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A nomogram for predicting low cardiac output syndrome in older patients undergoing acute type A aortic dissection surgery

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Abstract. – OBJECTIVE: Low cardiac output syndrome (LCOS) is a dangerous postoperative complication in patients with acute type A aortic dissection (ATAAD). This study aims to develop and evaluate a nomogram model that can reliably identify risk variables for postoperative LCOS in elderly patients suffering from ATAAD.

PATIENTS AND METHODS: In this retrospective study, a total of 310 elderly patients with ATAAD admitted to Fujian Medical University Union Hospital were included and categorized into the LCOS and non-LCOS groups. Stepwise logistic regression was used to analyze independent predictors of LCOS, and a nomogram was constructed. The best clinical decision points were found using decision analysis and a clinical impact curve.

RESULTS: Postoperative LCOS occurred in 22 (7.1%) of elderly patients with ATAAD. Independent risk factors for postoperative LCOS were age, smoking history, aortic cross-clamp (ACC), coronary heart disease (CHD), and preoperative shock. The nomogram constructed based on the identified risk factors showed good performance.

CONCLUSIONS: Our results suggest that preventive treatment can be administered when needed when the risk of LCOS in older patients with ATAAD after surgery is >60%. This study contributes to developing a methodology that may improve therapeutic decision-making in older patients and provides insights for assessing the risk of LCOS.

Key Words:
Low cardiac output syndrome, Nomogram, Decision-making curve, Acute type A aortic dissection surgery, Cardiac function.

Introduction

Low cardiac output syndrome (LCOS) is a serious complication of surgical intervention for acute type A aortic dissection (ATAAD) and is considered a primary cause of postoperative death in these patients[1,2]. The pathogenesis of LCOS involves an imbalance between the energy supply and demand in myocardial cells, leading to myocardial injury, decreased cardiac ejection fraction (EF), peripheral vascular contraction, and insufficient tissue perfusion[3]. LCOS following cardiac surgery not only leads to tissue malperfusion, but also multiple organ dysfunction of brain, lung, liver, kidney, and gastrointestinal tract, thereby increasing health care resource utilization and associated costs. Recent studies[4] have shown that the LCOS after cardiac surgery is associated with a 3%-45% mortality rate, higher intensive care unit (ICU) admission rates, more respiratory support, and increased hospitalization costs[1,5].

Current research[4,6-8] identified left ventricular ejection fraction (LVEF), female sex, aging, surgical history, hemodynamic burden of uncorrected defects, cardiopulmonary bypass (CPB) induced stimulation of the inflammatory and complement cascades, preoperative renal failure, circulating temperature, and preoperative shock as the most frequent predictors of LCOS. However, risk factors for LCOS in aortic dissection (AD) have not been reported. Early detection of high-risk populations before the onset of LCOS following AD surgery aids in improving the clinical outcomes of AD surgery and may influence the selection of surgical techniques and operation possibilities.

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Moreover, the clinical benefits of treating patients at high risk of postoperative LCOS before the onset of disease symptoms are unknown.

Although machine learning models has been developed to predict LCOS in patients following cardiac surgery, nomogram has not been constructed for predicting LCOS in elderly patients undergoing ATAAD[9]. Numerous illnesses have been predicted, and their prognosis has been examined using nomograms that have great effectiveness[10-13]. Thus, the purpose of this study was to investigate the risk variables related to older patients' postoperative LCOS, develop a nomogram prediction model with good accuracy to predict the risk of postoperative LCOS, offer practical information regarding medical services.

Patients and Methods

Patients

In this retrospective study, clinical data of elderly patients (≥65) with ATAAD who were treated in our center from January 1, 2013, to December 31, 2021, were reviewed. To validate the anatomical diagnosis, all imaging modalities [including computed tomography (CT) and echocardiography] were examined. The surgeries were performed by experienced surgeons at our hospital. The study involved 310 eligible patients.

The inclusion criteria were as follows: (1) Age ≥65; (2) Clinical diagnosis of ATAADs confirmed using computed tomography angiography or ultrasonography; (3) Symptoms, such as chest pain that occurred within 14 days of diagnosis; (4) Individuals who had an emergency surgery within 48 hours after being admitted; (5) Preoperative New York Heart Association (NYHA) grades <3.

The exclusion criteria were as follows: (1) Patients with other systemic diseases requiring simultaneous surgical treatment; (2) Serious mental illnesses; (3) Patients with malignant tumors or serious medical diseases; (4) History of ongoing systemic corticosteroid therapy within one month; (5) Incomplete clinical data; (6) Patients who experienced sudden serious complications before surgery.

Patients were categorized into the LCOS (patients with postoperative LCOS, n=22) and non-LCOS groups (patients without postoperative LCOS, n=288). Comparisons were made between the two groups in terms of baseline characteristics, intraoperative features, mortality rate, length of intensive care unit (ICU) stay, length of hospital stay, and length of mechanical ventilator support. The associations between these characteristics and LCOS were investigated using regression analysis to identify independent risk factors and produce nomograms. The best risk intervention threshold for postoperative LCOS in older patients with AD was evaluated by combining decision and clinical influence curves.

Study Definitions

LCOS was defined as the need for inotropic drugs (dobutamine, levosimendan, and norepinephrine) or a cardiac index (CI) of at least 2.2 for a minimum of 12 hours after ICU admission using an intra-aortic balloon pump and the existence of at least one of the following: urine output <0.5 mL/kg/h, central venous oxygen saturation <60%, or pulmonary capillary wedge pressure (PCWP) >18 mmHg.

Statistical Analysis

Numbers and percentages were used to represent categorical variables, whereas mean ± SD was used to represent continuous variables. Using all the important characteristics discovered in the multivariable logistic regression analysis, a logistic model was created using the "rms" (regression modeling methods) package of R software (https://www.r-project.org/) to predict the chance of postoperative LCOS. The nomogram's performance was assessed using the concordance index (C-index). The "rmda" (risk model decision analysis) package of R software (https://www.r-project.org/) was used to compute clinical impact curves, and decision curve analysis (DCA) was used to evaluate clinical value. The DCA was used to compare the net benefits of each prediction model at each threshold probability. For internal validation, the validation cohort's sensitivity, specificity, positive predictive value, and negative predictive value were determined. The two-tailed *p*-value of 0.05 indicates that statistical significance has been achieved.

Results

Baseline Characteristics of the Participants

A total of 310 patients (258 males and 52 females) were enrolled in the research. The average age of patients was 69.46±2.25 years, and the incidence rate of LCOS was 7.1% (22/310). Age, sex, history of smoking, coronary artery stenosis, ACC (min), preoperative shock, and type of operation were shown to be substantially different in older ATAAD patients with and without postoperative LCOS (**Supplementary Table I**).

Postoperative Complications and Follow-Up

Average durations of ICU stay, hospital stay, and mortality were all significantly higher in the LCOS group compared to the non-LCOS group (**Supplementary Table I**). At the conclusion of the follow-up period, there were 50 cases of mortality, of which 22 patients died during hospitalization and 28 died during follow-up after discharge. In the LCOS group, 8 patients died of low cardiac output, and 4 patients died of other causes. Overall, 38 patients died without a low cardiac output. We did not find any further potential cases of mortality related to reduced cardiac output after surgery, even though it was difficult to verify the cause of death in all cases (**Supplementary Table I**).

Risk Factors

The association of each clinical and demographic risk factor with postoperative LCOS was individually assessed using univariate logistic proportional hazard models. Age, sex, smoking history, coronary artery stenosis, aortic cross-clamp (ACC) (min), preoperative shock, and type of surgery were all identified as risk factors for postoperative LCOS (Table I). These factors were then analyzed using a multivariate logistic risk

Table I. Univariable logistic regression analysis for the association of clinical characteristics with LCOS.

Subgroup	n (%) or mean±σ	Hazard ratio (95% CI)	*p*-value*
Age (years)	69.46±2.25	1.777 (1.307-2.416)	0.043
BMI	25.08±3.31	0.941 (0.779-1.137)	0.528
Sex	/	5.167 (1.440-18.533)	0.012
Male	258 (83.23%)	/	/
Female	52 (16.77%)	/	/
History of smoke	278 (89.68%)	1.686 (1.214-2.342)	0.002
One cigarette in few days	144 (46.45%)	/	/
One cigarette per day	30 (9.68%)	/	/
2-3 cigarettes per day	10 (3.23%)	/	/
4-10 cigarettes per day	26 (8.39%)	/	/
10-20 cigarettes per day	32 (10.32%)	/	/
More than 20 cigarettes per day	36 (11.61%)	/	/
History of alcohol intake	110 (35.48%)	1.567 (0.455-5.389)	0.476
NYHA		1.033 (0.368-2.902)	0.435
I	134 (43.23%)	/	/
II	176 (52.77%)	/	/
Hypertension	262 (84.52%)	0.811 (0.164-4.011)	0.798
Diabetes	28 (9.03%)	2.444 (0.965-17.630)	0.286
Blood glucose (mmol/L)	5.82±0.82	1.145 (0.563-2.329)	0.709
Coronary artery stenosis	100 (32.26%)	2.799 (1.558-5.029)	0.001
Mild (<50%)	48 (15.48%)	/	/
Moderate (50-70%)	38 (12.26%)	/	/
Severe (>70%)	14 (4.52%)	/	/
Aortic regurgitation	262 (84.52%)	0.925 (0.442-1.939)	0.837
Mild	140 (45.16%)	/	/
Moderate	96 (30.97%)	/	/
Severe	26 (8.39%)	/	/
Moderate/severe pericardial effusion	54 (17.42%)	1.875 (0.464-7.584)	0.378
Preoperative shock (systolic blood pressure <80 mmHg)	24 (7.74%)	8.625 (1.81540.981)	0.007
LVEF	63.21±6.15	0.979 (0.888-1.080)	0.673
Leucocyte ($\times 10^9$/L)	4.04±0.65	0.775 (0.280-2.143/0	0.624
Erythrocyte ($\times 10^{12}$/L)	11.81±3.66	1.005 (0.850-1.189)	0.95
Hemoglobin ($g \cdot L^{-1}$)	129.36±18.67	1.010 (0.977-1.044)	0.545
PLT ($\times 10^9$/L)	189.25±77.28	1.001 (0.994-1.009)	0.766
PT (s)	14.78±3.90	1.082 (0.973-1.202)	0.146

Continued

Table I *(Continued)*. Univariable logistic regression analysis for the association of clinical characteristics with LCOS.

Subgroup	n (%) or mean±σ	Hazard ratio (95% CI)	*p*-value*
APTT (s)	39.14±8.32	1.023 (0.965-1.086)	0.445
TT (s)	18.21±5.65	1.012 (0.919-1.114)	0.81
INR	1.18±0.43	2.062 (0.811-5.239)	0.128
DD (mg/L)	10.08±7.34	0.989 (0.909-1.076)	0.797
FIB (g/L)	3.45±1.85	0.884 (0.609-1.284)	0.519
Albumin (g/L)	37.09±6.86	0.952 (0.856-1.058)	0.359
BUN (umol/L)	7.37±3.80	0.938 (0.754-1.167)	0.566
CR (umol/L)	102.34±61.81	0.999 (0.989-1.010)	0.891
BNP (pg/mL)	79.49±48.73	1.001 (0.978-1.012)	0.896
LDH (U/L)	376.28±299.77	1.000 (0.999-1.002)	0.642
Na^+ (mmol/L)	138.42±3.85	0.975 (0.835-1.139)	0.749
Ca^{2+} (mmol/L)	2.21±0.17	11.225 (0.102-1,240.062)	0.314
K+ (mmol/L)	3.98±0.72	1.281 (0.595-2.757)	0.526
Onset to surgery time (h)	31.41±7.48	1.019 (0.892-1.024)	0.673
Type of operation			
CABG	26 (8.33%)	1.100 (0.242-4.991)	0.902
Ascending aorta replacement	295 (95.14%)	1.073 (0.134-8.561)	0.947
Hemi-arch replacement	41 (13.19%)	0.979 (0.277-3.460)	0.974
Total-arch replacement	242 (77.78%)	1.286 (0.420-3.934)	0.66
Three branch aortic stent	218 (70.32%)	0.212 (0.086-0.526)	0.001
Blood transfusion			
Erythrocytes (U)	4.24±2.16	1.109 (0.853-1.442)	0.438
Cryoprecipitate (U)	0.55±0.47	0.425 (0.106-1.702)	0.227
Plasma (U)	554.45±338.93	0.999 (0.997-1.001)	0.432
Operating time (min)	293.87±66.45	1.000 (0.991-1.010)	0.916
CPBT (min)	159.60±39.74	1.005 (0.992-1.018)	0.525
ACC (min)	61.05±21.04	1.058 (1.023-1.095)	0.001
Deep hypothermic circulatory arrest (min)	19.37±3.41	1.121 (0.798-1.143)	0.692

BMI: body mass index; NYHA: New York Heart Association classification, LVEF: left ventricular ejection fraction; DD: D-Dipolymer; PLT: platelet; PT: prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; INR: international normalized ratio; FIB: fibrinogen; BUN: blood urea nitrogen; BNP: brain natriuretic peptide; CR: creatinine; LDH: lactate dehydrogenase; CABG: coronary artery bypass grafting; CPBT: cardiopulmonary bypass time; ACC: aortic cross-clamp. *Univariable logistic regression analysis.

model. The results showed that age, smoking history, coronary artery stenosis, ACC (min), and preoperative shock were independently associated with postoperative LCOS, while sex and type of operation were not independent risk factors for LCOS (Table II).

Survival Significance of Postoperative LCOS

The impact of postoperative LCOS on the survival of older patients with ATAAD was assessed using Kaplan-Meier survival, Cox analysis, and cumulative risk curves. As sur-

Table II. Multivariate logistic regression analysis associated with LCOS.

Subgroup	B	95% CI for OR	*p*-value*
Age	1.189	2.971 (1.869-10.162)	0.033
Sex	-2.465	3.167 (0.740-14.328)	0.146
History of smoke	2.365	3.172 (2.994-11.099)	0.035
Coronary artery stenosis	5.985	3.726 (2.869-13.701)	0.021
Preoperative shock	6.152	4.135 (3.912-15.125)	0.014
Three branch aortic stent	-1.55	0.778 (0.218-2.775)	0.279
ACC (min)	1.062	1.065 (1.932-1.168)	0.047

LCOS: low cardiac output syndrome, ACC: aortic cross-clamp. *Multivariate logistic regression analysis.

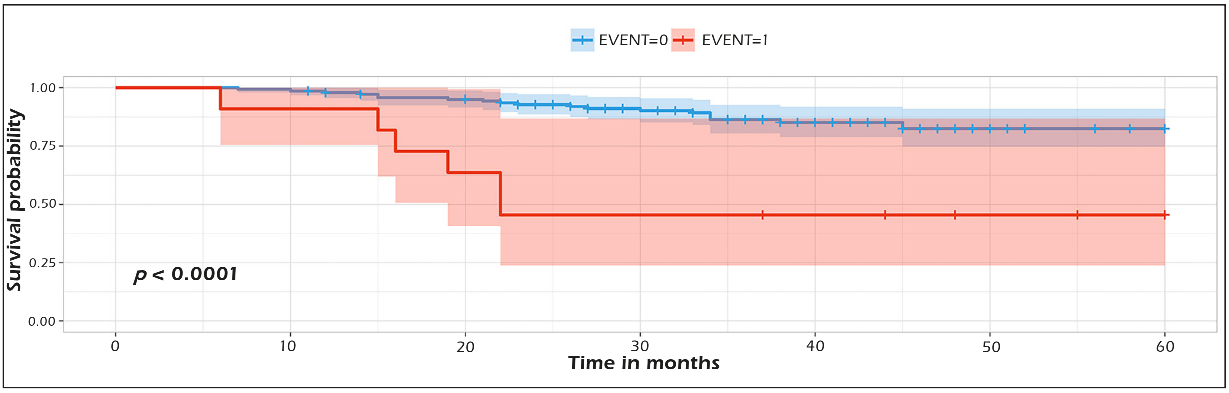

Figure 1. Effect of postoperative LCOS on postoperative survival in elderly patients with ATAAD and the cumulative risk (log-rank test).

vival time increased, postoperative LCOS risk cumulatively increased, patient survival probability decreased, and survival time decreased (Figure 1).

Establishment of the LCOS Score Using a Nomogram

Table II summarizes significantly different variables. Age, smoking history, coronary artery stenosis, ACC (min), and preoperative shock were added to the "rms" package in R for analysis to see the outcomes of the logistic proportional hazards model. The weights assigned to each factor's contribution were used to create a nomogram. For patients who underwent AD surgery, the estimation of each patient's specific postoperative risk for LCOS (Figure 2) and median survival time (**Supplementary Figure 1)** was made using the total score value of each risk factor corresponding to the maximum score on the scale.

Reaching the Decision Point for Optimal Clinical Benefit

The ideal choice points were established using clinical impact curves and decision analysis. Initially, the overall benefit of the nomogram and each individual risk factor for postoperative LCOS were assessed using DCA. The net benefit tended to increase as the risk threshold decreased as more patients received therapy below the low-

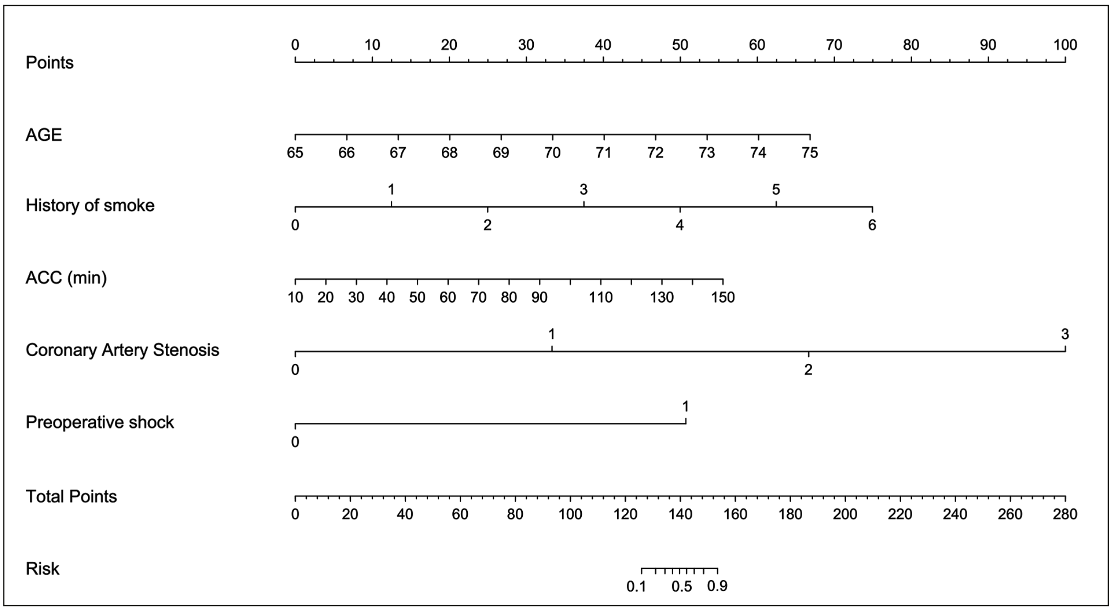

Figure 2. A nomogram to identify elderly patients with ATAAD who are at risk of developing postoperative LCOS. The scores for each independent variable were summed [i.e., age, history of smoke, coronary artery stenosis, ACC (min), preoperative shock] to obtain a total score. The total score was used to calculate the risk of postoperative LCOS.

risk threshold. Conversely, a low-risk threshold increases the chance of false-positive findings. Clinical impact curves were developed to investigate the percentage of patients classified as high-risk at each cutoff point and the percentage of patients considered high-risk. The difference between the overall number of patients thought to be at elevated risk for postoperative LCOS and the real number of patients increased as the risk threshold decreased, as seen in Figure 3. This suggests a rise in false-positive rates and ineffective treatment. Therefore, to balance increased net benefits and reduced false-positive rates, we changed the DCA in accordance with the clinical effect curve. The calibration findings demonstrated that with a score of just over 144, the risk threshold for postoperative LCOS at 0.6 offered the greatest substantial therapeutic benefit for the whole cohort (Figures 2 and 3). When the risk score was higher than 144, preventative therapy, tailored to the demands of the condition, was specifically advised.

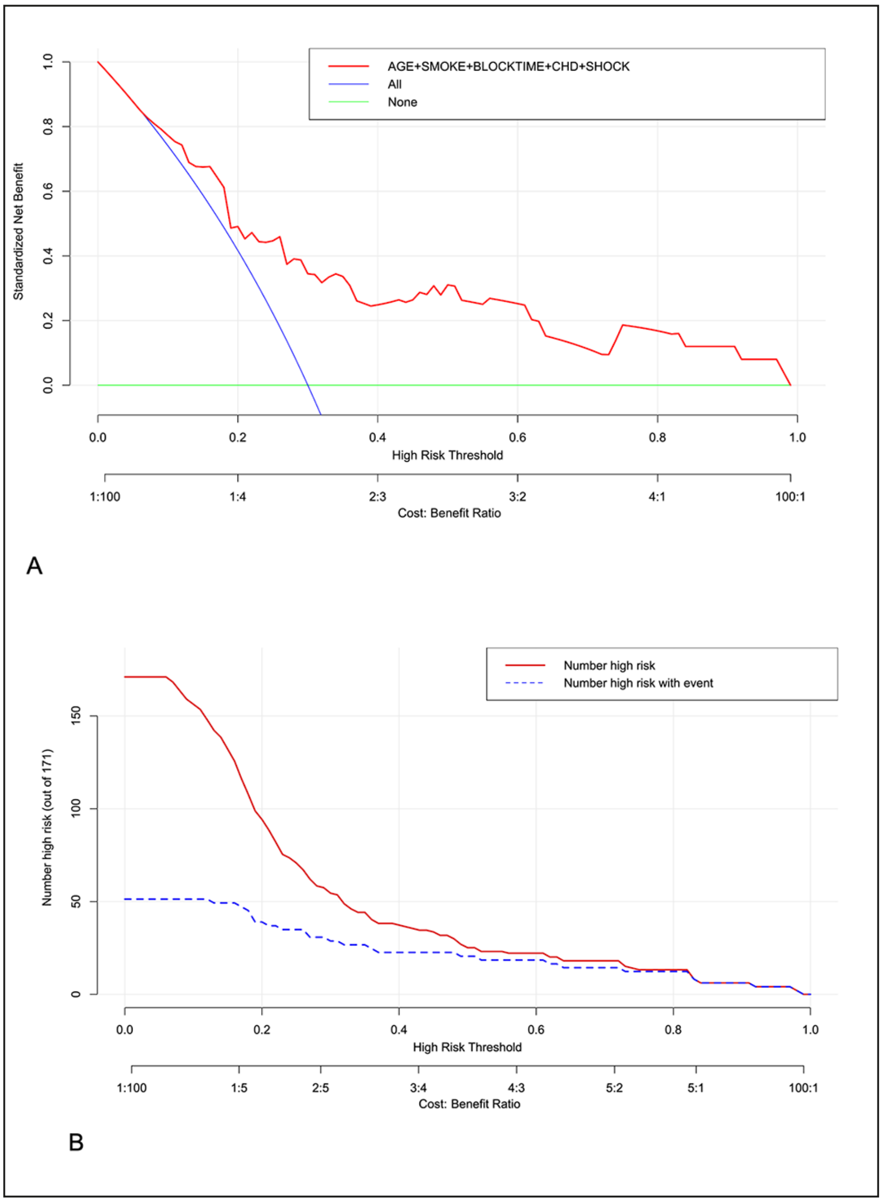

Figure 3. Selecting the optimal decision-making point. **A**, Decision curve. **B**, Clinical impact curve. A reduced false positive rate and a larger net benefit were obtained with a threshold of 0.6.

Internal Verification

Calibration and discrimination are the two main metrics used for prediction model validation. A good model distinguishes objects with various probabilities of endpoint events and reliably forecasts the probability of endpoint events.

With a C-index of 0.828>0.75 (95% CI: 0.804-0.852, p=0.001), our nomogram accurately estimated the risk of LCOS. The anticipated values of the correction curve closely matched the measured values, demonstrating a high consistency.

Discussion

This study identified age, smoking history, aortic cross-clamp (ACC), coronary heart disease (CHD), and preoperative shock as independent risk factors for postoperative LCOS in elderly patients after ATAAD and constructed a nomogram model to identify risk variables for postoperative LCOS.

The incidence rate of LCOS in the current investigation was 7.10%. Previous studies[1,2,6] report that the overall incidence rate of adult patients with heart disease and LCOS after surgery is approximately 2.4-9.1%. Interestingly, the overall incidence rates reported in different studies varied significantly. In some neonatal studies[14], the incidence of postoperative LCOS exceeded 50%. Hoffman et al[15] found that the incidence of LCOS in the first 36 hours after surgery was 25.9%, 17.5%, and 11.7% in pediatric patients treated with placebo, low-dose milrinone, and high-dose milrinone, respectively. Butts et al[16] found that following cardiac surgery, 32 out of 76 (42%) babies developed LCOS.

Postoperative LCOS is associated with higher rates of medical resource usage and higher mortality[1-3]. The mortality rate of patients with LCOS following heart surgery may surpass 20%[6], and the most common outcomes of LCOS include acute liver and kidney failure, pulmonary infection, hypoxemia, and sepsis[1,16-19]. In our study, the mortality rate of elderly patients with postoperative LCOS was as high as 66.67%. High-risk cardiac patients, particularly those with left ventricular (LV) systolic failure before surgery (LVEF 35%) who are more likely to develop LCOS, require special care during the perioperative phase[20]. Therefore, in order to optimize oxygen delivery (DO_2) levels and restore tissue metabolism and organ function, LCOS must be diagnosed as soon as possible and treated with goal-directed therapy.

Previous studies[21-25] identified advanced age (>65 years), sex (female), impaired LV function (<50%), hemoglobin index, total lymphocyte count, N-terminal pro-brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), hypertension, on-pump coronary artery bypass grafting, CPB, and emergency surgery as independent risk factors for LCOS. Additionally, malnutrition was another risk factor that has been connected to a two-fold increase in the probability of needing inotropic care after surgery[26]. Nutrition is crucial for the prevention of cardiovascular disease[27], and severe nutritional deficiencies may play a causative role in LCOS[28]. Malnutrition affects the course of disease and prognosis in elderly people[29]. In the current study, we identified the following independent risk variables for postoperative LCOS in older patients with ATAAD: advanced age, smoking history, coronary artery stenosis, ACC (min), and preoperative shock. While sex and surgical type were identified as risk factors for postoperative LCOS, they were not independently associated. Our results differed slightly from those found in earlier research[21-26]. We may speculate that the difference may be attributed to the participants' varied demographics, initial diseases, degrees of severity, and surgical techniques[5].

Research on risk variables and prediction models has been focused on coronary artery disease, congenital heart disease, and rheumatic heart disease. Relevant reports in the field of AD are scarce[30,31]. As previously mentioned, advanced age (>65 years) is a risk factor for LCOS. With the increasing aging of the general population, there is a gradual increase in the number of high-risk older patients who are undergoing AD. The expansion of cardiac surgery for high-risk older patients has resulted from improved surgical techniques and perioperative myocardial protection. However, despite continuous improvements in preoperative cardioprotection and other strategies, the incidence rate of postoperative LCOS is still not low, and delayed treatment misses the best treatment opportunity, greatly affecting the prognosis of patients. Therefore, early diagnosis and treatment are very important.

As was already noted, significant markers are strongly correlated with postoperative LCOS occurrence. The benefit of our model is that it provides a quantitative foundation for postoperative LCOS. Every patient in our study had AD surgery, yet some did not experience LCOS thereafter. Since it is impossible to predict whether postoperative LCOS will occur after surgery, it will likely lead to incorrect judgment of surgical decisions and intraoperative risks. As a result, patients may undergo traumatic surgery that would not be beneficial. Therefore, our study provides a valuable basis for clinical preoperative decision-making, including the selection of surgical methods, optimization of surgical procedures, and perioperative management. Additionally, this is the first study that has measured the risk of surgical LCOS, which may be imperative for patient prognosis advice and postoperative LCOS risk classification.

Limitations

However, this study had some limitations. First, the retrospective design warrants further research to confirm our findings and to broaden the therapeutic applicability of the nomogram. Additionally, only a single-center sample was included in this study, so the generalization of its findings to other demographics may be limited. And, despite the thoroughness of the investigation, we were unable to conduct a more informative subgroup analysis due to the small sample size. Finally, due to the limited sample size, we did not perform external validation of the model. Depending solely on internal validation may lead to overly optimistic performance assessment of the model. We hope to have more cases in the future to validate the model's performance in the real world.

Conclusions

This study developed a nomogram model that may provide an initial, impartial insight for medical decisions and postoperative LCOS. Our results allow clinicians to offer prognostic guidance by establishing distinct risk assessment and prognostic counseling for each older patient with ATAAD.

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Ethics Approval

The study was approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2022KY031; date: March 9, 2022).

Data Availability

Data are available from Liangwan Chen (chengliangwan@tom.com) for researchers who meet the criteria for access to confidential data.

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Conflicts of Interest

The authors declare no competing interest.

Informed Consent

Patient informed consent was waived because of the retrospective nature of the study.

AI Disclosure

No AI was used for conducting and drafting this article.

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