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PRESEPSIN AS A POTENTIAL BIOMARKER OF SEPSIS IN PEDIATRIC PATIENTS UNDERGOING OPEN-HEART SURGERY

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ABSTRACT

Sepsis after pediatric open-heart surgery is rare but highly lethal. Diagnosis is challenging because sepsis symptoms often overlap with postoperative inflammatory responses. This study assessed presepsin as a biomarker for postoperative sepsis in children with congenital heart disease. In this prospective diagnostic accuracy study at Cipto Mangunkusumo National Central Hospital, Jakarta, 49 children undergoing open-heart surgery were enrolled. Plasma presepsin and procalcitonin (PCT) levels were measured on postoperative day 1 (T1) and day 3 (T3). Diagnostic performance was evaluated using ROC analysis. Presepsin levels were higher in septic than non-septic patients at T1 (415 vs. 141.5 pg/mL) and T3 (624 vs. 75.9 pg/mL), with a significant difference at T3 ($p = 0.001$). Presepsin was unrelated to surgical complexity but was associated with 7-day mortality ($p = 0.013$). At T3, presepsin showed better diagnostic accuracy than PCT (AUC 0.945 vs. 0.895). Optimal cut-offs were 404 pg/mL (T1) and 203.5 pg/mL (T3). PCT levels declined over time in septic patients. Presepsin is a promising biomarker for detecting postoperative sepsis in pediatric open-heart surgery patients, demonstrating diagnostic performance comparable to or superior to PCT, particularly on postoperative day 3. Serial monitoring may facilitate earlier identification of septic complications.

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1. INTRODUCTION

Congenital heart disease (CHD) is a prevalent disorder that affects heart structure and function, and disrupts blood circulation and heart hemodynamics[1]. CHD poses a significant public health challenge, is a leading cause of infant mortality, and necessitates frequent hospitalization and long-term monitoring of children. Indonesian Ministry of Health indicate that among the 4.6 million live births in Indonesia, approximately 36,000 were affected by CHD. Annually, only 2.3% of these patients receive treatment at Harapan Kita National Heart Center Hospital, Jakarta. [2] Corrective interventions, such as open-heart surgery, invasively address anatomical and functional heart abnormalities. [3] The mortality rate of pediatric heart surgery patients with RSCM between 2014 and 2015 was 13%, with a 17.5% incidence of sepsis[4].

Cardiopulmonary bypass (CBP) combined with ischemia-reperfusion injury, hypothermia, and surgical trauma triggers a complex systemic inflammatory response [5], [6], [7]. This involves complement cascade activation, endotoxin release, leukocyte and vascular endothelium activation, and proinflammatory cytokine secretion. Consequently, inflammation leads to temporary immunosuppression and an increased susceptibility to infection. [3] Postoperative infections significantly impact morbidity and mortality rates, increase antibiotic usage, and extend intensive care unit stays [4], [8], [9].

CD14, a glycoprotein of the Toll-like receptor (TLR) family, is membrane-associated (mCD14) and soluble (sCD14). Its primary ligand, bacterial lipopolysaccharide (LPS), binds to LPS-binding protein (LPBP), which triggers TLR recognition and produces sCD14, which can attach to epithelial and endothelial cells [10], [11]. Soluble CD14 is cleaved by cathepsin D into 13 kDa molecules, forming a new molecule called presepsin (sCD14-ST) [12]. Blood culture is recognized as the gold standard for diagnosing sepsis but has limitations, including long result times, false negatives, and a sensitivity of 35.4%. Presepsin, an immunological biomarker, has shown high accuracy in detecting adult infections [13]. Its use as an early marker for postoperative infections has been reported in adult cardiac surgery patients [14].

Saito et al. found that presepsin levels increased before procalcitonin (PCT) and CRP levels in adults undergoing cardiovascular surgery. Research on presepsin in pediatric sepsis is limited, with only one systematic review and meta-analysis available [14]. Studies on the role of presepsin in pediatric postoperative infections in Indonesia are scarce [13]. These findings suggest that serial presepsin evaluations after surgery may be useful for diagnosing infectious complications in pediatric patients. However, no studies have explored the presepsin levels in children undergoing cardiac surgery. This study aimed to assess the efficacy of presepsin as a sepsis biomarker in children after open-heart surgery and to compare it with that of procalcitonin (PCT), an established marker.

2. RESEARCH METHOD

This prospective diagnostic accuracy study with repeated measures aimed to evaluate the efficacy of presepsin as a biomarker of postoperative sepsis in pediatric patients undergoing open-heart surgery. The study was conducted in the Cardiac Intensive Care Unit (CICU), part of the Integrated Cardiac Care Unit (PJT) at Cipto Mangunkusumo National Central Hospital (RSCM), Jakarta, Indonesia, between January and May 2023. The study adhered to the ethical principles of the Declaration of Helsinki and was approved by the Medical Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo National Central Hospital (No. 108/UN2.F1/ETIK/PPM.00.02/2023; January 23, 2023).

Consecutive pediatric patients aged 1 month to 18 years who underwent open-heart surgery with cardiopulmonary bypass (CPB) were screened for eligibility. Patients presenting with postoperative fever (core temperature $> 38.5°C$ or axillary temperature $> 37.9°C$) and clinically suspected sepsis, as determined by the attending physician, were enrolled. Sepsis was defined according to the criteria established by the International Pediatric Sepsis Consensus Conference, namely the presence of suspected or proven infection accompanied by systemic inflammatory response syndrome (SIRS) and evidence of organ dysfunction appropriate for pediatric patients. Confirmation of infection was supported by microbiological culture results when available. Patients with chronic inflammatory or systemic diseases, including rheumatic heart disease, systemic lupus erythematosus, chronic renal failure, and diabetes mellitus, those undergoing surgery for non-congenital cardiac conditions, patients who died within three days of observation, or those whose parents or legal guardians declined participation were excluded from the study. Written informed consent was obtained from parents or legal guardians prior to enrollment.

Demographic and clinical characteristics, including sex, age group, nutritional status, Aristotle Basic Score, CPB duration, aortic cross-clamp duration, and postoperative complications, were collected from medical records. Venous blood samples were obtained within 24 hours after surgery (T1) and repeated 72 hours postoperatively (T3) in surviving patients. Laboratory evaluation included complete blood count, plasma presepsin, procalcitonin (PCT), and blood cultures. Additional microbiological cultures were obtained when clinically indicated. Plasma presepsin levels were measured using the PATHFAST™ immunoanalyzer (Mitsubishi Chemical Medience Corporation, Tokyo, Japan), while PCT levels were analyzed using the Immulite 2000™ immunochemiluminescence system. Blood cultures were processed using the BACTEC™ BacT/Alert system (Biomerieux, France), with

microorganism identification performed using the Vitek Compact System 5.

Continuous variables are presented as medians (min-max), while categorical variables are expressed as frequencies and percentages. Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Diagnostic accuracy analyses were conducted using 2×2 contingency tables to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LRs), cut-off values, and area under the receiver operating characteristic curve (AUC-ROC), along with corresponding 95% confidence intervals (CIs). Comparisons between sepsis and non-sepsis groups were performed using the independent t-test or Mann–Whitney U test, depending on data distribution. Because of the limited number of sepsis events ($n = 5$), multivariable analysis and adjustment for potential confounders such as CPB duration, nutritional status, age, and Aristotle Basic Score were not feasible. Similarly, no correction for multiple comparisons was applied; therefore, findings should be interpreted cautiously and considered exploratory. The limited sensitivity of blood culture as the reference standard was acknowledged as a potential source of misclassification bias. Statistical significance was defined as $p < 0.05$.

3. RESULT AND ANALYSIS

Table 1 presents the characteristics of 49 paediatric patients, among whom 10.2% (5 patients) were diagnosed with sepsis. The gender distribution was equal. Approximately 55% of the groups comprised toddlers aged 1–5 years old. While 46.9% of patients had a good nutritional status, 22.4% (11 patients) had severe malnutrition. Additionally, 57.2% of patients had acyanotic CHD. Infections were predominantly caused by gram-negative bacteria, notably Klebsiella pneumoniae and Acinetobacter sp., which were identified in two blood cultures.

Table 1: Demographic Features of the Study Population

Variables	All (n = 49)	Sepsis (n = 5)	Nonsepsis (n = 44)
Sex, n (%)			
Male	25 (51.0)	4 (80.0)	21 (47.7)
Female	24 (49.0)	1 (20.0)	23 (52.3)
Age (year), n (%)			
1 month–1 year	8 (16.3)	1 (20.0)	7 (15.9)
1–5 years	27 (55.1)	2 (40.0)	25 (56.8)
>5 years	14 (28.6)	2 (40.0)	12 (27.3)
Nutritional Status, n (%)			
Severely malnourished	11 (22.4)	1 (20.0)	10 (22.7)
Underweight	14 (28.6)	2 (40.0)	12 (27.3)
Well-nourished	23 (46.9)	2 (40.0)	21 (47.7)
Overweight	1 (2.0)	0 (0)	1 (2.3)
Principal Diagnosis, n (%)			
Acyanotic CHD	28 (57.2)	1 (20.0)	27 (61.4)
Cyanotic CHD	21 (42.8)	4 (80.0)	17 (38.6)
Secondary Diagnosis, n (%)			
Down syndrome	7 (14.3)	1 (20.0)	6 (13.6)
Other syndromes	2 (4.0)	0 (0)	2 (4.5)
None	40 (81.7)	4 (80.0)	36 (81.8)
Aristotle Basic Score, n (%)			
Level 1	2 (4.1)	0 (0)	2 (4.5)
Level 2	8 (16.3)	0 (0)	8 (18.2)
Level 3	22 (44.9)	2 (40.0)	20 (45.5)
Level 4	17 (34.7)	3 (60.0)	14 (31.8)
Duration of CPB, n (%)			
≤90 mins	30 (61.2)	1 (20.0)	29 (65.9)
>90 mins	19 (38.8)	4 (80.0)	15 (34.1)
Duration of Aortic Cross Clamp, n (%)			
≤40 mins	30 (61.2)	3 (60.0)	27 (61.4)
>40 mins	19 (38.8)	2 (40.0)	17 (38.6)
Surgery Complications, n (%)			
Delayed sternal closure	4 (8.2)	3 (60.0)	1 (2.3)
None	45 (91.8)	2 (40.0)	43 (97.7)
Sputum Culture, n (%)			
Positive	26 (53.1)	5 (100.0)	21 (47.7)
Negative	23 (46.9)	0 (0)	23 (52.3)
Length of CICU Care, n (%)			
≤7 days	37 (75.5)	0 (0)	37 (84.1)

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Table 1 – Continued from Previous Page

Variables	All (n = 49)	Sepsis (n = 5)	Nonsepsis (n = 44)
>7 days	12 (24.5)	5 (100.0)	7 (15.9)
Presepsin Levels Change After 72 h, n (%)			
Decreased	43 (87.8)	3 (60.0)	40 (90.9)
Increased	6 (12.2)	2 (40.0)	4 (9.1)
Percentage of Decreased Presepsin Levels Reduction, n (%)*			
<50%	19 (44.2)	3 (100.0)	16 (40.0)
50–79%	20 (46.5)	0 (0)	20 (50.0)
≥80%	4 (9.3)	0 (0)	4 (10.0)
Percentage of Increased Presepsin Levels, n (%)†			
<50%	1 (16.7)	0 (0)	1 (25.0)
50–79%	1 (16.7)	1 (50.0)	0 (0)
≥80%	4 (66.7)	1 (50.0)	3 (75.0)

*Calculated among patients with decreased presepsin levels after 72 h (n = 43).

†Calculated among patients with increased presepsin levels after 72 h (n = 6).

Table 2 compares the presepsin and PCT levels on the first (T1) and third (T3) postoperative days between the sepsis and non-sepsis groups. In the sepsis group, presepsin levels increased on the third day, whereas the non-sepsis group demonstrated a decline. The sepsis group had significantly higher presepsin levels on the third postoperative day than the non-sepsis group ($p = 0.001$). Median PCT levels also differed significantly between the sepsis and non-sepsis groups on both the first postoperative day ($p = 0.016$) and the third postoperative day ($p = 0.004$) (Figure 1).

Table 2: Median Values of Presepsin and Procalcitonin in the Sepsis and Non-Sepsis Groups on the First and Third Day

Parameters	Sepsis (n = 5)	Non-Sepsis (n = 44)
Presepsin (pg/mL)		
T1	415 (102–3,004)	141.5 (37.9–2,010)
T3	624 (208–1,529)	75.9 (20.6–915)
Delta Presepsin	146 (-209–1,475)	71.95 (-154–1,475)
Procalcitonin (ng/mL)		
T1	340 (61.79–1,407)	43.85 (2.37–1,710)
T3	104.7 (28.71–500.70)	4.5 (0.12–844.20)

*Data are presented as median (minimum–maximum). P-values were obtained using the Mann–Whitney U test. *Statistically significant at $p < 0.05$. T1 = postoperative day 1; T3 = postoperative day 3.*

The delta presepsin value, representing the change in presepsin levels between T1 and T3, was calculated to evaluate biomarker trends over time. However, no statistically significant difference in delta presepsin values was observed between the sepsis and non-sepsis groups ($p = 0.895$). This finding suggests that absolute presepsin levels at specific postoperative time points, particularly on the third day, may provide greater diagnostic utility than changes in serial values alone. The lack of significant difference in delta presepsin trends may also reflect the limited sample size and the small number of sepsis cases in this study.

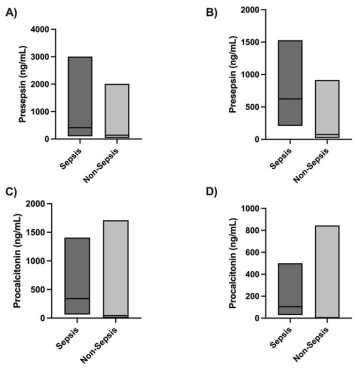
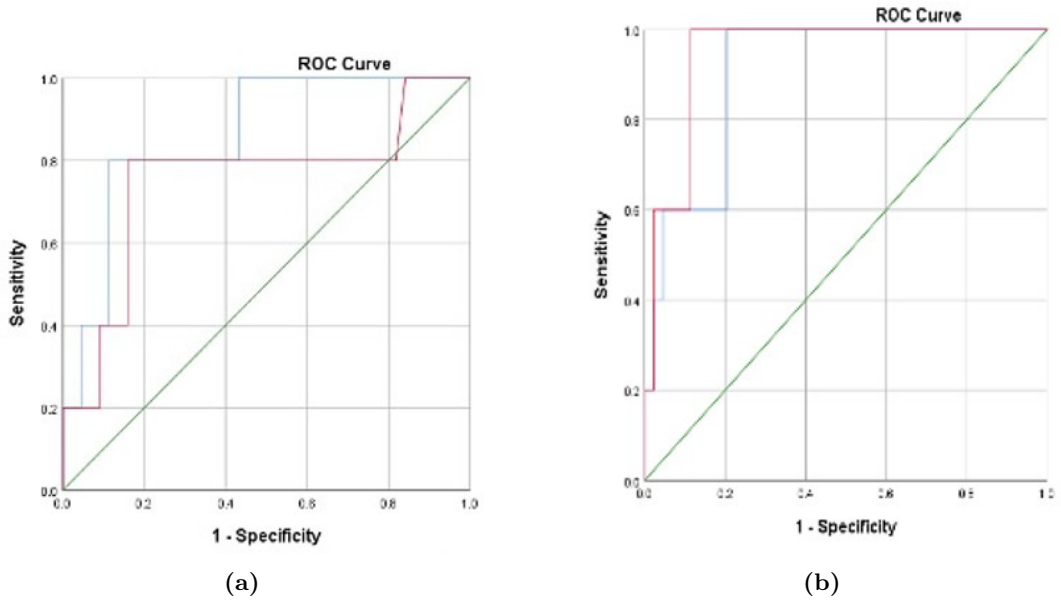


Figure 1. The levels of presepsin on the first day (A) and third day (B) and PCT levels on the first day (C) and third day (D). Solid lines indicate the median biomarker values.

The ROC curve for patients diagnosed with sepsis on the first day after open heart surgery indicated an AUC

of 0.752 for presepsin, which was lower than that for PCT (AUC of 0.832) (Figure 2A). The optimal presepsin cut-off according to the ROC curve was 404 ng/ml, which is close to the clinical cut-off of 500 pg/ml. Three days after surgery, the ROC curve showed an AUC of 0.945 for presepsin, which was higher than that for PCT (0.895). The optimal cutoff values were 203.5 pg/ml for presepsin and 28.54 ng/ml for PCT. On the first day (T1), presepsin had an optimal threshold of 404 pg/ml, while PCT had 226.85 ng/ml, both with a sensitivity of 80%. The specificity values for presepsin T1 (84.09%) and PCT (86.36%) are similar. The positive predictive value, negative predictive value, and positive likelihood ratio of presepsin were lower than those of PCT levels. However, the negative likelihood ratio was slightly higher (0.238) than that for PCT (0.232).



(a) **(b)**

Figure 2. Receiver operating characteristic (ROC) curves for presepsin and procalcitonin (PCT) levels in pediatric patients according to blood culture results on postoperative day 1 (A) and postoperative day 3 (B) following open-heart surgery.

These findings indicate that the effectiveness of presepsin as a blood culture indicator in children after open-heart surgery is slightly lower than that of procalcitonin. The optimal cut-off values for presepsin and PCT were 203.5 pg/mL and 28.545 ng/mL, respectively. On the third postoperative day, the area under the ROC curve was marginally higher for presepsin (0.945) than for procalcitonin (0.895) (Figure 2B). Both markers had 100% sensitivity, but presepsin showed a higher specificity (88.64%) than PCT (79.55%). ROC curve analysis identified a presepsin level of 203.5 pg/mL as the optimal cut-off for predicting sepsis, with 88.64% sensitivity and specificity, 50% positive predictive value (PPV), and 100% negative predictive value (NPV) (Table 3).

Table 3: Diagnostic Performance of Presepsin and Procalcitonin

Parameter	**Presepsin**		**PCT**	
	Day 1 (404 pg/mL)	Day 3 (203.5 pg/mL)	Day 1 (226.85 ng/mL)	Day 3 (28.54 ng/mL)
Sensitivity (95% CI)	80 (44.94–115.06)	100	80 (44.94–115.06)	100
Specificity (95% CI)	84.09 (73.28–94.90)	88.64 (79.26–98.01)	86.36 (76.22–96.50)	79.55 (67.63–91.46)
PPV (95% CI)	36.36 (7.94–64.79)	50 (19.01–80.99)	40 (9.64–70.36)	35.71 (10.62–60.81)
NPV (95% CI)	97.37 (92.28–102.46)	100	97.44 (92.48–102.40)	100
LR (+) (95% CI)	5.029 (2.241–11.286)	8.80 (3.856–20.085)	5.867 (2.475–13.908)	4.889 (2.730–8.755)
LR (-) (95% CI)	0.238 (0.041–1.379)	0	0.232 (0.040–1.342)	0
AUC–ROC (95% CI)	0.752 (0.483–1.022)	0.945 (0.878–1.013)	0.832 (0.685–0.978)	0.895 (0.794–0.997)

PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; AUC = area under the curve; ROC = receiver operating characteristic; CI = confidence interval.

This study investigated the seven-day survival rates of paediatric patients with sepsis and the relationship between mortality on the seventh day and presepsin levels on the first day (T1). The results indicated a significant correlation between seventh-day mortality and first-day presepsin levels ($p = 0.013$) (Table 4).

Table 4: Association Between First-Day Presepsin Levels and 7-Day Mortality

Parameter	Non-survivors (n = 4)	Survivors (n = 45)
Presepsin (pg/mL)	1212.5 (167–3004)	138 (37.9–1074)

*Data are presented as median (minimum–maximum). Comparisons were performed using the Mann–Whitney U test. *Statistically significant at $p < 0.05$ ($p = 0.013$).*

In general, significant differences were observed in presepsin and procalcitonin levels among the four complexity levels of the Aristotle Basic Score on the first and third days post-surgery; however, there was no significant relationship between the Aristotle Basic Score and the presepsin and PCT levels (Table 5).

Previous studies have predominantly examined adults with acquired or congenital heart disorders, resulting in limited paediatric specific data. This study assessed the efficacy of presepsin as a sepsis biomarker in children with congenital heart disease (CHD) who underwent open heart surgery with cardiopulmonary bypass (CPB). Additionally, we explored the changes in presepsin levels on the third postoperative day. The overall prevalence of sepsis was 10.2% compared to 17.4% in adults with congenital cyanotic heart disease. Yavuz et al. reported a 4.74% sepsis rate in children post-open-heart surgery [15]. Notably, 4.8% (211 of 2,230) of adults underwent cardiac surgery without CPB, indicating a relatively higher incidence of sepsis in the paediatric population. An immature immune system is a risk factor for postoperative infections in children [16], [17].

Table 5: Median Comparison of Presepsin and PCT Levels Based on the Aristotle Basic Score

Parameters	Aristotle Basic Score				p-value
	Level 1 (n = 2)	Level 2 (n = 8)	Level 3 (n = 22)	Level 4 (n = 17)	
Presepsin (pg/mL)					
T1	597.5 (121–1074)	130 (37.9–854)	145.5 (79.4–3004)	205 (67.6–2010)	0.487
T3	75.55 (50.1–101)	71.1 (30–150)	103.9 (20.6–1529)	89.3 (24.8–915)	0.673
Procalcitonin (ng/mL)					
T1	52.11 (20.39–83.82)	26.48 (11–1414)	55.52 (2.37–1407)	113.1 (3.39–1710)	0.873
T3	6.35 (2.43–10.27)	4.63 (0.12–165.06)	5.51 (0.22–500.70)	26.15 (0.26–844.20)	0.917

Data are presented as median (minimum–maximum). Comparisons among Aristotle Basic Score groups were performed using the Kruskal–Wallis test. T1 = postoperative day 1; T3 = postoperative day 3.

Surgical site infections (ISBs) significantly contribute to nosocomial infections in children post-cardiac surgery. Studies indicate that extended CPB time and duration are key risk factors for nosocomial infections after paediatric cardiac surgery. [16], [17] Perioperative factors, such as the duration and type of surgery, surgery site, CPB and aortic clamping duration, and hypothermia induction, affect postoperative fever, often resulting from surgery-related systemic inflammatory response syndrome [18], [19], [20].

Postoperative fever is common in children with CHD, raising concerns for both surgeons and patients. It can result from a metabolic trauma response, systemic response to cardiopulmonary bypass, hypothermia, drainage tubes, medications, blood transfusion, or infection. Addressing post-cardiac surgery fever requires a methodical approach; however, data on its occurrence are limited, with prevalence rates ranging from 12 to 73%. [21] Most children experience fever within 24 h post-surgery, typically resolving within 48–72 hours without specific treatment, requiring only symptomatic care. [19] Fever persisting beyond 48 h is more likely to indicate infection. Post-cardiac surgery fever is often linked to cardiopulmonary bypass, hypothermia, post-perfusion syndrome, infection, and blood transfusion [16].

In the present study, four of the five patients who developed sepsis had CPB times exceeding 90 min. Regarding aortic cross-clamp time, three out of five patients had a cross-clamp duration of $\leq$ 40 min (data not shown). A CPB duration of $\geq$ 90 min was linked to a 5.538-fold increased risk of postoperative sepsis compared to $\leq$ 90 min (80% vs. 25%, $RR = 5.538, p = 0.006$) [2]. Additionally, both the intensity and duration of inotropic use are associated with infection risk and the prolonged use of mechanical ventilation [14]. Gram-negative bacteria are the most commonly isolated bacteria in blood cultures, with Klebsiella pneumoniae being the most frequent (78%) in the Paediatric Intensive Care Unit (PICU) at RSCM Hospital between July and December 2020. [22] Variations in microbial patterns may result from the specific bacterial mapping used in each treatment center [23].

Beyond its diagnostic performance, presepsin may have important clinical and public health implications, particularly in resource-limited settings. Early identification of postoperative sepsis could facilitate timely and targeted antimicrobial therapy, potentially reducing unnecessary broad-spectrum antibiotic exposure and supporting antibiotic stewardship programs [9], [12]. Although the cost-effectiveness of routine presepsin testing was not evaluated in this study, serial biomarker monitoring may help optimize resource utilization by improving diagnostic accuracy and reducing prolonged intensive care stays or unnecessary investigations. In addition, implementation of

presepsin measurement appears feasible within routine postoperative monitoring workflows because the assay can be performed rapidly using automated immunoanalyzer systems already available in many tertiary-care centers. Further multicenter studies evaluating economic impact, accessibility, and integration into clinical decision-making protocols are warranted [24], [25].

Procedure complexity was assessed using the Aristotle Basic Score (ABS), which evaluates the potential mortality, morbidity, and technical challenges. ABS remained consistent for cardiac surgery patients regardless of institution or location.[26] Among patients who developed sepsis, 80% died more than seven days postoperatively. However, no significant correlation was found between ABS and postsurgical sepsis, as indicated by the number of patients who died at Level 3. ABS primarily reflects anticipated surgical difficulty rather than infection risk or postoperative sepsis [23]. These findings are consistent with previous studies, which also concluded that ABS did not predict sepsis after open-heart surgery [2].

Not all infected patients develop sepsis, however all sepsis cases result from infection [15]. Sepsis is a severe condition characterized by a systemic inflammatory response to infection, potentially leading to organ damage and mortality [6]. Studies at RSPJNHK revealed a significant incidence of sepsis (35%) among infants with an ABS of 6 who underwent open-heart surgery [2]. Presepsin levels in the blood typically rise within 1.5 to 2 hours after infection onset [27]. Compared to PCT, presepsin is more specific for identifying bacterial infections because of its direct role in the pathomechanism of infections [28].

In patients wth cardiac disease, presepsin levels may increase, even in the absence of infection. This study found that the presepsin levels on the first postoperative day were significantly higher in the sepsis group than in the non-sepsis group. Conversely, PCT levels did not show a similar increase from the first to the third postoperative day in either group, with median values significantly lower than those reported in other studies (404 pg/mL and 203 pg/mL on the first and third postoperative days, respectively). Reported median values of 806.5 pg/mL in the infection group and 571 pg/mL in the non-infection group on the first postoperative day in children and 980 pg/mL and 516 pg/mL on the third postoperative day [13]. Our findings also indicate that the first-day presepsin levels do not accurately predict postoperative sepsis. These findings are consistent with those of [10] who found that initial presepsin levels are unreliable for predicting septic shock in children with sepsis [29].

Procalcitonin levels, which are currently used in clinical settings, were significantly different between the sepsis and non-sepsis groups on the first and third days. Area under the curve (AUC) analysis using receiver operating characteristic (ROC) curves revealed that presepsin was a more effective diagnostic marker than PCT. The area under the curve for presepsin was 0.945, which was greater than that of PCT (0.895). This result was similar to those of other studies in which the AUC of presepsin was 0.772 and that of PCT was 0.717 in children postoperatively. [13] Presepsin levels on the third day demonstrated greater accuracy than PCT levels in diagnosing sepsis in pediatric patients who underwent open-heart surgery.

Both markers had a sensitivity of $> 80\%$. Presepsin and PCT levels were 84.09%, while PCT had 86.36%, respectively. The AUCs for third-day presepsin and PCT levels were 0.945 and 0.895, respectively. These results are consistent with those of Khera et al. (2022), who found that higher presepsin levels at 72 h post-admission indicated more severe sepsis, especially in patients with shock. In our study, the third-day presepsin and PCT sensitivity values were higher than the first-day values, reaching 100% sensitivity. This suggests that presepsin may be more accurate than PCT in diagnosing sepsis in paediatric post-open-heart surgery patients after 72 h.

A meta-analysis by Yoon et al. examined presepsin threshold values from 240 pg/mL to 1014 pg/mL to diagnose sepsis in children, and found an average cut-off of 635.8 pg/mL. Sensitivity was higher for presepsin concentrations above 650 pg/mL at 0.84, compared to 0.99 below 650 pg/mL [24]. Specificity for levels above 650 pg/mL was 0.42, while below 650 pg/mL it was 0.90. The AUC values indicated higher diagnostic accuracy, with 0.827 for levels above 650 pg/mL and 0.983 for levels below 650 pg/mL.

In addition to its diagnostic value at the individual patient level, presepsin may also have important implications for hospital-wide sepsis surveillance and antimicrobial stewardship programs, particularly in pediatric cardiac intensive care settings. Early differentiation between postoperative systemic inflammatory response syndrome and true sepsis remains a major clinical challenge after open-heart surgery. The incorporation of serial presepsin monitoring into institutional sepsis screening protocols could support earlier identification of high-risk patients, facilitate more targeted microbiological investigations, and assist clinicians in optimizing antimicrobial initiation and de-escalation strategies. Such an approach may reduce unnecessary prolonged broad-spectrum antibiotic exposure, which is especially relevant in tertiary referral centers facing increasing rates of antimicrobial resistance. Furthermore, standardized presepsin-based monitoring algorithms could improve consistency in postoperative sepsis detection across multidisciplinary teams and potentially strengthen quality improvement initiatives focused on pediatric sepsis management.

From a broader health-system perspective, the implementation of presepsin testing may offer potential benefits in middle-income and resource-limited healthcare systems, although considerations regarding cost-effectiveness and laboratory accessibility remain important. Compared with prolonged empiric antibiotic treatment or delayed

recognition of postoperative sepsis, earlier diagnostic clarification through presepsin measurement may contribute to shorter CICU stays, improved ICU bed turnover, and reduced utilization of high-cost supportive therapies. These effects could ultimately decrease healthcare expenditures and improve resource allocation in high-volume cardiac centers. In countries such as Indonesia, where specialized pediatric cardiac intensive care resources remain limited, the use of reliable biomarkers to support timely clinical decision-making may have meaningful population-level implications for postoperative mortality reduction and healthcare efficiency. Nevertheless, further multicenter studies evaluating economic feasibility, assay availability, and integration into national sepsis management pathways are still required before routine large-scale implementation can be recommended.

This study had several limitations that warrant careful consideration. First, the relatively small sample size and low number of sepsis events resulted in limited statistical power and wide confidence intervals for diagnostic accuracy estimates. The study was also conducted using a cross-sectional diagnostic design with repeated postoperative measurements, which limited the ability to establish temporal or causal relationships between biomarker elevation and sepsis progression, although serial assessments at T_1 and T_3 partially mitigated this limitation. In addition, the inclusion of patients with clinically suspected sepsis may have introduced verification bias by enriching the study population with higher-risk cases, potentially affecting diagnostic performance estimates, particularly specificity.

Another important limitation relates to the imperfect reference standard used for sepsis diagnosis. Blood cultures, while considered the gold standard, have limited sensitivity and may yield false-negative results, potentially leading to misclassification of septic patients and biasing diagnostic accuracy estimates toward the null. Furthermore, the limited number of patients precluded multivariable analyses to adjust for potential confounding variables such as CPB duration, nutritional status, age, and surgical complexity. No correction for multiple statistical comparisons was performed; therefore, the findings should be interpreted as exploratory.

Although serial biomarker measurements were planned for all surviving patients, several critically ill patients died before completion of follow-up, which may have influenced longitudinal comparisons between T_1 and T_3. Nevertheless, this study remains the first to evaluate presepsin levels in pediatric patients undergoing open-heart surgery with cardiopulmonary bypass in Indonesia.

Future multicenter prospective studies with larger cohorts are needed to validate the optimal presepsin cut-off values identified in this study and to improve the precision of sensitivity and specificity estimates. Such studies should include formal sample size calculations for diagnostic accuracy analyses, multivariable modeling, and external validation cohorts. In addition, future research should explore clinical algorithms incorporating presepsin into routine postoperative monitoring alongside conventional biomarkers and clinical assessment, as well as evaluate the cost-effectiveness and potential impact of presepsin-guided strategies on antibiotic stewardship and intensive care resource utilization.

4. CONCLUSION

Monitoring presepsin levels and their trends may assist clinicians in identifying postoperative septic complications in paediatric patients after open heart surgery. Further research is required to assess the practicality and efficacy of presepsin as a diagnostic tool for paediatric sepsis. Given the relatively small sample size and single-center design, the findings of this study should be considered preliminary and hypothesis-generating. Larger multicenter studies are required to validate the diagnostic performance and clinical utility of presepsin in pediatric patients undergoing open-heart surgery.

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