Prediction Model For Postoperative Severe Acute Lung Injury In Patients Undergoing Acute Type A Aortic Dissection Surgery

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Abstract

Objective: This study aimed to establish a risk assessment model to predict postoperative severe acute lung injury (ALI) risk in patients with acute type A aortic dissection (ATAAD). *Methods*: Consecutive patients with ATAAD admitted to our hospital were included in this retrospective assessment and placed in the postoperative severe ALI and non-severe ALI groups based on the presence or absence of ALI within 72 h postoperatively (oxygen index (OI) [?]100 mmHg). Patients were then randomly divided into training and validation groups in a ratio of 8:2. Logistic regression analyses were used to statistically assess data and establish the prediction model. The prediction model's effectiveness was evaluated via tenfold cross-validation of the validation group to facilitate construction of a nomogram. *Results*: After screening, 479 patients were included in the study: 132 (27.5%) in the postoperative severe ALI group and 347 (72.5%) in the postoperative non-severe ALI group. Based on logistics regression analyses, the following variables were included in the model: coronary heart disease (CHD), cardiopulmonary bypass (CPB) [?]257.5 min, left atrium (LA) diameter [?]35.5 mm, hemoglobin [?]139.5 g/L, preCPB OI [?]100 mmHg, intensive care unit (ICU) OI [?]100 mmHg, left ventricular posterior wall thickness (LVPWT) [?]10.5 mm, and neutrophilic granulocyte percentage (NEUT) [?]0.824. The area under the receiver operating characteristic (ROC) curve of the modeling group was 0.805, and differences between observed and predicted values were not deemed statistically significant via the Hosmer–Lemeshow test (χ2=6.037, df=8, P=0.643). For the validation group, the area under the ROC curve was 0.778, and observed and predicted value differences were insignificant when assessed using the Hosmer–Lemeshow test (χ ^{2}=3.3782, df=7; P=0.848). The average tenfold cross-validation score was 0.756. *Conclusions*: This study established a prediction model and developed a nomogram to determine the risk of postoperative severe ALI after ATAAD. Variables used in the model were easy to obtain clinically and the effectiveness of the model was good.

Introduction

Acute type A aortic dissection (ATAAD) is a cardiovascular disease that requires urgent care. Emergency surgery is currently the primary treatment option for patients with ATAAD. Despite continual improvements in surgical techniques and perioperative management strategies, postoperative complications including paraplegia, stroke, acute kidney injury, low cardiac output syndrome, and acute lung injury (ALI) are common.[1] In particular, the incidence of postoperative ALI after ATAAD is 30–50%.[2]Perioperative ALI significantly increases postoperative mortality, mechanical ventilation duration, intensive care unit (ICU) stay duration, and hospitalization cost in patients who undergo ATAAD repair, and outcomes are poor.[3] Currently, variables included in the commonly used ALI score scales including LIPS and Murray are insufficient for predicting ALI occurrence after ATAAD. In addition, due to the lack of effective treatments for severe ALI, early identification of patients at high risk of developing ALI after ATAAD is highly important because it facilitates early intervention, and this prevents the progression to severe ALI. This study aimed to analyze risk factors of severe ALI after ATAAD and establish a prediction model that facilitates the identification of high-risk patients in order to allow physicians to make timely medical decisions.

Methods

Study design

This study involved the retrospective assessment of data from 522 consecutive patients who underwent ATAAD at our Hospital from September 2017 to June 2021, including patients who were diagnosed at our hospital and those who were transferred to our center from other hospitals. All patients were diagnosed using transthoracic echocardiography (TTE) and computed tomography angiography. The following exclusion criteria were applied: history of lung diseases (chronic obstructive pulmonary disease, asthma, lung tumor, respiratory failure); New York class III or IV; preoperative liver and kidney insufficiency; severe neurological and psychiatric disease; history of nonsteroidal anti-inflammatory drug and hormone therapy; and died within 48 h post-surgery. Overall, 479 patients were included after the exclusion criteria were applied. Based on the Berlin definition,[4] ALI severity was classified as follows: mild ALI (200 mmHg < oxygen index [OI] [?] 300 mmHg), moderate ALI (100 mmHg < OI [?] 200 mmHg), and severe ALI (OI [?] 100 mmHg). Patients were placed in postoperative severe and non-severe ALI groups according to whether severe ALI occurred within a 72-h postoperative period. Ethical approval for this study (Identifier: 2020-298H-1) was provided by the Guangdong Provincial People's Hospital's Clinical Research Ethics Committee on July 8, 2021. Due to the retrospective retrieval of the patients data, the informed consent was waived.

Data collection

Data from our institution were preferentially considered compared to those from other institutions in order to eliminate selection bias in data from different hospitals. If patients who had been transferred were unable to undergo examination at our institution owing to their critical condition, data collected at other institutions were used. Perioperative data of all patients, including general characteristics, disease history, comorbidities, physical examination findings, laboratory test results, imaging data, and outcomes, were collected, entered by specialists, and reviewed by experienced and senior doctors.

Statistical analysis

Patient data were divided between training (384 patients) and validation datasets (95 patients) at a ratio of 8:2 using simple random sampling. Normally distributed continuous variables (expressed as means and standard deviations) were compared using two-sample t-tests. Non-normally distributed variables (expressed as medians and interquartile range [IQR]) were compared using the Mann–Whitney U test. Categorical variables (expressed as frequency and percentage) were analyzed using χ^2 or Fisher's exact tests. All non-binary variables were dichotomized via univariable logistic regression, and optimal cut-off points were estimated via receiver operating characteristic (ROC) curve analysis and determined based on the maximum Youden index. Stepwise multivariate analysis was performed to identify variables that were independently associated with severe postoperative ALI. Odds ratios (ORs) were presented with corresponding 95% confidence intervals (CIs), and P-values were considered statistically significant at $P < 0.05$. Variables with values of $P < 0.05$ were included in a multivariate logistic regression, as follows:

$$logit\ p = ln\left[p/(1 - p)\right] = B0X0 + B1X1 + \cdots + BkXk,$$

Where p denotes postoperative severe ALI, and each B value is expressed as a coefficient of an independent risk factor in the final model for a particular risk. Observed and predicted incidence of postoperative severe ALI was compared. The model was calibrated using the validation dataset and assessed using the area under the ROC curve. The goodness of fit of the final model was tested using the Hosmer–Lemeshow test, and tenfold cross-validation was conducted by randomly dividing the dataset into 10 equally sized samples, refitting the model to each of the 10 sets comprising 90% of the data, calculating the area under the ROC curve for the unused 10% in each case, and averaging 10 areas under ROC curves. We excluded variables with missing rates that were >20%. Furthermore, missing data were not filled in. Statistical analyses were performed using SAS software (version 9.4; Cary, NC, USA).

Results

Patient inclusion

Overall, 522 patients were enrolled in the study, of which 43 were excluded due to preoperative severe hepatic and renal insufficiency, cardiac insufficiency, neuropsychiatric complications, or death within 48 hours after surgery. Overall, 479 patients were included.

Baseline characteristics

The incidence of postoperative severe ALI was 27.5% in this study, which included 404 male (84.3%) and 75 female patients (15.7%), with a mean age of 51.96 $\pm$ 10.75 years. Postoperative non-severe and severe ALI groups contained 347 and 132 patients, respectively. Surprisingly, patients in the postoperative non-severe ALI group appeared to be older than those in the postoperative severe ALI group (52.48 $\pm$ 10.77 versus 50.61 $\pm$ 10.61, respectively; P = 0.089); however, the difference was not statistically significant. In the postoperative severe ALI group, more patients were obese, and more patients had hypertension and coronary heart disease (CHD) compared to the non-severe ALI group (Table 1).

[Insert Table 1 here]

Preoperative laboratory and TTE findings

Preoperative laboratory and TTE findings of patients in the severe and non-severe ALI groups are shown in Table 2. The following parameters were determined to be significantly associated with postoperative severe ALI: albumin [?] 35.34 mg/L, aspartate aminotransferase [?] 22.5 U/L, glucose [?] 6.44 mmol/L, serum creatinine [?] 105.16 µmol/L, hemoglobin [?] 139.5 g/L, neutrophilic granulocyte percentage (NEUT) [?] 0.824, D-Dimer [?] 4,835 ng/mL, TT [?] 18.45 s, left atrium (LA) diameter [?] 35.5 mm, left ventricular posterior wall thickness (LVPWT) [?] 10.5 mm, left ventricular diastolic dysfunction.

[Insert Table 2 here]

Intraoperative data and clinical outcomes

When postoperative non-ALI and ALI groups were compared, the following intraoperative and clinical outcome data significantly differed: cardiopulmonary bypass (CPB) duration [?] 257.5 min, preCPB OI [?] 100 mmHg, ICU OI [?] 100 mmHg, ICU lactate [?] 3.75 mmol/L, and delayed chest closure. Aortic cross clamp (ACC) and deep hypothermic circulatory arrest (DHCA) duration, intraoperative transfusion volume, lowest nasopharyngeal temperature, and lowest rectal temperature did not affect the occurrence of postoperative severe ALI. Patients in the postoperative severe ALI group had higher postoperative mortality rates, and longer ICU stay, hospital stay, and mechanical ventilation durations than those in the non-severe ALI group. Further, patients in the postoperative severe ALI group had an increased incidence of postoperative adverse events, such as tracheotomy, reintubation, low cardiac output syndrome, and stroke (Table 3).

[Insert Table 3 here]

Prediction model training, calibration, and effectiveness

The above statistically significant variables were incorporated into the multivariable logistics regression analysis to identify those variables that were independent risk factors for postoperative severe ALI (Table 4).

[Insert Table 4 here]

Based on the results of the multiple regression analysis, a risk-scoring model was established. The formula used to determine the preoperative risk score was as follows:

logit p = ln [p/(1 - p)] = -2.974 + 1.497 × (CHD) + 0.938 × (CPB duration [?] 257.5 min) + 0.722 x (LA diameter [?] 35.5 mm) - 0.814 x (hemoglobin [?] 139.5 g/L) + 0.771 x (ICU OI [?] 100 mmHg) + 0.953 x (LVPWT [?] 10.5 mm) + 0.869 x (NEUT [?] 0.824) + 0.976 x (preCPB OI [?] 100 mmHg).

The area under the ROC curve of the model was 0.805 (95% CI: 0.746–0.864), and the Hosmer–Lemeshow goodness of fit for the logistic regression model was determined to be significant ($\chi 2 = 6.037$, df = 8, P = 0.643) (Figure 1). The model was used to predict which patients should be placed in the validation group and to evaluate its calibration and discrimination. The area under the ROC curve of the validation group was 0.778 (95% CI: 0.667–0.889), and the Hosmer–Lemeshow test showed that the optimal cut-off value was 0.848 ($\chi 2 = 3.3782$, df = 7) (Figure 2). The resulting average area of tenfold cross-validation was 0.756 (range, 0.628–0.839), which was very similar to the results produced via assessment of the validation set.

[Insert Figures 1 and 2 here]

Nomogram creation for predicting postoperative severe ALI

Based on the characteristics of patients in the training group that were predictive of postoperative severe ALI, a nomogram was developed. Eight independent predictors of postoperative severe ALI were used (Figure 3). Each factor in the nomogram received an individual score according to the value of the factor, and a total score was obtained by summarizing the scores of eight factors used to estimate postoperative severe ALI risk. A bootstrap method with 1,000 repetitions was used to test the nomogram, and a calibration curve revealing the probability that the nomogram accurately estimated postoperative severe ALI risk was created (Figure 4).

[Insert Figures 3 and 4 here]

Discussion

ATAAD progresses rapidly, and the surgical procedure used to treat the condition is complex and difficult to perform. Therefore, postoperative lung injury after ATAAD repair is not rare. Studies have shown that the incidence of severe ALI after surgery is 15.9–36.6%[3, 5] , which is in line with our results. In this study, a prediction model for severe ALI after ATAAD was successfully established, and its effectiveness was evaluated. Finally, a nomogram was constructed. Since all preoperative data used in this study were findings that were determined upon admission to the emergency room, our prediction model may potentially better facilitate the identification of patients at high risk of postoperative severe ALI than those that have been described previously.[6] This will facilitate the early diagnosis of postoperative severe ALI, and allow clinicians to provide timely treatment.

In previous studies, different methods were used to designate postoperative ALI and postoperative non-ALI groups. Most studies distinguished patients based on OI values > or [?] 200 mmHg at 24 h or 48 h post-surgery.[2, 7] Some patients did not develop lung injury immediately after surgery. Further, the incidence of mild and moderate ALI after surgery was close to 50%, and there was no significant difference between mild, moderate, and non-ALI patients regarding prognosis. Contrastingly, mortality and postoperative complication rates of patients with and without severe ALI differed.[8, 9] Therefore, in this study, groups were designated based on at least one occurrence of OI [?] 100 mmHg in arterial blood gas analysis within a 72-h period post-surgery, and we were able to show that the model obtained using this grouping method showed good calibration and discrimination.

The mechanism by which ALI forms after ATAAD has not been completely elucidated; however, it is generally believed that inflammation plays an important role in the process. Some inflammatory factors such as C-reactive protein (CRP), interleukin-6 (IL-6), and white blood cell count have been confirmed to be related to ALI after ATAAD.[10, 11] However, the role of neutrophils, which are key contributors to acute inflammatory responses that are associated with adverse outcomes in various cardiovascular diseases,[12, 13] remain unclear. In this study, CRP and IL-6 levels were not statistically analyzed due to their high missing rates. However, we found that a NEUT level of [?] 0.824 was a risk factor for severe ALI after ATTAD and incorporated the parameter into the model after multivariate analysis. There have been many studies on the influence of CPB duration on the occurrence of adverse events after aortic dissection surgery.[14] In our study, patients with a CPB duration of [?] 257.5 min were more likely to suffer severe ALI after surgery than those with a CBP duration of < 257.5. Decreased hemoglobin levels have been associated with poor prognosis in a variety of cardiovascular diseases.[15-17] However, interestingly, hemoglobin levels of [?] 139.5 g/L were determined to be associated with a reduction in postoperative severe ALI risk in this study.

TTE is widely used to evaluate patients with ATAAD as it is non-invasive, is a convenient bedside operation, and has high sensitivity and specificity in the diagnosis of ATTAD[18] . Compared with previous studies,[6, 19] this study innovatively assessed and evaluated the influence of preoperative echocardiographic data of patients. After analysis, it was concluded that an LA diameter [?] 35.5 mm and LVPWT [?] 10.5 mm were independent risk factors for severe ALI after surgery (OR: 2.384, 95% CI: 1.167–5.763, P = 0.019). However, elucidation of the mechanism by which LA diameter and LVPWT contribute to ALI require further studies.

In our study, the length of ICU stay and duration of mechanical ventilation were significantly higher than those reported previously. We believe that as an authoritative cardiovascular center in the southern region, the preoperative condition of ATAAD patients admitted to our hospital tends to be severe, and in addition to ALI, a relatively high proportion of patients experience complications that contribute to difficulties associated with removal of tracheal intubation postoperatively, such as low cardiac output, stroke, and delirium. For such patients, we time tracheal intubation removal conservatively. Therefore, the average length of ICU stay and the duration of mechanical ventilation were longer in this study compared to those of previous studies.

This study has several limitations. First, it was a single-center, retrospective study, which may have led to a selection bias. Second, the end point assessed was the occurrence of severe ALI within the 72-h period that followed surgery, but the status of patients with severe ALI after discharge was not followed-up. Additional studies are needed to explore the impact of severe ALI after ATAAD on the long-term patient survival.

Conclusion

This study identified the following as risk factors for severe ALI after ATAAD: CHD, CPB duration [?] 257.5 min, LA diameter [?] 35.5 mm, hemoglobin [?] 139.5, ICU OI [?] 100 mmHg, LVPWT [?] 10.5 mm, NEUT [?] 0.824, and preCPB OI [?] 100 mmHg. The identified factors were included in a prediction model, and a nomogram was drawn to facilitate risk assessment. The variables identified are easy to obtain in clinical settings and will allow clinicians to predict the occurrence of severe ALI after ATAAD more rapidly and effectively.

References

1.Wei J, Chen Z, Zhang H, Sun X, Qian X, Yu C. In-hospital major adverse outcomes of acute Type A aortic dissection. *Eur J Cardiothorac Surg.*2019;55:345-350.

2.Liu N, Zhang W, Ma W, Shang W, Zheng J, Sun L. Risk factors for hypoxemia following surgical repair of acute type A aortic dissection.*Interact Cardiovasc Thorac Surg.* 2017;24:251-256.

3.Gong M, Wu Z, Xu S, et al. Increased risk for the development of postoperative severe hypoxemia in obese women with acute type A aortic dissection. *J Cardiothorac Surg.* 2019;14:81.

4.Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307:2526-2533.

5.Su IL, Wu VC, Chou AH, et al. Risk factor analysis of postoperative acute respiratory distress syndrome after type A aortic dissection repair surgery. *Medicine (Baltimore).* 2019;98:e16303.

6.Ge H, Jiang Y, Jin Q, Wan L, Qian X, Zhang Z. Nomogram for the prediction of postoperative hypoxemia in patients with acute aortic dissection.*Bmc Anesthesiol.* 2018;18:146.

7.Wang Y, Xue S, Zhu H. Risk factors for postoperative hypoxemia in patients undergoing Stanford A aortic dissection surgery. *J Cardiothorac Surg.* 2013;8:118.

8.Zhou J, Pan J, Yu Y, et al. Independent risk factors of hypoxemia in patients after surgery with acute type A aortic dissection. *Ann Palliat Med.* 2021.

9.Chen MF, Chen LW, Cao H, Lin Y. Analysis of risk factors for and the prognosis of postoperative acute respiratory distress syndrome in patients with Stanford type A aortic dissection. *J Thorac Dis.*2016;8:2862-2871.

10.Girdauskas E, Kuntze T, Borger MA, et al. Acute respiratory dysfunction after surgery for acute type A aortic dissection. *Eur J Cardiothorac Surg.* 2010;37:691-696.

11.Yuan SM. Profiles and Predictive Values of Interleukin-6 in Aortic Dissection: a Review. *Braz J Cardiovasc Surg.* 2019;34:596-604.

12.Liew PX, Kubes P. The Neutrophil's Role During Health and Disease.*Physiol Rev.* 2019;99:1223-1248.

13.Bhutta H, Agha R, Wong J, Tang TY, Wilson YG, Walsh SR. Neutrophil-lymphocyte ratio predicts medium-term survival following elective major vascular surgery: a cross-sectional study. *Vasc Endovascular Surg.*2011;45:227-231.

14.Zhang K, Pan XD, Dong SB, et al. Cardiopulmonary bypass duration is an independent predictor of adverse outcome in surgical repair for acute type A aortic dissection. *J Int Med Res.* 2020 Nov 2020;48:1220768002.

15.Cattadori G, Agostoni P, Corrà U, et al. Heart failure and anemia: Effects on prognostic variables. *Eur J Intern Med.* 2017;37:56-63.

16.Wang Y, Qiao T, Zhou J. The short-term prognostic value of serum platelet to hemoglobin in patients with type A acute aortic dissection.*Perfusion.* 2020:1054062802.

17.Grammer TB, Kleber ME, Silbernagel G, et al. Hemoglobin, iron metabolism and angiographic coronary artery disease (The Ludwigshafen Risk and Cardiovascular Health Study). *Atherosclerosis.* 2014;236:292-300.

18.Sobczyk D, Nycz K. Feasibility and accuracy of bedside transthoracic echocardiography in diagnosis of acute proximal aortic dissection.*Cardiovasc Ultrasound* . 2015;13:15.

19.Ju F, Liu N, Pan XD, et al. [A prediction model for severe postoperative hypoxemia after surgery for Standford type A aortic dissection].*Zhonghua Yi Xue Za Zhi.* 2016;96:1001-1006.

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