Prognostic utility of biomarker levels and clinical severity scoring in sepsis: a comparative study

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ABSTRACT

Procalcitonin (PCT) is one of the best validated biomarkers in the management of sepsis. However, its prognostic utility remains poorly studied. The present study sought to assess the prognostic utility of serial PCT assessments in patients with sepsis, and to compare the prognostic predictive capability of serial measurements of PCT with conventional markers of inflammation and validated intensive care unit (ICU) severity scoring systems. We recruited consecutive patients admitted to the medical units of a tertiary care center with suspected or proven bacterial infection and sepsis. Measurement of serum PCT levels, inflammatory markers, and ICU severity scores were performed at admission and repeated every 48 hours subsequently for the duration of hospital stay. 99 patients with bacterial infection and sepsis were recruited and followed until death or discharge. Median serum PCT level was similar between survivors and non-survivors on day 1, but was significantly lower at days 3, 5 and 7 in the survivors. The analysis found Acute Physiology and Chronic Health Evaluation (APACHE IV) score on all days (1, 3, 5, and 7), PCT on days 5 and 7, and Sequential Organ Failure Assessment score at 24 hours to have good predictive accuracy for adverse patient outcome. PCT clearance on days 3 and 5 of admission was measured and demonstrated predictive accuracy comparable to day-matched APACHE IV scores. While serial levels of serum PCT in patients with sepsis are accurate in the prediction of adverse patient outcome, they do not offer any additional clinical benefit over existing severity of illness scores and may be cost prohibitive in resource-limited settings. While serial levels of serum PCT in patients with sepsis are accurate in the prediction of adverse patient outcome, they do not offer any additional clinical benefit over existing severity of illness scores and may be cost prohibitive in resource-limited settings.

Significance of this study

What is already known about this subject?

- Severe bacterial infections and sepsis represent a significant cause of morbidity and mortality in tertiary care medical centers across the world. The utility of biomarkers in the diagnosis, management and prognostic prediction of sepsis has been well established.
- Serum procalcitonin (PCT) is the best validated sepsis biomarker. The utility of serum PCT in the diagnosis of sepsis and in antimicrobial stewardship is well established.
- The prognostic utility of this sepsis biomarker, however, remains less well validated. Furthermore, its prognostic predictive utility as compared with conventional markers of inflammation and intensive care unit (ICU) severity scores remains poorly established

What are the new findings?

- The study demonstrates that while baseline serum PCT levels were poor predictors of patient outcome, serial biomarker levels and calculated kinetics could be used to accurately predict adverse patient outcome.
- However, it was noted that PCT kinetics was only as accurate as established ICU severity scores in the prediction of adverse patient outcomes.
- This analysis proposes the relative futility of serial PCT levels to assess prognosis in resource-limited settings where a clinical score-based approach would possibly be more cost-effective and equally informative.

How might these results change the focus of research or clinical practice?

- Further study is needed to develop composite scoring systems combining the use of PCT with other physiological parameters to improve prognostic prediction in patients with sepsis.

INTRODUCTION

Severe bacterial infections and sepsis represent a significant cause of morbidity and mortality in tertiary care medical centers across the world.[1 2] The changing definition of sepsis over the years reflects the changing understanding of the scientific community of the underlying pathophysiology of the disorder. The most recent iteration, the third international consensus definition for sepsis (Sepsis-3), currently defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[3] While the new definition fulfilled multiple domains of usefulness and validity, a gold standard

diagnostic test to diagnose sepsis remains lacking. This, along with recognition that sepsis involves multiple organs, with the consequent alteration in expression patterns of a variety of endogenous substances, has led to the description of a plethora of sepsis biomarkers of clinical or scientific utility.[4]

A recent systematic review identified almost 180 distinct molecules that have been proposed for use as biological markers of sepsis.[5] The utility of biomarkers in clinical practice has been limited, however, owing to a lack of sensitivity and specificity and the frequently high cost of test implementation for the newer molecules in routine clinical practice.[6] Serum procalcitonin (PCT), ostensibly the most widely studied of these biomarkers, has found utility in distinguishing infectious from non-infectious fever and in antimicrobial stewardship.

The prognostic value of serum PCT levels is, however, less well validated. PCT as a prognostic indicator has not been incorporated into standard guidelines owing to the lack of high-quality evidence supporting specific times of measurement and cut-off values.[7] Furthermore, the vast majority of prognostic data on sepsis biomarkers have been extrapolated from data from high-income countries.[8] The utilization of these biomarkers, including PCT, makes less economic sense in limited resource settings. The limited data on the prognostic utility of serum PCT in comparison with conventional markers of inflammation and clinical disease severity scoring systems necessitate further investigation.

The present study seeks to analyze the prognostic utility of serial PCT assessments in patients with sepsis and to compare to prognostic predictive capacity of serial PCT measurements with serial measurements of conventional markers of inflammation and clinical severity scoring systems.

MATERIALS AND METHODS

We conducted a prospective observational study among patients admitted to the medical wards and medical intensive care unit (ICU) of a tertiary care center in north India from October 2018 to January 2020. The study included patients (≥14 years of age) admitted with features suggestive of acute bacterial infection and sepsis (defined as life-threatening organ dysfunction identified by an acute change in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points). It has been observed that a variety of medical conditions other than sepsis may alter serum levels of PCT by altering pathways involved in its synthesis or elimination. All patients in the terminal stages of chronic diseases (Child class C cirrhosis, end-stage renal disease, terminal stages of incurable malignancies), those on hemodialysis, and patients inherited or acquired immunocompromised (eg, all stages of HIV infection, neutropenia) were thus excluded from our study.

All newly admitted patients satisfying the inclusion and exclusion criteria were enrolled for the study after taking valid informed written consent from the patient or legally authorized representative. All patients received standard, guideline-based care as prescribed by the treating physician. Patients and the public were not involved in the design, conduct or dissemination of data gathered in this study.

One hundred consecutive patients meeting the inclusion criteria were enrolled for the study. A thorough clinical assessment with history and examination was performed for each patient at admission, and demographic characteristics, medical and surgical history and current symptoms and duration of illness were noted. Examination included vitals (blood pressure, pulse rate, capillary refill time, temperature and respiratory rate) and a general and systemic physical evaluation with emphasis on detection of the source of infection and complications of sepsis. Laboratory and radiological testing was ordered by the treating physician as needed to localize the source of sepsis (including a chest radiography, urine routine examination, and abdominal ultrasonography in all patients) and identify end-organ dysfunction (including hemogram, liver and renal function tests, arterial blood gas analysis, and coagulation profile). A microbiological diagnosis was sought in each case with a blood and urine culture performed for all patients on the day of admission, preferably prior to the initiation of antibiotics, and processed per standard protocol. Body fluid or swab samples for culture (including sputum, endotracheal aspirate, pleural fluid, cerebrospinal fluid, and wound swab) were obtained as per the decision of the treating physician. The study subjects were followed up longitudinally for the duration of their hospital stay (ie, until hospital discharge or mortality).

A serum sample at admission was used to measure PCT levels using a Food and Drug Administration-approved commercially available enzyme-linked fluorescent assay (VIDAS BRAHMS PCT, Thermo Fisher Scientific and license partner: bioMérieux, Delhi, India)[9] with a measurement range of 0.05–200 µg/L. Serial PCT levels were determined every 48 hours for the first week of hospital admission, that is, on days 1 (admission), 3, 5, and 7. Subsequent measurements were performed as deemed appropriate by the treating physician but were not included in the analysis. Procalcitonin clearance (PCTc) was measured for days 3, 5 and 7, which is the percentage decrease in serum PCT levels on day X compared with baseline (PCTc on day $(X) = 100 \times (\text{PCT on day } X - \text{PCT on day 1})/\text{PCT on day 1}$). Serial measurements of other biomarkers of inflammation including total leucocyte count (TLC), erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels were performed similarly every 48 hours.

Anonymized, numerically coded records thus obtained were analyzed using a statistical software package (IBM SPSS Statistics V.25.0) and STATA V.14.0 (Texas, USA).[10] Patient outcome at end of hospital stay (discharge or mortality) was the primary outcome variable. Assessed secondary outcome measures included duration of hospital stay and duration of ICU stay. Categorical variables were represented as frequencies and percentages, and compared using the χ^2 test or Fisher's exact test as appropriate. Continuous variables were tested for normality using the Shapiro-Wilk test. Distributions of variables were reported as percentages and mean±SD. Non-normally distributed included the outcomes of interest (PCT, Acute Physiology and Chronic Health Evaluation (APACHE IV), SOFA, Simplified Acute Physiology Score (SAPS 3)), were represented as median (IQR) and were tested for significant difference between the survivors and non-survivor groups using the Wilcoxon rank-sum test. A p value <0.05 was

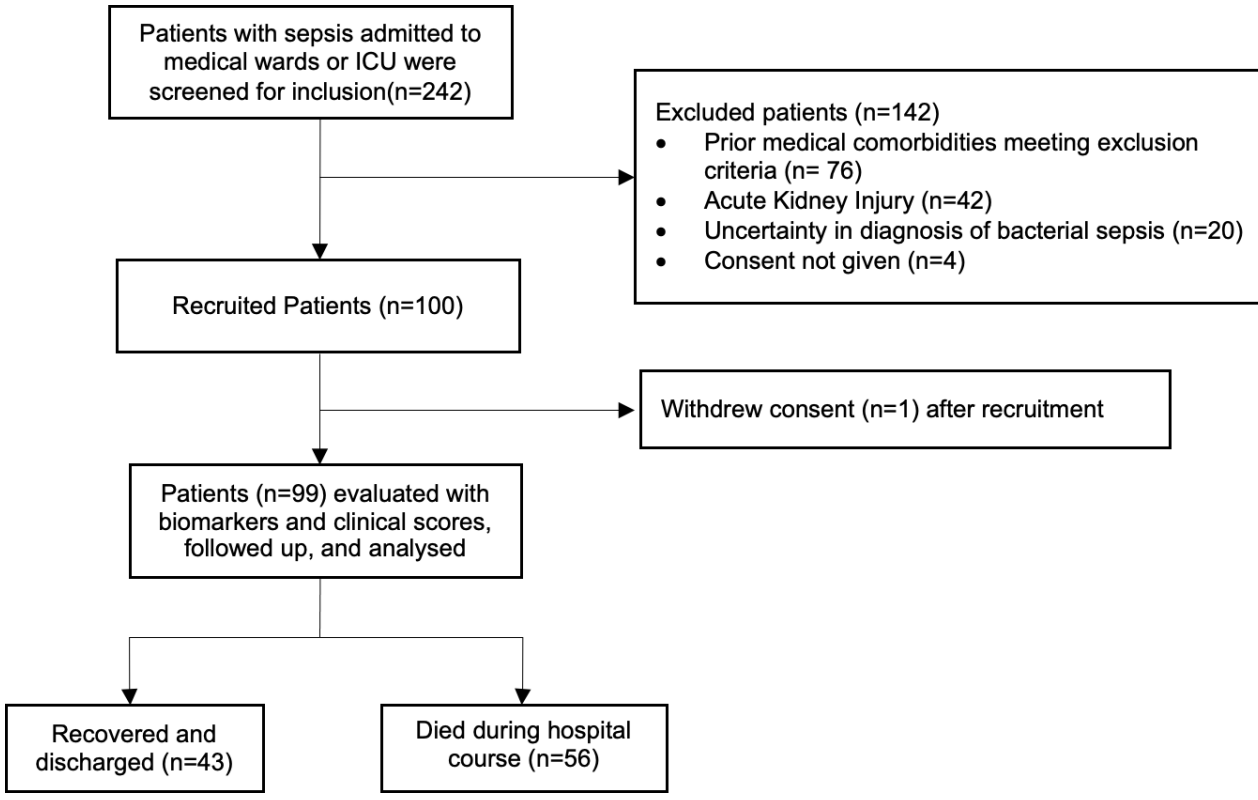

Figure 1 Patient recruitment and follow-up. ICU, intensive care unit.

considered to be statistically significant. Predictive accuracy was tested using receiver operating characteristic (ROC) analysis. ROC curves thus obtained were compared using the Hanley and McNeil method.[11]

RESULTS

A total of 242 patients with suspected or proven bacterial infection and acute rise in SOFA score of ≥2 were screened for inclusion into the study. After screening for prespecified inclusion and exclusion criteria, 100 patients were included in the study. We were able to follow-up 99 of these patients to the prespecified endpoint of death or discharge from hospital. Of these, 43 (43.4%) were discharged following recovery and 56 (56.6%) succumbed to their illness in the course of their hospital stay (figure 1).

The recruited patients had a mean age of 45.9±18.5 years with the majority (53%) of patients older than 45 years of age. Patients who succumbed to their illness in hospital were significantly (p=0.031) older (49.4±18.2 years) than patients who were successfully discharged (41.2±18.5 years). The study had a greater number of male (59%) patients with no significant difference in outcomes between the 2 genders. Comorbid illnesses were common among the recruited patients with 72 (72%) of patients having at least 1 comorbid illness. Septic shock was observed more frequently (p<0.01) among non-survivors (75%) as compared with survivors (46.5%). Dysfunction of other organs including acute kidney injury (25% overall) and acute respiratory distress syndrome (15% overall) was evenly distributed among the survivors and non-survivors. The demographic, etiological and disease severity indices at baseline are detailed in table 1.

Serial serum PCT levels on days 1, 3, 5, and 7 were analyzed for association with patient outcome. A significantly higher serum PCT level was found among non-survivors as compared with survivors on day 3 (p=0.016) and day 5 (p<0.001). While serum PCT was higher among non-survivors on day 7 as well, this difference did not attain statistical significance, possibly owing to the smaller sample size (n=23) on day 7. These results are elaborated on in table 2. ROC curve analysis was subsequently undertaken to define the capabilities of serial PCT levels. PCT levels quantified on day 3 (p=0.010) and day 5 (p<0.001) significantly predicted an adverse outcome in tested patients with area under the curve (AUC) of 0.492 (0.394–0.590) and 0.819 (0.754–0.884), respectively. Based on the data points thus obtained, we defined cut-off points for absolute values of day 3 and day 5 serum PCT as predictors of adverse patient outcome, attempting to maximize the sensitivity of the test. On day 3, a PCT level of more than 2.34 ng/mL had a sensitivity of 84% and a specificity of 56.4% to predict an adverse outcome. Similarly, a PCT level more than 1.82 ng/mL on day 5 predicted adverse patient outcome with a sensitivity of 89.5% and a specificity of 71.9%.

Further, the percentage clearance of serum PCT levels on days 3 and 5 compared with baseline (PCTc; see above) was analyzed. PCTc on both days was found to be predictive of adverse outcome with obtained AUCs of 0.848 (0.793–0.903; p<0.001) and 0.854 (0.796–0.912; p<0.001) for days 3 and 5, respectively. The ROC curves obtained following analysis are depicted in figure 2. ORs were

Table 1 Baseline demographic and clinical characteristics

Variables	All patients	Survivors (n=43)	Non-survivors (n=56)	P value
Age (mean±SD)	45.9±18.5	41.2±18.5	49.4±18.2	0.031*
Male sex, n (%)	59 (59)	24 (55.8)	35 (62.5)	0.502
Source of sepsis (%)				0.301
Pulmonary	68 (68)	29 (67.4)	39 (69.6)	
Intra-abdominal	11 (11)	4 (9.3)	7 (12.5)	
Skin and soft tissue	7 (7)	4 (9.3)	3 (5.4)	
Meningitis	6 (6)	1 (2.3)	4 (7.2)	
Urosepsis	4 (4)	1 (2.3)	3 (5.6)	
Catheter-related bloodstream infection	1 (1)	1 (2.3)	0	
Other	3 (3)	3 (6.9)	0	
Comorbid conditions (%)				
Any	72 (72)	29 (67.4)	43 (76.8)	0.72
Hypertension	20 (20)	4 (9.3)	16 (28.6)	0.018*
Diabetes	19 (19)	5 (11.7)	14 (25.9)	0.094
Chronic neurological disease	21 (21)	10 (23.3)	11 (19.7)	0.663
Chronic lung disease	14 (14)	7 (16.2)	7 (12.5)	0.593
Chronic heart disease	10 (10)	2 (4.7)	8 (14.3)	0.179
Malignancy	7 (7)	2 (4.6)	5 (8.9)	0.696
Chronic liver disease	3 (3)	0	3 (5.4)	0.253
Others	3 (3)	1 (2.3)	2 (3.7)	
Severity scoring				
APACHE score (mean±SD)	83.6±29.3	78.9±23.9	94.7±28.5	<0.001*
SOFA score (mean±SD)	7.32±3.0	6.28±2.73	8.14±3.02	0.002*
SAPS 3 (mean±SD)	52.01±15.57	44.07±12.55	58.19±14.94	<0.001*
Organ dysfunction (%)				
Septic shock	62 (62)	20 (46.5)	42 (75)	0.004*
Acute kidney injury	25 (25)	7 (16.2)	18 (32.1)	0.072
Acute respiratory distress syndrome	15 (15)	5 (11.6)	10 (17.9)	0.392

*p-value less than the pre-defined level of significance (i.e. < 0.05)
APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

computed to compare baseline and serial PCT levels for the outcome of patient mortality and are presented in table 3.

Data were accrued for toxic granulations on peripheral smear analyses at admission and serial levels of serum CRP, ESR and TLC. Of the analyzed inflammatory markers, only serum CRP levels on day 3 (median: 101.4; IQR: 117.15) were found to be significantly (p=0.035) lower in survivors (median: 86.75; IQR: 77.03) as compared with non-survivors (median: 136.19; IQR: 114.72). ROC analysis was thus undertaken to assess the value of day 3 serum CRP as a diagnostic marker for adverse patient outcome. Day 3 CRP was found to be a significant predictor of adverse outcome (p=0.035) with an AUC of 0.658 (0.513–0.803). The 2 ROC curves thus obtained on day 3 CRP and PCT levels were compared. The performance of the CRP curve was significantly inferior (p=0.027) as compared with the PCT curve.

Furthermore, ROC analysis was undertaken to study the accuracy of each of the 3 studied severity scores (APACHE IV, SAPS 3, SOFA) at baseline in predicting adverse outcome. All 3 scoring systems were accurate as predictors of adverse outcome (table 4). Change in serial APACHE IV score over the course of hospital stay was significantly different among survivors ((mean±SD%) day 1 to day 3: −9.9±22.4%, day

Table 2 Serial serum PCT levels: association with outcome

Variables	Day 1 serum procalcitonin (n=99) (ng/mL)	Day 3 serum procalcitonin (n=72) (ng/mL)	Day 5 serum procalcitonin (n=52) (ng/mL)	Day 7 serum procalcitonin (n=23) (ng/mL)
All patients (n=99) (Median (IQR))	7.57 (24.18)	2.8 (17.36)	1.815 (6.41)	0.47 (3.02)
Survivors (n=43) (Median (IQR))	7.1 (18.53)	1.74 (9.4)	0.87 (2.15)	0.34 (0.69)
Non-survivors (n=56) (Median (IQR))	10.83 (26.92)	6.02 (29.14)	7.13 (16.93)	6.66 (9.02)
P value (non-parametric)	0.683	0.016*	<0.001*	0.164

*p-value less than the pre-defined level of significance (i.e. < 0.05)
PCT, procalcitonin.

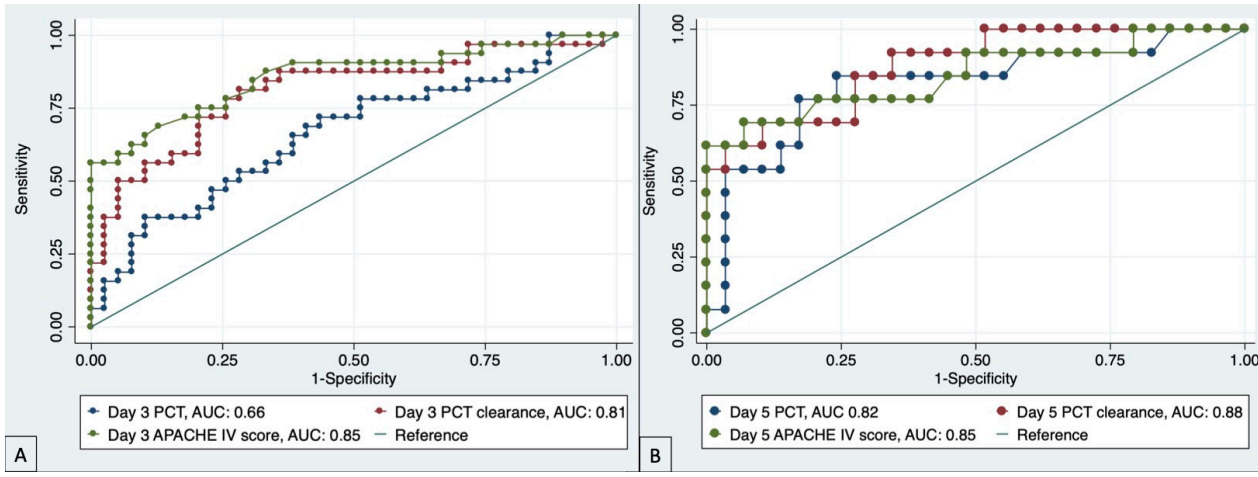

Figure 2 Receiver operating characteristic (ROC) analysis for serial procalcitonin (PCT), PCT clearance (PCTc) and day-matched Acute Physiology and Chronic Health Evaluation (APACHE IV) scores. AUC, area under the curve.

1 to day 5: −23±24.6%) as compared with non-survivors ((mean±SD%) day 1 to day 3: +12.3%±20.4%, day 1 to day 5: +19%±44.6%) (p<0.001 on both days). Baseline SAPS was the best marker followed by baseline APACHE IV and SOFA scores, respectively. Serial APACHE IV scores were subsequently compared with serial values of PCTc on admission days 3 and 5. As the performance of baseline SOFA score was significantly inferior to that of the APACHE score and SAPS, and the SAPS 3 has not been validated for serial assessments, only serial APACHE scores were selected for the purpose. The comparison of ROC curves yielded no significant difference in the predictive accuracy for adverse outcomes on day 3 (p=0.28) or day 5 (p=0.14) (table 4). It may thus be concluded that the prognostic predictive performance of PCTc is only as good as day-matched APACHE IV score.

A multivariate (logistic) regression model was designed considering predictive variables (viz day 3 and day 5 APACHE IV scores, and day 3 and day 5 PCTc) as independent variables and patient outcome as the dependent variable. The model was a good fit to outcome data, predicted 43.5% of the variation in outcome and was significantly (p=0.002) associated with patient outcome. The only variable to associate independently with adverse outcome was day 5 APACHE IV score with an adjusted OR of 1.310 (1.005–1.708).

Table 3 Analyses of trends in procalcitonin clearance

Test variable	OR (95% CI)	P value
Rise in serum procalcitonin (baseline to day 3)	13.6 (2.82 to 66.05)	<0.001
Fall in serum procalcitonin <45% (baseline to day 3)	8.61 (3.03 to 24.44)	<0.001
Rise in serum procalcitonin (baseline to day 5)	38.33 (2.044 to 718.68)	<0.001
Fall in serum procalcitonin <75% (baseline to day 5)	8.37 (2.26 to 31.01)	0.002

DISCUSSION

As elaborated above, the role of serum PCT levels in predicting patient outcome remains poorly studied. In particular, in a setting of resource constraints, whether the marker will offer additional prognostic predictive benefit when compared with conventional biomarkers of infection and severity scoring systems remains controversial. This study was thus conceived with an aim to determine the utility of serial serum PCT levels as a predictor of adverse patient outcome and compare the predictive accuracy of this marker to conventional markers of inflammation and disease severity scoring systems.

Our study evaluated the associations of patient outcome with PCT levels measured serially over the first week of admission. Baseline PCT levels, measured at the time of hospital admission, demonstrated no significant association with adverse patient outcome. However, non-parametric testing of serial PCT levels on days 3 and 5 demonstrated higher levels to be significantly associated with adverse outcome. Furthermore, a day 3 PCT more than 2.34 ng/mL and a day 5 PCT more than 1.85 ng/mL were indicative of adverse outcome with ORs of 3.08 (1.19–7.93) and 22.7 (4.34–118.42), respectively. Similarly, a PCT on day 3 of

Table 4 Comparison of predictive accuracy for adverse outcomes: PCTc and severity of illness scores

Test result variable(s)	Area under the curve	P value
Baseline APACHE IV score	0.756 (0.663–0.850)	<0.001
Baseline SOFA score	0.677 (0.571–0.784)	0.003
Baseline SAPS 3	0.767 (0.673–0.862)	<0.001
Test result variable(s)	**Area under the curve**	**Comparison of day-matched predictors (P value)**
Percentage day 1 to day 5	0.879 (0.770–0.989)	0.14
Day 5 APACHE IV score	0.846 (0.702–0.991)	
Percentage day 1 to day 3	0.838 (0.709–0.966)	0.28
Day 3 APACHE IV score	0.823 (0.672–0.974)	

APACHE, Acute Physiology and Chronic Health Evaluation; PCTc, PCT clearance; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

more than 45.14% of baseline and on day 5 of more than 75.48% of baseline predicted adverse outcome with ORs of 8.61 (3.03–24.44) and 8.37 (2.26–31.01), respectively.

As was expected, higher baseline levels of all 3 studied severity scores, namely the APACHE IV score, SAPS 3 and SOFA score, were significantly associated with adverse patient outcome. Comparison of predictive analysis of the 3 scores demonstrated baseline SAPS 3 to have the highest predictive accuracy for adverse patient outcome. However, as the SAPS 3 is not validated for serial assessments, the serial prognostic predictive value of serial APACHE IV score was compared with day-matched PCTc on days 3 and 5. The 2 prognostic ROC curves were found not to be significantly different, suggesting that the predictive value of PCTc was only as much as day-matched APACHE IV score.

There remains considerable ambiguity in the results from prior studies as regards the association of serum PCT level at baseline with patient outcome.[12–14] There is, however, greater consensus on the applicability of PCT kinetics as indicator of outcome. The first study to address this was undertaken by Karlsson *et al*,[15] demonstrating a clearance <50% at 48 hours to be indicative of adverse outcome. Subsequently, the multicenter procalcitoonin monitoring sepsis (MOSES)[16] study and a study by Schuetz *et al*[17] published in 2013 demonstrated PCT clearance less than 80% at 4 days and 72 hours, respectively, to be associated with adverse outcome. Each of these studies used predefined cut-points and times of measurement, leaving significant ambiguity about the optimal level of each. Our literature review demonstrated 2 prior small-sized prospective studies on the topic.[13 18] The first study[13] by Ruiz-Rodríguez *et al* analyzed 27 patients with sepsis and demonstrated PCT levels at 24 and 48 hours to be associated with adverse patient outcome. As our study also suggests, Rios-Toro *et al*[18] found SOFA and APACHE II scores to be superior to PCT levels in predicting patient outcome. This was, however, a small study with a short duration of follow-up.

Our study suffered from certain limitations. Our study has a small sample size and trends thus found may need to be validated in a larger cohort. Superadded hospital-acquired infections could not be ruled out and may have affected biomarker levels on serial testing. There was an over-representation of respiratory infections ascribed to the exclusion of patients with renal dysfunction at baseline. Additionally, patients with renal dysfunction at the time of admission were excluded from the study. The impact of this on serial biomarker levels remains unknown. Finally, the overall study population was younger as compared with global estimates. This may be problematic when extrapolating these data to older patients with more comorbid illnesses.

In spite of these limitations our study is one of the first to recruit sufficient patients to evaluate the prognostic capability of PCT and PCTc in patients with sepsis from low and middle-income countries and compare it with existing disease severity scoring systems. This analysis proposes the relative futility of serial PCT levels to assess prognosis in resource-limited settings where a clinical score-based approach using APACHE IV would possibly be more cost-effective and equally informative. While a cost-benefit analysis may be more revealing of its utility, in resource-rich settings, a single measurement of PCT on day 5, or PCT clearance on day 3 and day 5, may be measured to predict in-hospital mortality. Further study may develop composite scoring system combining the use of PCT with other physiological parameters that improves prognostic prediction in patients with sepsis.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The study protocol, study questionnaire, patient information sheet and patient informed consent form were reviewed and approved by the AIIMS Institutional Ethics Committee for Post-Graduate Research and ethical clearance was obtained on September 13, 2017 (Ref No IECPG-328/07.09.2017). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. All anonymized patient data used in the analysis and preparation of this study will be made available upon reasonable request.

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