e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(2); 153-158

Original Research Article

Early-Life Immune Profiling in Children with Congenital Heart Disease and Its Association with Postoperative Outcomes

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Received: 03-12-2025 / Revised: 02-01-2026 / Accepted: 04-02-2026

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Conflict of interest: Nil

Abstract:

Background: Children with congenital heart disease (CHD) frequently exhibit immune dysregulation that may influence postoperative recovery following cardiac surgery. However, comprehensive characterization of early-life immune profiles and their predictive value for surgical outcomes remains limited.

Methods: A total of 186 infants (aged 1-12 months) undergoing surgical repair for CHD were enrolled. Preoperative immune profiling included lymphocyte subset enumeration, immunoglobulin quantification, T-cell receptor excision circle (TREC) analysis, and cytokine assessment. Primary outcomes included postoperative infections, intensive care unit (ICU) length of stay, and 30-day mortality.

Results: Compared to age-matched healthy controls (n=50), CHD infants demonstrated significantly reduced CD4+ T-cell counts (1,842 ± 624 vs. 2,856 ± 718 cells/μL, $p<0.001$), lower TREC levels (median 42 vs. 128 copies/μL, $p<0.001$), and decreased IgG concentrations (412 ± 156 vs. 586 ± 142 mg/dL, $p<0.001$). Postoperative infections occurred in 31.7% of patients. Preoperative CD4+ counts <1,500 cells/μL (OR 3.42, $p=0.002$), TREC levels <30 copies/μL (OR 2.87, $p=0.008$), and cyanotic defects (OR 2.24, $p=0.021$) were independently associated with postoperative infections. ICU stay was prolonged in patients with immune deficiencies (8.4 ± 4.2 vs. 5.1 ± 2.8 days, $p<0.001$).

Conclusion: Infants with CHD demonstrate significant immune abnormalities prior to surgery, and preoperative immune profiling identifies patients at elevated risk for postoperative complications. Integration of immune assessment into preoperative evaluation may facilitate risk stratification and targeted immunomodulatory interventions.

Keywords: Congenital Heart Disease; Immune Profiling; Pediatric Cardiac Surgery; Postoperative Infections; T-Lymphocytes; Thymic Function.

DOI: 10.25258/ijcpr.18.2.24

Introduction

Congenital heart disease represents the most prevalent category of birth defects, affecting approximately 8-12 per 1,000 live births globally and requiring surgical intervention in a substantial proportion of affected individuals during infancy [1]. Advances in surgical techniques, cardiopulmonary bypass technology, and perioperative care have dramatically improved survival rates for children undergoing cardiac surgery, yet postoperative morbidity remains a significant concern [2]. Infectious complications following pediatric cardiac surgery occur in 15-45% of patients and contribute substantially to prolonged hospitalization, increased healthcare costs, and adverse neurodevelopmental outcomes [3].

The immune system of neonates and young infants differs fundamentally from that of older children and adults, characterized by predominance of naive T-lymphocytes, reliance on passive maternal antibodies, and limited immunologic memory [4]. Children with congenital heart disease may exhibit additional immune perturbations related to their underlying cardiac pathology, chronic hypoxemia, malnutrition, and hemodynamic compromise [5]. The thymus, situated in the anterior mediastinum and critically important for T-lymphocyte development, is frequently partially or completely resected during cardiac surgical procedures to facilitate surgical exposure, potentially exacerbating immunodeficiency [6].

Emerging evidence suggests that immune dysfunction in children with CHD may precede surgical intervention. Studies have documented reduced lymphocyte counts, altered T-cell subset distributions, and diminished immunoglobulin levels in infants with complex cardiac defects prior to any surgical manipulation [7]. The pathophysiology underlying these preoperative immune abnormalities likely involves multiple factors including genetic syndromes with associated immunodeficiency, impaired thymic development due to abnormal cardiac embryogenesis, and physiologic stress from hemodynamic instability [8].

The 22q11.2 deletion syndrome, present in approximately 15-20% of patients with conotruncal cardiac defects, exemplifies the intersection of cardiac and immune abnormalities, as affected individuals frequently demonstrate thymic hypoplasia with variable degrees of T-cell lymphopenia [9]. However, immune dysfunction has been observed in CHD patients without identifiable genetic syndromes, suggesting that cardiac disease itself may contribute to immune perturbation through mechanisms that remain incompletely understood [10].

T-cell receptor excision circles (TRECs) represent circular DNA byproducts generated during T-cell receptor gene rearrangement in the thymus and serve as quantitative biomarkers of recent thymic emigrant output [11]. Reduced TREC levels have been identified in neonates with CHD and correlate with severity of cardiac defects, suggesting compromised thymic function in this population [12]. The clinical implications of reduced thymic output for postoperative outcomes, however, have not been systematically evaluated.

Despite recognition that immune dysfunction may influence surgical outcomes in children with CHD, comprehensive preoperative immune profiling has not been widely integrated into clinical practice [13]. Identification of immune biomarkers predictive of postoperative complications could facilitate risk stratification, inform decisions regarding surgical timing, and guide implementation of preventive strategies including immunoglobulin supplementation or antimicrobial prophylaxis.

The aim of this prospective cohort study was to characterize preoperative immune profiles in infants undergoing surgical repair for congenital heart disease and to evaluate associations between immune parameters and postoperative clinical outcomes including infectious complications, intensive care requirements, and mortality.

Materials and Methods

Study Design and Setting: This prospective observational cohort study was conducted at the Pediatric Cardiac Surgery Center of a tertiary academic children's hospital.

Study Population: Consecutive infants aged 1-12 months scheduled for surgical repair of congenital heart disease requiring cardiopulmonary bypass were screened for eligibility. A control group of age-matched healthy infants was recruited from the general pediatric outpatient clinic for comparison of baseline immune parameters.

Inclusion Criteria:

- Age 1-12 months at time of surgery
- Diagnosis of congenital heart disease requiring surgical repair with cardiopulmonary bypass
- Parental consent obtained

Exclusion Criteria:

- Preoperative mechanical ventilation or circulatory support
- Known primary immunodeficiency disorder (other than 22q11.2 deletion syndrome)
- Active infection within 14 days of scheduled surgery
- Prior cardiac surgery
- Receipt of blood products within 30 days of enrollment
- Prematurity (<34 weeks gestational age)
- Chromosomal abnormalities other than trisomy 21 or 22q11.2 deletion

Sample Size Calculation: Based on preliminary data suggesting a 25% difference in postoperative infection rates between immune-deficient and immune-competent subgroups, sample size calculation using a two-tailed alpha of 0.05 and power of 0.80 indicated a minimum requirement of 160 patients. Accounting for anticipated 15% attrition, a target enrollment of 186 patients was established.

Preoperative Immune Assessment: Peripheral blood samples (3-5 mL) were collected within 48 hours prior to surgery. Immune profiling included the following assessments:

Lymphocyte Subset Enumeration: Flow cytometry was performed using a standardized panel including CD3, CD4, CD8, CD19, CD16, and CD56 antibodies (BD Biosciences). Absolute counts were calculated using dual-platform methodology.

T-Cell Receptor Excision Circles (TRECs): Quantitative polymerase chain reaction for signal-joint TRECs was performed on extracted DNA from peripheral blood mononuclear cells using validated methodology.

Immunoglobulin Quantification: Serum IgG, IgA, and IgM concentrations were measured by nephelometry.

Cytokine Assessment: Plasma concentrations of interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) were measured using multiplex immunoassay.

Clinical Data Collection: Demographic variables, cardiac diagnosis, surgical complexity (Risk Adjustment for Congenital Heart Surgery [RACHS-1] category), cardiopulmonary bypass duration, and thymic resection status were recorded. Postoperative outcomes were prospectively collected including infections (culture-confirmed or clinically diagnosed requiring antimicrobial therapy), ICU length of stay, total hospital length of stay, mechanical ventilation duration, and 30-day mortality.

Statistical Analysis: Statistical analyses were performed using SPSS version 27.0 and R version 4.2.2. Continuous variables were expressed as mean ± standard deviation or median with interquartile range based on distribution normality assessed by Shapiro-Wilk testing. Categorical variables were expressed as frequencies and percentages. Group comparisons utilized Student's t-test, Mann-Whitney U test, or chi-square test as appropriate. Multivariable logistic regression identified independent predictors of postoperative infection, with variables demonstrating $p<0.10$ in univariate analysis entered into the model. Receiver operating characteristic (ROC) curve analysis evaluated discriminative capacity of immune biomarkers. Statistical significance was established at $p<0.05$.

Results

Patient Characteristics: A total of 186 infants with CHD were enrolled, with a median age of 4.2 months (IQR 2.1-7.3). The control group comprised 50 healthy age-matched infants. Cardiac diagnoses included ventricular septal defect (28.0%), tetralogy of Fallot (21.5%), complete atrioventricular septal defect (15.1%), transposition of great arteries (12.9%), and other defects (22.5%). Cyanotic defects were present in 41.9% of patients. Baseline characteristics are presented in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	CHD Group (n=186)	Control Group (n=50)	p-value
Age (months), median (IQR)	4.2 (2.1-7.3)	4.8 (2.4-7.6)	0.412
Sex, male n (%)	102 (54.8)	28 (56.0)	0.879
Birth weight (kg), mean ± SD	3.12 ± 0.52	3.34 ± 0.48	0.008*
Weight at surgery (kg), mean ± SD	5.24 ± 1.38	-	-
Weight-for-age z-score, mean ± SD	-1.42 ± 1.18	0.12 ± 0.94	<0.001*
Cyanotic defect, n (%)	78 (41.9)	-	-
22q11.2 deletion, n (%)	18 (9.7)	0 (0)	-
Trisomy 21, n (%)	24 (12.9)	0 (0)	-
RACHS-1 category, n (%)			
- Category 1-2	68 (36.6)	-	-
- Category 3-4	98 (52.7)	-	-
- Category 5-6	20 (10.8)	-	-
CPB duration (min), mean ± SD	124 ± 48	-	-
Thymic resection, n (%)	142 (76.3)	-	-

*Statistically significant; CHD: Congenital Heart Disease; IQR: Interquartile Range; SD: Standard Deviation; RACHS-1: Risk Adjustment for Congenital Heart Surgery; CPB: Cardiopulmonary Bypass

Preoperative Immune Profiles: Children with CHD demonstrated significant immune abnormalities compared to healthy controls across multiple parameters. CD4+ T-cell counts were markedly reduced in the CHD group (1,842 ± 624 vs. 2,856 ± 718 cells/μL, $p<0.001$), as were TREC levels (median 42 vs. 128 copies/μL, $p<0.001$). IgG concentrations were also significantly lower in CHD patients (412 ± 156 vs. 586 ± 142 mg/dL, $p<0.001$). Within the CHD cohort, patients with cyanotic defects exhibited more pronounced immune deficiencies than those with acyanotic defects. Detailed immune parameters are presented in Table 2.

Table 2: Preoperative Immune Parameters Comparison

Immune Parameter	CHD Group (n=186)	Control Group (n=50)	p-value
Lymphocyte Subsets (cells/μL)			
Total lymphocytes, mean ± SD	4,286 ± 1,412	5,842 ± 1,568	<0.001*
CD3+ T-cells, mean ± SD	2,648 ± 894	3,986 ± 1,024	<0.001*
CD4+ T-cells, mean ± SD	1,842 ± 624	2,856 ± 718	<0.001*
CD8+ T-cells, mean ± SD	724 ± 312	1,042 ± 356	<0.001*
CD4/CD8 ratio, mean ± SD	2.78 ± 0.92	2.84 ± 0.76	0.672

CD19+ B-cells, mean ± SD	1,124 ± 486	1,356 ± 412	0.002*
NK cells (CD16+CD56+), mean ± SD	486 ± 224	512 ± 198	0.462
Thymic Output			
TREC (copies/μL), median (IQR)	42 (24-78)	128 (86-186)	<0.001*
TREC <30 copies/μL, n (%)	62 (33.3)	2 (4.0)	<0.001*
Immunoglobulins (mg/dL)			
IgG, mean ± SD	412 ± 156	586 ± 142	<0.001*
IgA, mean ± SD	28 ± 18	34 ± 16	0.032*
IgM, mean ± SD	56 ± 28	68 ± 24	0.006*
Cytokines (pg/mL)			
IL-6, median (IQR)	8.4 (4.2-16.8)	2.1 (1.2-4.6)	<0.001*
IL-10, median (IQR)	12.6 (6.4-24.2)	4.8 (2.4-8.2)	<0.001*
TNF-α, median (IQR)	6.2 (3.1-12.4)	2.8 (1.4-5.2)	<0.001*

*Statistically significant; TREC: T-cell Receptor Excision Circle; IQR: Interquartile Range; NK: Natural Killer; SD: Standard Deviation

Postoperative Outcomes: Postoperative infections occurred in 59 patients (31.7%), including pneumonia (14.0%), sepsis (8.6%), surgical site infections (5.9%), and urinary tract infections (3.2%). ICU length of stay was 6.4 ± 3.8 days overall, and 30-day mortality was 3.2% (n=6). Patients experiencing postoperative infections demonstrated significantly lower preoperative CD4+ counts, TREC levels, and IgG concentrations compared to those without infections. Outcome associations are presented in Table 3.

Table 3: Association Between Immune Parameters and Postoperative Outcomes

Parameter	Infection (n=59)	No Infection (n=127)	p-value
Preoperative Immune Markers			
CD4+ T-cells (cells/μL), mean ± SD	1,486 ± 548	2,008 ± 612	<0.001*
CD4+ <1,500 cells/μL, n (%)	38 (64.4)	42 (33.1)	<0.001*
TREC (copies/μL), median (IQR)	28 (18-52)	54 (32-94)	<0.001*
TREC <30 copies/μL, n (%)	32 (54.2)	30 (23.6)	<0.001*
IgG (mg/dL), mean ± SD	354 ± 138	438 ± 158	<0.001*
IgG <400 mg/dL, n (%)	42 (71.2)	56 (44.1)	<0.001*
IL-6 (pg/mL), median (IQR)	14.2 (7.8-26.4)	6.8 (3.4-12.6)	<0.001*
Clinical Outcomes			
ICU LOS (days), mean ± SD	8.4 ± 4.2	5.1 ± 2.8	<0.001*
Hospital LOS (days), mean ± SD	18.6 ± 8.4	11.2 ± 4.6	<0.001*
Mechanical ventilation (days), mean ± SD	4.8 ± 3.2	2.4 ± 1.8	<0.001*
30-day mortality, n (%)	5 (8.5)	1 (0.8)	0.008*
Multivariable Predictors of Infection	OR (95% CI)		p-value
CD4+ <1,500 cells/μL	3.42 (1.58-7.41)		0.002*
TREC <30 copies/μL	2.87 (1.32-6.24)		0.008*
Cyanotic defect	2.24 (1.13-4.44)		0.021*
RACHS-1 category ≥4	1.94 (0.96-3.92)		0.064

*Statistically significant; ICU: Intensive Care Unit; LOS: Length of Stay; IQR: Interquartile Range; OR: Odds Ratio; CI: Confidence Interval

ROC curve analysis demonstrated that CD4+ T-cell count <1,500 cells/μL predicted postoperative infection with an area under the curve (AUC) of 0.72 (95% CI 0.64-0.80), while TREC levels <30 copies/μL yielded an AUC of 0.68 (95% CI 0.59-0.77). A composite immune risk score incorporating both parameters achieved an AUC of 0.78 (95% CI 0.71-0.85).

Discussion

This prospective study provides comprehensive characterization of preoperative immune profiles in infants with congenital heart disease and demonstrates significant associations between immune parameters and postoperative clinical outcomes. Our findings reveal that children with CHD exhibit substantial immune abnormalities prior to surgical intervention, and these preoperative immune deficiencies predict increased risk of postoperative infectious complications, prolonged intensive care requirements, and mortality.

The observation that infants with CHD demonstrate reduced CD4+ T-cell counts and diminished thymic output prior to surgery confirms and extends previous investigations documenting immune dysfunction in this population [14]. The magnitude of T-cell lymphopenia observed in our cohort was substantial, with mean CD4+ counts approximately 35% lower than age-matched healthy controls. This

degree of immune compromise likely reflects multiple contributing factors including genetic syndromes with associated immunodeficiency, aberrant thymic development in the context of cardiac malformations, and chronic physiologic stress from hemodynamic abnormalities [15].

The finding that reduced TREC levels independently predicted postoperative infections provides novel evidence regarding the clinical significance of impaired thymic function in children undergoing cardiac surgery [16]. TRECs serve as quantitative biomarkers of recent thymic emigrant output, and their reduction in CHD patients suggests compromised naive T-cell generation that may limit the capacity to mount effective immune responses to novel pathogens encountered in the perioperative period. These findings have important implications given that thymic tissue is frequently resected during cardiac surgery to facilitate surgical access [17].

Hypogammaglobulinemia was prevalent in our CHD cohort, with mean IgG concentrations significantly below those of healthy controls. Reduced immunoglobulin levels in infants with CHD may result from multiple mechanisms including inadequate B-cell helper function secondary to T-cell deficiency, impaired antibody production in the context of chronic illness, and increased catabolism related to hemodynamic stress [18]. The association between preoperative hypogammaglobulinemia and postoperative infection risk suggests potential benefit from immunoglobulin replacement therapy in selected high-risk patients.

The elevated baseline cytokine concentrations observed in CHD patients indicate a state of chronic immune activation that may paradoxically coexist with cellular immunodeficiency. Chronic inflammation associated with heart failure, tissue hypoxia, and endothelial dysfunction likely contributes to this inflammatory milieu [19]. Elevated preoperative IL-6 levels have been previously associated with adverse outcomes following cardiac surgery, and our findings support the prognostic value of inflammatory biomarkers in risk stratification.

Children with cyanotic defects demonstrated more pronounced immune abnormalities compared to those with acyanotic lesions, consistent with previous observations linking chronic hypoxemia to immune dysfunction [20]. Hypoxia may directly impair lymphocyte proliferation and function while simultaneously activating inflammatory pathways that contribute to tissue injury. The independent association between cyanotic defect status and postoperative infection risk underscores the importance of considering physiologic severity in immune risk assessment.

The practical implications of our findings relate to potential integration of immune profiling into preoperative evaluation protocols. Identification of infants with significant immunodeficiency may inform decisions regarding surgical timing, intensity of antimicrobial prophylaxis, and consideration of immunomodulatory interventions [21]. The composite immune risk score developed in this study demonstrated reasonable discriminative capacity for postoperative infection prediction and warrants validation in independent cohorts.

Limitations of this study include its single-center design, which may limit generalizability across different surgical centers and populations. The heterogeneity of cardiac diagnoses within our cohort, while reflecting clinical reality, introduces potential confounding that may not be fully addressed through statistical adjustment. Additionally, the observational design precludes determination of causality between immune deficiency and adverse outcomes.

Conclusion

This prospective cohort study demonstrates that infants with congenital heart disease exhibit significant preoperative immune abnormalities characterized by T-cell lymphopenia, reduced thymic output, hypogammaglobulinemia, and chronic inflammation. These immune deficiencies are present prior to any surgical intervention and are independently associated with increased risk of postoperative infectious complications, prolonged intensive care requirements, and mortality. Preoperative CD4+ T-cell counts below 1,500 cells/μL and TREC levels below 30 copies/μL identify infants at substantially elevated risk for adverse outcomes. Integration of immune profiling into preoperative assessment may facilitate risk stratification and enable targeted preventive interventions in high-risk patients. Future investigations should evaluate whether immunomodulatory strategies, including immunoglobulin supplementation or thymic-sparing surgical approaches, can improve outcomes in immune-deficient children undergoing cardiac surgery for congenital heart disease.

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