



ISSN:2687-4245

Role of Neutrophil Lymphocyte Ratio in Predicting Disease Severity in COVID-19

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ABSTRACT

Background To evaluate the role of NLR as a prognostic indicator for severe COVID-19, due to its positive correlation with disease severity, easy accessibility and low cost.

Material and Methods A multicenter retrospective observational study was conducted in COVID-19 wards of two tertiary care hospitals of Faisalabad city, Pakistan, treating COVID-19 patients between May 2021 - July 2021. A predesigned proforma was filled to collect the data. SPSS 21 was used for the statistical analysis of this research.

Results A record of 100 COVID-19 patients admitted between May 2021 - July 2021, fulfilling the inclusion criteria was included in the study. All patients were divided into two groups. The non-severe group included 37 patients while the severe group included 63 patients. The mean age of the study population was 56 years with male predominance (63%). Overall, 50% of patients in the non-severe group and 71% in the severe group had some co-existent comorbidity. Fever and cough were the most commonly reported symptoms in both groups while shortness of breath was more widely reported in the severe group (74.2%). The mean NLR in the non-severe group was 4 as compared to 12 in the severe group.

Conclusions Higher neutrophil lymphocyte ratio (NLR) is associated with severe COVID -19 and can be used as an effective tool to predict the progression of the non-severe disease to severe disease.

Turk J Int Med 2022;4(1):6-12

DOI: [10.46310/tjim.1011041](https://doi.org/10.46310/tjim.1011041)

Keywords: COVID-19, coronavirus, SARS- COV-2, neutrophil/lymphocyte ratio.



Turkish
Journal of
Internal
Medicine

Received: October 21, 2021; Accepted: November 26, 2021; Published Online: January 29, 2022

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Introduction

COVID-19, an extremely contagious and rapidly spreading viral infection caused by a novel corona virus SARS-COV-2 was first reported in China on December 5, 2019. It was declared a pandemic by WHO on March 11, 2020.¹ The pandemic has affected millions of people since the emergence of the first case. Till October 01, 2021, 219 million people worldwide got infected and almost 4.55 million deaths.² The statistical data of Pakistan till October 01, 2021, report 2.16 million diagnosed cases of COVID-19 with almost 28k fatalities.² The SARS-COV-2 is transmitted primarily through respiratory droplets and direct contact with infected body fluids or people.^{3,4} The median incubation period reported is four to five days (range: 2-14 days).⁵ The disease manifests most commonly as fever, cough, fatigue, shortness of breath, loss of taste and smell et cetera.^{6,7} The novel infection under research exhibits a broad spectrum of severity ranging from no symptom to severe pneumonia leading to death. The majority of affected people have a mild form of the illness (81%) while some deteriorate and progress to moderate (14%) or severe disease (5%). Patients with moderate symptoms develop dyspnea due to pneumonia after the seventh day of illness, whereas severe disease is complicated by ARDS, acute respiratory failure, coagulopathy, septic shock, multi-organ failure and metabolic acidosis ending up in ventilator support and death.³ This alarming situation highlights the urgent need to evaluate any reliable, widely available and cost-effective prognostic indicator to identify the patients likely to experience deterioration and progression to critical disease status and mortality. Early identification of high-risk cases may facilitate patient prioritization, arranging appropriate health care facilities, and tailoring appropriate treatment plans to enable good supportive care and reduce mortality.⁸

Sustained neutrophilia and lymphopenia have been witnessed in severe COVID at the onset of the disease compared to mild COVID (84.6% vs. 44.4%).⁹ Neutrophil to lymphocyte ratio (NLR), one of the leading indicators for prediction of high-risk COVID-19 cases, can be easily calculated from differential leucocyte count (NLR [million per liter]=absolute neutrophil count/

lymphocyte count) on admission. It has been hypothesized to be an effective screening tool for identifying patients likely to have complicated diseases. Available literature shows higher NLR values in patients with severe COVID symptoms as compared to mild or moderate symptoms.^{1,10,11} Higher NLR has also been found to be positively correlated with bilateral pulmonary involvement in 80% of cases.⁷ To predict severe COVID and low survival rate, the so far suggested NLR cut-off value is >3.3.^{11,12}

To evaluate the role of NLR as a prognostic indicator for severe COVID-19, due to its positive correlation with disease severity, easy accessibility and low cost. COVID-19, a highly contagious and rapidly spreading viral infection caused by a novel coronavirus SARS-COV-2 was first reported in China on December 5, 2019. The novel infection under research exhibits a broad spectrum of severity ranging from no symptom to severe pneumonia leading to death.

Material and Methods

It was a multicenter retrospective observational study conducted in COVID wards of two tertiary care hospitals (Allied Hospital and DHQ hospital, Faisalabad) treating COVID-19 patients between May 2021-July 2021. Informed consent was waived after permission from the Institutional ethics committee due to this study's retrospective and observational character. Anonymity and confidentiality were ensured. This study was approved by the Institutional ethics committee of Allied hospital (Faisalabad Medical University) with approved no. AHF-402-FMU-04/15.

Hospital record was reviewed and patients with age >18 years and positive COVID-19 RT PCR for nasopharyngeal swab specimens were enrolled in the study. Cases were diagnosed based on the interim guidance of the WHO and divided in two groups named non-severe and severe. The patients meeting the following conditions were enrolled in the non-severe group: (1) Epidemiology history, (2) Fever or other respiratory symptoms, (3) Typical chest X-ray abnormalities of COVID-19, and (4) Positive result of RT-PCR for SARS-CoV-2 RNA. Patients having at least one of the following in addition to the above criteria were enrolled in the severe group: (1) Shortness of breath, respiratory

Table 1. Demographics and clinical features of patients.

Variables	All patients (n=100)	Non-severe group (n=37)	Severe group (n=63)	p value
Age (mean±SD)	56.82 (15.61)	51.71 (18.90)	59.03(13.13)	0.03
Gender, n (%)				
Male	63 (63%)	20 (58.82%)	43 (65.15%)	0.39
Female	37 (37%)	14 (41.18%)	23 (34.85%)	0.39
Comorbidity, n (%)	64 (64%)	17 (50%)	47 (71.21%)	0.04
Symptoms, n (%)				
Fever	77 (77%)	26 (76.47%)	51 (77.27%)	0.93
Cough	55 (55%)	16 (47.06%)	39 (59.09%)	0.25
SOB	57 (57%)	8 (23.53%)	49 (74.24%)	0.000
Myalgia	26 (26%)	9 (26.47%)	17 (25.76%)	0.94
Diarrhea	9 (9%)	1 (2.94%)	8 (12.12%)	0.13
Sore throat	8 (8%)	2 (5.88%)	6 (9.09%)	0.58
Headache	7 (7%)	1 (2.94%)	6 (9.09%)	0.25

rate (RR) ≥ 30 times/min, (2) Oxygen saturation (resting-state) $\leq 93\%$ or PaO₂/FiO₂ ≤ 300 mmHg. Patients with COVID symptoms but negative PCR were excluded from the study.

Data Collection

A predesigned proforma was filled to collect the data. Demographic details, clinical symptoms and signs, and laboratory findings including CBC, TLC, DLC, NLR, CRP, serum ferritin, D-dimer, LDH, liver function tests, renal function tests on the first day of hospitalization were obtained from medical records. In addition, the number of days of hospital stay, need for mechanical ventilation, ICU admission, mortality, recovery and discharge from hospital were also noted.

Statistical Analysis

SPSS 21 was used for the statistical analysis of this research. Continuous variables were expressed as means±standard deviation or medians and interquartile ranges. Categorical variables were summarized as frequency and percentages in each category. Pearson product-moment correlation and independent-sample t-test was used to find out the relationship of

NLR with different parameters of COVID and compare severe and non-severe groups in various parameters of COVID respectively.

Results

Records of 100 COVID-19 patients admitted between May 2021 - July 2021 fulfilling the inclusion criteria was included in the study. The non-severe group included 37 patients while the severe group included 63 patients. The mean age of the study population was 56 years with male predominance (63%). Overall, 50% of patients in the non-severe group and 71% in the severe group had some co-existent comorbidity. Fever and cough were the most commonly reported symptoms in both groups while shortness of breath was more widely reported in the severe group (74.2%). The rest of the symptoms like myalgia, diarrhea, and headache were equally noted in both groups (Table 1).

The severe group showed a higher mean respiratory rate/min (36.24, $p < 0.001$) as compared to the non-severe group. Similarly, oxygen requirement was also found to be higher in the severe group (7.48±5.09). Mean SpO₂ was

Table 2. Comparison of investigations and disease outcome.

Parameters	All patients (n=100)	Non-severe group (n=37)	Severe group (n=63)	p value
Clinical parameters (mean±SD)				
RR (/minute)	33.60 (5.86)	19.72 (2.76)	36.24 (5.65)	0.000
SPO ₂ (%)	87.52 (11.78)	95.81 (2.04)	83.30 (12.44)	0.000
Oxygen requirement (L)	5.06 (5.21)	1.09 (1.71)	7.48 (5.09)	0.000
Lab investigation (Mean±SD)				
TLC (*10 ³ /UL)	11.67 (5.55)	9.54 (3.99)	12.90 (6.02)	0.005
NLR	9.53 (9.52)	4 (2.29)	12.81 (10.65)	0.000
D-dimers (mg/L)	1.21 (1.36)	1.14 (1.40)	3.27 (1.65)	0.04
CRP (mg/L)	31.7 (25.99)	23.59 (22.83)	35.76 (26.69)	0.03
Ferritin (ng/mL)	743.74 (543.09)	603.75 (574.93)	807.80 (520.35)	0.03
LDH (U/L)	476.13 (373.14)	327.55 (262.69)	575.55 (406.04)	0.001
S.ALT (U/L)	48.09 (37.37)	37.75 (17.95)	54.69 (44.33)	0.04
Chest X-ray (PA view), n (%)				
<50% involvement	37 (37%)	16 (47.06%)	21 (31.82%)	0.14
>50% involvement	44 (44%)	2 (.61)	42 (63.64)	0.000
Duration of ICU stay (mean±SD)	4.42 (6.34)	0.84 (1.79)	6.59 (7.04)	0.000
Duration of hospital stay (mean±SD)	10.67 (5.38)	9.28 (3.73)	11.81(5.83)	0.01
Outcome, n (%)				
Expired	11 (11%)	0 (0%)	11 (16.67%)	0.01
Discharge	89 (89%)	34 (100%)	55 (83.33%)	0.01

RR: respiratory rate, SPO₂: Oxygen saturation, ICU: intensive care unit, CRP: C-reactive protein, LDH: lactate dehydrogenase, ALT: alanine aminotransaminase.

significantly lower in the severe group (83.30, $p < 0.001$). The mean NLR in the non-severe group was 4 as compared to 12 in the severe group. Other Lab investigations like D-dimer, ferritin, LDH, troponin I, serum creatinine and serum ALT were significantly higher in the severe group than the non-severe group (Table 2). On average, patients of the severe group stayed in ICU for almost 6.6 days compared to 0.84 days in the non-severe group. The total duration of hospital stay was 9 days in the non-severe group while 11 days in the severe group. Overall, 89% of patients recovered and were discharged from hospitals. We noted 11 mortalities in the severe group whereas all patients recovered and were discharged in the non-severe group (Table 2).

Pearson product moment correlation was used to determine the relationship of NLR with different COVID symptoms experienced by patients. NLR showed a significant positive relationship with

respiratory rate, oxygen usage, LDH, troponin I, serum ALT, serum creatinine, D-dimer, CRP, ferritin, >50% involvement on chest x-ray, duration of ICU stay, duration of hospital stay and mortality. Moreover, NLR showed a significant negative relationship with SpO₂ and chest x-ray <50% involvement. The NLR value did not influence the occurrence of symptoms (Table 3).

Discussion

COVID-19 has spread exponentially worldwide causing devastating loss of human life and economic crisis in developed and developing countries. The disease is under research worldwide; the literature available so far reports higher morbidity and mortality in severe disease than the non-severe disease, emphasizing the importance of early identification of patients at risk of developing severe disease. Prediction of severe disease may facilitate

Table 3. Relationship of NLR with different Severity Parameters of COVID-19 (n=100).

Severity parameters	NLR and parameter relationship (correlation coefficient r)
RR (/min)	.36***
SPO ₂ (%)	-.28**
Oxygen requirement (L)	.33**
Shortness of breath	.35***
Chest X-ray <50% involvement	.43***
Chest X-ray >50% involvement	.43***
ICU days	.55***
Hospital days	.46***
D-dimers (mg/L)	.33**
CRP (mg/L)	.32**
Ferritin (ng/mL)	.35**
LDH (U/L)	.40***
Troponin-I (ng/L)	.25*
Serum ALT (U/L)	.27*
Serum creatinine (mg/dL)	.29**
Mortality	-.44***

***p<.001, **p<.01, *p<.05. RR: respiratory rate, SPO₂: oxygen saturation, ICU: intensive care unit, CRP: C-reactive protein, LDH: lactate dehydrogenase, ALT: alanine aminotransaminase.

timely hospitalization, anticipation and prevention of complications and initiation of appropriate management.^{13,14} For this purpose, simple, easily available, quick and cost-effective investigations are required. NLR is one of the leading tests under research in this context.¹ We recovered and analyzed data of 100 COVID-19 PCR positive patients from two different tertiary care hospitals and divided them into severe and non-severe groups according to the criteria mentioned above and found 63 patients with severe disease and 37 with the non-severe disease. We found higher NLR (12.8) in severe disease as compared to the non-severe group (4.0). In accordance with our results other researchers also found NLR >4.7 to be an independent risk factor for severe disease.^{11,15} Lagunas-Rangel¹ also reported higher NLR levels to suggest a poor prognosis reflecting exaggerated inflammatory response. Many other researchers also established the role of NLR and even platelet lymphocyte ratio (PLR) as independent prognostic markers for early recognition of the severe disease facilitating early triage and well-timed commencement of appropriate management.¹⁶

In our study mean RR was significantly less (19.72/min) in the non-severe group in comparison to the severe group (36.24/min). In the non-severe group, patients presented with a mean SpO₂ of 95.81% while 83.30% was the mean SpO₂ in the severe group. The non-severe group of patients used 1.09 liters of oxygen in the mean, while the other group used 7.48 liters as mean. Then regarding blood tests, a noticeable difference was noted among both groups out of which NLR we have already discussed above. Mean TLC was 9.54x10 in the non-severe group while 12.9x10 in the severe group.³ Inflammatory markers were also found to be raised in the severe group. Ferritin, LDH, CRP had a mean value of 807.80, 575.55, 35.76 respectively in the severe group as compared to 603.75, 327.55, 23.59 respectively in the non-severe group. D-dimer was also raised in the severe group with a mean of 3.27, while in non-severe 1.14 value was noted. Chest X-ray involvement >50% was more commonly present in the severe group as compared to the non-severe group. ICU stay and total hospital stay were also more in the severe group than the non-severe group. It was also seen that different severity parameters had direct concordance with the increased NLR, like increased RR, decreased saturation at time of admission, increased oxygen usage, and more frequently having shortness of breath as patients' presenting symptoms. Chest x-ray involvement of more than 50%, which is also a feature of COVID severity had a direct relation with NLR and the same finding was noted in CRP, ferritin and D-dimer levels that they were raised with increased NLR depicting that increased NLR has a direct relationship with all the severity parameters of COVID-19 disease. However, no relationship was noted between NLR and the general symptoms of COVID patients, i.e., cough, fever, headache, myalgias, and diarrhea.

Moreover, in our study patients with increased NLR were observed to have prolonged hospital and ICU stay. In addition, all patients who died had increased NLR correlating with other studies showing 8% higher risk of in-hospital mortality for each unit increase of NLR.^{14,15,17} Thus, NLR seems to be a useful and easily approachable tool to predict the severity of COVID-19

disease. Different studies suggest NLR should be monitored starting from the first day of hospitalization to predict disease progression from mild to severe.¹⁸⁻²⁰

Conclusion

Higher NLR is associated with severe COVID-19 and can be used as an effective tool to predict the progression of the non-severe disease to severe disease.

Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: KA; Study Design: KA; Supervision: KA; Materails: FA; Data Collection and/or Processing: FA; Statistical Analysis and/or Data Interpretation: KA, FA; Literature Review: FA; Manuscript Preparation: KA, FA; Critical Review: KA, FA.

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