

# Neutrophil to Lymphocyte Ratio (NLR) in Predicting Severity of COVID-19 Pneumonia

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**Abstract:** *The NLR has been used for the past two decades to assess prognosis in acute and systemic inflammatory conditions. Neutrophilia and lymphopenia have individually been found to correlate with severity and outcome of COVID-19 pneumonia. NLR can act as a potential marker of deteriorating clinical condition in patients of COVID-19, thereby proving to be an important marker to use, in prospective triaging of patients in resource and time limited settings.*

**Keywords:** Neutrophil-Lymphocyte ratio, COVID-19 pneumonia, severity, A-DROP scoring system.

## 1. Introduction

COVID has reached almost all countries in the World, and even though the rate of spread of COVID-19 has slowed down considerably over the past few months, transmission continues and many countries internationally are now facing the threat of another wave of COVID-19 caused by one of the many genetic variants of the virus.<sup>1</sup>

Neutrophil-to-lymphocyte ratio (NLR): NLR is simply the ratio of neutrophil to lymphocyte count in venous blood. Usually during periods of physiological stress, the neutrophil count increases while the lymphocyte count decreases. The NLR accounts for both changes and is therefore a sensitive marker of inflammatory processes, although an increase in NLR may also be encountered in non-inflammatory conditions of physiological stress (such as hypovolemic shock). Since NLR has been found to increase after episodes of acute physiological stress (within the first 6 hours) as compared to more chronic processes, it has been found to be a sensitive marker of acute inflammatory processes.<sup>2,3,4</sup>

### Aims and Objectives

- To correlate the Neutrophil-to-Lymphocyte ratio with severity of COVID-19 pneumonia on its presentation.
- To use the NLR in low resource settings to prioritise and triage attribution of health care services in view of prognosis based on the NLR.

## 2. Methods

A cross-sectional study was done from May 2020 to May 2021 on 300 COVID positive patients (100 of mild, moderate and severe category each), with the aim of correlating Neutrophil-to-Lymphocyte ratio (NLR), with the severity of COVID-19 disease on presentation of participants.

All the patients who came to SSG Hospital with either signs or symptoms suggestive of COVID-19 infection, or those who were asymptomatic for COVID, but had radiological evidence of pneumonia were screened, and subsequently enrolled according to the inclusion/exclusion criteria.

Rapid Antigen Test (RAT) was conducted to identify patients with SARS-CoV-2 infection, with those testing positives considered as COVID-19 positive and directly admitted to the COVID Positive Isolation Ward or COVID Intensive Care Unit (as required). Those who tested negative on RAT but were still suspected to be COVID positive based on clinical/radiological findings were ruled out using RT-PCR. RAT negative suspected patients were admitted in COVID Suspect Isolation Ward/ COVID ICU till confirmed reports were obtained. RT-PCR Positive patients were shifted to COVID Positive Isolation Ward/COVID ICU and subsequently approached for participation in the study.

Patients were classified into mild, moderate and severe pneumonia based on the severity of the illness. All medical record information including demographics, symptoms, underlying comorbidities, clinical examination and laboratory data were obtained and recorded.

The A-DROP scoring system was used for assessing the severity of COVID-19 pneumonia. The A-DROP scoring system assesses the following parameters: (i) Age (ii) Dehydration (iii) Respiratory failure (iv) Orientation disturbance and (v) low blood Pressure.

Investigations: Patients were subjected to detailed investigations comprising Complete blood counts (CBC) (including NLR (Neutrophils to lymphocytes ratio), Renal Function Tests, Liver Function Tests, Chest x-ray PA view or HRCT Thorax, RBS, ECG, Other investigations (as deemed necessary).

A-Drop Score (For assessment of severity of pneumonia)

Criteria	Score 0	Score 1
Age	In Males <70 In Females <75	In Males >70 In Females >75
Dehydration	BUN <21mg/dl	BUN =or >21mg/dl
Respiratory Failure	Spo2>90% on Room Air	Spo2 < or= 90% on Room Air
Orientation	Conscious	Confused
Blood Pressure	>90mm hg Systolic Pressure	< or = 90mm hg Systolic Pressure

Based on A-Drop Score

Score	Risk	Preferred treatment modality	Mortality
0-1	Low	Home isolation with frequent monitoring or hospitalization if comorbidities are present or symptoms not resolving even on treatment	<5%
2	Immediate	Hospital Admission	<20%
3-5	High	ICU admission	>40%

Clinical severity and assessment parameters according to MOHFW guidelines

Clinical Severity	Clinical Presentation	Clinical Parameters
Mild	Patients with uncomplicated upper respiratory tract infection, may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise headache	Without evidence of breathlessness or hypoxia (normal saturation)
Moderate	Pneumonia with no signs of severe disease	Adolescent or adult with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2. <94 % (range 90-94) on room air, respiratory rate more than or equal to 24 per minute
Severe	Severe Pneumonia	Adolescent or adult: with clinical signs of pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 < 90% on room air.

**Inclusion and Exclusion Criteria:**

**Inclusion criteria:** Participation in the study was solicited from all the patients who:

Age 12 years and above

Diagnosed case of COVID-19 Pneumonia

Admitted in the COVID isolation ward or the COVID ICU in the hospital.

**Exclusion criteria:** Patients with

Viral infections like dengue, chikungunya, acute and chronic hepatitis, HIV

Malignancy

Chronic kidney disease

Pregnant and postpartum females;

Unwilling to participate in the study

**3. Results**

- The AUC for NLR was found to be 0.895 (95%CI = 0.857 – 0.932). It was found that for NLR, if we consider a cut-off of 3.875, it is able to differentiate between mild and moderate/severe cases with a sensitivity of 85% and a specificity of 76%.
- Most of the patients 216 (72.0%) exhibited neutrophilia, while only one patient (0.3%) exhibited neutropenia. Most of the participants in our study exhibited lymphopenia 206 (68.7%), while only 4 (1.3%) of the participants exhibited lymphophilia. On applying tests of significance, it was found that Neutrophilia and Lymphopenia were significantly associated with severe/moderate disease than mild disease.
- As can be seen from table 1, most of the patients (72.0%) exhibited neutrophilia, while only one patient exhibited neutropenia.

**Table 1:** Categorization of participants on the basis of total neutrophil count (n = 300)

Particular	n	%
Neutropenia	1	0.3
Normal	83	27.7
Neutrophilia	216	72.0
Total	300	100

The table 2 depicts the categorization of participants according to lymphocyte count. Most of the participants in our study exhibited lymphopenia (68.7%), while only 1.3% of the participants exhibited lymphophilia.

**Table 2:** Categorization of participants on the basis of total neutrophil count (n = 300)

Particular	n	%
Lymphopenia	206	68.7
Normal Lymphocyte Count	90	30.0
Lymphophilia	4	1.3
Total	300	100

On comparing participants based on categorization of neutrophil count with clinical manifestations of COVID-19, we found that most participants with neutrophilia had severe clinical manifestations, while most participants with a normal neutrophil count had mild COVID-19. On applying chi-square test, the  $\chi^2$  value was 92.656, while the p-value was 0.000, indicating significant association between neutrophil count categorization and clinical severity of COVID-19. (Table 3)

Table 3

		Severity of the disease on admission			Total
		Mild	Moderate	Severe	
Categorization of neutrophil count	Neutropenia	1 (100%)	0 (0%)	0 (0%)	1 (100%)
	Normal	62 (74.7%)	14 (16.9%)	7 (8.4%)	83 (100%)
	Neutrophilia	37 (17.1%)	86 (39.8%)	93 (43.1%)	216 (100%)
Total		100	100	100	300

$\chi^2 = 92.656$ ; p-value = 0.000

On comparing participants based on categorization of lymphocyte count with clinical manifestations of COVID-19, we found that most participants with lymphopenia had severe clinical manifestations, while most participants with a normal lymphocyte count had mild COVID-19. On applying

chi-square test, the  $\chi^2$  value was 117.859, while the p-value was 0.000, indicating significant association between lymphopenia and severe clinical severity of COVID-19. (Table 4)

Table 4

		Severity of the disease on admission			Total
		Mild	Moderate	Severe	
Categorization of lymphocyte count	Lymphopenia	28	85	93	206
	Normal Lymphocyte Count	68	15	7	90
	Lymphophilia	4	0	0	4
Total		100	100	100	300

$\chi^2 = 117.859$ ; p-value = 0.000

#### 4. Discussion

- Multiple studies have shown neutrophilia to be associated with severe manifestations and poor outcomes in COVID-19. A narrative analysis of studies which have examined haematological changes associated with COVID-19 found that neutrophilia was common in patients with severe COVID-19.<sup>6</sup> Similarly; a meta-analysis conducted by Shi et al also found that higher neutrophil counts were indicative of more severe outcomes of COVID-19 in patients.<sup>7</sup> Henry et al had similar findings, wherein neutrophilia at admission was found to be associated with severe outcomes in COVID-19 later on, and recommended aggressive monitoring of patients who displayed neutrophilia on admission.<sup>8</sup> It has been speculated that Neutrophil Extracellular Traps (NETs) may have a role to play in the detrimental pathology associated with severe COVID-19, but the evidence is still being generated and no conclusions can be drawn.
- Similarly, lymphopenia has also been found to be associated with higher mortality and more severe outcomes of COVID-19 in many studies. Decreased lymphocyte count was found to be associated with severe outcomes in COVID-19 by Huang et al<sup>9</sup> and Li Tan et al<sup>10</sup>. A meta-analysis by Henry et al also found that lymphopenia was associated with higher mortality increased severity during COVID-19.<sup>14</sup> The inflammatory cytokine storm is likely a key factor behind the observed lymphopenia. The serum level of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6, have been closely correlated with lymphopenia. It has also been speculated that the numbers of suppressive immature neutrophils and/or G-MDSCs expanded during severe COVID-19 infection are associated with lymphopenia and disease severity. Recent works that identified the presence of G-MDSCs (HLA-DRneg, Linneg, 67 CD33+, CD11b+, CD15+, CD14neg) by flow cytometry in the peripheral blood of COVID-19 patients

provided mechanistic insights by which these cells can impair T cell activity and cause lymphopenia.

- In our study, we found that NLR had a relatively high sensitivity and specificity for differentiating mild versus moderate/severe COVID-19, with AUC for NLR being 0.895 (95%CI: 0.857-0.932). It was also found that at a cut-off of 3.875 for NLR, sensitivity was 85% while specificity was 76%. Given that our findings are based on haematological findings in the participants on admission, NLR can act as a potential marker of deteriorating clinical condition in patients of COVID-19, thereby aiding in prospective triaging of patients.

#### 5. Conclusion

The NLR yielded high AUCs and had a high cut-off point of discerning presence of mild versus moderate/severe disease. This indicates that this parameter can be used as a prognostic indicator for identifying patients who would develop moderate or severe disease, thereby helping in triaging of patients for admission in resource-limited settings.

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