

ORIGINAL ARTICLE

Neutrophil-to-Lymphocyte ratio in moderate and severe COVID-19 among hospitalized adults: A retrospective study from a resource limited setting in Pakistan



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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has a broad clinical spectrum. Simple and inexpensive inflammatory markers may help characterize patients with more severe illness in resource-limited settings. The neutrophil-to-lymphocyte ratio (NLR), derived from a routine complete blood count, has been associated with COVID-19 severity in previous studies.

Methods: A retrospective study included 635 adults who were hospitalized with reverse-transcription polymerase chain reaction (RT-PCR)-confirmed COVID-19 in Lahore, Pakistan. Demographic, clinical, and laboratory information was reviewed. NLR was calculated from complete blood count parameters and is reported as median (interquartile range [IQR]). Categorical associations with disease severity were assessed from the retained aggregate counts using Pearson's chi-square test for age categories and two-sided Fisher's exact test for 2 x 2 comparisons.

Results: Severe disease was recorded in 490 (77.2%) patients and moderate disease in 145 (22.8%). Median NLR was 11.1 (IQR 12.7) in the severe group and 2.6 (IQR 2.4) in the moderate group. Sex was not associated with severity (two-sided Fisher's exact $p=0.482$). Obesity showed a borderline but non-significant association with severity ($p=0.054$). Overall, 200 (31.5%) patients died and 435 (68.5%) were discharged.

Conclusion: NLR was markedly higher in the severe group than in the moderate group and may be a simple marker associated with disease severity in hospitalized patients. Because patient-level data were unavailable for receiver operating characteristic (ROC) analysis, effect-size estimation, and multivariable adjustment, these findings do not establish NLR as an independent predictor or define its clinical discriminatory performance.

Keywords: COVID-19; Neutrophil-to-Lymphocyte Ratio; Disease Severity; Biomarker; Pakistan

INTRODUCTION: The first patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was identified in Wuhan, China, in 2019. By early 2020, the disease had become a global pandemic, presenting variably across patients and causing an exponential increase in cases and mortality. SARS-CoV-2 is a single-stranded RNA virus causing COVID-19. The virus was formally named the virus SARS-CoV-2 and the disease COVID-19 by World Health Organization, which was soon declared a global health emergency. The initial infection was reported in December 2019, after which the virus quickly spread to multiple continents, including Europe and the US [1-3]. Whilst 75 percent of patients recover with no complication; however, 25 percent of patients can develop severe life-threatening complications and require intensive care unit admission and even die [4]. Infectious diseases trigger immune responses leading to pneumonias in viral infections including COVID-19 [5]. Dysregulated immunity can create imbalances. Circulating biomarkers serving as indicators of inflammation and immune status can predict COVID-19 prognosis [6]. Indicators like peripheral white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), derived NLR (d-NLR: neutrophil count

divided by WBC count minus neutrophil count), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are broadly used to assess severe systemic inflammation and predict viral pneumonia outcomes [7]. Majority of COVID-19 patients have mild or moderate disease a small number develop life-threatening complications, hence effective & safe therapeutic agents and required to address this novel virus. Supportive therapy is standard care at present with multiple ongoing research trials. Multiple antiviral and immunomodulating agents are being evaluated to treat COVID-19 and are at various stages of experimentation and development. Severe COVID-19 presents high mortality, showing the need to clarify its causes and find new therapeutic options. Recognizing elevated NLR early and initiating proactive steps to avoid ICU admission may improve outcomes for critically ill patients. A recent study showed that lymphopenia can occur in some patients can be severe [8]. The immunologic findings in peripheral blood of COVID-19 were studied by other colleagues [9]. Their work showed elevated NLR as an independent biomarker associated with progression of pneumonia in COVID-19. Reactive oxygen radicals released by Neutrophils (NEU) cause cell DNA damage hence facilitation the exit of virus from the cells. This cytotoxicity (ADCC) can directly inactivate/kill the virus and/or induce immunity [10-12]. Virus related inflammatory cytokines such as interleukin-6 and interleukin-8 produced by lymphocytes and endothelial cells can stimulate neutrophils [13-15]. Whilst human immune response to a viral infection predominantly depends on lymphocytes, generalized inflammatory conditions can suppress cellular immunity. The immune response triggered by viral infection, is predominantly lymphocyte dependent [16], whilst systemic inflammation significantly suppresses cellular immunity, reducing CD4+ T lymphocytes and increasing CD8+ suppressor T lymphocytes [17]. NLR is thus is increased by inflammation caused by viral infection. Elevated NLR promotes COVID-19 progression thus leading to severe infection, shorter duration of transfer to ICU from admission and fastened need for mechanical ventilation.

COVID-19: Coronavirus disease 2019 is the clinical spectrum of symptoms and signs caused by infection with SARS-CoV-2. In this study, diagnosis was established by a positive reverse-transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2.

Neutrophil-to-lymphocyte ratio (NLR): From complete blood count absolute neutrophil count was derived and then divided by absolute lymphocyte count.

METHODS: Retrospective observational study of 635 hospitalized adults with RT-PCR-confirmed COVID-19, selected by convenience sampling. It was a retrospective study, and data from all COVID-19 patients admitted to Fatima Memorial Hospital and Jinnah Hospital, Lahore, were collected. 635 patients; convenience sampling. Data was collected in two months from 1st August 2020 to 30th September 2020.

Inclusion criteria:

- Positive SARS-CoV-2 RT-PCR test confirming COVID-19.
- Age 18-90 years.
- Both male and female patients.
- Hospitalized patients categorized in the original study as having moderate or severe COVID-19.
- Clinical symptoms of with COVID-19, including fever and respiratory or non-respiratory symptoms.
- Chest radiographic abnormalities compatible with viral pneumonia.
- Severe COVID-19 was defined in the original manuscript by the presence of at least one of the following criteria:

1) Respiratory rate ≥ 30 breaths/min;

2) Resting oxygen saturation $\leq 93\%$; or

3) Ratio of arterial oxygen partial pressure to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ≤ 300 mmHg.

Exclusion criteria:

- Malignancy with an expected survival of less than one year.
- Malignancy requiring chemotherapy or radiotherapy.
- Current treatment with methotrexate, azathioprine, cyclosporine, or cyclophosphamide.
- Previously diagnosed aplastic anemia.

Ethical approval was granted by the Institutional Review Board of Fatima Memorial Hospital, Lahore (FMH07-2020-IRB-768-M; 23 July 2020).

Retrospective records were reviewed for demographic characteristics, comorbidities, CBC parameters (including absolute neutrophil and lymphocyte counts), disease severity, and clinical outcome. Absolute neutrophil count was divided by the absolute lymphocyte count to get the NLR. SPSS version 25.0 was used in the original analysis. Categorical variables were summarized as frequencies and percentages. Using the aggregate counts retained in the manuscript, the association between age category and disease severity was assessed with Pearson's chi-square test, while two-sided Fisher's exact tests were used for 2 x 2 comparisons of sex and individual comorbidities with disease severity. NLR is presented as median (IQR). All p values were two-sided, $p < 0.05$ was considered to be of statistical significance. Because the original patient-level dataset is no longer available, the inferential test originally used for the NLR comparison cannot be independently reproduced, and no ROC analysis, NLR cut-off estimation, effect-size calculation, or multivariable logistic regression is reported. Missing-data patterns and any original procedures used to handle missing observations also cannot be reconstructed from the retained aggregate information.

RESULTS: Among 635 hospitalized patients, 145 (22.8%) were categorized as having moderate COVID-19 and 490 (77.2%) as having severe COVID-19. The distribution of disease severity did not differ significantly across the five age categories (Pearson chi-square $p = 0.472$) (Table 1). Of 427 male patients, 94 were in the moderate group and 333 were in the severe group. Of 208 female patients, 51 were in the moderate group and 157 were in the severe group. Sex was not significantly associated with disease severity (two-sided Fisher's exact $p = 0.482$) (Table 1). Median NLR (IQR) was 2.6 (2.4) in the moderate group and 11.1 (12.7) in the severe group (Table 2). Because patient-level data are unavailable, the original inferential comparison cannot be independently reproduced; therefore, no p value, effect size, confidence interval, ROC-AUC, or NLR cut-off is reported for this comparison. Among 74 patients with obesity, 64 were in the severe group and 10 were in the moderate group. The association between obesity and severity was borderline but did not reach the conventional threshold for statistical significance (two-sided Fisher's exact $p = 0.054$). Other comorbidity comparisons are shown in Table 1. Overall, 200 (31.5%) patients died and 435 (68.5%) were discharged. Severity-by-outcome inferential analysis is not reported because the retained aggregate information is insufficient to verify the original cross-tabulation.

Table 1: Demographic and clinical characteristics according to COVID-19 disease severity

Characteristic	Category	Moderate n (%)	Severe n (%)	Total n (%)	Overall p-value
Age group	≤30 years	10 (6.9)	48 (9.8)	58 (9.1)	0.472
	31–45 years	29 (20.0)	118 (24.1)	147 (23.1)	
	46–60 years	51 (35.2)	166 (33.9)	217 (34.2)	
	61–75 years	46 (31.7)	125 (25.5)	171 (26.9)	
	>75 years	9 (6.2)	33 (6.7)	42 (6.6)	
Sex	Male	94 (64.8)	333 (68.0)	427 (67.2)	0.482
	Female	51 (35.2)	157 (32.0)	208 (32.8)	
Diabetes mellitus	Present	67 (46.2)	202 (41.2)	269 (42.4)	0.294
Hypertension	Present	68 (46.9)	225 (45.9)	293 (46.1)	0.850
Cardiovascular disease	Present	24 (16.6)	76 (15.5)	100 (15.7)	0.795
Chronic kidney disease	Present	8 (5.5)	33 (6.7)	41 (6.5)	0.703
Obesity	Present	10 (6.9)	64 (13.1)	74 (11.7)	0.054

Table 2: Neutrophil-to-lymphocyte ratio according to COVID-19 disease severity

Disease severity	n	NLR median (IQR)
Moderate	145	2.6 (2.4)
Severe	490	11.1 (12.7)

Note: NLR is presented descriptively because the original patient-level dataset is unavailable to reproduce the inferential comparison or perform ROC, effect-size, cut-off, and multivariable analyses.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; IQR, interquartile range; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease; CKD, chronic kidney disease. Percentages in the moderate and severe columns are column percentages. For individual comorbidities, p values compare presence versus absence using two-sided Fisher's exact tests. The age-group p value is from Pearson's chi-square test

DISCUSSION: The principal finding of this study is the large descriptive difference in NLR between hospitalized patients categorized as having severe and moderate COVID-19. Median NLR was 11.1 (IQR 12.7) in the severe group compared with 2.6 (IQR 2.4) in the moderate group. Published reference values for healthy adults are substantially lower, although reference intervals vary and comparison with a healthy reference range does not establish diagnostic or predictive performance. The observed pattern is consistent with previous COVID-19 literature. Toori and colleagues reported higher NLR in severe disease in a Pakistani cohort, while Ulloque-Badaracco and colleague found in a systematic review and meta-analysis, that higher baseline NLR was associated with both severe disease and mortality. [18-19] Moradi in his study similarly reported higher NLR in patients with greater mortality risk.[20] These comparisons support biological and clinical plausibility but do not substitute for predictive validation in the present dataset.

NLR should therefore be interpreted here as an associated inflammatory marker rather than a stand-alone predictor. Prior studies have reported different NLR thresholds and different levels of discrimination. This variability is expected because NLR can change with timing of blood sampling, stage of illness, age, comorbidities, treatment exposure, severity definitions, study population, and statistical methodology. A threshold derived in one cohort may not perform similarly in another population.

The demographic findings in this cohort also require cautious interpretation. Age category was not significantly associated with severity ($p=0.472$), and sex was not significantly associated with severity ($p=0.482$). Consequently, this study should not claim that age was associated with severity. Obesity showed a borderline but non-significant association with severe disease ($p=0.054$), and it should not be described as a statistically significant risk factor in this dataset. Comorbidities are important potential confounders because they may influence both systemic inflammatory markers and COVID-19 outcomes. Previous studies have described adverse outcomes in patients with obesity, diabetes, hypertension, cardiovascular disease, and other chronic illnesses [21-24]. In the present study, individual comorbidity comparisons were unadjusted; therefore, causal or independent effects cannot be inferred. The observed mortality rate of 31.5% is high and should be interpreted in the context of the sampling frame. This was a convenience sample of hospitalized patients, 77.2% of whom were categorized as having severe disease. The cohort was therefore enriched for clinically ill patients and is not representative of all individuals with SARS-CoV-2 infection. The mortality proportion should not be generalized to community COVID-19, and elevated NLR alone should not be interpreted as explaining mortality. From a clinical perspective, NLR remains appealing because it is rapidly available from a routine CBC and does not require specialized assays. However, clinical usefulness depends on discrimination, calibration, reproducible cut-offs, and incremental value beyond established clinical variables. Because ROC analysis and multivariable regression cannot be performed from the retained aggregate data, the present study cannot determine sensitivity, specificity, an optimal NLR threshold, adjusted odds ratios, or whether NLR adds independent prognostic information. The present findings are therefore best interpreted as descriptive and hypothesis-supporting. They demonstrate that NLR was higher in the severe group within this hospitalized cohort, but additional patient-level analyses would be required to determine whether NLR independently predicts severity and whether it has clinically useful discriminatory performance. A Pakistan-based study by

Minhas et al also reported higher NLR and neutrophil counts in severe COVID-19, providing local context for the present observations. Nevertheless, study design variations, selection of patients, timing of laboratory assessment, treatment practices, and severity classification limit direct comparison across cohorts. [25-27]

CONCLUSION: In this hospitalized cohort, median NLR was substantially higher in patients categorized as having severe COVID-19 than in those with moderate infection. NLR may therefore be a simple and inexpensive inflammatory marker associated with disease severity in resource-constrained settings. However, this study does not establish NLR as an independent predictor, because patient-level ROC analysis, effect-size estimation, cut-off determination, and multivariable adjustment could not be performed. Prospective or retrospectively re-analyzable studies with clearly defined sampling times, severity criteria, treatment data, and validated predictive analyses are needed before NLR can be used as a stand-alone risk-stratification tool.

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