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ORIGINAL ARTICLE

Prognostic role of serum procalcitonin in neonatal sepsis at a tertiary care hospital.

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ABSTRACT... Objective: To analyze the prognostic role of serum procalcitonin in neonatal sepsis at a tertiary care hospital. **Study Design:** Cross-sectional study. **Setting:** Department of Pediatric, Dr. Ziauddin University Hospital, Kemari, Karachi, Pakistan. **Period:** October 2023 to March 2024. **Methods:** Neonates of both genders aged between 1 to 28 days having confirmed neonatal sepsis were included. At baseline, demographic characteristics were noted and necessary laboratory investigations were performed. At baseline, serum procalcitonin levels were evaluated in all neonates. The prognostic value of baseline PCT was assessed by comparing its association with the mortality. Other outcome variables like need for non-invasive ventilation, mechanical ventilation, need for inotropics, and acute kidney injury were also documented. **Results:** In a total of 131 neonates, 76 (58.0%) were male. The median age was 2.00 days (IQR=1-7 days). The median baseline procalcitonin level was 3.17 ng/ml (IQR=0.55 to 10.34 ng/ml). Need for non-invasive ventilation, and mechanical ventilation was noted in 93 (71.0%), and 19 (14.5%) neonates, respectively. Need for inotropics was documented in 23 (17.6%) neonates. The median duration of NICU stay was 3.00 (2.00-5.00 days). Among neonates who died, procalcitonin levels were significantly higher than those who survived (p=0.015). Mortality was found to have significant association with need for mechanical ventilation (p<0.001), and need for inotropics (p<0.001). **Conclusion:** High serum procalcitonin was found to be a significant predictor of mortality in neonatal sepsis. Mortality was significantly associated with need for mechanical ventilation, and need for inotropics.

Key words: Mechanical Ventilation, Mortality, Neonate, Procalcitonin, Sepsis.

INTRODUCTION

Neonatal sepsis, characterized by systemic immune dysregulation due to a bloodstream infection in infants less than 28 days old, is a major contributor to neonatal morbidity and mortality.[1,2] The prevalence neonatal sepsis varies geographically[3,4] and the global estimates are primarily derived from data in high-income countries, despite the fact that the burden of morbidity and mortality from neonatal sepsis is significantly higher in "Low- and Middle-Income Countries (LMICs)".[5-8] Sepsis in neonates can be categorized as "early-onset neonatal sepsis (EONS)" if it occurs within the first 72 hours of life, and "late-onset neonatal sepsis (LONS)" if it presents after 72 hours. Risk factors for EOS include maternal infections, preterm birth, and prolonged rupture of membranes.[9] LONS is often associated with healthcare-associated infections.[10]

Neonatal sepsis requires accurate diagnosis and risk stratification as early recognition and appropriate management are crucial for improving outcomes. Conventional diagnostic methods, such as blood culture, have limitations in terms of sensitivity and turnaround time. Procalcitonin (PCT), a precursor of calcitonin, has emerged as a potential biomarker for diagnosing and predicting outcomes in neonatal sepsis. Researchers have shown that mean levels of procalcitonin among cases having neonatal sepsis is significantly elevated when compared to controls (5.70±8.72 ng/ml vs. 0.69±0.54 ng/ml, p<0.05).[11]

A study by Nanda et al shsowed that sensitivity, and specificity of PCT in neonatal sepsis were 85.7%, and 25.4%, respectively.[12] A study by

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Chawdhary et al found that baseline PCT levels were significantly high among non-survivor neonates versus those who survived (6.32±3.66 ng/dl vs. 5.05±3.83 ng/dl, p=0.04).[13] Another study done by Aygun Fatih showed that higher PCT levels were significantly associated with mechanical ventilation application (19.76±33.98 ng/ml vs. 6.75±18.89 ng/ml, p<0.001), inotropic drug administration (27.83±37.92 ng/ml vs. 5.01±15.48 ng/ml, p<0.001), mortality (57.41±46.96 ng/ml vs. 9.38±22.97 ng/ml), acute kidney injury (30.08±38.79 ng/ml vs. 4.92±15.22 ng/ml, p<0.001), length of ICU stay above or equal to 7 days (16.23±30.30 vs. 7.43±21.02, p<0.001), and blood product transfusions (23.14±34.60 ng/ml vs. 2.34±9.21, p<0.001).[14]

It is anticipated that baseline PCT levels might be significantly high among those cases neonatal sepsis who have unfavorable outcomes. If PCT comes out as a reliable predictor of neonatal sepsis outcomes, it could have a substantial impact on clinical decision-making, allowing for more timely and targeted interventions. Ultimately, this research was expected to contribute to improve the management and outcomes of neonatal sepsis. The present study was also thought to provide important insights about the monitoring of PCT concentrations as it may provide valuable information on treatment response and the need for further interventions. Our objective was to analyze the prognostic role of serum procalcitonin in neonatal sepsis at a tertiary care hospital.

METHODS

This hospital based cross-sectional study was conducted at the Pediatric Department at "Dr. Ziauddin University Hospital", Kemari, Karachi, Pakistan from October 2023 to March 2024. Considering 95% confidence level with 6% margin of error and taking the sensitivity of PCT as 85.7% in neonatal sepsis, the sample size was calculated to be 131. Neonates of both genders aged between 1 to 28 days having neonatal sepsis were included. Exclusion criteria were neonates who had birth asphyxia, very low birth weight <1500 grams, gestational age <32 weeks and neonates who already had taken antibiotics in the last 3 days. Neonatal sepsis was diagnosed based on positive blood culture results combined with clinical and pathological signs of perinatal risk factors.[7,9,10] Non-probability consecutive sampling technique was adopted.

Approval form "Institutional Ethical Committee" was taken prior to commencement of this study (Reference Code: 7770923PKPED) dated: 11-10-23. Informed and written consents were taken from the patents or guardians of the neonates included in this study. Relevant laboratory investigations were sent to institutional laboratory. Three ml blood sample was withdrawn from enrolled neonates and processed for blood culture, detection of serum level of PCT by immunoluminometric assay on day-1. Outcomes was noted as need for mechanical ventilation, need for non-invasive ventilation, need for inotropic drug use, acute kidney injury, duration of NICU stay and mortality. Need of mechanical ventilation application criteria included; severe respiratory distress: Ggrunting, nasal flaring, retractions (visible sinking of the chest or ribs during breathing), and significant tachypnea (rapid breathing); Sever hypoxemia: SpO2 < 85% and PaO2 < 40 mmHg; hypercapnia: PaCO2 > 65 mmHg; Apnea or Bradycardia: Apnea as cessation of breathing for a period lasting 20 seconds or longer. Bradycardia was labeled as heart rate < 100 beats per minute (bpm) for at least 10 seconds in pre-term and in term neonates as heart rate < 100 bpm for at least 5 seconds; metabolic acidosis as arterial pH < 7.35 and bicarbonate (HCO3) < 18 mmol/L. Need of non-invasive ventilation application was when neonate had severe respiratory distress. Need for inotropic drug administration was when there was hypotension and signs of poor perfusion like cool extremities, prolonged capillary refill time, and altered mental status. Acute kidney injury was labeled as the presence of decreased urine output (<0.5 ml/kg/h for more than 8 hours). The prognostic value of baseline PCT was assessed by comparing its association with the outcomes.

The data was entered and analyzed using "IBM-SPSS Statistics, version 26.0". Qualitative data like gender, types of sepsis and outcomes were represented as frequency and percentages.

Quantitative data were represented as mean and standard deviation or median and inter-quartile range. Comparisons of qualitative data will be done utilizing chi-square test whereas quantitative data were compared using independent sample t-test or Mann-Whitney U test. P value below 0.05 was taken as significant.

RESULTS

In a total of 131 neonates, 76 (58.0%) were male. The median age was 2.00 days (IQR=1-7 days). The mean gestational age was 36.51±2.40 weeks (ranging between 31 to 41 weeks. The median birth weight was 2.53±0.65 kg (ranging between 1.10 to 4.00 kg). The median baseline procalcitonin level was 3.17 ng/ml (IQR=0.55 to 10.34 ng/ml). Need for non-invasive ventilation, and mechanical ventilation was noted in 93 (71.0%), and 19 (14.5%) neonates, respectively. Need for inotropics was documented in 23 (17.6%) neonates. AKI was found in 7 (5.3%) neonates. The median duration of NICU stay was 3.00 (2.00-5.00 days). Among neonates who died, procalcitonin levels were significantly higher than those who survived (p=0.015). Table-I is showing overall distribution of baseline and outcome variables as well as their association with procalcitonin levels.

Mortality was found to have significant association with need for mechanical ventilation (p<0.001), and need for inotropics (p<0.001). Table-II is showing details about the association of mortality with baseline characteristics and outcome variables.

Baseline and Outcome Variables		Total (n=131)	Procalcitonine, ng/ml Median (IQR)	P-Value
Gender	Male	76 (58.0%)	2.91 (0.37-10.93)	0.850
	Female	55 (42.0%)	3.21 (1.38-8.54)	
Age (days)	≤7	100 (76.3%)	3.08 (0.96-9.87)	0.537
	>7	31 (23.7%)	3.74 (0.15-9.59)	
Gestational age	Pre-term	69 (52.7%)	3.62 (0.55-8.83)	0.803
	Term	62 (47.3%)	2.77 (0.43-11.13)	
Birth Weight	Normal	76 (58.0%)	3.17 (0.72-10.73)	0.789
	Low birth weight	55 (42.0%)	3.07 (0.51-9.18)	
Sepsis type	Early-onset neonatal sepsis	87 (66.4%)	3.08 (1.32-9.86)	0.483
	Late-onset neonatal sepsis	44 (33.6%)	3.74 (0.18-9.63)	
Need for non-invasive ventilation	Yes	93 (71.0%)	4.09 (1.39-11.23)	<0.001
	No	38 (29.0%)	0.83 (0.19-4.55)	
Need for mechanical ventilation	Yes	19 (14.5%)	7.30 (1.71-17.97)	0.206
	No	112 (85.5%)	3.08 (0.50-8.70)	
Need for inotropics	Yes	23 (17.6%)	8.19 (0.55-16.75)	0.392
	No	108 (92.4%)	3.08 (0.42-8.70)	
AKI	Yes	7 (5.3%)	2.77 (0.20-9.40)	0.732
	No	124 (94.7%)	3.16 (0.55-10.10)	
Mortality	Yes	7 (5.3%)	9.40 (6.06-16.34)	0.015
	No	124 (94.7%)	2.99 (0.47-9.28)	

Table-I. Association of baseline and outcome variables with respect to procalcitonin levels

Baseline and Outcome Variables		Mortality		P-Value
		Yes (n=7)	No (n=124)	
Gender	Male	2 (28.6%)	74 (59.7%)	0.105
	Female	5 (71.4%)	50 (40.3%)	
Age (days)	≤7	5 (71.4%)	95 (76.6%)	0.754
	>7	2 (28.6%)	29 (23.4%)	
Gestational age	Pre-term	5 (71.4%)	64 (51.6%)	0.307
	Term	2 (28.6%)	60 (48.4%)	
Birth Weight	Normal	3 (42.9%)	52 (41.9%)	0.962
	Low birth weight	4 (57.1%)	72 (58.1%)	
Sepsis type	Early-onset neonatal sepsis	4 (57.1%)	83 (66.9%)	0.594
	Late-onset neonatal sepsis	3 (42.9%)	41 (33.1%)	
Need for non-invasive ventilation	Yes	7 (100%)	86 969.4%)	0.082
	No	-	38 (30.6%)	
Need for mechanical ventilation	Yes	6 (85.7%)	13 (10.5%)	<0.001
	No	1 (14.3%)	111 (89.5%)	
Need for inotropics	Yes	7 (100%)	16 (12.9%)	<0.001
	No	-	108 (87.1%)	
AKI	Yes	1 (14.3%)	6 (4.8%)	0.280
	No	6 (85.7%)	118 (95.2%)	

DISCUSSION

In this study, we note that median PCT levels were significantly high among neonates who reported mortality (9.40 (6.06-16.34) ng/ml, vs. 2.99 (0.47-9.28) ng/ml, p=0.015). A study done by Meng and colleagues showed that higher PCT level at the time of admission in ICU admission was a significant predictor of short-term mortality.[15] Another study by Bustos et al analyzing the predictive value of procalcitonin in pediatric sepsis documented that PCT proved its prognostic importance in predicting mortality in PICU.[16] Ruetsch et al from France demonstrated that high PCT levels were significant prognostic biomarker in neonates with LONS.[17] In NICUs, infections and sepsis are significant contributors to illness and death. Early identification of infections in NICUs is crucial. PCT has recently been extensively studied and commonly used biochemical markers for evaluating infections in clinical practice.[18] Procalcitonin levels increase more rapidly than other markers like CRP during infections and decrease more swiftly upon recovery. PCT has also been proposed to be closely linked with the severity of systemic inflammation and bacterial infections.[19] A meta analysis analyzing the diagnostic accuracy of PCT for diagnosing neonatal sepsis showed moderate accuracy but the present study and reinforced the prognostic value of PCT in predicting short term outcomes in NICU.[20] Vouloumanou et al exhibited good diagnostic accuracy of PCT in diagnosing neonatal sepsis.[21] All these studies show that whether diagnosed or suspected neonatal sepsis, serum PCT evaluation can prove to be a significant marker of diagnosis as well as short-term outcome in neonatal sepsis.

While much of the literature focuses on sepsis, higher PCT have been identified as poor prognostic factor in sepsis. Various other factors can influence patient mortality in intensive care units. “Acute respiratory failure” needing mechanical ventilation (MV) is a primary reason for NICU admission. Mechnical ventilation not only provides respiratory support but also enhances gas exchange and reduces pulmonary workload. Studies have shown that mechanical ventilation is associated with a poor prognosis in NICU patients as was found in this research as mortality was significantly associated with the need of mechanical ventilation in neonatal sepsis. AKI is another factor linked to mortality and prolonged hospital stays, serving as an independent factor behind poor outcomes but it was not exhibited in this study.

Being a single center study, conducted on a

relatively small sample size were some of the limitations of this research. The prognostic value of serum PCT should be compared with other biomarkers like CRP in NICU settings in large multicenter trials in the future.

CONCLUSION

High serum procalcitonin was found to be a significant predictor of mortality in neonatal sepsis. Mortality was significantly associated with need for mechanical ventilation, and need for inotropics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	Sagar	Proof reading, Literature review.	
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