



"Neutrophil – Lymphocyte ratio (NLR) as a prognostic marker in COVID-19"

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ABSTRACT: The Coronavirus disease 2019 (COVID-19) is a disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. This disease had a major impact on global health in the last few years and continues to live with us. The disease causes the asymptomatic disease to severe respiratory illness and can lead to the death of the patients. There is immune dysregulation seen in these patients which is responsible for varied presentation. Identifying patients who are at risk of progressing to severe disease is of at most importance considering this is a pandemic disease. In this study with this aim Neutrophil Lymphocyte ratio was used as a marker to assess the severity of COVID-19 disease.

OBJECTIVE: Neutrophil – Lymphocyte ratio as a prognostic marker for disease severity and mortality in COVID-19 patients admitted to a tertiary care centre.

MATERIALS AND METHODS: All RT-PCR Positive COVID-19 cases admitted between March to May 2021 in AJ Institute of Medical Sciences were included in the study. Descriptive statistical analysis like median and Chi-square test was used to assess statistical significance.

RESULTS: The relationship between NLR and COVID-19 disease severity was statistically significant according to our study with a p-value of 0.001.

CONCLUSION: Patients with higher NLR at admission are at more risk of getting severe COVID-19 disease and also are found to have increased mortality risk.

KEYWORDS: Coronavirus disease 2019 (COVID-19), Neutrophil-Lymphocyte ratio (NLR), C Reactive Protein (CRP)

I. INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had a major impact on global health, it put a strain on healthcare systems and disrupted socioeconomic life. Since the start of the pandemic

in late 2019, SARS-CoV-2 has taken more than six million human lives and continues to spread worldwide with more than 620 million confirmed cases today. Now sub-variants are being identified regularly and COVID-19 remains a serious threat. It is important to identify the poor prognostic factors and identify the patients at risk, to devote more time and resources to patients who need it the most. Neutrophils are the first line of defence of the host immune response against pathogens, by mechanisms of chemotaxis, phagocytosis, ROS generation, granular proteins, and cytokine release(1). The Neutrophil-Lymphocyte ratio (NLR), is the ratio between the neutrophil count and lymphocyte count. Neutrophils represent innate immune response, while lymphocytes represent adaptive immunity(2). NLR is a proven prognostic indicator in various disease conditions namely sepsis, bacterial pneumonia, cardiovascular disease, cancer, and now even in COVID-19 disease according to a few published studies. In COVID-19 pneumonia T cells and NK cells, necessary to contain viral infection are reduced in number and this rate of reduction also is inversely related to disease severity(3). Based on this pathophysiology current study was undertaken. To check the hypothesis that Neutrophil - Lymphocyte ratio is a predictor of the severity of COVID-19.

OBJECTIVE OF THE STUDY

Neutrophil – Lymphocyte ratio as a prognostic marker for disease severity and mortality in COVID-19 patients admitted to a tertiary care centre

II. MATERIALS AND METHODS

- **Source of Data:** Data for the study was collected from the patients admitted to A.J. Institute of Medical Sciences, Mangalore.
- **Study Design:** Hospital-based retrospective observational study.
- **Study period:** All cases were admitted between March to May 2021.



- **Place of study:** A.J. Institute of Medical Sciences, Mangalore.
- **Sample size:** All cases were admitted between March to May 2021 at AJ Institute of Medical Sciences.
- **Data Collection:** Hospital files of all patients admitted with RTPCR Positive cases were analysed. Being a retrospective study, data about patient information like demographic details, co-morbid associations, vitals at admission, admission to ward/ ICU, days of ICU stay, mode of ventilation, laboratory investigation, etc were collected and analysed.

Ethical committee clearance was obtained for this study by Institutional Ethics Committee of A J Institute of Medical Sciences, Mangalore.

- **Inclusion Criteria:**

Patients aged 18 and above, with a confirmed Covid -19 diagnosis by RT-PCR or RAT COVID TEST.

- **Exclusion Criteria:**

- a. Patients below 18 years of age.
- b. RTPCR negative Severe acute respiratory illness.
- c. Patients with a medical history or treatment that altered their blood counts and, therefore, their circulating lymphocytes or neutrophils (e.g., chemotherapy, immunosuppressive therapy, preadmission corticosteroid therapy, pre-admission antibiotic therapy, active cancer, or haematological malignancies) were also excluded from our study.

- **Case definitions and classification:** A standard protocol that included case definitions for categorization of SARS -CoV-2 infection, a detailed management plan, baseline, and

follow-up investigations, and treatment according to clinical severity as categorized by WHO was followed. The consensus treatment algorithm was developed after reviewing the guidelines of various international societies and revised national clinical management guidelines for COVID-19 by the MoHFW, Government of India, dated March 31, 2020.

- a. Patients were categorized into mild, moderate, or severe diseases.
- b. Patients with upper respiratory tract infection symptoms without shortness of breath or hypoxia were classified to have mild disease.
- c. Patients with respiratory rate $> 24/\text{min}$, $\text{SpO}_2 < 94\%$ as a moderate disease.
- d. Patients with respiratory rate $\geq 30/\text{min}$, $\text{SpO}_2 < 90\%$ as severe disease

- **Statistical analysis :**

The chi-square test was used to analyse the association of NLR with covid severity.

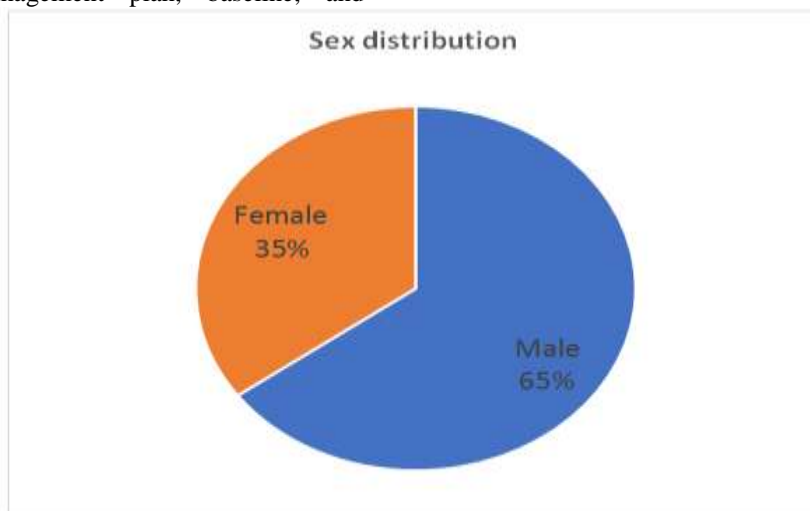
Mild and moderate-severity patients were grouped and compared with severe covid patients.

The same test was also applied to CRP to assess the association with Covid severity.

SPSS software was used for statistical analysis.

III. RESULTS

- **Demographics and baseline clinical characteristics :** During the study period, 102 patients were diagnosed to have COVID -19 and were included in the study.
- Among study population median age was 53 years (min - 18, max - 84).
- It included 66 male (64.7%) and 36 female (35.29%) patients

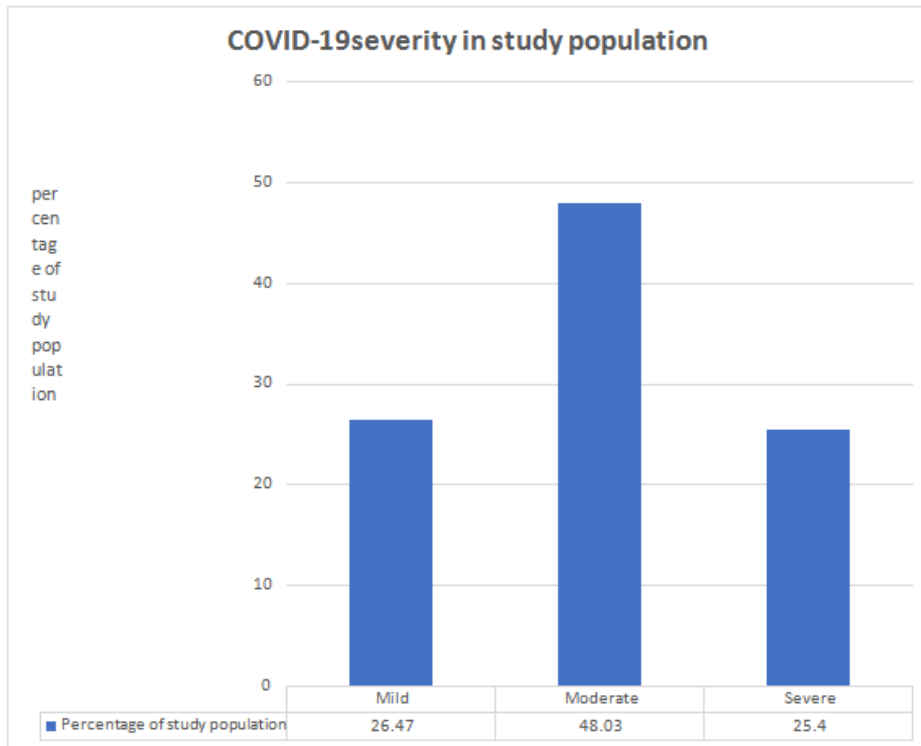




- Among them 43.13% had diabetes and 39.21% were having hypertension as co-morbidities.

- Mild – 27 (26.47%)
- Moderate – 49 (48.03%)
- Severe – 26 (25.49%)

Classification of COVID 19 according to WHO in the study population



- NLR mean in a different subgroup of COVID severity was for mild disease 2.8, moderate disease 6.21, and severe disease 8.925. The median value of all the patients included in the study was 5.6
- There is a significant relationship between NLR and covid severity, χ^2 (1, N=102) = 11.333, p = 0.001.
- This shows that patients who had a higher Neutrophil to lymphocyte ratio at admission had a higher risk of getting severe coronavirus disease and NLR could be used to predict the severity of covid.

- Mortality was also seen more in the patients who had higher NLR at admission (11.76%) compared to patients with lower NLR at admission (5.88%). The median NLR value of survivors in the study was 5.56, while non-survivors had an NLR value of 8.81
- Also, there was a significant relationship between CRP value and Covid severity. χ^2 (1,N=102) = 9.763, p = 0.002. This shows that patients with higher CRP values at admission had a risk of severe COVID disease.
- Mortality was also seen more in the patients who had higher CRP values at admission (12.12%) compared to patients with lower CRP values at admission(3.7%).

Admission NLR and CRP comparison between COVID-19 severity subgroups

COVID-19 Severity	Mild	Moderate	Severe	p-value
Admission NLR	2.8 (1.2-24.89)	6.21 (0.81-33.7)	8.925 (1.78 - 26.1)	0.001
CRP	5.39 (0-228)	20 (0- 241.59)	119.6 (1-362)	0.002



IV. DISCUSSION

The neutrophil-to-lymphocyte ratio (NLR), which is determined as a straightforward ratio between the counts of neutrophils and lymphocytes in peripheral blood, is a biomarker that combines the innate immune response, which is primarily supported by neutrophils, and adaptive immunity, which is supported by lymphocytes. Acute stroke, myocardial infarction, atherosclerosis, severe trauma, cancer, post-surgery problems, and any illness characterized by tissue damage that triggers SIRS can all result in an isolated increase in neutrophil count and, as a result, a higher NLR. Studies have proven NLR significance in predicting mortality in heart diseases, chronic lower respiratory diseases, bacterial pneumonia, and kidney diseases(4). There are few studies conducted to prove NLR as a prognostic marker in COVID-19 patients, but there were not any studies conducted by the southern part of India at the time of starting this study, to the best of our knowledge. NLR is also known to be an independent marker of endothelial dysfunction. It is observed that progressive endothelial damage in diseases like COVID-19 is responsible for increasing NLR as the disease progresses(5). In our study median NLR was 5.6 for the total study population, for mild cases 2.80, for moderate cases 6.21 and for severe cases had a median value of 8.92. This is similar to the study conducted by AbensurVuillaume et al (6) where the total study population had a median NLR value of 5.4, moderate cases had 5.2, and severe cases had a median value of 6.6. In our study on applying the chi-square test, there was statistical significance ($p = 0.001$) for NLR at admission and COVID-19 disease severity. In a study conducted by Lian et al (7), he showed a significant relationship between NLR and COVID-19 disease progression.

CRP level in our study had a mean value of 22 including all study populations. Mild cases had a median of 5.39, moderate cases of 20, and severe cases of 119.6. In a study conducted by AbensurVuillaume et al (6) similar results were found, moderate cases had a CRP of 68, while severe cases had a value of 124. CRP level also showed statistical significance on applying the chi-square test with a p -value of 0.002 against the severity of COVID-19 disease.

Mortality was also most commonly seen in patients with higher NLR at admission at 11.76% compared to 5.88% in patients with NLR less than the median found in the study. This is similar to a study conducted by Saliccioli et al (8) who found NLR measured at the time of admission to the ICU to be associated with 28-day mortality

in critically ill patients. In another study by Bg et al (9) there was different trend, they observed NLR was significantly higher in survivors than non-survivors. But most studies including the studies conducted by Liu et al (10), and Yang et al (11) showed similar results as in our study, where they concluded higher NLR at admission to be a predictor of the severity of COVID-19. These studies and the study we conducted reinforce the fact that Coronavirus Disease is associated with dysregulated immune response, particularly inducing lymphopenia with a frequent decrease in CD 4+ T cells (6).

V. CONCLUSION

This study was conducted on 102 patients admitted to A J Institute of Medical Sciences, Mangalore, and diagnosed to have COVID-19 from March to May 2021. The study included 66 male (64.7%) and 36 female (35.29%) patients. The most common comorbidities were diabetes (43.13%) and hypertension (39.21%).

Among the patients included 27 (26.47%) patients had mild disease, 49 (48.03%) had moderate disease and 26 (25.49%) had severe COVID-19 disease. In our study median NLR was 5.6 for the total study population, for mild cases 2.80, for moderate cases 6.21 and for severe cases had a median value of 8.92. The relationship between NLR and COVID-19 disease severity was statistically significant according to our study. Conventional inflammatory marker like CRP was also studied here, which also showed statistical significance for COVID-19 disease severity. Considering NLR is widely available and relatively cheap, it can be very useful in resourcepoor places to optimize patient management and to accurately triage and treat patients in need.

VI. ADDITIONAL INFORMATION

Disclosures

Human subjects: Consent was obtained by all participants in this study. Institutional Ethics Committee, A J Institute of Medical Sciences issued approval N/A. This study was approved by the Institutional Ethics Committee of A J Institute of Medical Sciences.**Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within



the previous three years with any organizations that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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