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Role Neutrophil to Lymphocyte Ratio on Admission as a Predictor of in Hospital Mortality in Septic Patients

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Abstract

Background: Sepsis has high mortality globally. The key factor in decreasing the mortality is early diagnosis and the initiation of appropriate treatment within hours. Various biomarkers are in use for timely diagnosis but none is without limitation. It's imperative to predict the mortality early in order to sensitize those involved in the care. We studied Neutrophil to Lymphocyte Ratio (NLR) as a prognostic marker in sepsis.

Methodology: It was a retrospective study, conducted at Aga khan university hospital from 30th November 2020 to 31st March 2021. Data was calculated from patient medical record after approval from ERC. Multiple linear regression technique was used to determine the association between increased NLR with mortality.

Results: Our study included 168 patients. The median (IQR) NLR of the patients was 10.4 (13.4). The mean SOFA score of the patients was noted to be 5.7 ± 2.9, mortality was reported in 26.1% (n=44) patients. Multiple linear regression showed NLR increased by 2.0 times with every mg/dl increased in average total bilirubin level (95% CI: 0.4-3.2), and by 1 times with every one unit increase in SOFA score (95% CI: 0.1-1.5). However, there was no significant association found between NLR and mortality rate.

Conclusion: NLR is an effective marker for predicting sepsis; however, its role in predicting mortality is yet to be established.

Keywords: Neutrophil to lymphocyte ration; Sepsis mortality

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Introduction

Sepsis is an unfettered inflammatory response to infection and demonstrates as a variety of illness that ranges clinically from bacteremia to severe sepsis to septic shock [1]. The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) defined sepsis as life-threatening organ dysfunction resulting from dysregulated host responses to infection and defined septic shock as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase the risk of mortality [1] Sepsis is a public health issue globally and is associated with high mortality.

Most data describing the incidence of sepsis are from high-income countries, where 2.8 million deaths per year are attributable to sepsis [2]. Angus et al. reported the incidence of severe sepsis in USA to be more than 300 cases per 100000 populations [3]. The reported prevalence of sepsis in UK is 27% of all ICU admissions, whereas the prevalence is 12% in the USA [4]. In low income countries the morality ranges from 60-80% [5] which is very high and in Pakistan it was documented to be 37% in a tertiary care hospital [5].

In clinical setting various bio markers and scoring systems can be used to diagnose sepsis and forecast it mortality [6], However these markers are either very expensive or not readily available so there is a lot of emphasis on tools that are cost effective, readily available and not only helpful in early diagnosis but can also predict the mortality.

Understanding that sepsis is a medical emergency so efforts are made to intervene at the earliest and markers which can guide

this immediate response has been studied. Neutrophils to Lymphocytes Ratio (NLR) is well known among the most readily available marker of sepsis diagnosis and prognostication [6], however its role in the prognosis is not studied in local population. Our objective in this retrospective study is to determine the association between NLR and hospital mortality rate among patients with sepsis.

Materials and Methods

A retrospective observational study conducted from 30th November 2020 to 31st March 2021 in tertiary care hospital of Karachi, Pakistan. Data was collected from patient's medical record after obtaining permission from institute ethical review committee (ERC# 2020-5643-14944). We included all adult patients of age above 18 years of either gender, admitted in Medicine department of Aga khan university hospital with diagnosis of sepsis on arrival or during hospital stay. Patients were diagnosed as septic based on the SOFA score. We excluded patients with massive blood loss and having severe disease complication such as myocardial infraction, pulmonary embolism, rheumatoid arthritis. No patient identifiers were recorded to protect patient's privacy.

A trained research staff collected the data based on the inclusion criteria which included all data on patient's demographic, data of inflammatory markers along with important vital and physical signs. A total of 168 patients has been selected using 10% level of significance, 90% confidence interval and 5% margin of error with 50% anticipated proportion of Sepsis. Patients were included within the period of 3 months. Data was entered and analysed in SPSS version 25. Descriptive analysis was performed on all the variables. Categorical variables were presented in form of frequency and percentages whereas quantitative variables were presented in form of mean (SD) or Median (IQR) depending upon the distribution of the Variable. Data was stratified according to age and gender. An appropriate statistical test was applied post stratification. P-value equal or less than 0.05 was considered significant.

Results

Our study included 168 patients, of which 55.3% (n=93) were male and remaining 44.6% (n=75) were females. Most participants (61.9%) were aged greater than 60 years. Out of 168 patients, 43.4% (n=73) were on inotropic support and 25% (n=42) of the patients were on ventilator support. The mean SOFA score of the patients was noted to be 5.7 ± 2.9. Majority of the patients i.e., 66% had elevated level of total leucocytes counts. The median (IQR) Neutrophil-Lymphocyte Ratio (NLR) of the patients was 10.4 (13.4). Also, 20% and 27.9% cases of positive blood and urine cultures were identified. Among a total of 168 cases, mortality was reported in 26.1% (n=44) patients. **Table 1** elaborates the baseline demographics and clinical parameters of patients.

Multiple linear regression technique was used to determine the association between increased NLR with mortality. All independent variables were considered for their potential association with increased NLR in univariate analysis using linear regression for which unadjusted Betas (β) were calculated. Age, SOFA score, TLC, creatinine level, procalcitonin, systolic blood pressure and sputum culture were all associated with increased NLR among patients in univariate analysis on P-value for selection (<0.25) as mentioned in **Table 2**.

The findings from multiple linear regression models examining the association between NLR and the mortality on P-value for selection (<0.05) are given in **Table 3**.

The main model showed that NLR was 9.5 times higher among patients who reported higher total leucocytes count as compared to patients who had normal total leucocytes count (95% CI: 4.7-14.4). The model also showed that NLR increased by 2.0 times with every one milligram per decilitre (mg/dL) increased in average total bilirubin level (95% CI: 0.4-3.2). The NLR level increased by 0.03 times with every millimetres of mercury (mmHg) increased in systolic blood pressure level (95% CI: 0.004 -0.04). The model also showed that the NLR level increased by 1 time with every one unit increase in SOFA score (95% CI: 0.1-1.5). However, there was no significant association found between NLR and mortality rate.

Discussion

In this current study we could not find NLR as a useful marker for predicting in hospital mortality among septic patients. However it's among the most readily available marker for predicting sepsis and positively correlated with other markers of sepsis [7]. Savran et al. and colleagues had the same observations where they found NLR to be useful in prediction the severity of sepsis but not positively related to the mortality in same patients [8].

At least two studies have shown a concordance conclusion of non-significant association of NLR with mortality in sepsis Vis-a-Vis non septic patients [9,10]. Ham et al. found NLR to be useful in predicting 28 days intensive care unit mortality in patients without sepsis; however the same relation was not seen in patients with sepsis [9]. Ni et al. also proposed a low NLR to be independent predictor of in hospital mortality in patients with sepsis [10].

However, in divergence to our finding, Hwang et al. recognized NLR to be a very useful marker in forecasting mortality in sepsis and septic shock [11]. The possible reason for this discordance include higher number of patient on inotropic support (62.9% vs. 43%) and higher mean SOFA score (7vs 5.7). In addition, significant number of patient in their cohort compromised of having comorbid conditions like hypertension (33.4%), diabetes mellitus (22%) and cardiovascular diseases, all of which contributed to higher mortality in sepsis [11].

The association of NLR with outcome in sepsis can be explained by physiological link between neutrophil and lymphocyte count with systemic inflammation and stress [12]. Patients response to inflammatory insult include rise in neutrophil count, if this rise in neutrophil count is overwhelming it may that lead to lymphocyte

Table 1 Basic characteristics of study participants (n=369). Values are either in mean ± SD or n (%) or Median (IQR).

Characteristics	n	(%)
Age (years)		
18-40	20	11.9
41-60	44	26.1
>60	104	61.9
Gender		
Males	93 75	(55.3)
Females		(44.6)
Pulse (beats/min)^	98	± 21.3
Inotropic Support		
Yes	73	(43.4)
No	95	(56.5)
Ventilator Support		
Yes	42	(25)
No	126	(75)
Temperature		
Febrile	14	(8.3)
Afebrile	154	(91.6)
SOFA score ^	5.7	± 2.9
Hemoglobin level (Hb)^	10.7	± 2.4
Platelets Count*	229	160.5
Total Leucocytes Count (TLC)		
Low counts level	10	(5.9)
Normal counts level	47	(27.9)
High counts level	111	(66)
Serum Creatinine level*	1.8	2.4
Neutrophil-Lymphocyte Ratio (NLR)*	10.4	13.4
Total bilirubin level*	0.6	0.8
Lactate level*	2	1.5
Procalcitonin level*	2	5.1
Systolic Blood pressure*	118	31
Diastolic Blood pressure*	70	20
Urine Culture		
Positive	47	(27.9)
Negative	121	(72)
Blood Culture		
Positive	34	(20.2)
Negative	134	(79.7)
Pus Culture		
Positive	18	(10.7)
Negative	150	(89.2)
Sputum Culture		
Positive	34	(20.2)
Negative	134	(79.7)
Shock Condition		
Yes	29	(20.8)
No	110	(79.1)
Mortality		
Yes	44	26.1
No	124	73.8
Primary Diagnosis		
Pneumonia	74	(44.0)
Urinary Tract Infection	44	(26.1)
Intra-abdominal Infection	9	(5.3)
Central Nervous System (CNS)	8	(4.7)
Skin, soft tissue and bone infections	33	(19.6)

For symmetry distribution: (^Means (SD=Standard Deviation)); For asymmetry distribution (*Median (IQR=Interquartile Range); For categorical variable n (%)

Table 2 Univariate analysis of factors associated with increased NLR among patients of Karachi, Pakistan (n=168).

Risk factors	Unadjusted Beta (β)	95% CI	P-value
Age (years) 18-40 41-60 >60	 - 4.9 7.9	 2.6 - 12.5 1.0 - 14.8	0.06*
Gender Males Females	 1.2 -	 3.4- 5.5	0.633
SOFA score	1.1	0.2 - 1.7	0.039*
Total Leucocytes Count (TLC) Low counts level Normal counts level High counts level	 - -4.2 10.6	 13.5 - 4.9 6.0-15.2	<0.001*
Serum Creatinine level	1.1	0.1 - 2.0	0.032*
Total bilirubin level	2.2	0.6 - 3.7	0.006*
Procalcitonin level	0.1	0.03 - 0.2	0.010*
Systolic blood pressure	0.02	0.004 - 0.05	0.021*
Diastolic blood pressure	-0.08	0.20 -0 .03	0.177*
Mortality Yes No	0.8	5.9 - 4.1	0.729
Shock Condition Yes No	0.4	4.6 - 5.5	0.862
Lactate level	-0.4	1.6 - 0.7	0.461
Inotropic Support Yes No	1.0	3.4 - 5.4	0.652
Sputum Culture Positive Negative	3.9	1.5 - 9.4	0.154*

death and higher NLR, causing unfavourable inflammatory response to sepsis and other inflammatory stresses which ultimately results in adverse outcome [13-16].

Sequantional Organ Failure Assessment Score (SOFA) has been validated a useful score for predicting mortality in septic patients in various studies [17,18] and SOFA score with coagulopathy or hepatic involvement is the strongest predictor of mortality in sepsis [19]. We also found NLR to be positively co-related with SOFA score and total bilirubin levels, however in multi-logistic regression the relation between NLR and mortality was not statistically significant.

As NLR is one of the earliest available, cost effective and efficacious markers of sepsis so its role in predicting mortality

Table 3 Multi-variables analysis of factors associated with increased NLR among patients of Karachi, Pakistan (n=168).

Risk factors	Adjusted Beta (β)	95% CI	P-value
Total Leucocytes Count (TLC)			
Low counts level	-8.5	18.3 - 1.2	0.121
Normal counts level	-		
High counts level	9.9	4.7 - 14.4	<0.001*
SOFA score	1.0	0.1- 1.5	0.032*
Total bilirubin level	2.0	0.4 - 3.2	0.012*
Systolic blood pressure	0.03	0.004- 0.04	0.019*
Mortality			
Yes	0.5	4.4 - 5.4	0.87
No			

should be studied in better designed, multi-centre studies with larger sample size.

Conclusion

NLR does have role in predicting sepsis and sepsis severity, however it part in forecasting sepsis mortality is yet to be established.

Ethical Approval

This study was reviewed and approved by ethical review committee of Aga Khan University.

Conflict of Interest

Authors declared no conflict of interest.

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