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Medicine

PROGNOSTIC SIGNIFICANCE OF NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) IN CRITICALLY- ILL SEPTIC PATIENTS

Dr. A K Chaurasia	Associate Professor, Dept of Medicine, MLN Medical College, Prayagraj, UP.
Prof. Poonam Gupta	Professor and Head of Department, Dept of Medicine, MLN Medical College, Prayagraj, UP.
Dr Manoj Kumar Mathur	Associate Professor, Dept of Medicine, MLN Medical College, Prayagraj, UP.
Dr Rajendra Kumar Singh*	Junior Resident, Dept of Medicine, MLN Medical College, Prayagraj, UP. *Corresponding Author

ABSTRACT **Objectives:** For early detection of sepsis, when the treatment is most effective, various biomarkers have been used but the cost, facilities limit their use. In this context NLR (neutrophil to lymphocyte ratio) can be a suitable marker of sepsis which can predict the outcome of sepsis patient not hampered by the constraint of sensitivity, specificity, practicality and financing.The objective of the study was to study the role in early detection and prognostic significance of NLR as a marker of sepsis in critically ill septic patients.

Methods: A prospective observational study was done in a total of 320 patients with suspected or documented sepsis at the time of admission falling under inclusion criteria. The values from different hematological, biochemical, radiological and other clinical investigations were used to derive NLR and SOFA score on Day 0, Day 3 and Day 7 and were compared to establish the efficacy in prognosticating septic patients.

Result: For comparision two groups, survivor (n=249, 77.8%) and non-survivor (n=71, 22.2%) group were made. The mean values of NLR and SOFA both were found to be significantly higher in expired group. When ROC cut off limit kept for NLR ≥15(sen.86%; spec.68%; OR 17.1; RR 4.49) and SOFA (sen 86%; spec 76%; OR 21.96; RR 7.75) at admission, we found comparable efficacy in early predicting the prognostic outcome. A significant positive correlation ($p<0.01$) between change in NLR and SOFA values at admission(rho=0.42) and on day 3rd (rho=0.43) and 7th (rho=0.28) was seen in both groups. It was also seen that in patients with higher the values of NLR and SOFA, had significant correlation($p<0.001$) with prolonged hospital stay (day3, rho=0.45 and day7, rho=0.84). NLR also predicted therapeutic response, as after treatment initiation, its values decreased on following days in the survivor group whereas patients with rising trend either succumbed or had prolonged duration of hospital stay and more incidence organ dysfunction.

Conclusion: It is concluded from the study that SOFA scores and NLR values both independently as well as in association with other parameter are relatively comparable in terms of sensitivity, specificity and discriminatory power in predicting mortality and prognosis among sepsis patients admitted to ICU.

KEYWORDS :

INTRODUCTION

Sepsis is now recognized to involve early activation of both pro- and anti-inflammatory responses, with loss of homeostasis and disruption of fine balance between pro- and anti-inflammatory mediators [1,2]. The broader perspective also emphasizes the significant biological and clinical heterogeneity in affected individuals, with age, underlying comorbidities, concurrent injuries (including surgery) and medications, and source of infection adding further complexity. Despite of all these efforts, the reported annual incidence of sepsis is approximately 750,000 cases in United States, out of which about one-third are fatal [3]. At global level, approximately 31.5 million new cases of sepsis are reported every year, of which 5.3 million fail to survive [4].

Although, no systematic records of sepsis in India are available, yet the magnitude of sepsis could be assumed to be much higher as compared to the west. In India, the average annual incidence of SIRS and sepsis were recorded as nearly 465 and 243 cases per 10,000 respectively, with mortality rates as high as 59.26% for the cases of severe sepsis [5]. Although the true incidence is unknown, conservative estimates indicate that sepsis is a leading cause of mortality and critical illness worldwide [6]. Furthermore, there is increasing awareness that patients who survive sepsis often have long-term physical, psychological, and cognitive disabilities with significant health care and social implications [3].

It is also clear that there is a significant risk of missing early identification of sepsis when the treatment is most effective, as it involves early activation of both pro- and anti-inflammatory responses, along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation, all of which have prognostic significance [1,2,7]. For early detection of sepsis, various biomarkers like CRP, procalcitonin, IL-6, 8, TNF, CD64, etc have been used but the cost, and the facilities for their testing limits their use [7]. Therefore, the search continues for preferable infection markers that may facilitate the early prognosis prediction of sepsis.

One of the physiological responses in immune system against inflammation is an acute increase in the number of neutrophils and decrease in the lymphocyte number. Due to change in the dynamics, delay of apoptosis of recruited neutrophils and increased apoptosis of the lymphocyte at the site of inflammation, prolongs the systemic effects of inflammation. It is seen that after 4-6 hrs of initiation of inflammation, there is a 300% rise in circulating neutrophils, 85% decrease in lymphocytes and 96% decrease in monocytes levels [7]. In this context NLR (neutrophil to lymphocyte ratio) has gained interest as an independent marker of sepsis [2].

NLR is based primarily on physiological link between neutrophilia and lymphopenia with systemic inflammation [7-10]. It can be obtained easily, cheaply and rapidly and can provide relevant information for necessary intervention within first few hours of admission, not hampered by the constraint of sensitivity, specificity, practicality and financing. NLR has not only gained interest in early prediction of sepsis but also an independent predictor of survival in various clinical conditions, ranging from cardiovascular to oncological cases [11-13].

In this study we aim to study neutrophil to lymphocyte ratio (NLR) as a marker of sepsis in patients with sepsis and to find prognostic significance of neutrophil to lymphocyte ratio in critically ill patients with sepsis.

MATERIALS AND METHODS

This prospective observational cohort study was conducted in SRN Hospital, MLN Medical College, Prayagraj, U.P. India. Total 320 suspected septic adult patients were enrolled. Patients already admitted and developing septic secondarily, underlying malignancy, immunosuppressive drugs, aplasia or immunosuppressive disease (HIV), pregnancy and critically ill patients of etiology other than sepsis were excluded from the study. After obtaining informed written

consent, detail history and relevant clinical examinations, biochemical and radiological examination in patients who qualified inclusion criteria was done.

Blood samples and other relevant investigations like CBC, LFT, KFT, Serum Electrolyte, RPG, ABG ,Blood/urine culture, site specific culture, X-ray, USG abdomen and ECG, 2DECHO were recorded. The values from the investigations were used to derive NLR ratio and SOFA score on Day 0, Day 3 and Day 7.

SOFA score includes parameters depicting possible effect of sepsis on major organ systems [14].

SOFA SCORING

ORGAN SYSTEM	0	1	2	3	4
Glasgow Coma Scale	15	14-13	12-10	9-6	less than 6
pO2/fio2 mmHg	>400	<400	<300	<200	<100
Platelet Count (lac/mm)	>1.5	<1.5	<1	<0.5	<0.2
Serum Bilirubin (mg/dl)	<1.2	1.2-1.9	2-5.9	6-11.9	>12
Cardiovascular (vasopressor dosage in ug/kg/min)	>70 mmHg	MAP<70 mmHg	Dopamine <5 Or, dobutamine (any dose)	Dopamine 5-5, or, epinephrine ≤0.1, Norepinephrine≤0.1	Dopamine >15 or, epinephrine >0.1 or, Norepinephrine>0.1
Serum creatinine (mg/dl) Urine output(ml/d)	<1.2	1.2-1.9	2-3.4	3.5-4.9 <500	>5 <200

Statistical Analysis

The statistical analysis was done using the SPSS v.20.0 (IBM Corp., Armonk, NY, USA) portable package program. The continuous numerical values of the binary groups were compared using Student's t-test for uniform distribution and expressed as the mean ± standard deviation. Nonuniform distribution was assessed using the Mann–Whitney U test and median quarter-to-quarter ratio. Dichotomous values were summarized using the chi-square test. Comparisons of 2 or more groups were compared using the Kruskal–Wallis test for unevenly distributed data. Assessment of mortality markers was shown using the receiver operating characteristic (ROC) curve and the area under the curve (AUC).

RESULTS

Table 1 shows the baseline characteristics of the patients. The mean age of the patients was 46.30 ±17.33. Total 61.3% patients had male and 38.8% female.

Table 1: Baseline Characteristics Of The Patients

All Parameters	Mean ± SD
Age (Years)	46.30 ±17.33
Gender	
Male	196 (61.3%)
Female	124 (38.8%)
TLC (/cu.mm)	20101.31 ± 8222.39
Neutrophils (%)	85.50 ± 7.95
Lymphocytes (%)	10.22 ± 7.90
SGOT (U/L)	85.44 ± 72.78
SGPT (U/L)	76.39 ± 77.86
ALP (U/L)	322.55 ± 287.19
T. Bilirubin (mg/dL)	1.20 ± 0.97
T. Protein (g/dL)	6.11 ± 9.10
S. Creatinine (mg/dL)	1.67 ± 1.13
Blood Urea (mg/dL)	74.96 ± 62.13
BUN (mg/dL)	36.74 ± 29.41
S. Sodium (mEq/L)	138.25 ± 6.58
S. Potassium (mEq/L)	4.29 ± 0.63
S. Calcium (mEq/L)	0.97 ± 0.63
Systolic BP (mmHg)	113.96 ± 27.73
Diastolic BP (mmHg)	74.47 ± 17.23
MAP (mmHg)	87.63 ± 20.42
Random Plasma Glucose (mg/dL)	149.44 ± 96.40
paO2/fio2	
100-200	21 (6.6%)
200-300	32 (10.0%)
300-400	267 (83.4%)
Platelet Count (Lacs/cu.mm)	1.67 ± 0.76
GCS	13.18 ± 2.96
SOFA (Admission)	4.03 ± 3.47
NLR (Admission)	11.56 ± 6.05

The change in SOFA score and NLR score from admission to day 7 are shown in Table 2. The SOFA score was significantly decreased from admission (4.03±3.47) to day 3 (2.42±3.00) and day 7 (0.87±1.57). The NLR was also decreased from admission (11.56±6.05) to day 3 (7.09±5.65) and day 7 (2.36±2.85).

Table 2: Change In SOFA And NLR From Admission To Day 7

	Admission (n=320)		Day 3 (n=320)		Day 7 (n=320)		p-Value
	Mean	± SD					
SOFA Score	4.03	3.47	2.42	3.00	0.87	1.57	<0.001*
NLR	11.56	6.05	7.09	5.65	2.36	2.85	<0.001*

*=Significant (p<0.05)

Table 3 shows the comparisons of SOFA score and NLR in between discharge/referred and expired patients at admission, day 3 and day 7. Out of 320, total 249 (77.81%) patients were discharge/referred and 71 (22.19%) patients were expired. The mean SOFA score was 2.93 ± 2.69, 1.86 ± 2.27 and 0.90 ± 1.37 in discharge/referred patients and 7.87 ± 3.17, 4.41 ± 4.19 and 0.77 ± 2.11 in expired patients at admission, day 3 and day 7, respectively. The SOFA score was significantly higher in expired patients at admission and day 3 and significantly lower at day 7 in between discharge/referred and expired patients. The mean NLR was 9.91±4.61, 6.75±3.76 and 2.95±2.80 in discharge/referred patients and 17.35 ± 6.92, 8.27 ± 9.67 and 0.28 ± 1.87 in expired patients at admission, day 3 and day 7, respectively. The mean NLR was significantly higher at admission and significantly lower at day 7. NLR was comparable at day 3 in between discharge/referred and expired patients.

Table 3: Comparisons Of SOFA Score And NLR In Between Discharge/referred And Expired Patients At Admission, Day 3 And Day 7.

	Outcome		p-Value
	Discharged/Referred (n = 249)	Expired (n = 71)	
SOFA (Admission)	2.93 ± 2.69	7.87 ± 3.17	<0.001*
SOFA (Day 3)	1.86 ± 2.27	4.41 ± 4.19	<0.001*
SOFA (Day 7)	0.90 ± 1.37	0.77 ± 2.11	0.003*
NLR (Admission)	9.91 ± 4.61	17.35 ± 6.92	<0.001*
NLR (Day 3)	6.75 ± 3.76	8.27 ± 9.67	0.242
NLR (Day 7)	2.95 ± 2.80	0.28 ± 1.87	<0.001*

*=Significant (p<0.05)

Spearman correlation coefficient of SOFA was significantly negatively correlated with the duration of hospital stay at admission whereas SOFA (Day 3), SOFA (Day 7), NLR (Admission), NLR (Day 3) and NLR (Day 7) was significantly positively correlated with the duration of hospital stay.

Table 4: Correlation Between SOFA Score And NLR With The Duration Of Hospital Stay At Admission, Day 3 And Day 7

	Duration Of Hospital Stay (Days)	[1]p value
SOFA (Admission)	-0.21	<0.001*
SOFA (Day 3)	0.09	0.111*
SOFA (Day 7)	0.25	<0.001*

NLR (Admission)	0.02	0.695*
NLR (Day 3)	0.45	<0.001*
NLR (Day 7)	0.84	<0.001*

*=Significant (p<0.05), *1: Spearman Correlation*

The Sensitivity, specificity positive productive value (PPV) and negative productive value (NPV) of diagnosing of outcome by SOFA score and NLR are shown in Table 5. The cut-off value for SOFA was 5 at admission, 6 at day 3 and 0 at day 7 (ROC) to make a diagnosis of outcome (expired). With these cut-off values, SOFA had more sensitivity of 85.9%, specificity of 76.3%, PPV of 50.8% and NPV of 95.0% in the diagnosis of outcome (expired) at admission. Whereas it was 45.1%,92.4%, 62.7%, 85.5%, respectively at day 3 and 80.3%, 41.8%, 28.2% and 88.1% respectively at day 7.

The cut-off value for NLR was 15 at admission, 0 at day 3 and day 7 (ROC) to make a diagnosis of outcome (expired). With these cut-off values, SOFA had sensitivity of 85.9%, 52.1% and 97.2% specificity of 67.5%, 99.6%, and 65.9%, PPV of 43.0%, 97.4%, and 44.8% and NPV of 94.4%, 87.9% and 98.8% in the diagnosis of outcome (expired) at admission, day 3 and day7, respectively. These tests were demonstrating the accuracy of risk factors. SOFA score were showed significant large area under the curve (AUC) on the ROC curve at admission and day 3. NLR were showed significant large area under the curve (AUC) on the ROC curve at admission (Figure 1).

Table 5: Sensitivity, Specificity Positive Productive Value (PPV) And Negative Productive Value (NPV) Of Diagnosing Of Outcome By SOFA Score And NLR

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
SOFA (Admission) (Cutoff: 5 by ROC)	85.9% (76-93)	76.3% (71-81)	50.8% (42-60)	95.0% (91-98)	78.4% (74-83)
SOFA (Day 3) (Cutoff: 6 by ROC)	45.1% (33-57)	92.4% (88-95)	62.7% (48-76)	85.5% (81-89)	81.9% (77-86)
SOFA (Day 7) (Cutoff: 0 by ROC)	80.3% (69-89)	41.8% (36-48)	28.2% (22-35)	88.1% (81-93)	50.3% (45-56)
NLR (Admission) (Cutoff: 15 by ROC)	85.9% (76-93)	67.5% (61-73)	43.0% (35-52)	94.4% (90-97)	71.6% (66-76)
NLR (Day 3) (Cutoff: 0 by ROC)	52.1% (40-64)	99.6% (98-100)	97.4% (86-100)	87.9% (84-92)	89.1% (85-92)
NLR (Day 7) (Cutoff: 0 by ROC)	97.2% (90-100)	65.9% (60-72)	44.8% (37-53)	98.8% (96-100)	72.8% (68-78)

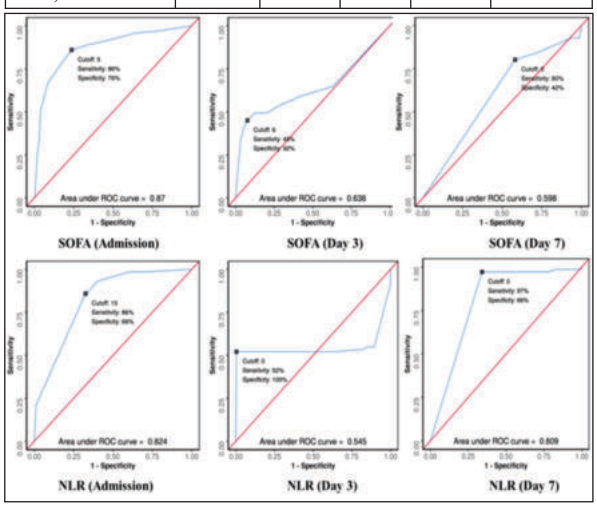

Figure 1: Receiver operating characteristic (ROC) curve analysis of diagnosing of outcome (expired). Each receiver characteristic curve is expressed as a solid line. AUC: area under the curve.Spearman correlation coefficient of NLR was significantly positive correlated with the SOFA score at admission, day 3 and day 7 (Table 6). Moreover, there was a moderate positive correlation between NLR (Admission) and SOFA (Admission), and this correlation was statistically significant (rho = 0.42, p = <0.001). There was a moderate positive correlation between NLR (Day 3) and SOFA (Day 3), and this correlation was statistically significant (rho = 0.34, p = <0.001). There was a weak positive correlation between NLR (Day 7) and SOFA (Day 7), and this correlation was statistically significant (rho = 0.28, p = <0.001).

Table 6: Correlation Between NLR And SOFA Score In Patients

Correlation	Spearman Correlation Coefficient	P Value
NLR (Admission) vs SOFA (Admission)	0.420	<0.001
NLR (Day 3) vs SOFA (Day 3)	0.340	<0.001
NLR (Day 7) vs SOFA (Day 7)	0.280	<0.001

*=Significant (p<0.05), *1: Spearman Correlation*

The following variables were significantly associated (p<0.05) with the variable 'SOFA (Admission)', NLR (Admission) Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

DISCUSSION

Sepsis is one of the most important and common cause for ICU admission. Sepsis involves magnitude of change in different physiological, hematological and biochemical parameters, thus these can be considered to be useful for prediction of outcome among sepsis patients admitted to an ICU.. SOFA score not only complex, time consuming and inconvenient but also costly assessment, particularly in low resource settings in a developing country like ours. Hence, there has always been an emphasis on exploration and validation of such parameters that can be obtained easily and have enough applicability in clinical settings. NLR is one such parameter, which in wake of increasing use of autoanalyzers is easily available and have been found to have adequate efficacy in prediction of ICU outcome in general and outcome of sepsis patients admitted to an ICU in particular [1-10].

Encouraged by the outcomes reported in previous studies, the present study was carried out to assess its prognostic efficacy in sepsis patients in our setup. The SOFA score was significantly decreased from admission (4.03±3.47) to day 3 (2.42±3.00) and day 7 (0.87±1.57) . The NLR was also significantly decreased from admission (11.56±6.05) to day 3 (7.09±5.65) and day 7 (2.36±2.85). Previous various studies reported that the range of baseline SOFA scores and NLR were 3-8 and 6.72-10.2 [15-19]. However, this difference could be owing to inclusion of exclusively severe sepsis cases in their study. As noted by most of the studies, the increasing severity of sepsis is associated with increased NLR values, the higher scores in our study thus could be well justified.

In this study the SOFA score was significantly negatively correlated with the duration of hospital stay at admission, Day 3 and Day 7 whereas the NLR was significantly positively correlated at Admission, Day 3 and Day 7 with the duration of hospital stay. Pantzaris et al. (2018) showed that the NLR correlation with either the days of hospitalization or the sepsis prognostic scores [17]. Karagoz et al. (2019) found that the hospital stay duration for patients in the survived and deceased groups were 3 (1-118) and 6 (0-97) days, respectively and this difference was statistically significant [20]. On the other hand, Gharebaghi et al. (2019) found that there was no significant correlated the length of hospital stay with NLR, or, SOFA score [21]. Martins et al. (2019) in a case-control study found that NLR (r = 0.3), has a positive and statistically significant correlation with length of hospital stay and also patients who had a diagnosis of sepsis at admission to the ICU remained longer in the department, and the hospitalization time and death rate were higher in these patients [22].

Keeping in view the correlation of NLR and SOFA values with the severity of sepsis as observed in previous studies, the difference in different studies could be attributable to the difference in proportion of patients with different severities of sepsis. Liu et al. (2016) observed that the increased NLR levels were independently associated with an unfavorable clinical prognosis [19]. Hwang et al. (2017), revealed that the initial NLR measured at ED admission was independently associated with the 28-day mortality [16]. Additionally, a change in the

NLR may be used as a valuable prognostic marker.

In present study, there were 71 (22.2%) mortalities. Out of 320, total 249 (77.81%) patients were discharge/referred and 71 (22.19%) patients were expired. The SOFA score was significantly higher in expired patients at admission and day 3 and significantly lower at day 7 in between discharge/referred and expired patients. Whereas, the mean NLR was significantly higher at admission and significantly lower at day 7. NLR was comparable at day 3 in between discharge/referred and expired patients. Akilli et al. (2014) reported that the high NLR was independently associated with in-hospital mortality and 6-month mortality [15]. In addition, high NLR was also related to a risk of multi-organ failure and sepsis development. Riche et al. (2015) revealed an association between NLR and risk of death in patients with septic shock [18]. They also suggested that NLR could be used as an indicator of early (before day 5) and late (on or after day 5 after septic shock onset) death. In a study conducted by Salciccioli et al. (2015) NLR measured at the time of ICU admission was associated with 28-day mortality in unselected critically ill patients [23]. In subgroup analysis, however, there was no association between NLR and mortality in sepsis patients. The evaluation criteria in different studies taking into account different landmarks, viz. in-hospital mortality, 30-day mortality and mortality even after discharge upto a definite time of follow-up as well as different severities of sepsis which also determines the mortality rate and that is why mortality rates might vary in different studies.

In our study the cut-off value for SOFA was 5 at admission, 6 at day 3 and 0 at day 7 (ROC) to make a diagnosis of outcome (expired). With these cut-off values, SOFA had more sensitivity of 85.9%, specificity of 76.3%, PPV of 50.8% and NPV of 95.0% in the diagnosis of outcome (expired) at admission. Whereas it was 45.1%, 92.4%,62.7%,85.5%, respectively at day 3 and 80.3%, 41.8%, 28.2% and 88.1% respectively at day 7. The cut-off values of NLR was 15 at admission the sensitivity of 85.9%, 52.1% and 97.2% specificity of 67.5%, 99.6%, and 65.9%, PPV of 43.0%, 97.4%, and 44.8% and NPV of 94.4%, 87.9% and 98.8% at admission, day 3 and day 7 (ROC) in the diagnosis of outcome (expired) at admission, respectively. These tests were demonstrating the accuracy of risk factors. SOFA score were showed significant large area under the curve (AUC) on the ROC curve at admission and day 3. NLR were showed significant large area under the curve (AUC) on the ROC curve at admission. In a study by Jain et al (2016) that investigated the SOFA score and ICU mortality relationship, determined that the higher the SOFA score on the 1st, 3rd, and 5th day of ICU stay, the higher the ICU mortality [24]. Liu et al. (2019) compared different evaluating systems to predict the prognosis of patients with sepsis outside of the ICU [25]. During the first 12 h before clinical worsening, they reported the AUC for the SOFA score as 0.78 significantly comparable to APACHE II score. Martins et al. (2019) evaluated the neutrophil-lymphocyte ratio, band neutrophils and total leukocytes for sepsis prediction [22]. The ROC curve values were 0.62 (95%CI 0.55 - 0.69) for NLR, 0.98 (95%CI 0.97 - 1.0) for band neutrophils, and 0.51 (95%CI 0.44 - 0.59) for total leukocytes. Among the three parameters, the best performance was observed for band neutrophil count followed by the NLR with sensitivity greater than 80% but with low specificity. Liu et al. (2019) reported that the AUC for the SOFA score as 0.78 significantly comparable to APACHE II score for predicting the prognosis [25]. Shinde et al. (2016) reported that the NLR has 100% sensitivity and 67.24% specificity in predicting outcome [26]. Shimoyama et al. (2018) reported that the cut-off value for mortality was kept at 15.6, they found sensitivity, 81.8%; specificity, 68.2% of NLR for prediction of outcome [27].

In the present study the NLR was significantly positive correlated with the SOFA score at admission, day 3 and day 7. Moreover, there was a moderate positive correlation between NLR (Admission) and SOFA (Admission), and this correlation was statistically significant (rho = 0.42, p = <0.001). There was a moderate positive correlation between NLR (Day 3) and SOFA (Day 3), and this correlation was statistically significant (rho = 0.34, p = <0.001). Similarly, Velissaris et al. (2018) found that NLR was positively correlated with the sepsis, comparable with other severity prognostic scores on admission (SOFA, rs = 0.497, p < 0.001; APACHE II, rs = 0.411, p = 0.003; SAPS II, rs = 0.445, p = 0.001) [28] whereas Pantzaris et al. (2018) in their study failed to show a statistical significant relationship between the NLR and the SOFA in their study [17]. Similarly, Shimoyama et al. (2018) showed no correlation between the NLR and SOFA score at ICU admission in the non-survivors group [27].

CONCLUSION:

Our study has indicated that the NLR could be a good tool to stratify the patient according to their NLR values even at the time of admission, which could help us in providing early intervention to the patient and even timely referral to the higher centres. It also indicated that higher values of NLR predict ensuing multiple organ dysfunction and prolonged hospital stay. SOFA is cumbersome tool, as it requires multiple parameters and requires a good functioning lab, NLR on the other hand is routinely done as a part of complete blood count, inexpensive, and easily available so may be a good prognostic marker of sepsis in developing country likes India. Further studies with larger sample size and longer duration of follow up to corroborate the findings of present study are recommended.

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