

# Predictive efficacy of procalcitonin, platelets, and white blood cells for sepsis in pediatric patients undergoing cardiac surgeries who are admitted to intensive care units: Single-center experience

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## ABSTRACT

- Background** : Sepsis is one of the major contributor of morbidity and mortality in pediatric cardiac surgeries.
- Aim** : The aim of this study was to compare the predictive efficacy of total leukocyte counts (TC), platelet count (PC), and procalcitonin (PCT) for sepsis in patients undergoing cardiac surgeries who are admitted to the Intensive Care Unit.
- Materials and Methods** : This prospective, single-center study included 300 neonates, infants, and pediatric patients who had undergone various open heart surgeries at our center from September 2014 to November 2015.
- Results** : Overall, the incidence of sepsis was 14% in pediatric patients undergoing cardiac surgeries. TC of postoperative 48 h were significantly lower ( $11889.19 \pm 5092.86$  vs.  $14583.22 \pm 6562.96$ ;  $P = 0.004$ ) in septic patients. The low levels of platelets on postoperative 24 h and 72 h were observed in patients with sepsis as compared to patients without sepsis, whereas the levels of PCT at various time intervals (preoperative, postoperative - 24 h, 48 h, and 72 h) had shown no association with sepsis in the study population. Low PC (24 h) was the strongest predictor of sepsis showing an odds ratio of 1.9 (95% confidence interval [CI]: 1.42–3.51;  $P = 0.001$ ) and area under curve of 0.688 with 95% CI of 0.54–0.83 ( $P = 0.018$ ).
- Conclusion** : We may conclude that in Indian pediatric population platelet levels are highly associated with sepsis as compared to any other hematological parameter. The immediate postoperative level of platelet is the strongest predictor of sepsis and could be effectively used in the clinical settings.
- Keywords** : Congenital cardiac surgeries, procalcitonin, sepsis, thrombocytopenia

## INTRODUCTION

Sepsis in postoperative pediatric cardiac surgery is one of the major concerns in developing countries due to its high association with mortality and morbidity.<sup>[1]</sup> Prompt identification and diagnosis of sepsis in neonates and

pediatric patients is a challenging task due to multifactorial and nonspecific nature of the condition.<sup>[2,3]</sup> Till date, blood cultural identification of causative microorganism

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remains the gold standard for sepsis diagnosis in this population; however, it suffers from a significant drawback of delayed result availability (results could be obtained only after 24–72 h of sampling).<sup>[4,5]</sup> Due to the absence of rapid diagnostic techniques and severity of the condition, an “Antibiotic therapy” in this population of patients is often started with clinical suspicion and symptom onset. On the other hand, this practice has exposed patients to other complications such as: over usage of antibiotics, resistance to antibiotics, increased incidences of antibiotic associated side effects, and prolonged hospitalization along with increased health-care cost.<sup>[6-8]</sup>

The quest for a standardized diagnostic marker of sepsis in postoperative pediatric cardiac patients is of utmost importance. Apart from blood culture assessment, various other assays such as C-reactive protein, procalcitonin (PCT), white-blood cell (WBC) count, and platelet count (PC) are gaining scientific attention. Although studied extensively the reliable data reporting its efficacy for diagnosing early infection and sepsis in postoperative pediatric cardiac surgery is limited as the “cardio pulmonary bypass (CPB) factor” also affects the biochemical markers, postcardiac surgery.<sup>[9,10]</sup>

Numerous times the clinicians have tried proposing several hematological parameters as possible markers of infection in pediatric cardiac surgery. Herewith, we aim to assess the predictive efficacy of total leukocyte counts (TC), PC, and PCT at postoperative 24 h, 48 h, and 72 h in this population undergoing cardiac surgeries who are admitted to Intensive Care Unit (ICU) for the prediction of sepsis and compare its predictive power with each other.

## MATERIALS AND METHODS

This single-center prospective observational study ( $n = 300$ ) of neonates and children undergoing surgery for congenital heart disease was approved and clear by the institutional ethics committee (UNMICRC/CARDIOANESTHESIA/14/52). The patients were enrolled from September 2014 to November 2015 at our superspeciality cardiac center. Prior consent was taken from legal guardians of the patients. Baseline, demographic, and surgical information such as gender, ethnicity, age and weight at the time of surgery, anatomic diagnosis, surgical procedure, cardiopulmonary bypass time, aortic cross-clamp time, and deep hypothermic circulatory arrest time were collected for all the patients. All patients were preoperatively evaluated and were screened for any preoperative infection. None of the patients had perioperative culture positive. The routine investigations were done before surgery in entire study group. In all patients, anesthesia protocol during surgery was same that is induction with ketamine, glyco fentanyl, and vecuronium; maintenance was done with

high dose of fentanyl with vecuronium and sevoflurane. Cardiopulmonary bypass (CPB) protocol was identical in these patients. Surgeries were performed by the same surgeons of the institute. All patients were weaned from CPB using same inotropes that are injection milrinone 0.5–0.75 mcg/kg/min and injection adrenaline 0.04–0.08 mcg/kg/min.

Cardiopulmonary bypass was performed using a Quadrox 10,000 (Maquet, Rastatt, Germany) for neonates, infants, and pediatric patients up to 10 kg and patients up to 20 kg quadrox 30,000 (Maquet, Rastatt, Germany). Neonates and infants flow were maintained to get confidence interval (CI) index up to 3.2 L/m<sup>2</sup>/min, and for pediatric patient, flow was maintain to achieve cardiac index up to 2.8 L/m<sup>2</sup>/min other parameters were monitor according to the institutional protocols. Before bypass, 400 units/kg of heparin was systemically administered in order to achieve optimal anticoagulation. Initially, St. Thomas cardioplegia at the dose of 30 ml/kg was used to accomplish cardioplegia which was subsequently continued at the dose of 20 ml/kg after 20 min of aortic cross-clamp time. According to the protocol, during CPB conventional ultrafiltration was used, which was replaced by modified ultrafiltration technique after bypass. Cefuroxime was given <60 min before incision (after induction of anesthesia), and repeat dose was given at every 4 h in case of prolonged surgeries or 1 h after completion of bypass. In post-operative ICU, 2 doses were given at every 8 h.

The monitoring of invasive arterial and central venous pressure was performed in study participants, where the initiation of inotropic and vasoactive medications was mutually decided by the surgical team. As our study was about early identification of infection and sepsis, we had taken either increase or decrease in TC, patients requiring vasopressors to maintain stable hemodynamics after ruling out any residual, or additional cardiac issue. Sepsis was confirmed by blood culture testing.

### Unit policy for blood culture testing

Blood cultures in postoperative patients were performed in two conditions:

1. Suspicion of sepsis (48 h)
2. Before changing the antibiotics.

After taking culture, we have stepwise escalated the antibiotics according to the antibiotic protocol as mentioned below:

- Step 1 - Surgical prophylaxis was given to all the patients according to standard threshold shift criteria (injection cefuroxime 3 doses)
- Step 2 - Injection piperacillin + tazobactam and injection levofloxacin/injection netilmicin)
- Step 3 - Injection meropenem and injection levofloxacin/injection netilmicin. Injection colistin was reserved for multi-drug resistant culture positive organisms.

The sepsis was suspected in patients having requirement for additional fluid resuscitation or vasopressors to maintain adequate hemodynamics in the absence of any residual or additional postoperative defects. In all the suspected patients, the antibiotic treatment was started after collecting 48 h blood sample (all other patients having an early requirement for antibiotic were excluded from the study).

#### Inclusion criteria for this research study

All routine pediatric patients coming for open heart surgery were selected for this study.

#### Exclusion criteria for this research study

Patients requiring emergency surgeries were excluded from this study.

#### Statistical analysis

The statistical calculations were performed using SPSS software v 20.0 (Chicago, IL, USA). Quantitative data were expressed as mean  $\pm$  standard deviation whereas qualitative data were expressed as percentage. Univariate analysis of the continuous data was performed using Student's *t*-test, whereas Chi-square test was used for the categorical data. One-way analysis of variance was applied to compare the results of three cohorts. The cutoff value of  $P < 0.05$  was considered for the statistical significance. Stepwise logistic regression was performed to establish the independent associative value of each of potential risk factors after controlling the effect of all the others (low birth weight, complexity of surgery, cardiopulmonary bypass time, aortic cross-clamp time, postoperative unstable hemodynamics, postoperative requirement for inotropes, and low cardiac output). Receiver operating curve (ROC) analysis was performed to assess the diagnostic accuracy of various parameters.

## RESULTS

The overall incidence of sepsis in pediatric patients undergoing various cardiac surgeries was 14% ( $n = 42$ ). The demographic details, operative and postoperative details of the study cohort are shown in Table 1. The type of organisms isolated and its frequencies are mentioned in Table 2.

The comparison of patients with positive blood culture with that of negative is shown in Table 3. The patients with sepsis were younger ( $153.8 \pm 241$  days vs.  $460.7 \pm 603$  days), had longer-CPB time ( $99.4 \pm 52.3$  min vs.  $82.4 \pm 47$  min), ICU stay ( $16.8 \pm 11.21$  days vs.  $8.31 \pm 6.43$  days), and ventilator stay ( $9.7 \pm 9$  h vs.  $3.8 \pm 5.08$  h) as compared to patients without sepsis. Overall, postoperative morbidity (incidence of cardiac arrest, reintubation, and reoperation) and mortality were significantly ( $P < 0.05$ ) higher in patients with sepsis as

**Table 1: Demographic details and surgery details of the study population**

Demographic details	Mean $\pm$ SD/n (%)
Total	300
Age (days)	417.78 $\pm$ 576.2
Females	122 (40.6)
Males	178 (59.3)
Cardiopulmonary bypass time	84.85 $\pm$ 48.6
Aortic cross clamp time	55.37 $\pm$ 37.88
Total ICU stay	9.5 $\pm$ 7.82
Ventilator stay	4.67 $\pm$ 6.13
Cardiac arrest	24 (8)
Mortality	19 (6.3)
Reintubation	65 (21.6)
Resepsis	8 (2.66)
Neurological issues	17 (5.6)
Renal issues	12 (4)
Type of surgeries	
TAPVC repair	79 (26.3)
VSD closure	70 (23.3)
ICR with trans annular patch	55 (18.3)
ASO	37 (12.3)
ASD closure	13 (4.3)
BDG	12 (4)
BT shunt	7 (2.3)
AVSD repair	6 (2)
PA band	5 (1.7)
AP window closure	3 (1)
Norwood	2 (0.6)
Aortic arch repair	2 (0.6)
Unifocalization	2 (0.6)
ALCAPA repair	2 (0.6)
HOCM repair	1 (0.3)
Hemitruncus	1 (0.3)
Rastelli	1 (0.3)
SAM resection	1 (0.3)
Senning	1 (0.3)

ALCAPA: Anomalous left coronary artery from the pulmonary artery, AP: Aortopulmonary, ASD: Atrial septal defect, ASO: Arterial switch operation, AVSD: Atrioventricular septal defect, BDG: Bidirectional glenn shunt, BT: Blalock-Taussig, HOCM: Hypertrophic obstructive cardiomyopathy, ICR: Intracardiac repair, PA: Pulmonary artery, VSD: Ventricular septal defect, SAM: Subaortic membrane, SD: Standard deviation, ICU: Intensive Care Unit, TAPVC: Total anomalous pulmonary venous connection

**Table 2: Organisms isolated in study population (n=42)**

Organism	n (%)
<i>Klebsiella pneumoniae</i>	20 (47.6)
<i>Pseudomonas aeruginosa</i>	9 (21.4)
<i>Acinetobacter baumannii</i>	5 (11.9)
<i>Candida albicans</i>	4 (9.5)
<i>Escherichia coli</i>	2 (4.8)
<i>Enterococcus faecalis</i>	2 (4.8)

compared to their counterparts. The neurological and renal complications were comparable in both the groups.

Univariate analysis showed that the level of PC on postoperative 24 h, 48 h, and 72 h were significantly ( $P < 0.05$ ) lower in patients with sepsis as compared to patients without sepsis [Table 4]. Apart from platelet, TC of postoperative 48 h were significantly ( $P = 0.004$ ) altered in patients with sepsis. Logistic regression analysis showed highest odds of 1.9 (95% CI: 1.42–3.51;  $P = 0.001$ ) for postoperative

**Table 3: Comparison of operative variables and postoperative complications in blood culture negative versus blood culture positive groups**

Demographic details (300)	Mean±SD/n (%)		Significance
	Blood culture negative (258)	Blood culture positive (42)	
Age (days)	460.7±603	153.8±241	<0.0001
Females	109 (42.2)	13 (31)	0.112
Males	149 (57.75)	29 (69)	
Cardiopulmonary bypass time (min)	82.4±47	99.4±52.3	0.036
Aortic cross clamp time (min)	53.7±37.1	64.8±40.98	0.08
Total ICU stay (days)	8.31±6.43	16.8±11.21	<0.0001
Ventilator stay (days)	3.8±5.08	9.7±9	<0.0001
Cardiac arrest	17 (6.6)	7 (16.6)	0.035
Mortality	13 (5)	6 (14.28)	0.035
Reintubation	46 (17.8)	19 (45.2)	<0.0001
Resepsis	3 (1.16)	5 (12)	0.002
Neurological issues	17 (6.6)	0	0.071
Renal issues	9 (3.5)	3 (7.1)	0.228

SD: Standard deviation, ICU: Intensive Care Unit

**Table 4: Comparison of biochemical variables in blood culture negative versus blood culture positive groups**

Variables	Blood culture	Mean±SD	Significance
Preoperative total leukocyte (/cmm)	Negative	11,393.98±3819.37	0.386
	Positive	12,375.71±5311.56	
Preoperative platelet (/cmm)	Negative	364,586.38±147,441.96	0.437
	Positive	390,964.29±156,697.85	
Preoperative PCT (ng/ml)	Negative	1.37±7.59	0.331
	Positive	0.25±0.20	
Total leukocyte 24 h (/cmm)	Negative	15,790.49±6538.50	0.079
	Positive	13,890.71±5570.33	
Platelet 24 h (/cmm)	Negative	197,167.36±97,600.46	0.025
	Positive	167,994.05±101,502.20	
PCT 24 h (ng/ml)	Negative	56.13±66.86	0.612
	Positive	54.17±73.94	
Total leukocyte 48 h (/cmm)	Negative	14,583.22±6562.96	0.004
	Positive	11,889.19±5092.86	
Platelet 48 h (/cmm)	Negative	152,979.88±88,804.00	0.151
	Positive	129,310.48±77,446.93	
PCT 48 h (ng/ml)	Negative	50.19±60.69	0.651
	Positive	50.36±63.04	
Total leukocyte 72 h (/cmm)	Negative	12,518.03±6175.04	0.164
	Positive	11,020.79±5201.52	
Platelet 72 h (/cmm)	Negative	132,861.72±75,950.33	0.041
	Positive	106,835.71±67,783.74	
PCT 72 h (ng/ml)	Negative	55.15±65.33	0.734
	Positive	34.74±34.80	

PCT: Procalcitonin, SD: Standard deviation

platelet levels (24 h), followed by 48 h TC (1.04; 95% CI: 0.96-1.07; *P* = 0.06), and 72 h (1.026; 95% CI: 0.96-1.04; *P* = 0.05) PC [Table 5]. According to ROC analysis, postoperative 24 h PC was the strongest predictor of sepsis in neonates showing an area under curve (AUC) of 0.688 with 95% CI of 0.54-0.83; significance - 0.018 [Table 6].

**Table 5: Logistic regression analysis for prediction of sepsis**

Variables	<i>P</i>	Exp (B)	95% CI
Platelet 24 h	0.001	1.9	1.42-3.51
Total leukocyte 48 h	0.06	1.04	0.96-1.07
Platelet 72 h	0.05	1.026	0.96-1.04

Linear regression model analysis. Exp (B): Exponentiation of the coefficients/OR of the predictors, CI: Confidence interval, ORs: Odds ratios

**Table 6: Receiver operative characteristic curve of various biochemical variables for diagnosis of sepsis**

Test result variable(s)	Area under the curve				
	Area	SE <sup>a</sup>	Asymptotic significant <sup>b</sup>	Asymptotic 95% CI	
				Lower bound	Upper bound
Platelet 24 h	0.688	0.073	0.018	0.545	0.831
Total leukocyte 48 h	0.475	0.080	0.755	0.319	0.632
Platelet 72 h	0.563	0.079	0.425	0.408	0.719

<sup>a</sup>Under the nonparametric assumption, <sup>b</sup>Null hypothesis: True area=0.5. SE: Standard error, CI: Confidence interval

## DISCUSSION

Sepsis is a life-threatening and a complex process which triggers various inflammatory and immune responses. Sepsis induced pro-inflammatory responses often lead to the alterations in coagulation systems.<sup>[11]</sup> In neonates, sepsis is the most common complication with highly nonspecific nature making its early identification challenging.<sup>[12-14]</sup> Moreover, initiation of antibiotic treatment in case of suspicion of sepsis often leads to alteration in postoperative levels of biochemical markers. However, in our study, the postoperative 24 h platelet level showed the highest predictive potency for sepsis in pediatric population, which eliminates this bias as in most of the cases, as sepsis was suspected only after 24 h, and treatment was started accordingly.

In pediatric literature, the connection of thrombocytopenia and mean platelet volumes (MPV) with various bacterial and fungal infection is well known. The incidence of low platelet level was found to vary from 20% to 50% in neonates according to various reports.<sup>[15-17]</sup> However, the nature of relationship between platelets and infectious disease has been controversial as MPV was identified as both - a positive and a negative acute phase reactant. Moreover, the conclusion of comparative predictive potencies of PC, WBC, and PCT has also been subjected to variations.

There is always a need to develop easily accessible, reliable, and inexpensive prognostic marker of sepsis in developing countries like India, where resources are highly limited.<sup>[18]</sup> The thrombocytopenia observed in the current study in patients with sepsis could be

due to increased production of cytokines, endothelial damage, and bone marrow suppression. The endothelial damage under the septic condition is often associated with bacterial product induced platelet adhesion and aggregation. As a response to this, body accelerates platelet clearance from circulation. Few reports have also indicated a role of immune systems in sepsis linked thrombocytopenia due to the presence of circulatory, immune and complement complexes.<sup>[19-22]</sup> Moreover, with the current study data and earlier reports, we may suggest that the sequential assessment of PC throughout the course of sepsis is more beneficiary than single PC levels.

We, herewith, compared the potential predictive hematological markers of sepsis in postoperative pediatric cardiac surgery patients at various time intervals. Our data showed that the level of platelet at postoperative 24 h is the strongest predictor (AUC - 0.688; 95% CI - 0.545-0.831;  $P = 0.018$ ) of sepsis in patients undergoing pediatric cardiac surgeries. Univariate analysis showed that WBC counts are also associated with the infection incidence, however, that significance was lost in ROC analysis, suggesting the inferior potency of this marker. Recently, Aydemir *et al.* had showed that the in adult patients with Gram-positive sepsis the level of MPV raised for 3 days whereas in case of fungal infection, it was increased for 5 days. In neonates also, thrombocytopenia and increased MPV were found to be associated with sepsis incidences, which were further correlated with low birth weight.<sup>[23]</sup>

Recently, there is an increasing clinician population proposing PCT as a better and early marker of infection in neonates and adults. It is proposed that PCT is produced and secreted by various organs of the body in response to severe infection and septic conditions. However, there is difference of opinion regarding the usefulness of PCT as a marker of infection in postoperative cardiac surgeries, as emerging reports are questioning its accuracy. We have measured PCT level in an immediate postoperative period which varies from first 24 h to 72 h. We herewith report that PCT levels in postoperative pediatric cardiac patients will not able to predict early sepsis and hence neither the single value nor the sequential values of PCT are helpful in diagnosing or prognosing sepsis in early postoperative patients. Moreover, the marker is less affordable as compared to other simple hematological parameters such as TCs and platelets.

## CONCLUSION

We may conclude that platelet levels in postoperative pediatric cardiac surgery are strongly associated with sepsis as compared to any other hematological parameter. The immediate postoperative level of

platelet is the strongest predictor of sepsis and could be effectively used in the clinical settings.

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## Conflicts of interest

There are no conflicts of interest.

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