



## Role of Neutrophil- Lymphocyte Ratio and Other Routine Hematological Parameters in Determining Severity of Disease in Covid-19 Positive Patients

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### Abstract

**Background:** Coronavirus disease 2019 (COVID-19) is an ongoing global pandemic with second and third waves sweeping through different countries. Patients with severe disease have a poor prognosis and it is essential for us to identify these cases to initiate timely management. Neutrophil-to-lymphocyte ratio (NLR) has been documented to be higher in the severe patients. **Aim:** The aim is to assess the NLR and other routine hematological parameters in severe versus Non severe patients on admission to the hospital. **Methods:** The blood counts at admission of 551 RT PCR positive Covid-19 patients (Non severe and Severe) were documented including Hemoglobin, Hematocrit, red cell indices, White blood counts (WBC), Platelet count, Absolute neutrophil count (ANC), Absolute lymphocyte count (ALC), Neutrophil-Lymphocyte ratio (NLR) and Platelet-Lymphocyte ratio (PLR). **Results:** A total of 551 patients were grouped into Non severe (450) and Severe (61) and complete blood counts were assessed. The two groups showed a statistically significant difference ( $p < 0.05$ ) between Hemoglobin, WBC, ANC, ALC, NLR, Platelet count and PLR. **Conclusions:** These routine blood count parameters especially NLR play an important role in determining disease severity and progression.

**Keywords:** -COVID-19, Complete blood counts, Neutrophil Lymphocyte ratio, Hemoglobin.

### INTRODUCTION

On 29 December 2019, pneumonia cases were detected in a hospital in Wuhan, China.<sup>[1]</sup> The Chinese Centre for Disease Control and Prevention then confirmed, after studying throat cultures from patients, that these cases were caused by a new type of beta-coronavirus that was named Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19.<sup>[2]</sup> This was followed by a pandemic that has affected millions worldwide. Most of the individuals affected have been

asymptomatic to mildly symptomatic, however severe respiratory disease can be seen in the elderly and specific patient groups, such as those with underlying medical conditions.<sup>[3]</sup> This is a systemic disease and can affect nearly all the organ systems especially the respiratory, haematopoietic, renal, liver etc, leading to multi-organ involvement and death.<sup>[4]</sup>

Due to the rapid spread as well as deterioration seen in patients, intensive care is required in many patients and the health care system has been overwhelmed.

Hence it is important for us to identify the severe or critical cases so that we may offer them timely management.

Blood tests play a vital role in early diagnosis as they provide a lot of information regarding the inflammatory process. The usual panel of haematological and serological investigations includes leukocyte count, platelet counts, coagulogram, acute inflammatory markers like C- reactive protein (CRP), serum Ferritin, D-Dimer, Lactate dehydrogenase, Renal Function tests and Liver function tests.<sup>[5]</sup>

As essential as this full battery of tests may be, complete blood counts (CBC) are often the cheapest, fastest and most readily available investigation that can be performed. Included in the CBC are values such as white blood count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and platelet count (PLT), mean platelet volume (MPV) and Neutrophil lymphocyte ratio (NLR) = absolute neutrophil count/absolute lymphocyte count. Platelet lymphocyte ratio (PLR) = absolute PLT/absolute lymphocyte count.<sup>[6]</sup>

## MATERIAL AND METHODS

This was a retrospective study, and involved analysis of complete blood counts in cases admitted in tertiary care hospital that were RT-PCR positive for SARS-CoV-2 RNA. These cases were diagnosed and categorized as per the Clinical Guidance for management of COVID-19 patients by ICMR- COVID-19 national Task Force and Ministry of Health and family Welfare, Government of India into mild, moderate or severe disease.<sup>[7]</sup> Mild disease included patients with upper respiratory symptoms with or without fever but without

any shortness of breath or hypoxia, moderate disease will include respiratory rate  $\geq 24$ /min, breathlessness or oxygen saturation between 90-93% on room air.

Patients with respiratory rate  $\geq 30$  times/min, breathlessness or oxygen saturation  $\leq 90\%$  on room air were categorized as suffering from severe disease. For purposes of analysis mild and moderate were clubbed as Non severe cases.

### Exclusion Criteria:

All Covid- 19 positive patients with a known or past underlying history of hematologic malignancies or myeloproliferative as well as lymphoproliferative disorders were excluded from the study.

The age, gender, severity of symptoms, complete blood counts including Hemoglobin, Hematocrit, Red cell indices, WBC, Differential leukocyte count (DLC), ANC, ALC, platelet count, MPV, NLR and PLR were documented on admission. NLR was further subdivided on the basis of severity in each group as mild ( $< 3.5$ ), moderate (3.5- 5) and severe ( $>5.0$ ). Continuous variables were expressed as the appropriate means and standard deviations. Categorical variables were summarized as the counts and percentages in each category.

All the above mentioned parameters were statistically analyzed using SPSS software version 16 and Mann Whitney test was used to compare the different variables in the two groups. P value  $<0.05$  was considered significant. The study is in accordance with the declaration of Helsinki of 1975, as revised in 2008 and approval has been granted from the Institutional Ethics Committee.



## RESULTS

A total of 551 patients were included, 490 (88.9%) were mildly symptomatic and 61(11.1%) had severe symptoms requiring admission in the intensive care unit. Their age ranged from 6 years to 90 years with 349 males (63.3%) and 202 females (36.7%). No significant difference was seen in severe and non severe cases with respect to age or gender[Table 1].

There was a statistically significant difference between the Hemoglobin, Hematocrit Mean cell hemoglobin (MCH), Mean cell Hemoglobin concentration (MCHC), Platelet count, WBC, ANC, ALC, NLR as well as PLR

between the Severe and Non severe categories [Table 1].

Lymphopenia was seen in only 35(7.1%) non severe cases and documented in 27 (44.2%) of the severe cases. Thrombocytopenia on the other hand was seen in 45 (9.1%) non severe cases and 4 (6.5%) of the severe cases.

Amongst the Non severe group it was seen that the NLR values ranged from 0.3-15.9 with a mean value of 2.6±1.8 and the severe group ranged from 1.0- 18.9 with a mean value of 6.1 ±3.5. Similarly PLR values showed a statistically significant difference between the non severe [110 ±69.9] and severe [211.5±121.5] categories of patients.

**Table 1:**Demographics and complete blood counts of Non severe and Severe COVID-19 positive patients on hospital admission

Variables/Parameters	Total (n=551)	Non-severe (n=490)	Severe(n=61)	p-value
Age	44.4±17.3	43.5± 17.1	51.0± 17.3	10.2
Sex (M/F)	349/202	311/179	38/23	0.8
Hemoglobin (g/ dL)	12.8 ±1.95	12.9±1.89	11.9±2.22	0.001*
RBC count (10 <sup>6</sup> / μL)	4.5 ±0.6	4.5 ±0.6	4.3±0.8	0.06
Hematocrit (%)	37.9±5.2	38.2±5.1	35.9±6.3	0.002*
MCV (fL)	83.0±9.4	83.2±9.3	81.4±9.8	0.16
MCH (pg)	28.1±3.5	28.2±3.5	27.1±3.7	0.02*
MCHC (%)	33.7±1.3	33.8±1.3	33.7±1.3	0.004*
WBC(10 <sup>3</sup> / μL)	7.1±2.4	6.9±2.2	8.4±3.5	0.001*
ANC (10 <sup>3</sup> / μL)	4.8±2.8	4.6±2.6	6.7±3.2	0.001*
ALC (10 <sup>3</sup> / μL)	1.9±7.9	2.0±7.7	1.3±6.7	0.001*
NLR	2.9±2.3	2.6±1.8	6.1±3.5	0.001*
PLR	121.6±83.4	110.4±69.9	211.5±121.6	0.001*
Platelet count (10 <sup>5</sup> /μL)	1.9±0.7	1.9±0.6	2.3±0.8	0.001*
MPV(fL)	7.8±1.6	7.9±1.6	7.4±1.6	0.07

\*- p value-significant (<0.05)

Mean cell volume (MCV), Mean cell hemoglobin (MCH), Mean cell hemoglobin concentration (MCHC), White blood count cell (WBC), Absolute neutrophil count (ANC), Absolute lymphocyte count (ALC), Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Mean platelet volume (MPV)

Further break-up of NLR as Mild (<3.5), moderate (3.5-5) and severe (>5.0) was

assessed. On admission, in the Non severe category, 82.8% of the patients had NLR<3.5,

followed by moderate NLR (3.5-5.0) in 10.4% and severe NLR (>5.0) in only 6.7% of the patients.

In the Severe category, however, 60% of the patients had severe NLR on admission, followed by moderate NLR in 11% and mild NLR in 29% cases. On follow up, it was seen that NLR value increased further in most of the patients who required prolonged duration of intensive care.

## DISCUSSION

As of 7<sup>th</sup> September 2021 according to the World Health Organization COVID dashboard webpage, Covid-19 has infected more than 221 million people worldwide and more than 4.5 million people have succumbed to this disease. India has had over 33 million cases of which more than 441,411 people have died. With record rise of cases daily, there is a large backlog of diagnostic testing and a longer waiting period for the reports. Both oxygen and ICU care facilities now in short supply.

In the current scenario, it becomes even more important to turn to simple, cheap and readily available blood tests. D-Dimer and CRP provide extremely valuable information, however they are both expensive as well as relatively time consuming investigations and not widely available especially in the periphery.

Chen et al. showed that, compared to cases with moderate disease severity, those with a severe disease status more frequently had lymphopenia as was seen in our study.<sup>[8]</sup>

Mo et al. found that patients with refractory and severe disease had higher neutrophil levels than general COVID-19 patients.<sup>[9]</sup> Our

study showed similar findings with significant difference between the two groups. (Severe vs Non-severe,  $6771 \pm 4870$  vs  $4633 \pm 2677$  per  $\mu\text{L}$ , P value-0.001).

As documented in numerous other studies and meta-analyses, in this study patients with severe COVID-19 infection had a higher NLR than those with non-severe COVID-19 infection.<sup>[10,11,12,13]</sup>

NLR has been studied earlier prior to the advent of Covid-19 and was seen to be raised in a multitude of conditions like tumor-related diseases, autoimmune diseases, bacterial pneumonia etc.<sup>[14,15,16]</sup>

Several reasons have been suggested that may account for this. Neutrophils are an integral part of the leukocyte population and quickly migrate to the affected organ systems, where by releasing reactive oxygen species, they cause cell DNA damage and free the virus from the cells. Neutrophils also interact with other cells that produce cytokines and vascular endothelial growth factor (VEGF). Neutrophils can also be triggered by virus-related inflammatory factors, like interleukin-6 and interleukin-8, granulocyte colony stimulating factor, tumor necrosis factor-alpha, and interferon-gamma factors.<sup>[17]</sup> Systemic inflammation triggered by SARS-CoV-2 decreases T cells cytopathic effects on the infected T cells and by suppressing cellular immunity.<sup>[18,19,20]</sup>

Hence, NLR is cost effective, and is associated with both progression and prognosis of Covid-19. It has proved to be an efficient tool or means of screening patients who are more likely to need intensive care, and helps in timely treatment and appropriate management

On studying PLR, it was seen that it was significantly higher on admission in the severe cases [211.5±121.6] in comparison to the Non severe cases [110.4±69.9]. This has been documented in several other studies, however no universal laboratory reference cut off value has been suggested that has high specificity as well as sensitivity.<sup>[21,22]</sup>

In contrast to a study by Lian et al,<sup>[23]</sup> which did not show any significant difference between the hemoglobin levels and RBC count in groups divided on the basis of severity, our study observed a significantly lower hemoglobin, hematocrit, MCH and MCHC in the Severe group compared to the Non-severe group. This was similar to a study by Huang et al which was based on a larger group size and showed significantly lower mean hemoglobin levels in the severe cases as compared to the non severe cases.<sup>[4]</sup>

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On comparison of platelet count it was surprising to note that the mean platelet count in the severe group [2.3±0.8] was significantly higher than the non severe group [1.9±0.6]. This differed from other studies and maybe explained by the fact that these values were only noted on admission.<sup>[23,24]</sup> On follow-up during the duration of ICU stay, the platelet values decreased further in nearly 30% of the severe patients.

## CONCLUSIONS

It is imperative to highlight the significance of a rapid, simple and cost effective test which is easily accessible in all laboratories especially in rural and peripheral health care settings. Complete blood counts with NLR provide useful information regarding severity of COVID-19 disease and help in guiding timely and targeted management.

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