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Lactate Kinetics and Procalcitonin Clearance as Predictors of 28-Day Mortality in Patients With Sepsis Admitted to a Medical Intensive Care Unit: A Prospective Observational Study

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Abstract

Background: Sepsis-associated organ failure is a major cause of mortality in intensive care units (ICUs) worldwide. Timely risk stratification using reliable biological markers may help identify patients at increased risk of adverse outcomes and support clinical decision-making. This study evaluated the prognostic performance of serial lactate measurements and procalcitonin (PCT) clearance for predicting 28-day mortality in patients with sepsis admitted to a tertiary-level medical ICU.

Materials and methods: This single-center prospective observational study was conducted in the Department of Critical Care Medicine, Jaypee Hospital (now Max Super Speciality Hospital), Sector 128, Noida, Uttar Pradesh, India, over an 18-month period from August 2022 to February 2024. Adults aged ⩾18 years admitted with sepsis, operationally defined as an increase in the Sequential Organ Failure Assessment score of ⩾2 points, were consecutively enrolled (n = 100). Whole-blood lactate was measured at admission and at six, 12, and 24 hours, while PCT was measured at admission and on day 3. Absolute lactate clearance, relative lactate clearance (RLC), lactate clearance rate (LCR), and PCT clearance were calculated. The primary outcome was all-cause mortality within 28 days. Receiver operating characteristic curve analysis was used to evaluate discriminatory performance and identify exploratory cutoffs.

Results: The mean age was 57.8 ± 13.6 years, and 56% of participants were male. Twenty-one patients (21%) died within 28 days. Compared with survivors, nonsurvivors had higher admission lactate concentrations (median, 8.6 mmol/L (IQR, 6.4-12.4) vs. 3.7 mmol/L (IQR, 2.6-4.4); $p < 0.0001$) and admission PCT levels (median, 100 ng/mL (IQR, 44.5-100) vs. 11.5 ng/mL (IQR, 5.5-27.3); $p < 0.0001$). PCT clearance demonstrated an apparent AUC of 1.000 (95% CI, 0.964-1.000) at an exploratory cutoff of ⩽38.65%. RLC and LCR each had an AUC of 0.999, while 24-hour lactate had an AUC of 0.996. These estimates were obtained and evaluated in the same cohort and have not been independently validated.

Conclusions: Serial lactate measurements and PCT clearance may provide useful prognostic information in ICU patients with sepsis. Although these biomarkers demonstrated high apparent discriminatory performance in this cohort, the identified cutoffs are exploratory and have not been independently validated. Larger, multicenter studies are needed to establish their reproducibility and clinical utility before these thresholds can be considered for clinical implementation.

Categories: Pulmonology, Internal Medicine, Infectious Disease
Keywords: 28-day mortality, biomarker, icu, lactate clearance, lactate kinetics, procalcitonin clearance, roc analysis, sepsis, sofa score

Introduction

Sepsis, characterized by life-threatening organ dysfunction resulting from a dysregulated host response to infection, remains a major challenge in critical care. It triggers a cascade of pathophysiological events encompassing endothelial injury, coagulation dysregulation, cardiovascular compromise, and ultimately multiorgan failure, culminating in death in a substantial proportion of affected individuals [1]. The 2017 Global Burden of Disease analysis cataloged approximately 49 million new cases worldwide each year, accounting for an estimated 11 million fatalities, nearly one-fifth of all global deaths that year [1]. Indian data are equally sobering; a multicenter survey spanning 35 ICUs documented a Sepsis-3 prevalence of 33% among critically ill admissions and a 30-day mortality of 27.6%, with discharge against medical advice accounting for a further 12.8% [2].

Early identification of high-risk patients is essential for effective sepsis management. Guidelines such as the Surviving Sepsis Campaign 2021 edition advocate a bundle of hemodynamic, antimicrobial, and monitoring interventions that, when instituted promptly, can attenuate organ injury [3]. Severity scoring instruments,

including SOFA [4], the National Early Warning Score (NEWS) [5], and APACHE II [6], provide clinicians with structured prognostic frameworks, yet their reliance on point-in-time physiological parameters limits their ability to track the dynamic biological response to resuscitation.

Blood lactate concentrations reflect changes in cellular metabolism. When oxygen delivery to peripheral tissues falls short of demand, whether from hemodynamic failure, microcirculatory dysfunction, or mitochondrial impairment, pyruvate is preferentially reduced to lactate via anaerobic glycolysis [7]. The magnitude and persistence of hyperlactatemia have been correlated with adverse outcomes across multiple critical illness syndromes. More recently, lactate clearance, defined as the reduction in lactate concentration during early resuscitation, has emerged as a potential indicator of therapeutic response that may provide additional information beyond a single measurement [8].

Procalcitonin (PCT), the 116-amino-acid calcitonin precursor synthesized by multiple tissues during systemic bacterial infection, has been adopted as both a diagnostic adjunct and a treatment-monitoring tool in sepsis. Its serum concentration rises steeply within hours of bacterial stimulus and declines as the infectious burden diminishes [9]. Several investigators have proposed that the proportional reduction in PCT between admission and a later time point, referred to as PCT clearance, may serve as a surrogate for clinical improvement and a predictor of survival [10].

Comparative data evaluating lactate kinetics and PCT clearance within the same patient cohort remain limited, particularly among patients admitted to ICUs in India, where demographic characteristics, pathogen profiles, and resource availability may differ from those in Western settings. This study addresses this gap by measuring serial lactate and PCT concentrations in patients with sepsis and linking their clearance trajectories to 28-day mortality and ICU length of stay.

Therefore, this study aimed to evaluate the prognostic performance of serial lactate measurements and PCT clearance in predicting 28-day mortality among patients with sepsis admitted to the intensive care unit (ICU). The secondary objectives were to compare the discriminatory performance of admission lactate, 24-hour lactate, lactate clearance indices, and PCT clearance for predicting 28-day mortality and to assess the relationship between these biomarkers and ICU length of stay. The study also explored biomarker cutoff values using receiver operating characteristic (ROC) curve analysis. These cutoff values were derived from the study dataset and were not independently validated.

Materials And Methods

Study design and setting

This prospective, single-center observational cohort study was conducted in the Department of Critical Care Medicine, Jaypee Hospital (now Max Super Speciality Hospital), Sector 128, Noida, Uttar Pradesh, India, over an 18-month period from August 2022 to February 2024. The institution has 504 inpatient beds, a 56-bed ICU, and comprehensive diagnostic and therapeutic facilities.

Ethical considerations

The Institutional Ethics Committee of Jaypee Hospital, Noida, Uttar Pradesh, India, approved the study protocol on July 23, 2022 (approval number: IEC/JH/IM/01/2022/DR001026). Written informed consent was obtained from each participant or an appropriate surrogate decision-maker before enrollment.

Eligibility criteria

Inclusion

Adult patients aged ⩾18 years admitted to the ICU with confirmed or clinically suspected sepsis were eligible for inclusion. Sepsis was defined according to the Sepsis-3 criteria as life-threatening organ dysfunction caused by a dysregulated host response to infection, operationalized as an acute increase in the Sequential Organ Failure Assessment (SOFA) score of ⩾2 points. In patients without documented pre-existing organ dysfunction, the baseline SOFA score was assumed to be zero. Patients were required to remain in the ICU for at least 72 consecutive hours.

Exclusion

Patients younger than 18 years, pregnant women, and individuals with a pre-existing diagnosis of HIV infection, active malignancy, chronic liver disease, chronic kidney disease, or polytrauma were excluded, as were those who had undergone major surgery within the preceding 30 days or acquired a new nosocomial infection that was not present at the time of ICU admission.

Sample size determination

The sample size was estimated using previously published area under the ROC curve (AUC) values for PCT

and 24-hour lactate [9-11]. The original calculation used a precision margin (δ) of 0.07 and a two-sided type I error rate of 5%, yielding a minimum required sample size of 91 participants. To account for potential data attrition and improve estimate precision, we increased the target sample size to 100 participants. However, the original calculation did not explicitly account for the expected number of mortality events. In the final cohort, 21 of the 100 participants died within 28 days. Therefore, the number of outcome events should be considered when interpreting the stability and precision of the prognostic performance estimates.

Clinical assessment and laboratory protocol

On ICU admission, standardized data were collected for each patient, including demographic characteristics, the nature and duration of comorbid conditions, and vital signs such as heart rate, systolic and diastolic blood pressure, and peripheral oxygen saturation (SpO_2). Glasgow Coma Scale (GCS) [12], Sequential Organ Failure Assessment (SOFA) [4], and National Early Warning Score (NEWS) [5] scores were also calculated. Prior to initiating antimicrobial therapy, blood specimens were drawn for a full blood count, serum electrolytes, renal biochemistry, liver biochemistry including albumin and bilirubin, coagulation indices (prothrombin time and international normalized ratio), serum PCT, and arterial blood gas analysis. Microbiological specimens, including blood, urine, and expectorated or tracheal sputum, were obtained simultaneously and submitted for Gram staining, culture, and antimicrobial susceptibility testing. Thoracic radiographs and abdominal ultrasonography were performed where clinically indicated to localize the infectious source.

Whole-blood lactate concentrations were measured at four predefined intervals: immediately upon ICU admission (0 hours), at six hours, 12 hours, and 24 hours. PCT was quantified at the time of admission and repeated on the third ICU day. The following derived indices were computed: absolute lactate clearance (ALC) = $\mathrm{Lactate}_{0\mathrm{h}} - \mathrm{Lactate}_{24\mathrm{h}}\ (\mathrm{mmol/L})$, relative lactate clearance (RLC, %) = $\dfrac{\mathrm{Lactate}_{0\mathrm{h}} - \mathrm{Lactate}_{24\mathrm{h}}}{\mathrm{Lactate}_{0\mathrm{h}}} \times 100$, lactate clearance rate (LCR, %/h) = $\dfrac{\mathrm{RLC}}{24}$, and PCT clearance (%) = $\dfrac{\mathrm{PCT}_{0\mathrm{h}} - \mathrm{PCT}_{\mathrm{day\ 3}}}{\mathrm{PCT}_{0\mathrm{h}}} \times 100$.

Outcome definitions

The primary endpoint was all-cause mortality within 28 days of ICU admission, and the secondary endpoint was total ICU stay duration, recorded in days. The 28-day mortality status of five patients who left the hospital against medical advice could not be ascertained; therefore, these patients were classified as having an unknown 28-day outcome rather than being considered survivors or nonsurvivors.

Statistical methods

Raw data were entered into Excel (Microsoft Corp., Redmond, WA, USA) and transferred to SPSS Statistics version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY) for analysis. Normally distributed continuous variables, as assessed using the Shapiro-Wilk test, are presented as the mean ± standard deviation (SD), whereas non-normally distributed variables are presented as the median and interquartile range (IQR; 25th-75th percentiles). Categorical data are expressed as counts and percentages. Between-group comparisons of non-normally distributed variables employed the Mann-Whitney U test; the independent-samples t-test was used for normally distributed measures. Chi-square or Fisher's exact test was applied to categorical comparisons depending on expected cell counts. Monotonic associations between continuous variables were quantified by Spearman's rank correlation coefficient. Variables with univariate significance were entered simultaneously into a binary logistic regression model to identify independent mortality predictors; a linear regression model was constructed to identify determinants of ICU stay duration. The discriminatory performance of each biomarker for 28-day mortality was characterized by ROC curve analysis, generating AUC estimates with 95% confidence intervals (CIs) alongside sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy at Youden-index-optimized cutoff points. A two-tailed $p < 0.05$ was prespecified as the threshold for statistical significance. Patients with an unknown 28-day mortality outcome were excluded from analyses requiring a known mortality status. The number of patients included in each mortality analysis was reported accordingly.

Results

Patient characteristics

All 100 consecutively enrolled patients completed the 28-day observation period. The cohort had a mean age of 57.8 ± 13.6 years (median 57.5 years; range 28-86 years). More than half were male (56 patients, 56%). The modal age group was the sixth decade (32 patients, 32%), followed by the seventh decade (23 patients, 23%). At least one comorbid condition was documented in 82 patients (82%); the most prevalent were diabetes mellitus (55 patients, 55%), systemic hypertension (44 patients, 44%), coronary artery disease (16 patients, 16%), and hypothyroidism (12 patients, 12%). Table *1* summarizes the baseline demographic and clinical

characteristics.

Characteristic	Value	Range/IQR
Age (years)	57.8 ± 13.6	28-86
Male sex, n (%)	56 (56%)	-
Female sex, n (%)	44 (44%)	-
Heart rate (beats/min)	104.79 ± 16.31	57-138
Systolic BP (mmHg)	111.13 ± 22.99	60-190
Diastolic BP (mmHg)	66.09 ± 14.11	40-98
SpO_2 (%)	94.17 ± 2.74	86-100
GCS score	13.04 ± 2.23	6-15
SOFA score	6.59 ± 3.63	1-16
NEWS score	7.01 ± 4.21	0-17
Diabetes mellitus, n (%)	55 (55%)	-
Hypertension, n (%)	44 (44%)	-
Coronary artery disease, n (%)	16 (16%)	-
Hypothyroidism, n (%)	12 (12%)	-
No comorbidity, n (%)	18 (18%)	-

TABLE 1: Baseline demographic and clinical characteristics (n = 100)

BP: blood pressure, GCS: Glasgow Coma Scale, NEWS: National Early Warning Score, SOFA: Sequential Organ Failure Assessment, SpO_2: peripheral oxygen saturation, IQR: interquartile range

At admission, the mean heart rate was 104.79 ± 16.31 beats/min, mean systolic blood pressure was 111.13 ± 22.99 mmHg, and mean SpO_2 was 94.17 ± 2.74%. Regarding GCS classification, 67 patients (67%) had scores of 13-15, 28 patients (28%) had scores of 9-12, and five patients (5%) had scores of ⩽8. Regarding SOFA score distribution, 61 patients (61%) scored 0-6, 18 patients (18%) scored 7-9, and 21 patients (21%) scored ⩾10. NEWS score stratification showed that 45 patients (45%) were high risk (⩾7), while 33 patients (33%) and 22 patients (22%) were low risk (0-4) and medium risk (5-6), respectively.

Biomarker kinetics

Mean whole-blood lactate concentrations progressively decreased across the four measurement time points, from 5.01 ± 3.12 mmol/L at admission to 4.01 ± 2.94 mmol/L at six hours, 3.23 ± 3.01 mmol/L at 12 hours, and 2.59 ± 3.32 mmol/L at 24 hours. The mean ALC was 2.42 ± 1.86 mmol/L, the RLC was 58.57 ± 29.76%, and the LCR was 2.44 ± 1.24%/h. PCT likewise declined from a mean of 30.83 ± 32.95 ng/mL at admission to 16.00 ± 28.71 ng/mL by day 3, corresponding to a mean PCT clearance of 67.58 ± 29.12%. Table *2* summarizes the serial lactate and PCT kinetics.

Parameter	Mean ± SD	Median (IQR)	Range
Lactate at admission (mmol/L)	5.01 ± 3.12	3.85 (2.80-6.08)	1.8-15.0
Lactate at 6 h (mmol/L)	4.01 ± 2.94	3.00 (2.00-4.60)	1.3-14.2
Lactate at 12 h (mmol/L)	3.23 ± 3.01	2.00 (1.40-3.53)	0.8-14.0
Lactate at 24 h (mmol/L)	2.59 ± 3.32	1.20 (0.70-2.10)	0.4-14.2
ALC (mmol/L)	2.42 ± 1.86	2.20 (1.70-3.00)	−2.4-9.8
RLC (%)	58.57 ± 29.76	69.23 (56.6-77.8)	−37.5-88.4
LCR (%/h)	2.44 ± 1.24	2.88 (2.34-3.24)	−1.56-3.68
PCT at admission (ng/mL)	30.83 ± 32.95	18.00 (6.53-39.61)	1.49-100
PCT on day 3 (ng/mL)	16.00 ± 28.71	3.18 (1.49-8.10)	0.04-100
PCT clearance (%)	67.58 ± 29.12	79.04 (66.7-85.8)	0-98.9

TABLE 2: Serial lactate measurements and PCT kinetics in the study cohort (n = 100)

ALC: absolute lactate clearance, IQR: interquartile range, LCR: lactate clearance rate, PCT: procalcitonin, RLC: relative lactate clearance, SD: standard deviation

Clinical outcomes

Over the 28-day observation window, 74 patients (74%) were discharged alive, 21 (21%) died in the ICU, and five patients (5%) self-discharged against medical advice. The median ICU length of stay was 5.5 days (IQR 4-8 days; mean 7.37 ± 5.18 days; range 3-28 days).

Comparative analysis: survivors versus nonsurvivors

Patients who died within 28 days exhibited substantially different biomarker profiles compared with survivors (Table *3*). At ICU admission, nonsurvivors had a median lactate of 8.6 mmol/L (IQR 6.4-12.4), compared with 3.7 mmol/L (IQR 2.6-4.4) among survivors (Mann-Whitney $U = 115.5$; $p < 0.0001$). Admission PCT concentrations were also substantially higher among nonsurvivors than survivors, with median values of 100 ng/mL (IQR, 44.5-100) and 11.5 ng/mL (IQR, 5.5-27.3), respectively.

Parameter	Survivors (n = 79)	Nonsurvivors (n = 21)	Test statistic	p-value
Lactate at admission (mmol/L)	3.7 (2.6-4.4)	8.6 (6.4-12.4)	Mann-Whitney U = 115.5	<0.0001
ALC (mmol/L)	2.86 ± 1.55	0.76 ± 2.01	Student's t(98) = 5.18	<0.0001
RLC (%)	72.32 ± 9.10	6.83 ± 22.45	Welch's t(21.8) = 13.09	<0.0001
LCR (%/h)	3.01 ± 0.38	0.28 ± 0.93	Welch's t(21.8) = 13.10	<0.0001
PCT at admission (ng/mL)	11.5 (5.5–27.3)	100 (44.5–100)	Mann–Whitney U = 248.0	<0.0001
PCT clearance (%)	81.76 ± 8.90	14.24 ± 10.33	Student's t(98) = 29.85	<0.0001
GCS score	13.91 ± 1.25	9.76 ± 2.05	Student's t(98) = 11.65	<0.0001
SOFA score	5.00 ± 1.89	12.57 ± 1.94	Student's t(98) = 16.25	<0.0001
NEWS score	5.37 ± 2.83	13.19 ± 2.34	Student's t(98) = 11.63	<0.0001
Age (years)	57.29 ± 14.49	59.71 ± 9.74	Welch's t(46.3) = 0.91	0.37
Comorbidity present (%)	81.01	85.71	Fisher's exact test	0.757
Male sex (%)	53.16	66.67	Pearson $\chi^2(1) = 1.23$	0.268

TABLE 3: Comparison of biomarker and clinical parameters between survivors and nonsurvivors (n = 100)

Values are presented as mean ± SD or median (IQR), as appropriate. Admission lactate and PCT were compared using the Mann-Whitney U test. Other continuous variables were compared using the independent-samples t-test (Student's or Welch's, as appropriate). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate.

GCS: Glasgow Coma Scale, NEWS: National Early Warning Score, PCT: procalcitonin, RLC: relative lactate clearance, SOFA: Sequential Organ Failure Assessment, SD: standard deviation, IQR: interquartile range, LCR: lactate clearance rate, ALC: absolute lactate clearance

With respect to clearance parameters, nonsurvivors exhibited substantially lower ALC (0.76 ± 2.01 versus 2.86 ± 1.55 mmol/L; Student's t(98) = 5.18; p < 0.0001), RLC (6.83 ± 22.45% versus 72.32 ± 9.10%; Welch's t(21.8) = 13.09; p < 0.0001), and LCR (0.28 ± 0.93 versus 3.01 ± 0.38%/h; Welch's t(21.8) = 13.10; p < 0.0001). PCT clearance was similarly lower among nonsurvivors than survivors (14.24 ± 10.33% vs. 81.76 ± 8.90%; Student's t(98) = 29.85; p < 0.0001), with a median of only 14.28% (IQR 6-18%) compared with 82.48% (IQR 76.6-87.7%) in survivors.

Severity scores differed substantially between survivors and nonsurvivors. Nonsurvivors had lower GCS (9.76 ± 2.05 versus 13.91 ± 1.25; Student's t(98) = 11.65; p < 0.0001), higher SOFA scores (12.57 ± 1.94 versus 5.00 ± 1.89; Student's t(98) = 16.25; p < 0.0001), and higher NEWS scores (13.19 ± 2.34 versus 5.37 ± 2.83; Student's t(98) = 11.63; p < 0.0001). Notably, all patients who died had NEWS scores in the high-risk category (⩾7). In contrast, age, sex distribution, and comorbidity status did not differ significantly between survivors and nonsurvivors in the univariate analyses.

In the multivariable logistic regression analysis incorporating nine clinically relevant predictors (GCS, SOFA, NEWS, admission lactate, admission PCT, ALC, RLC, LCR, and PCT clearance), no individual parameter retained independent statistical significance (p > 0.05 for all), a finding attributable to substantial multicollinearity among these interrelated predictors within a 100-patient sample.

Correlation with ICU length of stay

ALC showed a weak but statistically significant positive correlation with ICU length of stay (Spearman r = 0.318, t(98) = 3.33; p = 0.001), indicating that patients with greater absolute lactate reductions tended toward marginally longer ICU stays, possibly reflecting more complex recoveries requiring extended monitoring. Admission lactate also showed a weak positive correlation with ICU length of stay (r = 0.228; p = 0.023). RLC (r = 0.010, t(98) = 0.09; p = 0.925), PCT clearance (r = 0.086, t(98) = 0.85; p = 0.397), SOFA score (r = 0.190, t(98) = 1.92; p = 0.059), NEWS score (r = 0.174, t(98) = 1.75; p = 0.083), and GCS (r = −0.070, t(98) = −0.70; p = 0.486) did not reach significance. Neither sex (Mann-Whitney U = 1155.0; p = 0.589) nor comorbidity status (Mann-Whitney U = 867.5; p = 0.241) was associated with ICU length of stay. Multivariable linear regression identified no independent predictors of ICU length of stay.

Discriminatory performance: ROC curve analysis

All six evaluated parameters showed apparent discriminatory performance for 28-day mortality, with AUC values exceeding 0.80. Table 4 summarizes the complete performance matrix.

Variable	AUC	Cutoff	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Accuracy (%)
Lactate (0 h)	0.930	>4.65 mmol/L	90.5	81.0	55.9	97.0	83
Lactate (24 h)	0.996	>2.80 mmol/L	95.2	100.0	100.0	98.7	99
ALC	0.839	≤1.60 mmol/L	76.2	93.7	76.2	93.7	90
RLC	0.999	≤52.38%	100.0	97.5	91.3	100.0	98
LCR	0.999	≤2.18%/h	100.0	97.5	91.3	100.0	98
PCT clearance	1.000	≤38.65%	100.0	100.0	100.0	100.0	100

TABLE 4: ROC curve analysis for prediction of 28-day ICU mortality (n = 100)

AUC: area under the ROC curve, LC: lactate clearance, LCR: lactate clearance rate, NPV: negative predictive value, PCT: procalcitonin, PPV: positive predictive value, RLC: relative lactate clearance, Sens.: sensitivity, Spec.: specificity, ROC: receiver operating characteristic, ICU: intensive care unit, ALC: absolute lactate clearance

PCT clearance demonstrated an apparent AUC of 1.000 (95% CI, 0.964-1.000). At the exploratory cutoff of ⩽38.65%, sensitivity, specificity, positive predictive value, and negative predictive value were each 100% within the analyzed cohort. Both RLC (⩽52.38%) and LCR (⩽2.18%/h) attained AUCs of 0.999 with 100% sensitivity and 97.5% specificity. Lactate at 24 hours (>2.80 mmol/L) had an AUC of 0.996 with 95.2% sensitivity and 100% specificity, for 99% overall accuracy. Admission lactate (>4.65 mmol/L; AUC 0.930) achieved 90.5% sensitivity and 81.0% specificity (83% accuracy). ALC (⩽1.60 mmol/L; AUC = 0.839) demonstrated the lowest AUC among the evaluated parameters, with 76.2% sensitivity and 93.7% specificity (90% accuracy). Overall, clearance-based measures demonstrated higher apparent AUC values than admission lactate, with PCT clearance yielding the highest numerical AUC among the evaluated biomarkers.

Discussion

This prospective observational study evaluated the prognostic performance of serial lactate and PCT measurements in predicting 28-day mortality among patients with sepsis admitted to the ICU. The findings suggest that changes in lactate concentrations over the first 24 hours and PCT concentrations over the first 72 hours may provide prognostic information within the studied cohort. PCT clearance of ⩽38.65% demonstrated an area under the receiver operating characteristic curve (AUC) of 1.000, with 100% sensitivity and specificity in the study sample. However, these estimates were derived and evaluated in the same cohort and should be interpreted as apparent, exploratory performance rather than validated clinical accuracy. The lack of independent validation, together with the relatively small number of mortality events, suggests the reported performance estimates may be optimistic. Independent validation in larger, multicenter cohorts is required to determine whether this discriminatory performance can be reproduced in other patient populations and whether the identified threshold has potential clinical utility.

The 21% mortality rate observed in this cohort falls within the range reported by comparable single-center Indian studies. Chaudhari and Agarwal documented a 23.5% 28-day mortality rate among ICU patients with sepsis using a similar lactate-kinetics framework [13]. International studies have reported varying mortality rates, potentially reflecting differences in patient characteristics, illness severity, ICU resources, and access to organ support. Suranadi and colleagues reported mortality exceeding 57% in an Indonesian cohort [11], whereas Lee et al. reported a mortality rate of 40.8% in a Korean series [14]. These differences highlight the heterogeneity of sepsis outcomes across clinical settings and the importance of considering population characteristics when interpreting prognostic findings. Although the mortality rate in the present study is broadly comparable to that reported in some previous studies, such agreement does not establish the external validity or generalizability of the biomarker thresholds identified here. Furthermore, the 28-day outcomes of five patients who left the hospital against medical advice could not be ascertained, which should be considered when interpreting the observed mortality proportion.

The association between lactate measurements and adverse outcomes aligns with prior research on lactate kinetics in sepsis. In a study of 111 patients with sepsis presenting to the emergency department, Nguyen et al. reported that increasing early lactate clearance was associated with a lower risk of death and that clearance of at least 10% within six hours was associated with improved 60-day survival [15]. Arnold et al. also reported that impaired lactate clearance was associated with mortality in a multicenter investigation [16]. In the present study, admission lactate had an AUC of 0.930, whereas 24-hour lactate concentration and derived lactate clearance indices had AUCs of 0.996 and 0.999, respectively. These findings indicate strong

apparent discriminatory performance in the current cohort and suggest that serial lactate measurements may provide additional prognostic information compared with a single admission measurement. Nevertheless, these estimates require cautious interpretation because the cutoff values were derived and evaluated in the same dataset and were not independently validated. Therefore, the high AUC estimates should be considered exploratory rather than definitive evidence of performance in other clinical settings.

PCT clearance also demonstrated high apparent discriminatory performance in the present study. Karlsson et al. found that ICU patients whose PCT levels dropped by more than 50% in 72 hours had a lower death rate than those whose levels dropped by less than 50% (12.2% vs. 29.8%) [17]. Mat Nor and Md Ralib reported that 48-hour PCT clearance was associated with survival in a separate Malaysian cohort, with an AUC of 0.69; a clearance exceeding 30% was also associated with a survival advantage [10]. In the present study, PCT clearance demonstrated an apparent AUC of 1.000. This numerical difference does not show that PCT clearance is statistically superior to the lactate-derived indices or intrinsically more accurate in the present population. Formal statistical comparison of correlated ROC curves was not performed; therefore, the statistical superiority of one biomarker over another cannot be established from the numerical AUC estimates alone. Differences in study design, patient characteristics, outcome distributions, biomarker measurement times, and analytical methods may also contribute to variations in reported AUC values. Additionally, the relatively small sample size and the selection and evaluation of the cutoff within the same cohort may have produced optimistic performance estimates. The upper measurement limit of the PCT assay may also have affected clearance calculations if concentrations at or above that limit were reported as capped values; however, this possibility requires confirmation from the assay documentation. Larger studies with independent validation are needed to determine whether the identified threshold is reproducible and clinically useful.

The severity scores evaluated in this study also differed between survivors and nonsurvivors. The observed differences in SOFA, GCS, and NEWS scores are consistent with the established relationship between physiological derangement, organ dysfunction, and adverse outcomes in critically ill patients [18,19]. The finding that none of the patients who died had a NEWS score below the high-risk threshold of ⩾7 suggests that NEWS may have been useful for identifying high-risk patients in this cohort. However, this finding alone does not establish NEWS superiority or show that lactate and PCT clearance improve risk classification beyond established severity scores. Such incremental prognostic value would require formal comparative analyses, including assessment of whether the addition of biomarkers improves discrimination or other measures of prognostic performance. Similarly, the absence of statistically significant associations between age, sex, or comorbidity status and mortality in this sample should not be interpreted as evidence that these characteristics have no prognostic relevance. The relatively small cohort and only 21 deaths limited the precision of the estimates and the ability to identify independent associations in multivariable analyses.

The distinct biological processes reflected by lactate and PCT may explain their potential complementary prognostic value. Lactate concentrations may reflect disturbances in tissue perfusion, cellular metabolism, and other physiological processes associated with critical illness. Changes in lactate concentrations during early resuscitation may therefore reflect the patient's evolving clinical condition [7]. PCT is associated with the systemic inflammatory response to bacterial infection, and changes in its concentration over time may reflect changes in the inflammatory response and the course of infection [9]. These biomarkers therefore represent different, though potentially overlapping, aspects of sepsis pathophysiology. However, the present study did not directly investigate the underlying biological mechanisms or establish that changes in either biomarker caused changes in clinical outcomes. Therefore, their potential complementary prognostic contribution should be evaluated through appropriately designed comparative studies.

Biomarker assessment timing is important when interpreting prognostic performance. In the present cohort, admission PCT showed less discriminatory performance than PCT clearance calculated from admission and day-3 measurements, while 24-hour lactate concentration had a higher AUC than admission lactate. These findings suggest that serial measurements may provide additional prognostic information among patients who remain available for assessment at the relevant time points. However, admission lactate, 24-hour lactate measurements, and day-3 PCT clearance do not represent predictions made at equivalent clinical time points. Admission lactate reflects information available at ICU admission, whereas 24-hour lactate indices and day-3 PCT clearance require subsequent measurements and continued observation until their respective assessment times. Consequently, the reported AUC estimates should not be interpreted as directly comparable measures of admission-time predictive performance. The prognostic value of these serial measurements should instead be evaluated in relation to the time at which the measurements become available, ideally using appropriately defined landmark analyses and independent validation.

An important methodological limitation is the requirement for a minimum ICU stay of 72 continuous hours. Because calculation of PCT clearance required a day-3 measurement, this eligibility criterion may have introduced selection and survivorship bias by excluding patients who died, were discharged, or were transferred before completing the required period. Patients experiencing very early deterioration or recovery may therefore have been underrepresented, potentially affecting the observed mortality rate and the apparent prognostic performance of the biomarkers. Additionally, the 28-day outcomes of five patients who left the hospital against medical advice could not be ascertained. This incomplete outcome ascertainment may have affected mortality estimation and the assessment of prognostic performance. The findings should

therefore be interpreted in the context of these potential sources of bias and should not be assumed to apply equally to all patients with sepsis admitted to the ICU.

The multivariable findings also require cautious interpretation. Only 21 deaths occurred in the cohort, whereas nine predictors were reportedly entered simultaneously into the multivariable regression model. This limited number of outcome events relative to the number of predictors raises concerns regarding model overfitting and the stability of the estimated associations. Furthermore, RLC and LCR are mathematically dependent because LCR was calculated by dividing RLC by 24. Their simultaneous inclusion as separate predictors may introduce substantial collinearity and limit the interpretation of their independent effects. Consequently, the reported associations should be regarded as exploratory, and the model requires evaluation in a larger cohort with an adequate number of outcome events and an appropriately specified predictor set. The extensive exclusion criteria, including the exclusion of patients with several pre-existing conditions, may also restrict generalizability to broader ICU populations with more heterogeneous clinical profiles.

Finally, associations involving ICU length of stay should be interpreted cautiously because death may represent a competing event. Patients who die early may have shorter ICU stays despite having more severe illness, whereas patients who survive may remain hospitalized for longer periods. Consequently, a simple association between biomarkers and ICU length of stay may not fully reflect the relationship between biomarker kinetics and clinical recovery. The present observational study also cannot establish whether serial biomarker monitoring changes clinical decisions or improves patient outcomes. Although the findings support further investigation of lactate kinetics and PCT clearance as potential prognostic markers, the derived thresholds should not be considered ready for routine clinical implementation. Future prospective, multicenter studies should recruit patients at ICU admission, account for early deaths and other early outcomes, ensure adequate follow-up, prespecify appropriate statistical analyses, and validate the proposed thresholds in independent populations. Such studies are needed to establish the reproducibility, comparative prognostic value, and potential clinical utility of serial lactate and PCT measurements in sepsis.

Limitations

Several limitations should be considered when interpreting the findings of this study. First, the single-center observational design may limit the generalizability of the findings to other ICU settings and patient populations. The requirement for a minimum ICU stay of 72 hours may have introduced selection and survivorship bias because patients who died, were discharged, or were transferred before completing this period may have been excluded. These post-baseline exclusions may have resulted in the underrepresentation of patients who experienced early adverse outcomes and may have influenced the observed mortality rate and apparent prognostic performance of the biomarkers. The number and outcomes of patients excluded before 72 hours should be clarified from screening records, if available.

Second, although 100 patients were included, only 21 deaths occurred within 28 days. This limited number of mortality events reduces the precision and stability of prognostic estimates and increases the risk of overfitting, particularly in multivariable analyses. Furthermore, ALC, relative lactate clearance, and LCR are mathematically related measures. Evaluating them simultaneously may introduce multicollinearity, complicating interpretation of their independent prognostic contributions.

Third, the ROC-derived cutoff values were selected and evaluated in the same dataset, potentially resulting in optimistic estimates of discriminatory performance. The near-perfect AUCs observed for PCT clearance and lactate-derived indices should therefore be interpreted cautiously. The authors performed no internal validation (e.g., bootstrapping or cross-validation) or independent external validation. Accordingly, the reported AUCs and cutoff values should be considered exploratory and require validation in larger, multicenter cohorts before they can be considered reliable clinical decision thresholds.

Fourth, the upper measurement limit of the PCT assay may have affected the accuracy of PCT clearance estimates if concentrations at or above this limit were reported as a capped value. Such assay ceiling effects could have influenced the apparent discriminatory performance of PCT clearance. This possibility should be considered when interpreting the observed AUC of 1.000.

Fifth, the study evaluated short-term mortality and ICU length of stay but did not assess longer-term patient-centered outcomes, such as physical functioning, cognitive status, or health-related quality of life. Additionally, death may act as a competing event for discharge alive when analyzing ICU length of stay. If this competing-risk structure is not appropriately accounted for, conventional analyses of ICU stay duration may yield incomplete or potentially misleading interpretations of the relationship between biomarkers and length of stay.

Finally, the study was observational and was not designed to determine whether protocolized serial measurement of lactate or PCT improves clinical decision-making or patient outcomes. Therefore, the observed prognostic associations do not establish clinical benefit from implementing these measurements as routine components of sepsis management. Future prospective, multicenter studies with adequate

mortality events, appropriate handling of early exclusions and competing risks, and independent validation are needed to confirm the prognostic utility and generalizability of these findings.

Strengths

This study's strengths include its prospective design, consecutive patient enrollment, predefined serial lactate measurements, longitudinal PCT assessment, and comparative evaluation of static and kinetic biomarker measures within the same cohort. The predefined sampling intervals and clearly specified clearance calculations facilitated a consistent assessment of biomarker changes in relation to 28-day mortality. However, the identified cutoff values remain exploratory and require independent validation before their clinical utility can be established.

Conclusions

Among patients with sepsis admitted to a tertiary-level medical ICU, serial lactate measurements and PCT clearance demonstrated strong apparent discriminatory performance for predicting 28-day mortality. However, the identified cutoffs are exploratory because they were derived and evaluated in the same cohort, potentially resulting in overestimated predictive performance. The findings should also be interpreted in light of the single-center design, limited number of mortality events, and potential selection bias associated with the requirement for a minimum ICU stay of 72 hours. Furthermore, the biomarkers were assessed at different time points, and their predictive performance should be interpreted accordingly. Larger, multicenter prospective studies with independent external validation are needed to establish the reproducibility and clinical utility of these thresholds before their incorporation into routine clinical decision-making.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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