

Neutrophil-to-lymphocyte ratio as an alternative to chest CT for assessing disease severity in COVID-19: evidence from a resource-limited setting

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ABSTRACT

Background: The COVID-19 pandemic created enormous challenges worldwide and also placed considerable burden on Bangladesh's healthcare system, economy, and social structure. Chest CT scans were identified as a key diagnostic and prognostic tool, however, in resource-limited settings, cheaper and more accessible alternatives are required. Neutrophil-to-lymphocyte ratio (NLR), an inflammatory marker, may be a potential prognostic marker for morbidity and mortality of COVID-19 patients. This study aimed to evaluate the NLR as a cost-effective prognostic marker for COVID-19 severity and mortality by assessing its correlation with CT findings in a resource-limited setting.

Methods: This was an observational retrospective study carried out in Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, between May 2020 and July 2021 among 237 patients with COVID-19 who fulfilled both inclusion and exclusion criteria. Hematological (neutrophil lymphocyte ratio and inflammatory indicators) and HRCT severity was also evaluated. Mann-Whitney U test, Spearman correlation and ROC curve were used to analyse data using SPSS version 21.0 and p value < 0.05 was taken as significant.

Results: Among 237 patients, 165 (69.9%) were males and most patients (23.2%) were aged 51–60 years. Diabetes mellitus (20.6%) and hypertension (18.5%) were the most common comorbidities. Positive correlation of CT severity with inflammatory markers (CRP, ferritin, and D-dimer; $\rho = 0.434, 0.446, 0.425$ respectively) was observed with $p < 0.001$ for each. An NLR cut-off of ≥ 4.9 demonstrated 78% sensitivity and 75.3% specificity for predicting severe CT findings on ROC analysis.

Conclusion: An NLR ≥ 4.9 , together with high ferritin, CRP, and D-dimer levels, may predict disease severity in COVID-19 patients and may offer a cost-effective prognostic alternative in resource-limited settings where CT imaging is unavailable or contraindicated.

Key words: COVID-19, Neutrophil-to-Lymphocyte Ratio, Chest HRCT

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INTRODUCTION

As of April 2024, the Worldometer had reported 704,753,890 confirmed cases of COVID-19 worldwide, including 7,010,681 deaths. And a total of 2,049,377 people had been infected with COVID-19 in Bangladesh, with 29,493 reported deaths.¹ According to the Directorate General of Health Services (DGHS) press

release, between 8 March and 27 December 2020, 509,148 COVID-19 cases were confirmed by RT-PCR, GeneExpert, and antigen testing, including 7,452 related deaths (case fatality rate 1.46%). Bangladesh ranked 27th globally and accounted for approximately 0.64 % of the global COVID-19 disease burden.²

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COVID-19 is a respiratory and systemic illness, initially presents with fever, dry cough, and fatigue. Within a few weeks, it may progress to acute respiratory distress syndrome (ARDS), metabolic acidosis, shock, multi-organ failure, and other fatal complications.³ Approximately two-thirds to three-quarters of individuals with positive RT-PCR throat swab results remain asymptomatic, and only around 10 % of symptomatic patients develop interstitial pneumonia, ARDS, or sepsis with multi-organ failure.⁴

Appropriate medical management has aided in the complete recovery of patients with mild to moderate illness. However, the death rate of patients with severe illness, especially with underlying co-morbidities, is higher.⁵

The cytokine storm, characterized by an exaggerated release of pro-inflammatory cytokines, is considered one of the major causes of mortality in severe COVID-19.⁴ Circulatory biomarkers reflecting systemic inflammation can be used as plausible predictors of prognosis in COVID-19 patients. The contributory role of hematological investigations, including CBC (Complete Blood Count), has been widely standardized in etiological detection, prognostications, patient follow up and therapeutic monitoring of COVID-19 patients. Neutrophil-to-lymphocytic ratio (NLR) is a lucid calculated parameter from differential leucocyte count, which has been largely studied as a potential prognostic and diagnostic circulating biomarker that is easily available and feasible in all hospital settings.³

Recent studies continue to support the prognostic significance of NLR and related inflammatory indices such as the Systemic Immunoinflammatory Index (SII) in assessing COVID-19 severity across multiple populations.^{6,7} However, most of these data originate from high-resource settings, highlighting the need for validation in low- and middle-income contexts such as Bangladesh.

Non-contrast high-resolution computed tomography (HRCT) plays a decisive role in the early disease detection, particularly in patients with false-negative RT-PCR results.⁸ Determination of disease severity from imaging findings has played a pivotal role in the clinical judgment of patients, ensuring effective and timely

management. Prognosis can also be affected by the severity of the disease in the critically ill patient allows appropriate selection of early involvement of intensive care. Multiple studies explored the utility of NLR as a prognostic marker in COVID-19 infection and also evaluated the association with chest CT severity.⁷⁻¹⁰

This study aimed to assess whether NLR could serve as a practical alternative to chest CT in determining COVID-19 severity in settings where imaging resources are limited.

METHODS

Study design

This retrospective cross sectional observational study was conducted at BSMMU in Dhaka, Bangladesh, based on the data collected on a research project that was completed previously between May 2020 to July 2021.

Demographic variables (age, sex) and co-morbidities (hypertension, diabetes mellitus, bronchial asthma, chronic kidney disease, hypothyroidism, organ transplantation and chronic liver disease) hematological parameters and chest high-resolution computed tomography (HRCT) scan severity scoring were secondarily evaluated from archived data of the original research database of all RT-PCR-confirmed COVID-19 patients. A total of 237 patients were taken as sample by non-probable consecutive sampling technique.

All patients diagnosed with COVID-19 based on RT-PCR positivity, who underwent HRCT chest and routine blood tests within 24 hours of admission.

Patients with negative RT-PCR results for COVID-19 or a known diagnosis of diffuse parenchymal lung disease (DPLD).

CBC analysis was performed on an automated analyzer using whole blood samples collected in an EDTA vial. Parameters recorded included total leukocyte count, Neutrophil percentage, lymphocyte percentage, and their calculated ratio (NLR), along with D-dimer, fibrin degradation products (FDP), C-reactive protein (CRP), and serum ferritin.

HRCT scans of the chest were performed using a multidetector CT scanner and interpreted by a single

radiologist with five years of experience. HRCT images were assessed for ground-glass opacity (GGO), crazy paving pattern, consolidation, reverse halo sign, subpleural linear band fibrosis, traction bronchiectasis, and pleural effusion. The CT scoring was done by CT severity score (CT-SS) classification system and categorized as minimal (0–5), mild (6–10), moderate (11–15), and severe (16–20), following the method of Cheng M et al.¹¹ Patients were subsequently grouped as mild-to-moderate (0–10) and severe (11–20) based on total scores.

Statistical analysis was performed using SPSS for Windows version 21.0. Descriptive statistics were expressed as mean $\pm$ standard deviation or percentage as appropriate. Mann–Whitney U test was used for group comparisons, Spearman's rho test for correlation analysis, and receiver operating characteristic (ROC) curve analysis to determine the diagnostic accuracy of NLR. A p -value < 0.05 was considered statistically significant.

RESULTS

A total of 237 patients were included in this study. Among them, 165 (69.9%) were male and 72 (30.1%) were female. Most patients belonged to the 51–60-year of age group, comprising 23.2% of the study population, and the mean age of the participants was 52.18 ± 16.33 years. The most common co-morbidity was diabetes mellitus in 49 (20.6%) followed by hypertension in 44 (18.5%) cases (Table I).

The mean Ferritin, WBC, NLR, and CRP were $8.99.74 \pm 1042.24$, 10653 ± 8044 , 7.38 ± 7.69 , and 63.51 ± 127.29 respectively (Table II).

The NLR values between mild-moderate and severe CT chest groups were compared using the Mann–Whitney U test, revealing a statistically significant difference ($p < 0.001$) (Table III).

Receiver operating characteristic (ROC) curve analysis of NLR for predicting HRCT chest severity demonstrated an optimal cut-off value of 4.93, with a sensitivity of 78.0%, specificity of 75.3% and AUC of 0.77 (Table 4; Figure 1).

The correlation between CT severity and inflammatory markers (CRP, ferritin, and D-dimer) was assessed using Spearman's rho correlation, which showed statistically significant positive associations ($\rho = 0.434, 0.446, 0.425$ respectively; $p < 0.001$ for each) (Table 5).

Table I. Age, gender and comorbidities among studied participants (N=237)

Age (years)	Number (n)	Percentage (%)
≤ 20	5	2.1
21 – 30	21	8.9
31 – 40	31	13.1
41 – 50	49	20.7
51 – 60	55	23.2
61 – 70	42	17.7
> 70	34	14.3
Mean $\pm$ SD (years)	52.18 ± 16.33	
Gender		
Male	165	69.9
Female	72	30.1
Co-morbidities		
DM	49	20.6
HTN	44	18.5
Asthma	14	5.9
Chronic kidney disease (CKD)	26	0.8
IHD	17	7.7
Hypothyroidism	3	1.3
Carcinoma	4	1.7
Organ transplant	1	0.4
CLD	1	0.4
Dengue	1	0.4

Table II. Laboratory Parameters of the studied participants (N=237)

Laboratory Parameter	Mean $\pm$ SD*	Min – max
Ferritin	899.74 ± 1042.24	23.00 - 4720.00
CBC	10655 ± 8044	2890 – 77000
NLR	7.38 ± 7.69	0.11 - 41.30
CRP	63.51 ± 127.29	0.83 - 1000.00

*SD- Standard deviation

Table III. Comparison of mean value of Neutrophil-Lymphocyte ratio (NLR) and severity of the participants (N=237)

NLR	Moderate	Severe	p-value*
Mean $\pm$ SD	4.72 $\pm$ 5.71	11.25 $\pm$ 8.57	<0.001
Min – max	0.11 – 40.00	0.82 – 41.30	
Median (IQR)	2.82 (3.12)	8.70 (11.08)	

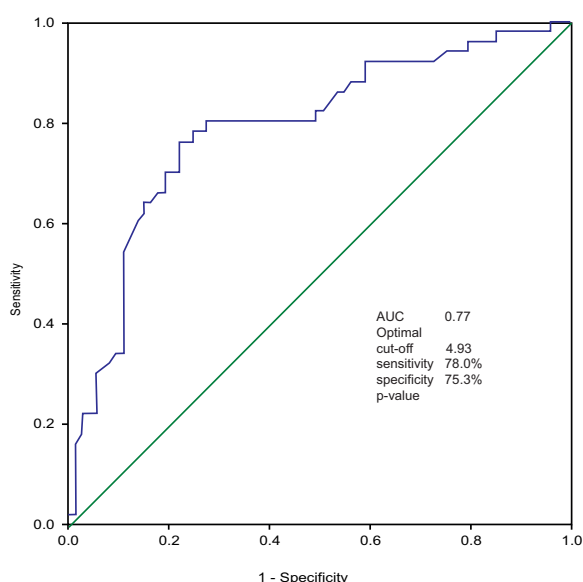
*p-value was calculated using Mann-Whitney U test.
A p-value <0.05 was considered for statistically significant.

Table IV. Diagnostic accuracy of Neutrophil-Lymphocyte ratio (NLR) in the assessment of severity of COVID-19 compared to HRCT of the chest (N=237)

NLR	Sn*	Sp**	PPV ^S	NPV ^{SS}	YI ^{SSS}
4.365	0.800	0.712	0.656	0.709	0.512
4.455	0.800	0.726	0.667	0.713	0.526
4.555	0.780	0.726	0.661	0.693	0.506
4.750	0.780	0.740	0.672	0.697	0.520
4.930	0.780	0.753	0.684	0.701	0.533
5.030	0.760	0.753	0.679	0.683	0.513
5.170	0.760	0.767	0.691	0.686	0.527
5.305	0.760	0.781	0.704	0.690	0.541
5.395	0.740	0.781	0.698	0.673	0.521

*Sn- Sensitivity, **Sp- Specificity, ^SPPV- Positive predictive value, ^{SS}NPV- Negative predictive value

^{SSS}YI- Youden index

**Figure 1.** Receiver operating characteristic (ROC) curve of Neutrophil-Lymphocyte ratio (NLR) in the studied participants (N=237)**Table V.** Correlation of severity of HRCT of the chest with CRP, ferritin, D-dimer, and serum creatinine

Parameter	Rho*	p-value**
CRP	0.434	<0.001
Ferritin	0.446	<0.001
D-dimer	0.425	<0.001
Serum creatinine	0.231	0.040

*Rho- correlation coefficient

**p- value was calculated using Spearman correlation analysis.
A p-value <0.05 was considered for statistically significant.

DISCUSSION

The present study investigated the association between the Neutrophil-to-lymphocyte ratio (NLR) as well as CT chest severity in patients with confirmed COVID-19, along with its correlation to other inflammatory markers such as CRP, D-dimer, and ferritin. Among all parameters analyzed, NLR emerged as the most important marker associated with disease severity.

Following COVID-19 infection, activation of CD8+ T lymphocytes leads to an inflammatory cascade that promotes neutrophil proliferation and lymphocyte apoptosis. This imbalance increases the NLR, reflecting the extent of systemic inflammation and cytokine storm. Several studies have reported that elevated NLR is associated with poor prognosis and higher mortality in COVID-19.¹²

Man et al. found that an NLR below 5.04 predicted mild CT severity with 94% probability, while Zhang et al. reported a significant increase in NLR among patients with severe disease.^{3,13} In line with these findings, our study demonstrated that patients with severe CT involvement had significantly higher NLR values, with a cut-off of 4.93 yielding 78% sensitivity and 75.3% specificity an AUC of 0.77.

Our findings are consistent with recent multicentre and molecular studies demonstrating that elevated NLR correlates with disease severity and inflammatory cytokine activation in COVID-19.^{6,7} Similar trends have also been observed in the pediatric cohorts, where NLR and PLR were associated with disease progression.¹⁴

Ferritin, a key acute-phase reactant involved in macrophage activation, is another marker of inflammation. Elevated serum ferritin levels have been reported in viral infections and correlate with disease severity.⁵ Consistent with this, our study found significantly higher ferritin levels among patients with severe CT findings ($p < 0.001$). Likewise, CRP and D-dimer levels were also positively correlated with increasing CT severity ($p < 0.001$), indicating the contribution of inflammation and coagulation activation to lung involvement.

Overall, our findings show that NLR, along with ferritin, CRP, and D-dimer, can serve as useful prognostic

biomarkers for assessing the disease severity in COVID-19 patients. In resource-limited settings or in patients for whom CT imaging is contraindicated (e.g., pregnant women), these simple and inexpensive laboratory markers may provide valuable guidance for clinical monitoring and management.

This study has several limitations that should be acknowledged. It was a single-center, retrospective study with a relatively modest sample size, which may limit the generalizability of the findings to other populations. The study included only hospitalized patients, potentially introducing selection bias toward more severe cases. HRCT scoring was performed by a single experienced radiologist to maintain consistency, the absence of inter-observer validation may have affected the reproducibility of CT severity grading. Therefore, future multicenter study with larger sample size and interobserver validation of radiological assessments are recommended to reduce selection bias.

Conclusion

In resource-limited settings or when CT scanning is contraindicated, the neutrophil-to-lymphocyte ratio (NLR), with a cut-off value of 4.93 can be used as a marker of disease severity assessment due to its acceptable sensitivity, specificity along with CRP, D-dimer, and serum Ferritin level in patients with COVID-19.

Authors' contribution:

Raihan Kamal Galib: conceptualization, methodology, data curation, investigation, formal analysis, visualization, resources, writing – original draft, writing – review and editing, funding acquisition. Khujjista Akter: conceptualization, methodology, data curation, investigation, writing – review and editing. Shuvo Majumder: conceptualization, methodology, software, data curation, formal analysis, writing – review and editing. Mohammad Khalid Hasan: investigation, writing – review and editing. Munzur-E-Murshid: Investigation, writing – review and editing. Susanta Kumar Paul: resources, writing – review and editing. Mohammed Atiqur Rahman: conceptualization, methodology, validation, writing – review and editing. Rajashish Chakraborty: conceptualization, methodology, validation, supervision, project administration, writing review and editing.

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