Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Surgical Determinants of Biomarker Profiles and Outcomes After the Fontan Procedure in Children

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Abstract

Objective: Early prediction of severe hemodynamic instability following the Fontan procedure is clinically important. This study aimed to investigate the association between early postoperative systemic immune-inflammation index (SII), hemoglobin–albumin–lymphocyte–platelet (HALP) score, and MELD-XI values and the requirement for extracorporeal membrane oxygenation (ECMO) in pediatric Fontan patients. **Materials and Methods:** Seventy-seven pediatric patients who underwent Fontan completion using the extracardiac total cavopulmonary connection technique between 2016 and 2021 were retrospectively evaluated. SII, HALP, and MELD-XI values measured within the first 24–72 postoperative hours were analyzed. The primary endpoint was ECMO requirement. Due to the limited number of ECMO events, univariable logistic regression analysis was performed. Discriminatory performance was assessed using receiver operating characteristic (ROC) curve analysis. **Results:** ECMO support was required in 14 patients (18.2%). In the ECMO group, cardiopulmonary bypass time was longer, SII and MELD-XI values were higher, and HALP scores were lower (all comparisons $p < 0.001$). In univariable analysis, CPB time (OR 1.06; 95% CI 1.02–1.10), SII (OR 1.005; 95% CI 1.002–1.007), HALP (OR 0.77; 95% CI 0.68–0.88), and MELD-XI (OR 2.78; 95% CI 1.64–4.73) were associated with ECMO requirement. ROC analysis demonstrated an AUC of 0.983 (95% CI 0.953–1.000) for SII, 0.955 (95% CI 0.885–0.997) for MELD-XI, and 0.844 (95% CI 0.677–0.989) for HALP. **Conclusion:** Increased inflammatory and organ dysfunction markers and reduced immunonutritional reserve in the early postoperative period may be associated with ECMO requirement after the Fontan procedure. Given the limited sample size, these findings should be interpreted as exploratory. Larger prospective studies are needed to clarify the role of these parameters in early risk stratification.

Keywords: Fontan procedure; pediatric cardiac surgery; biomarkers; ECMO; systemic inflammation

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1. Introduction

The Fontan procedure represents the final stage of palliative surgical management in patients with functional single-ventricle physiology, enabling the separation of pulmonary and systemic circulations in series. Advances in surgical techniques, improvements in perioperative care, and more careful patient selection have led to a significant reduction in early postoperative mortality following Fontan surgery in recent years. Nevertheless, the Fontan circulation is characterized by limited cardiac output, elevated systemic venous pressures, and non-pulsatile pulmonary blood flow, resulting in a unique physiology that may affect multiple organ systems[1–3].

Although the Fontan procedure is typically performed in early childhood in most centers, surgery may be delayed in some patients due to socioeconomic, anatomical, or clinical factors. In patients undergoing Fontan completion at a later age, prolonged exposure of the ventricle to volume and pressure overload, a potential increase in pulmonary vascular resistance, and limited cardiac reserve have been associated with a higher incidence of postoperative complications. This subgroup may exhibit clinical and hemodynamic characteristics that differ from standard Fontan cohorts and may therefore be at increased risk during the early postoperative period[3–5].

Identifying parameters that can predict early clinical course after Fontan surgery is important for risk stratification and patient management[2]. Although operative duration and technical factors have long been used to assess clinical outcomes, these variables may not fully explain postoperative course, particularly in patients considered to be at higher risk[6]. In recent years, biomarkers reflecting cardiac load, systemic inflammation, nutritional status, and hepatic function have been suggested to have potential prognostic value in the evaluation of Fontan physiology[7,8]. However, the relationship between these biomarkers and surgical factors, as well as their role in predicting early postoperative outcomes, has been limitedly investigated in pediatric populations and particularly in patients undergoing Fontan completion at a relatively later age.

In this study, we analyzed the association between surgical and perioperative characteristics and early postoperative biomarker profiles in pediatric patients undergoing the Fontan procedure, and evaluated the relationship between these biomarkers and early clinical outcomes. By focusing on patients undergoing Fontan completion at a relatively later age and those considered to be at increased perioperative risk, we aimed to identify objective parameters that may contribute to early risk assessment following Fontan surgery.

2. Materials and Methods

2.1.Study Design and Ethical Approval

This study was designed as a single-center retrospective cohort analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all data were anonymized prior to analysis. Ethical approval was obtained from the institutional ethics committee (date: January 9, 2026; decision no: 162; session no: 37). Due to the retrospective design and the use of anonymized data, the requirement for individual informed consent was waived.

2.2Patient Population

Seventy-seven consecutive pediatric patients who underwent Fontan completion using the extracardiac total cavopulmonary connection (TCPC) technique at our center between 2016 and 2021 were included. Patients with functional single-ventricle physiology and available early postoperative laboratory data were eligible for analysis. Patients with missing key demographic, surgical, or postoperative biochemical data were excluded.

At our institution, Fontan completion may occasionally be performed beyond the conventional timing. In this study, the term "high-risk Fontan" does not refer to a universally accepted risk classification but reflects an operational definition based on institutional clinical practice.

2.3.Surgical Technique and Operative Variables

All patients underwent the extracardiac TCPC technique. Operative data were retrospectively obtained from surgical reports and perfusion records. The recorded variables included:

• Cardiopulmonary bypass (CPB) time (minutes)
• Aortic cross-clamp time (minutes)
• Total operative time (minutes)
• Conduit diameter (mm)
• Presence of fenestration

Fenestration was selectively performed based on intraoperative hemodynamic assessment and the patient’s clinical risk profile.

2.4.Biomarker Assessment

Laboratory values obtained during routine clinical practice within the first 24–72 postoperative hours were analyzed. This time interval reflects the period during which early hemodynamic stabilization and inflammatory response are typically observed at our center.

The analyzed parameters were:

• Systemic immune-inflammation index (SII): platelet × neutrophil / lymphocyte
• HALP score: hemoglobin × albumin × lymphocyte / platelet
• MELD-XI score: calculated using the standard formula based on serum creatinine and total bilirubin

These parameters were considered indicators of systemic inflammation, immunonutritional reserve, and hepatorenal function, respectively.

Preoperative biomarker values were not included in the analysis, as they were not consistently available within a standardized time frame.

2.5.Clinical Outcomes and Endpoints

Primary Endpoint:

• Postoperative requirement for extracorporeal membrane oxygenation (ECMO)

Secondary Endpoints:

• Early mortality (evaluated descriptively only)
• Duration of mechanical ventilation
• Length of intensive care unit (ICU) and hospital stay

ECMO was initiated in cases of refractory low cardiac output syndrome or severe hemodynamic instability despite maximal medical therapy.

Given the limited number of mortality events, no inferential statistical analysis was performed for mortality, and it was presented descriptively.

2.6.Statistical Analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics, version 29.0). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Non-normally distributed variables were presented as median (minimum–maximum), and categorical variables were expressed as number and percentage.

Comparisons between patients with and without ECMO requirement were performed using the Mann–Whitney U test for continuous variables and Fisher’s exact test for categorical variables.

Variables associated with ECMO requirement were evaluated using univariable logistic regression analysis, and results were reported as odds ratios (OR) with 95% confidence intervals (CI). For CPB time, the OR was calculated per minute increase.

Given the limited number of ECMO events, multivariable modeling was not performed to avoid the risk of overfitting. Findings were interpreted as univariable associations rather than independent predictive effects.

The discriminatory performance of biomarkers for ECMO requirement was assessed using receiver operating characteristic (ROC) curve analysis. Area under the curve (AUC) values were reported with 95% confidence intervals. Optimal threshold values were determined using the Youden index, and corresponding sensitivity and specificity values were calculated.

A two-tailed p value < 0.05 was considered statistically significant in all analyses.

3. Results

3.1. Demographic and Preoperative Characteristics

A total of 77 pediatric patients were included in the study. Of these, 41 (53.2%) were male and 36 (46.8%) were female. The median age was 11 years (range, 2–17). The median height was 143 cm (90–185) and the median body weight was 38 kg (14–68) (Table 1).

Table 1. Demographic and Preoperative Characteristics of the Study Population

Variable	Value
Number of patients	77
Male / Female, n (%)	41 (53.2) / 36 (46.8)
Age (years), median (min–max)	11 (2–17)
Height (cm), median (min–max)	143 (90–185)
Weight (kg), median (min–max)	38 (14–68)

Values are presented as median (minimum–maximum) or number (percentage), as appropriate.

3.2. Surgical and Operative Data

All patients underwent the extracardiac total cavopulmonary connection (TCPC) technique. The median cardiopulmonary bypass (CPB) time was 100 minutes (54–180), the median aortic cross-clamp time was 0 minutes (0–93), and the median total operative time was 246 minutes (160–359). The median conduit diameter was 20 mm (16–22). Fenestration was performed in 44 patients (57.1%) (Table 2).

Table 2. Operative and Surgical Characteristics

Variable	Median (min–max)
Cardiopulmonary bypass time (min)	100 (54–180)
Aortic cross-clamp time (min)	0 (0–93)
Total operative time (min)	246 (160–359)
Conduit diameter (mm)	20 (16–22)
Fenestration, n (%)	44 (57.1)

Values are presented as median (minimum–maximum) or number (percentage). CPB, cardiopulmonary bypass.

3.3. Early Postoperative Biomarker Profiles

The distribution of early postoperative biomarkers demonstrated heterogeneity. The median SII value, reflecting systemic inflammation, was 379 (110–2664). The median HALP score was 37 (11–48), and the median MELD-XI score was 12 (8–20) (Table 3).

Table 3. Early Postoperative Biomarker Profiles

Biomarker	Median (min–max)
Systemic immune-inflammation index (SII)	379 (110–2664)
HALP score	37 (11–48)
MELD-XI score	12 (8–20)

Values are presented as median (minimum–maximum). SII, systemic immune-inflammation index; HALP, hemoglobin–albumin–lymphocyte–platelet score; MELD-XI, Model for End-Stage Liver Disease excluding INR.

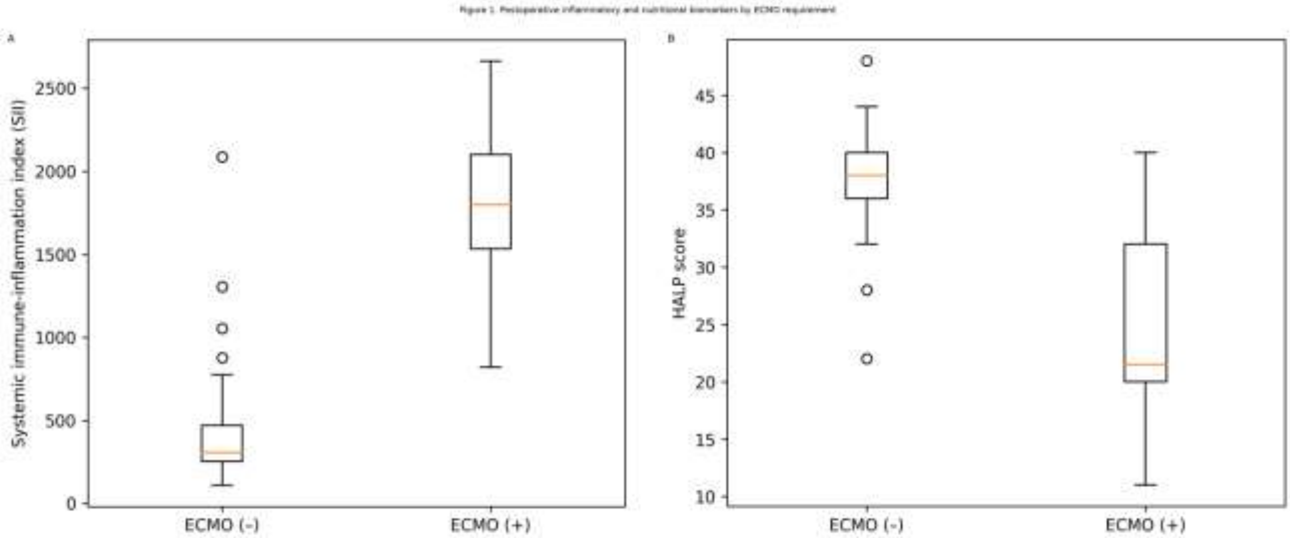

Figure 1. Comparison of Postoperative Inflammatory and Nutritional Biomarkers According to ECMO Requirement *(A) Systemic immune-inflammation index (SII) values according to ECMO requirement. (B) HALP score values according to ECMO requirement. Box-and-whisker plots demonstrate that patients requiring extracorporeal membrane oxygenation (ECMO) exhibited significantly higher postoperative SII values and significantly lower HALP scores compared with patients without ECMO requirement.*

3.4.Early Postoperative Clinical Outcomes

The median duration of mechanical ventilation was 19 hours (4–144), the median intensive care unit (ICU) stay was 3 days (1–10), and the median hospital stay was 9 days (2–22).

The primary endpoint, ECMO requirement, occurred in 14 patients (18.2%).

Early mortality was observed in 5 patients (6.5%) and, due to the limited number of events, was evaluated descriptively only.

3.5.Comparison Between Patients With and Without ECMO Requirement

Patients who required ECMO had significantly longer CPB times compared with those who did not require ECMO (median 132 minutes [98–180] vs 95 minutes [54–140], p < 0.001).

SII values were significantly higher in the ECMO group (median 2140 [877–2664] vs 342 [110–812], p < 0.001), whereas HALP scores were significantly lower (median 22 [11–30] vs 38 [28–48], p < 0.001). MELD-XI scores were also significantly higher in patients requiring ECMO (median 16 [13–20] vs 11 [8–15], p < 0.001).

There was no statistically significant difference in age between the groups (p = 0.112). All comparisons according to ECMO requirement are summarized in Table 4.

3.6.Univariable Logistic Regression Analysis

Variables associated with ECMO requirement were evaluated using univariable logistic regression analysis:

- CPB time: OR 1.06 per minute increase (95% CI 1.02–1.10; p = 0.001)
- SII: OR 1.005 per unit increase (95% CI 1.002–1.007; p < 0.001)
- HALP score: OR 0.77 per unit increase (95% CI 0.68–0.88; p < 0.001)
- MELD-XI score: OR 2.78 per unit increase (95% CI 1.64–4.73; p < 0.001)

Given the limited number of ECMO events, multivariable analysis was not performed, and results are presented as univariable associations. The results of the univariable analysis are summarized in Table 5.

Table 4. Comparison of Patients with and Without ECMO Requirement

Variable	ECMO (+) (n=14)	ECMO (–) (n=63)	p value
Age (years)	9 (4–16)	11 (2–17)	0.112
Cardiopulmonary bypass time (min)	132 (98–180)	95 (54–140)	<0.001
Systemic immune-inflammation index (SII)	2140 (877–2664)	342 (110–812)	<0.001
HALP score	22 (11–30)	38 (28–48)	<0.001
MELD-XI score	16 (13–20)	11 (8–15)	<0.001

Values are presented as median (minimum–maximum) or number (percentage), as appropriate. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. ECMO, extracorporeal membrane oxygenation; SII, systemic immune-inflammation index; HALP, hemoglobin–albumin–lymphocyte–platelet score; MELD-XI, Model for End-Stage Liver Disease excluding INR.

Table 5. Univariable Logistic Regression Analysis for ECMO Requirement

Variable	Odds Ratio (OR)	95% Confidence Interval	p-value
CPB time (per minute increase)	1.06	1.02 – 1.10	0.001
SII (per unit increase)	1.005	1.002 – 1.007	<0.001
HALP (per unit increase)	0.77	0.68 – 0.88	<0.001
MELD-XI (per unit increase)	2.78	1.64 – 4.73	<0.001

OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; CPB: Cardiopulmonary bypass; SII: Systemic immune-inflammation index; HALP: Hemoglobin–albumin–lymphocyte–platelet score; MELD-XI: Model for End-Stage Liver Disease excluding INR.

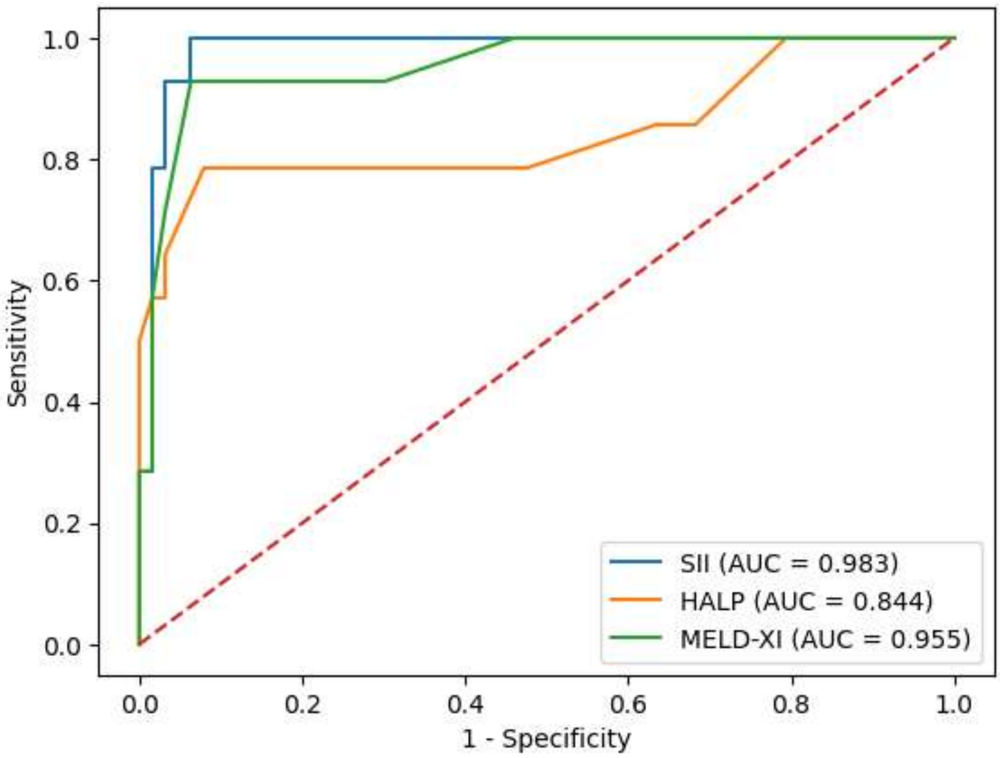

Figure 2. Receiver Operating Characteristic (ROC) Curves of Biomarkers for Predicting ECMO Requirement

Receiver operating characteristic (ROC) curve analysis demonstrating the predictive performance of SII, HALP, and MELD-XI scores for ECMO requirement in the early postoperative period following the Fontan procedure.

3.7.ROC Curve Analysis

The discriminatory performance of biomarkers for predicting ECMO requirement was assessed using ROC curve analysis.

For SII, the AUC was 0.983 (95% CI 0.953–1.000). At the optimal threshold of 820 determined by the Youden index, sensitivity was 100% and specificity was 93.7%.

For HALP, the AUC was 0.844 (95% CI 0.674–0.989). At a cut-off value of 32, sensitivity was 78.6% and specificity was 92.1%.

For MELD-XI, the AUC was 0.955 (95% CI 0.886–0.997). At a threshold of 15, sensitivity was 92.9% and specificity was 93.7% (Figure 2).

These findings suggest that, within the present cohort, these biomarkers may have the capacity to discriminate ECMO requirement. However, given the limited sample size, these results should be interpreted as exploratory rather than confirmatory.

4. Discussion

In this study, we evaluated the association between early postoperative SII, HALP, and MELD-XI values and ECMO requirement in pediatric patients undergoing the Fontan procedure. Our findings indicate that prolonged cardiopulmonary bypass (CPB) time, elevated SII and MELD-XI values, and decreased HALP scores were associated with ECMO requirement. However, given the retrospective design and the limited number of events, these findings should be interpreted as exploratory rather than indicative of independent predictive effects[2,8–10].

The Fontan circulation is characterized by limited cardiac output and chronic venous congestion[2]. This unique physiology may accentuate cardiac, inflammatory, and metabolic responses in the early postoperative period. Surgical stress and prolonged CPB duration further contribute to these responses. In our cohort, CPB time was significantly longer in patients who required ECMO, supporting the role of operative duration as an important determinant of early postoperative hemodynamic instability after Fontan surgery[9].

SII, a marker reflecting systemic inflammation, was significantly higher in patients requiring ECMO. This finding suggests that surgical stress and the associated inflammatory response may play a role in early clinical deterioration[11,12]. In our ROC analysis, SII demonstrated a high AUC value. Nevertheless, particularly the very high AUC observed for SII may partly reflect threshold optimization in a limited cohort and should therefore be interpreted with caution. The limited sample size and event number may contribute to overestimation of discriminatory performance.

The HALP score represents a composite indicator of immunonutritional reserve[13]. Lower HALP values may reflect reduced physiological reserve and increased inflammatory burden. In our study, lower HALP scores were observed in patients requiring ECMO, suggesting that diminished immunonutritional status may be associated with early postoperative instability. However, data regarding HALP in pediatric Fontan populations remain limited, and further confirmatory studies are required.

Chronic venous congestion is a well-recognized feature of Fontan physiology and may adversely affect hepatic function[6,14]. We observed significantly higher MELD-XI scores in the ECMO group, suggesting that even early postoperative hepatorenal dysfunction may be associated with adverse clinical course[15,16]. Despite the high AUC observed for MELD-XI, this finding should also be interpreted cautiously in light of the limited sample size.

An important aspect of this study is the simultaneous evaluation of inflammatory status, immunonutritional reserve, and hepatorenal function within the same cohort.

However, the absence of multivariable modeling precludes assessment of independent effects, and the results should therefore be interpreted as associative rather than causal.

The term "high-risk Fontan" used in this study reflects an operational definition based on institutional clinical practice and does not correspond to a standardized risk classification. Accordingly, the generalizability of the findings may be limited. In addition, biomarker measurements were obtained within a 24–72-hour postoperative window, which may introduce temporal heterogeneity and may not fully capture dynamic inflammatory changes. The absence of preoperative biomarker values limited our ability to assess surgery-related changes. Furthermore, no adjustment was performed for potential confounders such as fenestration, which represents another limitation.

Overall, these findings suggest that the evaluated biomarkers should not be considered stand-alone decision-making tools but rather as supportive parameters that may contribute to early risk awareness. Larger, prospective studies are required to validate these associations and to clarify how such biomarkers could be integrated into clinical decision-making algorithms.

5. Conclusion

In this single-center retrospective study, early postoperative SII, HALP, and MELD-XI values were found to be associated with ECMO requirement following the Fontan procedure. Prolonged CPB duration, increased inflammatory and organ dysfunction markers, and reduced immunonutritional reserve may accompany early hemodynamic instability in this population.

However, given the limited sample size and event count, these findings should be considered exploratory and hypothesis-generating rather than definitive evidence of independent predictive value. These biomarkers may provide supportive information in identifying patients at increased early risk rather than serving as stand-alone clinical decision tools.

Further large-scale, prospective studies are needed to better define their role in early postoperative risk stratification after the Fontan procedure.

genAI: No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by the author.

Statement of Ethics: The study was conducted in accordance with the principles of the Declaration of Helsinki, and all data were anonymized prior to analysis. Ethical approval was obtained from the institutional ethics committee (date: January 9, 2026; decision no: 162; session no: 37). Due to the retrospective design and the use of anonymized data, the requirement for individual informed consent was waived.

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

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Conflict of Interest: The author declares no conflict of interest.

Author Contributions: Study concept and design: O.B.; Data collection: O.B.; Surgical procedures and clinical follow-up: O.B.; Data analysis and interpretation: O.B.; Statistical analysis: O.B.; Writing of the manuscript: O.B.; Critical revision: O.B. The author has read and approved the final version of the manuscript.

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