Prognostic value of neutrophil-to-lymphocyte ratio in patients with sepsis at the emergency department

Wiem Demni, Emna Ben Mhamed, Yessmine Walha, Dhekra Hamdi, Fadoua Lachter, Wided Bahria, Nourelhouda Nouira

Emergency department, Mongi Slim Hospital, Faculty of Medicine of Tunis, University of Tunis Elmanar

Corresponding author: Wiem Demni; Emergency department, Mongi Slim Hospital, Faculty of Medicine of Tunis, University of Tunis Elmanar, email: wiem.demni@fmt.utm.tn

Abstract

Introduction: Sepsis represents a diagnostic and therapeutic emergency, responsible for significant morbidity and mortality. The prognostic value of the neutrophil-to-lymphocyte ratio has been studied in different pathologies, particularly in septic patients. This study aimed to evaluate the prognostic value of the neutrophil-to-lymphocyte ratio in septic patients admitted to the emergency department.

Methods: This was a prospective, observational, descriptive, and analytical study. We included all patients with sepsis admitted to the emergency department. We collected epidemiological, clinical, biological, therapeutic, and evolutionary data and calculated the neutrophil-to-lymphocyte ratio at admission. To determine the prognostic value of the neutrophil-to-lymphocyte ratio, we established and analyzed the ROC curve.

Results: We included 106 patients. The average age was 65 ± 15 years. The sex ratio (F/M) was 1.4. The main medical histories were diabetes (52.8%), hypertension (46.2%), coronary artery disease (16%), and chronic renal failure (12.3%). The main reasons for consultation were general deterioration (84.9%), digestive signs (43.4%), and respiratory signs (43.4%). The most frequently selected infectious entry points were respiratory (37.7%), urinary (30.2%), and cutaneous (20.8%). Septic shock was diagnosed on admission in 26 patients (24.5%). The median neutrophil-to-lymphocyte ratio at admission was 9 [5-23]. After 72 hours of hospitalization, the intra-hospital mortality rate was 25.5%. In univariate analysis, the neutrophil-to-lymphocyte ratio appeared as a predictive factor for early intra-hospital mortality (p=0,003, OR= 2.96, CI95% = [3.23-14.97]). The area under the ROC curve of the neutrophil-to-lymphocyte ratio according to mortality was 0.75 (p<0.001, CI95%=0.66-0.85). A neutrophil-to-lymphocyte ratio cut-off of 6 was predictive of early mortality (p=0.003, Se=92%, Sp=68%, PPV=42%, NPV=97%) and outcomes in septic shock (p=0.04).

Conclusion: The neutrophil-to-lymphocyte ratio has prognostic value in septic patients, mainly for the identification of patients at high risk of poor outcomes.

Keywords: Biomarkers, Lymphocytes, Mortality, Neutrophils, Prognosis, Sepsis, Septic shock

Introduction

Sepsis represents a major public health problem, as it can lead to organ failure and rapidly become life-threatening. The identification and management of patients with sepsis remain a daily challenge for frontline physicians in emergency departments. In 2021, 166 million cases of sepsis and 21.4 million sepsis-related deaths from all causes were recorded worldwide, accounting for 31.5% of total global deaths (1).

Several biomarkers have been studied to assess the prognosis of patients with sepsis. According to Paskaline et al. (2), the persistence of elevated biological marker levels in septic patients admitted to intensive care units is correlated with an increased risk of clinical deterioration and mortality. In 2001, Zahorec et al. (3) reported a correlation between neutrophil and lymphocyte counts and prognosis in critically ill patients admitted to intensive care units.

Since the 1990s, the neutrophil-to-lymphocyte ratio (NLR) has attracted increasing scientific interest due to its pathophysiological relevance, wide availability, and low cost. This parameter has been explored in numerous studies across various medical specialties and has demonstrated its usefulness as both a diagnostic and prognostic marker. Thus, NLR represents a novel approach derived from the complete blood count that, according to some studies, can predict mortality in septic patients.

To date, few Tunisian studies have focused on the prognostic performance of the neutrophil-to-lymphocyte ratio in patients with sepsis.

This study aimed to evaluate the prognostic value of the neutrophil-to-lymphocyte ratio in patients admitted to the emergency department with sepsis.

Methods

This was a prospective, observational, descriptive, and analytical study conducted in the emergency department over 10 months (April 2022–January 2023).

Inclusion criteria: Patients aged 18 years and older, admitted to the emergency department for the management of sepsis, defined by a Sequential Organ Failure Assessment (SOFA) score ≥ 2.

Non-inclusion criteria: Patients younger than 18 years, and patients who did not meet the diagnostic criteria for sepsis or septic shock.

Exclusion criteria: Patients transferred to another healthcare facility for further management.

This study was based on the definitions of sepsis and septic shock established by the Third International Consensus (Sepsis-3) published in 2016 (4).

The primary outcome of the study was **early mortality**, defined as death occurring within the first 72 hours of management.

Study protocol: After enrollment, all included patients were admitted to the emergency room. Following initial stabilization, blood samples were collected at admission, including a complete blood count.

The management protocol for septic patients in the emergency department was based on the Surviving Sepsis Campaign guidelines (2021 update) (5). All patients received fluid resuscitation, with or without vasoactive agents, and empirical antibiotic therapy. Adjunctive treatments were administered according to the patient's clinical presentation and subsequent outcomes (low-dose systemic corticosteroids, oxygen therapy, etc.).

The neutrophil-to-lymphocyte ratio (NLR) was calculated from the baseline biological assessment at admission for all included patients.

For statistical analysis and to assess the prognostic value of the neutrophil-to-lymphocyte ratio, patients were divided into two groups: **Survivors and non-survivors**

Absolute and relative frequencies (percentages) were calculated for qualitative variables. Quantitative variables were expressed as means, medians, standard deviations, and ranges (minimum and maximum values).

Comparisons of proportions were performed using the Pearson chi-square test or Fisher's exact test when appropriate. Comparisons of means between independent groups were performed using Student's T test or the non-parametric Mann–Whitney test when required. A *p*-value < 0.05 was considered statistically significant.

To determine the prognostic value of the NLR, a receiver operating characteristic (ROC) curve was constructed. After confirming that the area under the ROC curve was greater than 0.5, the optimal cut-off value for the NLR was determined as the point corresponding to the best sensitivity–specificity balance.

Oral informed consent was obtained from all patients to allow the use of their medical data and follow-up of their clinical outcomes.

Results

A total of 106 patients were included in the study. The mean age was 65 ± 15 years, and the male-to-female ratio was 1.4. The main clinical presenting features at admission were general deterioration (84.9%), abdominal signs (43.4%), respiratory signs (43.4%), fever (34%), and urinary signs (20%)

The main sources of infection were respiratory (37.7%), urinary (30.2%), abdominal (18.9%), and cutaneous (20.8%). The mean SOFA score was 4 ± 2, with values ranging from 2 to 11.

Septic shock was diagnosed at admission in 26 patients (24.5%). An additional nine patients (8.5%) developed septic shock during their stay in the emergency department.

The median neutrophil-to-lymphocyte ratio (NLR) at admission was 9 [5–23]. Early in-hospital mortality was 25.5%.

The epidemiological, clinical, and biological characteristics of patients according to mortality status are presented in Table 1.

The area under the ROC curve (AUC) for the NLR in predicting mortality was 0.75 (95% CI: 0.66–0.85; p < 0.001), with a cut-off value of 6 (sensitivity 92%, specificity 68%, positive predictive value 42%, negative predictive value 97%) (Figure 1).

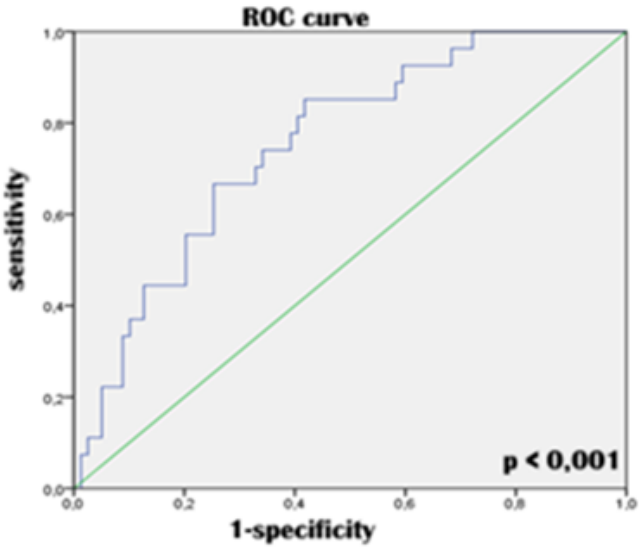

Figure 1: ROC curve of the neutrophil-to-lymphocyte ratio according to early mortality

The NLR was identified as a significant predictor of early in-hospital mortality (OR 2.96, 95% CI: 3.23–14.97; p = 0.003) in univariate analysis.

The clinical course of included patients according to the NLR cut-off is shown in Table 2.

Discussion

The neutrophil-to-lymphocyte ratio (NLR), calculated as the simple ratio of neutrophil to lymphocyte counts measured in peripheral blood, is readily available in the emergency setting.

Table 1: Epidemiological characteristics of patients with sepsis

Parameters	All patients n =106	Non-survivors n =27	survivors n=79	p-value
Age, years; mean± SD	65 ± 15	68 ± 10	64 ± 16	**0.03**
Female, n (%)	62 (59)	14 (52)	48 (61)	NS
Medical, n (%)	56 (53)	15 (53)	41 (52)	NS
Diabetes	49 (46)	9 (33)	40 (51)	NS
Hypertension	13 (12)	4 (15)	9 (12)	NS
Chronic	12 (11)	4 (15)	8 (10)	NS
kidney	17 (16)	10 (37)	7 (9)	**0.002**
disease	10 (9)	6 (22)	4 (5)	**0.02**
Heart failure				
Coronary heart disease				
Stroke				
Clinical parameters				
SpO2, %	90 ± 8	88 ± 10	92 ± 8	**0.02**
Respiratory rate, cycles/min	22 ± 5	25 ± 7	21 ± 5	**0.02**
Systolic blood pressure, mmHg	112 ± 28	108 ± 31	113 ± 27	NS
Diastolic blood pressure, mmHg	61 ± 17	57 ± 18	60± 17	NS
Heart rate, beats/min	97 ± 28	101 ± 27	87 ± 29	**0.04**
Glasgow Coma Scale	13 ± 2	12 ± 3	14 ± 2	**<0.001**
Septic shock, n (%)	26 (25)	14 (52)	2 (3)	**<0.016**
Sepsis scores at admission	4 ± 2	6 ± 2	4 ± 1	**0.001**
SOFA	1 [1-2]	2 [1-3]	1 [1-2]	**0.04**
qSOFA				
Laboratory data				
White blood cells (10^9 /L)	12830 [8515-19400]	12830 [8515-19400]	12540 [8500-16300]	NS
Neutrophils (10^9 /L)	10585 [6315-16520]	12928 [6315-10585]	9800 [6200-13880]	NS
Lymphocytes (10^9/L)	1000 [677-1692]	1000 [677-1692]	1570 [700-1880]	**0.009**
NLR	**9 [5-23]**	**20 [10-28]**	**8 [5-17]**	**0.004**

SpO2: peripheral oxygen saturation, *SOFA*: sequential organ failure assessment, q*SOFA*: quick sequential organ failure assessment, *NLR*: neutrophil to lymphocyte ratio

It is a biomarker that integrates two major components of the immune system: innate immunity, primarily mediated by neutrophils, and adaptive immunity, mediated by lymphocytes (6).

Table 2: Clinical outcomes of included patients according to the NLR cut-off.

Outcomes	NLR ≥ 6 n=74	NLR < 6 n=32	p-value
Development of septic shock, n (%)	26 (35)	5 (15,6)	**0.04**
Use of mechanical ventilation, n (%)	8 (11)	6 (19)	NS
Length of stay in the ED, hours	94 ± 10	84 ± 8	NS
Early mortality, n (%)	20 (27)	5 (16)	**0.003**

NLR: neutrophil to lymphocyte ratio, NS: non-significant, ED: emergency department

Indeed, neutrophils are the first immune cells mobilized by the host in response to invading pathogens. Their activity relies on several mechanisms, including chemotaxis, phagocytosis, the release of reactive oxygen species (ROS), exocytosis of granular proteins, and cytokine secretion. Regarding lymphocytes, the decrease in their circulating levels is explained by their marginalization and redistribution to the lymphatic system.

Thus, the NLR reflects the balance between neutrophil and lymphocyte levels in the body and serves as an indicator of systemic inflammation. This biomarker, which is easily accessible, non-invasive, and cost-effective, has attracted considerable interest in scientific literature. The NLR has been extensively studied in various fields, including surgery (as a predictor of postoperative complications and mortality), oncology (for monitoring patients undergoing treatment), and cardiology (to predict prognosis in patients with acute coronary syndromes, heart failure, and infective endocarditis) (7–10).

In this study, we investigated the prognostic value of the NLR in patients with sepsis. According to previous studies, an elevated NLR has been reported as an early indicator of complications and short-term mortality, thereby enabling the

identification of septic patients at higher risk of adverse outcomes and facilitating the optimization of initial therapeutic management.

Compared with the biological results of our study, Riché et al. (11) reported mean white blood cell and neutrophil counts that were very similar to ours, whereas lymphocyte counts and NLR values were lower. The median lymphocyte count and NLR were 770 [510–1030] cells/µL and 2.5 [6.5–21.2], respectively. Regarding the NLR, our study found a lower mean value than that reported by Liu X. et al. (12), who observed a mean NLR of 17.85 [9.61–28.19].

In an observational cohort study conducted in the emergency department of a university hospital in Turkey and including 373 patients with sepsis, Nazire B.A. et al. (13) demonstrated that the area under the receiver operating characteristic (ROC) curve of the NLR for predicting mortality was 0.61 (p = 0.01), with an optimal NLR cut-off value of 11.9, yielding a sensitivity of 37% and a specificity of 81.8%. In the same study, the NLR emerged as an independent predictor of mortality (OR = 1.63, p = 0.01, 95% CI= [1.11–2.41]).

In a 2020 meta-analysis including 14 studies (11,564 patients with sepsis), Huang Z. et al. (14) demonstrated that NLR values were significantly higher in non-survivors than in survivors (p=0.002). Furthermore, they showed that an elevated NLR was significantly associated with poor prognosis in patients with sepsis. Similarly, a 2024 meta-analysis including 10,811 patients reported a significant association between elevated NLR values and unfavorable clinical outcomes (15).

However, in contrast to these findings, other studies did not observe a significant association between NLR and in-hospital mortality among patients with sepsis (16,17).

The areas under the ROC curves of the NLR, reported in different comparable studies, according to mortality outcomes, are summarized in Table 3.

The results of our study demonstrate that the neutrophil-to-lymphocyte ratio (NLR) shows a satisfactory prognostic performance for predicting early mortality in patients with sepsis, with an area under the ROC curve (AUC) of 0.75.

Table 3: Performance of the NLR in predicting early mortality in patients with sepsis

Studies	AUC	p-value	Cut-off	Sensitivity	Specificity
X. Liu et al. (12)	0.69	<0.001	23.8	81	54
Riché et al. (11)	0.70	<0.001	5.3	78	55
Mandal and al.(18)	0.77	<0.001	10	98	93
Stoian and al *(19)*	0.76	<0.001	17.1	53	93
Our study	0.75	<0.001	6	92	68

AUC: Area under the curve

This finding is consistent with previously published studies and supports the potential utility of NLR as a prognostic biomarker in this clinical setting. Indeed, the AUC values reported in the literature range from 0.69 to 0.77 (11,12,18,19). These results indicate a moderate to good discriminative ability of NLR for mortality prediction in sepsis, although some variability exists across studies.

Considerable heterogeneity is also observed in the optimal NLR cut-off values, which range from 5.3 to 23.8. This variability may be explained by differences in study design, patient populations, sepsis definitions, timing of blood sampling, and outcome measures.

Nevertheless, the overall performance of NLR observed in our study, combined with its rapid availability, low cost, and non-invasive nature, supports its role as a valuable adjunct in the early prognostic assessment of patients with sepsis. Future research should focus on integrating NLR into multimodal prognostic models alongside clinical scores and other biomarkers to enhance its predictive accuracy and clinical applicability.

Conclusion

The neutrophil-to-lymphocyte ratio was associated with early mortality in patients with sepsis admitted to the emergency department. It may therefore help optimize initial clinical management to prevent unfavorable outcomes.

However, further evaluation of the optimal cut-off and target values of this ratio, as well as its dynamic changes during hospitalization, is necessary to enable more effective use of this biological parameter in routine clinical practice.

Conflict of interest: All the authors declare no conflicts of interest related to this study.

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