxic to some extent, HB poses significant harm to the human body, impacting prognosis, and in severe cases, even jeopardizing the patient's life. The incidence of HB after cardiac surgery ranges from 10% to 40% and is associated with increased postoperative morbidity and mortality [4,5]. However, the specific cause of postoperative HB in ATAAD patients remains unclear, and there is a scarcity of relevant studies.

The purpose of this study was to retrospectively analyze the clinical data of patients who underwent surgery for acute type A aortic dissection (ATAAD) and investigate the risk factors associated with postoperative HB.

Materials and Methods

General Information

The clinical data of patients with ATAAD who underwent ascending aortic replacement + Sun's surgery in the First Affiliated Hospital of Gannan Medical University from January 2021 to November 2023 were collected. The study included patients of all genders and ages above 18 years old. Exclusion criteria for the study were patients who had undergone other types of cardiac surgery, secondary surgery, preoperative HB, chronic liver and renal insufficiency, or postoperative extracorporeal membrane oxygenation (ECMO) placement. Postoperative HB was defined as a postoperative plasma total bilirubin (TBIL) level greater than $51.3 \mu\text{mol/L}$. The patients were divided into two groups: the HB group and the non-hyperbilirubinemia (NHB) group. This study was approved by the hospital ethics committee.

Data Acquisition

The following data was collected for each patient: age, gender, smoking history, systolic blood pressure, diastolic blood pressure, preoperative D-dimer, preoperative white blood cells, preoperative alanine aminotransferase (ALT), preoperative aspartate aminotransferase (AST), preoperative creatinine, preoperative total bilirubin, preoperative direct bilirubin; intraoperative data such as operation time, CPB time, blocking time, and blood transfusion status; postoperative data including postoperative ALT, postoperative AST, postoperative creatinine, postoperative total bilirubin, and postoperative direct bilirubin.

Surgical Methods

After establishing extracorporeal circulation, the patient is cooled down to induce cardiac arrest. The ascending aorta is then blocked and incised, and the thrombus in the false lumen is removed. Cardioplegia is infused directly through the openings of the left and right coronary arteries, and the four-branch artificial blood vessel is connected to the aorta for arterial root anastomosis. Once the nasal temperature drops to 28°C , the brachiocephalic trunk artery, left common carotid artery, and left subclavian artery are individually blocked. At the same time, selective cerebral perfusion is performed through the right axillary artery, leading to circulatory arrest. The ascending aorta is incised up to the aortic arch and transected, and three bifurcated blood vessels are used. The proximal end of the left subclavian artery is sutured with 4/0 prolene sutures. An appropriate type of stent elephant trunk is selected and implanted into the true lumen of the descending aorta through the distal part of the aortic arch. The aortic arch tissue is trimmed to match the diameter of the stent elephant trunk.

During the operation, the stent is implanted in the distal descending aorta and anastomosed end-to-end with the distal end of the four-branch artificial blood vessel, with intermittent reinforcement. The artificial blood vessel perfuses the branches to restore circulation, and the corresponding three branches are first anastomosed to the left common carotid artery using continuous 5/0 prolene sutures. After opening the exhaust, rewarming is initiated to restore cardiac circulation, and finally, the brachiocephalic trunk artery and the left subclavian artery are anastomosed.

Statistical Analysis

Data analysis was performed using SPSS 26.0 software (IBM Corp., Chicago, IL, USA). Count data were presented as the number of cases and percentage (%), while measurement data were presented as mean \pm standard deviation ($\bar{x} \pm s$). A two independent samples *t*-test was used to compare groups, and predictors in the one-way analysis of variance (ANOVA) test were included in the binary logistic regression model to analyze risk factors for HB after ATAAD surgery. An receiver operating characteristic (ROC) curve was plotted to analyze the area under the curve and the critical values of the risk factors. Statistical significance was set at $p < 0.05$.

Result

This study examined 150 patients with acute type A aortic dissection who underwent ascending aorta replacement combined with Sun's surgery. Of the participants, 117 were male and 33 were female. Upon admission, the study cohort consisted of 88 cases with hypertension, 27 cases with diabetes, 5 cases with coronary atherosclerotic heart disease, 43 cases with pulmonary infection, 21 cases with shock, 1 case with celiac artery malperfusion, and 6 cases with pericardial effusion. In the HB group, the male to female ratio was 65/20, with an average age of 55.48 ± 12.23 years, the mean systolic blood pressure on admission was (138.55 ± 29.82) mmHg, with a corresponding mean diastolic blood pressure of (76.68 ± 20.97) mmHg and a smoking history rate of 38.82%. In the NHB group, the male to female ratio was 52/13, with an average age of 54.80 ± 9.66 years, the mean systolic blood pressure on admission was (131.32 ± 34.01) mmHg, with a mean diastolic blood pressure of (73.57 ± 18.55) mmHg and a smoking history rate of 43.08%. Postoperative hyperbilirubinemia occurred in 56.7% of cases, with 85 cases in the HB group and 65 cases in the NHB group. The HB group had significantly higher preoperative plasma total bilirubin levels ($p < 0.001$) compared to the NHB group. Additionally, the HB group had longer operation time ($p < 0.001$), CPB time ($p < 0.001$), and aortic cross-clamp time ($p < 0.001$) than the NHB group. No statistically significant differences were found in other indicators between the two groups (Table 1).

Table 1. Comparison of two groups of sample data.

Variable	Hyperbilirubinemia (n = 85)	Non-hyperbilirubinemia (n = 65)	p-value
Male/female ratio	65/20	52/13	
Age	55.48 ± 12.23	54.80 ± 9.66	0.71
Smoking habit	38.82%	43.08%	0.60
Systolic pressure, mmHg	138.55 ± 29.82	131.32 ± 34.01	0.17
Diastolic pressure, mmHg	76.68 ± 20.97	73.57 ± 18.55	0.35
D-dimer, mg/L	18.41 ± 24.53	20.89 ± 23.20	0.53
Preoperative white blood cells, ×10 ⁹ /L	12.54 ± 4.19	13.87 ± 4.61	0.07
Preoperative ALT, U/L	19.27 ± 10.81	22.69 ± 19.38	0.17
Preoperative AST, U/L	30.32 ± 19.65	47.22 ± 71.98	0.07
Preoperative creatinine, μmol/L	118.72 ± 134.30	116.68 ± 102.43	0.92
Preoperative TBIL, μmol/L	14.32 ± 4.92	10.98 ± 3.17	0.00
Preoperative DBIL, μmol/L	5.18 ± 1.95	4.25 ± 1.16	0.00
Preoperative IBIL, μmol/L	9.14 ± 3.46	6.74 ± 2.45	0.00
Postoperative ALT, U/L	93.55 ± 447.09	64.85 ± 109.96	0.61
Postoperative AST, U/L	169.51 ± 563.43	165.74 ± 266.04	0.96
Postoperative creatinine, μmol/L	157.42 ± 73.34	150.15 ± 85.50	0.58
Postoperative TBIL, μmol/L	72.36 ± 16.17	29.72 ± 10.21	0.00
Postoperative DBIL, μmol/L	42.49 ± 14.02	16.35 ± 8.06	0.00
operation time, min	455.20 ± 77.37	340.11 ± 43.04	0.00
CPB time, min	215.42 ± 40.23	169.23 ± 19.43	0.00
Aortic cross-clamp time, min	122.75 ± 29.66	103.46 ± 20.22	0.00
RBC, U	3.38 ± 2.37	2.72 ± 1.40	0.05
Plasma transfusion, mL	422.35 ± 148.10	397.69 ± 138.47	0.30

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; RBC, red blood cell; CPB, cardiopulmonary bypass.

Table 2. Logistic regression analysis of risk factors.

Risk factors	OR	95% CI	p-value
Preoperative TBIL	1.213	1.044–1.410	0.012
Operation time	1.019	1.008–1.030	0.001
CPB time	1.053	1.019–1.087	0.002
Aortic cross-clamp time	1.030	1.006–1.055	0.015

OR, odds ratio; CI, confidence interval.

Predictive factors were analyzed using binary logistic regression, and it was found that preoperative plasma TBIL (odds ratio (OR): 1.213, 95% confidence interval (CI): 1.044–1.410, $p = 0.012$), operation time (OR: 1.019, 95% CI: 1.008–1.030, $p = 0.001$), CPB time (OR: 1.053, 95% CI: 1.019–1.087, $p = 0.002$), and aortic cross-clamp time (OR: 1.030, 95% CI: 1.006–1.055, $p = 0.015$) were significant predictors of postoperative HB (Table 2).

The preoperative plasma TBIL had a critical value of 12.96 μmol/L, with an area under the curve of 0.707. The critical value for operation time was 387.5 minutes, with an area under the curve of 0.914. The critical value for CPB time was 190.5 minutes, with an area under the curve of 0.885. The critical aortic cross-clamp time was 117.5 minutes, with an area under the curve of 0.714 (Table 3, Fig. 1).

Yoden Index: The Youden index is a method used to assess the accuracy of a screening test, particularly when

false negatives and false positives are considered equally harmful. It is calculated by adding sensitivity and specificity and then subtracting 1. This index reflects the overall effectiveness of a screening method in distinguishing true patients from non-patients. A higher index value indicates a better screening test with increased accuracy.

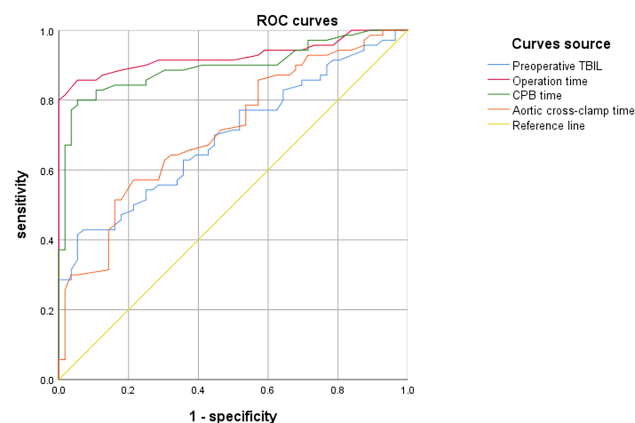


Fig. 1. The ROC curve of preoperative total bilirubin, operation time, CPB time and blocking time was analyzed. ROC, receiver operating characteristic.

Table 3. The critical value of ROC curve of risk factors.

Risk factors	Yoden Index	Critical value	Areas under curve
Preoperative TBIL	0.422	12.95	0.707
Operation time	0.778	387.50	0.914
CPB time	0.695	190.50	0.885
Aortic cross-clamp time	0.338	117.50	0.714

The postoperative hospitalization time for patients in the HB group was (28.30 ± 19.13) days, with an intensive care unit (ICU) hospitalization time of (101.75 ± 54.42) hours. In comparison, patients in the NHB group had a hospitalization time of (20.75 ± 11.55) days and ICU hospitalization time of (89.20 ± 53.47) hours. The difference between the two groups was statistically significant. The mortality rate for patients in the HB group during hospitalization was 2.35%, while the remaining patients were successfully treated and discharged with positive follow-up outcomes.

Discussion

HB is a common complication following surgery for ATAAD and is associated with increased mortality [6]. In this study, the incidence of HB after ATAAD surgery was found to be 55.6%, which is significantly higher compared to patients undergoing valve repair or replacement (36.2%) and coronary artery bypass grafting during the same period (34.1%) [7]. The higher incidence in ATAAD surgery can be attributed to its more challenging nature, longer operation time, and prolonged intraoperative CPB time, which result in greater damage to red blood cells and more severe liver dysfunction. The destruction of red blood cells leads to the production of bilirubin during hemoglobin metabolism, and impaired liver function hinders the proper excretion of bilirubin, thereby increasing the occurrence of postoperative HB.

This study demonstrates that operation time, CPB time, and aortic cross-clamp time are risk factors for HB after ATAAD. Prolonged operation time results in increased tissue exudation and bleeding, as well as intraoperative destruction and loss of red blood cells and coagulation factors [8]. This further contributes to postoperative multi-organ dysfunction, including liver dysfunction, which leads to elevated bilirubin levels. An *et al.*'s study [9] also found that prolonged operation time is an independent risk factor for postoperative HB, aligning with our findings. During ATAAD surgery, organ and tissue hypoperfusion can occur, causing damage. Prolonged operation time exacerbates the damage to organs and tissues, particularly liver function, ultimately resulting in postoperative HB.

Extracorporeal circulation is a vital procedure in the surgical treatment of ATAAD [10]. However, due to its non-physiological nature, CPB can trigger a series of stress

and inflammatory reactions in the body, potentially exacerbating liver damage and hepatocellular HB [11]. Liver cell destruction, micro-emboli, cytotoxic substances, and inadequate local perfusion during extracorporeal circulation contribute to liver dysfunction. Furthermore, CPB-induced hemodilution can reduce tissue oxygen delivery and result in ischemic injury [12]. Additionally, extracorporeal circulation causes mechanical damage to red blood cells and triggers systemic inflammatory responses, leading to red blood cell destruction [13]. These factors contribute to the excessive accumulation of bilirubin in the plasma, ultimately leading to HB. Studies have shown that prolonged CPB time is a risk factor for liver dysfunction following aortic dissection [14]. Longer CPB duration increases hemolysis, alters visceral perfusion, and intensifies inflammation. CPB can also induce hypoperfusion, hypoxia, or inflammatory reactions in abdominal organs, thereby causing liver and kidney damage [6].

Preoperative serum TBIL is an independent risk factor for postoperative HB after ATAAD. Poor liver perfusion during the progression of ATAAD affects the blood supply to the liver, resulting in liver dysfunction. This impairment in the liver's ability to excrete bilirubin leads to an increase in total plasma bilirubin concentration. Elevated preoperative plasma TBIL levels can indicate the presence of preoperative liver dysfunction in ATAAD patients and may also serve as an indicator of the severity of dissection and predict the occurrence of postoperative HB.

The mechanisms underlying the complications and poor prognosis associated with HB are intricate and not yet fully understood [11]. Bilirubin itself possesses a certain level of toxicity, leading to an accumulation of bilirubin in the bloodstream. In mild cases, this can result in severe jaundice, while in severe cases, it can even pose a life-threatening risk to patients. Moreover, the buildup of bilirubin in the liver exacerbates liver damage. Elevated bilirubin levels can initiate cellular oxidative stress and trigger cell apoptosis [15], contributing to various pathological processes. For instance, it induces inflammatory responses and apoptosis in the brain [16], alveolar epithelial cell apoptosis leading to pulmonary edema and injury [17], and can worsen renal ischemia-reperfusion injury [18]. Consequently, HB following ATAAD not only impacts the patient's prognosis and prolongs hospitalization and intensive care unit (ICU) monitoring time but also diminishes the patient's survival rate.

Conclusion

Postoperative HB is a frequently observed complication in patients with ATAAD following surgery. It is associated with a high incidence rate, unfavorable prognosis, and extended hospitalization and ICU monitoring and treatment duration. Our study reveals that several factors, including preoperative serum TBIL levels, operation time, CPB time, and aortic cross-clamp time, contribute to the development of HB in these patients.

Abbreviations

ATAAD, acute type A aortic dissection; HB, hyperbilirubinemia; TBIL, total bilirubin; OR, odds ratio; CI, confidence interval; CPB, cardiopulmonary bypass; DBIL, direct bilirubin; IBIL, indirect bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit.

Availability of Data and Materials

The raw data supporting the conclusions of this article will be made available by the corresponding authors.

Author Contributions

The literature review and manuscript were conducted by WY. WY and YL collected the data. JY, WL, CT and ZL conceptualized the research direction and provided guidance in writing. XZ and PL provided medical records. JG compiled the overall clinical data of the patients involved in the research. JX developed the study concept and reviewed and edited the initial draft. All authors contributed to and approved the submitted manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study obtained the informed consent of the patient and signed the informed consent form. All procedures and data collection involving human participants were performed in accordance with the ethical standards of the First Clinical Medical College of Gannan Medical University and National Research Committee (s) and with the Helsinki Declaration (as revised in 2013). Ethics approval number(s)/ID(s) is LLSC-2023 NO.412.

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Conflict of Interest

The authors declare no conflict of interest.

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