Original Article

Neutrophil Lymphocyte Ratio (NLR) as a Prognostic Marker in COVID-19 Infection

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ABSTRACT

Objectives: To determine the efficacy of Neutrophil/Lymphocyte ratio (NLR) as a marker of the severity of COVID-19 pneumonia. The neutrophil-to-lymphocyte ratio (NLR) in peripheral blood has been studied as a systemic inflammatory marker and various studies have shown that it is a valid prognostic factor in various solid tumours and other chronic diseases such as lung, cardiovascular and kidney diseases. Emerging evidences suggested that peripheral blood neutrophil to lymphocyte ratio (NLR) can be used as a marker of systemic inflammation. Furthermore, NLR has shown good predictive values on progression and clinical outcomes in Covid-19 severity. Our study aims at evaluating whether NLR can help clinicians identify potentially severe cases early, conduct early triage and initiate effective management in time, which may reduce the overall mortality of COVID-19.

Material and Methods: This was a retrospective study done from January 2021 to August 2021 in Breach candy hospital Mumbai. A group of 100 patients with confirmed COVID-19 infection hospitalised in our centre were retrospectively analysed. COVID-19 diagnosis was performed via RTPCR from nasopharyngeal and oropharyngeal swabs. For each patient, demographic data, clinical history, laboratory tests specially CBC and treatment measures during hospitalisation were collected.

Results: NLR can be used to determine on disease severity and mortality in patients with COVID infection.

Conclusion: Evaluating NLR can help clinicians identify potentially severe cases early, conduct early triage and initiate effective management in time, which may reduce the overall mortality of COVID-19.

Keywords: Neutrophils, Lymphocytes, Coronavirus disease (COVID)

INTRODUCTION

Coronavirus is a large virus family, members of which are known to cause common cold and serious illnesses, such as the Middle East respiratory syndrome and severe acute respiratory syndrome.[1-4] It was found that the coronavirus disease 2019 (COVID-19) was the cause of unexplained viral pneumonia in Wuhan, China in December 2019, and this virus was recognised by the World Health Organization (WHO) on January 12, 2020. In the following month, COVID-19 was reported to spread throughout the Hubei Province and China and even to other countries.[5]

Most patients infected with the novel coronavirus had mild and moderate illness and severe illness often experienced dyspnoea after 1 week. In cases of critical illness, patients progressed rapidly to acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy and septic shock. Early identification of risk factors for critical illness facilitated appropriate provision of supportive care and rapid access to the intensive care unit (ICU) when required. For patients with mild and moderate illness, general isolation treatment is required and ICU care is not needed unless the condition worsens. Thus, early prognosis prediction would definitely help reduce mortality.

Of note, a high incidence of lymphopenia in COVID-19 patients has been reported by Huang *et al*.[6] In addition, the baseline neutrophil-to-lymphocyte ratio (NLR) has been confirmed as a potential short-term prognostic indicator for patients with acute-on-chronic hepatitis B liver failure. Formerly, NLR was mainly used in oncological conditions, autoimmune diseases and bacteriological infections.[7-9] Thus, NLR can be a potential predictor for critical illness of COVID-19.

Different immunity parameters in the human body have been identified to combat the disease. These tests are often expensive and time delay occurs in the results of these tests, hampering the patient's treatment. Therefore, we should have a clinical indicator or marker that is inexpensive, has a rapid turnaround time and is simultaneously specific and sensitive. One such marker is a complete blood count (CBC) profile, out of which neutrophils and lymphocytes are especially important. The neutrophils are increased in bacterial infection and lymphocytes are reduced during viremia. Examining these two parameters can greatly help assess the COVID-19 infection.

MATERIAL AND METHODS

This was a retrospective study done from January 2021 to August 2021 in Breach candy hospital Mumbai. A group of 100 patients with confirmed COVID-19 infection hospitalised in our centre were retrospectively analysed. COVID-19 diagnosis was performed through reverse transcription polymerase chain reaction (RTPCR) from nasopharyngeal and oropharyngeal swabs. For each patient, demographic data, clinical history, laboratory tests especially CBC and treatment measures during hospitalisation were collected. Patients taken in our study were categorised into –

Mild cases

Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test RTPCR) but who have no symptoms that are consistent with COVID-19 or Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) but who do not have shortness of breath, dyspnoea or abnormal chest imaging[10] (Chest CT score <7).

Moderate illness

Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO$_2$) ≥94% on room air at sea level (Chest CT score 8–17).[10]

Severe illness

Individuals who have SpO$_2$ <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 mm Hg, respiratory frequency >30 breaths/min or lung infiltrates >50%. Moreover, individuals who have respiratory failure, septic shock and/or multiple organ dysfunction (Chest CT score >18).[10]

CBC sample was taken on day 1 of the admission and was analysed using the hospital laboratory system, Sysmex analyzer. NLR were calculated by the formula- ABSOLUTE NEUTROPHIL COUNT/ABSOLUTE LYMPHOCYTE COUNT, from the haemogram and 1–3 being normal the normal reference range. NLR ratios of the patients were calculated and their correlation with the severity and the survival of the patient Results were analysed according to the presence or absence of symptoms, comorbidities and survival of the patient.

Inclusion criteria

COVID-19 RTPCR-positive hospitalised patients were included in the study.

Exclusion criteria

The following criteria were excluded from the study:
1. Patients who were having fever but were RTPCR-negative
2. COVID-19-positive with solid tumours.

RESULTS

One hundred patients in the study were evaluated and the results and observations are as follows –

There was a male preponderance with a Male: Female ratio that was 2.57. Age range of patients was 18–90 years with mean age of 57.92 ± 19.03. As shown in [Table 1], NLR range was 1.5–30.1 with mean NLR of 12.06 ± 9.09.

As shown in [Table 2], 31% of patients were in age group below 45 years.

29% in 46–60 and 40% in more than 60 age group.

In age group of more than 60 years, mean NLR was the highest.

Table 1: NLR range in the patients.

NLR Range	Patient n (100)
1.1–5.1	40
5.2–10.1	13
10.2–15.1	15
15.2–20.1	5
20.2–25.1	11
25.2–30.1	16

NLR: Neutrophil-to-lymphocyte ratio, n = Total number of cases (100), n = Total number of cases included in the study

Table 2: Mean NLR in different age groups.

Age	Mean NLR
<45	7.38
45–60	8.88
>60	18.1

NLR: Neutrophil-to-lymphocyte ratio

There is significant correlation between symptomatic patients and high NLR.

P = 0.00001 and 86.07% of total symptomatic patients have NLR >3.

Fever and breathlessness were the most common symptoms in our study and 21 of our total patients were asymptomatic. Sixty-eight of our total patients had comorbidities and 32 were without comorbidities.

About 100% of the patients with diabetes mellitus (DM) and other comorbidities have NLR >3.

About 75.92% of the patients with DM have NLR >3.

Hence, P value is statistically significant for the patients having DM to have NLR >3 (P = 0.0009).

NLR more than 3 has a 72.6% of survival rate and 27.3% of death rate.

NLR <3 has 100% survival rate. Hence, the mortality rate is higher in patients with higher NLR.

Sensitivity of NLR for detection of severe disease is 27.02 and specificity is 1.

DISCUSSION

The WHO has officially recognised COVID-19 as a pandemic and countries worldwide are now facing huge challenges trying to prevent its further spread as well as treating the growing number of COVID-19 patients. In fact, although the majority of cases are usually self-limiting with mild symptoms such as low-grade fever and cough, the disease can be fatal. Serious COVID-19 cases can develop severe pneumonia, acute respiratory distress syndrome and multiple organ failure leading to death; the mortality rate is much higher in elder patients with comorbidities.[11] The NLR in peripheral blood has been studied as a systemic inflammatory marker and various studies have shown that it is a valid prognostic factor in various solid tumours[12] and other chronic diseases such as lung, cardiovascular and kidney diseases.

Emerging evidences suggested that peripheral blood NLR can be used as a marker of systemic inflammation. Furthermore, NLR has shown good predictive values on progression and clinical outcomes in various disease, such as solid tumours, chronic obstructive pulmonary disease, cardiovascular disease and pancreatitis.[13-15] Recently, several studies have reported that NLR may differentiate between mild/moderate and severe/critical groups and probability of death in patients with COVID-19 infection. In addition, a series of studies have suggested NLR is a reliable predictor of COVID-19 progression and elevated NLR is associated with high mortality.[16,17]

In our study, we found a statistically significant correlation between the patients with symptoms and high NLR

Table 3: NLR values in symptomatic and asymptomatic patients.

NLR	COVID symptoms present	Symptoms absent	Total
<3	11	15	26
>3	68	6	74
Total	79	21	100

NLR: Neutrophil-to-lymphocyte ratio

Table 4: Commonest symptoms.

Symptoms	No. of patients
Fever	58
Cough	40
Breathlessness	40
Vomiting	7
Sore throat	6
No symptoms	21

Table 5: NLR values in patients with comorbidities.

Comorbidities	NLR <3	NLR >3	Total
DM	7	18	25
HTN	8	12	20
DM with HTN OR MI	0	23	23
No comorbidity	11	21	32
Total	26	74	100

NLR: Neutrophil-to-lymphocyte ratio, DM: Diabetes mellitus, HTN: Hypertension, MI: Myocardial infarction

values [Tables 3 and 4]. Furthermore, the patients with comorbidities had invariably high NLR values and mortality was high if NLR value is high [Table 5]. [Figure 1] shows pie chart showing most common symptoms. About 100% of the patients with DM and other comorbidities have NLR >3. NLR <3 has 100% survival rate. Hence, the mortality rate is higher in patients with higher NLR. There is significant correlation between symptomatic patients and high NLR in our study. About 86.07% of total symptomatic patient have NLR >3. In our study, 60% of patient in more than 60 age group have high NLR which shows that severity of their disease is also more [Table 2].

In study conducted by Ciccullo et al., an NLR of greater than four was seen as a predictor of the admission of COVID-19 patients to the ICU. The duration of hospital stay was prolonged and the time lag for nucleic acid results to become negative was increased. It is a valuable tool for screening critically ill patients with confirmed SARS-CoV-2 infection, as it can contribute to the evaluative acumen of the physician.[18]

A recent systematic review and meta-analysis by Feng et al. regarding immune-inflammatory parameters in COVID-19 infection concluded that NLR is associated with
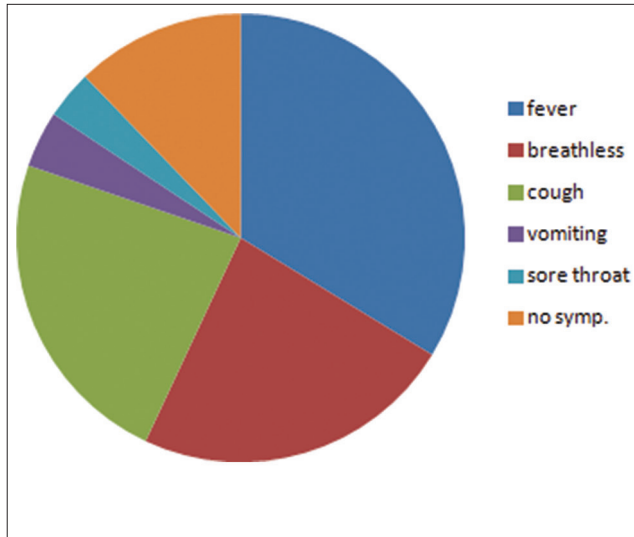
Figure 1: PIE chart showing symptoms.

the progression of the infection and can be utilised by the physicians to identify high risk or deteriorating patients at an early stage.[19] Several other studies have reported their findings that NLR can be used as an early warning signal of severe COVID-19 infection[20] and considered as an independent marker for poor clinical outcomes and mortality in COVID-19 infection.[21]

Neutrophils are one of the human body's vital immune cells. When pathogenic microorganisms invade the body, immune cells tend to rapidly chemotactically gather to the infection site and play the role of host defence and immune regulation.[22] When the body's neutrophils are significantly reduced, the body's immunity is compromised and thus the risk of infection is significantly increased.[23] Lymphocytes are the main effector cells of the human immune response. The number of lymphocytes in the body is closely related to the body's immunity and defence system against pathogenic microorganisms and is negatively correlated with the degree of inflammation. NLR encompasses two types of leukocyte subtypes, reflecting the balance of the body's neutrophil and lymphocyte count levels and the degree of systemic inflammation. More accurately, it reflects the balance between the severity of the inflammation and the body's immunity status[24] and is thus considered an important marker of systemic inflammatory response. Based on this, we speculated that heavy COVID-19 infection can have significant systemic inflammation and that NLR may have a role in predicting the infection's severity.

In a study conducted by Yang *et al.*, it was found to be an independent prognostic factor in patients with COVID-19. This reinforces the belief in the relationship between hyper-inflammation and SARS-CoV-2.[25,26] This NLR is a crucial screening and prognostic tool as it is readily available with

the help of a complete hemogram. This is an investigation modality that is widely accessible even in remote areas and resource-limited setting NLR has good predictive values on disease severity and mortality in patients with COVID-19 infection. Evaluating NLR can help clinicians identify potentially severe cases early, conduct early triage and initiate effective management in time, which may reduce the overall mortality of COVID-19.

CONCLUSION

NLR can be used to determine disease severity and mortality in patients with COVID-19 infection. Evaluating NLR can help clinicians identify potentially severe cases early, conduct early triage and initiate effective management in time, which may reduce the overall mortality of COVID-19.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, *et al*. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263-70.
2. Drosten C, Gunther S, Preiser W, van der Werf S, Brodt HR, Becker S, *et al*. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003;348:1967-76.
3. De Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, *et al*. Middle East respiratory syndrome coronavirus (MERS-CoV): Announcement of the Coronavirus Study Group. J Virol 2013;87:7790-2.
4. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814-20.
5. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, *et al*. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929-36.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
7. Liu H, Zhang H, Wan G, Sang Y, Chang Y, Wang X, *et al*. Neutrophil-lymphocyte ratio: A novel predictor for short-term prognosis in acute-on-chronic hepatitis B liver failure. J Viral Hepat 2014;21:499-507.
8. Ying HQ, Deng QW, He BS, Pan YQ, Wang F, Sun HL, *et al*.

The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol 2014;31:305.

9. Uslu AU, Küçük A, Şahin A, Ugan Y, Yılmaz R, Güngör T, et al. Two new inflammatory markers associated with disease activity Score-28 in patients with rheumatoid arthritis: Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Int J Rheum Dis 2015;18:731-5.

10. Saeed GA, Gaba W, Shah A, Al Helali AA, Raidullah E, Al Ali AB, et al. Correlation between Chest CT severity scores and the clinical parameters of adult patients with COVID-19 Pneumonia. Radiol Res Pract 2021;2021:6697677.

11. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62 Errata in: Lancet 2020;395:1038; Lancet 2020;395:1038.

12. Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. J Natl Cancer Inst 2014;106:dju124.

13. Kim S, Eliot M, Koestler DC, Wu WC, Kelsey KT. Association of neutrophil to-lymphocyte ratio with mortality and cardiovascular disease in the Jackson heart study and modifcation by the Dufy antigen variant. JAMA Cardiol 2018;3:455-62.

14. Paliogiannis P, Fois AG, Sotgia S, Mangoni AA, Zinellu E, Pirina P, et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: Recent evidence and future perspectives. Eur Respir Rev 2018;27:147.

15. Kong W, He Y, Bao H, Zhang W, Wang X. Diagnostic value of neutrophil lymphocyte ratio for predicting the severity of acute pancreatitis: A meta analysis. Dis Markers 2020;2020:9731854.

16. Lian J, Jin C, Hao S, Zhang X, Yang M, Jin X, et al. High neutrophil-to-lymphocyte ratio associated with progression to critical illness in older patients with COVID-19: A multicenter retrospective study. Aging (Albany NY) 2020;12:13849-59.

17. Zhang JJ, Cao YY, Tan G, Dong X, Wang BC, Lin J, et al. Clinical, radiological and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. Allergy 2021;76:533-50.

18. Ciccullo A, Borghetti A, Dal Verme L, Tosoni A, Lombardi F, Garcovich M, et al. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: A report from the Italian front line. Int J Antimicrob Agents 2020;56:106017.

19. Feng X, Li S, Sun Q, Zhu J, Chen B, Xiong M, et al. Immune-inflammatory parameters in COVID-19 cases: A systematic review and meta-analysis. Front Med (Lausanne) 2020;7:301.

20. Xia X, Wen M, Zhan S, He J, Chen W. An increased neutrophil/lymphocyte ratio is an early warning signal of severe COVID-19. Nan Fang Yi Ke Da Xue Xue Bao 2020;40:333-6.

21. Yang A, Liu J, Tao W, Li H. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020;84:106504.

22. Mercier J, Voutsadakis I. The platelets-neutrophils to lymphocytes ratio: A new prognostic marker in metastatic colorectal cancer. J Gastrointest Oncol 2018;9:478-86.

23. Yeo A, Henningham A, Fantino E, Galbraith S, Krause L, Wainwright CE, et al. Increased susceptibility of airway epithelial cells from ataxia-telangiectasia to S. pneumonia infection due to oxidative damage and impaired innate immunity. Sci Rep 2019;9:1-10.

24. Soylu K, Gediklio O, Ekşi A, Avcıoğlu Y, Soylu AI, Yüksel S, et al. Neutrophil-to-lymphocyte ratio for the assessment of hospital mortality in patients with acute pulmonary embolism. Arch Med Sci 2016;12:95-100.

25. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. Lancet 2020;395:514.

26. Yang Y, Shen C, Li J, Yuan J, Wei J, Huang F, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. J Allergy Clin Immunol 2020;146:119-127.e4.