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# LYMPHOCYTE COUNT AND NEUTROPHIL/LYMPHOCYTE RATIO IN SEVERITY OF COVID-19 PATIENTS

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#### Abstract

TO

Background: Many people are exposed to the corona-virus once in their lifetime, which often causes diseases such as pneumonia or bronchitis. The objective is to analyze the outcome of COVID 19 patients in terms of severity and outcome in association with Absolute Lymphocyte Count and N/L (Neutrophil/ lymphocyte) ratio. Materials and Methods: This hospital based observational study was conducted in the Tertiary care hospital in central India. 246 COVID-19 patients were studied, who were admitted with RTPCR positive fulfilling the requisite criteria. Result: The males were more affected (66.9%) than the females (32.1%). The most affected age group was 41-50 years (37.4%). Most of the cases were symptomatic (96.7). Among the patients, 36.6% has diabetes mellitus alone. The N/L ratio was high significantly from the day of admission (day 0) to day 9 in patients with chest X-ray score  $\geq$ 4/6 ( P value <0.001). The N/L ratio was high significantly from the day of admission (day 0) to day 9 (P value <0.001) in patients with HRCT score 8-16 and >16. The N/L ratio was high significantly from the day of admission (day 0) to day 12 in patients with NEWS2 score  $\geq 4$  (P value <0.001). ALC was low significantly from the day of admission (day 0) to day 12 in patients with NEWS2 score  $\geq$ 4 (P value <0.001). Conclusion: Absolute Lymphocyte Count and Neutrophil to Lymphocyte ratio are simple biomarkers that reflect the presence of systemic inflammation, and are associated with allcause mortality in COVID-19.

# **INTRODUCTION**

The fundamental particle of an infectious virus composed of nucleic acid and an external protein shell is called a virion.<sup>[1]</sup> In the modern world, a record for detecting respiratory infections caused by the virus in children and adults date back to the 1960s,<sup>[2]</sup> one of the essential viruses available that cause respiratory syndromes are coronaviruses. This family is called Coronaviridae. Coronaviruses are single-stranded, enveloped RNA viruses with a 80-120 nm diameter and are divided into four groups: Alpha coronaviruses, Beta coronaviruses.<sup>[3]</sup>

Nevertheless, two types of coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS- CoV), caused two deadly epidemics.<sup>[4]</sup> In 2003, due to the SARS-CoV emergency in southern

China and its widespread prevalence, extensive research was conducted to control and treat the disease. In addition, in 2012, another outbreak of the acute respiratory disease was reported in Saudi Arabia where MERS-COV was identified as the cause of the epidemic. According to published reports, the mortality rate was over 35%.<sup>[5]</sup> It was stated that market civets and dromedary camels were the primary sources of SARS-CoV transmission and MERS-CoV transmission to humans.<sup>[4]</sup>

COVID-19 could induce symptoms including fever, dry cough, headache, anorexia, nausea, vomiting, loose stool, sore throat, myalgia, dyspnea, fatigue in infected patients. In more severe cases, infections causing viral pneumonia may lead to severe acute respiratory syndrome and even death.<sup>[6]</sup>

The poor outcome of the disease appears to be associated with initial high viral load, neutrophil infiltration in lungs with exclusive elevated levels of proinflammatory cytokines and chemokines (cytokine storm) with a decrease of peripheral T lymphocytes. Pathogenesis depends on virus induced cytopathic effect along with maladjusted immune response. The neutrophil to lymphocyte ratio (NLR) is a simple marker of the systemic inflammatory response. Not only for infectious diseases, it is also reported as an independent prognostic factor for non-infectious diseases like acute MI, stroke, malignancy. NLR can be used as a potential predictor of severity and outcome of many diseases especially in COVID -19 cases in present scenario.

The present study was designed to analyze the outcome of COVID 19 patients in terms of severity and outcome in association with Absolute Lymphocyte Count and N/L (Neutrophil/ lymphocyte) ratio.

# **MATERIALS AND METHODS**

This hospital based observational study was conducted in the Tertiary care hospital in central India. 246 COVID-19 patients who were admitted with RTPCR positive for fulfilling the requisite criteria. The duration of the study was 2 years (November 2020 to October 2022).

#### **Inclusion Criteria**

All RTPCR positive COVID-19 patients (symptomatic and asymptomatic), age more than 18 years.

#### **Exclusion Criteria**

- 1. Pediatric age group
- 2. Patients having autoimmune disorders
- 3. Patients on long term steroid therapy
- 4. Patients having hematogical malignancy
- 5. Patients on radiation therapy/chemotherapy
- 6. Pregnant females
- 7. Not willing to participate

Sampling technique: Universal Sampling Technique Sample size – 246

- Expected proportion- 0.8
- Absolute precision(alpha)-5%
- Desired confidence interval- 95%
- Minimal sample size required- 246

#### **Data Collection Method**

• Patients with positive RTPCR for COVID 19 were included in the study

- Demographic, epidemiologic, clinical, laboratory and radiological and group according to WHO classification was collected.
- Case id, age, gender, address was obtained.
- Following which detailed clinical history and examination was done which was followed by laboratory investigations (Complete blood count, liver Function test, Kidney function tests) and radiological investigations (Chest xray and HRCT).

#### **Statistical Analysis**

The data was tabulated in Microsoft excel and analysed with SPSS v.24 software. The continuous variables are expressed with mean and standard deviation. The categorical variables are expressed with frequency and percentage. Independent t test and one way ANOVA are used for the comparisons. The p value  $\leq 0.05$  is considered as statistically significant.

### RESULTS

Among 246 patients studied, 167 patients (66.9%) were males and 79 patients(32.1%) were females. 10 patients age was less than 20 years, 24 patients were between 21 to 30 years, 48 patients were between 31 to 40 years, 92 patients were between 41 to 50 years, 32 patients were between 51 to 60 years, 16 patients were between 61 to 70 years, and rest 24 patients were between 71 to 80 years. So maximum number of patients (37.4%) were in the age group 41 to 50 years and minimum number of patients (4.1%) were less than 20 years of age.

Most of the cases were symptomatic (96.7%) while a very few cases were asymptomatic (3.3%). 68.2% had Fever, 56.0% had Cough, 42.6% had Breathlessness, 6.0% had Sore throat, 3.0% had Anosmia, 39.0% had Myalgia/Body ache and 2.0% had Diarrhoea.

238 patients were symptomatic, among which, 11(4.7%) patients had only one symptom, 185(77.7%) patients had two symptoms and 42(17.6%) patients had three symptoms, hence majority of the patients had two symptoms.

36.6% has diabetes mellitus alone and 26.8% had hypertension alone, 19.5% had both diabetes and hypertension, 7.3% had diabetes, hypertension and COPD, 3.3% had diabetes, hypertension, IHD and CCF.

Table 1: Distribution of comorbidities		
Comorbidities	Ν	%
DM	90	36.6%
HTN	66	26.8%
DM+HTN	48	19.5%
DM+HTN+COPD	18	7.3%
DM+HTN+IHD+CCF	8	3.3%

On the day of admission(day 0), the mean ALC was  $1888.0 \pm 1798.5$  in the patients with chest X-ray score  $\geq 4/6$  and  $2203.2 \pm 1115.2$  in the patients with chest X-ray score< 4/6 with no statistically significant difference. On the day 3, the mean ALC was  $1739.1 \pm 903.1$  in the patients with chest X-ray score $\geq 4/6$  and  $1597.1 \pm 949.7$  in the patients with chest X-ray score < 4/6 with no statistically significant difference. On the day 6, the mean ALC was  $1376.0 \pm 668.5$  in the patients with chest X-ray score  $\geq 4/6$  and  $1834.8 \pm 1110.1$ in the patients with chest X-ray score <4/6 with statistically significant difference.

On the day 9, the mean ALC was  $1550.0 \pm 634.6$  in the patients with chest X-ray score  $\geq 4/6$  and  $2260.0 \pm 716.8$ in the patients with chest X-ray score <4/6 with statistically significant difference.

On the day 12, the mean ALC was 400 in the patients with chest X-ray score  $\geq$ 4/6 but there was no patients with chest X-ray score <4/6.

Table 2: Distribution of ALC based on Chest X Ray									
Days from symptom onset	Chest x-ray	Mean	SD	Minimum	Maximum	Р			
Day 0	≥4/6	1888.0	1798.5	300	6400	0.226			
	<4/6	2203.2	1115.2						
Day 3	≥4/6	1739.1	903.1	310	3600	0.370			
	<4/6	1597.1	949.7						
Day 6	≥4/6	1376.0	668.5	290	4200	0.010*			
	<4/6	1834.8	1110.1						
Day 9	≥4/6	1550.0	634.6	800	2600	0.010*			
	<4/6	2260.0	716.8						
Day 12	≥4/6	400.0	0.0	400	400	-			
	<4/6	-	-						

On the day of admission(day 0), the mean N/L ratio was  $6.3 \pm 2.8$  in the patients with chest X-ray score  $\geq 4/6$ and  $4.3 \pm 2.8$  in the patients with chest X-ray score <4/6 with statistically significant difference.

On the day 3, the mean N/L ratio was  $5.9 \pm 2.1$  in the patients with chest X-ray score  $\geq 4/6$  and  $4.0 \pm 2.7$  in the patients with chest X-ray score <4/6 with statistically significant difference.

On the day 6, the mean N/L ratio was  $5.8 \pm 1.9$  in the patients with chest X-ray score  $\geq 4/6$  and  $3.7 \pm 2.8$  in the patients with chest X-ray score <4/6 with statistically significant difference.

On the day 9, the mean N/L ratio was  $4.4 \pm 1.1$  in the patients with chest X-ray score  $\geq 4/6$  and  $3.2 \pm 2.2$  in the patients with chest X-ray score <4/6 with statistically significant difference.

On the day 12, the mean N/L ratio was 7.2  $\pm$  0.1 in the patients with chest X-ray score  $\geq$ 4/6 but there was no patients with chest X-ray score <4/6.

Table 3: Distribution of N/L Ratio based on Chest X Ray									
Days from symptom onset	Chestx-ray	Mean	SD	Minimum	Maximum	Р			
Day 0	≥4/6	6.3	2.8	0.27	10.0	< 0.001*			
	<4/6	4.3	2.8						
Day 3	≥4/6	5.9	2.1	0.45	12.0	< 0.001*			
	<4/6	4.0	2.7						
Day 6	≥4/6	5.8	1.9	0.38	13.0	< 0.001*			
	<4/6	3.7	2.8						
Day 9	≥4/6	4.4	1.1	2.10	7.20	0.045*			
	<4/6	3.2	2.2						
Day 12	≥4/6	7.2	0.1	7.20	7.20	-			
	<4/6	-	-						

On the day of admission(day 0), the mean ALC was  $2196.0 \pm 1324.0$  in the patients with HRCT score <8,  $2035.5 \pm 772.6$  in the patients with HRCT score 8-16 and  $1892.2 \pm 1135.1$  in the patients with HRCT score>16 with no statistically significant difference.

On the day 3, the mean ALC was 2060.0  $\pm$  988.6 in the patients with HRCT score <8, 1721.5  $\pm$  625.1 in the patients with HRCT score 8-16 and 1686.6  $\pm$  847.3 in the patients with HRCT score>16 with no statistically significant difference.

On the day 6, the mean ALC was  $2477.8 \pm 941.6$  in the patients with HRCT score<8,  $2451.5 \pm 1228.4$  in the patients with HRCT score 8-16 and 1825.4  $\pm$  1301.8 in the patients with HRCT score>16 with statistically significant difference.

On the day 9, the mean ALC was 2200.0 in the patients with HRCT score < 8, 1000.0 $\pm$  421.6 in the patients with HRCT score 8-16 but there was no patients with HRCT score >16.

Table 4: Distribution of ALC based on HRCT Score.									
Days from symptom onset	HRCT score(out of 25)	Mean	SD	Minimum	Maximum	Р			
Day 0	<8	2196.0	1324.0	300	6400	.538			
	8-16	2035.5	772.6						
	>16	1892.2	1135.1						
Day 3	<8	2060.0	988.6	310	3600	.209			
	8-16	1721.5	625.1						
	>16	1686.6	847.3						
Day 6	<8	2477.8	941.6	290	4200	0.054*			
	8-16	2451.5	1228.4						
	>16	1825.4	1301.8						

Day 9	<8	2200.0	0.0	800	2600	< 0.001
-	8-16	1000.0	421.6			
	>16	-	-			*

On the day of admission (day 0), the mean N/L ratio was  $2.0 \pm 1.7$  in the patients with HRCT score <8,  $4.0 \pm 2.6$  in the patients with HRCT score 8-16 and  $4.4 \pm 2.1$  in the patients with HRCT score >16 with statistically significant difference.

On the day 3, the mean N/L ratio was  $2.9 \pm 0.7$  in the patients with HRCT score  $<8,4.1 \pm 2.3$  in the patients with HRCT scores-16 and  $5.2 \pm 3.1$  in the patients with HRCT scores-16 with statistically significant difference. On the day 6, the mean N/L ratio was  $2.6 \pm 0.6$  in the patients with HRCT score $<8, 5.1 \pm 3.9$  in the patients with HRCT score >16 with statistically significant difference. On the day 9, the mean N/L ratio was 3.0 in the patients with HRCT score  $<8, 5.3 \pm 0.7$  in the patients with HRCT score >16 with statistically significant difference.

Table 5: Distribution of N/L Ratio based on HRCT score								
Days from symptom onset	HRCT score(out of 25)	Mean	SD	Minimum	Maximum	Р		
Day 0	<8	2.0	1.7	0.27	10.0	0.002*		
	8-16	4.0	2.6					
	>16	4.4	2.1					
Day 3	<8	2.9	0.7	0.45	12.0	0.009*		
	8-16	4.1	2.3					
	>16	5.2	3.1					
Day 6	<8	2.6	0.6	0.38	13.0	0.001*		
	8-16	5.1	3.9					
	>16	5.2	2.5					
Day 9	<8	3.0	0.0	2.10	7.20	< 0.001*		
	8-16	5.3	0.7					
	>16	-	-					

On the day of admission(day 0), the mean ALC was  $2041.6 \pm 1453.5$  in the patients with NEWS2 <4 and 1727.8  $\pm 1240.3$  in the patients with NEWS2 ≥4 with no statistically significant difference.

On the day 3, the mean ALC was  $2123.5 \pm 830.9$  in the patients with NEWS2 <4 and  $1334.1 \pm 861.4$  in the patients with NEWS2  $\geq 4$  with statistically significant difference.

On the day 6, the mean ALC was  $2556.4 \pm 915.6$  in the patients with NEWS2 <4 and  $1196.5 \pm 922.8$  in the patients with NEWS2  $\geq 4$  with statistically significant difference.

On the day 9, the mean ALC was 2291.7  $\pm$  226.4 in the patients with NEWS2 <4 and 983.4  $\pm$  383.4 in the patients with NEWS2  $\geq$ 4 with statistically significant difference.

On the day 12, the mean ALC was 400.0 in the patients with NEWS2  $\geq$ 4 but there was no patients with NEWS2 <4.

Table 6: Distribution of ALC based on NEWS2 score									
Days from symptom onset	NEWS2score	Mean	SD	Minimum	Maximum	Р			
Day 0	<4	2041.6	1453.5	300	6400	0.079			
	≥4	1727.8	1240.3						
Day 3	<4	2123.5	830.9	310	3600	< 0.001*			
	≥4	1334.1	861.4						
Day 6	<4	2556.4	915.6	290	4200	< 0.001*			
	≥4	1196.5	922.8						
Day 9	<4	2291.7	226.4	800	2600	< 0.001*			
	≥4	983.4	383.4						
Day 12	<4	-	-	400	400	-			
	≥4	400.0	0.0						

# Table 6: Distribution of ALC based on NEWS2 score

On the day of admission(day 0), the mean N/L ratio was  $3.6 \pm 2.6$  in the patients with NEWS2 <4 and  $5.3 \pm 2.7$  in the patients with NEWS2 ≥4 with statistically significant difference.

On the day 3, the mean N/L ratio was  $3.0 \pm 1.5$  in the patients with NEWS2 <4 and  $5.7 \pm 2.5$  in the patients with NEWS2  $\geq 4$  with statistically significant difference.

On the day 6, the mean N/L ratio was  $2.8 \pm 1.1$  in the patients with NEWS2 <4 and  $6.0\pm 2.4$  in the patients with NEWS2 ≥4 with statistically significant difference.

On the day 9, the mean N/L ratio was  $2.9 \pm 0.6$  in the patients with NEWS2 <4 and  $5.7 \pm 1.0$  in the patients with NEWS2  $\geq 4$  with statistically significant difference.

On the day 12, the mean N/L ratio was  $7.2 \pm 0.1$  in the patients with NEWS2  $\geq$ 4 but there was no patients with NEWS2  $\leq$ 4.

Table 7: Distribution of N/L Ratio based on NEWS2 score							
Days from symptom onset	NEWS2 score	Mean	SD	Minimum	Maximum	Р	
Day 0	<4	3.6	2.6	0.27	10.0	< 0.001*	

	≥4	5.3	2.7			
Day 3	<4	3.0	1.5	0.45	12.0	< 0.001*
	≥4	5.7	2.5			
Day 6	<4	2.8	1.1	0.38	13.0	< 0.001*
	≥4	6.0	2.4			
Day 9	<4	2.9	0.6	2.10	7.20	< 0.001*
	≥4	5.7	1.0			
Day 12	<4	-	-	7.20	7.20	-
	≥4	7.2	0.1			

### DISCUSSION

The neutrophil to lymphocyte ratio (NLR), a routinely measured inflammatory biomarker, reflects the immune status of the human defense system against infection. A higher NLR, which results in an increased neutrophil or/and decreased lymphocyte count, might indicate that the patient had severe inflammatory progression.<sup>[7]</sup> Some studies have reported that the NLR could be useful for the diagnosis of sepsis and might be a good predictor for a poor prognosis of acute respiratory distress syndrome, which has the same disease characteristics as COVID-19, to some extent.<sup>[8]</sup> Previous studies of COVID-19 have noted the predictive power of the NLR for clinical deterioration and mortality among COVID-19 patients.<sup>[9]</sup>

We studied 246 patients, amongst them, maximum number of patients (37.4%)were in the age group 41 to 50 years and minimum number of patients (4.1%) were less than 20 years of age. The males were more affected (66.9%) than the females (32.1%). Most of the cases were symptomatic (96.7) while a very few cases were asymptomatic (3.3%). Liu et al in 2020 stated that, out of the 61 patients with 2019-nCoV infection included in their study, 44 were diagnosed as mild (mild group) and 17 as moderate or severe(severe group) on admission. The median age of the two groups was statistically different, the mild group was 41 years old and the severe group was 56 years old. Study of Liu et al,<sup>[10]</sup> declared that patients with aged greater than 50 years and with an NLR greater than 3.13 were more likely to develop severe COVID- 19, and they suggested that these patients should be sent to the ICU, among the patients, 36.6% has diabetes mellitus alone and 26.8% had hypertension alone, 19.5% had both diabetes and hypertension, 7.3% had diabetes, hypertension and COPD, 3.3% had diabetes, hypertension, IHD and CCF. Ding et al in 2020 stated that out of 72 patients with COVID-19, the most common comorbidities found in the infected patients included hypertension (9 [12.5%]), cardiovascular disease (6 [8.3%]) and diabetes (5 [6.9%]).<sup>[11]</sup>Toori et al n 2021 conducted a study to identify association of neutrophil to lymphocyte ratio with COVID -19 disease severity and mortality. The mean age of patients was 40  $\pm$ 12.4 years with 96% being males. Majority patients (76.5%) were asymptomatic. Diabetes mellitus was most common recorded co-morbidity.

The mean duration of hospital stay was  $9.90 \pm 2.80$ in patients with N/L ratio  $\leq 3.5$  and  $8.44 \pm 3.42$  in patients with N/L ratio >3.5 with statistically significant difference. The mean duration was  $8.65 \pm 2.70$  in patients with ALC  $\leq 1000$  and  $9.19 \pm 3.39$ in patients with ALC >1000 with no statistically significant difference.

In our study On the day of admission (day 0), the mean ALC was  $1888.0 \pm 179$  in the patients with chest X-ray score  $\geq 4/6$  and  $2203.2 \pm 1115.2$  in the patients with chest X-ray score <4/6 with no statistically significant difference. On the day 12, the mean ALC was 400 in the patients with chest Xray score  $\geq 4/6$  but there was no patients with chest X-ray score <4/6. Like severe acute respiratory syndrome (SARS) and Middle East Respiratory syndrome (MERS),<sup>[12]</sup>changes in circulating blood cells were also important features in patients with COVID-19, including abnormalities in the number and function of lymphocytes. Lymphopenia on admission was reported in numerous studies, of which the proportion varied from 36.9% to 83.2%.<sup>[13]</sup> In the study, lymphopenia was found in 54.2% of patients on admission. Lymphocyte count in severe patients was much lower compared with non-severe patients on admission and appeared more difficult to recover during hospitalization Disturbance of the immune system including lymphopenia, imbalance of lymphocyte subgroups and cytokine storm had been found to occur in patients with COVID-19, and the extent of disturbance might be linked to the severity of COVID-19.<sup>[14]</sup>

On the day 0, the mean N/L ratio was  $6.3 \pm 2.8$  in the patients with chest X-ray score  $\geq 4/6$  and  $4.3\pm$ 2.8 in the patients with chest X-ray score <4/6 with statistically significant difference. On the day 0, the mean N/L ratio was  $2.0 \pm 1.7$  in the patients with HRCT score <8, 4.0  $\pm$  2.6 in the patients with HRCT score 8-16 and  $4.4 \pm 2.1$  in the patients with HRCT score >16 with statistically significant difference. NLR had become another important laboratory parameter of patients with COVID-19 due to the characteristic changes in lymphocyte count. The NLR was considered to be a marker for evaluation of the progression and prognosis in patients with infection and tumors, and increased NLR indicated poor prognosis. Similar clinical value had been proven as NLR was applied in COVID-19. Elevated NLR on admission was considered an independent risk factor for severe illness and mortality of COVID-19 patients.<sup>[16]</sup> Ding et al stated that dynamic NLR had implications for better evaluating the hospitalization time of patients with COVID-19.<sup>[11]</sup>

Shang et al in 2020 stated that NLR and CRP were independent risk factors for severe COVID-19. Xisheng et al stated that NLR value of non survival group was higher than that of the survival group in the patients of COVID 19 disease. Yang et al stated that elevated NLR and age are independent factors for poor clinical outcome in COVID 19.As it is known, the human immune system plays a major role in putting out viral infections. The NLR reflects that the high systemic inflammatory response is associated with the poor prognosis of infectious diseases. Several studies have manifested that severe cases (including patients who died) of COVID-19 were more likely to have higher neutrophil counts and lower lymphocyte counts, when compared with non-severe cases. Thus, the elevated NLR tends to predict the severity of COVID-19. Through a retrospective analysis of 452 patients, Qin et al,<sup>[17]</sup> reported that severe cases are likely to have higher NLRs caused by the higher neutrophil counts, but these cases would have lower lymphocyte counts, when compared to non-severe patients, indicating that the surveillance of NLRs might be helpful for the early screening of the critical illness of COVID-19.

Jianhong et al stated that NLR of the severe group was higher than the mild/moderate on days 1, 4 and 14 (P < 0.01), hence dynamic change of NLR can distinguish severe COVID 19 cases from mild/moderate. In this study also, NLR was on higher side and gradually increasing in successive follow up for the patients that succumed in due course, and the majority of patients with declining NLR in follow up were improved and hence discharged.

# **CONCLUSION**

The initial values of ALC and NLR were great predictors of severe COVID-19 and could help clinicians identify the potentially critical patients early and decide the allocation of vital resources. The reduction of ALC and elevation of NLR are useful biomarkers to predict the mortality in COVID-19. Further studies are needed to ascertain the dynamic values of ALC and NLR in predicting all- cause mortality in COVID-19, and explore more useful markers to timely detect critical patients.

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