

Original Research Article

The role of neutrophil/lymphocyte ratio in predicting the severity of sepsis in a tertiary care hospital in South India: a retrospective study

Alfy Ann George¹, Teju P. Thomas^{2*}, Abdul Gaffor²

¹Department of Pathology, ²Department of Critical Care Medicine, Travancore Medical College and Hospitals, Kollam, Kerala, India

Received: 13 March 2020

Accepted: 20 March 2020

***Correspondence:**

Dr. Teju P. Thomas,

E-mail: tejupt@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Sepsis, a syndrome of dysregulated host response to infection leading to life-threatening organ dysfunction, is having a substantial burden in health system. The outcome in sepsis is often time dependent. None of the clinical manifestations nor the age-old markers like ESR, CRP, etc. have proven diagnostic or prognostic of sepsis. This study aims to assess the role of neutrophil: lymphocyte ratio (NLR) in assessing the severity of sepsis within the initial 24 hrs of admission.

Methods: Authors did a retrospective observational study in 208 sepsis patients admitted in the MDICU. The NLR was calculated and the study population was grouped into those with an NLR of more than or equal to 5 and those with less than 5. The patients were also grouped based on the number of organs impaired due to sepsis. The association between these groups were then assessed.

Results: 46 patients (60.5%) with single organ involvement had NLR <5; 30 patients (39.5%) had NLR >5; 27 patients (42.2%) with two organ involvement had NLR <5 and 37 patients (57.8%) had NLR >5. Among patients with more than two organ involvement, 8 patients (21.6%) had NLR <5 and 29 patients (78.4%) had NLR >5. It was found that there is statistically significant association between increase in number of organs involved and NLR more than 5. The chi square test value was 15.691 with a p value was less than 0.001.

Conclusions: In the current study, we have evaluated the role of NLR in sepsis. NLR calculated on the day of admission is a simple parameter that helps to stratify patients into severe risk category. A significant association was found with higher NLR and the number of organs impairment in sepsis.

Keywords: Neutrophil/lymphocyte ratio, Organ involvement, Sepsis, WBC count

INTRODUCTION

Sepsis is now defined as a life-threatening organ dysfunction where the host has a dysregulated immune response to infection. In the early 1990s, a consensus statement was developed by the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM). They defined sepsis as Systemic Inflammatory Response Syndrome (SIRS) with or without positive blood culture. In 2016, The Third

International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) was published.¹

The main changes were (Table 1):

- The terminology of SIRS and severe sepsis were eliminated.
- Sepsis is now considered as a life-threatening organ dysfunction caused by a dysregulated host response to infection.

- Organ dysfunction is newly defined as change in SOFA (sequential organ failure assessment) score.
- Septic shock is considered to be a subset of sepsis in which underlying circulatory and cellular or metabolic abnormalities are profound enough to increase mortality substantially. The burden of sepsis is very high in low- and middle-income countries. The mortality is very high too. Thus, early diagnosis of sepsis is of utmost importance in initiating treatment in sepsis.²⁻⁵

In sepsis, a hyper-inflammatory response is followed by an immunosuppressive phase during which multiple organ dysfunction develops which will lead to hospital acquired infections.

Biomarkers to diagnose sepsis may allow early intervention which can reduce the risk of death. Although lactate is currently the most commonly used biomarker to identify sepsis; other biomarkers may help to enhance lactate's effectiveness.

Table 1: The third international consensus definitions for sepsis and septic shock (sepsis-3).

Category	Definition
Previous definitions	
SIRS (systemic inflammatory response syndrome)	Two of the following; Temperature >38 Celsius or <36 Celsius Heart rate >90 beats /min Respiratory rate > 20 / minute or arterial carbon dioxide <32mmHg White blood cell count >12* 10 ⁹ or <4 * 10 ⁹ /L
Sepsis	SIRS with infection (proven or probable)
Severe sepsis	Sepsis with evidence of acute organ dysfunction
Septic Shock	Sepsis with persistent hypotension after fluid resuscitation
Revised definitions	
Sepsis	Life threatening organ dysfunction caused by a dysregulated host response to infection
Septic shock	Sepsis and vasopressor therapy needed to increase mean arterial pressure to >65 mm Hg and lactate >2 mmol/L despite adequate fluid resuscitation

Other biomarkers are pro-inflammatory cytokines and chemokines; proteins such as C-reactive protein and procalcitonin which are synthesized in response to infection and inflammation. Recently, markers of the immunosuppressive phase of sepsis, such as anti-inflammatory cytokines, and alterations of the cell surface markers of monocytes and lymphocytes have been examined. Combinations of pro- and anti-inflammatory biomarkers may help identify patients who

are developing severe sepsis before MODS (multi-organ dysfunction) has advanced too far. But most of the biomarkers are expensive, not easily available and not validated.^{6,7} Though the initial consensus statement of sepsis definition included leucocytosis, it was later found to have a low predictive value.^{8,9} NLR is a calculated parameter derived from the absolute neutrophil and lymphocyte count.

The hypothesis of high NLR in sepsis is related to the neutrophilia and increased lymphocyte apoptosis seen in systemic inflammation and stress that was first reported by Zahorec et al.¹⁰ In this background, we conducted a retrospective study in a tertiary care hospital in south India during the period June 2016 to May 2017. Different variables like total WBC count, NLR (neutrophil lymphocyte ratio) and its relation to severity of sepsis was assessed.

METHODS

This study was a retrospective study done at department of critical care medicine, Travancore medical college, Kollam. The study period was between June 2016 and May 2017. The study population were adult patients admitted in multidisciplinary critical care ICU with sepsis. Pregnant females and immune compromised participants were excluded from the study. The sample size of study population was 208.

Convenient sampling was done. A diagnosis of sepsis was made based on the diagnosis documented at the point of admission by the treating clinician. NLR was calculated from the complete blood counts of the blood sample collected at the time of admission. The patients were then grouped into two, based on the NLR as those with a N:L ratio of less than 5 and those with an N:L ratio of more than or equal to 5. The number of organs impaired, the total white blood cell (WBC) count, the platelet count and the clinical profile of these patients were assessed.

Inclusion criteria

- Patients admitted with sepsis with age more than 18.

Exclusion criteria

- Paediatric patients, pregnant women, immunocompromised individuals and patients on steroid therapy for more than 5 days were excluded from the study. Required data was collected from the clinical records of patient fitting the criteria.

Statistical analysis

The data collected was entered in Microsoft Excel and analysed using SPSS V.16. Descriptive analysis was done by calculating frequencies and proportions. Chi square test was used to calculate statistical significance.

RESULTS

Clinical characteristics of patients

As shown in Table 2, 117 study population (56.3%) was above 60 years and 59 patients (28.4%) was between the age group 40 to 60. Majority of the patients (59.1%) were males. Female patients were 85 (40.9%).

Table 2: Age and gender distribution.

Age group	Frequency (n=208)	Percentage
18-40	32	15.4
40-60	59	28.4
>60	117	56.3
Gender		
Male	123	59.1
Female	85	40.9

As shown in Table 3, among the co-morbidities hypertension was seen in 137 patients (65.9%) followed by diabetes mellitus in 116 (55.8%) patients. 62 patients (29.8%) had coronary artery diseases and 53 patients (25.5%) had chronic kidney disease. From table 4, single organ involvement was seen in 76 patients (42.9%), two organ involvement was seen in 64 patients (36.2%). 37 patients (20.9%) had more than 2 organs involved.

As shown in table 5 neutropenic sepsis (total WBC count <4500) was seen in 43 patients (20.7%). 89 patients

(42.8%) had total count more than 11,000. 76 patients (36.5%) had total WBC count between 4500 and 11,000.

Table 3: Comorbidities.

Comorbidities	Frequency (n=208)	Percentage
Diabetes mellitus	116	55.8
Hypertension	137	65.9
CKD	53	25.5
CAD	62	29.8
CVA	32	15.4

Table 4: Organ involvement.

Organ involvement	Frequency (n=177)	Percentage
Single organ involvement	76	42.9
Two organ involvement	64	36.2
More than two organ involvement	37	20.9
Total	177	100.0

Table 5: WBC count.

TC group	Frequency	Percentage
<4500	43	20.7
4500-11000	76	36.5
>11000	89	42.8
Total	208	100.0

Table 6: WBC count and organ involvement.

TC	Organ involvement			Chi square test	p value
	Single organ involvement	Two organ involvement	More than two organ involvement		
<4500	20 (26.3%)	9 (14.1%)	5 (13.5%)	8.445	0.077
4500-11000	28 (36.8%)	24 (37.5%)	9 (24.3%)		
>11000	28 (36.8%)	31 (48.4%)	23 (62.2%)		

Table 7: Organ involvement and N/L ratio.

Organ involvement	N/L ratio		Chi square test	p value
	<5	>5		
Single organ involvement	46 (60.5%)	30 (39.5%)	15.691	0.001*
Two organ involvement	27 (42.2%)	37 (57.8%)		
More than two organ involvement	8 (21.6%)	29 (78.4%)		

As shown in table 6 the total WBC count was compared with the severity of sepsis assessed by the number of organs involved was assessed. No significant association was found between the total WBC count and the organ involvement (p value= 0.077). As shown in table 7, 46 patients (60.5%) with single organ involvement had NLR <5. 30 patients (39.5%) had NLR more than 5. 27

patients (42.2%) with two organ involvement had NLR less than 5 and 37 patients (57.8%) had NLR more than 5. Among patients with more than two organs involved 8 patients (21.6%) had NLR less than 5 and 29 patients (78.4%) had NLR of more than 5. There is statistically significant association between increase in number of organs involved or deranged by sepsis and NLR of more

than 5. The chi square test value was 15.691 with p value of less than 0.001.

DISCUSSION

NLR is a calculated parameter derived from the absolute neutrophil and lymphocyte count. The hypothesis of high NLR in sepsis is related to the neutrophilia and increased lymphocyte apoptosis seen in systemic inflammation and stress that was first reported by Zahorec et al.¹⁰ A similar association was observed in trauma patients with SIRS by Herfferman et al. He postulated that lymphocytes are vital for the regulation of an adequate inflammatory response. Once the regulation is lost due to apoptosis, cellular exhaustion and down regulation may lead to a deleterious inflammatory state.¹¹ In comparison with other biomarkers, NLR is an economic and easily available parameter that is derived from the complete blood cell count. Though it cannot be used independently for the diagnosis of sepsis, it can be used to assess the severity of the disease in patients with features of systemic inflammatory response. Gurol et al assessed the NLR cut off values according to procalcitonin values and found that NLR > or equal to 5 was associated with bacteraemia. They found that NLR had a higher sensitivity than CRP or total WBC count in septicemia.¹² These authors also found that NLR was a more convenient marker for infection than CRP, with a high specificity (83.9%) but moderate sensitivity for diagnosing septicemia in critically ill patients.¹³

Lymphocytes are cells that mount an immune response against microorganisms and other foreign substances. In the event of sepsis, a low lymphocyte count will detrimentally affect the immune response and eventually lead to increased morbidity. As seen in our study, high NLR is also found to be associated with increasing morbidity and severity in sepsis. Increased NLR levels were independently associated with unfavourable clinical prognosis in patients with sepsis in the study conducted by Xuan Liu et al.¹⁴

In the study conducted by Hwang et al, on a total of 1395 patients, the initial NLR measured on the day of admission was associated with 28-day mortality. He also suggested a change in NLR may be a valuable prognostic marker for sepsis.¹⁵ Lee et al, in their study stated that the NLR in the Asian population was generally lower than other races. The mean NLR across all ages in men and women was 1.63 and 1.66, respectively.¹⁶

The association of neutrophilic leucocytosis with bacteraemia and lymphocytosis with viremia is well known.¹³ In the current study, the NLR was found to be higher in patients with bacterial infection compared to those with viral infection. However, in a study conducted on HIV and hepatitis C infected individuals, NLR was associated with higher illness severity.¹⁷

Elevated NLR is not diagnostic of sepsis and is seen in many other conditions. Elevated NLR is found to be associated with trauma, surgery, pancreatitis, cardiac and rheumatic disease. It is also associated with poor outcomes in cancer patients and those with acute coronary syndrome too.^{18,19}

In the current study, we have evaluated the role of NLR in sepsis. NLR calculated on the day of admission is a simple parameter that helps to stratify patients into severe risk category. A significant association was found with higher NLR and the number of organs impairment in sepsis. However, this is more relevant in sepsis due to bacterial causes. NLR is of limited use in viral infections such as dengue.

Our study had few limitations. Comparison of NLR with sepsis severity indicators such as SOFA, APACHE II and SAPS II was not included in our study. A larger sample size would be needed in order to derive a statistically significant association between the severity indicators and NLR which was limited in the current study. Hence the morbidity of the disease assessed by the number of organs impaired by sepsis was taken into consideration in this study.

CONCLUSION

Timely diagnosis and prompt administration of treatment is pertinent in the outcome of sepsis. Compared to the other time consuming and expensive biomarkers and diagnostic tests used in sepsis, NLR is a simple parameter that is calculated from the complete blood counts. Though NLR is not of diagnostic use, it can be used as a prognostic tool to predict the severity in sepsis even in resource limited hospitals.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA.* 2016 Feb 23;315(8):801-10.
2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Resp Criti Care Med.* 2016 Feb 1;193(3):259-72.
3. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Criti Care Med.* 2013 May 1;41(5):1167-74.
4. Rello J, Valenzuela-Sanchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: a review of advances in

- management. *Advan Therapy.* 2017 Nov 1;34(11):2393-411.
5. Dellinger RP, Levy MM, Carlet JM. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. *Criti Care Med.* 2008;36:296-327.
 6. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 sccm/esicm/accp/ats/sis international sepsis definitions conference. *Inten Care Med.* 2003 Apr 1;29(4):530-8.
 7. Faix JD. Biomarkers of sepsis. *Criti Rev Clin Lab Sci.* 2013 Jan 1;50(1):23-36.
 8. Bogar L, Molnar Z, Kenyeres P, Tarsoly P. Sedimentation characteristics of leucocytes can predict bacteraemia in critical care patients. *J Clini Pathol.* 2006 May 1;59(5):523-5.
 9. Davis BH, Bigelow NC. Comparison of neutrophil CD64 expression, manual myeloid immaturity counts, and automated hematology analyzer flags as indicators of infection or sepsis. *Lab Hematol.* 2005;11(2):137-51.
 10. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratislavske lekarske listy.* 2001 Feb;102(1):5-14.
 11. Heffernan DS, Monaghan SF, Thakkar RK, Machan JT, Cioffi WG, Ayala A. Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern. *Criti Care.* 2012 Feb 1;16(1):R12.
 12. Gurol G, Ciftci IH, Terizi HA, Atasoy AR, Ozbek A, Koroglu M. Are there standardized cutoff values for neutrophil-lymphocyte ratios in bacteremia or sepsis? *J Microbiol. Biotechnol.* 2015;25:521-5.
 13. Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. *Infection.* 2017 Jun 1;45(3):299-307.
 14. Liu X, Shen Y, Wang H, Ge Q, Fei A, Pan S. Prognostic significance of neutrophil-to-lymphocyte ratio in patients with sepsis: a prospective observational study. *Media Inflamm.* 2016;2016.
 15. Hwang SY, Shin TG, Jo IJ, Jeon K, Suh GY, Lee TR, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in critically-ill septic patients. *Am J Eemerg Med.* 2017 Feb 1;35(2):234-9.
 16. Lee JS, Kim NY, Na SH, Youn YH, Shin CS. Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine.* 2018 Jun;97(26).
 17. Hanberg JS, Freiberg MS, Goetz MB, Rodriguez-Barradas MC, Gibert C, Oursler KA, et al. Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios as Prognostic Inflammatory Biomarkers in Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), and HIV/HCV Coinfection. *InOpen forum infectious diseases* 2019;6(10):347.
 18. Shah N, Parikh V, Patel N, Patel N, Badheka A, Deshmukh A, et al. Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary heart disease mortality: insights from the National Health and Nutrition Examination Survey-III. *Inter J Cardiol.* 2014;171:390-7.
 19. Li MX, Liu XM, Zhang XF, Zhang JF, Wang WL, Zhu Y, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. *Inter J Cancer.* 2014;134:2403-13.

Cite this article as: George AA, Thomas TP, Gaffor A. The role of neutrophil/lymphocyte ratio in predicting the severity of sepsis in a tertiary care hospital in south India: a retrospective study. *Int J Res Med Sci* 2020;8:1624-8.