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Initial Neutrophil-To-Lymphocyte Ratio as a Predictor of Unfavorable Outcome in Sepsis

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Abstract:
Background*: High world-wide sepsis-related mortality and morbidity have highlighted the need of rapid, accurate and cost-effective tool for assessing sepsis severity to ensure timely intervention and therefore better outcomes. Although neutrophil lymphocyte ratio (NLR) has been used as a prognostic factor in various conditions, none of the currently available sepsis scores have utilized it yet.*
This study aimed to assess NLR as a prognostic factor for patient with sepsis in ICU, and to define its cut-off value for prediction of mortality in sepsis.
Materials and Methods*: This is an analytical cross-sectional study where initial NLR and relevant data were collected from immunocompetent adult patients with sepsis in ICU departments at four different hospitals in Khartoum, Sudan (2018-2019). Statistical Package for Social Studies Program (SPSS), ANOVA, Pearson's correlation and receiver operating characteristic curve (ROC) were used for analysis. P value < 0.05 was considered as statistically significant.*
Results*: NLR showed negative correlation with GCS (r=-0.350; P=0.000) and positive correlation with EWS (r=0.331; P=0.000), SOFA (r= 0.620; P= 0.000), and CRP (r=0.839; P= 0.000). Furthermore, NLR was negatively associated with PO2/FIO2 (P= 0.000). Regarding the outcome, NLR was significantly high in the non-survivor group of patients (P= 0.000). Using ROC, the AUC of NLR was found to be 0.882 (95% CI: 0.819–0.945; P=0.000) with a cut-off value of >9.8 (sensitivity= 94.3% and specificity= 97.1%).*
Conclusion: *This study concluded that initial NLR and NLR trend have a prognostic role for sepsis outcome.*
Key Word*: ICU, Mortality, Neutrophile-lymphocyte ratio (NLR), Sepsis, Outcome, Prognosis.*

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I. Introduction

Sepsis is defined as "life-threatening organ dysfunction caused by a deregulated host response to an infection"[1]. Sepsis is estimated to affect around 30 million people worldwide every year, and causes about 5.3 million deaths annually[2]. The clinical manifestations and patients' outcome of sepsis depend on the balance between pro-inflammatory and anti-inflammatory components[3].

The appropriate activation of Toll Like Receptors (TLRs) in neutrophils releases pro- inflammatory mediators such as; cytokines, chemokines and other mediators that play an important role in fighting against sepsis. However, in some studies persistent activation of neutrophils resulted in reduced expression of pro- inflammatory cytokines[4]. In sepsis, over-activation of complement system can cause impaired neutrophils' killing ability[5]. In some patients despite the adequate neutrophils' phagocytic capacity, there is an increase in the number of circulating immature neutrophils with altered chemotaxis and oxidative burst capacity. All those factors can lead to increased risk of death in septic shock[4].

High neutrophils number in sepsis was found to be due to increased expression of anti-apoptotic proteins like Mcl-1 and Bcl-xL and reduced both expression pro-apoptotic BIM protein as well as formation of apoptosomes[4]. In contrast, low lymphocyte count was observed in sepsis due to increased apoptosis and some studies showed that a drop in certain T and B cell populations are associated with poor prognosis in sepsis[6]. Considering the above mentioned factors, neutrophil-to-lymphocyte ratio (NLR) was found to be high in severe infection or systemic inflammation; therefore it was considered as biomarker in clinical evaluation for systemic inflammation[7].

Initial NLR measured at admission was found to be associated with an increase in 28-day mortality in patients with severe sepsis and septic shock[8]. Moreover, the use of NLR as a predictor factor for clinical outcome has been documented in a number of malignancies including lung and ovarian cancers and in patients undergoing colorectal cancer resection[9–11].

Acute critical care predictive scoring systems such as Acute Physiologic and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) utilize total white blood cells count and platelets count respectively to assess risk for mortality in sepsis[12].

The aim of this study was to assess the usefulness of initial neutrophil to lymphocyte ratio (NLR) as a marker of sepsis outcome in adult patients with sepsis admitted to intensive care units and to assess if there is a predicting value for point NLR in relation to outcome.

II. Material And Methods

This is an analytical cross-sectional hospital-based study conducted from November 2018 to March 2019 in ICU departments at Royal Care, Fedail, Omdurman Military and Ibrahim Malik Hospitals in Khartoum, Sudan.

Study population was adult patients admitted to the ICU with sepsis. Immunodeficient patients or those on immunosuppressive treatment were excluded. Demographic, physiological, clinical and laboratory data were collected and initial NLR was calculated on admission. Data was analysed using Statistical Package for Social Studies Program (SPSS, V. 21.0. IBM; Chicago). ANOVA and Pearson's correlation were used to determine the factors related to NLR in bivariate analysis. Receiver operating characteristic curve (ROC) showing sensitivity, 1- specificity and area under the curve (AUC) was used to evaluate the accuracy and cut-off value of NLR as a prognostic factor. *P* value < 0.05 was considered as statistically significant. Ethical approval was obtained from obtained from Sudan Medical Specialization Board (SMSB) and permissions were taken from hospitals' administrations.

III. Result

A total of 116 patients with sepsis admitted to ICUs during the study period were recruited. Males and females were 76 (65%) and 40 (35%) respectively. Their age ranged from 25 to 98 years with a mean of 65.2±17.7 years. The majority of the patients 76 (65.5%) were above 60 years. Pneumonia 67 (57.7%) was the major cause of sepsis in the study population followed by urosepsis 9(7.8%) and meningioencephalitis 6 (5.2%). Hypertension, diabetes, chronic liver disease, cardiac disease, chronic renal disease and cancer were recorded in 59 (50.9%), 43 (37.1%), 13 (11.2%), 7 (6%), 6 (5.2%) and 3 (2.6%) respectively.

According to the physiological parameters, the mean of respiratory rate (RR) was 25.3±7.2 and the majority of the patients 86 (74.1%) had respiratory rate below 30 breath/ minute. Mean of oxygen saturation (SPO2) was 91.4±10.1% with the majority of the patients 67(57.8%) had oxygen saturation more than 95%. Mean of heart rate (HR) was 99.1±21.3 with 7(6%) patients developing bradycardia (HR<60) and 51(44%) developing tachycardia (HR>100). Systolic blood pressure below 120 mmHg and diastolic blood pressure below 80 mmHg were found in 73 (62.9%) and 85(73.3%) of the patients, respectively. The mean of mean arterial pressure (MAP) was 89.3±17.8 with 89 patients (76.7%) who had a MAP above 70 mmHg. Eighty (69%) patients received oxygen supplementation while only 40(34.5%) patients received inotropes. Mean of fraction of inspired oxygen (FIO2) was 56.3±30.9 and the majority of the patients 80 (68.9%) had FIO2 above 40%. Mean of PaO2 was 93.9±32.5 with 91 (78.4%) patients who had PaO2 >75 mmHg. The means of temperature, Glasgow coma score (GCS), EWS and SOFA were 37.1±1.1, 11.5±3.7, 8.9±3.3 and 7.1±4.5 respectively.

Laboratory investigations revealed leukocytes count mean of 13.6±6.2 x 10^3 cell/mm^3, neutrophils count mean of 11.4±6.0x10^3 cell/mm^3, and lymphocyte count mean of 1.3±0.6 x 10^3 cell/mm^3, while platelets count mean was 410.9±54.8 x 10^3 cell/mm^3. The mean of CRP levels was 224.4±76.9; and those of creatinine and bilirubin were 2.1±0.7 mg/dl and 2.8±1.8 mg/dl, respectively. The neutrophil to lymphocyte ration (NLR) mean was 10.6±7.4. Regarding outcomes, 55 (48%) patients died, 28 (24%) had organ dysfunction and 33(28%) were discharged.

Pearson's correlation was used to identify relation between NLR and other variables. Glasgow coma score (GCS) was significantly negatively correlated with NLR (r= - 0.350; P= 0.000). Furthermore, EWS score showed moderate positive correlation with NLR (r= 0.331; P= 0.000) while both SOFA score and CRP levels showed strong positive correlation with NLR ,(r= 0.620; P= 0.000) (r= 0.839; P= 0.000) respectively. (table 1)

The association between NLR and outcomes showed that patients who died had the highest NLR mean (15.7±6.8) followed by the subjects with organ dysfunction (7.6±3.2) and those who were discharged (4.8±4.5), with statistically significant P value (P= 0.000) (table 2).

The association between NLR and PO2/FIO2 showed that patients with PO2/FIO2 less than 100 had the highest NLR mean (12.7±5.3) followed patients with PO2/FIO2 between 100- 200 (9.7±1.7), patients with

PO2/FIO2 between 201-300 (5.9±3.7), patients with PO2/FIO2 between 301-400 (3.2±2) and those with PO2/FIO2 more than 400 (2.8±1.2). The difference was statistically significant (P= 0.000) (table 3).

Multiple receiver operating characteristic curve (ROC) was drawn to evaluate validity of NLR in predicting mortality among patients with sepsis admitted to ICU. The area under the curve (AUC) of NLR was 0.882 (95% CI: 0.819–0.945; P= 0.000) (figure 1).

Furthermore, using the interactive Dot ROC an optimal cut-off NLR value for predicting mortality among patients with sepsis admitted to ICU NLR was calculated to be >9.8 (sensitivity = 94.3% and specificity = 97.1%) (figure 2).

Table 1: Pearson's correlation between NLR with GCS, EWS, SOFA and CRP (N= 116)

	Pearson's coefficient (r)	***P*. value**
GCS * NLR	-0.350	0.000
EWS * NLR	0.331	0.000
SOFA * NLR	0.620	0.000
CRP * NLR	0.839	0.000
Stay length * NLR	0.088	0.350

Table 2: Association between NLR and outcomes (N= 116)

Outcomes	**Mean**	**SD**	***P* value**
Discharge	4.8	4.5	0.000
organ dysfunction	7.6	3.2	
Death	15.7	6.8	

Table 3: Association between NLR and PO2/FIO2(N= 116)

PO2/FIO2	**Mean**	**SD**	***P* value**
>400	2.8	1.2	0.000
301-400	3.2	2.0	
201-300	5.9	3.7	
100-200	9.7	1.7	
<100	12.7	5.3	

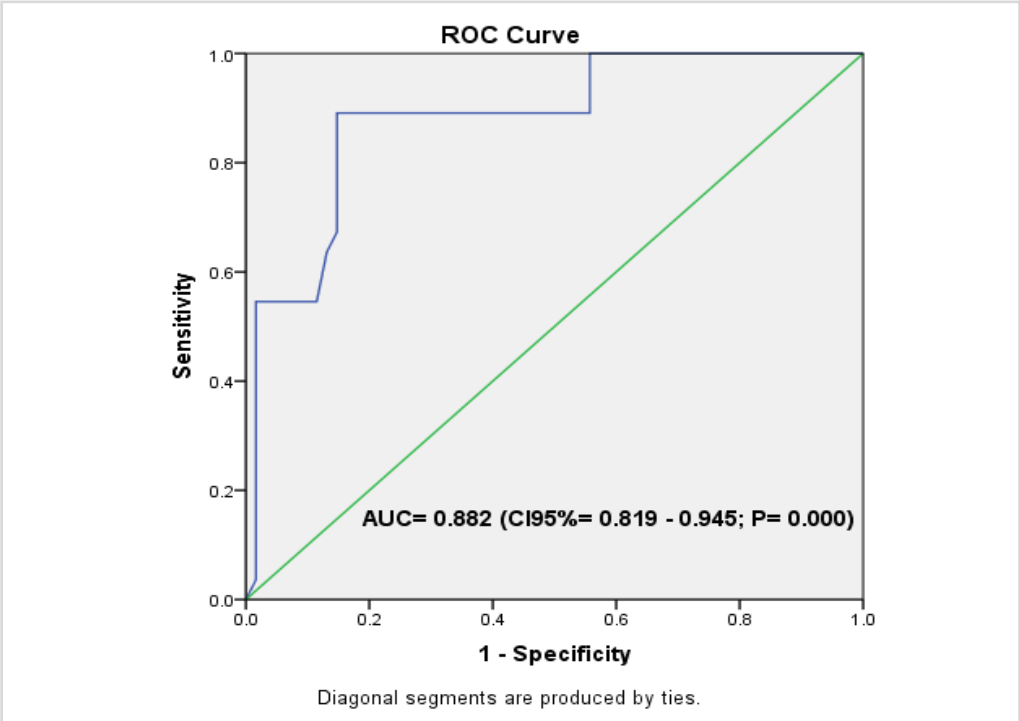

Figure 1: Shows multiple receiver operating characteristic curve (ROC) and the accuracy of NLR for predicting the outcome in patents with sepsis admitted to ICU. (AUC): area under the curve.

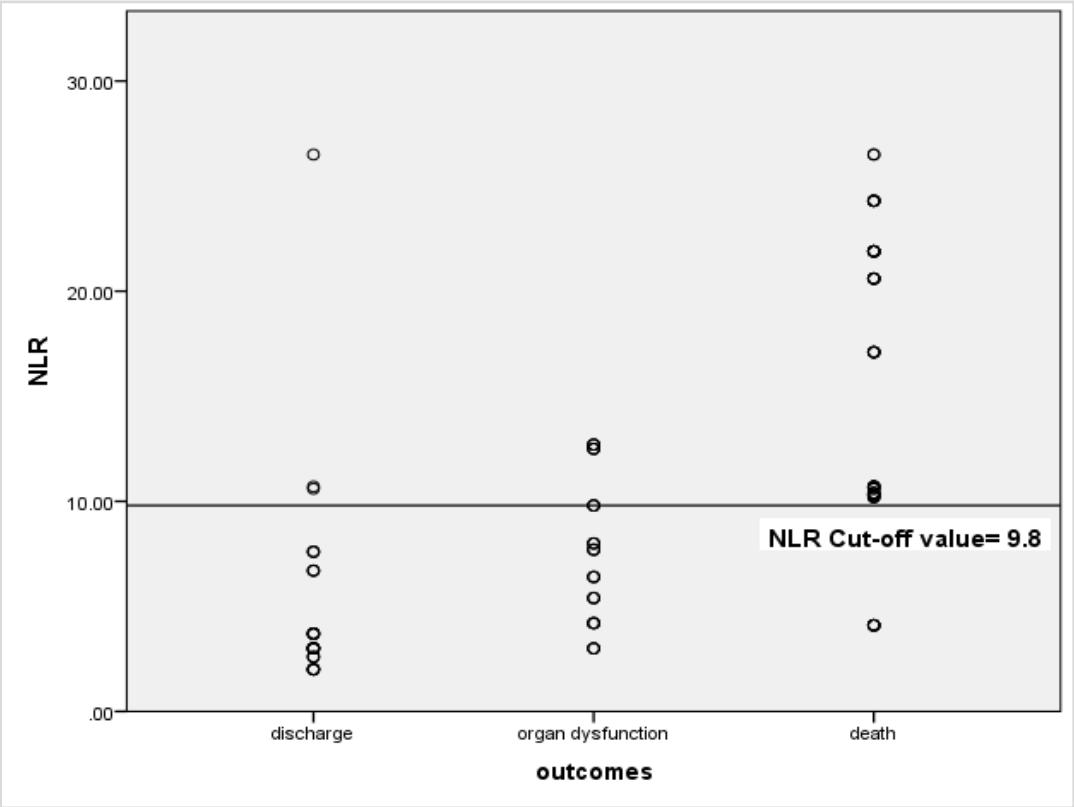

Figure 2: Interactive Dot ROC curves showing the cut-off NLR value for prognosis in patients with sepsis admitted to ICU.

IV. Discussion

In this study we aimed to assess the value of initial neutrophil to lymphocyte ratio (NLR) as an indicator of severe sepsis and a predictor of the outcome in patients with sepsis admitted to ICU. In systemic inflammation, demarginating and reduced apoptosis of neutrophil and increased lymphocyte apoptosis lead to increased neutrophil lymphocyte ratio (NLR)[13]. The use of NLR as a predictor of poor outcome in ICU was also studied in other conditions such as stroke and liver failure[14,15].

Our patients were mainly males and the majority were above 60 years. In a study done by *Xuan Liu et al*, among adult patients with sepsis, more than half of the patients were male and the mean of age was around 70 years which was associated significantly with unfavourable outcomes[16].

Hypertension and DM were the main comorbidities documented among our study group which is comparable to what was reported by Xuxan L et al, and Rajnish K et al [16,17]. Pneumonia and urosepsis were reported as the main causes of sepsis among patients admitted to ICU. Analysis of data related to 2973 patients with sepsis globally revealed that the most common source of sepsis was the respiratory tract[18]. Moreover, *Mayr FB et* al, found that respiratory and genitourinary tracts were the most common sites of infection in sepsis and were associated with higher mortality[19].

Assessing the outcomes of patients under study showed that almost half (48%) of the patients died. In Africa, the ICU mortality rate in patients with sepsis ranges between 39.5% and 47.2%[18]. Recently, WHO has estimated that nearly 20% of global deaths per year are sepsis-related and the rate of mortality is higher in low-middle income countries[20]. In 2018, we conducted a study regarding ICU admission in Sudan; in which we found that stroke and septic shock were the two major reasons for ICU admissions. The overall ICU mortality rate was 56%[21].

The range of normal NLR is variable in different studies, but mostly recorded as a value of less than 3.5[22–24]. In the current study, the neutrophil lymphocyte ration (NLR) mean was 10.6±7.4. Similarly, in a case control study that involved 226 patients with sepsis admitted to ICU, the NLR was 10.7 in patients with sepsis and this value was significantly different between the case group and control group[25].

Our study revealed that the overall correlation between NLR and sepsis poor outcome was significantly positive; as the highest level of NLR were correlated with the worst outcome (death) ($P< 0.05$). Several researches were conducted to assess the validity of NLR as a diagnostic and prognostic factor in sepsis which found significant correlation between high NLR and poor outcome in sepsis and critical illness[16,17,26].

However, another retrospective cohort study showed no correlation between NLR and 28-day hospital mortality[27].

Interestingly, this study didn't only show the significant association between NLR and patients' outcomes, but it also demonstrated the significant associations between NLR and other known risk factors for death in sepsis.

The links we found between NLR and both SOFA score and CRP levels were significant (P= 0.000), as higher NLR was correlated with higher SOFA score and higher CRP level. A similar result was reported by *Rehman FU et al*,[28]. According to sepsis-3, SOFA score of ≥ 2 is associated with severe sepsis and organ dysfunction as well as 10% increase in mortality. SOFA score of 13-14 can increase mortality rate up to 50%[1]. In this study the mean SOFA score was around 7. A high CRP level of more than 100 mg/L was also known to be a risk factor for mortality in sepsis[29]. Notable, the average CRP level in this study was around 200 mg/L.

Additionally, we found a positive correlation between NLR and Early Warning Score (EWS). It is worth mentioning that EWS is a quick monitor of physiological parameters which identifies deteriorating patients and those who need quick interventions, and in some studies it was found to be more sensitive than SOFA score in predicting death due to infection in ICU[30,31]. However, another study showed inaccuracy of EWS for mortality prediction[32]. The average EWS for patients in this study was around 9. *E Siddiqui et al*, reported an EWS of more than 7 to have a high sensitivity for detecting patients with sepsis and severe sepsis[33]. In the same way of our study, *Wang J-l et al*, reported a positive correlation between monocyte lymphocyte ratio (MLR) and national early warning score (NEWS) ($P<.001$)[34].

This study revealed significant negative correlation between NLR and GCS. GCS is a sensitive tool for detecting sepsis, therefore, a GCS of ≤ 14 has been used for calculation of both SOFA and qSOFA scores[1]. The lower GCS, the higher risk of mortality in sepsis[35]. Also, a negative association between NLR and PO_2/FIO_2 ratio was significant. PO_2/FIO_2 has been used as a component of SOFA score to assess the respiratory dysfunction[1]. Analysis of data in the current study showed that the highest NLR mean was observed in patients with the lowest PO_2/FIO_2 (<100). In a study done by *Santana AR et al*, among patients with sepsis, respiratory tract and urinary tract where the main sites of infection and non-survivor patients had lower PO_2/FIO_2 ratio than those who survived ($P< 0.05$)[36].

On the other hand, the association between NLR and the length of ICU or hospital stay was not significant ($P= 0.350$). In contrast, in a retrospective study involved more than 21000 patients admitted to ICU between 2001 and 2012, patients with high level of NLR had longer hospital and ICU stay ($P< 0.001$)[37]. This insignificant association might be due to small sample size.

Finally, our study revealed a NLR cut-off value of ≥ 9.8 with high sensitivity (94.3%), specificity (97.1%) and high accuracy (AUC = 0.882 (95% CI: 0.819–0.945; P= 0.000)) as a predictor of mortality in patients with sepsis admitted to ICU. This is comparable to a study done by *Ni J et al*, which defined a NLR cutoff value of 9.1 as marker for in-hospital mortality due to sepsis[27].

This significant positive correlation between NLR and SOFA score, CRP levels and EWS as well as NLR's negative association with GCS and PO_2/FIO_2 ratio can explain the significance of NLR as an indicator of poor outcome in sepsis. This raises the possibility of using NLR as an easy and cheap tool to predict outcome in patients with sepsis especially in limited-resource areas.

V. Conclusion

This study concludes that the initial NLR measured at admission was independently associated with mortality and severity of disease in patients with sepsis admitted to ICU. In addition, the change in the NLR may prove to be a valuable prognostic marker in patients with sepsis.

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