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Neutrophil to Lymphocyte Ratio: A Simple, Quick, and Independent Predictor of Severity and Outcome in COVID-19 Disease

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Abstract

Coronaviridae belongs to an enveloped RNA virus family and is kenned to cause the common cold and sometimes astringent illnesses. The most recently discovered coronavirus is COVID-19, referred to as severe acute respiratory syndrome caused by SARS-CoV-2. Current classification criteria for moderate and severe disease are respiratory rate, oxygen saturation, and PaO_2/FiO_2. These markers are significant but have no COVID-19 specificity. NLR is suggested as a simple marker of the systemic inflammatory response in critically ill patients and is an independent indicator of both short-term and long-term mortality in critical patients. The ease of using NLR as a systemic inflammatory marker and a potential predictor of clinical risk and outcome in critically ill patients reinforce its use in the COVID scenario. The aim of our study was to evaluate NLR as a COVID-19 disease severity marker and to evaluate the role of NLR in COVID-19 disease outcome. We included the demographics and clinical characteristics of 117 admitted patients who were RT-PCR positive for COVID-19. As per age and gender-wise distribution, 74 patients were male, and 43 were female, with a mean age of 49.11 ± 18.63 years. Mild patients had a mean NLR of 4.76 (2.03 to 7.77), the moderate disease had a mean NLR of 5.21 (2.00 to 9.88), and severe disease had a mean NLR of 6.19 (0.2 to 25) at admission. Our results show a strong relationship between higher NLR values with mortality (AUC = 97.4) with a sensitivity of 92.3% and specificity of 86.6% and is statistically significant. We recommend that NLR can be a quick, inexpensive, accessible, reproducible marker for gauging severity and outcome in COVID-19.

Introduction

Coronaviridae belongs to an enveloped RNA virus family and is kenned to cause the common cold and sometimes astringent illnesses. Sometimes zoonotic coronaviruses infect humans and propagate further, as shown in the MERS-CoV, SARS-CoV and recently COVID-19, via human-to-human transmission. The most recently discovered coronavirus is COVID-19, referred to as severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2)[1]. In mid-December 2019, Wuhan city in Hubei Province of China reported a COVID-19 outbreak, declared as the Public Health Emergency of International Concern (PHEIC) by the World Health Organisation (under International Health Regulations) on 30 January 2020, and later on 11 March 2020 as a pandemic[2]. COVID-19 halted the world, with over 20.5 million of lives being lost to COVID-19 globally[3]. While the majority of the cases are self-limiting, the disease has a 2 - 3% death rate[4]. Though COVID-19 has been chiefly characterised and noticed as a respiratory condition, up to 20% of patients with COVID-19 have a severe infection, including coagulopathy and septic shock, with severe extra-pulmonary symptoms[5]. which can have consequences, such as severe pneumonia, ARDS, and multi-organ failure that ultimately lead to death[6]. The gold standard for the diagnosis of COVID-19 is the RT-PCR test, which detects viral RNA and usually produces a result within two to five hours. Nevertheless, the severity of the condition remains clinically based. The current classification criteria for moderate and severe disease are respiratory rate, oxygen saturation, and PaO_2/FiO_2. These markers are significant but have no COVID-19 specificity. In severe disease, patients rapidly deteriorate to respiratory distress/failure, metabolic acidosis, coagulation defects, and septic shock. Early identification of severe risk factors enables adequate assistance to provide support and quick access to a health facility or an intensive care unit (ICU) if necessary. The early identification would assist decrease mortality and avoid medical scarcity in the early triage. COVID-19 associated sepsis demonstrates decreased eosinophils, CD4+, CD8+, CD19+, and total lymphocytes; and significantly elevated liver enzymes, C-reactive protein, erythrocyte sedimentation rate (ESR), ferritin, and IL-6 levels in severe disease[7], with an exceptionally high incidence of lymphopenia in COVID- 19 patients[8]. Separately testing all these markers becomes challenging, particularly in resource-poor settings. The world is facing considerable challenges in the management of COVID patients and preventing further disease spread. Lockdowns and curfews have created a resource crunch. Resource-poor settings struggle to match the expanded need for appropriate diagnosis and management, which has also

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sparked fears of global economic crisis and recession. In such a scenario, the simplest objective tests gain utmost importance. One such test is the neutrophil to lymphocyte ratio or NLR. The NLR is suggested as a simple marker of the systemic inflammatory response in critically ill patients and is an independent indicator of both short-term and long-term mortality in critical patients[9-11]. The ease of using NLR as a systemic inflammatory marker and a potential predictor of clinical risk and outcome in critically ill patients reinforce its use in the COVID scenario.

To our knowledge, there is still no validation of the usefulness of NLR for predicting mortality in COVID-19 patients, especially in Indian patients. Hence, we discussed the role of NLR as a valuable, inexpensive, readily available, reproducible objective marker for the assessment of clinical severity and outcome in COVID-19.

Aims and objective

1. To evaluate NLR as a COVID-19 disease severity marker.
2. To evaluate the role of NLR in COVID-19 disease outcome.

Material and methods

Study design

We analysed the data retrospectively on clinical characteristics of RT-PCR confirmed COVID-19 patients admitted in corona wards between March 2020 to August 2020 in Dr Ram Manohar Lohia Hospital, New Delhi, India. Informed consent was taken from relatives of the patients to use their data for this research. Based on the COVID-19 management guidelines published by the Ministry of Health and Family Welfare (MoHFW), from time to time, patients were characterised on clinical severity as mild, moderate, and severe[12]. Mild COVID-19 was defined as patients presenting with uncomplicated upper respiratory tract infection; mild symptoms such as fever, cough, sore throat, nasal congestion, malaise and headache. Moderate COVID-19 was defined as clinical features of dyspnoea and or hypoxia, fever, cough, including SpO_2 < 94% (range 90 - 94%) on room air, the respiratory rate more than or equal to 24 per minute. Severe COVID-19 was defined as clinical signs of Pneumonia plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, SpO_2 < 90% on room air. Two other patient groups were made based on the clinical outcomes, i.e., Discharge and Death. The following patients were excluded from the study:-

1. Patients on any prolonged immunosuppression, prolonged steroids (prolonged being defined as > = four weeks),
2. Pregnant women,
3. Patients with known malignancy and autoimmune diseases,
4. Patients with HIV/AIDS,
5. Patient's age less than 18 years.

Blood samples for NLR were collected during admission and again after seven days in EDTA vials. The samples were processed in Medonic M series analysers within 1 hour of collection. The neutrophil to lymphocyte ratio was calculated as the absolute neutrophil count and absolute lymphocyte count ratio (ALC). The normal value of NLR identified in healthy, non-geriatric adults ranges from 0.75 to 3.53[13].

Continuous and normally distributed variables were described by the mean and standard deviation (SD). Variables that did not show a normal distribution were defined using medians and interquartile ranges. Comparisons between all three groups were performed using the Kruskal-Wallis H-tests, followed by Bonferroni-corrected Mann–Whitney U-tests as a post-hoc analysis. With $P < 0.05$, the results were considered statistically significant, and the predictive value of NLR was calculated by using ROC.

Results

Table I shows the demographics and clinical characteristics of 117 admitted patients who were RT-PCR positive for COVID-19. As per age and gender-wise distribution, 74 patients were male, and 43 were female, with a mean age of 49.11 ± 18.63 years. Of these 117 patients, 59.8% (n = 70) had co-morbidities in the form of diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, bronchial asthma, etc. Severity categorisation into mild, moderate, and severe was 32%, 31%, and 37%, respectively. Of these 117 patients, 67% (n = 78) were discharged and 33% (n = 39) died.

Table I: Demographic profile of COVID patients.

Total number of patients (N)	117
Gender (M/F)	74 /43
Mean age	49.11 ± 18.63
Patients with co-morbidities	70
Clinical category	Mild - 38 Moderate - 36 Severe - 43
Clinical outcome	Discharged - 78 Death - 39

Table II shows the trend of severity correlation of NLR in COVID-19 patients. Mild patients had a mean NLR of 4.76 (2.03 to 7.77), the moderate disease had a mean NLR of 5.21 (2.00 to 9.88,) and severe disease had a mean NLR of 6.19 (0.2 to 25) at admission. However, the NLR ratio further decreased at seven days to 3.59 (0.9 to 8.8) for mild patients, 3.64 (1.3 to 18.4) for moderate patients but increased to 6.70 (0.02 to 21.6) in severe disease. Likewise, the discharged patients showed a decreasing trend of NLR from a mean of 5.14 at admission to 3.32 at seven days. The NLR of patients who scummed the COVID-19 increased from a mean value of 5.99 at admission to 7.59 at seven days (Table III).

Table II: NLR as per disease severity (severity correlation).

Outcome	Early NLR	Late NLR	Significance
Discharge	4.76 ± 1.52	3.59 ± 1.95	0.042
Death	5.21 ± 2.06	3.64 ± 3.59	0.001
Severe COVID	6.19 ± 4.77	6.70 ± 4.96	0.04

Table III: Neutrophil lymphocyte ratio (NLR) as per disease outcome.

Outcome	Early NLR	Late NLR	Significance
Discharge	514 ± 2.07	3.32 ± 1.90	0.00
Death	5.99 ± 4.82	7.59 ± 5.50	0.004

ROC plot showed the cut-off value of the NLR as 7.69 at the time of admission. The result shows a strong relationship between higher NLR values with mortality (AUC = 97.4) with a sensitivity of 92.3% and specificity of 86.6% and is statistically significant P = 0.00 (Fig. 1).

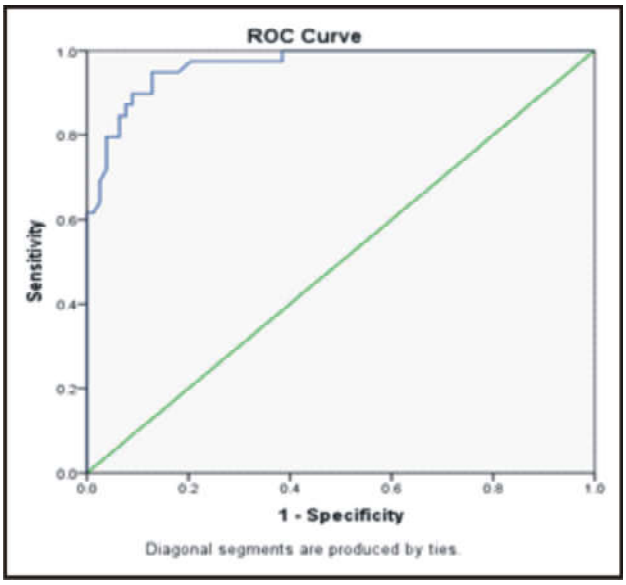

Fig. 1: *ROC for prognostic value of early NLR.*

Furthermore, we found that the cut-off value of the NLR after seven days was reduced to 4.65, providing strong evidence that patients with values above this are more likely to develop mortality (AUC = 96.5) with a sensitivity of 94.9% and specificity of 83.6%, at a significance of p = 0.00 (Fig. 2).

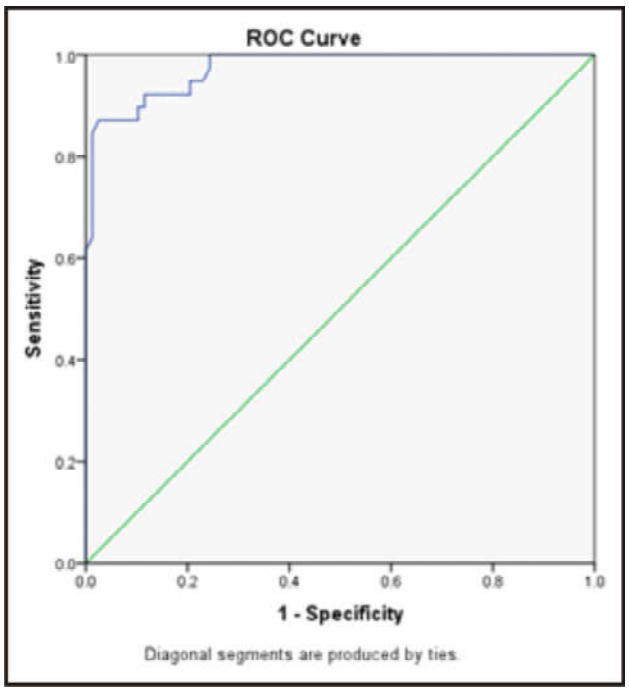

Fig. 2: ROC for prognostic value of late NLR.

Discussion

COVID-19, a highly infectious disease, has been spreading rapidly throughout the world and continues to pose a severe threat to global public health. The prognosis for patients with severe COVID is poor. As a result, we must identify potentially severe cases early and treat these patients as soon as possible. In our hospital's clinical practice of treating COVID-19 patients, we've found that the NLR is a quick and inexpensive predictor of severity and outcome.

There is strong evidence that immune system dysregulation plays a role in the development of viral hyper-inflammation. Serum Ferritin, IL-6 levels, lactate dehydrogenase (LDH), C-reactive protein (CRP), D Dimer levels, and serum Procalcitonin are some of the available laboratory parameters to monitor this hyper-inflammation[14]. The difficulty of obtaining most laboratory tests makes early, objective prognostication difficult and, as a result, morbidity and mortality rise. The lack of standardised management protocols emphasizes the value of early risk assessment even more. The absolute value of peripheral white blood cells in patients with COVID-19 is usually normal or low in laboratory examinations, and lymphopenia is common[4]. As

the lymphocyte count declines, the neutrophil count rises[15], owing to severe COVID-19's biphasic event of hyper-inflammation and immunosuppression, similar to severe sepsis[16]. Sepsis has two phases: an early phase (which lasts 5 days) and a late phase[17]. The distinction between early and late sepsis is increasingly being researched, and the two conditions may have different underlying mechanisms that require different treatment approaches[18-20]. Using the same reasoning as we did with COVID-19, we tested the NLR in the early phase and then in the late phase of the study. NLR has been studied in the context of sepsis as a diagnostic and prognostic marker, according to the reviewed literature[21]. Although there have been several studies, none have examined the NLR in early and late COVID-19 sepsis to determine whether it is a predictor of severity or outcome. Using NLR cut-off values of 4.3, Shang *et al* evaluated 443 patients and reported in their study that the AUC was 0.74, the sensitivity was 56.3 per cent, and the specificity was 83.7 per cent, indicating that the NLR cut-off value of 4.3 was indicative of severe disease. 22 Li *et al* discovered an NLR cut-off value of 11.3 in 93 patients to predict severe COVID-19, with a sensitivity of 78.1 per cent and specificity of 92.0 per cent in patients with severe COVID-19, respectively. 23 In another study, Basbus *et al* discovered that an NLR cut-off value of 3.0 among 131 patients could predict severe disease with 80.9 per cent sensitivity and 67.3 per cent specificity, indicating that the NLR cut-off value was accurate[24].

Wang *et al* proposed a still higher NLR cut-off value of 13.4 to indicate severe disease, with an AUC of 0.89 and sensitivity and specificity of 83.3 and 82.4 per cent, respectively, indicating severe disease[25]. Qin *et al* also found that a high NLR was associated with severe illness in 452 patients admitted to the hospital with COVID[26]. A study by Cheng *et al* looked at 456 patients and found that at an NLR of 3.2 and an AUC of 0.81, they could predict mortality with an accuracy of 78.3 percentage points and a specificity of 73.9 per cent[27]. As an example, Tatum *et al* studied 125 patients and found that an NLR cut-off value of 10 was associated with an AUC of 0.71, a sensitivity of 52.4 per cent, and a specificity of 96.7 per cent (with an AUC of 0.71)[28].

Despite the fact that cut-offs vary depending on the patient's demographic profile and have varying sensitivity and specificity, several researchers have come to the conclusion that a raised NLR is a predictor of COVID-19 severity and, in some cases, mortality.

Conclusions

NLR can be a quick, inexpensive, accessible, reproducible marker for gauging severity and outcome in COVID-19. The higher the NLR, the greater the risk. High NLR at admission in early disease is a predictor of disease severity and can objectively help triage and guide management. An elevated NLR at the end of the first week is a predictor of mortality. Additional studies are needed to strengthen its role.

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