Congenital Heart Disease

Tech Science Press

Doi:10.32604/chd.2025.070345

ARTICLE

Correlation between Syndecan-1 in Inter Category of RACHS-1 Score and Immediate Clinical Outcomes

Novik Budiwardhana[1,*], Indah Kartika Murni[2], Eva Miranda Marwali[1], Pribadi Wiranda Busro[3], Fildza Intan Rizkia[4], Muhamad Faza Soelaeman[4] and Yunita Widyastuti[5]

[1]Pediatric Cardiac Intensive Care Unit, Harapan Kita National Cardiovascular Centre, Jakarta, 11420, Indonesia
[2]Department of Pediatrics, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Jogyakarta, 55281, Indonesia
[3]Pediatric Cardiac Surgery, Department of Cardiac surgery, Harapan Kita National Cardiovascular Centre, Jakarta, 11420, Indonesia
[4]Research Assistant of Pediatric Cardiac Intensive Care Unit, Harapan Kita National Cardiovascular Centre, Jakarta, 11420, Indonesia [5]Department of Anesthesiology and Intensive therapy, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Jogyakarta, 55281, Indonesia
*Corresponding Author: Novik Budiwardhana. Email: novikdrspa@gmail.com

Received: 14 July 2025; Accepted: 10 November 2025; Published: 30 November 2025

ABSTRACT: Background: Low cardiac output syndrome (LCOS) is a frequent and serious complication after pediatric cardiac surgery. Endothelial glycocalyx (EG) degradation, indicated by elevated syndecan-1, contributes to microvascular dysfunction and postoperative instability. The relationship between syndecan-1 dynamics and surgical risk categories remains unclear. **Objective:** To examine the association between perioperative syndecan-1 levels and clinical outcomes across Risk Adjustment for Congenital Heart Surgery (RACHS-1) categories. **Methods:** We analyzed 106 children (RACHS-1 categories 2–4) undergoing elective cardiac surgery with cardiopulmonary bypass (CPB). Syndecan-1 was measured at baseline (T0), 4 h (T4), and 72 h (T72). Outcomes included LCOS, vasoactive inotropic score (VIS), Pediatric Logistic Organ Dysfunction (PELOD-2), pediatric intensive care unit (PICU) stay, and mortality. Analyses used Kruskal–Wallis, Bonferroni post hoc tests, Spearman correlation, and multivariable regression adjusted for CPB duration, cross-clamp time, and pre-PICU status. **Results:** Syndecan-1 differed significantly across RACHS groups at T0 ($p = 0.044$) and T72 ($p = 0.015$). RACHS score was weakly correlated but significant with syndecan-1 at T72 (r = 0.238, $p = 0.019$) and decline from T4–T72 (r = 0.249, $p = 0.013$), indicating delayed recovery at higher risk. RACHS-4 patients had the highest VIS and PELOD-2 scores and longer PICU stay. In adjusted models, RACHS-3 was associated with higher syndecan-1 at T72 ($\beta = +51.9$, $p = 0.016$), higher VIS 0–4 h ($\beta = +4.9$, $p = 0.008$), and increased LCOS risk (OR 5.99, 95% CI 1.61–25.70, $p = 0.010$). RACHS-4 showed greater organ dysfunction but LCOS risk was attenuated (OR 0.19 vs. RACHS-3, $p = 0.035$). Mortality was highest in RACHS-4 (17.6%) but not statistically significant ($p = 0.368$). **Conclusion:** Higher RACHS categories are linked with delayed EG recovery, greater vasoactive support, and more severe organ dysfunction. Syndecan-1 kinetics at 72 h, alongside VIS and LCOS, may serve as adjunctive markers for postoperative risk stratification in pediatric cardiac surgery.

KEYWORDS: Endothelial glycocalyx; RACHS-1 score; Syndecan-1 level

1 Introduction

Low cardiac output syndrome (LCOS) is a common and potentially life-threatening complication in the immediate postoperative period following pediatric cardiac surgery. While length of stay (LOS) is a known contributor to mortality, it also significantly increases morbidity, leading to prolonged stays in the pediatric intensive care unit (PICU) and hospital care. A study by Murni et al. in Indonesia reported an

LCOS incidence of nearly 20% among 257 children undergoing pediatric cardiac surgery. Approximately 20% of these patients experienced major adverse events, including cardiac arrest, multi-organ failure, and deaths [1].

The cause of LCOS is a complex interplay of factors including myocardial immaturity, ischemia-reperfusion injury, and microvascular dysfunction. Preoperative contributors may include myocardial dysfunction due to congestive heart failure, chronic hypoxia, single-ventricle physiology or prior myocardial infarct. Post-operative factors also play a critical role, especially in neonates and infants, whose immature myocardium is less capable of compensating for stress. Another factor is endothelial glycocalyx (EG) degradation, which has been increasingly recognized as a key contributor. The EG, a proteoglycan-rich layer lining the vascular endothelium, maintains vascular barrier function, regulates leukocyte adhesion, and protects myocardial perfusion. Its disruption leads to the release of circulating fragments such as syndecan-1, which serve as biomarkers of endothelial injury and disease severity. Recent advances have also highlighted that inhibition of EG degradation may protect cardiac function. Experimental models suggest that therapeutic strategies including heparin, heparanase antagonists, corticosteroids, neutrophil elastase inhibitors, and recombinant thrombomodulin, can attenuate glycocalyx shedding and preserve myocardial integrity [2–4].

Previous studies have shown that the risk of LCOS and other adverse postoperative outcomes is influenced not only by physiological and intraoperative factors, but also by the complexity of the surgical procedure itself. The Risk Adjustment for Congenital Heart Surgery (RACHS-1) score is a widely validated tool for stratifying the severity of congenital heart surgery and predicting postoperative morbidity and mortality. Higher RACHS-1 categories are associated with increased incidence of LCOS, prolonged mechanical ventilation, and higher inotropic support requirements. Therefore, RACHS-1 can serve as a surrogate marker of surgical risk when exploring the underlying pathophysiological mechanisms of early postoperative outcomes, including endothelial injury [5,6].

Continuing effort to reduce the burden of LCOS in pediatric cardiac surgery have highlighted the importance of preserving endothelial integrity. Preventing EG degradation may offer new avenues for improving postoperative care. Endothelial glycocalyx breakdown is believed to contribute significantly to microvascular dysfunction, including microthrombi formation, capillary leakage, leukocyte rolling, and red blood cell clumping (rouleaux formation). However, the precise mechanisms remain incompletely understood, and further studies are needed to elucidate the role of endothelial injury in LCOS development. Several therapeutic approaches targeting microcirculatory dysfunction are currently under exploration [3,4].

Given that the pathogenesis of LCOS is multifactorial and its prevention requires a multimodal approach, understanding the extent to which EG degradation contributes to postoperative instability across different surgical risk categories is important. The RACHS-1 scoring system provides a robust framework for this analysis [5,6]. Therefore, this study aims to examine the correlation between surrogate markers of EG shedding and clinical outcomes in RACHS-1 categories. The findings may inform targeted strategies for LCOS prevention and enhance postoperative management in pediatric cardiac surgery.

2 Methods

2.1 Study Design

This prospective study was conducted using data from a previously collected dataset involving pediatric patients who underwent elective cardiac surgery with cardiopulmonary bypass (CPB) in National Cardiovascular Center Harapan Kita from January 2023 to May 2024. This analysis focuses specifically on the correlation between Syndecan-1 levels and immediate postoperative clinical outcomes across different categories of the RACHS-1 stratification.

2.2 Eligibility Criteria

Only patients within RACHS-1 categories 2 to 4 were included [7], yielding a total of 106 subjects: 37 in category 2, 35 in category 3, and 34 in category 4. All patients were infants and children under 120 months of age undergoing elective cardiac surgery with CPB. Ethical clearance was obtained from the institutional review board (LB.02.01/VII/003/KEP003/2023). As all participants were minors, informed consent was obtained from their parents or legal guardians.

2.3 Outcomes

Syndecan-1 levels were measured at three time points: before surgery (T0), 4 h postoperatively (T4), and 72 h postoperatively (T72). These were analyzed in relation to key immediate postoperative outcomes: low cardiac output syndrome (LCOS), mortality, Pediatric Logistic Organ Dysfunction (PELOD)-2 score, vasoactive-inotropic score (VIS), length of stay in the PICU, and duration of intubation.

LCOS was defined as a cardiac index <2.0 L/min/m^2 with clinical and laboratory signs of hypoperfusion, including oliguria, metabolic acidosis, and elevated lactate levels (>2 mmol/L). Pulmonary over circulation was indicated by SaO_2 >85% in room air, widened pulse pressure, persistent metabolic acidosis, and low cardiac output.

The VIS score was used to quantify cardiovascular support in the first 24 h post-surgery, based on dosages of inotropic and vasoactive medications such as dopamine, epinephrine, norepinephrine, milrinone, and vasopressin. Additional clinical outcomes assessed included PICU length of stay and duration of mechanical ventilation.

2.4 Statistical Analysis

All statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. Categorical variables were summarized as frequencies and percentages. The normality of numerical variables was assessed using the Kolmogorov–Smirnov or Shapiro–Wilk test, as appropriate. Normally distributed data were presented as mean ± standard deviation (SD), while non-normally distributed data were expressed as median and interquartile range (IQR).

Group comparisons were conducted using bivariate analyses. Categorical variables were compared using the chi-square test where applicable. For numerical variables, one-way ANOVA was used for normally distributed data. If ANOVA results were statistically significant, post hoc pairwise comparisons were conducted. Tukey's Honestly Significant Difference (HSD) test was applied when the assumption of equal variances was met; otherwise, the Games–Howell test was used, which does not assume equal variances or equal sample sizes. For non-normally distributed data, the Kruskal–Wallis test was employed. When significant differences were found ($p < 0.05$), post hoc pairwise comparisons were performed using Dunn's test with Bonferroni correction to adjust for multiple comparisons.

Spearman's rank correlation coefficient was used to assess the monotonic relationship between RACHS-1 score and key outcomes, including Syndecan levels (T0, T4, T72, T40, T724), VIS score (0–4 h, 4–24 h, and 24–72 h), PELOD-2 scores at 24 h and 72 h, PICU length of stay, and LCOS. Correlation coefficients (r) with corresponding p-values were reported.

To evaluate the association between RACHS-1 score and postoperative outcomes, multivariable regression analyses were performed. RACHS-1 score was entered into the models as a categorical variable (levels 2, 3, and 4). For continuous outcomes (Syndecan levels at T0, T4, T72, T40, and T724; VIS at 0–4 h, 4–24 h, and 24–72 h; PELOD-2 score at 24 h and 72 h; and PICU length of stay), linear regression models were applied. For binary outcomes logistic regression was used and results were expressed as odds ratios (OR) with 95% confidence intervals (CI).

All models were adjusted for potential confounders, including CPB duration (>120 min), aortic cross-clamp time, pre-PICU status, age, height, and weight. Regression coefficients (β) with corresponding *p*-values were reported for continuous outcomes, while ORs with 95% CIs and *p*-values were presented for LCOS. A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using R software (version 2023.09.1+494; R Foundation for Statistical Computing, Vienna, Austria).

3 Result

This study included 106 patients who underwent various cardiac surgeries, stratified by RACHS-1 categories. As shown in Table 1, patients in category 3 were generally older and larger in size, while those in category 4 were the youngest and smallest. This reflects the nature of procedures in RACHS-1 category 4, which typically involve neonates and young infants undergoing complex surgeries such as arterial switch with VSD repair or total anomalous pulmonary venous return correction. Gender distribution was relatively balanced across all groups (Table 1).

Table 1: Patient characteristics.

Variable	RACHS 2	RACHS 3	RACHS 4
	n = 37	n = 35	n = 34
Age, median (IQR), months	33.7 (12.6–48.4)	63.1 (28.1–90.5)	14.9 (4.6–31.1)
Weight, median (IQR), kg	9 (6.4–13)	14 (11.5–17)	7.3 (5.2–10.1)
Length, median (IQR), cm	79 (69.5–96.5)	104 (94–115)	74.5 (59.8–84)
Gender, n (%) Male Female	 20 (54.1) 17 (45.9)	 20 (57.1) 15 (42.9)	 18 (52.9) 16 (47.1)
Aortic cross clamp Time, median (IQR), minutes	41 (32–61)	30.5 (0–61)	94 (62–122)
CPB Time, median (IQR), minutes	76 (62–99)	103 (72.5–141.5)	164 (126–190)

Table 2 summarizes clinical outcomes across RACHS-1 categories. Syndecan-1 levels rose at 4 h postoperatively (T4) across all groups but declined significantly by 72 h (T72), suggesting early endothelial glycocalyx (EG) degradation followed by partial recovery. The smallest decline at T72 was observed in RACHS-4 patients, possibly due to their younger age and slower recovery. While Syndecan-1 levels at T0 and T4 showed no significant correlation with RACHS-1 scores, levels at T72 and the change from T4 to T72 were positively correlated with higher surgical risk, highlighting the association between delayed EG recovery and increased surgical complexity.

RACHS-4 patients also had the highest vasoactive-inotropic scores (VIS) at all time points, indicating greater hemodynamic support needs. Similarly, ICU stay was significantly longer in this group. Post hoc analysis revealed several significant pairwise differences, particularly between RACHS-2 and RACHS-4, for VIS, PELOD scores, and hospital length of stay, reinforcing the link between higher surgical risk and greater postoperative severity (Table 3).

Table 4 shows a positive correlation between early and late VIS scores and clinical outcomes, indicating that vasoactive support in the immediate and late postoperative periods is associated with patient status. In contrast, VIS during the intermediate period showed no significant correlation, likely reflecting a more stable phase with less consistent dose adjustments. PICU length of stay showed only a weak association with these scores.

PELOD scores were significantly higher in RACHS-1 category 4 patients at both 24 and 72 h, suggesting more severe organ dysfunction and slower recovery in this group. LCOS incidence was also significantly higher in RACHS categories 3 and 4 compared to category 2, reflecting the complexity of procedures within

these groups. Although mortality was highest in RACHS-4, the differences across categories were not statistically significant. PELOD scores showed a moderate positive correlation with RACHS-1 categories, particularly at 72 h (Table 4).

Table 2: Patient outcomes between RACHS-1 scores.

Variables	RACHS 2 n = 37	RACHS 3 n = 35	RACHS 4 n = 34	*p* Value
Syndecan T0, median (IQR), ng/ml	70.4 (41.5–133.8)	41.3 (32.7–87.1)	59.6 (42.8–102.5)	0.044
Syndecan T4, median (IQR), ng/ml	230.9 (185.9–265.7)	223.7 (210.8–263.6)	231.4 (185.5–254.4)	0.88
Syndecan T72, median (IQR), ng/ml	71.6 (49.3–111.7)	102.4 (71.7–219.4)	103.4 (64.8–229)	0.015
Syndecan T4–T0, mean (SD), ng/ml	124.5 (65.9)	156.0 (65.3)	139.0 (56.4)	0.105
Syndecan T72–T4, mean (SD), ng/ml	−125.5 (64.6)	−86.7 (78.0)	−83.3 (72.9)	0.026
VIS 0–4 h, median (IQR)	7.5 (5–10)	8.8 (8.8–14.4)	10 (7.6–14.7)	0.003
VIS 4–24 h, median (IQR)	8.5 (6.3–10.5)	10 (8.4–15.6)	10 (8.2–13.6)	0.02
VIS 24–72 h, median (IQR)	3.9 (3–8)	6.9 (4.8–11.5)	9.4 (6.4–14.7)	0.007
PICU LOS, median (IQR), days	3 (1–5)	2 (2–7)	7 (3–9.8)	0.02
PELOD-2 Score 24 h, median (IQR)	6 (0–9)	4 (0.5–10)	9 (4–11)	0.032
PELOD-2 Score 72 h, median (IQR)	0 (0–5)	1 (0–10)	4 (1–10.8)	0.01
LCOS, n (%)	12 (32.4)	22 (62.9)	20 (58.8)	0.019
Mortality, n (%)	3 (8.2)	3 (8.6)	6 (17.6)	0.368

Low Cardiac Output Syndrome (LCOS), Length of Stay (LOS), Paediatric Logistic Organ Dysfunction 2 (PELOD-2) score, Pediatric Intensive Care Unit (PICU), Vaso-Inotropic Score (VIS).

Table 3: Post Hoc analysis.

Variable	Comparison	Adjusted *p*-Value (Bonferroni Correction)
PICU LOS	RACHS-2 vs. RACHS-3	1.000
	RACHS-2 vs. RACHS-4	0.027
	RACHS-3 vs. RACHS-4	0.081
VIS 0–4 h	RACHS-2 vs. RACHS-4	0.015
	RACHS-2 vs. RACHS-3	0.009
	RACHS-4 vs. RACHS-3	1.000
VIS 4–24 h	RACHS-2 vs. RACHS-4	0.101
	RACHS-2 vs. RACHS-3	0.027
	RACHS-4 vs. RACHS-3	1.000
VIS 24–72 h	RACHS-2 vs. RACHS-3	1.000
	RACHS-2 vs. RACHS-4	0.045
	RACHS-3 vs. RACHS-4	0.106
PELOD 24 h	RACHS-2 vs. RACHS-3	0.966
	RACHS-2 vs. RACHS-4	0.008
	RACHS-3 vs. RACHS-4	0.136
PELOD 72 h	RACHS-2 vs. RACHS-3	0.241
	RACHS-2 vs. RACHS-4	0.046
	RACHS-3 vs. RACHS-4	1.000
Syndecan T0	RACHS-3 vs. RACHS-4	0.064
	RACHS-3 vs. RACHS-2	0.025
	RACHS-4 vs. RACHS-2	1.000
Syndecan T72	RACHS-2 vs. RACHS-4	0.094
	RACHS-2 vs. RACHS-3	0.052
	RACHS-4 vs. RACHS-3	1.000
Syndecan T72-4	RACHS-2 vs. RACHS-3	1.000
	RACHS-2 vs. RACHS-4	0.027
	RACHS-3 vs. RACHS-4	0.081

Table 4: Patient outcome and correlation.

Variables	Correlation Coefficient	*p* Value
Syndecan T0	−0.071	0.473
Syndecan T4	0.009	0.93
Syndecan T72	0.238	0.019
Syndecan T4–T0	0.079	0.436
Syndecan T72–T4	0.249	0.013
VIS 0–4 h	0.258	0.008
VIS 4–24 h	0.177	0.07
VIS 24–72 h	0.276	0.004
PICU LOS	0.161	0.099
PELOD Score 24 h	0.222	0.023
PELOD Score 72 h	0.263	0.008

Low Cardiac Output Syndrome (LCOS), Length of Stay (LOS), Paediatric Logistic Organ Dysfunction 2 (PELOD-2) score, Pediatric Intensive Care Unit (PICU, Vaso-Inotropic Score (VIS)).

In multivariable analyses adjusted for perioperative confounders (CPB duration, aortic cross-clamp time, PICU pre-status, age, weight, and height), RACHS category 3 consistently emerged as the group most strongly associated with endothelial injury and adverse outcomes. Compared with RACHS 2, RACHS 3 patients had significantly higher Syndecan-1 levels at 72 h (β = +51.95, p = 0.016, Table 5) and greater vasoactive support requirements in the early postoperative phase, reflected by an increase of 4.94 points in VIS 0–4 h (p = 0.008). They also demonstrated a six-fold higher risk of developing LCOS (OR = 5.99, 95% CI 1.61–25.70, p = 0.010, Table 5). RACHS 4 patients had an 81% lower risk (OR = 0.19, 95% CI 0.04–0.83, p = 0.035, Table 5).

Table 5: Significant multivariate analysis between RACHS score and outcomes.

Outcome	Comparison	β/OR (95% CI)	*p*-Value
Syndecan T72	RACHS 3 vs. 2 (ref = 2)	β = +51.95	0.016
VIS 0–4 h	RACHS 3 vs. 2 (ref = 2)	β = +4.94	0.008
LCOS	RACHS 3 vs. 2 (ref = 2) RACHS 4 vs. 3 (ref = 3)	OR = 5.99 (1.61–25.70) OR = 0.19 (0.04–0.83)	0.010 0.035

4 Discussion

This study explored the association between syndecan-1 levels and surgical complexity as stratified by RACHS-1 scores in pediatric cardiac surgery. Our findings highlight that syndecan-1 levels did not significantly correlate with RACHS-1 categories in the early postoperative period (T0 and T4), but a significant correlation emerged by 72 h (T72), suggesting that EG recovery is more closely linked to postoperative care than to the immediate impact of surgery alone.

The elevation of Syndecan-1 and delayed glycocalyx recovery reflect a multifactorial endothelial response involving inflammation, oxidative stress, and impaired shear-dependent mechanotransduction. Previous *in-vivo* study showed that enzymatic or cytokine-induced glycocalyx degradation triggers systemic inflammation and oxidative stress, delaying endothelial healing for 5–7 days and inhibiting regeneration in the absence of physiological shear stress [8]. Clinically, cardiopulmonary bypass has been shown to induce

persistent microcirculatory disturbances and prolonged glycocalyx shedding, with plasma Syndecan-1 and heparan sulfate levels inversely correlated with perfusion indices ($r = -0.51$, $p < 0.0001$). Together, these findings indicate that restoration of glycocalyx integrity depends on resolving inflammation, re-establishing physiological shear stress, and restoring oxidative balance [9].

In theory, higher RACHS categories represent greater surgical complexity and physiological stress, which are expected to induce more pronounced endothelial glycocalyx degradation. Our study showed that the change in syndecan-1 from T4 to T72 (ΔT72–T4) showed a stronger correlation with RACHS-1 scores than the change from T0 to T4 (ΔT4–T0), reinforcing that recovery dynamic are more indicative of surgical complexity. These findings imply that EG shedding is a near-universal response to cardiopulmonary bypass and surgical trauma, but the degree of recovery is modulated by patient and procedural factors.

In particular, patients in RACHS-1 category 3 showed the highest syndecan-1 elevation at T4, possibly reflecting more pronounced endothelial disruption in moderately complex procedures. Conversely, patients in RACHS-1 category 4 exhibited the least reduction in syndecan-1 by T72, pointing to a delayed recovery in this high-risk group. This pattern underscores the value of syndecan-1 as a potential marker not only for early endothelial injury but also for monitoring recovery and guiding postoperative care strategies.

These observations align with previous studies showing that syndecan-1 levels rise early after surgery and are exacerbated by CPB use [10]. The novel contribution of this study lies in its demonstration that syndecan-1 trends in the recovery phase (rather than the immediate postoperative period) better reflect the burden of surgical complexity and may help identify patients at risk of prolonged endothelial dysfunction.

Although syndecan-1 levels at baseline (T0) and 4 h postoperatively (T4) did not correlate with RACHS-1 scores, a significant positive correlation emerged at 72 h (T72). This novel finding suggests that syndecan-1 levels in the recovery phase may more accurately reflect clinical severity or ongoing endothelial dysfunction than levels measured immediately after surgery. Notably, the change in syndecan-1 between T72 and T4 correlated significantly with RACHS-1 scores, while the earlier change from T0 to T4 did not, thus highlighting the importance of recovery dynamics over initial injury.

These results underscore the potential of syndecan-1 as a dynamic marker of postoperative endothelial health. Specifically, its level at 72 h and the rate of decline may serve as indicators of surgical complexity and recovery trajectory. Further studies are warranted to validate these findings and assess whether targeted strategies to preserve or restore the endothelial glycocalyx can improve outcomes, particularly in high-risk pediatric cardiac surgery patients [5,6]. This aligns with growing evidence that the glycocalyx is not only a marker of endothelial injury but also a potential therapeutic target. Recent studies have reported that pharmacological agents such as sulodexide, albumin, fresh frozen plasma, glucocorticoids, and sphingosine-1-phosphate may attenuate glycocalyx shedding, preserve endothelial barrier function, and improve microcirculatory stability. Although our study did not evaluate these interventions, the association between higher RACHS categories, elevated syndecan-1, and adverse outcomes (higher VIS and LCOS incidence) provides clinical relevance and supports the rationale for future trials investigating EG-preserving therapies in pediatric cardiac surgery [3,4].

The observed differences in VIS across RACHS categories highlight the increased hemodynamic support required with greater surgical complexity. Patients in the highest RACHS category (RACHS-4) consistently showed the highest VIS at all postoperative intervals, reflecting prolonged cardiovascular instability and the need for aggressive pharmacologic support. These findings are consistent with the understanding that more complex congenital heart surgeries impose greater physiological stress. This is further supported by Wasniewski et al., who demonstrated that combining VIS and RACHS-1 scores provides good predictive accuracy for adverse events in pediatric cardiac surgery [11].

The significantly longer hospital stays observed in RACHS-1 category 4 patients further highlight the greater clinical burden associated with higher surgical complexity. Prolonged elevation of VIS likely reflects not only immediate postoperative instability but also a delayed recovery trajectory, possibly due to more extensive surgical trauma, longer cardiopulmonary bypass duration, or intrinsic patient vulnerabilities. These findings align with prior studies indicating that higher RACHS categories predict more complicated postoperative courses, extended recovery periods, and increased healthcare resource use. However, as Boethig et al. noted, while RACHS-1 classification has good predictive value at the group level, its accuracy in forecasting individual outcomes like length of stay and mortality remains limited [5].

Notably, PELOD scores were significantly higher in patients within the RACHS 4 group at both 24 and 72 h postoperatively, indicating more severe and prolonged organ dysfunction in those undergoing higher-risk procedures. These findings suggest that RACHS classification correlates not only with intraoperative complexity but also with the early postoperative physiological burden and severity of organ impairment [12].

Importantly, PELOD scores at both 24 and 72 h showed significant positive correlations with outcome measures, with a stronger association at 72 h. This suggests that persistent organ dysfunction beyond the immediate postoperative phase may better predict adverse outcomes than early assessments alone. These findings highlight the importance of serial organ function monitoring for early identification of patients needing intensified care.

In addition, the higher incidence of LCOS in RACHS-3 and RACHS-4 groups reinforces the link between surgical complexity and postoperative hemodynamic instability. LCOS, a known complication associated with poor perfusion and increased morbidity, was significantly more common in these higher-risk groups. While specific studies linking RACHS-1 categories to LCOS are lacking, Navero et al. found VIS scores to be independently associated with LCOS development, supporting our observations [13]. Although mortality rates were highest in RACHS-4 and lowest in RACHS-2, the difference was not statistically significant, potentially due to limited sample size or improved perioperative care. Nonetheless, the overall trends align with prior studies, affirming that higher RACHS categories are associated with more complex and risk-prone postoperative courses [14–16].

This study has several limitations that should be acknowledged. First, this was a single-center study with a relatively modest sample size, which may limit the generalizability of the findings and reduce statistical power, especially for subgroup comparisons. Second, syndecan-1 was only measured at three time points, which may not fully capture the dynamic trajectory of glycocalyx shedding and recovery.

To address these limitations, future studies should enroll a larger and more diverse patient population including lower and higher RACHS categories, and perform more frequent syndecan-1 monitoring to capture the full temporal pattern of EG injury and recovery. Long-term outcome assessments such as neurodevelopmental follow-up or organ-specific complications would provide additional clinical relevance. Including a comparator group without CPB exposure or a less invasive surgical cohort could further clarify the specific contribution of surgical trauma to endothelial dysfunction. These steps would enhance causal inference and support the clinical application of glycocalyx-based monitoring in pediatric cardiac surgery.

Despite these limitations, the study has strengths. It is one of the few to explore endothelial glycocalyx injury in pediatric cardiac surgery using syndecan-1 as a biomarker, and it integrates both biochemical and clinical parameters in the analysis. The prospective design and use of validated scoring systems (RACHS-1, PELOD, VIS) strengthen the methodological rigor.

5 Conclusion

This study demonstrates that surgical complexity, as reflected by RACHS-1 categories, is closely associated with endothelial glycocalyx injury and adverse early postoperative outcomes in pediatric cardiac

surgery. Patients in RACHS-1 category 4 showed the highest clinical severity, with elevated Syndecan-1 levels at 72 h, prolonged PICU stay, higher VIS and PELOD scores, and a greater incidence of LCOS. Multivariable analysis further revealed that RACHS-3 patients also had significantly increased Syndecan-1 levels and early VIS requirements, indicating that both intermediate and high surgical risk categories carry distinct hemodynamic and endothelial burdens. While early Syndecan-1 levels did not distinguish surgical risk, delayed recovery-phase elevations provide a stronger reflection of endothelial dysfunction. These findings emphasize that Syndecan-1 kinetics, together with VIS and LCOS, may serve as complementary markers of surgical complexity and postoperative instability. Incorporating these markers into postoperative risk stratification could help guide tailored monitoring and interventions to improve outcomes in high-risk pediatric cardiac surgery patients.

Acknowledgement: We sincerely thank the participants for their invaluable contribution to this study. We also appreciate the support provided by the Harapan Kita National Cardiovascular Centre and Gadjah Mada University which was crucial for the successful completion of this research.

Funding Statement: This study was conducted without financial support from any organizations, institutions, or third parties.

Author Contributions: The authors confirm contribution to the paper as follows: Study conception and design: Novik Budiwardhana, Indah Kartika Murni, Eva Miranda Marwali, Pribadi Wiranda Busro, Yunita Widyastuti. Data collection: Novik Budiwardhana, Fildza Intan Rizkia, Muhamad Faza Soelaeman. Analysis and interpretation of results: Novik Budiwardhana, Fildza Intan Rizkia, Muhamad Faza Soelaeman. Draft manuscript preparation: Novik Budiwardhana, Fildza Intan Rizkia, Muhamad Faza Soelaeman. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval: This study has been approved by Harapan Kita Ethics Committee under approval number LB.02.01/VII/003/KEP003/2023, and written informed consent was obtained from all participants. Our study complied with the 1975 Declaration of Helsinki principles.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

References

1. Murni IK, Djer MM, Yanuarso PB, Putra ST, Advani N, Rachmat J, et al. Outcome of pediatric cardiac surgery and predictors of major complication in a developing country. Ann Pediatr Cardiol. 2019;12(1):38–44. [CrossRef].
2. Epting CL, McBride ME, Wald EL, Costello JM. Pathophysiology of post-operative low cardiac output syndrome. Curr Vasc Pharmacol. 2016;14(1):14–23. [CrossRef].
3. Villalba N, Baby S, Yuan SY. The endothelial glycocalyx as a double-edged sword in microvascular homeostasis and pathogenesis. Front Cell Dev Biol. 2021;9:711003. [CrossRef].
4. Suzuki A, Tomita H, Okada H. Form follows function: the endothelial glycocalyx. Transl Res. 2022;247:158–67. [CrossRef].
5. Boethig D, Jenkins KJ, Hecker H, Thies WR, Breymann T. The RACHS-1 risk categories reflect mortality and length of hospital stay in a large German pediatric cardiac surgery population. Eur J Cardiothorac Surg. 2004;26(1):12–7. [CrossRef].
6. Larsen SH, Pedersen J, Jacobsen J, Johnsen SP, Hansen OK, Hjortdal V. The RACHS-1 risk categories reflect mortality and length of stay in a Danish population of children operated for congenital heart disease. Eur J Cardiothorac Surg. 2005;28(6):877–81. [CrossRef].
7. Thiagarajan RR, Laussen PC. Risk adjustment for congenital heart surgery-1 (RACHS-1) for evaluation of mortality in children undergoing cardiac surgery. In: Pediatric and congenital cardiac care. London, UK: Springer; 2014. p. 327–36. [CrossRef].

8. Potter DR, Jiang J, Damiano ER. The recovery time course of the endothelial cell glycocalyx *in vivo* and its implications *in vitro*. Circ Res. 2009;104(11):1318–25. [CrossRef].
9. Dekker NM, Veerhoek D, Koning NJ, van Leeuwen AI, Elbers PG, van den Brom CE, et al. Postoperative microcirculatory perfusion and endothelial glycocalyx shedding following cardiac surgery with cardiopulmonary bypass. Anaesthesia. 2019;74(5):609–18. [CrossRef].
10. Passov A, Schramko A, Salminen US, Aittomäki J, Andersson S, Pesonen E. Endothelial glycocalyx during early reperfusion in patients undergoing cardiac surgery. PLoS One. 2021;16(5):e0251747. [CrossRef].
11. Geier L, Menzel C, Germund I, Trieschmann U. RACHS-1 score as predictive factor for postoperative ventilation time in children with congenital heart disease. Cardiol Young. 2020;30(2):213–8. [CrossRef].
12. Russell RA, Ghanayem NS, Kuhn EM, Jeffries HE, Scanlon MC, Rice TB. Relationship between risk-adjustment tools and the pediatric logistic organ dysfunction score. World J Pediatr Congenit Heart Surg. 2014;5(1):16–21. [CrossRef].
13. Pérez-Navero JL, Merino-Cejas C, de la Rosa II, Jaraba-Caballero S, Frias-Perez M, Gómez-Guzmán E, et al. Evaluation of the vasoactive-inotropic score, mid-regional pro-adrenomedullin and cardiac troponin I as predictors of low cardiac output syndrome in children after congenital heart disease surgery. Med Intensiva. 2019;43(6):329–36. [CrossRef].
14. Bajracharya SM, Joshi D, Pradhan S. Predicting surgical mortality after congenital heart surgeries using risk adjustment in congenital heart surgery-1 (RACHS-1) risk scoring system: a retrospective analysis in a single tertiary center. Nepal Heart J. 2023;20(2):27–31. [CrossRef].
15. Baquerizo P, Clavería C, Becker P, Ibáñez S, Villablanca P, Cerda J. Surgical mortality in pediatric congenital heart surgery: 10-year experience in a Chilean cardiac surgery center. Clinics of Surgery. 2024;9:3687.
16. de Melo Bezerra Cavalcante CT, de Souza NMG, Pinto VC Jr, Branco KMPC, Pompeu RG, de Oliveira Teles AC, et al. Analysis of surgical mortality for congenital heart defects using RACHS-1 risk score in a Brazilian single center. Braz J Cardiovasc Surg. 2016;31(3):219–25. [CrossRef].