European Journal of Clinical Pharmacy
Print ISSN: 2385-409X, **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Comparison between the Accuracy of TLC and Neutrophil-to-Lymphocyte ratio as Predictive Biomarker for the Development of Sepsis

Article History:

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Received*:* 02-11-2025
Revised*:* 26-11-2025
Accepted*:* 06-12-2025
Published*:* 20-12-2025

Abstract: Background: Objective: To evaluate Total Leukocyte Count (TLC) and the Neutrophil-to-Lymphocyte Ratio (NLR) as early markers for predicting septic evolution in patients who had acute surgical conditions, as a diagnostic tool.**Study Design:** Prospective, comparative cohort study.**Place and Duration of Study:** Department of General Surgery, Combined Military Hospital, Lahore, Pakistan, from March 2025 to October 2025.**Methods**: One hundred eighty (180) adult patients with acute surgical conditions requiring an operation either in the emergency department or out-patient clinics of the hospital were prospectively recruited. At admission, venous blood was drawn to determine the baseline TLC, and thus calculate NLR. Sepsis was then sought for the next 7 days using Sepsis-3 criteria of an acute increase of at least 2 SEPSIS (Sequential Organ Failure Assessment) points due to suspected or proven infection. Two variables, namely the area under the curve (AUC) and optimal cut-off values, with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used to assess the diagnostic performance of both of the biomarkers. IBM SPSS Statistics (version 29.0) was used to perform statistical analyses.**Results:** After 7 days follow up, of 180 included patients, 42 (23.3%) developed sepsis. Patients who developed sepsis had significantly higher baseline TLC than those who remained free of sepsis (14.2 ± 3.9 × 10^9/L vs. 10.8 ± 2.8 × 10^9/L; P < 0.001). Similarly, the baseline NLR was significantly elevated in the sepsis group compared with non-sepsis group (8.4 ± 2.9 vs. 3.6 ± 1.4, P < 0.001). ROC analysis demonstrated that NLR had superior predictive performance compared with TLC, with an AUC of 0.884 (95% CI: 0.824–0.944; P < 0.001) versus 0.742 (95% CI: 0.658–0.826; P < 0.001). The best cut-off value for NLR was 5.2 with a sensitivity of 85.7% and specificity of 81.2%, while the best cut-off value for TLC was 11.5 × 10^9/L with a sensitivity of 71.4% and a specificity of 64.5%.**Conclusion**: NLR was more accurate at predicting early sepsis among patients with acute surgical conditions than were TLC. NLR is an easily accessible, inexpensive, and stable biomarker, which can improve early risk stratification and facilitate prompt decision making in the emergency of general surgery.

Keywords: Sepsis; Neutrophil-to-Lymphocyte Ratio; Total Leukocyte Count; Predictive Biomarker; Acute Surgical Abdomen; Diagnostic accuracy.

INTRODUCTION

The recognition of sepsis is still a significant issue in ED general surgery and intensive care settings as diagnosis is essential to improving outcomes [1].

Sepsis according to the Sepsis-3 consensus definition is a life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection [5]. Patients with acute surgical diseases like perforated hollow viscus, necrotizing soft tissue infections, complicated appendicitis, and severe ascending cholangitis are especially susceptible to rapid clinical deterioration with localized disease potentially degrading into a systemic inflammatory dysfunction very quickly. If sepsis is not identified quickly enough, then appropriate antimicrobial, and definitive source control, which are strongly associated with reduced morbidity and mortality, may be delayed [1,5]. Hence, identification of simple, readily available biomarkers, which can lead to early stratification of risks in surgical practice, become an important priority [2,4].

The Total Leukocyte Count (TLC) which is part of the basic complete blood count (CBC) has long been considered a starting point laboratory indicator of systemic inflammation/infection. One of the main criteria of the Systemic Inflammatory Response Syndrome (SIRS) was traditionally leukocytosis (TLC>12.0 × 10^9/L) or leukopenia (TLC<4.0 ×10^9/L). However, there are significant limitations in the use of TLC for diagnostic purposes, especially in the context of acute surgical conditions, in which a high leukocytic count may exist without infection [4,6]. Circulating leukocytes also can be increased independently by surgical stress, tissue injury, ischemia, trauma and corticosteroid therapy, making the specificity as an indicator of true sepsis less [3]. Thus, the use of TLC alone could not always be used to differentiate von infectious systemic inflammation from a physiological stress response.

Inflammatory markers based on the differential leukocyte count have gained increasing interest in order to improve the accuracy of the diagnosis, including the Neutrophil-to-Lymphocyte Ratio (NLR) [1,2]. The NLR is the ratio of the absolute value of the neutrophils to the lymphocytes, and reflects the balance of innate and adaptive immunity [1]. In the early stages of sepsis inflammatory cytokines induce a rapid release of neutrophils from the bone marrow and induce apoptosis and depletion of circulating lymphocytes, particularly CD4+ cells and CD8+ T cells [5,8]. All the above-mentioned immune alterations occur concurrently and result in a significant rise in the NLR level, which could make the NLR a more useful parameter of the immune imbalance of the body rather than the total leucocyte count alone [1,8].

While biomarkers like procalcitonin (PCT) and C-reactive protein (CRP) show promise for the early diagnosis of sepsis, their cost and availability are limited and they are not infrequently used in LMICs, including Pakistan, especially in low-resource settings [4]. In contrast, both are easily available from a routine complete blood count done under automation (CBC), which does not require extra testing, making them low cost and easily utilized in the clinical routine evaluation [1,6]. However, direct comparative data on the predictive ability of the two biomarkers in acute surgical patients within the context of the Pakistani health-care system is scarce. Hence, the present study was conducted to compare the diagnostic accuracy of baseline TLC and NLR for prediction of sepsis in patients admitted in the surgical admission ward with acute surgical diseases in a tertiary care hospital of Lahore, Pakistan.

MATERIALS AND METHODS

Design and setting of the studies

This is a prospective comparative cohort study done in Department of General Surgery, Combined Military Hospital (CMH), Lahore, Pakistan. CMH Lahore is a Tertiary Care Teaching Hospital which offers emergency and elective surgical facilities to the Military and the general public of Punjab.The events lasted for a total of eight months from March 2025 to October 2025. The study protocol was approved by the Institutional Review Board and Ethics Committee of Combined Military Hospital, Lahore (IRB No. CMH/GS/2024-045) and registered in Pakistan National Trial Registry (PNTR202401000456). All procedures performed in the studies were in line with the principles of the Declaration of Helsinki. All the individuals who were eligible for the study or their legal representative if applicable, were given a detailed description of the objective of the study before enrolment and were asked to sign an informed consent form. All patient records were anonymised with alphanumeric ID numbers for the purpose of keeping the information confidential.

Sample Size Calculation

The Buderer formula for diagnostic accuracy studies was used to calculate the required sample size. It was based on the assumed sensitivity of 85% and 65% for Neutrophil-to-Lymphocyte Ratio (NLR) and Total Leukocyte Count (TLC) respectively in diagnosis of sepsis with the determined margin of error as 10, 95% confidence level and the estimated prevalence of sepsis as 22% among the patients admitted with acute surgical condition [1,5]. The smallest calculated sample size was 165 participants. Considering the possible losses due to poor laboratory documentation, absence of follow-up data or early transfer of patients, the sample size was expanded to 180 consecutive eligible patients.

Selection Criteria
Inclusion Criteria:

- Male and female adult patients (ages 18-75) years.
- Patients who are admitted to the emergency department or outpatient clinics with acute surgical conditions of various types, which need surgical exploration or close inpatient monitoring such as complicated acute appendicitis, acute cholecystitis, mechanical intestinal obstruction, hollow viscus perforation, intra-abdominal abscess or necrotising fasciitis [3,6,7].
- Prompt availability of a FBC that includes an automated DBC within two hours of presentation to the hospital and prior to the start of empirical antimicrobial therapy [1].

Exclusion Criteria
- Those who, at admission, have known sepsis or septic shock [1].
- A history of haematological malignancy, bone marrow disorders, currently on chemotherapy or high dose corticosteroids/immunosuppressive agents [5].
- Patients in end stage chronic kidney disease on maintenance hemodialysis or in advanced liver cirrhosis (Child – Pugh Class C).
- Patients who died within 24 hours of admission due to catastrophic haemorrhagic shock, or non-infectious polytrauma.

Operational Definitions
1. Total Leukocyte Count (TLC): Count the number of leukocytes in the venous blood as ×10^9/L using automated hematology analyzer.
2. Neutrophil-to-Lymphocyte Ratio (NLR): This is a ratio index which is calculated from the differential count of leukocytes in the following manner [1,2]

NLR refers to Absolute Neutrophil Count / Absolute Lymphocyte Count

3. Primary Outcome (Development of Sepsis): Primary outcome was development of sepsis during 7 days follow up period. Sepsis was diagnosed using the consensus-based definition of sepsis (Sepsis-3): an acute. increase of ≥2 points in Sequential Organ Failure Assessment (SOFA) score due to suspected or proved infection [5]. The SOFA score assesses failure in each of six organ systems – respiratory, coagulation, hepatic, cardiovascular, neurological and renal.

Data collection and laboratory analysis
The principal investigator recorded demographic characteristics at admission (age/sex), presenting complaints and baseline vital signs (heart rate, respiratory rate, blood pressure, temperature) and provisional clinical diagnosis on a data collection sheet. A 3 mL venous blood sample was obtained in an ethylenediaminetetraacetic acid (EDTA) tube within 2 hours of hospital presentation and was analyzed within the institutional pathology laboratory using an automated an automated hematology analyzer in regard to total leukocyte count, absolute neutrophil count and absolute lymphocyte count [1].

In both groups, all patients were managed with standard surgery along with judicious fluid resuscitation and culture directed antibiotics or empirical antibiotic therapy, and definitive source control (laparotomy, laparoscopy and/or wound debridement) was performed when indicated [3]. Organ dysfunction and sepsis were assessed on 7th day after admission in the patients. Every day clinical and biochemical parameters (arterial blood gas analysis, platelet count, serum bilirubin, serum creatinine, Glasgow Coma Scale (GCS) score and urine output) were recorded to calculate the SOFA score and determine the occurrence of sepsis [5].

Statistical Analysis
SPSS Statistics 29.0 for Windows, IBM Corp., Armonk, NY, USA, was used for data analysis. The Shapiro–Wilk test was used to explore the distribution of continuous variables. All continuous variables were normally distributed and presented as mean ± standard deviation (SD), and were statistically compared using independent Student's t-test. Categorical data were presented as percentages and numbers; comparison was done with the Pearson chi-square and Fisher's exact test as appropriate.
The predictive performance of TLC and NLR was tested by Receiver Operating Characteristic (ROC) curve analysis [4] Area under the curve (AUC) and corresponding 95% confidence intervals (CI) were computed for both biomarkers [4,5]. Youden's index (J = Sensitivity + Specificity − 1) was used to obtain each marker's optimal cut-off value. At these cut-off values the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. A two-sided P-value of ≤0.05 was considered statistically significant.

RESULTS
All 180 patients with acute surgical disease met inclusion criteria and finished the 7-day follow-up. The age range of the study population was 19 to 73 years with the mean age of 44.6 ± 14.8 years. Males constituted 61.1% (n = 110) of the cohort, while females accounted for 38.9% (n = 70). The most common diagnosis for admission was complicated acute appendicitis (30.0%), acute cholecystitis (22.8%), hollow viscus perforation with peritonitis

(21.1%), mechanical intestinal obstruction (16.1%) and necrotizing soft tissue infection (10.0%).
In the follow-up, 42 patients (23.3%) met the Sepsis-3 criteria for sepsis while 138 patients (76.7%) did not develop sepsis during the study. There were no statistically significant differences between the sepsis and non-sepsis groups in age, race, steroid use, distribution of primary surgical diagnosis (all P > 0.05). Table 1 shows detailed baseline characteristics.

Table 1: Baseline Demographics and Clinical Characteristics of the Study Cohort (N = 180)

Baseline Parameter Metric	Overall Cohort (N = 180)	Sepsis Group (n = 42)	Non-Sepsis Group (n = 138)	P-value
Age (years), Mean ± SD	44.6 ± 14.8	46.2 ± 15.1	44.1 ± 14.7	0.424
Gender: Male, n (%)	110 (61.1%)	27 (64.3%)	83 (60.1%)	0.631
Gender: Female, n (%)	70 (38.9%)	15 (35.7%)	55 (39.9%)	
Primary Surgical Presentation:				0.184
Complicated Appendicitis	54 (30.0%)	10 (23.8%)	44 (31.9%)	
Acute Cholecystitis	41 (22.8%)	7 (16.7%)	34 (24.6%)	
Hollow Viscus Perforation	38 (21.1%)	13 (31.0%)	25 (18.1%)	
Mechanical Intestinal Obstruction	29 (16.1%)	5 (11.9%)	24 (17.4%)	
Soft Tissue Infections	18 (10.0%)	7 (16.7%)	11 (8.0%)	

There was significant difference between the two groups in terms of initial haematological values. Patients who subsequently developed sepsis had a significantly higher mean TLC than those who did not develop sepsis (14.2 ± 3.9 × 10^9/L vs. 10.8 ± 2.8 × 10^9/L; P < 0.001). Similarly, baseline NLR mean value was significantly higher in the patients who developed sepsis (8.4 ± 2.9) than in non-sepsis group (3.6 ± 1.4, P < 0.001). A post hoc analysis revealed that absolute numbers of neutrophils were significantly, while absolute numbers of lymphocytes were significantly less in patients who developed sepsis. The results of these are summarised as follows in table 2.
Table 2 shows the differences in hematological biomarkers at baseline within the groups.Differences in hematological biomarkers at baseline for each group are presented in Table 2.

Table 2: Comparison of Baseline Hematological Biomarkers Between Groups

Biomarker Parameter	Sepsis Group (n = 42)	Non-Sepsis Group (n = 138)	t-value	P-value
Total Leukocyte Count (×10^9/L)	14.2 ± 3.9	10.8 ± 2.8	6.071	<0.001
Absolute Neutrophil Count (×10^9/L)	11.8 ± 3.4	7.8 ± 2.2	8.814	<0.001
Absolute Lymphocyte Count (×10^9/L)	1.4 ± 0.4	2.2 ± 0.6	-8.146	<0.001
Neutrophil-to-Lymphocyte Ratio	8.4 ± 2.9	3.6 ± 1.4	14.532	<0.001

A receiver operating characteristic (ROC) curve analysis was used for the comparison of predictive performance of both biomarkers. The NLR demonstrated better discrimination for predicting sepsis than TLC, with an AUC of 0.884 (95% CI: 0.824–0.944; P < 0.001), whereas the AUC for TLC was 0.742 (95% CI: 0.658–0.826; P < 0.001).

The best cut-off value of NLR based on Youden's index was 5.2 with sensitivity of 85.7%, specificity of 81.2%, positive predictive value (PPV) of 58.1% and negative predictive value (NPV) of 94.9%. For TLC, the optimal cut-off value was 11.5 × 10^9/L, corresponding to a sensitivity of 71.4%, specificity of 64.5%, PPV of 38.0%, and NPV of 88.1%. Table 3 provides a comparison of the diagnostic performance of both the biomarkers.

Table 3: Comparison of the diagnostic performance of NLR and TLC

Diagnostic Parameter	Neutrophil-to-Lymphocyte Ratio (NLR)	Total Leukocyte Count (TLC)
Optimal Cut-off Value	5.2	11.5 ×10^9/L
Area Under the Curve (AUC)	0.884 (95% CI: 0.824–0.944)	0.742 (95% CI: 0.658–0.826)
P-value	<0.001	<0.001
Sensitivity (%)	85.7	71.4
Specificity (%)	81.2	64.5
Positive Predictive Value (PPV) (%)	58.1	38.0
Negative Predictive Value (NPV) (%)	94.9	88.1

DISCUSSION

Our study demonstrated that the neutrophil to lymphocyte ratio (NLR) at admission had better diagnostic performance to predict sepsis in acute surgical patients than the total leukocyte count (TLC) [1,4]. This is consistent with the NLR being a readily available inflammatory indicator that expresses neutrophilia together with relative lymphopenia in the setting of systemic infection [1,5]. While TLC is commonly used to assess inflammation, it is not a reliable way to determine whether the inflammatory response is local or a dysregulated systemic inflammatory process seen in sepsis [4]. NLR on the other hand does include the change in neutrophils and lymphocytes level which is a more sensitive indicator of severe bacterial infection [5,8].

The results of the present study showed that NLR had a high diagnostic value with Area Under the Curve 0.884 as compared to TLC of 0.742. This has clinical significance in general surgical practice at the emergency department where early recognition of patients at risk of sepsis may allow timely intervention [3,6]. A high sensitivity was accompanied with a negative predictive value of 94.9% at an admission NLR cut off value of 5.2 (based on Youden's index). The results of this study indicate that patients having admission NLR value less than this threshold value are less likely to develop sepsis infection, and may have stratification of reduced risk settings when taken together with the routine clinical assessment.

On the other hand, TLC demonstrated relatively low specificity (64.5%) and positive predictive value (38.0%) with the best cutoff value of 11.5 × 10^9/L; leucocytosis induced by surgical trauma and/or tissue injury without systemic infection is common with a low diagnostic value of TLC alone in emergency surgical patients [3,4]. Thus, the use of TLC as a single parameter raises the possibility of false positive clinical suspicion of sepsis.

The findings of our study are in agreement with previous reports. Rehman et al. found NLR had higher performance characteristics when compared to traditional WBC parameters for early detection of sepsis [1]. In another study, Sarin et al also observed that alterations in differential WBC and high NLR value was correlated with developing sepsis after major abdominal surgery [2]. Giacometti et al. also showed that a higher admission NLR was linked to extensive intraabdominal disease such as bowel ischemia and hence the results found in this study [3]. Patients who developed sepsis always had higher NLR values on admission than those who did not , irrespective of the main surgical diagnosis. If this finding proves to be correct, this could be a good low-cost screening tool for a wide array of emergency surgery cases [6,7]. As it is derived from a CBC, NLR can be easily included in the assessment process in the ED, at no extra cost, and without any specialized equipment [4].

There are several strengths to this study, being a prospective study with consecutive patient enrollment, the use of Sepsis-3 criteria, and the generation of data from an emergency general surgery population in a tertiary care hospital in Pakistan. Several limitations should, however, be recognized. First, it was a single center study limiting generalization of the results. Second, only NLR and TLC levels were assessed at admission and not serially to determine how these changed over time. Third, unfortunately due to resources and finances, comparison with other markers (such as procalcitonin or interleukin-6) was not possible.

The usefulness of the findings needs to be confirmed in further multicenter studies using larger and more heterogeneous patient groups in order to define optimal diagnostic cut-off values for different healthcare settings [4]. In addition, serial evaluation of NLR during the treatment process should also be conducted in future studies and associations of NLR with infection control, clinical outcomes, length of intensive care unit stay and survival should also be analyzed.

CONCLUSION

Overall, the NLR at admission exhibits superior predictive and diagnostic values for predicting sepsis onset in acute surgical patients when compared to TLC in acute surgical patients. NLR has a good sensitivity and specificity when used with a cut-off value of 5.2, and has high NPV, which could be useful for clinical risk stratification. The NLR is a practical, available screening tool that comes from a commonly ordered blood test, doesn't require any extra health care costs, can complement and augment clinical judgment, and can assist in making triage decisions and identify patients early in any condition.

ACKNOWLEDGMENT
The authors are grateful for the helpful assistance extended by the laboratory staff, nursing staff, and surgical residents of Combined Military Hospital (CMH) Lahore, Pakistan, in samples processing, data collection and patient management during the entire study.

CONFLICT OF INTEREST
None

FUNDING
None

ETHICAL APPROVAL
The study protocol was approved by the IRB No. CMH/GS/2024-045 Combined Military Hospital Lahore (IRB & EC) Institutional Review Board and Ethics Committee. The study has been registered in Pakistan National Trial Registry (PNTR202401000456). The study procedures were performed according to the Declaration of Helsinki and written informed consent was derived from all participants prior to their consent to participate.

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