


# Neutrophil Lymphocyte Ratio as a Marker of In-Hospital Deterioration in COVID-19: Observations From a Resource Constraint Setting

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## ABSTRACT

**INTRODUCTION AND OBJECTIVES:** The study was conducted to assess the association of neutrophil lymphocyte ratio (NLR) in COVID-19 and to identify the cut-off value that predicts mortality, need of respiratory support and admission to high-dependency or intensive care.

**METHODS:** A retrospective observational study was conducted to collect demographic data, clinical variables, the neutrophil-lymphocyte ratio on-admission and the outcome of confirmed COVID-19 patients admitted to a tertiary care center in Sri Lanka.

**RESULTS:** There were 208 patients with a median age of 56 years (IQR 43-67) and 98 (47.1%) males. The median neutrophil count was  $4.07 \times 10^3/\mu\text{L}$  (IQR 2.97-6.79) and the median lymphocyte count was  $1.74 \times 10^3/\mu\text{L}$  (IQR 1.36-4.75). The calculated NLR ranged from 0.12 to 48.28 with a median value of 2.32 (IQR 1.37-4.76). A NLR value  $>3.6$  predicted development of severe disease requiring respiratory support, transfer to a high-dependency or an intensive care unit and/or succumbing to the illness with a sensitivity 80% and specificity 80% (area under the curve 0.8, 95% CI 0.72-0.88,  $P < .0001$ ). The adjusted odds ratio of NLR  $>3.6$  on predicting severe disease was 11.1, 95% CI 4.5-27.0,  $P < .0001$ .

**CONCLUSIONS:** A NLR  $>3.6$  is a useful variable to be included in risk prediction scores in Sri Lanka.

**KEYWORDS:** COVID-19, neutrophil lymphocyte ratio, NLR, severe disease, SARS-CoV-2

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## Introduction

The COVID-19 pandemic has posed an enormous challenge to health care services throughout the world. Providing intensive care treatment and ventilatory support to the critically ill patients during the pandemic is a difficult task for resource-poor countries. Triage patients to the most appropriate health care setting is of paramount importance at the initial presentation for a better outcome. Many laboratory and clinical parameters have been identified as predictive markers of severe COVID-19 infection and scores such as “4C” is used in countries to identify patients likely to develop severe manifestations. However, use of multiple laboratory parameters is not feasible in resource constraint settings during massive outbreaks and it is vital to have simple, cheap and widely available tests for identifying patients likely to develop severe disease. Sri Lanka has reported approximately 660 000 cases so far with more than 16 000 deaths. The rapid surge in cases caused a massive strain on the government funded health sector and it is vital to identify patients needing admission and transfer to a health care with facilities to provide respiratory support promptly.

Neutrophil-lymphocyte ratio (NLR) is a simple parameter derived from the full blood count and its usefulness as a

predictive marker of mortality and disease progression has been explored in many conditions including sepsis,<sup>1</sup> ischaemic heart disease<sup>2</sup> and malignancy.<sup>3</sup> Studies also report an association of NLR and disease severity in COVID-19.<sup>4-6</sup> Combination of cycle threshold (Ct) value, absolute lymphocyte count and the NLR was suggested to predict respiratory compromise in a cohort of patients from a single center in Sri Lanka.<sup>7</sup> Diagnosis of COVID-19 is established more frequently using rapid antigen-based tests precluding the use of such predictive models in all settings. Due to the effect of diabetes,<sup>8</sup> metabolic syndrome<sup>9</sup> and non-alcoholic fatty liver disease<sup>10</sup> on the NLR, the cut-off values vary according to the studied population. We have conducted an observational study in Sri Lanka during the third wave of COVID-19 pandemic to derive the best cut-off value of NLR to predict patients at high risk of death, requiring respiratory support and patients needing high-dependency or intensive care unit admission.

## Methods

A retrospective observational study was performed by gathering data from confirmed COVID-19 patient (rapid antigen test and/or SARS-CoV-2 PCR positive) clinical records at



Colombo South Teaching Hospital, Kalubowila, Sri Lanka. Details were collected from records of patients admitted to the medical wards during July to August 2021. A data collection sheet was used to record demographic details, clinical and biochemical parameters on-admission to the healthcare setting and the need of respiratory support, escalation to a high-dependency unit (HDU) or intensive care unit (ICU) and all-cause mortality. The NLR was calculated by dividing the absolute neutrophil count from the absolute lymphocyte count. Due to the retrospective nature of the study and the sole use of secondary data, consent from the patients were not obtained. Ethical approval was obtained from the Ethics Review Committee of Colombo South Teaching Hospital and administrative approval obtained prior to data collection.

Shapiro–Wilk test was used to test the normality of data. Categorical data were displayed as frequencies (percentage) and continuous data in a skewed distribution were described as median (IQR). The non-parametric test, Mann Whitney U test was used to compare quantitative data and the Pearson chi-squared test was used to compare categorical data. Receiver operator characteristic (ROC) curve was used to identify the predictive ability of NLR value on-admission and a  $NLR > 3.6$  in identifying severe disease. Logistic regression was used to calculate the odds ratio of NLR in predicting a severe outcome and adjusted for age in multivariable logistic regression. Statistical significance was considered as  $P < .05$ .

## Results

### *Baseline characteristics of the study population*

There were 208 COVID-19 confirmed patients included in the study with a median age of 56 years (IQR 43–67) and 98 (47.1%) were males. Comorbidities seen in the study population were diabetes ( $n = 70$ , 33.7%), hypertension ( $n = 67$ , 32.2%), ischaemic heart disease ( $n = 15$ , 7.2%), dyslipidaemia ( $n = 39$ , 18.8%), chronic kidney disease ( $n = 11$ , 5.3%) and chronic liver disease ( $n = 6$ , 2.9%). Severity of illness was mild in 158 (76%) and moderate-severe in 50 (24%) patients. There were 26 (12.5%) patients requiring non-invasive ventilation, high-flow nasal oxygen or invasive ventilation and 39 (18.8%) required high-dependency or intensive care unit admission for organ support. There were 37 (17.8%) deaths in the study group. Patients who deteriorated in the hospital requiring respiratory support, transfer to a high-dependency unit (HDU) or an intensive care unit (ICU) and patients who succumbed to the illness were classified as the “severe disease” group.

A significantly higher heart rate (100.5 vs 91,  $P < .0001$ ) and a lower oxygen saturation ( $SpO_2$ ) (88.5 vs 98,  $P < .0001$ ) was seen on-admission to hospital in patients who developed severe disease compared to non-severe category (Supplemental Table 1). Investigations revealed a higher C-reactive protein (CRP) (134.4 vs 20.8,  $P < .0001$ ), a higher white cell count ( $9.3 \times 10^3/\mu L$  vs  $6.7 \times 10^3/\mu L$ ,  $P < .0001$ ), higher serum glutamic-oxaloacetic transaminase (SGOT) (56.5 vs 35.3,  $P < .01$ ) and higher serum creatinine (141.9 vs 79,  $P < .0001$ )

on-admission in patients who developed severe disease compared to others.

### *Absolute neutrophil, lymphocyte counts and NLR in the study population*

The median neutrophil count was  $4.07 \times 10^3/\mu L$  (IQR 2.97–6.79) and the median lymphocyte count was  $1.74 \times 10^3/\mu L$  (IQR 1.36–4.75) in the study population. The calculated NLR ranged from 0.12 to 48.28 with a median value of 2.32 (IQR 1.37–4.76). A higher absolute neutrophil, a lower absolute lymphocyte count and a higher NLR were significantly associated with the need for respiratory support in the form of non-invasive ventilation, high-flow nasal oxygen or invasive ventilation (Table 1). In addition, a higher neutrophil count, a lower lymphocyte count and a higher NLR was significantly associated with the need of escalation to a high-dependency unit, intensive care unit and associated with mortality (Table 1).

### *NLR is a predictor of severe disease*

Our data revealed that the NLR on-admission to the hospital in patients with COVID-19 predicted severe disease and in-hospital deterioration. We developed ROC curve for further identification of the association of NLR with severe disease (Figure 1). A NLR value higher than 3.6 was the best cut-off value identified to predict severe disease with a sensitivity of 80% and a specificity of 80%. Since the area under the curve (AUC) for the selected cut off for  $NLR > 3.6$  was 0.8 (95% CI 0.72–0.88,  $P < .0001$ ), respective NLR value on admission can be used as an excellent discriminator in identifying the severe disease outcome in Sri Lankan population.

Patients with  $NLR > 3.6$  were older and had a higher heart rate and a lower  $SpO_2$  on-admission (Table 2). The CRP, SGOT and creatinine were higher among patients with a  $NLR > 3.6$  compared to patients with a value  $\leq 3.6$  (Table 2).

The odds ratio  $NLR > 3.6$  on predicting severe disease was 15.4 (CI 6.5–36.5,  $P < .0001$ ) and the risk persisted after correcting for the possible confounding effect of age (adjusted OR 11.1, CI 4.5–27.0,  $P < .0001$ ).

## Discussion

Cheap and widely available markers are useful in triaging patients with COVID-19 at community level and in health care settings. We report the association of severe COVID-19 and the NLR performed on-admission to a tertiary care institution in Sri Lanka. We have derived the best cut-off value of NLR to be used to screen patients who are at high risk of deterioration at first presentation during the COVID-19 pandemic.

The age distribution and the presence of comorbidities in our study population were comparable to studies from the region.<sup>5,11</sup> Increasing age and male gender is known to be associated with severe disease.<sup>5</sup> Previous studies have revealed poor T-cell activation, higher ACE-2 levels and poor habits such as

**Table 1.** Association of neutrophils, lymphocytes and NLR with severe disease.

VARIABLE	NEED OF RESPIRATORY SUPPORT		P VALUE	NEED OF ESCALATION TO HDU/ICU		P VALUE	MORTALITY		P VALUE	SEVERE DISEASE		P VALUE
	YES	NO		YES	NO		YES	NO		YES	NO	
Neutrophils (x10 <sup>9</sup> /µL)	9.19 (4.44-11.32)	3.9 (2.90-5.70)	<.0001	8.10 (4.90-11.45)	3.79 (2.86-5.31)	<.0001	8.96 (5.35-11.57)	3.79 (2.83-5.34)	<.0001	8.1 (4.90-11.45)	3.79 (2.86-5.31)	<.0001
Lymphocytes (x10 <sup>3</sup> /µL)	1.01 (0.71-1.39)	1.89 (1.29-2.58)	<.0001	1.06 (0.66-1.47)	1.90 (1.33-2.59)	<.0001	0.97 (0.63-1.47)	1.90 (1.33-2.60)	<.0001	1.06 (0.66-1.47)	1.90 (1.33-2.59)	<.0001
NLR	6.84 (4.96-13.59)	2.08 (1.32-3.39)	<.0001	6.89 (4.46-13.19)	2.02 (1.28-3.13)	<.0001	7.78 (4.96-13.59)	2.02 (1.28-3.13)	<.0001	6.89 (4.46-13.19)	2.02 (1.28-3.13)	<.0001

All values are given as median (IQR). Statistical significance was assessed by Mann-Whitney U test.

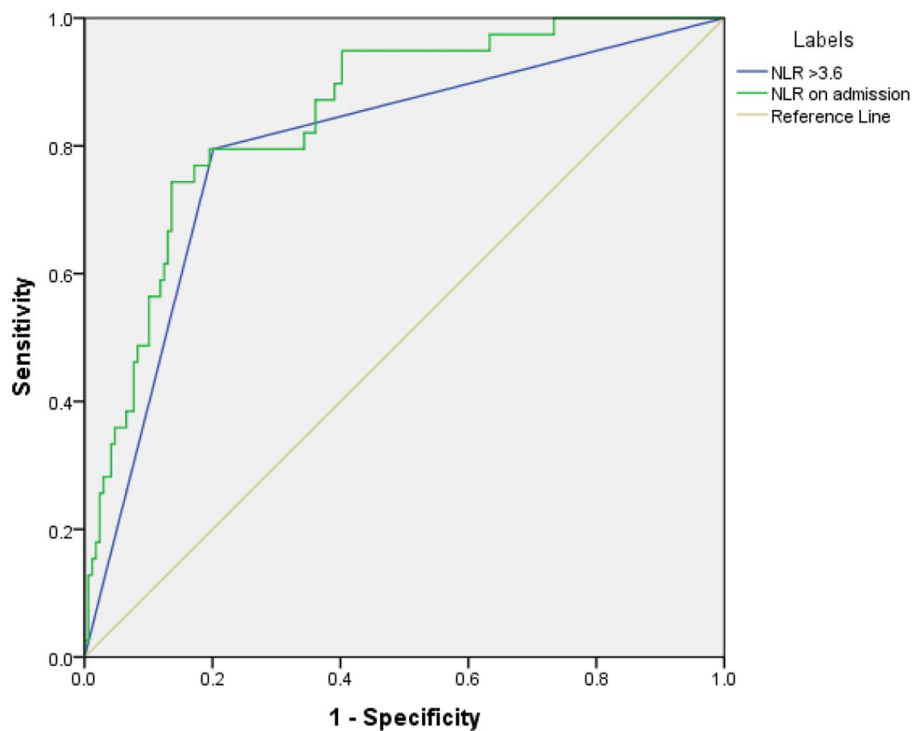
smoking contributing to a worse outcome in males compared to females.<sup>12-14</sup> Although not statistically significant, a higher frequency of diabetes and hypertension was seen in the severe COVID-19 category of our study. The lower numbers in the groups could have affected the power in identifying a significant association. The presence of tachycardia on-admission and a high CRP correlated with a severe disease outcome and both these parameters were associated with a high NLR suggesting that these patients had features of a systemic inflammatory response.

Neutrophils are components of the first line of defense in infections and they are involved in the inflammatory response to injury. A high neutrophil count initiates the systemic inflammation seen during the cytokine mediated response in COVID-19. Lymphocytes are important for initiating the immune response to infection and low lymphocytes have shown to be associated with a severe disease outcome.<sup>15,16</sup> NLR which incorporates both neutrophil and lymphocyte counts is therefore, a useful prognostic marker in COVID-19.

Despite the available literature on the association of NLR as a marker of disease severity in COVID-19, cut-off values identified are highly variable suggesting the heterogeneous distribution of this parameter. The NLR value considered normal for a healthy adult is not clear. Forget et al, reported a mean NLR of 1.65 in a Belgian population of apparent good health and the upper limit was reported as 3.5.<sup>17</sup> There are no data available in other regions. Studies conducted in COVID-19 patients in Asia report cut-off values ranging from 4 to 11 in predicting mortality and severe disease.<sup>5,11,15,18</sup> The presence of metabolic syndrome, non-alcoholic fatty liver disease and diabetes affect the baseline NLR of an individual. It is important to identify the population-specific NLR cut-off values in countries with a high prevalence of such metabolic conditions as Sri Lanka. Our data reveal that a NLR more than 3.6 had a sensitivity and specificity of 80% in identifying patients likely to develop severe COVID-19. A patient having a NLR>3.6 at first presentation had 11-times higher risk of dying, needing respiratory support or requiring HDU or ICU admission independent of age.

The limitations of this study were the relatively low number of patient data used in the study. Patient data was collected prior to initiation of the community-based care for COVID-19 in the country. This allowed the study investigators to use data from asymptomatic-mild to severe disease and helped derive most appropriate data for the study. The retrospective nature of the study was a limitation but yielded necessary information for us to make conclusions.

In conclusion, this retrospective study in a resource constraint setting has identified NLR as an appropriate marker in predicting a severe disease outcome and the use of the cut-off value 3.6 could help identify COVID-19 patients needing admission and close monitoring.



**Figure 1.** The ROC curve of NLR value on-admission and NLR>3.6 in determining a severe disease outcome.

**Table 2.** The association of clinical parameters and biochemical investigations with NLR > 3.6.

VARIABLES	TOTAL N=208	NLR ≤ 3.6 N=143	NLR > 3.6 N=65	STATISTICS P VALUE
Age	56 (47.5-66.5)	52 (35.5-60.0)	64 (53.2-73.0)	<.0001
Males (n, %)	98 (47.1)	64 (44.8)	34 (52.3)	.31
Heart rate (bpm)	93 (80.5-102.5)	92 (80.0-100.5)	98 (82.5-109.5)	.02
SpO <sub>2</sub> on room air (%)	98 (94-98.5)	98 (97.0-99.0)	92 (84.2-96.0)	<.0001
CRP (mg/L)	27.6 (7.3-89.5)	21.95 (4.9-50.5)	118.1 (28.4-183.1)	<.0001
SGOT (U/L)	36.3 (23.7-58.5)	35.5 (21.4-53.15)	44.05 (30.8-82.2)	.01
SGPT (U/L)	35.1 (20.8-48.3)	31.14 (15.7-48.2)	34.55 (22.2-80.8)	.11
Creatinine (μmol/L)	85.6 (68.3-105.2)	77.4 (65.5-93.8)	98.25 (79.2-214.1)	<.01

Abbreviations: CRP, C-reactive protein; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase. All values except male gender is given as median (IQR).

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### Author's Contributions

NP was involved in conceptualization, analysis and writing the manuscript. AD, MK was involved in conceptualization. RR was involved in data analysis. JI revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

### Availability of Data and Material

Data are available from the authors on reasonable request.

### Ethics Approval and Consent to Participate

Due to the retrospective nature of the study and the sole use of secondary data, consent from the patients were not obtained. Personal identification data were not used for the study. Ethical approval was obtained from the Ethics Review Committee of Colombo South Teaching Hospital and administrative approval was obtained prior to data collection.

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**Supplemental Material**

Supplemental material for this article is available online.

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