ORIGINAL ARTICLE

Comparison of Trends of Procalcitonin and Neutrophil to Lymphocyte Ratio in Patients of Sepsis in Intensive Care Unit

Aparna Jayara[1], Joanne Mascarenhas[2], Bhavesh Gandhi[3], Janardan Nimbolkar[4]

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Abstract

Background: This study examines the trends of procalcitonin (PCT), neutrophil-to-lymphocyte ratio (NLR), and sequential organ failure assessment (SOFA) scores in intensive care unit (ICU) sepsis patients from different infection sources. Elevations in PCT and NLR reflect infection severity and predict sepsis prognosis. Combining them may enhance diagnostic accuracy and prognostic capabilities, despite variations in cut-off values. The study emphasizes the significance of these biomarkers in improving sepsis management and patient outcomes.

Materials and methods: This was a prospective observation study of ICU sepsis patients from different infection sources. Procalcitonin and NLR levels were measured on days 0, 2, and 4 of admission. Sequential organ failure assessment scores on these days were also analyzed. The cut-off values were obtained for predicting the prognosis of sepsis ICU patients.

Results: The study included 100 sepsis patients with an equal distribution of males and females and a mean age of 72 years. Procalcitonin showed a significant decrease over time, while NLR initially increased before decreasing on day 4, and SOFA scores showed no significant changes. Deceased patients had significantly higher PCT and SOFA scores on days 2 and 4. Receiver operating characteristic curve analysis showed promising predictive results for PCT on day 4 and SOFA scores on days 2 and 4.

Conclusion: Understanding the trends of PCT and NLR concerning the infection source can provide deeper insights into their diagnostic and prognostic capabilities. This comparative analysis of PCT, NLR, and SOFA score trends contributes to the improvement of patient outcomes through accurate assessment of sepsis severity and progression, early diagnosis, and timely intervention.

Keywords: Inflammatory markers, Intensive care unit, Neutrophil–lymphocyte ratio, Procalcitonin.

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Highlights

This study highlights the value of procalcitonin (PCT) and neutrophil-to-lymphocyte ratio (NLR) in combination in predicting the prognosis of sepsis in ICU patients.

There is variation in cut-off values observed.

Introduction

Sepsis is characterized by a life-threatening condition, a dysregulated immune response to infection, resulting in organ dysfunction and high mortality rates in the intensive care unit (ICU).[1–3] The annual sepsis incidence was found to be 276–678/1,00,000 persons globally, with case fatalities ranging from 22.5 to 26.7%.[2] To improve patient outcomes, reliable biomarkers for accurately assessing sepsis severity and progression, early diagnosis, and timely intervention are necessary. Several biomarkers are studied to predict the prognosis and mortality in sepsis or severe infection cases. C-reactive protein (CRP), PCT, serum amyloid *P*, lactate, soluble urokinase plasminogen activator receptor (suPAR), mean platelet volume (MPV), pro-adrenomedullin, NLR, red-cell distribution width (RDW), α-2 macroglobulin (A2M), ferritin, fibrinogen, haptoglobin, serum amyloid A, and tissue plasminogen activator.[3–5] Among the numerous biomarkers studied, PCT and NLR have garnered significant attention due to their potential utility in the clinical management of sepsis.[5]

Calcitonin hormone has PCT as a peptide precursor produced in response to bacterial infections and systemic inflammation. It is a valuable marker for diagnosing diseases and guiding antibiotic treatment. Procalcitonin rises sharply within 6 hours in response to bacterial sepsis and decreases as the patient recovers, remaining low in viral infections.[6] A mild increase in PCT can occur in non-infectious conditions like heart failure, cardiogenic shock, myocardial infarction, or stroke, where higher levels are linked to worse outcomes. Despite its potential as a prognostic marker for cardiovascular diseases, limited evidence supports its use in general medical emergency settings.[6] Elevated PCT levels are associated with severe bacterial infections and have been proposed as a diagnostic and prognostic marker in sepsis.[7] It can aid in risk stratification; however, it has limitations and can sometimes be outperformed by a straightforward clinical examination. It has demonstrated efficacy in distinguishing sepsis (bacterial) from other causes of systemic inflammatory response syndrome (SIRS), guiding antibiotic therapy, and predicting patient outcomes.[5,8]

[1–4]Department of Critical Care Medicine, Breach Candy Hospital Trust, Mumbai, Maharashtra, India

Corresponding Author: Aparna Jayara, Department of Critical Care Medicine, Breach Candy Hospital Trust, Mumbai, Maharashtra, India, Phone: +91 7895646823, e-mail: aparna11.jayara@gmail.com

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The neutrophil-to-lymphocyte ratio (NLR), calculated from routine complete blood counts, reflects the blood's balance between neutrophil and lymphocyte count. Its increase hallmarks of the inflammatory response in sepsis.[9] Neutrophil–lymphocyte ratio is a cost-effective and easily accessible marker that has shown promise in predicting sepsis severity, patient prognosis, and monitoring therapeutic responses.[10]

Sepsis can arise from various infection sources, including respiratory, urinary, gastrointestinal, and bloodstream infections. Each source of infection can influence the inflammatory response, and thus, the levels of biomarkers such as PCT and NLR. Understanding the trends of these biomarkers concerning the infection source could provide deeper insights into their diagnostic and prognostic capabilities.[5]

The sequential organ failure assessment (SOFA) score for sepsis includes six organ systems to evaluate the extent of a patient's organ dysfunction.[11] These systems are:

- Respiratory system: Assessed by the PaO_2/FiO_2 ratio.
- Cardiovascular system: Evaluated by measuring mean arterial pressure (MAP) or administration of vasopressors.
- Liver function: Gauged by serum bilirubin levels.
- Coagulation: Assessed using platelet count.
- Renal function: Evaluated by serum creatinine levels or urine output.
- Central nervous system: Assessed using the Glasgow coma scale (GCS).

Each parameter is scored from 0 to 4, with higher scores indicating more significant dysfunction. The total SOFA score is the sum of these individual scores, helping to predict patient outcomes and mortality risk in sepsis.[11] It is vital for predicting survival in sepsis as it quantifies organ dysfunction, directly correlating with patient outcomes. The score aids in risk stratification, guiding clinical decisions, resource allocation, and treatment prioritization. Studies indicate that higher SOFA scores are associated with increased mortality, and understanding organ dysfunction severity allows for tailored, potentially more aggressive treatments.[12,13] The SOFA score is a crucial tool for assessing organ dysfunction, predicting outcomes, and guiding sepsis management.[14]

While PCT and NLR have individually shown potential as biomarkers for sepsis, their comparative trends and combined utility in the ICU setting still need to be explored. Understanding these markers' relationship and predictive value could enhance diagnostic accuracy, enable timely therapeutic interventions, and improve clinical outcomes for septic patients. Tracking SOFA scores over time helps monitor disease progression, with increasing scores often linked to higher mortality rates. The current study aimed to compare the trends of PCT and NLR ratio and SOFA score in sepsis patients admitted to the ICU, considering different sources of infection. By analyzing their trajectories and correlations with clinical outcomes, we seek to elucidate the potential complementary roles of PCT and NLR in sepsis management. This study shall provide valuable insights into the effectiveness of these biomarkers in guiding clinical decision-making and optimizing patient care in critical settings.

Materials and Methods

In sepsis patients admitted to the ICU, the prospective observation study was conducted in Breach Candy Hospital, Mumbai, from January 2020 to January 2021. Individuals aged >18 years, fulfilling sepsis criteria according to Sepsis-3 definition,[12] and giving consent for participation were included in the study. Individuals with the following conditions were excluded: anticipated life expectancy <48 hours; not able to be assessed for delirium (due to reasons like severe hearing loss, visual impairment, unable to communicate, severe mental retardation, etc.); were treated with glucocorticoids, either short-duration high-dose (e.g., > 5 days ≥1 mg/kg/day) or long-duration low-dose (e.g., >20 days ≥ 0.1 mg/kg/day); known or potential immunodeficiency. Sample size was estimated with the formula $n = [(Z_{\alpha/2})^2 \times \{\text{sensitivity} \times (1-\text{Sensitivity})\}]/L^2$ and found to be 100. An Institutional Ethics Committee (IEC) approval was obtained for the study. After obtaining written informed consent, information on each patient, including sociodemographic characteristics and clinical parameters, was obtained. Blood samples were collected at ICU admission (day 0), after 48 hours of admission (day 2), and after 96 hours of admission (day 4). Blood parameter values, such as total WBC count, differential WBC count, and PCT were obtained. Cultures of various samples, (e.g., abdominal fluid, bile, blood, feces, sputum, and urine) of all patients were sent to the laboratory to identify potential sources of sepsis. PCT, NLR, and SOFA score values were assessed on days 0, 2, and 4 of admission. The appropriate management, including empirical antibiotic therapy of all the patients, was immediately started from day 0. Additionally, they were followed up on ICU stay duration, the status of invasive mechanical ventilation, and the outcome.

Data Collection and the Statistical Analysis

The data collected were entered and cleaned in Microsoft Excel v2021 (©Microsoft Incorporation) and analyzed in SPSS v21 (©IBM Incorporation). Central tendency measures for continuous data (mean, standard deviation, range, etc.) and categorical data (median, interquartile range, percentage, etc.) were calculated. The normality of the continuous data was checked with the Shapiro–Wilk test. Correlation between different variables (ICU stay and age with NLR, PCT, and SOFA score) was calculated using Spearman's rank correlation test. Mann–Whitney *U* test was used to compare the means. Friedman test was used to compare the means of variables on different timelines. The receiver operating characteristic (ROC) curve was used to find the cut-off point of PCT, NLR, and SOFA score to predict mortality and ventilation requirements. An area under curve (AUC) value of >0.8 for ROC was considered good. Their association was analyzed using Chi-square test. A p-value of < 0.05 was considered significant for statistical significance.

Results

Baseline Patient Characteristics

Out of 100 patients studied, 41 (41%) were females and 51 (51%) were males. The overall mean age was 72 ± 10.90 years, the median was 73 years, and has a non-normal distribution (Shapiro–Wilk test, $p < 0.01$). In most cases ($n = 42$, 42%), the sepsis source was the lungs, followed by the urinary tract ($n = 25$, 25%), gastrointestinal region ($n = 13$, 13%), blood ($n = 9$, 9%), skin-soft tissue ($n = 5$, 5%) and urinary tract and lower respiratory tract ($n = 3$, 3% each). Most of the patients ($n = 63$, 63%) were treated with meropenem. The mean ICU stay was 20.99 ± 15.06 days with a median of 17 days. Out of 100 patients, invasive mechanical ventilation was needed in 47 (47%). A total of 14 (14%) patients died, whereas 86 (86%) patients survived from the sepsis.

Bacteriological Source of Infection

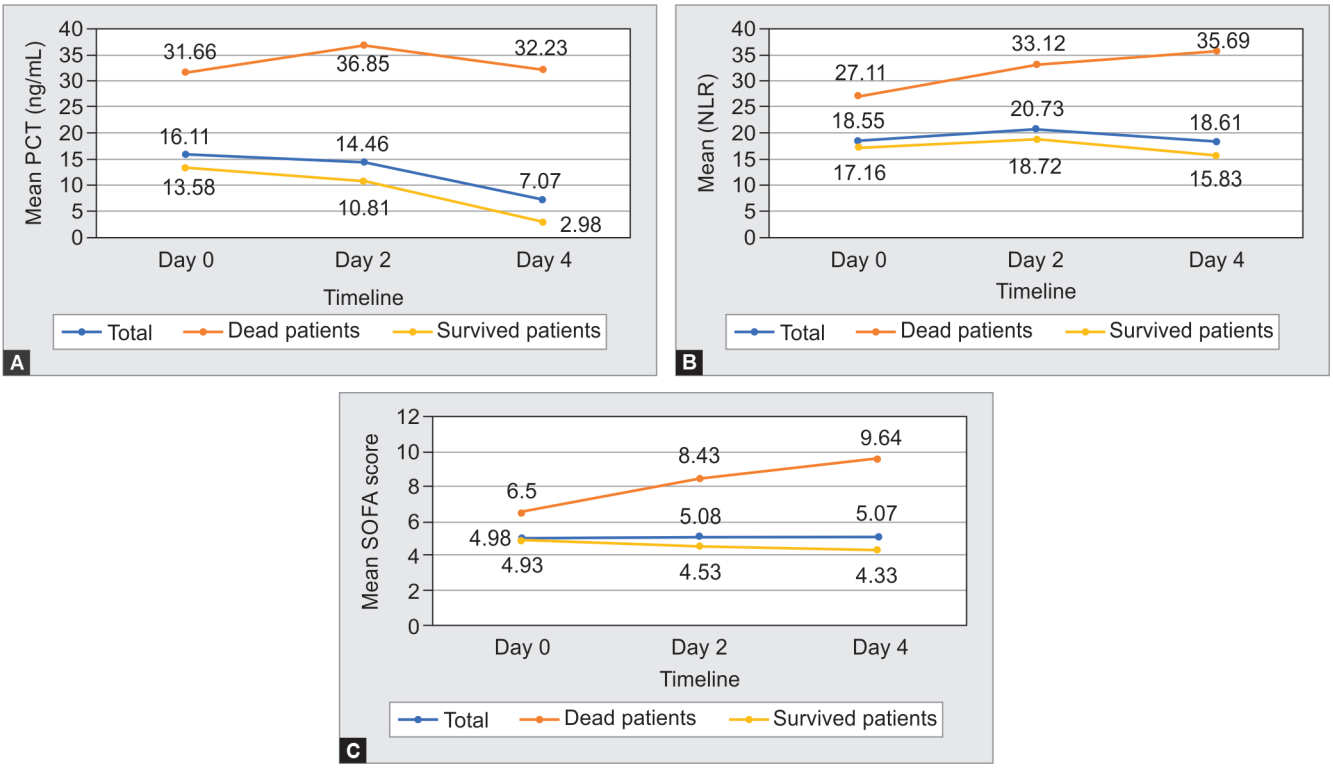
Out of 100 patients, culture reports of 80 patients were obtained, out of which 23 samples showed *Klebsiella* sp. as prominent growth. Eight samples had *Escherichia coli* growth. Three samples had

Methicillin-resistant *Staphylococcus aureus* (MRSA) growth. Bacteria species could not be identified in 27 samples. Four samples did not yield any growth.

PCT, NLR, and SOFA Score

All these parameters were noted respectively on day 0, 2, and 4. The mean PCT value showed a statistically significant decrease from day 0 (16.11 ± 41.85) to day 2 (14.46 ± 36.74) to day 4 (7.07 ± 23.08) (Friedman test, $\chi^2 = 9.654$, $p = 0.008$) (Fig. 1A). Neutrophil–lymphocyte ratio values increased from day 0 (18.55 ± 18.71) to day 2 (20.73 ± 19.61) and then decreased on day 4 (18.61 ± 23.30) being the lowest, with no statistically significant difference (Friedman test, $\chi^2 = 5.913$, $p = 0.052$) (Fig. 1B). Similarly, SOFA score increased from day 0 (4.98 ± 2.53) to day 2 (5.08 ± 2.79) and then decreased on day 4 (5.07 ± 3.45) without any statistically significant difference (Friedman test, $\chi^2 = 4.869$, $p = 0.088$) (Fig. 1C).

PCT, NLR, and SOFA scores were calculated separately for dead and survived patients. According to Mann–Whitney *U* test, PCT at day 2 ($Z = -3.344$, $p = 0.001$), PCT at day 4 ($Z = -4.512$, $p < 0.001$), SOFA score at day 2 ($Z = -4.144$, $p < 0.001$) and SOFA score at day 4 ($Z = -4.558$, $p < 0.001$) were statistically significantly higher in dead patients than that of survived patients (Table 1). A detailed



Figs 1A to C: Line trend showing progress of PCT, NLR, and SOFA scores. (A) Line trend showing PCT values (ng/mL); (B) Line trend showing NLR values; (C) Line trend showing SOFA scores

Table 1: Descriptive analysis of baseline patient characteristics

						Classification				
		Total patients (n = 100)				*Dead patients (n = 14)*		*Survived patients (n = 86)*		*Comparison*
Sr. No.	*Variable*	*Mean*	*Standard deviation*	*Median*	*Normality by Shapiro–Wilk test*	*Mean*	*Standard deviation*	*Mean*	*Standard deviation*	*p-value (by Mann–Whitney U test*
1	Age (years)	72.00	10.90	73.00	Non-normal	72.36	10.92	71.94	10.96	0.968
2	ICU stay (days)	20.99	15.06	17.00	Non-normal	27.00	22.93	20.01	13.29	0.640
3	PCT at day 0	16.11	41.85	2.06	Non-normal	31.66	55.33	13.58	39.05	0.122
4	PCT on day 2	14.46	36.74	2.20	Non-normal	36.85	53.23	10.81	32.28	0.001
5	PCT on day 4	7.07	23.08	1.11	Non-normal	32.23	55.10	2.98	5.91	<0.001
6	NLR at day 0	18.55	18.71	13.85	Non-normal	27.11	36.11	17.16	13.95	0.548
7	NLR on day 2	20.73	19.61	13.04	Non-normal	33.12	28.81	18.72	17.08	0.111
8	NLR on day 4	18.61	23.30	8.32	Non-normal	35.69	35.91	15.83	19.47	0.103
9	SOFA score on day 0	4.98	2.53	4.00	Non-normal	6.50	4.20	4.93	2.08	0.144
10	SOFA score on day 2	5.08	2.79	5.00	Non-normal	8.43	4.18	4.53	2.06	<0.001
11	SOFA score on day 4	5.07	4.00	3.44	Non-normal	9.64	4.41	4.33	2.62	<0.001

Table 2: Correlation table of age and ICU stay with PCT, NLR, and SOFA score ($n = 100$)

		Correlation with age (years)			*Correlation with ICU stay (days)*		
Sr. No.	*Variable*	*Spearman's ρ*	*p-value*	*Interpretation*	*Spearman's ρ*	*p-value*	*Interpretation*
1	PCT at day 0	0.122	0.228	Very weak positive monotonic	–0.175	0.081	Very week negative monotonic
2	PCT on day 2	0.077	0.444	Very weak positive monotonic	0.031	0.758	Very weak positive monotonic
3	PCT on day 4	–0.149	0.139	Very week negative monotonic	0.155	0.124	Very weak positive monotonic
4	NLR at day 0	0.093	0.358	Very weak positive monotonic	–0.051	0.612	Very week negative monotonic
5	NLR on day 2	0.236	0.018	Weak positive monotonic	0.084	0.406	Very weak positive monotonic
6	NLR on day 4	–0.024	0.814	Very week negative monotonic	0.064	0.529	Very weak positive monotonic
7	SOFA score on day 0	–0.175	0.081	Very week negative monotonic	–0.085	0.399	Very week negative monotonic
8	SOFA score on day 2	0.012	0.903	Very weak positive monotonic	0.072	0.477	Very weak positive monotonic
9	SOFA score on day 4	–0.019	0.853	Very week negative monotonic	0.329	0.001	Weak positive monotonic
10	Age (years)	–	–	–	–0.287	0.004	Weak negative monotonic
11	ICU stay (days)	–0.287	0.004	Weak negative monotonic	–	–	–

comparison of all values is given in Table 1. The trend of PCT, NLR, and SOFA scores in dead and survived patients is depicted in Figure 1.

Correlation Analysis

The correlation between age and ICU stay with PCT, NLR, and SOFA score was calculated using Spearman's rank test. The age of the patients was found to be statistically significantly correlated with NLR at day 2 ($\rho = 0.236$, $p = 0.018$, weak positive monotonic) and ICU stay ($\rho = -0.287$, $p = 0.004$, weak negative monotonic). Intensive care unit stay had a statistically significant correlation with SOFA score at day 4 ($\rho = 0.329$, $p = 0.001$, weak positive monotonic). All detailed correlation analyses are given in Table 2. All scatter plots are depicted in Figure 2.

Regression Analysis

The logistic regression model was performed to ascertain the effects of PCT, NLR, and SOFA scores on the need for invasive mechanical ventilation and the outcome. In case of outcome, that is, survival, PCT at day 2 (OR = 0.988, $p = 0.036$); PCT at day 4 (OR = 0.894, $p = 0.008$); NLR at day 2 (OR = 0.974, $p = 0.025$); NLR at day 4 (OR = 0.972, $p = 0.004$); SOFA score at day 0 (OR = 0.780, $p = 0.018$); SOFA score at day 2 (OR = 0.563, $p < 0.001$) and SOFA score at day 4 (OR = 0.625, $p < 0.001$) yielded statistically significant regression models. Details of logistic regression are given in Table 3.

ROC Curve

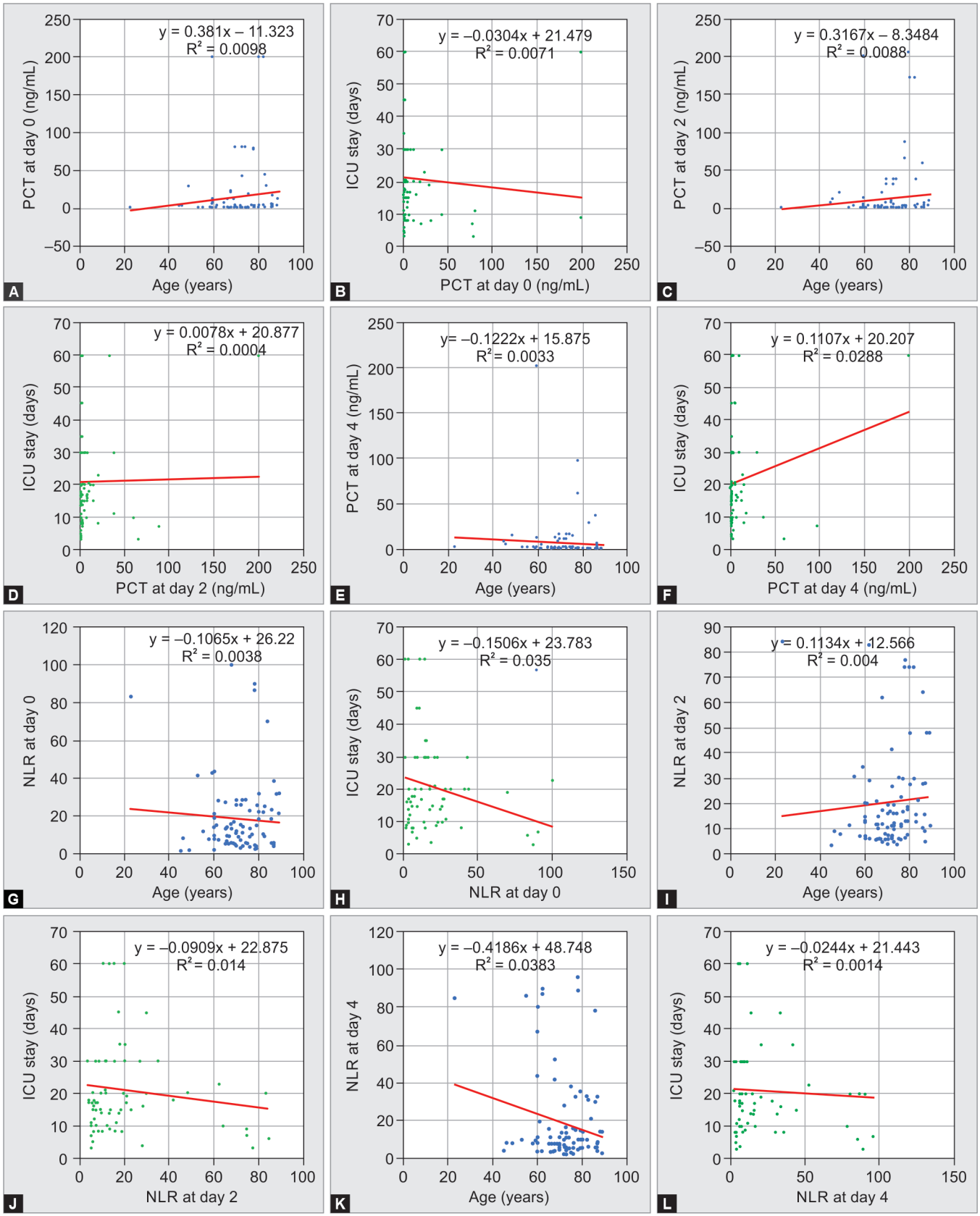
Receiver operating characteristic curve was used to find cut-off values of PCT, NLR, and SOFA score to estimate the outcome and need for invasive mechanical ventilation. When these variables are calculated against the outcome, PCT at day 4 (AUC = 0.886, $p < 0.001$), SOFA score at day 2 (AUC = 0.858, $p < 0.001$), and SOFA score at day 4 (AUC = 0.888, $p < 0.001$) yielded promising results with better sensitivity and specificity. Similarly, when calculated with the need for machinal ventilation, only the SOFA score at day 4 (AUC = 0.825, $p < 0.001$) yielded promising results with better sensitivity and specificity. All other ROC curves yielded either poor or negligible AUCs. All ROC curves are depicted in Figure 3, and their details are given in Table 4.

Association Analysis

As per the published standard literature, PCT, NLR, and SOFA score values were categorized into two groups, taking 0.25, 3, and 11 as their respective cut-off values.[15–17] According to the Chi-square test, a high SOFA score on day 4 was statistically significantly associated with mortality ($\chi^2 = 14.705$, $p = 0.003$). The rest of the variables could not yield a significant association with mortality. Details of the association are given in Table 5.

Discussion

Sepsis is a severe condition and is one of the most frequent causes of mortality globally. It is a prevalent, costly, and often deadly condition, causing as many annual deaths as acute myocardial infarction in the United States.[18] According to WHO key facts, for every 1,000 patients, 15 patients are expected to develop sepsis.[19] The elderly population, pregnant women, neonates, hospitalized patients, patients in the ICU, immunocompromised individuals, and those with chronic medical illness are at higher risk of sepsis development.[20,21] The present study is conducted in sepsis patients admitted to the ICU, with the majority of cases ($n = 42$, 42%) where the sepsis source was the lungs, followed by the urinary tract ($n = 25$, 25%), gastrointestinal region ($n = 13$, 13%), blood ($n = 9$, 9%), skin-soft tissue ($n = 5$, 5%) and urinary tract and lower respiratory tract ($n = 3$, 3% each). Microbiological culture has long


y = 0.381x – 11.323
R² = 0.0098
PCT at day 0 (ng/mL)
Age (years)
A
y = –0.0304x + 21.479
R² = 0.0071
ICU stay (days)
PCT at day 0 (ng/mL)
B
y = 0.3167x – 8.3484
R² = 0.0088
PCT at day 2 (ng/mL)
Age (years)
C
y = 0.0078x + 20.877
R² = 0.0004
ICU stay (days)
PCT at day 2 (ng/mL)
D
y= –0.1222x + 15.875
R² = 0.0033
PCT at day 4 (ng/mL)
Age (years)
E
y = 0.1107x + 20.207
R² = 0.0288
ICU stay (days)
PCT at day 4 (ng/mL)
F
y = –0.1065x + 26.22
R² = 0.0038
NLR at day 0
Age (years)
G
y = –0.1506x + 23.783
R² = 0.035
ICU stay (days)
NLR at day 0
H
y = 0.1134x + 12.566
R² = 0.004
NLR at day 2
Age (years)
I
y = –0.0909x + 22.875
R² = 0.014
ICU stay (days)
NLR at day 2
J
y = –0.4186x + 48.748
R² = 0.0383
NLR at day 4
Age (years)
K
y = –0.0244x + 21.443
R² = 0.0014
ICU stay (days)
NLR at day 4
L

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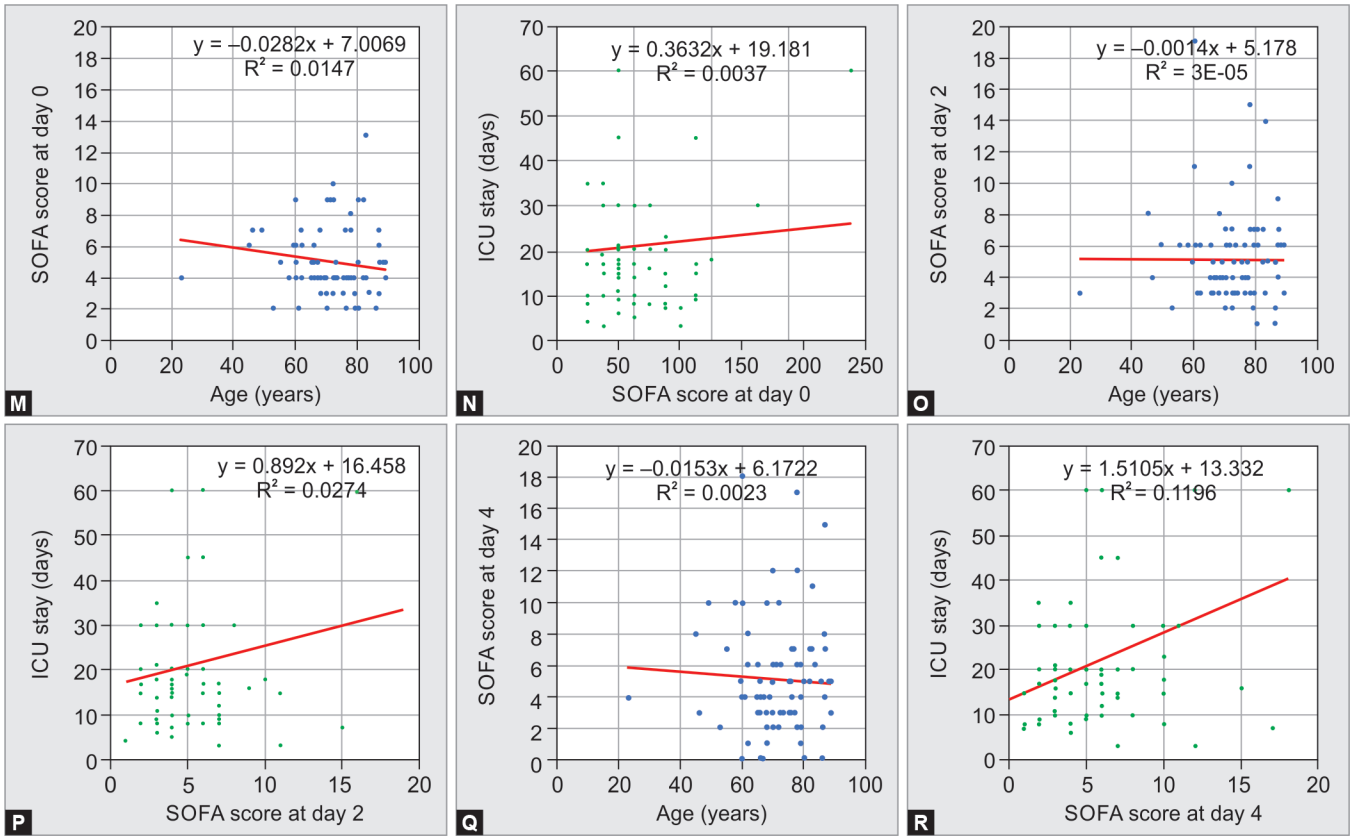


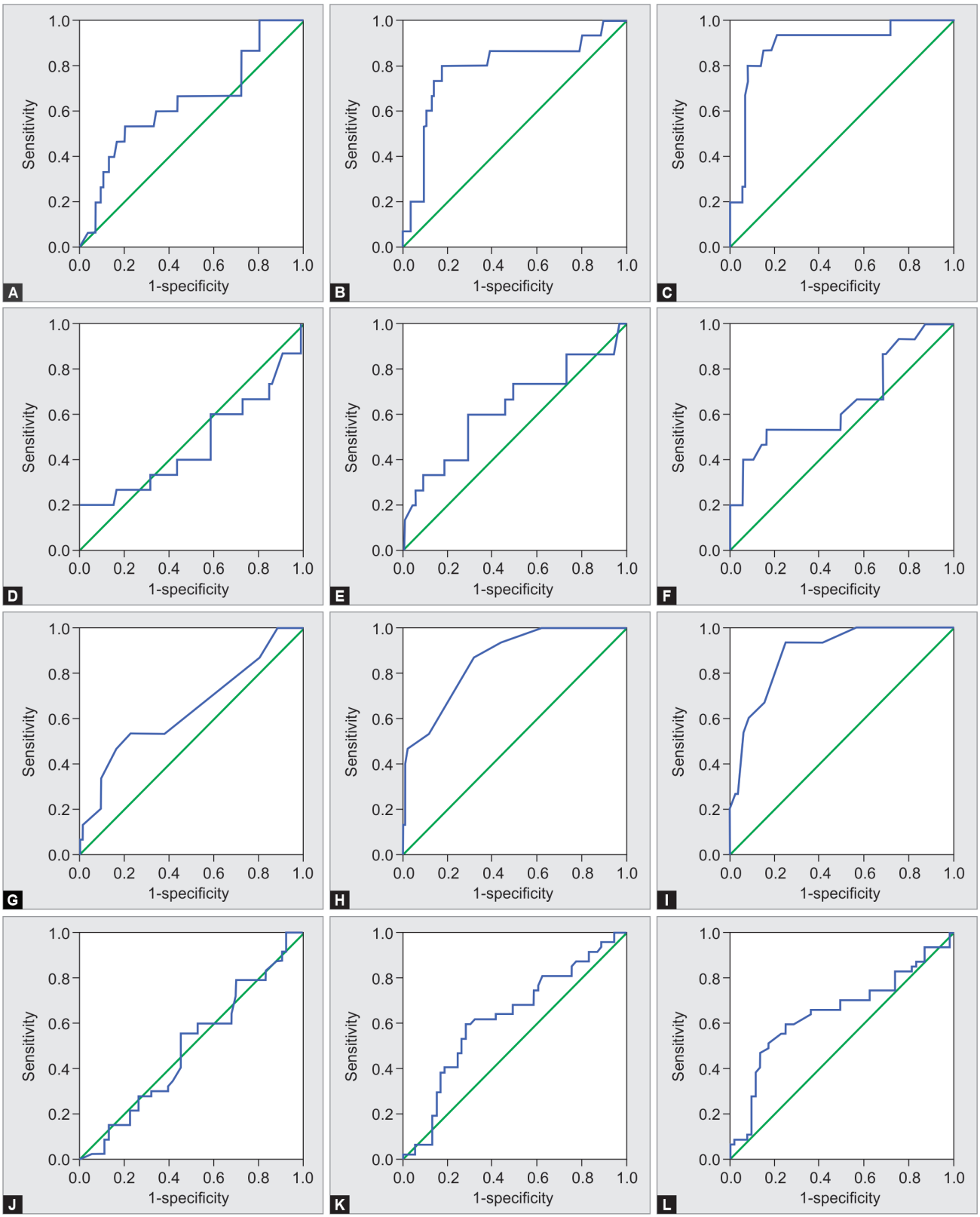
Figs 2A to R: Scatter plots showing correlations between different variables. (A) Correlation between age and PCT at day 0; (B) Correlation between ICU stay and PCT at day 0; (C) Correlation between age and PCT at day 2; (D) Correlation between ICU stay and PCT at day 2; (E) Correlation between age and PCT at day 4; (F) Correlation between ICU stay and PCT at day 4; (G) Correlation between age and NLR at day 0; (H) Correlation between ICU stay and NLR at day 0; (I) Correlation between age and NLR at day 2; (J) Correlation between ICU stay and NLR at day 2; (K) Correlation between age and NLR at day 4; (L) Correlation between ICU stay and NLR at day 4; (M) Correlation between age and SOFA score at day 0; (N) Correlation between ICU stay and SOFA score at day 0; (O) Correlation between age and SOFA score at day 2; (P) Correlation between ICU stay and SOFA score at day 2; (Q) Correlation between age and SOFA score at day 4; (R) Correlation between ICU stay and SOFA score at day 4

Table 3: Regression analysis between outcome and need for mechanical ventilation with PCT, NLR, and SOFA score ($n = 100$)

		Dependent variable: final outcome					
		Model summary			*95% Confidence interval*		*p-value*
Sr. No.	*Independent variable*	χ^2	*p-value*	*Odds ratio*	*Lower*	*Upper*	*(regression)*
1	PCT at day 0	11.696	0.165	0.993	0.983	1.003	0.186
2	PCT on day 2	23.443	0.003	0.998	0.977	0.999	0.036
3	PCT on day 4	32.426	<0.001	0.894	0.823	0.971	0.008
4	NLR at day 0	9.713	0.286	0.979	0.956	1.003	0.086
5	NLR on day 2	8.358	0.399	0.974	0.951	0.997	0.025
6	NLR on day 4	8.584	0.379	0.972	0.953	0.991	0.004
7	SOFA score on day 0	7.443	0.190	0.780	0.634	0.958	0.018
8	SOFA score on day 2	2.875	0.719	0.563	0.410	0.775	<0.001
9	SOFA score on day 4	7.079	0.314	0.625	0.499	0.782	<0.001

been regarded as the definitive method for diagnosing sepsis but is a time-intensive process with often low success rates, particularly when patients have been pretreated with antibiotics or when contamination occurs during sample collection. Out of 100 patients in the current study, culture reports were obtained for 80. Among these, 23 samples showed *Klebsiella* sp. growth, 8 had *Escherichia coli*, and 3 had MRSA.

In the present study, PCT, NLR, and SOFA values were assessed at days 0, 2, and 4 of admission to predict and compare the prognosis of sepsis in terms of mortality. In contrast, various studies assessed PCT, NLR, CRP, platelet indices, and other biomarkers as prognostic markers of suspected infections or sepsis in different settings.[5,6,8,22–27] Bloos et al. studied PCT to predict mortality in ICU patients with pneumonia, while Leroux et al. used PCT to predict



Figs 3A to L: ROC curve of various variables at different timelines. (A) ROC curve between PCT at day 0 and mortality; (B) ROC curve between PCT at day 2 and mortality; (C) ROC curve between PCT at day 4 and mortality; (D) ROC curve between NLR at day 0 and mortality; (E) ROC curve between NLR at day 2 and mortality; (F) ROC curve between NLR at day 4 and mortality; (G) ROC curve between SOFA score at day 0 and mortality; (H) ROC curve between SOFA score at day 2 and mortality; (I) ROC curve between SOFA score at day 4 and mortality; (J) ROC curve between PCT at day 0 and need of mechanical ventilation; (K) ROC curve between PCT at day 2 and need of mechanical ventilation; (L) ROC curve between PCT at day 4 and need of mechanical ventilation

Table 4: ROC curve statistics of values of PCT, NLR, and SOFA score to estimate outcome and need for invasive mechanical ventilation

ROC curve of PCT, NLR, and SOFA score to estimate the outcome									
					95% Confidence interval				
Sr. No.	*Variable*	*Area under curve (AUC)*	*Standard error*	*p-value*	*Upper bound*	*Lower bound*	*Sensitivity*	*Specificity*	*Cut-off value*
1	PCT at day 0	0.642	0.082	0.081	0.481	0.802	0.533	0.788	4.68
2	PCT on day 2	0.789	0.072	<0.001	0.648	0.931	0.800	0.788	4.51
3	PCT on day 4	0.886	0.049	<0.001	0.791	0.982	0.800	0.859	4.65
4	NLR at day 0	0.467	0.094	0.685	0.282	0.652	0.600	0.412	10.96
5	NLR on day 2	0.627	0.087	0.118	0.456	0.798	0.600	0.682	18.33
6	NLR on day 4	0.660	0.085	0.049	0.493	0.826	0.533	0.824	20.25
7	SOFA score on day 0	0.645	0.084	0.075	0.480	0.809	0.533	0.776	5.5
8	SOFA score on day 2	0.858	0.047	<0.001	0.766	0.950	0.867	0.682	5.5
9	SOFA score on day 4	0.888	0.039	<0.001	0.811	0.965	0.933	0.753	5.5
ROC curve of PCT, NLR, and SOFA score to estimate the need for invasive mechanical ventilation									
					95% Confidence interval				
Sr. No.	*Variable*	*Area under curve (AUC)*	*Standard error*	*p-value*	*Upper bound*	*Lower bound*	*Sensitivity*	*Specificity*	*Cut-off value*
1	PCT at day 0	0.490	0.058	0.860	0.376	0.604	0.553	0.547	2.06
2	PCT on day 2	0.622	0.057	0.036	0.510	0.733	0.596	0.698	2.72
3	PCT on day 4	0.649	0.057	0.010	0.537	0.761	0.596	0.755	1.36
4	NLR at day 0	0.468	0.059	0.583	0.353	0.583	0.255	0.798	25.43
5	NLR on day 2	0.519	0.060	0.743	0.402	0.636	0.298	0.887	29.48
6	NLR on day 4	0.593	0.057	0.111	0.480	0.705	0.447	0.755	12.13
7	SOFA score on day 0	0.560	0.058	0.302	0.446	0.674	0.298	0.868	6.5
8	SOFA score on day 2	0.752	0.049	<0.001	0.656	0.848	0.745	0.698	4.5
9	SOFA score on day 4	0.825	0.042	<0.001	0.742	0.907	0.787	0.774	4.5

Table 5: Association of outcome (death or survival) with different variables ($n = 100$)

Sr. No.	*Variable*	χ^2	*p-value*	*Cramer's V*	*Strength of association**
1	PCT at day 0	2.012	0.218#	0.142	Weak
2	PCT on day 2	1.416	0.366#	0.119	Weak
3	PCT on day 4	1.809	0.236#	0.134	Weak
4	NLR at day 0	1.327	0.589#	0.115	Weak
5	NLR on day 2	It cannot be computed			
6	NLR on day 4	1.416	0.366#	0.119	Weak
7	SOFA score on day 0	2.197	0.262#	0.148	Weak
8	SOFA score on day 2	7.125	0.051#	0.267	Moderate
9	SOFA score on day 4	14.705	0.003#	0.383	Moderate

#Fisher Exact test is applied. *Grades of Cramer's V: 0.00–0.10 = Negligible; 0.10–0.20 = Weak; 0.20–0.40 = Moderate; 0.40–0.60 = Relatively strong; 0.60–0.80 = Strong; 0.80–1.00 = Very strong

the outcome of suspected infections.[8,22] Kelly et al. conducted a prospective cohort study of 69 surgical ICU patients with suspected sepsis and observed the levels of different biomarkers at baseline and then at 24, 48, and 72 hours.[5] Sari et al. studied NLR as a predictive marker for treating sepsis in ICU patients by comparing NLR and CRP as inflammatory markers and APACHE II and SOFA scores as severity markers in patients with and without septic shock, both survivors and non-survivors.[28] Kaushik et al. analyzed NLR as a diagnostic and prognostic marker for sepsis.[29]

ROC curve was used to find cut-off values of PCT, NLR, and SOFA score to estimate the outcome and the need for invasive mechanical ventilation in the current study. When these variables are calculated against the outcome, PCT at day 4 (AUC = 0.886, $p < 0.001$), SOFA score at day 2 (AUC = 0.858, $p < 0.001$), and score at day 4 (AUC = 0.888, $p < 0.001$) yielded promising results with better sensitivity and specificity. Similarly, when calculated with the need for mechanical ventilation, only the SOFA score at day 4 (AUC = 0.825, $p < 0.001$) yielded promising results with better sensitivity and specificity. The AUC provides a comprehensive measure of sensitivity and specificity, encapsulating the intrinsic accuracy of diagnostic tests.[30] The AUC must be considered while interpreting the ROC curve. However, in the present study, all other ROC curves yielded either poor or negligible AUCs. In the ROC curve for sepsis cases studied by Kaushik et al., the NLR on day 1 was significantly higher compared with controls, with an AUC of 0.911, indicating high diagnostic accuracy ($p < 0.001$, sensitivity 87.5%, specificity 90% at NLR1 $\geq$ 3.3).

While NLR1 did not differ significantly between survivors (group I) and non-survivors (group II), the late-phase NLR on day 5 (NLR5) was significantly lower in survivors. The AUC for NLR5 was 0.732, showing moderate diagnostic accuracy ($p < 0.045$, sensitivity 73%, specificity 71% at NLR5 of 8.3).[29] Gürol et al. investigated PCT as a benchmark for predicting sepsis and septic shock, comparing its effectiveness with NLR, CRP, and leukocyte counts through ROC analysis. They found that NLR was the most reliable indicator for sepsis.[31] An NLR of 5 or higher indicated sepsis, necessitating treatment and infection follow-up in critically ill patients.[31]

Kelly et al. found that considerably higher PCT levels and lower A2M levels in bacterial sepsis at three different timelines. A negative predictive value of 75% was obtained by the combination of A2M (at baseline) and PCT (at 72 hours), which effectively distinguished sepsis of bacterial origin from other SIRS in suspected sepsis SICU patients.[5]

Jain et al. examined the relationship between the SOFA score and ICU mortality, finding that higher SOFA scores on the 1st, 3rd, and 5th days of ICU stay were associated with increased ICU mortality. However, they also found that SOFA scores on the 7th and 9th days did not correlate with mortality.[32]

ROC curve analysis indicated that PCT effectively distinguished survivors and non-survivors in the overall cohort, with an AUC of 0.75 in Sager et al.[6] They also observed the best results in patients with metabolic (AUC: 0.85) and cardiovascular diseases (AUC: 0.82). Including PCT in the quick sequential organ failure assessment (qSOFA) score significantly improved its prognostic accuracy, increasing the AUC from 0.61 to 0.76 ($p < 0.001$).[6]

Takada et al. conducted a study to evaluate the inflammatory markers in sepsis, that is, CRP, NLR, MPV, and RDW.[3] All markers except CRP showed added predictive value to vital signs.[3] Assessing the additional value of lactate in comparison to the studied inflammatory markers remains a compelling area for further research. Additionally, among newly developed markers, mid-regional pro-adrenomedullin has been shown to enhance the predictive accuracy of qSOFA in older patients with infectious conditions.[4] Zahorec found that the NLR is easily measurable and correlates better with sepsis severity and 28-day mortality than neutrophilia, lymphopenia, and the overall clinical course.[27]

Strength and Limitation of the Study

This study demonstrates that both PCT and NLR are valuable biomarkers in the diagnosis and prognosis of sepsis in ICU patients. Each marker offers unique insights into the inflammatory and infectious processes associated with the condition. Combining these biomarkers may enhance the accuracy of sepsis management and improve patient outcomes. However, in the present study, the sample size was limited, and other biomarkers were not explored.

Conclusion

This study shows that combining PCT and NLR is promising for predicting sepsis prognosis in ICU patients. It highlights the need for standardized cut-off values.

Orcid

Aparna Jayara https://orcid.org/0000-0002-3664-5551
Joanne Mascarenhas https://orcid.org/0000-0002-7371-8289
Bhavesh Gandhi https://orcid.org/0000-0003-3282-4007
Janardan Nimbolkar https://orcid.org/0000-0001-7131-3600

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