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Predictive value of neutrophil-to-lymphocyte ratio in in-hospital mortality in sepsis patients: A cross-sectional study

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ABSTRACT

Objective: To explore the predictive value of neutrophil-to-lymphocyte ratio (NLR) in in-hospital mortality in sepsis patients.

Methods: A prospective observational cross-sectional study was conducted on 100 patients with septicemia. The data about the patient's demography, medical history, general examination including pulse rate, blood pressure, *etc.*, use of vasopressor support, need for renal replacement therapy, mechanical ventilation, outcome, and lab parameters including total lymphocyte count with neutrophil-to-lymphocyte ratio were recorded. And parameters between survivals and non-survivals were compared.

Results: Out of 100 patients, 80% were from rural backgrounds. Most patients were 50 to 59 years old. 26 Patients were dead. The patients in the nonsurvivor group were older and more had a history of diabetes mellitus when compared with the survivor group. The non-survivor group had a higher NLR, APACHE II, and SOFA score.

Conclusions: NLR is a readily available parameter and can be used as a good prognostic indicator for mortality in sepsis patients.

KEYWORDS: Neutrophil-to-lymphocyte ratio; Sepsis; Intensive Care Unit; Mortality; APACHE score; SOFA score

1. Introduction

Sepsis is the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; (2) heart rate > 90 beats per minute; (3) respiratory rate >20 breaths per minute or $\text{PaCO}_2 < 32$ mmHg, and (4) white blood count $>12000/\text{mm}^3$, $<4000/\text{mm}^3$ or $>10\%$ immature

(band) forms[1]. Sepsis is one of the major causes of deteriorating medical conditions and death of patients admitted to intensive care units. The Global Burden of Disease study estimated that there were 48.9 million sepsis cases worldwide in 2017, which led to 11.0 million sepsis-related deaths (19.7% of all global deaths) that same year[2].

Neutrophil-to-lymphocyte ratio (NLR) is a very easily available, cost-effective parameter, in the developing country like India. It can be used as a prognostic indicator for disease mortality. It can be easily calculated from neutrophils and lymphocytes, from the complete blood count report even in remote areas. The objective of the study was to evaluate the predictive value of NLR in sepsis-related in-hospital mortality. We conducted a cross-sectional study and calculated NLR on day 1, day 3, and day 5, in patients with septicemia.

Significance

It is difficult to assess mortality in sepsis patients in resource-limited settings and countries like India. Our research found that neutrophil-to-lymphocyte ratio was elevated in sepsis patients and it can be used as a prognostic marker to assess mortality of sepsis patients.

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2. Patients and methods

A prospective cross-sectional was conducted in the Government Medical College and associated group of hospitals, Kota, Rajasthan from July 2023 to December 2023.

2.1. Ethical approval statements

The ethical clearance was taken from the institutional ethical committee of Government Medical College, Kota with clearance number (Acad/Ethical Clearance/2023/41).

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Patients aged older than 10 years and younger than 90 years; (2) at least one organ system failure that is acute and associated with septicemia; (3) confirmed foci of infection.

Patients aged younger than 10 years and older than 90 years, immunocompromised patients, patients with chronic corticosteroid treatment, pregnant patients, and patients not giving consent for the study were excluded from the study.

2.3. Methodology

The data about the patient's demography including age, sex, and residence were collected. History of smoking/alcohol, comorbidities, the main site of infection, and previous history of anti-hypertensive medication were also collected. General examinations including pulse rate, blood pressure, respiratory rate, and temperature, were performed. The use of vasopressor support, the need for renal replacement therapy, and mechanical ventilation, APACHE score, SOFA score, and $\text{PaO}_2/\text{FiO}_2$ and lab parameters including serum urea, creatinine, liver function test, serum calcium, serum uric acid, C reactive protein, serum electrolytes, and NLR were recorded. And parameters between survivals and non-survivals were compared.

2.4. Statistical analysis

Data analysis was conducted using SPSS 25.0 software. Normally distributed measurement data were summarized with the mean and standard deviation (SD) and analyzed using the independent sample *t*-test. For measurement data that were not normally distributed, the median and interquartile range were used for presentation and analyzed using the Mann-Whitney *U* test. Categorical data were analyzed using either the chi-square test or Fisher's exact test.

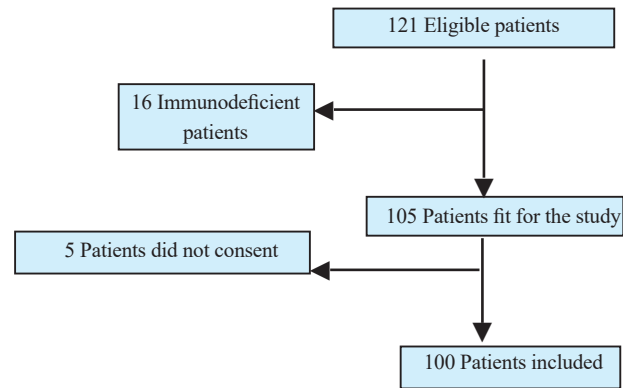


Figure 1. The study flowchart.

3. Results

A total of 121 patients were eligible for the study, out of them 16 patients were found to have chronic immunodeficiency disease and 5 patients did not consent to the study (Figure 1).

Out of 100 patients, 50 were male and 50 were females. The majority of them (80%) were from rural backgrounds. Most patients were 50 to 59 years, followed by 60 to 69 years. 48% Of them were chronic smokers and 22% were alcoholics. Comorbidities were present in 52%. Stroke and malignancy were the most common.

The most common infection site was the lung (58%) followed by urinary tract infection (18%), and abdominal infection (8%). 20% Of them were on anti-hypertensive medication, regularly. 26% Of patients were presented with tachycardia, 4% with bradycardia and 70% patients were with normal heart rate. The blood pressure of 24% of patients rose during admission. 22% Had tachypnea, and 78% had with normal respiratory rate. Only 5% of patients were febrile. 37% Of patients required ICU admission, and 63% of patients were managed in the wards only. Vasopressor support was needed in 16% of patients to manage blood pressure. After admitting into the ICU, 21% (21/100) of patients required ventilator support. And 3 (3%) patients required renal replacement therapy.

Out of 100 patients with septicemia, 66 patients survived and were discharged, 8 patients were referred to a higher center, and 26 patients died (Table 1).

In our study, it was found that patients in the nonsurvivor group were older than the survivor group ($P=0.02$). More patients had diabetes mellitus in the nonsurvivor group ($P<0.01$). The non-survivor group had a higher NLR, APACHE II, and SOFA score (Table 2).

Table 1. Patient characteristics (n=100, n, %).

Variables	n (%)
Age (years)	
10-19	6 (6)
20-29	12 (12)
30-39	8 (8)
40-49	10 (10)
50-59	30 (30)
60-69	16 (16)
70-79	14 (14)
80-89	2 (2)
≥ 90	2 (2)
Male	50 (50)
Residence	
Rural	80 (80)
Urban	20 (20)
Smoking	
Yes	48 (48)
No	52 (52)
Alcoholics	
Yes	22 (22)
No	78 (78)
Comorbidities	
Hypertension	6 (6)
Chronic obstructive airway disease	12 (12)
Diabetes mellitus	8 (8)
Coronary artery disease	10 (10)
Stroke	30 (30)
Malignancy	16 (16)
Rheumatoid arthritis	14 (14)
Asthma	2 (2)
Common infection sites	
Lung	58 (58)
Urinary tract	18 (18)
Abdomen	8 (8)
Anti-hypertensive medications	
Yes	20 (20)
No	80 (80)
Increased blood pressure	24 (24)
Abnormal heart rate	30 (30)
Abnormal respiratory rate	22 (22)
Febrile	5 (5)
ICU admission	37 (37)
Wards only	63 (63)
Vasopressor support	16 (16)
Ventilator support	21 (21)
Renal replacement therapy	3 (3)

Smoking: Smoking was considered when patients smoked 10 cigarettes/bidis per day for 10 years; Alcoholics: Alcoholism was considered when males consumed 100 mL of hard liquor per day and females consumed 50 mL of hard liquor per day on most days of the week, for more than 1 year.

4. Discussion

We conducted a study in 100 patients. In our study, the mean age of the nonsurvivor was older (mean age of 58 years), which is similar to the study by Loeches *et al*[3]. The blood pressure in the nonsurvivor group was lower than the survivor group, but it was within the normal range. The lower blood pressure in the nonsurvivor group may be due to severe inflammation and vasodilation. It was

associated with Tachycardia in the nonsurvivor group, which was statistically significant. The common risk factors for infection in our study include older age and history of diabetes mellitus. The most common site of infection was the lung in our study, followed by the urinary tract and abdomen, which is similar to the study by Burke *et al*[4].

Neutrophils are part of the body's innate immune system, responsible for eliminating harmful microorganisms and activating other immune cells[5]. Lymphocytopenia is a decrease in lymphocyte levels caused mainly by apoptosis. It could lead to immunosuppression and is linked to a higher risk of infections and mortality. The severity and duration of this condition correlate with increased infection risks and death rates. Platelets play a crucial role in regulating leukocyte recruitment and activation through serotonin secretion. This process promotes the release of cytokines and chemokines, influencing the activation of lymphocytes and neutrophils and regulating the functions of monocytes, macrophages, lymphocytes, and endothelial cells.

In the clinic, the counts of neutrophils, lymphocytes, or platelets alone are affected by many factors and do not strongly correlate with sepsis prognosis. During sepsis, the uncontrolled release of inflammatory mediators and cytokines disrupts the balance between pro-inflammatory and anti-inflammatory responses. This leads to an increase in neutrophils, a decrease in lymphocytes, reduced platelet production, and increased consumption.

NLR has previously been shown to predict adverse outcomes in patients with tumors[6] including lung[7,8], ovary[9], and breast malignancies[10]. However, NLR is rarely investigated and not given much importance in clinical practice. NLR reflects the balance between innate and adaptive immunity. These ratios, which consider neutrophils and lymphocytes, offer better prognostic indicators for sepsis. Higher NLR values indicate more severe sepsis and higher mortality rates. Kaushik *et al*[11] concluded that elevated levels of NLR are seen in the early phase of sepsis and thus helpful in diagnosis, especially considering limitations in terms of time and low-positive rate due to microbiological culture. In another study by Liu *et al*[12], it was concluded that the patients with severe sepsis or septic shock tended to have higher baseline levels of APACHE II score, neutrophil count, and NLR, as well as lower lymphocyte count.

In a country like India, which is developing it is not easy to investigate the patients in detail. The NLR can be considered as a prognostic marker in sepsis patients. In the study by de Jager *et al*[13], it was also proved that in an emergency care setting, both lymphocytopenia and NLR are better predictors of bacteremia. In our study, the NLR of the non-survival group was higher on days 1, 3, and 5 when compared with the survivor group, which is similar to the study by Ye *et al*[14]. So, NLR can be used as a prognostic indicator in assessing the mortality of sepsis patients.

Table 2. Risk factors of mortality.

Parameters	Survivors (n=74)	Non-survivors (n=26)	U/t/ χ^2	P
Age (Years, mean±SD)	47.4±19.7	57.8±18.1	-2.32	0.022
Blood pressure (mmHg, mean±SD)				
Systolic	134.26±16.21	113.10±14.20	5.90	<0.001
Diastolic	86.14±10.82	62.12±11.51	9.54	<0.001
Heart rate (per min, mean±SD)	78.44±12.68	97.85±14.69	6.43	<0.001
Respiratory rate (per min, mean±SD)	13.1±4.6	18.5±5.8	-4.80	<0.001
Temperature (°F, mean±SD)	98.5±1.4	98.8±1.9	-0.85	0.396
Smokers (n, %)	38 (51.35)	10 (38.46)	0.12	0.258
Alcoholics (n, %)	20 (27.03)	2 (7.69)	4.19	0.041
Comorbidities (n, %)				
Hypertension	16 (21.62)	8 (30.77)	0.88	0.347
Chronic obstructive airway disease	9 (12.16)	6 (23.08)	1.79	0.180
Diabetes mellitus	4 (5.41)	6 (23.08)	6.68	0.010
Coronary artery disease	8 (10.81)	2 (7.69)	0.21	0.648
Stroke	9 (12.16)	0	3.48	0.062
Malignancy	2 (2.70)	0	0.72	0.397
Common infection sites (n, %)				
Lung	40 (54.05)	18 (23.68)	1.82	0.177
Urinary tract	16 (21.62)	2 (7.69)	2.53	0.112
Abdomen	8 (10.81)	0	3.06	0.080
Serum urea (median, Q1, Q3)	40.0 (25.5, 81.3)	59.0 (42.0, 168.3)	624	<0.01
Creatinine (median, Q1, Q3)	1.1 (0.8, 2.6)	1.7 (1.08, 3.0)	714	0.051
Serum uric acid (mg/dL, mean±SD)	6.57±4.78	7.99±3.24	-1.33	0.187
AST (median, Q1, Q3)	48.5 (27.0, 88.3)	31.5 (81.0, 262.0)	792	0.246
ALT (median, Q1, Q3)	33 (19, 71)	49 (19, 158)	804	0.288
Serum albumin (g/dL, mean±SD)	2.91±0.64	2.97±0.54	-0.42	0.674
C-reactive protein (mg/dL, mean±SD)	8.1±6.8	36.4±28.6	-7.96	<0.001
Serum sodium (mEq/L, mean±SD)	134.14±8.03	136.85±7.27	-1.52	0.133
Serum potassium (mEq/L, mean±SD)	3.96±0.86	4.60±1.14	2.92	0.004
Serum calcium (mg/dL, mean±SD)	7.98±1.32	8.24±2.08	-0.68	0.498
NLR (Median, Q1, Q3)				
Day 1	9.0 (6.5, 15.8)	18.0 (13.2, 27.5)	548	0.002
Day 3	10.5 (7.1, 17)	18.8 (9.1, 27.1)	492	0.022
Day 5	8.4 (5.1, 13.5)	22.6 (6.8, 24.4)	402	0.009
APACHE II (mean±SD)	24.05±4.95	28.95±3.81	-4.59	<0.001
SOFA score (median, Q1, Q3)	8 (6-10)	9 (7-11)	244	0.004
PaO ₂ /FiO ₂ (mean±SD)	260.77±121.57	263.82±146.30	-0.10	0.917

ALT: alanine aminotransferase; AST: aspartate aminotransferase; NLR: Neutrophil-to=lymphocyte ratio.

In conclusion, NLR is an easily accessible and cost-effective marker. Our study suggests that a higher NLR on admission and an increasing trend during hospitalization are associated with higher in-hospital mortality in sepsis patients. This makes NLR a valuable tool, particularly in resource-limited settings where advanced diagnostic facilities may not be available.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

Concept, design, and definition of intellectual content were given by JPK. Literature search, data acquisition, manuscript preparation, manuscript editing, and manuscript review were done by SM and MV. Data analysis and statistical analysis were done by MDK.

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