ORIGINAL ARTICLE

NEUTROPHIL-LYMPHOCYTE RATIO AT PRESENTATION IN SEVERE COVID-19 PNEUMONIA AND ITS EFFECTS ON CLINICAL OUTCOMES

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ABSTRACT

Background: To determine the neutrophil-lymphocyte ratio (NLR) at presentation in hospitalized patients from Pakistan with severe COVID-19 pneumonia and assess its effect in predicting disease severity and clinical outcomes.

Material and Methods: A cross-sectional study was carried out at the COVID isolation ward of a major tertiary care government hospital in Karachi, Pakistan. The study included 190 patients who were admitted within a 5-month timeframe from 1/2/2021 till 30/6/2021. Patient demographic information, comorbidities, clinical manifestations of COVID-19 infection and laboratory values at the time of presentation, including Hemoglobin, platelets, NLR, glomerular filtration rate, markers of inflammation, liver function tests, and electrolytes were documented. Patient outcomes and requirement for mechanical ventilation were evaluated 28 days post admission and compared to the NLR at presentation.

Results: Mean NLR was 11.1. Mode and Median NLR were 8.6. The range of NLR was from 0.7 to 47.7. Mean NLR was higher in non-survivor's compared to survivors (p-value 0.043) and higher in patients who required mechanical ventilation compared to those who did not (p-value 0.028). There was no significant variation observed between NLR and the length of hospital stay. Using the ROC curve, the best cut-off value to predict mortality was 8.550, with a sensitivity of 0.643 and specificity of 0.417

Conclusion: Patients with severe COVID-19 pneumonia frequently have high neutrophil-lymphocyte ratios at presentation, and this is linked to a higher in-hospital mortality rate and need for mechanical ventilation.

Keywords: Neutrophil-lymphocyte ratio, COVID-19, Mortality rate, Mechanical ventilation

BACKGROUND

SARS-CoV-2 infection can range from being asymptomatic to showing symptoms that vary in severity, from mild to severe.[1] Severe illness is defined by an oxygen saturation level of less than 94% when breathing room air at sea level, a ratio of the partial pressure of oxygen in arteries to the fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory rate >30 breaths/min, or lung infiltrates >50% on imaging.[2] Patients who require hospitalization have a higher rate of critical or fatal disease outcomes.[3]

The most common finding in critically ill patients is respiratory failure due to acute respiratory distress syndrome.[4] SARS-CoV-2 infection initiates innate autoimmune response with T and B lymphocytes. This results in chemotaxis, activation of neutrophils, the release of cytokines, systemic inflammatory response, endothelial damage and multiorgan failure.[5] The release of proinflammatory cytokines, as well as direct viral invasion, causes lymphopenia.[6] Hence an increased neutrophil to lymphocyte count in COVID-19 patients, indicates more widespread inflammation and viral activity and is related to more severe disease and worse disease outcomes.[7]

Clinicians are looking for reliable prognostic markers for patients with COVID-19.[8] Neutrophil-lymphocyte ratio has been used as a marker of inflammation in many diseases and has been proposed as an inexpensive and widely available prognostic marker for patients infected with SARS-CoV-2[9] Research has demonstrated that NLR can serve as an early indicator of worsening severe COVID-19 infection.[10] Our study was conducted in the Intensive care unit (ICU) of Pakistan's largest tertiary care public hospitals, Jinnah postgraduate medical center. Our objective was to evaluate the trend in NLR in patients from Pakistan with severe SARS-CoV-2 pneumonia and to assess its impact in predicting the severity of disease and clinical outcomes.

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MATERIAL AND METHODS

A cross-sectional study was carried out at the COVID isolation ward of a major tertiary care government hospital in Karachi, Pakistan. The study included patients who were admitted within a 5-month time frame from 1/2/2021 till 30/6/2021. Ethical approval for the study was obtained from Jinnah Postgraduate Medical Center (No.F.2-81/2021-GENL/Conf-9/JPMC).

Inclusion criteria were adults over 18years of age, positive result on COVID-19 PCR test and evidence of severe infection. The study excluded patients with previous respiratory diseases including chronic obstructive pulmonary disease, pulmonary tuberculosis and interstitial lung disease; chronic kidney disease or chronic liver disease; heart failure; use of immunosuppressing medications including long term steroids; sepsis; previous or current history of cancer and recent major surgical procedures.

Severe illness was defined by an oxygen saturation level of less than 94% when breathing room air at sea level, a ratio of the partial pressure of oxygen in arteries to the fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory rate >30 breaths/min, or lung infiltrates >50% on imaging. NLR was calculated by dividing the number of neutrophils by the number of lymphocytes in a peripheral blood sample.

Blood samples were collected from all patients within 24 hours of their admission. The tests conducted included complete blood count, renal function tests, liver function tests, coagulation profile, arterial blood gas analysis and markers of inflammation (C-reactive protein, Lactate dehydrogenase, Ferritin and D-Dimers). A portable chest X-ray was performed for all patients within 24 hours of admission to assess the extent of lung involvement. The data from these investigations was utilized in the study.

Patient demographic information such as age, gender, and pre-existing medical conditions was also documented. The outcome variables were the length of hospital stay, requirement for mechanical ventilation and the patient's status 28 days after admission.

Data analysis was performed using SPSS version 26. Mean, Median and Standard deviation were calculated for quantitative variables like Age, Hemoglobin, Total leukocyte count, Platelets, Neutrophil-lymphocyte ratio, Urea, Creatinine, Glomerular filtration rate, CRP, LDH, and D-Dimers. Qualitative data, including gender and comorbidities, was analyzed using frequencies and percentages. The remaining data was organized into categorical variables, including oxygen requirement, PiO2/FiO2 ratio, and duration of hospital stay. Spearman correlation was used to assess the correlation of neutrophil-lymphocyte ratio with continuous and ordinal variables. An independent sample T-test was used to compare the differences of mean values between categories. Mann Whitney test was used to compare median values. A p value of less than 0.05 was considered statistically significant.

RESULTS

There were a total of 372 SARS-CoV-2 positive patients admitted during the period of the study. After following the inclusion and exclusion criteria, the data of 190 patients was obtained. Of the patients studied, 62.1% were male and 37.9% were female. The mean age of the patients was 57 years. Approximately half of the patients (50.0%) had diabetes mellitus, nearly half (44.7%) had hypertension and 6.8% had ischemic heart disease. The most frequently reported symptoms upon presentation were fever, cough, shortness of breath, and fatigue. Most patients (51.6%) presented with a PO_2/ FiO_2 ratio less than 100.

Table 1 summarizes the demographics, comorbidities, and clinical presentations of the patients.

Mean Hemoglobin at presentation was 12.4 mg/dl, Total leukocyte count 11.9, Neutrophil lymphocyte ratio 11.1, Platelets 238.5. Mode and Median NLR were 8.6. The range of NLR was from 0.7 to 47.7. The laboratory findings of patients upon admission are displayed in Table-2.

Intravenous methylprednisolone or dexamethasone was given to all patients. Remdesivir was given to 74.6% patients. Tocilizumab was only given to 4.2% of patients because of unavailability. 98.9% (n=188) were given anticoagulation. Two patients were not given anticoagulation because of contraindications.

Most patients had a hospital stay for greater than 7 days (61.6%). 65.3% of patients needed non-invasive ventilation support. Out of the patients who needed non-invasive ventilation, 44.7% required it for a period of less than 7 days. 41.6% of patients needed invasive ventilation. Out of those who required invasive ventilation, 81.4% received it for less than 7 days.

Table-3 displays the results of the study regarding patient outcomes. Most patients (61.6%) died within 28

days of hospital admission. 28.4% were discharged on room air without oxygen, 3.7% remained admitted with oxygen support, 3.7% remained admitted with non-invasive ventilation and 2.1% were discharged on home oxygen.

Mean NLR was significantly higher among non-survivors compared to survivors (p-value 0.043). It was significantly higher amongst patients who required mechanical ventilation vs those who did not (p-value 0.028). However, when accounting for standard deviations, there was a wide overlap between mean NLR values in survivors and non-survivors and those who required mechanical ventilation and those who did not. Mean NLR was not significantly impacted by the duration of hospital stay, non-invasive ventilation, and invasive ventilation. Table-4 compares the mean neutrophil lymphocyte ratio in different groups of patients.

Median NLR in survivors was significantly higher in non-survivors, 12.0, compared to survivors, 9.6, p-value 0.04. It was also higher in patients who required mechanical ventilation, 12.0, compared to those who did not, 9.1, p-value 0.03.

Correlation analysis showed that NLR was significantly correlated with the age and gender of the patient. It was higher in patients more than 60 years and in males, p-values 0.027 and 0.009 respectively. However, it did not show any significant correlation with comorbidities. There was a significant negative correlation between PO_2/ FiO_2 and NLR at presentation, p-value 0.037. Low PO_2/ FiO_2 was associated with higher NLR values. NLR showed significant positive correlation with other inflammatory markers, CRP and LDH, p-values 0.001 and 0.044 respectively.

The ROC curve was used to determine the area under the NLR curve and showed an AUC of 0.623 (95% CI). The largest Youden index was 0.06, corresponding to the optimum cut-off value of 8.550, sensitivity of 0.643 and specificity of 0.417. Figure-1 shows NLR critical value judgment in predicting mortality.

Table-1: Demographics, comorbidities and clinical characteristics of 190 patients.

Demographic/ comorbidity		Number of cases/ (percentages) n=190
Age	20-40	15 (7.9)
	40-60	79 (41.6)
	60 and above	96 (50.5)
Gender	Male	118 (62.1)
	Female	72 (37.9)
Co-morbidity	Diabetes Mellitus	95 (50.0)
	Hypertension	84 (44.2)
	Ischemic heart disease	18 (9.5)
	Others	12 (6.3%)
Oxygen saturation at room air	90-93%	4 (2.1%)
	70-89%	103 (54.2%)
	<70%	83 (43.7%)
Need for oxygen in liters at presentation	1-5L/min	21 (11.1%)
	6-15L/min	62 (32.6%)
	>15L/min	107 (56.3%)
PO2/FiO2 ratio	<100	98 (51.6%)
	100-300	91 (47.9%)
	>300	1 (0.5%)
Need for mechanical ventilation	Non-invasive ventilation	128 (67.4%)
	Invasive ventilation	76 (40.0%)

Table-2: Laboratory findings at presentation.

Laboratory value at presentation	Mean +/- Std Dev	Median
Hemoglobin (mg/dl)	12.4± 1.9	12.4
Total leukocyte count x 109L	11.9 ± 5.0	11.1
Neutrophil lymphocyte ratio	11.1 ± 8.2	8.6
Platelets x 109L	238.5±99.9	219.5
Blood Urea Nitrogen mg/dl	28.2±19.8	22.2
Creatinine mg/dl	1.4±1.5	1.02
C Reactive Protein mg/L	117.5±69.5	120.0

D Dimers mg/L	4.4±5.9	1.8
Lactate Dehydrogenase U/L	834.7.3±491.4	714.0
Ferritin mcg/L	903.1±573.9	860.0
International Normalized ratio	1.1±0.8	1.0
Serum sodium mmol/L	137.4±6.0	138.0
Serum potassium mmol/L	3.9±0.7	3.9
Total bilirubin mg/dl	0.6±0.4	0.5
Alkaline phosphatase U/L	150.5±110.4	112.5
Alanine aminotransferase U/L	65.9±138.4	37.5

Table-3: Outcome variables.

	Outcome	Number of cases (percentages)
Outcome after 28 days	Death	117 (61.6%)
	Discharged on room air	54 (28.4%)
	Discharged on home oxygen	4 (2.1%)
	Admitted with oxygen support via mask/nasal cannula	7 (3.7%)
	Admitted with non-invasive ventilation	7 (3.7%)
	Admitted with invasive ventilation	1 (0.5%)
Duration of hospital stay	0-7 days	73(38.4%)
	More than 7 days	117 (61.6%)
Duration of non-invasive ventilation	0-7 days	84 (44.2%)
	More than 7 days	44 (23.1%)
Duration of invasive ventilation	0-7 days	68 (35.8%)
	More than 7 days	8 (4.2%)

Table-4: Independent sample t-test- Comparing mean Neutrophil lymphocyte ratio in various groups of patients.

Grouping variable		Mean NLR +/- STD	T score	p-value
Need for mechanical ventilation	Yes	12.0±8.3	2.213	0.028
	No	9.1±7.7		
Outcome at 28 days	Non-Survivor	12.0±7.9	2.037	0.043
	Survivor	9.6±8.3		
Duration of hospital stay	0-7 days	10.6±7.1	-0.675	0.500
	More than 7 days	11.5±8.8		
Duration of non-invasive ventilation	0-7 days	11.8±7.7	-0.154	0.877
	More than 7 days	12.0±9.5		
Duration of invasive ventilation	0-7 days	11.4±7.0	-0.133	0.895
	More than 7 days	11.8±7.4		

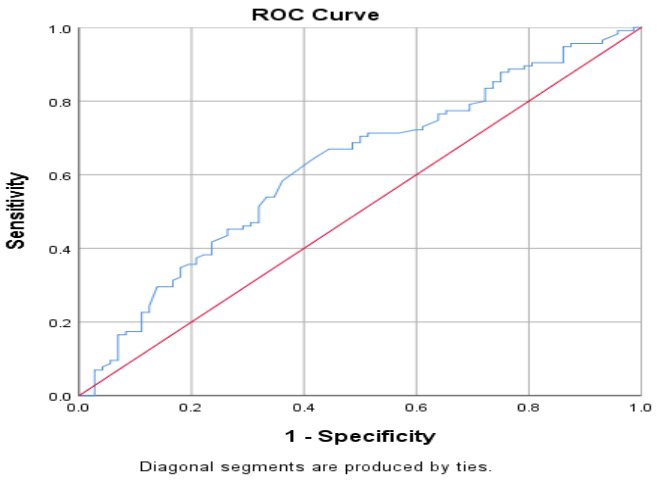

Figure-1: ROC curve for NLR critical value judgment in predicting mortality.

DISCUSSION

We studied the variation of NLR ratio only in patients with severe SARS-CoV-2 pneumonia and assessed its impact on clinical outcomes and disease progression. Our study took place at one of the largest, but resource constrained, public tertiary care hospital in Pakistan.

Among patients with severe COVID-19 pneumonia requiring ICU admission, our study showed a wide variation of NLR from 0.7- 47.7. 67% of patients had NLR between 2.7 and 12.7. Other studies have also shown a wide variation in NLR ratios among COVID-19 patients.[11,12] Studies have shown that NLR levels can be variable and are influenced by genetic constitution, age, sex, lifestyle including smoking and degree of systemic inflammatory response. [13,14]

In our study, NLR at presentation was associated with a lower PO_2/ FiO_2, indicating more severe disease.

NLR was also significantly higher in non-survivors vs survivors. A study with a similar methodology conducted on 720 patients in Islamabad, Pakistan found that a high NLR can indicate worsening severe COVID-19 pneumonia.[15] International studies carried out in different parts of the world including China, Ethiopia and Egypt have also concluded that neutrophil lymphocyte ratio is an independent predictor of disease severity and risk of death.[16-18] However, some studies carried out during the second wave of COVID-19 have shown that there are no significant differences in different severity subgroups of COVID-19 patients.[19]

A cut-off of NLR 8.550 was associated with increased mortality in our study. A meta-analysis of 19 studies revealed variability in cut-off ratios of NLR in predicting disease severity and mortality.[12] Some studies suggest cut-off ratios of less than 4.5 in predicting disease severity, while others suggest cut-off ratios of >4.5.[20-23] Similarly, in predicting disease mortality some studies suggest cut-off ratios of less than 6.5, while others suggest cut-off ratios of more than 6.5.[24-27]

Mean NLR was higher in patients who required mechanical ventilation vs those who did not. Other studies carried out on the South Asian population have also shown that higher NLR is associated with a greater need for mechanical ventilation. A study carried out in India on 93 patients showed that mean NLR in patients who required mechanical ventilation was 5.8 vs 3.9 in those who did not require mechanical ventilation.[28] Similarly, a study carried out in Pakistan on 31 patients reported that an NLR >3.1 was associated with a higher frequency of mechanical ventilation.[29] Our study which was carried out on a much larger cohort of patients validated these findings.

The main drawback of our study was the diverse clinical presentations among patients. In Pakistan, patients often seek help at local untrained centers and present late in the disease course to government tertiary care hospitals because of social stigmas and inadequate awareness. Moreover, IL-6 inhibitors were not readily available at the hospital. The hospital lacked proper infection control due to insufficient logistics and staff knowledge. The center was short of experienced anesthesiologists. All of these factors may have affected patient outcomes and disease course. Additionally, this was a single center study done over a short duration which limits the generalizability of the results. The analysis was not adjusted for confounding factors, including possible prior steroid use.

Our study showed a wide overlap between mean values of NLR in survivors and non-survivors. The NLR critical value to predict mortality calculated using the ROC curve showed a sensitivity of 0.643. This is why, even though NLR is higher in non-survivors and mechanically ventilated patients, NLR values may not be a very sensitive marker in predicting mortality and need for mechanical ventilation in severe COVID-19 pneumonia in resource-limited settings. Further validation of our study's results requires larger studies across multiple centers.

CONCLUSION

Patients with severe COVID-19 pneumonia frequently have high neutrophil-lymphocyte ratios at presentation, and this is linked to a higher in-hospital mortality rate and need for mechanical ventilation. On admission, NLR can be used as an inexpensive, but not very sensitive, prognostic indicator for mortality and a tool for risk categorization in severe COVID-19 disease in resource-limited settings.

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AUTHOR CONTRIBUTION

Mehak Hanif, Kamran Khan Sumalani: Designed the study and were involved in data collection, statistical analysis, and interpretation

Vishal Mandhan, Zarkesh Shaikh, Shahbaz Haider: Contributed to the drafting and critical review of the manuscript, approved the final draft

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