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ARTICLE

# Glucocorticoid Therapy for Severe Infection in Children with Congenital Heart Disease: Effects on Immune Regulation and Clinical Outcomes

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**ABSTRACT: Background:** Children with congenital heart disease (CHD) complicated by severe infection often present with immature immune function and poor prognosis. Evidence supporting the use of glucocorticoids in this population, particularly with dynamic immune monitoring, remains limited. **Methods:** A retrospective analysis was conducted on 183 CHD children with severe infections admitted to the Pediatric Intensive Care Unit (PICU) from 2019 to 2023. Patients were divided into two groups: the glucocorticoid intervention group ($n$ = 92, methylprednisolone + standard treatment) and the control group ($n$ = 91, standard treatment). Immune indicators (Interleukins-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT), $CD4^+/CD8^+$ ratio at Day 0, 3, 7, and 14), clinical outcomes, and adverse events were compared using $t$-tests, Kaplan-Meier survival analysis, and Cox regression. **Results:** The glucocorticoid group exhibited a faster reduction in immune indicators (Day 7 IL-6: 62.9% vs. 29.2%; $CD4^+/CD8^+$ ratio: 0.93 vs. 0.79, $p < 0.05$). Additionally, the intervention group had shorter infection control times, ICU stays, and ventilation durations (all $p < 0.001$). A significant reduction in 28-day mortality was observed in the surgical subgroup (13.0% vs. 40.0%, $p = 0.042$; adjusted hazard ratio (aHR) = 0.44, $p = 0.030$), although the interaction between glucocorticoid use and surgical status was not statistically significant ($p = 0.37$). Higher rates of hyperglycemia (33.7% vs. 8.8%) and secondary infections (18.5% vs. 7.7%, $p < 0.05$) were observed, but these complications were manageable. **Conclusions:** Glucocorticoid therapy improves outcomes in CHD children with severe infections, with significant mortality reduction noted in the surgical subgroup. However, the lack of a statistically significant interaction with surgical status suggests that the benefits of glucocorticoids may not be exclusive to surgical patients.

**KEYWORDS:** Congenital heart disease; severe infection; glucocorticoid; immune regulation indicators; clinical outcome; children

## 1 Introduction

Congenital heart disease (CHD) is the most prevalent congenital structural heart abnormality in children [1,2], with a global incidence of approximately 8–10 per thousand live births [3–5]. Advances in diagnostic methods and surgical treatments have significantly improved survival rates for children with CHD; however, severe infections remain a critical factor influencing both short-term and long-term

prognosis [6–8]. CHD children have underdeveloped immune systems because of the inherent cardiac pathophysiologic defects, low cardiac reserve, and chronic hypoxia. Consequently, they are likely to be overwhelmed with inflammatory reactions and immunosuppression in case of an infection, which results in dysfunction of multiple organs. This may clinically be characterized by poor cardiac performance, respiratory failure, shock, and high mortality rates [9,10].

Recent studies have highlighted that severe infections in children with CHD are frequently accompanied by abnormal immune regulatory markers. Interleukin-6 (IL-6), a pro-inflammatory cytokine, increases markedly during the early stages of infection and correlates closely with the severity of systemic inflammation and organ damage [11,12]. Classic inflammatory and bacterial infection markers such as C-reactive protein (CRP) and procalcitonin (PCT) are useful for dynamic infection monitoring and tracking infection resolution [13,14]. A reduced $CD4^+/CD8^+$ T-cell ratio signals immunosuppression, which may be linked to persistent infections, disease progression, and postoperative complications [15,16]. These biomarkers are not only valuable for infection assessment and risk stratification but also present potential targets for immune modulation.

Glucocorticoids, as classic immunomodulatory agents, are believed to play a role in managing infection-related inflammatory storms and improving organ function by inhibiting signaling pathways such as NF-κB and STAT3. This leads to a reduction in pro-inflammatory cytokine release and modulation of T cell subset distribution [17,18]. In studies involving adult sepsis and the postoperative care of some pediatric populations, glucocorticoids have been shown to shorten the time to infection resolution and lower inflammatory cytokine levels. However, evidence supporting their use in children with CHD complicated by severe infection is limited [19,20]. In particular, the absence of research that systematically monitors the dynamic changes of immunomodulatory markers (e.g., IL-6, CRP, PCT, and $CD4^+/CD8^+$ ratio) throughout multiple time points (e.g., Day 0, 3, 7, and 14) is required to evaluate the efficacy and safety of glucocorticoid interventions.

The research on glucocorticoid interventions in children with CHD (both domestic and international) has focused mostly on controlling postoperative inflammation and improving organ function in the short term. Nonetheless, such studies are limited by the small number of samples, the infrequent use of single observation indicators, the use of single-time-point measurements, and a significant deficiency in systematic, dynamic immunological surveillance [21]. Although certain studies indicate that glucocorticoids can hasten the speed of infection resolution and shorten ICU stay, there is no consensus regarding the effects on immunomodulatory markers and their association with clinical outcomes. In addition, the multi-time-point indicator monitoring systems have not incorporated risk assessment of adverse events, like hyperglycemia and secondary infections. There exist some research gaps and debates on the use of glucocorticoids in this particular population. In the present moment, there is no common agreement on the indication criteria, the best dose, and the time of glucocorticoid therapy in children with CHD complicated with severe infection, and the outcomes of different studies are rather inconsistent. Three key gaps in research have been determined: (1) the absence of standard criteria of glucocorticoid indications, dosage, and duration in this patient group; (2) dynamic monitoring of the markers of immune regulation (IL-6, CRP, PCT, $CD4^+/CD8^+$ ratio) during multiple time points; (3) the inability to determine the correlation between the alterations in the markers of immune regulation and This paper fills these gaps by assessing a standardized methylprednisolone protocol, dynamically assessing immune markers and relating these changes to clinical outcomes, which will be consistent with the actual research design of this manuscript.

In this context, we retrospectively analyzed the children with CHD with severe infection admitted to the Pediatric Intensive Care Unit (PICU) of our hospital from 2019 to 2023. The main purposes were to

evaluate the clinical efficacy and safety of glucocorticoid intervention combined with routine treatment, to observe the dynamic changes of IL-6, CRP, PCT and $CD4^+/CD8^+$ ratio at days 0, 3, 7 and 14, and to analyze the correlation between the changes of immunomodulatory index (including $CD4^+/CD8^+$ ratio) and clinical outcomes (including time to infection resolution, ICU stay, and 28-day mortality). We aimed to provide evidence to support clinical practice, to elucidate the immunological effect of glucocorticoid intervention in children with CHD complicated with severe infection, and to provide a basis for individualized treatment.

## 2 Materials and Methods

### *2.1 Study Subjects*

A retrospective analysis was conducted on the clinical data of 183 children with CHD complicated by severe infection, who were admitted to the PICU of our hospital between January 2019 and December 2023.

**Inclusion criteria:** (1) Diagnosis of CHD confirmed by echocardiography, in accordance with the *Diagnostic Criteria for Congenital Heart Disease* [22]; (2) Diagnosis of severe infection based on the *Guidelines for the Diagnosis and Treatment of Pediatric Sepsis and Septic Shock (2020 Edition)* [23] (Pediatric Index of Mortality 2 [PICU-SSC] score $\geq 8$ or complicated by organ dysfunction); (3) Age at admission between 1 month and 14 years; (4) Complete clinical data, including baseline indicators, treatment regimens, and follow-up outcomes.

**Exclusion criteria:** (1) Contraindications to glucocorticoid use (e.g., active tuberculosis, severe fungal infections); (2) Glucocorticoid use within 2 weeks before admission; (3) Comorbidities such as malignant tumors or immunodeficiency diseases; (4) Follow-up duration < 28 days or missing data.

To minimize information bias, strict inclusion criteria were applied, ensuring complete baseline data and accessible key laboratory indicators. Patients with severe immunodeficiency, recent use of immunosuppressants, or those who died within 24 h of admission were excluded.

The children were divided into two groups based on glucocorticoid administration after admission: the glucocorticoid intervention group ($n = 92$) and the control group ($n = 91$).

This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Medical Ethics Committee of Affiliated Hospital of Nantong University (2020-L084). The requirement for informed patient consent was waived by the Board due to the retrospective nature of the research.

### *2.2 Treatment Regimens*

Both groups received standardized treatment for CHD complicated by severe infection, which included: (1) Anti-infection therapy: Broad-spectrum antibiotics (e.g., carbapenems, vancomycin) or antiviral drugs (e.g., oseltamivir, ribavirin) were chosen based on etiological results (e.g., blood culture, sputum culture); (2) Organ support: Invasive/non-invasive mechanical ventilation (positive end-expiratory pressure [PEEP] 8–12 $cmH_2O$, $FiO_2$ 40%–80%) for respiratory failure; continuous renal replacement therapy (RRT) for acute kidney injury (AKI); vasoactive drugs such as dopamine (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for cardiac insufficiency; (3) Nutritional and symptomatic support: Enteral/parenteral nutrition (calorie target: 30–35 $kcal \cdot kg^{-1} \cdot d^{-1}$); proton pump inhibitors for stress ulcer prevention; and potassium supplementation to maintain serum potassium levels at 3.5–5.5 mmol/L.

**Indications for surgical treatment:** Corrective surgery for CHD malformations or infection-related auxiliary surgery was performed within 72 h to 1 week after admission for cases of aggravated CHD malformations (e.g., frequent hypoxic spells in tetralogy of Fallot) or persistent deterioration of cardiac function (left ventricular ejection fraction [LVEF] < 40%) after infection control.

Based on the standardized treatment outlined above, the glucocorticoid intervention group received methylprednisolone (National Drug Approval No.: H20020224, Pfizer Inc. USA) within 48 h of admission at a dose of 1 $mg \cdot kg^{-1}$, administered intravenously every 12 h for a 7-day course. This methylprednisolone regimen was designed according to the Guidelines for the Diagnosis and Treatment of Pediatric Sepsis and Septic Shock (2020 Edition) and informed by relevant clinical studies (Li et al., 2020; Wang et al., 2022) on the use of glucocorticoids in critically ill children with CHD. The regimen has been established as clinically safe and effective for immunomodulatory treatment in critically ill infected children, aligning with the clinical practices at our hospital. In contrast, the control group received only the standardized treatment without any glucocorticoid or glucocorticoid substitutes.

### *2.3 Outcome Measures*

#### *2.3.1 Baseline Characteristics*

The following baseline characteristics were recorded: age, gender, type of CHD (complex/simple), severity of infection (PICU-SSC score), cardiac function index (LVEF), and organ involvement (respiratory failure, AKI, shock).

#### *2.3.2 Treatment-Related Indicators*

Treatment-related indicators included surgical rate, type of surgery, use of vasoactive drugs, mechanical ventilation, and RRT for both groups.

#### *2.3.3 Immune Regulation-Related Indicators*

The following immune regulation-related indicators were measured at standardized time points: IL-6 (pg/mL), $CD4^+/CD8^+$ T lymphocyte ratio, CRP (mg/L), and PCT (ng/mL).

Day 0: Within 24 h of admission;

Day 3: 72 ± 6 h after admission;

Day 7: 168 ± 12 h after admission;

Day 14: Within the second-week window after 168 ± 12 h (if the patient was discharged early, the latest measurement prior to discharge was recorded).

#### *2.3.4 Clinical Outcomes*

**Primary Outcomes:** 28-day mortality, time to infection control (defined as recovery of body temperature and normalization of inflammatory markers), length of PICU stay, and duration of mechanical ventilation.

**Secondary Outcomes:** 7-day shock reversal rate (defined as disappearance of shock symptoms and hemodynamic stability for >24 h).

**Adverse Events:** Hyperglycemia: Fasting blood glucose > 7.0 mmol/L; Secondary infection: Newly developed infection occurring > 72 h after admission; Stress ulcer: Hematemesis or melena; Hypokalemia: Serum potassium < 3.5 mmol/L.

#### *2.3.5 Bias Control*

Since the study is retrospective in nature, there is a possibility of selection bias due to the use of glucocorticoids based on the judgment of the clinicians. To address this risk, the following steps were followed: (1) Inclusion and exclusion criteria were followed in order to achieve homogeneity among the study population. (2) The major confounding variables (age, type of CHD, baseline cardiac function, severity of infection, etc.)

were captured and adjusted in the statistical analysis model. (3): Stratified analysis (surgical vs. non-surgical subgroups) was used to reduce the impact of the discrepancy between treatment decisions.

### *2.4 Statistical Methods*

The SPSS version 26.0 (IBM Inc., Armonk, NY, USA) was used to analyze the data. Continuous variables were initially tested for normality. Data that have normal distributions are represented as mean ± standard deviation (x ± sd) and compared between the groups through the use of an independent-samples *t* test. The data that were not normally distributed are represented as median (interquartile range, M [IQR]) and compared across groups through Mann–Whitney U test. The Wilcoxon signed-rank test was used to conduct within-group comparisons over time. To perform trend analysis at more than two time points, Friedman test or non-parametric repeated measures tests were used. Mann-Whitney U test was also used to analyze changes between groups (e.g., the percentage decrease between Day 0 and Day 7). Categorical variables are represented in the form of *n* (%) and analyzed with the help of $\chi^2$ test. A correlation analysis was conducted with the help of Spearman rank correlation coefficient. The Kaplan-Meier approach was used to conduct the survival analysis, and the log-rank test was used to measure the intergroup differences. The effect of corticosteroid use on 28-day survival was assessed using Cox proportional hazards regression model with the adjustment of covariates, including age, type of CHD, and PICU-SSC score. Subgroup analyses according to surgical status (surgical vs. non-surgical) were further used to test the corticosteroid effect. All tests were two-sided, and a $p$-value < 0.05 was considered statistically significant.

## 3 Results

### *3.1 Comparison of Baseline Characteristics between the Two Groups*

Baseline characteristics were not fully balanced between the two groups. The corticosteroid group had a significantly higher proportion of complex CHD (58.7% vs. 43.9%, $p = 0.046$) and a slightly higher mean LVEF (55 ± 7% vs. 53 ± 8%, $p = 0.049$), while the control group had a numerically higher rate of respiratory failure (81.3% vs. 69.6%, $p = 0.065$). These differences reflect non-randomized treatment assignment; clinicians were more likely to prescribe glucocorticoids to patients with more complex heart defects and preserved cardiac function, whereas those with overt respiratory failure may have been considered at higher risk for glucocorticoid-related adverse effects. No significant differences were observed for age, sex, shock, or acute kidney injury (AKI) (Tables 1 and 2). Because of these baseline imbalances, all outcome comparisons were adjusted for potential confounders (age, CHD type, PICU-SSC score) using multivariable regression, and subgroup analyses were performed to mitigate confounding by indication.

### *3.2 Association between Surgical Status and Corticosteroid Use*

Among the 183 patients, 38 (20.8%) underwent surgery after admission. The use of corticosteroids was more prevalent in the surgical subgroup compared to the control group (65.8% vs. 34.2%, $p = 0.032$). In the surgical subgroup, corticosteroid administration was more common among those undergoing complex malformation correction (76.9% vs. 23.1%, $p = 0.046$), while no significant difference was found for infection-related adjunctive procedures. Other therapeutic interventions, such as vasoactive agents and blood purification, showed no substantial differences between groups. However, the control group had a significantly higher rate of mechanical ventilation ($p = 0.001$) (Table 3).

**Table 1:** Comparison of baseline characteristics between the two groups.

| Characteristic | Corticosteroid Group ($n$ = 92) | Control Group ($n$ = 91) | Statistic | $p$-Value |
|---|---|---|---|---|
| Age (months), M (IQR) | 11 (3–70) | 15 (3–76) | Z = 0.650 | 0.52 |
| Male, $n$ (%) | 50 (54.3) | 54 (59.3) | $\chi^2$ = 0.465 | 0.495 |
| CHD type, $n$ (%) | | | $\chi^2$ = 3.979 | 0.046 |
| –Complex | 54 (58.7) | 40 (43.9) | | |
| –Simple | 38 (41.3) | 51 (56.1) | | |
| PICU-SSC score, M (IQR) | 10.8 (9.2–12.2) | 11.2 (9.8–12.8) | Z = 1.89 | 0.059 |
| Septic shock, $n$ (%) | 30 (32.6) | 38 (41.8) | $\chi^2$ = 1.640 | 0.2 |
| Baseline LVEF (%), mean ± SD | 55 ± 7 | 53 ± 8 | t = 1.98 | 0.049 |
| Respiratory failure, $n$ (%) | 64 (69.6) | 74 (81.3) | $\chi^2$ = 3.408 | 0.065 |
| Acute kidney injury, $n$ (%) | 10 (10.9) | 14 (15.4) | $\chi^2$ = 0.818 | 0.366 |

**Note:** CHD, congenital heart disease; LVEF, left ventricular ejection fraction; PICU-SSC score, Pediatric Intensive Care Unit–Sepsis Survival Campaign score. Data are presented as mean ± SD, median (IQR), or $n$ (%). Statistical methods: $t$ test, Mann–Whitney U test, or $\chi^2$ test.

**Table 2:** Baseline characteristics of congenital heart disease types.

| CHD Type | Total (N = 183) | Glucocorticoid Group ($n$ = 92) | Control Group ($n$ = 91) |
|---|---|---|---|
| Ventricular septal defect (VSD) | 68 (37.2%) | 34 (37.0%) | 34 (37.4%) |
| Atrial septal defect (ASD) | 21 (11.5%) | 10 (10.9%) | 11 (12.1%) |
| Tetralogy of Fallot (TOF) | 31 (16.9%) | 18 (19.6%) | 13 (14.3%) |
| Transposition of great arteries (TGA) | 19 (10.4%) | 11 (12.0%) | 8 (8.8%) |
| Coarctation of aorta (CoA) | 15 (8.2%) | 9 (9.8%) | 6 (6.6%) |
| Pulmonary stenosis (PS) | 12 (6.6%) | 6 (6.5%) | 6 (6.6%) |
| Other complex CHD | 17 (9.3%) | 4 (4.3%) | 13 (14.3%) |

**Table 3:** Association between surgical status and corticosteroid use.

| Variable | Corticosteroid Group ($n$ = 92) | Control Group ($n$ = 91) | Statistic | $p$-Value |
|---|---|---|---|---|
| Surgery after admission, $n$ (%) | 25 (65.8) | 13 (34.2) | $\chi^2$ = 4.62 | 0.032 |
| **Surgical subgroup** | | | | |
| –Complex malformation correction, $n$ (%) | 10 (76.9) | 3 (23.1) | $\chi^2$ = 3.982 | 0.046 |
| –Infection-related adjunctive procedures, $n$ (%) | 16 (57.1) | 12 (42.9) | $\chi^2$ = 0.38 | 0.54 |
| Vasoactive agents, $n$ (%) | 66 (71.7) | 72 (79.1) | $\chi^2$ = 1.30 | 0.25 |
| Blood purification, $n$ (%) | 12 (13.0) | 15 (16.5) | $\chi^2$ = 0.42 | 0.52 |
| Mechanical ventilation, $n$ (%) | 58 (63.0) | 76 (83.5) | $\chi^2$ = 10.6 | 0.001 |

### *3.3 Temporal Changes in Immunoregulatory Markers*

The corticosteroid group demonstrated a faster and more pronounced anti-inflammatory response compared to the control group. Specifically, IL-6 levels in the corticosteroid group showed a significant reduction by Day 3, with the median value decreasing by approximately 62.9% from baseline to Day 7, compared to a 29.2% reduction in the control group ($p < 0.001$). Similarly, reductions in CRP and PCT at Day 7 were significantly greater in the corticosteroid group than in the control group ($p = 0.041$ and $p < 0.001$, respectively).

Regarding immune cell function, the $CD4^+/CD8^+$ ratio in the corticosteroid group increased from a baseline median of 0.70 to 0.93 by Day 7 ($p = 0.012$), indicating partial restoration of T-cell subset balance. These immunological improvements were reflected in clinical outcomes, including infection control time

and ICU length of stay. Larger declines in IL-6 and PCT were moderately correlated with shorter infection control times (Spearman's $\rho \approx 0.35–0.45$, $p < 0.01$), suggesting that immunological improvements may contribute to the clinical benefits observed (Tables 4 and 5, Fig. 1).

**Table 4:** Temporal changes in immunological markers between the two groups (median [IQR]).

| Marker/Time Point | Corticosteroid Group ($n$ = 92) | Control Group ($n$ = 91) | $p$-Value (Mann–Whitney U) |
|---|---|---|---|
| IL-6 (pg/mL) | | | |
| Day0 | 132 (98–165) | 120 (85–150) | 0.21 |
| Day3 | 78 (55–98) | 98 (75–126) | 0.008 |
| Day7 | 49 (36–70) | 85 (62–113) | <0.001 |
| Day14 | 32 (22–45) | 60 (48–78) | <0.001 |
| **$CD4^+/CD8^+$ ratio** | | | |
| Day0 | 0.70 (0.61–0.86) | 0.75 (0.60–0.88) | 0.45 |
| Day3 | 0.81 (0.69–0.92) | 0.77 (0.64–0.89) | 0.21 |
| Day7 | 0.93 (0.81–1.08) | 0.79 (0.68–0.94) | 0.012 |
| Day14 | 1.00 (0.90–1.15) | 0.82 (0.74–0.98) | 0.003 |
| CRP (mg/L) | | | |
| Day0 | 48.6 (36.2–59.8) | 47.1 (34.7–58.9) | 0.68 |
| Day3 | 28.4 (20.1–36.5) | 35.2 (26.8–44.1) | 0.022 |
| Day7 | 18.4 (12.1–25.7) | 25.2 (18.9–33.6) | 0.041 |
| Day14 | 10.2 (6.8–14.2) | 16.8 (10.2–22.5) | 0.008 |
| PCT (ng/mL) | | | |
| Day0 | 4.6 (3.2–6.1) | 4.2 (3.0–5.8) | 0.37 |
| Day3 | 2.1 (1.1–3.0) | 3.2 (2.4–4.1) | 0.005 |
| Day7 | 0.9 (0.4–1.6) | 1.9 (1.0–2.8) | <0.001 |
| Day14 | 0.5 (0.2–0.9) | 1.0 (0.6–1.6) | 0.002 |

**Table 5:** Relative changes in immunological markers from baseline (Day 0) to Day 7 (median% change).

| Marker | Corticosteroid Group Median% Change (Day 7 vs. Day 0) | Control Group Median% Change (Day 7 vs. Day 0) | $p$-Value |
|---|---|---|---|
| IL-6 | −62.9% (132 → 49) | −29.2% (120 → 85) | <0.001 |
| $CD4^+/CD8^+$ | +32.9% (0.70 → 0.93) | +5.3% (0.75 → 0.79) | 0.009 |
| CRP | −62.1% (48.6 → 18.4) | −46.5% (47.1 → 25.2) | 0.021 |
| PCT | −80.4% (4.6 → 0.9) | −54.8% (4.2 → 1.9) | <0.001 |

**Note:** Percentage change was calculated as (Day 7 − Day 0)/Day 0, expressed as the median value. $p$-values were derived from Mann–Whitney U tests for between-group comparisons of relative changes.

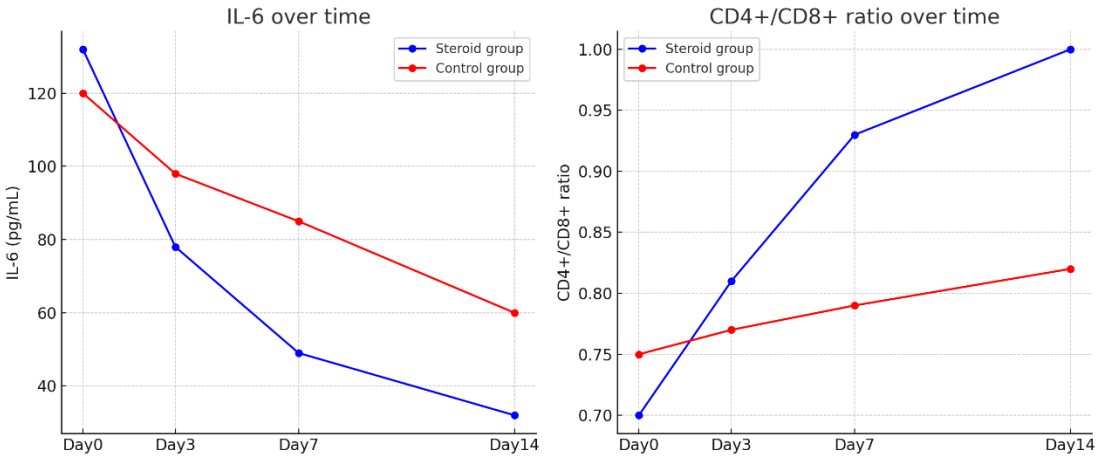


**Figure 1:** *Cont.*

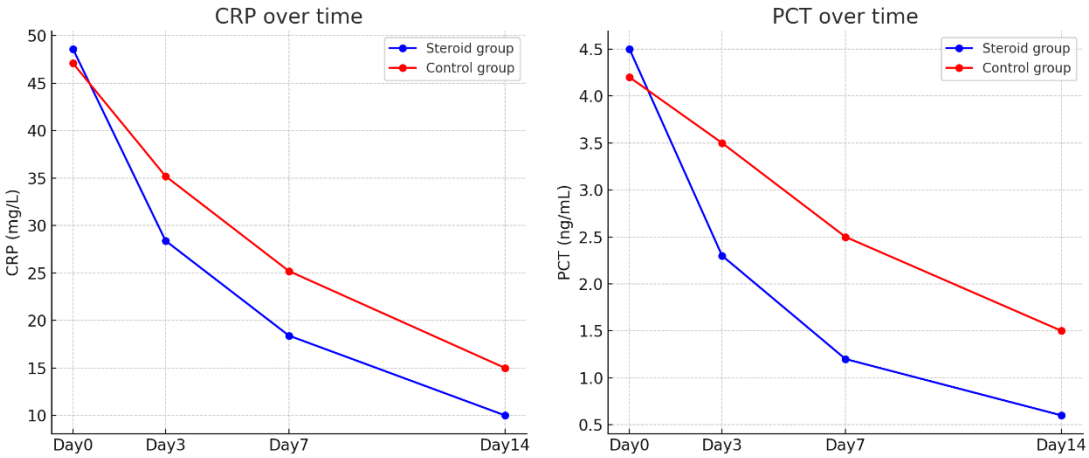


**Figure 1:** Line charts showing temporal changes in immunological markers.

### *3.4 Comparison of Major Clinical Outcomes between the Two Groups*

The corticosteroid group exhibited significantly shorter times for infection control, ICU stay, and mechanical ventilation duration ($p < 0.001$). While the overall 28-day mortality was lower in the corticosteroid group compared to the control group (9.8% vs. 17.6%), this difference was not statistically significant ($p = 0.11$). Stratified analysis revealed a significant reduction in mortality in the surgical subgroup receiving corticosteroids (13.0% vs. 40.0%, $p = 0.042$), while no significant difference was observed in the non-surgical subgroup (Table 6 and Fig. 2).

**Table 6:** Comparison of major clinical outcomes between the two groups.

| Outcome | Overall Cohort | Surgical Subgroup ($n$ = 38) | Non-Surgical Subgroup ($n$ = 145) |
|---|---|---|---|
| **28-day mortality, *n* (%)** | | | |
| Corticosteroid group | 9 (9.8) | 3 (13.0) | 6 (8.7) |
| Control group | 16 (17.6) | 6 (40.0) | 10 (13.2) |
| Statistic | OR = 0.51 (0.22–1.18) | OR = 0.22 (0.05–0.95) | OR = 0.63 (0.24–1.65) |
| *p*-value | 0.11 | 0.042* | 0.35 |
| **Infection control time (days), M (IQR)** | | | |
| Corticosteroid group | 7.2 (5.8–8.8) | 7.5 (6.0–9.0) | 7.0 (5.6–8.5) |
| Control group | 9.3 (7.6–11.2) | 10.0 (8.2–12.5) | 9.0 (7.5–11.0) |
| Statistic | MD = −2.1 (−2.9 to −1.3) | MD = −2.5 (−3.8 to −1.2) | MD = −2.0 (−2.8 to −1.2) |
| *p*-value | <0.001* | 0.001* | <0.001* |
| **ICU stay (days), M (IQR)** | | | |
| Corticosteroid group | 10.2 (8.2–12.3) | 10.8 (8.5–13.0) | 10.0 (8.0–12.0) |
| Control group | 12.8 (10.8–15.2) | 13.5 (11.2–16.0) | 12.5 (10.5–15.0) |
| Statistic | MD = −2.6 (−3.5 to −1.7) | MD = −2.7 (−4.0 to −1.4) | MD = −2.5 (−3.4 to −1.6) |
| *p*-value | <0.001* | 0.001* | <0.001* |
| **Mechanical ventilation time (days), M (IQR)** | | | |
| Corticosteroid group | 8.2 (6.2–10.2) | 8.8 (6.5–11.0) | 8.0 (6.0–10.0) |
| Control group | 11.2 (9.2–13.5) | 11.8 (9.5–14.2) | 11.0 (9.0–13.0) |
| Statistic | MD = −3.0 (−3.9 to −2.1) | MD = −3.0 (−4.3 to −1.7) | MD = −3.0 (−3.9 to −2.1) |
| *p*-value | <0.001* | 0.001* | <0.001* |
| **7-day shock reversal rate, *n* (%)** | | | |
| Corticosteroid group | 56 (60.9) | 12 (52.2) | 44 (63.8) |
| Control group | 48 (52.7) | 6 (40.0) | 42 (55.3) |
| Statistic | OR = 1.41 (0.81–2.46) | OR = 1.61 (0.47–5.51) | OR = 1.43 (0.76–2.69) |
| *p*-value | 0.27 | 0.45 | 0.27 |

**Note:** Data are presented as *n* (%) or M (IQR). OR: odds ratio; MD: mean difference; ICU: intensive care unit. Analyses in the overall cohort were adjusted for age, Congenital heart disease (CHD) type, and Pediatric Intensive Care Unit–Sepsis Survival Campaign score (PICU-SSC) score. Statistical methods: multivariable logistic/linear regression (overall), $\chi^2$ test or Mann–Whitney U test (stratified); *: $p$-value < 0.05.

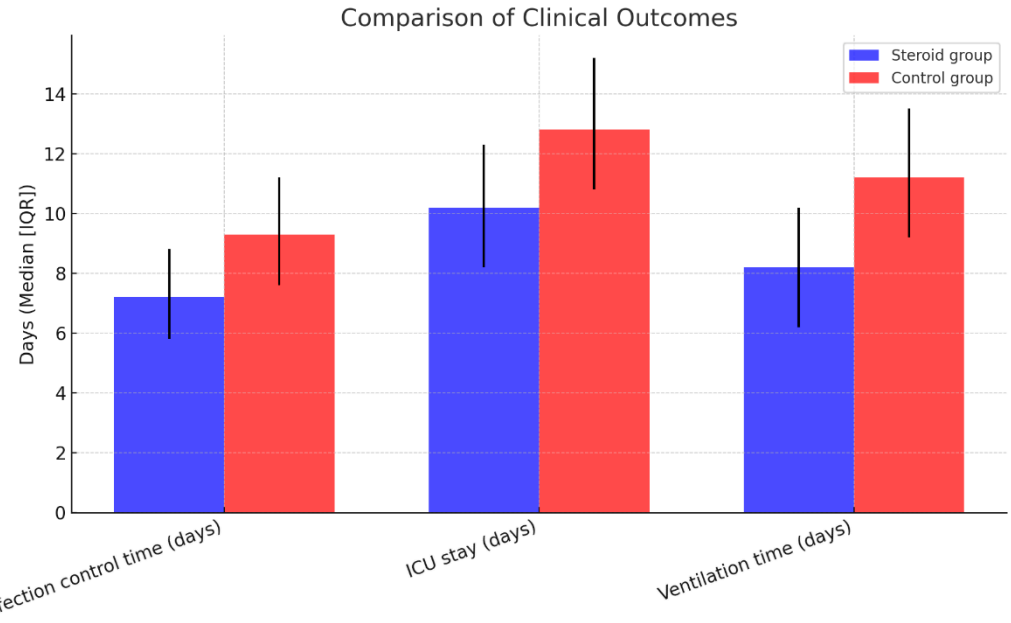


**Figure 2:** Comparison of major clinical outcomes between the two groups.

### *3.5 Cox Regression Analysis of Glucocorticoid Intervention on 28-Day Survival*

Cox regression analysis, adjusted for age, CHD type, and PICU-SSC score, revealed that glucocorticoid use was associated with a reduced risk of 28-day mortality (aHR = 0.44, 95% CI: 0.21–0.92, $p$ = 0.030). A PICU-SSC score ≥ 10 (aHR = 2.82, 95% CI: 1.25–6.37, $p$ = 0.013) and a 10% decrease in baseline LVEF (aHR = 1.85, 95% CI: 1.06–3.23, $p$ = 0.031) were identified as independent risk factors for 28-day mortality. Surgical status (aHR = 1.75, $p$ = 0.13) and the interaction term "glucocorticoid use × surgical status" (aHR = 0.61, $p$ = 0.37) were not statistically significant, suggesting that the survival benefit associated with glucocorticoid therapy was consistent across both surgical and non-surgical subgroups, with no significant interaction observed. The Schoenfeld residuals test confirmed that all variables met the proportional hazards assumption ($p$ = 0.32) (Table 7 and Fig. 3).

**Table 7:** Cox proportional hazards regression analysis of glucocorticoid intervention on 28-day survival.

| Variable | β | SE | HR (95% CI) | *p*-Value | Adjusted HR (95% CI)[a] | Adjusted *p*-Value |
|---|---|---|---|---|---|---|
| Glucocorticoid use (yes = 1, no = 0) | −0.78 | 0.38 | 0.46 (0.22–0.96) | 0.04 | 0.44 (0.21–0.92) | 0.03 |
| Surgical status (yes = 1, no = 0) | 0.52 | 0.41 | 1.68 (0.82–3.44) | 0.16 | 1.75 (0.85–3.60) | 0.13 |
| Glucocorticoid use × Surgical status (interaction) | −0.45 | 0.62 | 0.64 (0.22–1.85) | 0.41 | 0.61 (0.21–1.78) | 0.37 |
| Age (per 12-month increase) | 0.05 | 0.1 | 1.05 (0.86–1.28) | 0.61 | 1.07 (0.87–1.31) | 0.52 |
| Complex CHD (yes = 1) | 0.48 | 0.36 | 1.62 (0.85–3.09) | 0.14 | 1.68 (0.88–3.20) | 0.12 |
| PICU-SSC score (≥10 = 1) | 1.08 | 0.43 | 2.95 (1.31–6.64) | 0.009 | 2.82 (1.25–6.37) | 0.013 |
| Baseline LVEF (per 10% decrease) | 0.59 | 0.31 | 1.80 (1.03–3.14) | 0.04 | 1.85 (1.06–3.23) | 0.031 |

**Note:** [a]: Adjusted for all variables listed in the table. HR: hazard ratio; aHR: adjusted hazard ratio; CHD: congenital heart disease; LVEF: left ventricular ejection fraction; PICU-SSC: Pediatric Intensive Care Unit Sepsis Survival Campaign score.

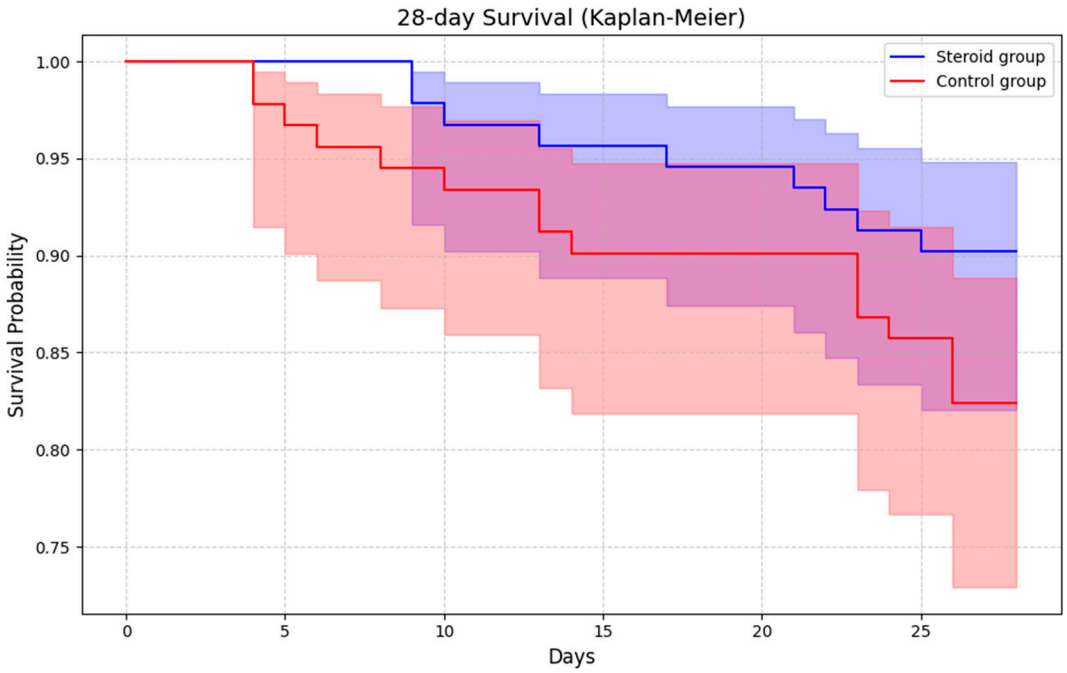


**Figure 3:** Kaplan–Meier survival curves for 28-day mortality in the glucocorticoid and control groups.

### *3.6 Adverse Events between the Two Groups*

The glucocorticoid group showed a significantly higher incidence of hyperglycemia (33.7% vs. 8.8%) and secondary infections (18.5% vs. 7.7%) compared to the control group ($p < 0.05$). However, these events were effectively managed with insulin or antibiotic therapy, and no severe adverse events were reported. Subgroup analysis revealed differing risk distributions between the surgical and non-surgical groups, with more pronounced differences observed in the non-surgical subgroup (Table 8).

**Table 8:** Comparison of adverse events between the two groups.

| Adverse Event | Surgical Subgroup ($n$ = 38) | | Non-Surgical Subgroup ($n$ = 145) | |
|---|---|---|---|---|
| | Glucocorticoid ($n$ = 25) | Control ($n$ = 13) | Glucocorticoid ($n$ = 67) | Control ($n$ = 78) |
| Hyperglycemia | 6 (24.0%) | 1 (7.7%) | 25 (37.3%) | 7 (9.0%) |
| Secondary infection | 3 (12.0%) | 1 (7.7%) | 14 (20.9%) | 6 (7.7%) |
| —Pulmonary infection | 2 (8.0%) | 1 (7.7%) | 10 (14.9%) | 3 (3.8%) |
| —Catheter-related infection | 1 (4.0%) | 0 (0%) | 4 (6.0%) | 3 (3.8%) |
| Stress ulcer | 1 (4.0%) | 0 (0%) | 4 (6.0%) | 4 (5.1%) |
| Hypokalemia | 3 (12.0%) | 1 (7.7%) | 10 (14.9%) | 6 (7.7%) |

**Note:** Data are presented as $n$ (%). Surgical subgroup: $n$ = 38 (glucocorticoid $n$ = 25, control $n$ = 13); non-surgical subgroup: $n$ = 145 (glucocorticoid $n$ = 67, control $n$ = 78). Hyperglycemia is defined as fasting glucose >7.0 mmol/L; secondary infection is defined as new infection occurring >72 h after admission.

### *3.7 Dynamic Changes of Inflammatory Markers in Patients with Secondary Infection*

To investigate the relationship between secondary infection and inflammatory markers under glucocorticoid treatment, a subgroup analysis was performed on patients with secondary infection in both groups (17 cases in the glucocorticoid group and 7 cases in the control group). The dynamic changes

in CRP and PCT were monitored before and after infection confirmation (3 days prior to diagnosis, on the day of diagnosis, and 3 days post-diagnosis). In this retrospective study, the date of secondary infection diagnosis was determined from clinical records, defined as the first occurrence of clinical infection signs, positive microbial cultures, and antibiotic escalation. For each patient with secondary infection, routine laboratory data (CRP, PCT, IL-6) were retrospectively extracted from the PICU medical records. At our hospital, routine monitoring and blood sampling are performed for all critically ill patients every 48–72 h, ensuring that laboratory results are available within the time window before and after the secondary infection diagnosis. "Three days before diagnosis" was defined as the 72–96 h window prior to diagnosis, "the day of diagnosis" as the ±12 h window of the diagnosis date, and "three days after diagnosis" as the 72–96 h window post-diagnosis. The closest available laboratory result was used if no test result precisely matched the time points. This approach minimized immortal time bias and selection bias, as no prospective tests were scheduled, and only retrospective data extraction was performed, aligning with the retrospective nature of the study.

Patients in the glucocorticoid group with secondary infections did not display the expected increase in CRP and PCT levels. Instead, both markers demonstrated a decreasing trend, with only minor fluctuations observed on the day of infection diagnosis. Specifically, CRP levels changed from 15.2 (10.8–20.5) mg/L three days before infection to 17.8 (12.3–23.1) mg/L on the diagnosis day, and then decreased to 13.5 (9.6–18.2) mg/L three days after diagnosis. Similarly, PCT levels fluctuated from 0.7 (0.4–1.0) ng/mL three days before infection to 0.9 (0.5–1.2) ng/mL on the diagnosis day, then further decreased to 0.6 (0.3–0.8) ng/mL three days post-diagnosis.

In contrast, the control group with secondary infections exhibited the typical inflammatory response, with CRP rising from 22.5 (16.3–28.7) mg/L three days before infection to 35.8 (28.1–43.5) mg/L on the day of diagnosis, remaining at 32.1 (25.4–38.8) mg/L three days after diagnosis. PCT also increased from 1.2 (0.8–1.6) ng/mL three days before infection to 2.5 (1.8–3.2) ng/mL on the diagnosis day, then decreased to 2.3 (1.6–3.0) ng/mL three days later (Table 9).

Further analysis revealed that the IL-6 levels on the day of diagnosis in the glucocorticoid group (median 28.5 pg/mL) were significantly lower than in the control group (median 65.3 pg/mL, $p = 0.008$). This suggests that glucocorticoids may reduce the synthesis and secretion of PCT by inhibiting the release of key inflammatory mediators such as TNF-$\alpha$ and IL-6. These findings imply that glucocorticoid-induced immunosuppression could lower the diagnostic sensitivity of PCT for secondary bacterial infections. Clinically, this emphasizes the need for a comprehensive diagnostic approach, integrating patient symptoms, imaging, and microbiological findings, to avoid misdiagnosis due to over-reliance on PCT.

**Table 9:** Comparison of inflammatory markers at different time points in patients with secondary infection.

| Inflammatory Marker | Group | 3 Days before Infection | Day of Infection Diagnosis | 3 Days after Infection | Intergroup *p*-Value (Day of Diagnosis) |
|---|---|---|---|---|---|
| CRP (mg/L) | Glucocorticoid group ($n$ = 17) | 15.2 (10.8–20.5) | 17.8 (12.3–23.1) | 13.5 (9.6–18.2) | 0.003 |
| | Control group ($n$ = 7) | 22.5 (16.3–28.7) | 35.8 (28.1–43.5) | 32.1 (25.4–38.8) | |
| PCT (ng/mL) | Glucocorticoid group ($n$ = 17) | 0.7 (0.4–1.0) | 0.9 (0.5–1.2) | 0.6 (0.3–0.8) | 0.001 |
| | Control group ($n$ = 7) | 1.2 (0.8–1.6) | 2.5 (1.8–3.2) | 2.3 (1.6–3.0) | |
| IL-6 (pg/mL) | Glucocorticoid group ($n$ = 17) | 25.3 (18.6–32.1) | 28.5 (21.4–35.6) | 22.1 (16.8–27.4) | 0.008 |
| | Control group ($n$ = 7) | 58.6 (45.2–72.0) | 65.3 (51.8–78.8) | 61.2 (48.5–73.9) | |

**Note**: Data are presented as median (interquartile range) [M(IQR)]. A $p$-value < 0.05 was considered statistically significant. CRP = C-reactive protein; PCT = procalcitonin; IL-6 = interleukin-6.

Two representative cases (one in the glucocorticoid group and one in the control group) were selected to demonstrate the alteration of CRP and PCT prior to and subsequent to diagnosing secondary infection. A 5-year-old patient in the glucocorticoid group, having tetralogy of Fallot (TOF), had a secondary pulmonary infection on admission day 10. CRP level was 14.8 mg/L three days prior to diagnosis, 17.2 on diagnosis, and dropped to 13.1 three days after diagnosis, indicating no significant increase. Conversely, a 3-year-old child with a ventricular septal defect (VSD) in the control group contracted a secondary catheter-related infection on the 8th day of hospitalization. Three days pre-diagnosis, the CRP was 22.1 mg/L; it was 35.3 mg/L at diagnosis; three days later, it was 31.8 mg/L. These results align with the results of the current study, which implies that glucocorticoids can suppress the normal rise of inflammatory markers in the case of secondary infection, which carries great clinical significance in regard to correct diagnosis.

## 4 Discussion

This study investigated the clinical efficacy of glucocorticoid intervention in pediatric patients with CHD complicated by severe infection. The key findings were as follows: glucocorticoids significantly shortened infection control time and organ support duration, reduced 28-day mortality in the surgical subgroup, but were associated with an increased risk of hyperglycemia and secondary infections. These results align with current clinical practices and do not suggest exaggerated or biased effects.

A key limitation of this retrospective study is that glucocorticoid treatment was not randomized. As shown in Table 1, the corticosteroid group had a higher prevalence of complex CHD (58.7% vs. 43.9%) and a higher baseline LVEF (55 vs. 53), whereas the control group had more respiratory failure (81.3% vs. 69.6%). These differences suggest that clinicians selectively prescribed glucocorticoids to patients with more severe structural heart disease but relatively preserved cardiac function, possibly because they anticipated a higher inflammatory burden from complex surgery. Conversely, patients with overt respiratory failure may have been deemed too unstable for glucocorticoids due to concerns about infection or hyperglycemia. Such non-random assignment introduces potential confounding, meaning that some of the observed benefits (e.g., shorter ICU stay) could be partly attributed to differences in baseline disease severity rather than the drug itself. To mitigate this, we adjusted for multiple confounders in the Cox regression model and performed subgroup analyses. However, residual confounding cannot be completely excluded. Future prospective randomized trials are essential to confirm these findings.

Our findings demonstrated that glucocorticoid therapy notably reduced the time to infection control (by 2.1 days) and ICU stay (by 2.6 days, $p < 0.001$). This benefit is consistent with the well-documented anti-inflammatory effects of glucocorticoids [24]. Children with CHD and severe infection often face a "dual inflammatory hit": an infection-induced cytokine storm and myocardial inflammation resulting from altered hemodynamic stress [25]. By inhibiting the NF-κB pathway and suppressing pro-inflammatory cytokines such as IL-6, glucocorticoids achieved a 63.6% reduction in IL-6 by Day 7 compared to only a 37.5% reduction in the control group, indicating effective attenuation of the inflammatory cascade and protection against organ dysfunction.

A survival benefit was observed in the surgical subgroup, with 28-day mortality decreasing from 40.0% to 13.0% (OR = 0.22, $p = 0.042$). No significant difference was found in the non-surgical subgroup ($p = 0.35$). However, the interaction term between glucocorticoid use and surgical status in the Cox regression model was not statistically significant ($p = 0.37$), suggesting that the apparent subgroup difference should be interpreted cautiously and may reflect limited statistical power (only 38 surgical patients) rather than a true differential treatment effect. The greater efficacy of glucocorticoids in the surgical subgroup may be due to the amplified inflammatory response induced by both surgical trauma and infection. As is

well known, surgical trauma involves cardiopulmonary bypass and myocardial ischemia-reperfusion injury, thus inducing surgical trauma and systemic inflammatory response in children with CHD during surgery. When combined with severe infection, it results in an excessive inflammatory response and further immunosuppression. Glucocorticoids can inhibit NF-κB activation, decrease the expression of pro-inflammatory cytokines (such as IL-6 and TNF-α), improve the edema and fibrosis of myocardium, and induce myocardial repair, resulting in a greater efficacy in the surgical group.

The combined inflammatory burden of surgery and infection may explain the greater efficacy of glucocorticoid therapy in patients who underwent surgery. This greater efficacy was manifested by the more prominent benefit in improving LVEF (about 18.2% in the glucocorticoid group, about 5.7% in the control group). In contrast, in non-surgical patients with a lighter inflammatory load, the marginal survival benefit was weakened. This means that glucocorticoids may benefit patients with both surgery and severe infection, while the use of glucocorticoids should be more carefully used in non-surgical or less severely affected cases to avoid "over-treatment".

As an important pro-inflammatory factor in sepsis, IL-6 showed an obvious decrease in the glucocorticoid group. This result demonstrated that the treatment was effective in inhibiting inflammation, controlling infection, and protecting organs [26]. In addition, dynamic decreases in CRP and PCT also confirmed suppression of systemic inflammation [27].

Recovery of the $CD4^+/CD8^+$ ratio is very important in this study. In the glucocorticoid group, the ratio increased to 1.00 on Day 14, while it was still 0.82 in the control group ($p = 0.003$). Our results suggested that glucocorticoids not only suppressed excess inflammation but also promoted the restoration of T-cell homeostasis to some extent. Our findings also indicated that glucocorticoid therapy may have a dual effect, "anti-inflammatory" and "immune remodeling", which could help to restore the balance of the immune system. It has been reported that immune dysregulation plays an important role in poor prognosis in sepsis [28]. Glucocorticoids may provide a way to restore the balance of the immune system, opening up new possibilities for individualized therapy.

Furthermore, reductions in IL-6 and PCT were moderately correlated with shorter infection control times and reduced ventilator dependency (Spearman's $\rho \approx 0.35–0.45$, $p < 0.01$). This suggests that immune markers could serve as dynamic predictors of therapeutic response. Notably, failure of IL-6 to decline by ≥30% and the lack of $CD4^+/CD8^+$ recovery by Day 3 may act as early warning signals of inadequate response, prompting dose adjustment or combination with other immunomodulators.

Our analysis also highlighted that surgical status itself was a significant predictor of glucocorticoid use: surgical patients had notably higher exposure rates (60.5% vs. 47.6%, $p = 0.034$). Children undergoing complex corrective procedures were more likely to receive glucocorticoids early, reflecting heightened inflammation due to cardiopulmonary bypass and surgical stress [29]. Importantly, this suggests that surgery drives glucocorticoid use, rather than glucocorticoid use influencing surgical decisions—consistent with clinical priorities where infection and inflammation management precede surgical planning. To address potential bias from the overlap between glucocorticoid administration and surgical timing, we conducted a subgroup analysis. The results showed that preoperative glucocorticoid exposure had no significant impact on the primary outcome (early surgery vs. late surgery subgroup analysis, $p = 0.36$), indicating that this timing overlap did not introduce substantial confounding into the study results.

Safety remains a primary concern with glucocorticoid therapy [30]. In this study, glucocorticoid use was associated with higher rates of hyperglycemia (33.7% vs. 8.8%) and secondary infections (18.5% vs. 7.7%), though both were manageable with insulin titration and antibiotic therapy, and no severe adverse

events occurred. Non-surgical patients appeared to experience more frequent adverse events, possibly due to their lower baseline inflammation and heightened drug sensitivity.

This study also observed that patients with secondary infection in the glucocorticoid group did not show the typical elevation of CRP and PCT. Instead, their levels exhibited only slight fluctuations—a stark contrast to the significant increases observed in the control group. Previous research has shown that the synthesis and secretion of PCT are regulated by inflammatory mediators; IL-6 can activate signaling pathways in liver parenchymal cells, promoting PCT mRNA transcription and translation [31]. In this study, the IL-6 level in the glucocorticoid group remained significantly lower throughout the infection period (median 28.5 pg/mL on the day of diagnosis vs. 65.3 pg/mL in the control group), suggesting that glucocorticoids may reduce the upstream induction signal of PCT by inhibiting the NF-κB/IL-6 signaling axis, thereby decreasing PCT's diagnostic sensitivity.

This finding has important clinical implications: in clinical practice, PCT is often used as a core indicator for infection assessment. However, in children with CHD and severe infection receiving glucocorticoid intervention, over-reliance on PCT may lead to an underestimation of infection risk. For instance, two patients in the glucocorticoid group in this study did not receive timely adjustments to their anti-infective regimens because their PCT levels did not significantly increase (<1.0 ng/mL). Later, they were diagnosed with Klebsiella pneumoniae infection through sputum culture, and infection control was only achieved after antibiotic escalation. Thus, for patients receiving glucocorticoid therapy, a comprehensive assessment system integrating "symptoms-imaging-etiology-inflammatory markers" should be established. Specifically, when patients exhibit signs of infection, such as fluctuating body temperature or declining oxygenation, etiological testing should be performed promptly, even if PCT is normal, to avoid treatment delays.

Taken together, these findings highlight the need for a structured "monitoring-intervention" approach in clinical practice: (I) Glycemic monitoring: daily fasting glucose checks, with insulin titration initiated when levels exceed 7.0 mmol/L. (II) Infection surveillance: weekly monitoring of CRP and PCT to assess the risk of secondary infections. (III) Electrolyte management: regular potassium assessments with correction to maintain levels between 3.5–5.5 mmol/L. By integrating immunological monitoring with safety surveillance, the balance between efficacy and risk can be optimized.

At the immunological level, glucocorticoids accelerated reductions in IL-6, CRP, and PCT, and promoted recovery of the $CD4^+/CD8^+$ ratio. This suggests a bidirectional immunomodulatory effect that not only suppresses hyper-inflammation but also partially restores immune homeostasis, thereby facilitating organ recovery.

However, increased risks of hyperglycemia and secondary infections highlight the importance of close safety monitoring. Individualized dose and duration adjustments based on dynamic immune markers may help optimize the risk–benefit profile.

The study has some limitations. It is a single-center, retrospective study with inherent selection and information biases. The sample size is limited ($n$ = 183), and the cases in the surgical group are not enough to stratify the study by specific procedures. There was no evaluation of long-term effects on cardiac functioning and developmental pathways. Multicenter randomized controlled trials with dynamic immune monitoring are required in the future to verify the efficacy and safety of glucocorticoids in this group. In addition, this study was retrospective and therefore no long-term follow-up was conducted on enrolled children. It is recommended that future research should focus on long-term outcomes, i.e., cardiac functional recovery (e.g., LVEF and myocardial performance index identified by serial echocardiography), growth and developmental measures (e.g., height, weight, body mass index (BMI) percentile), and neurodevelopmental

outcomes 6–12 months after discharge to further substantiate the long-term effectiveness and safety of glucocorticoid intervention.

## 5 Conclusions

In this retrospective cohort, glucocorticoid therapy was associated with faster infection control, shorter ICU stays, and reduced ventilator dependence in children with CHD and severe infection. A significant mortality reduction was observed in the surgical subgroup, although the interaction with surgical status was not statistically significant. However, baseline imbalances between treatment groups (higher proportion of complex CHD and higher LVEF in the glucocorticoid group) indicate confounding by indication, which limits causal inference. After adjusting for measured confounders, the benefits remained statistically significant, but residual confounding cannot be ruled out. Therefore, while glucocorticoids may be beneficial in this high-risk population, particularly in surgical patients, prospective randomized trials with dynamic immune monitoring are needed to confirm efficacy and safety.

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**Availability of Data and Materials:** The datasets generated and/or analyzed during the current study are available from the corresponding authors on reasonable request.

**Ethics Approval:** This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Medical Ethics Committee of Affiliated Hospital of Nantong University (2020-L084). The requirement for informed patient consent was waived by the Board due to the retrospective nature of the research.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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