Risk Factors for Acute Respiratory Distress Syndrome after Surgery for Severe and Complex Congenital Heart Disease in Children: A Postprint

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Abstract

Objective By comparing the clinical data of pediatric patients with critical and complex congenital heart disease (CCHD) who developed acute respiratory distress syndrome (ARDS) postoperatively with those who did not develop ARDS, to investigate the risk factors for ARDS following surgery for critical and complex congenital heart disease. Methods According to the 2011 Berlin Definition of ARDS, 75 pediatric patients with critical and complex congenital heart disease who did not develop ARDS, admitted to our cardiac surgery department from January 2009 to May 2014, were selected as Group I, while 80 patients who developed ARDS during the same period were selected as Group II. The clinical data of the two groups were compared and analyzed, with 39 indicators including age, gender, body weight, preoperative oxygen partial pressure and carbon dioxide partial pressure, preoperative and postoperative serum albumin, preoperative and postoperative serum creatinine, preoperative left ventricular EF, etc., selected for univariate analysis and multivariate Logistic regression analysis. Results In Group II, there were 17 deaths, with a mortality rate of 21%. Group II included 27 cases of mild ARDS, 25 cases of moderate ARDS, and 28 cases of severe ARDS. Univariate analysis revealed that 23 indicators showed statistically significant differences between the two groups ($P<0.05$), including body weight, preoperative PCO2, preoperative left ventricular ejection fraction, early postoperative serum globulin, intraoperative aortic cross-clamp time, cardiopulmonary bypass time, operation time, intraoperative blood loss, total intraoperative blood transfusion volume, 8-hour postoperative chest drainage volume, 8-hour postoperative blood transfusion volume, postoperative serum albumin, postoperative serum creatinine, initial postoperative lactate value, maximum lactate increase rate at 24 hours postoperatively, 24-hour postoperative B-type natriuretic peptide, 24-hour postoperative procalcitonin, 24-hour postoperative

C-reactive protein, 24-hour postoperative serum prealbumin, age, preoperative pulmonary artery pressure, preoperative pulmonary infection, and preoperative abnormal coagulation function. Logistic regression analysis demonstrated that five indicators were independent risk factors for ARDS after CCHD surgery: intraoperative aortic cross-clamp time, cardiopulmonary bypass time, maximum lactate increase rate at 24 hours postoperatively, 24-hour postoperative procalcitonin, and intraoperative blood loss. Conclusion ARDS is a serious complication following surgery for critical and complex congenital heart disease, which significantly increases the mortality rate in pediatric patients. Based on these main risk factors—aortic cross-clamp time, cardiopulmonary bypass time, maximum lactate increase rate at 24 hours postoperatively, 24-hour postoperative procalcitonin, and intraoperative blood loss—the occurrence of ARDS can be predicted and necessary measures can be taken early to improve the success rate of ARDS treatment in pediatric patients after CCHD surgery.

Full Text

Preamble

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Risk factors for acute respiratory distress syndrome following surgeries for pediatric critical and complex congenital heart disease

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Abstract

Objective: To explore the risk factors for acute respiratory distress syndrome (ARDS) in children receiving surgeries for critical and complex congenital heart disease (CCHD). **Methods:** According to the 2011 Berlin definition of ARDS, clinical data were collected from 75 children without ARDS (Group I) and 80 children with ARDS (Group II) following surgeries for CCHD performed in the Department of Cardiac Surgery of our hospital from January 2009 to May 2014. Univariate analyses and logistic regression were used to analyze 39 clinical parameters including age, gender, weight, preoperative blood gas values, serum albumin, creatinine, left ventricular ejection fraction, and various intraoperative and postoperative variables. **Results:** Among the 80 patients who developed ARDS postoperatively in Group II, 27 had mild ARDS, 25 had moderate ARDS, and 28 had severe ARDS; death occurred in 17 cases (21% mortality). Univariate analysis identified 23 parameters with statistically significant differences between groups ($P<0.05$). Logistic regression analysis revealed that intraoperative aortic cross-clamp time, cardiopulmonary bypass time, maximum lactate increase rate within 24 hours postoperatively, serum procalcitonin at 24 hours postoperatively, and intraoperative blood loss were independent risk factors for postoperative ARDS. **Conclusion:** ARDS is a severe complication following CCHD surgery that significantly increases mortality. The identified risk factors can predict ARDS occurrence and enable early intervention to improve treatment success rates.

Key words: critical and complex congenital heart disease; acute respiratory distress syndrome; risk factor

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Introduction

Critical and complex congenital heart disease (CCHD) encompasses complex cardiovascular malformations including tetralogy of Fallot, pulmonary atresia, double outlet right ventricle, and transposition of the great arteries. Pediatric critical CHD also includes intracardiac defects combined with severe pulmonary vascular damage (either pulmonary hypertension-type lesions or pulmonary vascular dysplasia), simple cardiovascular malformations complicated by cardiac insufficiency, and low birth weight infants. In this study, the term CCHD refers to both critical and complex congenital heart disease. These patients exhibit significantly higher perioperative complication rates and mortality compared to those with simple CHD, and their treatment outcomes serve as an important indicator of a center' s congenital heart disease management capability.

Acute respiratory distress syndrome (ARDS) is a common complication following cardiac surgery and cardiopulmonary bypass (CPB). Li et al. reported an ARDS incidence of 7.6% after tetralogy of Fallot repair, while Chen et al. observed ARDS in all 22 patients with tetralogy of Fallot complicated by unilateral pulmonary artery absence. Gajic et al. reported that ARDS incidence after cardiac surgery could reach as high as 20%. However, large-scale studies on ARDS incidence specifically in CCHD patients are lacking in the literature. Clinically, these critically ill children with complex malformations undergo difficult surgical procedures, and CPB can easily cause pulmonary ischemia-reperfusion injury, making ARDS a not uncommon occurrence that substantially increases postoperative management difficulty, prolongs mechanical ventilation and ICU stay, and represents a serious complication affecting survival.

To improve clinical understanding and management of ARDS following CCHD surgery, this study retrospectively analyzed data from 155 pediatric CCHD patients admitted to our surgical ICU between January 2009 and May 2014. Using multivariate logistic regression analysis, we investigated risk factors for postoperative ARDS to provide evidence for prevention and treatment strategies that may improve outcomes in this patient population.

1.1 Study Subjects

Initially, 176 pediatric patients with critical and complex congenital heart disease who underwent primary corrective surgery in our cardiac surgery department between January 2009 and May 2014 were screened. After applying inclusion and exclusion criteria, 155 patients with complete clinical data were enrolled. According to the Berlin definition of ARDS, patients meeting the following criteria were diagnosed with ARDS: (1) acute onset or deterioration within one week; (2) PaO /FiO 300 mmHg with PEEP 5 cm H O; (3) condition not fully explained by cardiac dysfunction or fluid overload; and (4) chest radiograph showing bilateral infiltrates not fully explained by pleural effusion, nodules, masses, or lobar collapse. Severity classification (mild, moderate, severe) followed Berlin criteria.

Exclusion criteria: (1) death within 24 hours postoperatively; (2) predominant manifestation of cardiac dysfunction; (3) onset after one week; (4) age >12 years. After exclusions, 155 patients were included: 80 who developed postoperative ARDS comprised the case group (Group II), while 75 without ARDS formed the control group (Group I). The ARDS group was further subdivided into mild (27 cases), moderate (25 cases), and severe (28 cases) subgroups. Among all 155 patients, 86 were male and 69 female; 24 were <3 months old and 131 were >3 months; 30 had weight <5 kg and 125 weighed 5 kg. The disease distribution is shown in Table 1 .

1.2 Surgical Methods

All surgeries were performed under general anesthesia with endotracheal intubation, hypothermia, and CPB. Primary intracardiac corrective procedures were completed in one stage. Postoperatively, patients were transferred to the SICU for routine mechanical ventilation. Low-dose dopamine, dobutamine, epinephrine, milrinone, or sodium nitroprusside were used to maintain hemodynamic stability. Electrolytes and blood gas analyses were monitored to maintain internal environment stability. Antibiotics were administered for infection prophylaxis, and bedside chest radiographs and echocardiography were performed to evaluate pulmonary and cardiac function.

ARDS typically developed early postoperatively, mostly within 72 hours, manifesting as restlessness, dyspnea, and refractory hypoxemia that could not be fully explained by cardiac dysfunction or fluid overload. Chest radiographs showed bilateral heterogeneous infiltrates, and lung compliance was markedly reduced under mechanical ventilation. As the disease progressed, some patients developed severe circulatory dysfunction and multiple organ failure; 17 patients in this series died from severe ARDS combined with multiple organ failure.

1.3 Clinical Observation Indicators

Thirty-nine perioperative clinical parameters were selected for analysis between groups: gender, age, weight, preoperative PaO and PaCO , preoperative serum albumin and creatinine, preoperative left ventricular ejection fraction (LVEF), preoperative pulmonary artery pressure, preoperative pulmonary infection, preoperative coagulation abnormalities, preoperative hemoglobin, intraoperative aortic cross-clamp (ACC) time, CPB time, operation time, intraoperative blood loss/kg, intraoperative fluid infusion/kg, intraoperative blood transfusion/kg, intraoperative fluid balance/kg, intraoperative average hourly urine output/kg, early postoperative serum globulin, completeness of surgical correction, postoperative pulmonary hypertension, postoperative 8-hour chest drainage/kg, postoperative 8-hour blood transfusion/kg, postoperative 8-hour average hourly urine output/kg, early postoperative hyperthermia, postoperative serum albumin, postoperative serum creatinine, initial postoperative lactate level, maximum lactate increase rate within 24 hours, B-type natriuretic peptide (BNP) at 24 hours, procalcitonin (PCT) at 24 hours, C-reactive protein (CRP) at 24 hours, serum prealbumin (PA) at 24 hours, mechanical ventilation duration, ICU stay, postoperative ventilator-associated pneumonia (VAP), and 28-day mortality.

Mechanical ventilation time, ICU stay, VAP occurrence, and 28-day mortality were not considered causative factors for ARDS but were included as prognostic indicators for comparison between groups. All volume measurements related to blood loss or fluids were standardized by body weight. Postoperative lactate levels were monitored continuously for 24 hours, and the maximum lactate increase rate was calculated using Schumacher' s method: lactate increase rate = (difference between consecutive measurements)/(time interval), with the maximum value identified from all intervals.

1.4 Statistical Methods

SPSS 19.0 software was used for statistical analysis. Continuous variables were compared using t-tests, multiple groups were compared using one-way ANOVA, and categorical variables were analyzed using chi-square tests. Variables with $P<0.05$ in univariate analysis were entered into multivariate logistic regression analysis using backward elimination (entry criterion $P<0.05$, removal criterion $P>0.10$). $P<0.05$ was considered statistically significant.

Results

ARDS occurred predominantly in patients with: (1) CHD combined with moderate-to-severe pulmonary hypertension, (2) severe tetralogy of Fallot, and (3) severe pulmonary atresia. These three categories accounted for 54.8% of all enrolled patients. The overall ARDS incidence in this cohort was 51.6%.

Univariate analysis revealed significant differences between groups in 23 parameters ($P<0.05$): weight, preoperative PaCO , preoperative LVEF, early postoperative serum globulin, ACC time, CPB time, operation time, intraoperative blood loss/kg, intraoperative blood transfusion/kg, postoperative 8-hour chest drainage/kg, postoperative 8-hour blood transfusion/kg, postoperative serum albumin, postoperative serum creatinine, initial postoperative lactate, maximum lactate increase rate within 24 hours, BNP at 24 hours, PCT at 24 hours, CRP at 24 hours, serum prealbumin at 24 hours, age distribution, pulmonary artery pressure, preoperative pulmonary infection, preoperative coagulation abnormalities, VAP occurrence, and 28-day mortality (Table 2).

ACC time, CPB time, PCT at 24 hours, and CRP at 24 hours showed progressively increasing trends across subgroups (Figure 1 [Figure 1: see original paper] through Figure 4 [Figure 4: see original paper]). One-way ANOVA demonstrated significant differences among the four groups for these four parameters ($P<0.05$, Table 3).

After excluding the four prognostic factors (VAP, 28-day mortality, mechanical ventilation time, and ICU stay), the remaining significant variables from univariate analysis were entered into multivariate logistic regression. The results identified five independent risk factors for postoperative ARDS: intraoperative ACC time, CPB time, maximum lactate increase rate within 24 hours, PCT at 24 hours, and intraoperative blood loss (Table 4).

Discussion

Congenital heart disease is the leading cause of birth defects in newborns. Domestic reports indicate an incidence of approximately 0.8%, with 180,000-220,000 new cases annually in China. Complex congenital heart disease and CCHD represent major challenges due to difficult correction, high complication rates, and high mortality. ARDS is a common perioperative complication associated with complex underlying disease, surgical trauma, CPB, postoperative pulmonary hemodynamic changes, and blood transfusion-related lung injury.

This study identified intraoperative ACC time, CPB time, maximum lactate increase rate within 24 hours, intraoperative blood loss, and PCT at 24 hours as independent risk factors for ARDS following CCHD surgery. ARDS fundamentally represents lung injury caused by systemic inflammatory response syndrome, resulting in pulmonary vascular endothelial damage, compromised respiratory barrier, and increased alveolar-capillary membrane permeability. Alten et al. found that surfactant deficiency or inactivation is a primary pathological mechanism in ARDS, causing atelectasis, intrapulmonary shunting, reduced lung volume, and decreased compliance. CPB leads to surfactant protein loss and inactivation, accompanied by interstitial edema and increased alveolar proteins, resulting in alveolar collapse.

Güvener et al. identified CPB duration, low body weight, and preoperative right-to-left shunt as independent risk factors for systemic inflammatory response syndrome and increased mortality after congenital heart surgery. Li et al. similarly found that inflammatory response and CPB injury were risk factors for postoperative ARDS. Hammer et al. demonstrated that prolonged ACC time was associated with significantly elevated PCT levels that remained high until postoperative day 4, and that circulating IL-6 levels correlated closely with ACC time. Aortic cross-clamping represents one of the most intense physiological and metabolic stressors the body can endure.

Our study found that both ACC time and postoperative PCT elevation were closely associated with ARDS development. The odds ratio for ACC time was 4.376, while PCT elevation carried an OR of 3.127, indicating that prolonged ACC time increased ARDS risk by 4.376-fold, and PCT elevation increased risk by 3.127-fold. The underlying mechanism likely involves ischemia-reperfusion injury and intense inflammatory response induced by CPB and aortic cross-clamping, leading to increased pulmonary vascular permeability. Verheij et al. found that up to 60% of patients developed increased pulmonary vascular permeability during CPB. Prolonged ACC time also extends CPB duration, which correlates closely with surgical complexity and disease severity. Meisner et al. similarly found that CPB duration and operation time correlated with PCT elevation. Li et al. also demonstrated that serum PCT could predict ARDS development.

In our study, the incidence of ARDS in CCHD patients was high, with ACC time, CPB time, PCT, and CRP showing clear increasing trends corresponding to ARDS severity. Statistical analysis confirmed significant differences in these parameters between ARDS and non-ARDS groups and among ARDS subgroups, with ACC time, CPB time, and PCT identified as independent risk factors—findings consistent with previous literature. Therefore, close monitoring for ARDS risk is essential in patients with prolonged ACC or CPB times and those with marked early postoperative PCT elevation.

Blood lactate level reflects microcirculatory perfusion and serves as an effective clinical indicator for early detection of tissue ischemia and prognosis prediction. Under anaerobic conditions, cellular lactate accumulation leads to hyperlactatemia, reflecting increased tissue oxygen debt. Hyperlactatemia is a common metabolic disturbance after CPB, and previous studies have shown that patients with hyperlactatemia have higher complication and mortality rates. Ghaffari et al. found that continuous lactate monitoring is crucial for postoperative management of congenital heart disease, with persistently elevated arterial lactate (>4 mmol/L) within 24 hours significantly increasing mortality.

Traditional lactate monitoring has focused on initial values, peak levels, or lactate clearance. However, initial lactate only reflects immediate postoperative pathophysiology, peak lactate is not the optimal indicator, and lactate clearance has limited value when lactate continues to rise postoperatively. Schumacher et al. continuously monitored arterial lactate for 24 hours in 231 pediatric patients after congenital heart surgery, finding that in the poor prognosis group, median initial lactate was 6.2 mmol/L, peak 24-hour lactate was 10.9 mmol/L, and maximum lactate increase rate was 2 mmol/(L · h), compared to 2.0 mmol/L, 2.4 mmol/L, and 0.25 mmol/(L · h) respectively in the good prognosis group.

In our ARDS patients, blood lactate showed a continuously rising trend postoperatively, making traditional lactate clearance less suitable. Adopting Schumacher's method, we combined initial lactate with dynamic lactate increase rate within 24 hours. Non-ARDS patients had median initial lactate of 2.25 mmol/L and median maximum lactate increase rate of 0.22 mmol/(L·h), while ARDS patients had corresponding values of 6.85 mmol/L and 2.25 mmol/(L·h), similar to Schumacher' s findings. Both parameters showed significant differences between groups, and the maximum lactate increase rate within 24 hours was an independent risk factor for ARDS, demonstrating that continuous dynamic monitoring of lactate increase rate can predict postoperative complications, particularly ARDS, enabling early warning and intervention.

Massive intraoperative blood loss was also closely associated with postoperative ARDS in CCHD patients. Maintaining effective circulating blood volume requires substantial blood product transfusion, which can cause transfusion-related acute lung injury (TRALI), defined as acute hypoxemia (PaO /FiO <300 mmHg) with bilateral pulmonary infiltrations within 6 hours of transfusion, pulmonary capillary wedge pressure <18 mmHg, and absence of left heart dysfunction. Vlaar et al. identified cardiac surgery as an independent risk factor for TRALI. Chen et al. also found that large postoperative chest drainage and transfusion volume were risk factors for ARDS after open-heart surgery.

Massive intraoperative blood loss with inadequate fluid and blood replacement reduces effective circulating volume and renal perfusion, predisposing to prerenal azotemia, fluid retention, and increased pulmonary edema that impairs gas exchange. Ware et al. found that leukocytes, platelet fragments, and denatured proteins in stored blood form microaggregates (20-400 m) that can widely occlude pulmonary capillaries, causing direct lung injury. Our study confirms that massive intraoperative bleeding and subsequent large-volume transfusion are closely related to postoperative ARDS, with massive intraoperative blood loss identified as an independent risk factor.

ARDS patients in our study had significantly longer mechanical ventilation times and ICU stays compared to non-ARDS patients, and all deaths occurred in the ARDS group. VAP incidence was also substantially higher in ARDS patients. Thus, ARDS is a major complication severely affecting prognosis in CCHD patients. Literature reports indicate extremely high mortality for postoperative ARDS, reaching up to 80%. Li et al. also identified ARDS as the leading cause of death after tetralogy of Fallot repair. Therefore, emphasizing ARDS prevention is crucial for improving CCHD surgical outcomes. Based on our findings, patients with prolonged ACC or CPB times, markedly elevated maximum lactate increase rate within 24 hours, elevated PCT, and massive intraoperative bleeding are at high risk for ARDS and require early attention and prompt intervention. Among the five independent risk factors, ACC time, CPB time, and intraoperative blood loss are directly related to surgical technique, while ACC time correlates closely with postoperative PCT elevation, and postoperative lactate changes reflect perioperative circulatory stability. Thus, improving surgical skills and minimizing operative time may reduce ARDS incidence.

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Note: Figure translations are in progress. See original paper for figures.