

Role of Neutrophil Lymphocyte Ratio (NLR) in Predicting Disease Severity in Covid -19: A Multicenter Retrospective Study

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ABSTRACT

Background: 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 as pandemic by WHO on March 11, 2020. The novel infection yet under research exhibits wide spectrum of severity ranging from no symptom to severe pneumonia leading even to death.

Aim: 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.

Methods: It was multicenter retrospective observational study conducted in COVID wards of two tertiary care hospitals of Lahore treating COVID-19 patients between March and June 2020. A predesigned proforma was filled to collect the data. SPSS 21 was used for statistical analysis of this research.

Results: Record of 100 COVID-19 patients admitted between March and June 2020 fulfilling the inclusion criteria was included in the study. All patients were divided into two groups. Non-severe group included 37 patients while severe group included 63 patients. The mean age of study population was 56 years with male predominance (63%). Overall, 50% patients in non-severe group and 71% patients in 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 commonly reported in severe group (74.2%). The mean NLR in non-severe group was 4 as compared to 12 in severe group.

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

Keywords: Covid 19, Corona Virus, SARS- COV 2, Neutrophil/Lymphocyte ratio.

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 as pandemic by WHO on March 11, 2020¹. The pandemic affected millions of people since the emergence of first case. Till November 2020 fifty-five million people all over world got infected and almost 1.34 million succumb to the deadly disease². The statistical data of Pakistan till October 2020 report 366,000 diagnosed cases of Covid-19 with almost 8000 fatalities². 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 etc^{6,7}. The novel infection yet under research exhibits wide spectrum of severity ranging from no symptom to severe pneumonia leading even to death. Majority of affected people have 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 seventh day of illness, whereas severe disease is complicated by ARDS, acute respiratory failure, coagulopathy, septic shock, multiorgan failure and metabolic acidosis ending up in ventilatory support and death³. 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, arrangement of appropriate health care facilities and tailoring appropriate treatment plan to enable good supportive care and reduce mortality⁸.

Sustained neutrophilia along with lymphopenia has been witnessed in severe COVID at the onset of the disease compared to mild COVID (84.6% versus 44.4%)⁹. Neutrophil to lymphocyte ration (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 identification of patients likely to have complicated disease. 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

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positively correlated with bilateral pulmonary involvement in 80% cases⁷. To predict severe COVID and low survival rate the so far suggested NLR cut-off value is >3.3^{11,12}.

MATERIALS AND METHODS

It was multicenter retrospective observational study conducted in COVID wards of two tertiary care hospitals of Lahore treating COVID-19 patients between March and June 2020. After permission from Institutional review board, informed consent was waived due to retrospective and observational character of this study. Anonymity and confidentiality was ensured.

Hospital record was reviewed and Patients with age > 18 years and positive COVID-19 RT PCR for nasopharyngeal swab specimens were enrolled in study. Cases were diagnosed on the basis of the interim guidance of the World Health Organization (WHO) and divided in two groups named non-severe and severe. The patients meeting following conditions were enrolled in Non-severe group: (1) Epidemiology history, (2) Fever or other respiratory symptoms, (3) Typical CXR 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 above criteria were enrolled in Severe group: (1) Shortness of breath, RR ≥ 30 times/min, (2) Oxygen saturation (Resting state) ≤ 93% or PaO₂/FiO₂ ≤ 300mmHg. 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 dimers, LDH, liver function tests, renal function tests on the first day of hospitalization were obtained from medical records. In addition, number of days of hospital stay, need of mechanical ventilation, ICU admission, mortality, recovery and discharge from hospital were also noted.

Statistical analysis: SPSS 21 was used for 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 relationship

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

RESULTS

Record of 100 COVID-19 patients admitted between March and June 2020 fulfilling the inclusion criteria was included in the study. Non-severe group included 37 patients while severe group included 63 patients. The mean age of study population was 56 years with male predominance (63%). Overall 50% patients in non-severe group and 71% patients in 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 commonly reported in severe group (74.2%). Rest of symptoms like myalgia, diarrhea, and headache were equally noted in both groups (Table 1).

Severe group showed higher mean respiratory rate / min (36.24 P=.000) as compared to non-sever group. Similarly, Oxygen requirement was also found to be higher in severe group (7.48± 5.09). Mean SPO₂ was significantly lower in severe group (83.30 P=.000). The mean NLR in non-severe group was 4 as compared to 12 in severe group. Other Lab investigations like D dimers, Ferritin, LDH, Trop I, Serum creatinine & Serum ALT were significantly higher in severe group than non-severe group (Table2). On average, patients of severe group stayed in ICU for almost 6.6days days compared to 0.84 day in non-severe group. Total duration of hospital stay was 9 days in non-severe group while 11 days in severe group. Overall 89% patients recovered and discharged from hospitals. We noted 11 mortalities in severe group whereas all patients recovered and discharged in non-severe group (table 2).

Pearson Product Moment Correlation was used to find out the relationship of NLR with different COVID symptoms experienced by patients. NLR showed significant positive relationship with respiratory rate, oxygen usage, LDH, Trop I, Serum ALT, Sr. Creatinine, D-dimers, CRP, ferritin, >50% involvement on chest x-ray, duration of ICU stay, duration of hospital stay and mortality. Moreover, NLR showed significant negative relationship with SPO₂ and chest x-ray<50% involvement. Occurrence of symptoms was not influenced by NLR value (table 3).

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				
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				
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

Table 2: Comparison of investigations and disease outcome

Clinical Parameters (Mean ± SD)	All patients N=100	Non-Severe group (n=37)	Severe group (n=63)	P value
RR/minute	33.60(5.86)	19.72(2.76)	36.24(5.65)	0.000
SPO2 %	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
ChestX-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

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***
SPO2 (%)	-.28**
Oxygen requirement(lit)	.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***
Trop-I(ng/l)	.25*
S. ALT(U/L)	.27*
S. Cr(mg/dl)	.29**
Mortality	-.44***

Note.***p<.001, **p<.01, *p<.05

DISCUSSION

COVID-19 has spread exponentially worldwide causing not only devastating loss of human life but also economic crisis in developed as well as developing countries. The disease is under research worldwide and literature available so far reports higher morbidity and mortality in severe disease as compared to the non-severe disease, emphasizing the importance of early identification of patients at risk of developing severe disease. Prediction of severe disease may facilitate 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. Neutrophil to Lymphocyte ratio (NLR) is one of the leading tests under research in this context¹.

We recovered and analyzed data of 100 COVID-19 PCR positive patients from 2 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 non-severe disease. We found higher NLR (12.8) in severe disease as compared to non-severe group (4.0). In accordance with our results other researchers also found NLR >4.7 to be independent risk factor for severe disease^{11,15}. Lagunas-Rangel FA also reported higher NLR levels suggest a poor prognosis actually reflecting exaggerated inflammatory response¹. 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 management¹⁶.

In our study mean respiratory rate (RR) was significantly less in (19.72/min) in non-severe group in comparison to severe group (36.24/min). In non-severe group, patients presented with mean Spo2 of 95.81% while 83.30% was the mean Spo2 in severe group. Non-severe group of patients used 1.09 liters of oxygen in mean, while other group used 7.48 liters as mean. Then regarding blood tests, an obvious difference was noted among both groups out of which NLR we have already discussed above. Mean TLC was 9.54*10³ in non-severe group while it was 12.9*10³ in the severe group. Inflammatory markers were also found to be raised in 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 non-severe group. D-dimers were also raised in severe group with mean of 3.27, while in non-severe 1.14 value was noted. Chest x-ray involvement >50% was more commonly present in severe group as compared to non-severe group. ICU stay and total hospital stay was also more in severe group as compared to the non-severe group.

It was also seen that different parameters of severity were having direct concordance with the increase NLR, like increase RR, decrease saturation at time of admission, increase oxygen usage and more frequently having shortness of breath as patients' presenting symptoms. CXR

involvement 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-dimers levels that they were raised with increase NLR depicting that increase NLR has direct relation 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, diarrhea.

Moreover, in our study patients with increased NLR were observed to have prolong hospital & 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 an easily approachable tool to predict severity of COVID-19 disease. As suggested by different studies, NLR should be monitored starting from first day of hospitalization to predict disease progression from mild to severe^{18,19,20}.

CONCLUSION

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

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