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Article

Risk Factors of Postoperative Infection in Newborns with Congenital Heart Disease

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Abstract

Aims: This study aims to explore the risk factors of postoperative infection in newborns with congenital heart disease. **Methods**: From January 2019 to January 2023, 78 neonates with congenital heart disease who were diagnosed and treated in our hospital with postoperative infection as well as an age- and sex-matched non-infected group (n = 78) were enrolled. After collecting the data and clinical information of 156 children, we compared the differences in the days of catheter indwelling, days of mechanical ventilation, times of blood transfusion, days of intensive care unit (ICU) stay, and survival status between postoperative infection and non-infection groups. Multivariate logistic regression was used to analyze the risk factors of postoperative infection in newborns with congenital heart disease. **Results**: Age (11 $\pm$ 4 *vs*. 10 $\pm$ 5 days) and sex (56.4% *vs*. 52.6%) were comparable between the infection and non-infection groups. Children in the infection group had lower birth weight, higher proportion of cesarean section, lower oxygen saturation levels, and higher risk adjustment in congenital heart surgery (RACHS-1) scores than those in the non-infection group. In terms of postoperative indicators, neonates in the infection group had longer catheter indwelling time, mechanical ventilation time, ICU hospitalization days, and more blood transfusion times than those in the non-infection group. Multivariate logistic regression analysis showed that oxygen saturation $<$85% (OR: 6.5; 95% CI: 3.7–15.4), catheter indwelling days $>$14 days (OR: 3.2; 95% CI: 2.1–10.7), and ICU stay $>$10 days (OR: 7.1; 95% CI: 3.6–18.5) were independent risk factors for postoperative infection in newborns with congenital heart disease. **Conclusion**: Low oxygen saturation, prolonged catheterization days, and prolonged ICU stay were independent risk factors for postoperative infection in neonates with congenital heart disease undergoing cardiac surgery.

Keywords

newborns; congenital heart disease; postoperative infection; risk factors

Introduction

Congenital heart disease is a type of malformation of the heart and large vessels that presents at birth due to abnormal development in the fetus [1]. Congenital heart disease can be caused by various genetic and environmental factors, and its clinical manifestations include palpitations, dyspnea, general cyanosis, and decreased oxygen saturation [2]. Common congenital heart diseases include atrial septal defect, ventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot [3]. Congenital heart disease is the most common congenital disease in newborns [4]. According to the epidemiological data, about 1.35 million newborns globally suffer from congenital heart disease every year. The reported prevalence rates of newborns with congenital heart disease in Asia, Europe, and North America are 9.3/1000 (95% confidence interval: 8.9–9.7), 8.2/1000, and 6.9/1000, respectively [5]. Congenital heart disease is an important cause of neonatal death, and early surgical treatment is the main method to improve the prognosis of children [6]. Preoperative status, perioperative preparation, and postoperative complications may affect the surgical treatment effect and prognosis because the cardiovascular and immune systems of newborns are not fully developed [7].

Postoperative infection is a common complication of neonatal congenital heart surgery and has a reported incidence rate as high as 15% to 30% [8]. Postoperative infections include surgical site infection, sepsis, ventilator-associated pneumonia, and catheter-associated infection. Most infections are caused by bacteria, and a few can be caused by fungi or viruses [9]. Postoperative infection can prolong neonatal hospital stay, increase medical costs, and even result in death in serious cases [10]. Several factors may contribute to postoperative infection in children undergoing surgery for congenital heart disease. A study of 4458 children suggested that younger age, ventilator use, and extracorporeal membrane oxygenation were risk factors for postoperative infection in heart transplant recipients [11]. Postoperative infection occurs frequently in the first month after heart transplantation, and bloodstream infections are the most common [11]. A 4-year survey suggested that con-

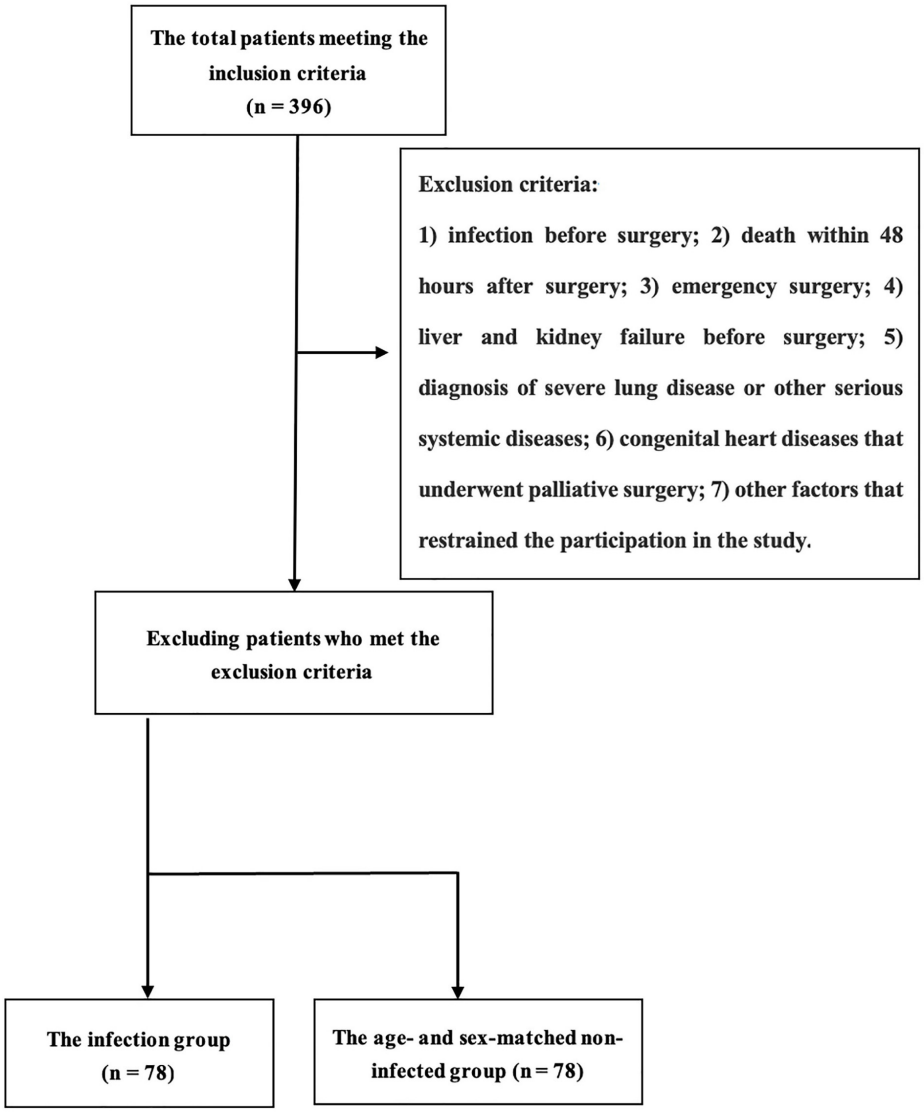

Fig. 1. Study flowchart.

genital malformations, other postoperative complications, and thoracotomy were risk factors for postoperative infection [12]. A study aimed at exploring risk factors for congenital heart disease with 11,651 patients found that Society for Thoracic Surgeons (STS) risk score, low or high body weight, and low lymphocyte/white blood cell were also important factors affecting postoperative infection [13]. However, most previous studies focused on postoperative infection in infants and children with congenital heart disease, and few reports are available on infection in neonates after surgery for congenital heart disease.

This study aimed to explore the risk factors of postoperative infection in newborns with congenital heart disease by comparing infection group with age- and sex-matched non-infection group in neonates with congenital heart disease. Results can help formulate countermeasures to reduce postoperative complications and provide a reference for clinical prevention.

Research Object and Method

Research Object

From January 2019 to January 2023, 396 neonates with congenital heart disease who were operated in our hospital met the inclusion criteria (Fig. 1). We excluded 240 patients who met the exclusion criteria. We retrospectively collected 78 neonates were diagnosed and treated with postoperative infection. Age and sex were important factors that could affect postoperative infection in newborns with congenital heart disease, so we performed the matching of age and sex by propensity score matched method. Finally, 156 children (the infection group [n = 78]; the age- and sex-matched non-infected group [n = 78]) were enrolled in the study. The inclusion criteria were as follows: (1) newborns aged 1–28 days; (2) diagnosed as congenital heart disease

Table 1. Clinical characteristics of postoperative infection and non-infection groups of newborns with congenital heart disease.

	Infection group	Non-infection group	*p* value
n	78	78	-
Age at surgery, days	11 ± 4	10 ± 5	0.623
Gender, n (%)			0.515
Male	44 (56.4)	41 (52.6)	
Female	34 (43.6)	37 (47.4)	
Gestational age, weeks	38 ± 4	39 ± 3	0.271
Birth weight, kg	2.7 ± 1.0	3.0 ± 1.3	0.032
Mode of delivery, n (%)			0.017
Caesarean section	58 (73.4)	43 (55.1)	
Vaginal delivery	20 (26.6)	35 (44.9)	
Apgar score at 5 min, n (%)			0.126
0–3	16 (20.5)	10 (12.8)	
4–7	25 (32.1)	33 (42.3)	
8–10	37 (47.4)	35 (44.9)	
Oxygen saturation, n (%)			0.003
<85	19 (24.4)	7 (9.0)	
85–94	20 (25.6)	30 (38.5)	
≥95	39 (50.0)	41 (52.5)	
Surgical risk (RACHS-1), n (%)			0.025
1–2	8 (10.3)	15 (19.2)	
3–4	67 (85.9)	59 (75.7)	
5–6	3 (3.8)	4 (5.1)	
Radical surgery	78 (100)	78 (100)	-

Note: RACHS-1, risk adjustment in congenital heart surgery.

based on the combination of clinical manifestations and echocardiography; (3) received cardiac surgery during hospitalization; and (4) completed surgical data and required variables. The exclusion criteria were as follows: (1) infection before surgery; (2) death within 48 h after surgery; (3) emergency surgery; (4) liver and kidney failure before surgery; (5) diagnosis of severe lung disease or other serious systemic diseases; (6) congenital heart diseases that underwent palliative surgery; and (7) other factors that restrained the participation in the study. All parents of the children signed written informed consent, and this study was approved by Affiliated Hospital of Inner Mongolia Medical College Hospital (Approval number: 20181219).

Data and Information Collection

The data and clinical information of children in the infection group (n = 78) and the non-infection group (n = 78) were collected and included age at operation, sex, gestational age, birth weight, mode of delivery, Apgar score at 5 min, oxygen saturation, surgical risk, and postoperative indicators. (1) Apgar score: Apgar score is a scoring system used to evaluate the organ system function and basic life status of newborns. It mainly consists of five indicators, namely, skin color, heart rate, response to stimulation, muscle tone, and respiration [14]. In the present study, the Apgar score at 5 min was recorded. (2) Oxygen saturation: The 24 h mean oxygen saturation after the surgery was recorded. (3) Surgical risk: The risk adjustment in congenital heart surgery (RACHS-1) was used to stratify surgical risk by score [9]. (4) Postoperative indicators: After reviewing the hospital database, we recorded catheter indwelling days and intensive care unit (ICU) hospitalization days. Mechanical ventilation days, blood transfusion times, and survival status were also recorded.

The criteria for judging postoperative infection are symptoms and signs of infection or imaging manifestations and evidence of microbiological infection, positive culture of blood or other specimens submitted for inspection, and postoperative infection judged by experienced doctors [8]. The types of postoperative infection include catheter-associated bloodstream infection (infections were diagnosed in patients with catheters or within 48 h after the removal of catheter), sepsis (systemic inflammatory response syndrome caused by the invasion of pathogenic microorganisms, such as bacteria, into the blood), ventilator-associated pneumonia (pneumonia that occurred 48 h after mechanical ventilation or within 48 h after extubation), pneumonia (lung infections caused by pathogens, such as bacteria and viruses, except ventilator-associated pneumonia), surgical site infection (infection that occurred in incisions or deep organs during the perioperative period), and infectious endocarditis (infection of the endocardium of the heart valve or ventricular wall caused by the direct infection of bacteria, fungi, and other microorganisms), *etc.* [15]. The indications of blood transfusion were as follows: (1)

Hemoglobin (Hb) <130 g/L for most children; (2) Hb <100 g/L for children with chronic anemia; (3) anemia-related symptoms, such as shortness of breath, difficulty breathing, apnea, tachycardia, or bradycardia, *etc.*; and (4) other situations considered necessary by professionals.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and *t*-test was used to evaluate differences between postoperative and non-infection groups. Categorical variables were represented by n (%), and chi-square test was used to assess differences between the two groups in terms of catheter indwelling days, mechanical ventilation days, blood transfusion times, ICU hospitalization days, and survival status. Multivariate logistic regression was used to analyze risk factors for postoperative infection in newborns with congenital heart disease. Receiver operation characteristic (ROC) curve was used to evaluate the performance of risk factors for determining postoperative infection. Statistical analysis was completed by IBM SPSS 26.0 software (IBM Corp., Armonk, NY, USA), and test level was set at $\alpha = 0.05$.

Results

Clinical Characteristics of Postoperative Infection and Non-Infection Groups

As shown in Table 1, 156 neonates with congenital heart disease who underwent surgery were included in this study and subjected to infection group (n = 78) and non-infection group (n = 78). Infected and non-infected groups were balanced and comparable in terms of age (11 ± 4 *vs.* 10 ± 5 days) and male proportion (56.4% *vs.* 52.6%).

Neonates in the infection group had gestational age of 38 ± 4 weeks and birth weight of 2.7 ± 1.0 kg. The proportions of cesarean section and vaginal delivery were 73.4% and 26.6%, respectively. The number of neonates with 5 min Apgar scores of 0–3, 4–7, and 8–10 were 16, 25, and 37, respectively. The proportions of children with blood oxygen saturation of <85%, 85%–94%, and ≥95% were 24.4%, 25.6%, and 50.0%, respectively. The number of neonates with RACHS-1 scores of 1–2, 3–4, and 5–6 were 8, 67, and 3, respectively.

The gestational age of neonates in the non-infected group was 39 ± 3 weeks, and the birth weight was 3.0 ± 1.3 kg. The proportions of cesarean section and vaginal delivery were 55.1% and 44.9%, respectively. The number of neonates with 5 min Apgar scores of 0–3, 4–7, and 8–10 were 10, 33, and 35, respectively. The proportions of children with blood oxygen saturation of <85%, 85%–94%, and ≥95% were 9.0%, 38.5%, and 52.5%, respectively. The number of neonates with RACHS-1 scores of 1–2, 3–4, and 5–6 were 15, 59, and 4, respectively.

Table 2. Types of postoperative infection in newborns with congenital heart disease.

Postoperative infection type	n	%
Surgical site infection	18	23.1
Pneumonia	7	9.0
Sepsis	21	26.9
Ventilator-associated pneumonia	14	17.9
Catheter related infection	15	19.2
Endocarditis	3	3.9
Total	78	100

Children in the infected group had lower birth weight, higher proportion of cesarean section, lower oxygen saturation levels, and higher RACHS-1 scores than those in the non-infected group. Gestational age and Apgar score at 5 min were not significantly different between infected and non-infected groups.

Types of Postoperative Infection in Neonates with Congenital Heart Disease

The children were divided into groups according to different types of postoperative infection. As shown in Table 2, the proportions of neonates with surgical site infection, pneumonia, sepsis, ventilator-associated pneumonia, catheter-related infection, and endocarditis were 23.1% (18/78), 9.0% (7/78), 26.9% (21/78), 17.9% (14/78), 19.2% (15/78), and 3.9% (3/78), respectively.

Comparison of Postoperative Indicators between Infection and Non-Infection Groups

Table 3 compares the postoperative indicators between the infection and non-infection groups. In the infection group, 21 and 57 neonates had catheter indwelling days of ≤14 and >14, respectively, and 33 and 45 neonates had mechanical ventilation days of ≤7 and >7, respectively. The proportions of neonates with blood transfusion <5 times and ≥5 times were 38.5% and 61.5%, respectively. The proportions of newborns with ICU hospitalization of ≤10 days and >10 days were 32.2% and 67.8%, respectively. The proportions of neonates whose postoperative status was survival and death were 96.2% and 3.8%, respectively.

In the non-infected group, 60 and 18 neonates had catheter indwelling days of ≤14 and >14, respectively, and 52 and 26 neonates with mechanical ventilation days of ≤7 and >7, respectively. The proportions of neonates with blood transfusion <5 times and ≥5 times were 60.3% and 39.7%, respectively. The proportions of newborns with ICU hospitalization ≤10 days and >10 days were 78.2% and 22.8%, respectively. The proportions of newborns whose postoperative status was alive and dead were 98.7% and 1.3%, respectively.

Table 3. Comparison of postoperative indicators between the infection and non-infection groups of neonates with congenital heart disease.

	Infection group	Non-infection group	*p* value
Catheter indwelling, n (%)			<0.001
≤14 days	21 (26.9)	60 (76.9)	
>14 days	57 (73.1)	18 (23.1)	
Mechanical ventilation, n (%)			<0.001
≤7 days	33 (42.3)	52 (66.7)	
<7 days	45 (57.7)	26 (33.3)	
Blood transfusions times, n (%)			<0.001
<5	30 (38.5)	47 (60.3)	
≥5	48 (61.5)	31 (39.7)	
ICU stay, n (%)			<0.001
≤10 days	19 (32.2)	61 (78.2)	
>10 days	59 (67.8)	17 (22.8)	
Survival status, n (%)			0.24
Survival	75 (96.2)	77 (98.7)	
Death	3 (3.8)	1 (1.3)	

Note: ICU, intensive care unit.

Table 4. Multivariate logistic regression analysis of risk factors for postoperative infection.

	B	S.E.	Wald χ^2	*p* value	OR (95% CI)
Oxygen saturation <85%	3.024	0.295	12.156	0.001	6.5 (3.7, 15.4)
Catheter indwelling >14 days	1.952	0.324	8.776	0.009	3.3 (2.1, 10.7)
ICU stay >10 days	3.964	0.310	15.241	0.001	7.1 (3.6, 18.5)

Neonates in the infection group had longer catheter indwelling time, mechanical ventilation duration, and ICU hospitalization days and more blood transfusion times than those in the non-infection group. Postoperative mortality was not significantly different between the two groups.

Multivariate Logistic Regression Analysis of Risk Factors for Postoperative Infection

Table 4 shows the risk factors for postoperative infection assessed by multivariate logistic regression analysis. A multivariate logistic regression model was established with the occurrence of postoperative infection as the dependent variable and variables with statistical significance and clinical significance in univariate analysis as the independent variables. Oxygen saturation <85%, catheter indwelling >14 days, and ICU hospitalization >10 days were independent risk factors for postoperative infection in newborns with congenital heart disease.

Neonates with oxygen saturation <85% had an OR (95% CI) of 6.5 (3.7, 15.4) for postoperative infection compared with oxygen saturation ≥85%. The OR (95% CI) for postoperative infection was 3.3 (2.1, 10.7) for neonates with >14 days of catheter indwelling compared with ≤14 days. The OR (95% CI) of neonates with >10 days in ICU for postoperative infection was 7.1 (3.6, 18.5) compared with ≤10 days.

ROC for Determining Postoperative Infection

Fig. 2 shows the ROC of oxygen saturation, time of catheter indwelling, and ICU stay for determining postoperative infection. The area under the curve (AUC), sensitivity, and specificity of oxygen saturation were 0.694, 57.7%, and 77.2% ($p < 0.001$). The Youden index and the cut-off value of oxygen saturation were 0.359 and 85%, respectively. The AUC, sensitivity, and specificity of time of catheter indwelling were 0.734, 41.0%, and 89.7%, respectively ($p < 0.001$). The Youden index and the cut-off value of catheter indwelling were 0.333 and 14, respectively. The AUC, sensitivity, and specificity of ICU stay were 0.687, 64.1%, and 62.8%, respectively ($p < 0.001$). The Youden index and the cut-off value of ICU stay were 0.269 and 10, respectively.

Discussion

Neonates in the postoperative infection group had longer catheter indwelling time, mechanical ventilation time, and ICU hospitalization days and more blood transfusion times than those in the non-infection group. Overall, oxygen saturation <85%, catheter indwelling >14 days, and ICU hospitalization >10 days are independent risk factors for postoperative infection in neonates with congenital heart disease.

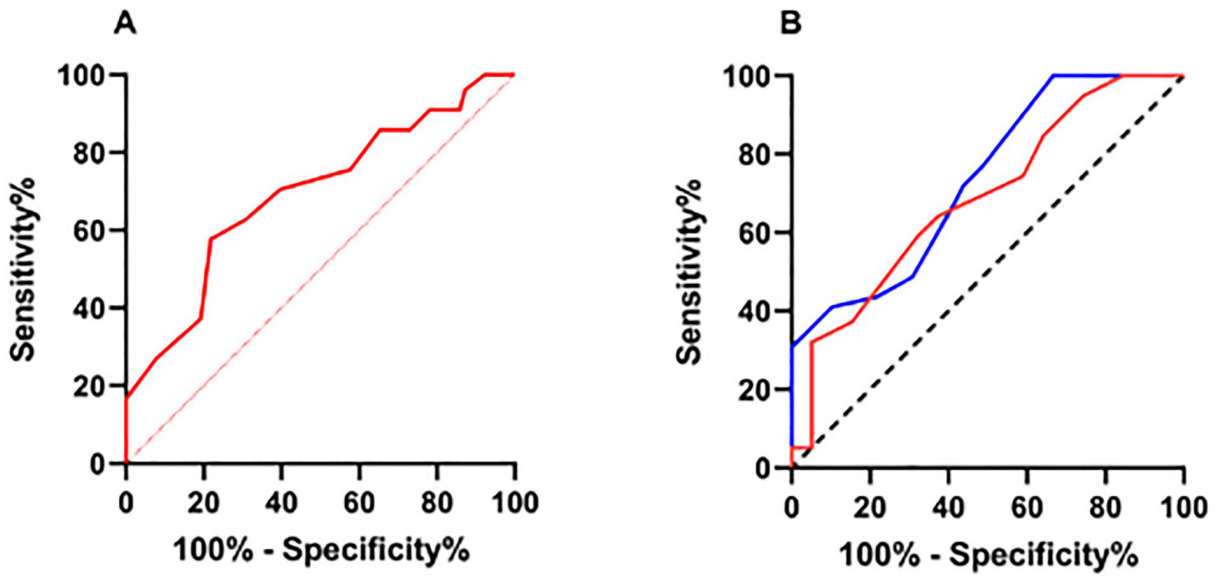

Fig. 2. ROC of oxygen saturation, time of catheter indwelling, and ICU stay for determining postoperative infection. (A) The red curve was the oxygen saturation. The AUC, sensitivity, and specificity of oxygen saturation were 0.694, 57.7%, and 77.2%, respectively ($p < 0.001$). The Youden index and the cut-off value of oxygen saturation were 0.359 and 85%, respectively. (B) The blue curve was time of catheter indwelling. The AUC, sensitivity, and specificity of catheter indwelling were 0.734, 41.0%, and 89.7%, respectively ($p < 0.001$). The Youden index and the cut-off value of catheter indwelling were 0.333 and 14, respectively. The red curve was time of ICU stay. The AUC, sensitivity, and specificity of ICU stay were 0.687, 64.1%, and 62.8%, respectively ($p < 0.001$). The Youden index and the cut-off value of ICU stay were 0.269 and 10, respectively. ROC, receiver operation characteristic; AUC, area under the curve.

Table 2 shows that among neonates with congenital heart disease, the most common postoperative infections were sepsis (26.9%), surgical site infection (23.1%), and catheter-related infection (19.2%). A study of 511 children found that among children undergoing cardiac surgery, surgical site infections (33.8, 27/80) and bloodstream infections (sepsis, 25%, 20/80) are the common types of postoperative infection [16]. Children with bloodstream infections have more severe symptoms and are more likely to have fever; the most common pathogens causing bloodstream infections are coagulase-negative staphylococci [17]. A multicenter study evaluated infection and outcomes after congenital heart surgery on 32,856 children at 28 centers; the results suggested that sepsis infection was the most common type of infection (51.3%), followed by surgical site infection (35.1%) [18]. Evidence indicates that catheter-associated infection is also a common type of infection after cardiac surgery in children [19].

A 2017 international multicenter study aimed at improving outcomes after cardiac surgery in children found that low blood oxygen saturation (<85%) is a risk factor for postoperative infection (OR: 1.5; 95% CI: 1.2–1.9; $p < 0.001$) [8]. This study also found that decreased oxygen saturation is independently associated with the increased risk of postoperative infection in newborns with congenital heart disease. This finding indicates that these patients have poorer cardiopulmonary function and weaker resistance to infection [20].

Evidence indicates that catheter indwelling duration (deep venous catheters, *etc*.) is an independent risk factor for postoperative infection, and the OR value is 6.2 (95% CI: 1.4–27.4) when the indwelling time is 7–10 days; the OR value increases when the indwelling time is >10 days (OR: 14.3) [21]. The present results also suggest that prolonged catheter indwelling is associated with an increased risk of postoperative infection. Catheter indwelling is an invasive diagnosis and treatment operation. Fibrin deposition will occur after 24 to 48 h, providing a good parasitic place for microorganisms and allowing bacteria to multiply and cause infection [22]. Long ICU stays and total hospital stays may increase the exposure of children to microorganisms, thereby increasing the risk of postoperative infections [23]. Other studies also suggested some important factors that may affect postoperative infection, including age, body mass index (BMI), neutrophils and lymphocytes, *etc*. [9,13].

Analysis and identification of risk factors for postoperative infection are important for identifying high-risk children and developing strategies to prevent postoperative infection. However, this study has the following limitations. First, this study adopted a single-center cross-sectional design, which cannot explain the relationship between risk factors and postoperative infection. Second, considering the small sample size, we did not have sufficient statistical power to perform subgroup analysis. Third, the data of laboratory tests and pathogenic bacteria were not

recorded in detail, and possible confounding factors in these variables may affect the results. Fourth, we did not record the severity of infection and did not follow up the treatment outcome of postoperative infection, which require further studies for confirmation.

Conclusion

In conclusion, in neonates with congenital heart disease undergoing cardiac surgery, low oxygen saturation, prolonged catheter indwelling days, and prolonged ICU stay were independent risk factors for postoperative infection. This study provides clinical implications for developing responses to these risk factors.

Availability of Data and Materials

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Author Contributions

Both the listed authors in the study participated in the design of the study and performed the statistical analysis, conceived of the study, and helped to draft the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both 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

All parents of the children signed written informed consent, and this study was approved by Affiliated Hospital of Inner Mongolia Medical College Hospital (Approval number: 20181219).

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Conflict of Interest

The authors declare no conflict of interest.

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