Association between serum procalcitonin levels and outcomes of patients admitted to two tertiary paediatric intensive care units in Bloemfontein: A retrospective analytical study

A M L Sanchez, FCPaed (SA), MMed Paed; **M A Pienaar,** FCPaed (SA), Cert Crit Care (SA) Paed, PhD

Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

Corresponding author: *M A Pienaar (PienaarMA1@ufs.ac.za)*

Background. Procalcitonin (PCT) is used in the diagnosis of sepsis. Its capability as a prognostic marker is unclear. The association between PCT and paediatric intensive care unit (PICU) outcomes has not been investigated in the South African setting.
Objectives. To determine the association between admission PCT, and trends within 72 hours of admission, and outcomes of patients admitted to the PICU at two tertiary academic hospitals.
Methods. The study was a two-year, double centre, retrospective, analytical cross-sectional medical record review.
Results. A total of 381 participants were included in the study; 55 died and 220 required mechanical ventilation. Non-survivors had a higher median admission PCT than survivors (p<0.0001, 95% confidence interval (CI) 1.28 - 15.12). Non-survivors had a higher median PCT at 48 - 72 hours than survivors (p<0.0001, 95% CI 2.50 - 21.72). Non-survivors had less of a median decrease in PCT than survivors (p=0.22, 95% CI -0.59 - 4.72). The area under the receiver operating characteristics curve (AUROCC) for admission PCT to discriminate for mortality was 0.6702 and for the 48 - 72 hour PCT it was 0.7369. There was a positive correlation between PCT and number of ventilator days (Spearman correlation co-efficient =0.1477, p=0.0138). There was no correlation between the length of PICU stay and admission PCT (p=0.7579) or PCT change (p=0.2034).
Conclusion. Single PCT measurements display some ability to discriminate for PICU mortality. Serial PCT measurements provide greater prognostic information. Non-survivors had a significantly greater median admission PCT, median PCT at 48 - 72 hours and a lower median PCT decrease than survivors.

Keywords: Biomarkers, procalcitonin, mortality

South Afr J Crit Care 2025;41(1):e2247. https://doi.org/10.7196/SAJCC.2025.v41i1.2247

Contribution of the study
This study clarifies the role and limitations of procalcitonin measurements and trends in PICU outcomes.

Various independent risk factors for mortality and morbidity have been described among patients admitted to the paediatric intensive care unit (PICU).[1-4] Bacterial sepsis remains a major risk factor for mortality and morbidity in the paediatric population both in and out of the PICU setting.[1-3,5-7] Procalcitonin (PCT) and C-reactive protein (CRP) have been identified as important biomarkers in the management of sepsis.[1,2,5,6,8] PCT is an endogenous peptide primarily secreted by the parafollicular C cells of the thyroid gland. It rises in response to certain pro-inflammatory stimuli and various bacterial endotoxins. Although inflammatory conditions such as burns, surgery and bowel wall ischaemia may cause a transient rise in PCT levels, the elevations are substantially lower than those caused by bacterial infections.[1,2,5,6,9] The efficiency of PCT to aid in the early diagnosis of bacterial sepsis has been widely reported.[5,6,8] Other uses of PCT are frequently being investigated including its use in guiding antimicrobial duration and its prognostic capabilities.[1,2,4-6,9-13] The prognostic capability of PCT in the paediatric setting is unclear.[1,4,6,10,12] In South Africa, evaluation of the prognostic capability of PCT in the critical care setting has been evaluated in the adult population. Naidoo *et al.* reported an increased risk of mortality in patients who had an increasing PCT trend or a PCT that remained above 10 ng/mL within 48 hours of admission to the ICU. Therefore, evaluating the trend of PCT at 48 hours of admission to the ICU may assist in risk stratification of a critically ill patient.[9] Considering this evidence, the evaluation of PCT trends in the PICU setting may similarly provide insight into the prognostic capability of PCT. The present study aimed to investigate the association between PCT on admission and the trend within the first 48 - 72 hours of admission, and outcomes in the PICU thereby evaluating prognostic capability of PCT in this setting.

Methods

This study was a retrospective analytical cross-sectional medical record review of consecutive patients admitted to the PICUs in two tertiary academic hospitals (Universitas Academic Hospital and Pelonomi Hospital) in Bloemfontein in Free State Province, over the period

1 January 2017 to 31 December 2018. Participants were identified from the electronic admissions registry available at each PICU. All patients between the ages of 1 month (30.44 days) and 60 months were assessed for eligibility. This was to emphasise under-5 mortality which is a central health concern. It also reflects most patients in these PICUs and excludes most trauma-related admissions in these units. Patients who did not have PCT measured on admission, patients who were elective post-surgery PICU admissions, patients who were admitted owing to trauma or burn injuries, and patients who had missing critical information were excluded from the study. Data collected included demographic characteristics, laboratory results and outcomes. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools. REDCap is a secure, web-based software platform designed to support data capture for research studies.[14,15] Demographic characteristics included age on admission, sex, HIV status and primary diagnosis as listed in the admissions registry. Laboratory results included the participant's PCT value on admission and the PCT value within 48 - 72 hours of admission. These hospitals made use of the National Health Laboratory Services (NHLS), where quantitative serum PCT levels are determined using the Elecsys BRAHMS PCT assay in the Cobas e immunoassay analyser (Roche Diagnostics, Mannheim, Germany). PCT values on admission included the first PCT value recorded within 24 hours of admission. PCT values within 48 - 72 hours of admission included the first recorded PCT within this time frame. The difference in PCT from admission to 48 - 72 hours of admission was calculated and recorded as an integer rounded to 2 decimal points (PCT change). The difference was also calculated as a percentage change from the admission value (PCT percentage change). Outcome data included PICU outcome at discharge, duration of mechanical ventilation and length of PICU stay.

De-identified data from the registered REDCap secure database were exported to a Microsoft Excel spreadsheet and submitted to the Department of Biostatistics, University of the Free State, for statistical analysis using SAS Software, Version 9.4 (copyright 2002 - 2012 by SAS Institute, Cary, USA). Data were summarised by reporting frequencies and percentages for categorical data, and means and standard deviations or medians and percentiles for numerical data. Appropriate statistical tests (chi-square, Fisher's exact, *t*-tests, Kruskal-Wallis etc.) were performed at 5% significance level. Data were used to plot receiver operating curves, with calculation of the J-statistic used to reflect optimum thresholds.

The research was approved by the Human Research Ethics Committee of the Faculty of Health Science of the University of the Free State (UFS-HSD2019/2251/203).

Results

A total of 953 patients were admitted to the PICU from 1 January 2017 to 31 December 2018. A total of 650 patients fell within the age range 1 month - 60 months. Of these, 216 were excluded due to a diagnosis of either trauma, burns or elective post-surgery admission. Fifty-one patients were excluded due to no admission PCT being done. Two patients were excluded due to missing information. A total of 381 participants were eligible to be included in the study.

The demographic characteristics of the final participant sample are summarised in Table 1.

The median age of the participant sample was 7.1 months. Just over half of the participants were male. Almost all the participants had a known HIV status, with 1 (0.3%) being unknown and most (91.3%) being negative. The most common primary diagnosis was sepsis followed by respiratory tract infections, which together comprised most of the participant sample.

Table 1. Demographic characteristics

Demographics		All (*N*=381)
Age (months)		1.0 - 59.7 (m=7.1; IQR 3.0 - 18.0)
Gender	Male	216 (56.7%)
	Female	165 (43.3%)
HIV status	Negative	348 (91.3%)
	Positive	32 (8.4%)
	Unknown	1 (0.3%)
Primary diagnosis	Sepsis	144 (37.8%)
	Respiratory tract disease	131 (34.4%)
	Intoxications	31 (8.1%)
	Neurological disease	25 (6.6%)
	Cardiovascular disease	24 (6.3%)
	Other	20 (5.3%)
	Haematolog/ Oncology	6 (1.5%)

m = median; IQR = interquartile range.

PCT was measured on admission in all participants. The value for PCT on admission ranged from 0.06 ng/mL to 100 ng/mL, with some values reported as >100 ng/mL. The median admission PCT was 1.86 ng/mL. Most (303; 79.5%) participants had a PCT measurement within 48 - 72 hours of admission. From admission to within 48 - 72 hours of admission, 87 (29.7%) patients had an upward trend in their PCT, 2 (<0.1%) participants showed no change in their PCT and 206 (67.9%) patients had a downward trend in their PCT. The PCT change from admission to within 48 - 72 hours ranged from -94.18 to +77.61, the median PCT change being -0.39 (interquartile range (IQR) -4.88 - 0.07). The percentage PCT change from admission PCT to the PCT within 48 to 72 hours ranged from -95.7% to +13 300%, with the median change being -42.0% (IQR -69.2% - 25.5%).

Of the 381 participants in this study, 55 (14.4%) died. The median admission PCT value for non-survivors (13.94 ng/mL, IQR 1.0 - 100.0) was significantly higher than for survivors (1.45 ng/mL, IQR 0.36 - 13.08) (p<0.0001, 95% CI 1.28 - 15.12). The median PCT at 48 - 72 hours for the non-survivors (12.79 ng/mL, IQR 2.08 - 100.00) was significantly higher than for the survivors (1.31 ng/mL, IQR 0.29 - 7.15) (p<0.0001, 95% CI 2.50 - 21.72). The median PCT change in the non-survivors (-0.12 ng/mL, IQR -3.68 to +4.125) was less than the median PCT change in the survivors (-0.40 ng/mL, IQR -4.88 to +0.05) (p=0.22, 95% CI -0.59 - 4.72). The median percentage PCT change in the non-survivors (-17.85%, IQR -61.00 to +105.10) was less than the median percentage PCT change in the survivors (-44.20%, IQR -69.5 to +16.8) (p=0.12, 95% CI -5.20 - 66.00). Of those who had a decreasing PCT trend, 13 (6.3%) died compared with 11 (12.6%) of those who had an increasing PCT trend (p=0.24). The relative risk of mortality in those with a decrease in PCT v. those with an increase in PCT was 2.00 (95% CI 0.93 - 4.30).

Fig. 1 displays the receiver operating characteristics (ROC) curve for an admission PCT to discriminate for mortality (area under curve (AUC) =0.6702). Table 2 shows the sensitivity, specificity and J-statistic

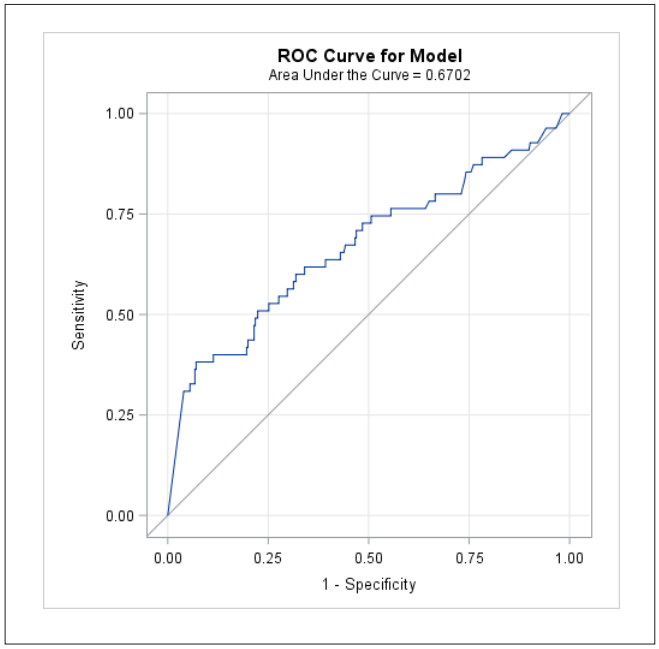

Fig. 1. Receiver operating characteristics (ROC) curve of admission procalcitonin to discriminate for mortality. (Area under the curve = 0.6702.)

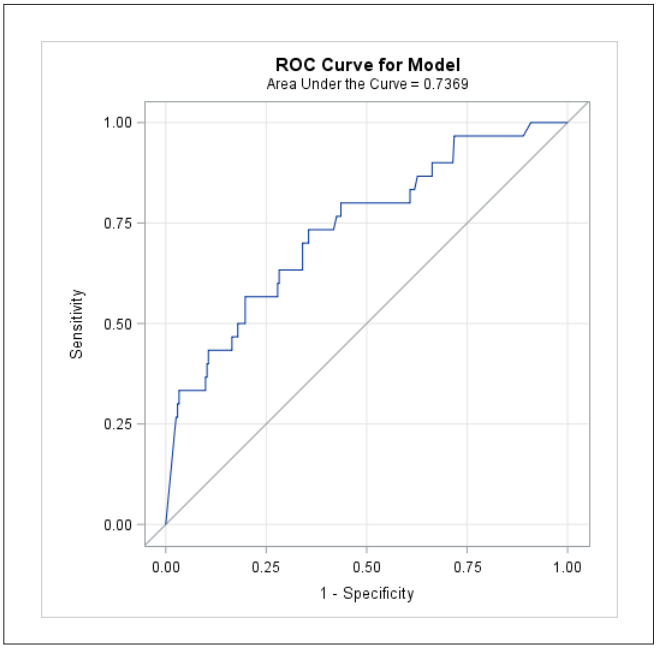

Fig. 2. Receiver operating characteristics(ROC) curve of procalcitonin within 48 - 72 hours of admission to discriminate for mortality. (Area under the curve = 0.7369.)

of the admission PCT to predict mortality calculated at various cut-off points. The optimal threshold for admission PCT to discriminate for mortality was at 70.76 ng/mL which had a sensitivity of 38.2% and specificity of 92.9%.

Fig. 2 displays the ROC curve for PCT at 48 - 72 hours to predict mortality (AUC=0.7369). Table 3 shows the sensitivity, specificity and J-statistic of PCT at 48 - 72 hours of admission to discriminate for mortality at various cut-off points. The optimal threshold for the 48 - 72 hour PCT to discriminate for mortality was at 3.16 ng/mL which had a sensitivity of 73.3% and specificity of 64.5%.

A total of 220 participants in this study required ventilation. The number of ventilation days for the participants requiring ventilation ranged from 1 day to 66 days (median=2 days). The median admission PCT value for participants requiring ventilation (2.03 ng/mL, IQR 0.45 - 19.96) was higher than for those not requiring ventilation (1.49 ng/mL, IQR 0.34 - 12.81) (p=0.1792, 95% CI 0.63 - 0.060). The median PCT change in participants requiring ventilation (-0.23 ng/mL, IQR -2.72 to +0.52) was significantly less than for those not requiring ventilation (-0.76 ng/mL, IQR -6.34 to -0.05) (p=0.0044, 95% CI -1.67 - -0.16). The median percentage PCT change in participants requiring ventilation (-34.3%, IQR -69.10 to +70.30) was significantly less than for those not requiring ventilation (-51.95%, IQR -70.10 to -17.45) (p=0.0367, 95% CI -28.4 - -0.70). Table 4 displays the Spearman correlation coefficients between admission PCT, PCT change and percentage PCT change and ventilation. The relative risk of requiring ventilation for those with an increase in PCT compared with those with a decrease in PCT was 1.40 (95% CI 0.19 - 1.66).

The length of PICU for the total participant sample ranged from 1 to 66 days (median=6). There was no significant correlation between the length of PICU stay and admission PCT(p=0.7579), the PCT change (p=0.2034) or the percentage PCT change (p=0.2625).

Discussion

The aim of this study was to evaluate the association between PCT and PICU mortality, length of PICU stay and mechanical ventilation in our setting. Findings in this study revealed a higher median admission PCT and PCT at 48 - 72 hours in the non-survivor group compared with the survivor group. Similar findings were reported in a study by Hatherill *et al.* (273 ng/mL v. 82 ng/mL, p=0.03)[6] as well as Aygun *et al.* where the researchers reported a difference in the mean admission PCT between the non-survivor and survivor groups (57.41 ng/mL v. 9.38 ng/mL, p=0.022).[1] In the latter study, the researchers reported that an admission PCT at a threshold of 6.38 ng/mL had a sensitivity of 81.8% and a specificity of 80.8% to discriminate for mortality and an AUC of 0.838.[1] In the present study, the strongest and more comparable profile was found using the 48 - 72-hour PCT with a AUC of 0.73 and an optimum threshold of 3.16 ng/mL. One might postulate that higher levels of PCT correlate with the severity of sepsis and therefore poorer outcomes.[1,11] However, the differing optimum PCT thresholds within various studies including the present one suggests that using single PCT thresholds is insufficient to discriminate for mortality risk. The present study also assessed trends in PCT and revealed that a greater percentage of the participants with an increasing PCT died than those who had a decreasing trend, with non-survivors also demonstrating a lesser decrease in PCT. Although not statistically significant, these findings are similar to the findings of Naidoo *et al.* which reported that a greater percentage of the study participants with an increasing PCT trend died than those with a decreasing PCT trend (66.7% v. 40.6%, OR=2.92, CI 1.18 - 7.22).[9] Furthermore, Hatherill *et al.* demonstrated that the absence of a decreasing PCT trend after initial antimicrobial treatment was associated with an increased mortality rate (44% v. 9%, p=0.02)[6] while Poddar *et al.* reported that a decrease in serum PCT levels within 4 days of admission was associated with survival. The use of serial PCT measurements therefore provides greater prognostic information than that of a single admission measurement.[4,6,12] In the present study, the poor discrimination for mortality of the admission PCT possibly reflects the unknown trend prior to ICU admission. A patient with a high admission PCT could have had a decreasing trend on admission, reflecting the start of recovery from sepsis. A lower optimum threshold within the 48 - 72-hour mark could therefore be a

Table 2. Predicting mortality from PCT on admission

PCT (ng/mL)	Sensitivity	Specificity	J-statistic
1.00	76.4%	44.5%	0.205
5.00	61.8%	64.7%	0.265
10.00	54.5%	72.1%	0.266
70.76	38.2%	92.9%	0.311

PCT = procalcitonin.

Table 3. Predicting mortality from PCT at 48 - 72 hours of admission

PCT (ng/mL)	Sensitivity	Specificity	J-statistic
1.00	80.0%	45.4%	0.254
5.00	63.3%	68.9%	0.322
10.00	56.7%	79.5%	0.362
3.16	73.3%	64.5%	0.378

PCT = procalcitonin.

Table 4. Spearman correlation co-efficients between PCT values and ventilation days

	PCT admission	PCT change	PCT percentage change
Spearman correlation co-efficients	0.046	0.144	0.1044
p-value	0.413	0.021	0.095

PCT = procalcitonin.

reflection of the progression of sepsis within the ICU, thereby making it a better predictor for mortality. Increasing trends during this time-frame is associated with an increased risk of mortality. Such correlation potentially reflects progression in the severity of disease or a lack of response to treatment. Static or increasing PCT trends should therefore prompt urgent re-evaluation of the patient.

The present study did not reveal any significant association between PCT, PCT change and length of PICU stay. Mechanical ventilation is a frequently used modality of treatment in the PICU which has been described as a strong independent risk factor for mortality.[1,3] Aygun *et al.* reported that the participants who required mechanical ventilation had high admission PCTs (>10 ng/mL, p=0.28).[1] The present study displayed a weak positive correlation between increasing PCT and ventilation days (Spearman correlation coefficient 0.14733, p=0.01).

Study limitations

This study had limitations. It was a retrospective study with a small sample size. Collected data were reliant on accurate registries and electronic records. Listed primary diagnosis lacked differentiation between sepsis and other organ-specific infections such as respiratory tract infections. Although comparisons were made with similar studies, population groups of other studies were notably different from that of the present study. Furthermore, the study excluded surgical and trauma patients and thus the results cannot be generalised to these groups of patients.

Conclusion

Procalcitonin is a valuable biomarker in the diagnosis of sepsis in the PICU. It also displays some ability to discriminate for mortality. A single measurement value cannot by itself be used to discriminate for risk of mortality. PCT trends from serial measurements provide greater prognostic information. Non-survivors had a significantly greater PCT at 48 - 72 hours and a lower PCT decrease than survivors. In this study, a PCT value above a threshold of 3.16 ng/mL at 48 - 72 hours of admission was optimal for mortality prediction. Although clinical judgement remains crucial, a PCT that remains above this threshold or that has an increasing trend during this time-frame could serve as a red flag for clinicians to re-evaluate the management plan of these patients. Owing to the small sample size of this study, further studies with a larger sample size are recommended. Furthermore, as this study excluded trauma and surgical patients, a study evaluating prognostic capabilities of PCT in this cohort of patients is also recommended.

Declaration. This work was submitted in partial fulfilment of the requirements for AMLS's MMed(Paed) degree.

Acknowledgements. We gratefully acknowledge Prof. G Joubert for assistance with statistical analyses.

Author contributions. AMLS: data collection, review and analysis, wrote the initial draft and revised the manuscript. MAP: research supervision, critically reviewed and assisted with revision of manuscript. Both authors approved the final version of the manuscript.

Funding. None

Confl ct of interest. None

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Received 22 May 2024. Accepted 16 January 2025.