

Prognostic Significance of Baseline Neutrophil to Lymphocyte Ratio and Lymphocyte to C-Reactive Protein Ratio in COVID-19 Patients

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ABSTRACT

Objective: To predict the disease severity, CURB-65 scores and outcome after 14 days of admission using two proxy biomarkers (neutrophil lymphocyte and lymphocyte C-reactive protein ratios) in Covid-19 patients.

Methods: A prospective study was done at the Department of Medicine, Pakistan Ordinance Factory (POF) hospital, Wah Cantt Pakistan from April to August 2022. A total of 123 coronavirus patients were included. Patients with clinical manifestation, decreased lymphocyte and leukocyte count, imaging characteristics of pneumonia, etiological evidence of positive real time PCR test of blood or respiratory samples and viral gene sequencing similar to known Covid-19 were measured. Patients were undergone laboratory measurements and imaging analysis for biomarkers indications. The analysis of data was conducted using SPSS v 23.

Results: The patients mean age was 53.83±16.2 years. Among 123 Covid-19 patients, 80 (65%) were males and 43 (35%) females. It was found high NLR and low LCR in severe disease ($p=0.05$, $p=0.01$). NLR and LCR showed 11% variance for disease severity ($\beta=0.143$, $p=0.00$ & $\beta=-0.293$, $p=0.01$). NLR and LCR showed 29% variance for CURB 65 scores ($\beta=0.48$, $p=0.634$ & $\beta=-0.159$, $p=0.08$). NLR and LCR showed 22% variance for outcome after 14 days of admission ($\beta=-0.53$, $p=0.562$ & $\beta=-0.132$, $p=0.149$).

Conclusion: Neutrophil to lymphocyte and lymphocyte to C-reactive protein ratios are effective prognostic biomarkers of measuring severity of disease in Covid-19 patients. High neutrophil to lymphocyte and low lymphocyte to C-reactive protein ratios significantly predict disease severity.

Keywords: Base ratios, Biomarkers, Coronavirus, C-reactive protein, Neutrophil, Lymphocyte.

Authors' Contribution:

^{1,2}Conception; *Literature research; manuscript design and drafting;* ^{3,4}Critical analysis and manuscript review; ^{5,6}Data analysis; *Manuscript Editing.*

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Introduction

The World Health Organization (WHO) declared Covid-19 a global public health emergency.¹ According to WHO in October 2022, there were 624 million confirmed Covid-19 cases including 6.5 million deaths, globally.² According to government of Pakistan, there were 1.5 million confirmed cases, 31,000 deaths of Covid-19 in July 2022 in Pakistan.³

Pathogen responsible for disease was identified as RNA (enveloped) beta coronavirus named as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus). These RNA viruses belong to Coronaviridae family (Coronavirinae sub family and order Nidovirales). Definition of coronavirus is related with the fact that it's a virus with crown like projection.⁴ All coronaviruses share similar genomic expression (16-nonstructural proteins and 4

structural proteins) and organization. These viruses are divided into four genera i) alpha, ii) Beta, iii) gamma, iv) delta. Coronaviruses can infect multiple hosts and showed different tissue tropism. SARS-CoV-2 mechanism of action is not well known, however, transmission of virus to human being is dependent upon its ability to bind human cells by binding its protein spikes to cells.⁵ Literature reported that host susceptibility to SARS-CoV-2 is determined by binding affinity between host receptor angiotensin 2 (ACE 2) and viral receptor binding domain (RBD).⁶

Neutrophil to lymphocyte ratio (NLR) is an important and simple marker systemic inflammatory response evaluation in critically ill patients of Covid-19. Studies reported NLR as an independent prognostic factor for several non-infectious diseases including stroke, acute myocardial infarction and various types of cancer.⁷ Evidence exists that NLR can be used as independent indicator short term and long-term outcomes and mortality in clinically serious patients. NLR can be easily calculated through blood test by dividing absolute neutrophil count by absolute lymphocyte count. High values of NLR are an important risk factor of mortality.⁸ A latest study reported that severe cases of Covid-19 are associated with increasing NLR and NLR is an important predictor of mortality in hospitalized Covid-19 patients.⁹ Another similar biomarker lymphocyte C-reactive protein (LCR) is used as prognostic marker in complex host tumor immunological interactions, systemic inflammatory responses and several types of cancers including colon and gastric carcinoma. LCR may also be a good proxy marker and carry prognostic value for Covid-19 patients.¹⁰ Present study is conducted to understand prognostic significance of NLR and LCR in Covid-19 patients. The data available on this topic is not enough to reach any conclusion in Pakistan. So, objective of our study was to predict disease severity, CURB-65 scores and outcome after 14 days of admission using two proxy biomarkers (neutrophil

lymphocyte and lymphocyte C-reactive protein ratios) in Covid-19 patients.

Methodology

A prospective study was done at the Department of Medicine, Pakistan Ordinance Factory (POF) Hospital, Wah Cantt, Pakistan from April to August 2022. A sample of 123 individuals was calculated using 95% confidence interval, 9.1% critical illness with Covid-19,¹¹ 5% significance level using WHO calculator. We took ethical approval from research approval committee of POF hospital. All the participating Covid-19 patients signed consent before participation in study. Inclusion criteria was based upon patients of all ages, both genders, confirmed Covid-19 cases diagnosed on the basis of criteria developed by center of disease control and prevention (CDC).¹² It was based upon travel history of patient, contact history of patients with Covid-19 confirmed cases, patients with clinical manifestation like fever and respiratory symptoms, decreased lymphocyte count, normal or decreased leukocyte count, imaging characteristics of pneumonia, etiological evidence of positive real time polymerase chain reaction (PCR) test of blood or respiratory samples and viral gene sequencing similar to known Covid-19. Exclusion criteria were based upon patients with autoimmune disorders, congenital anomalies, cardiovascular disorders, pregnant and breast-feeding mothers. The clinical classification of disease was done using Liu et al standards.¹¹ These are as follows; i) mild [slight symptoms without pneumonia on imaging], ii) moderate [involving respiratory symptoms, fever, and pneumonia on imaging], iii) severe [indicated by conditions such as a respiratory rate \geq 30 beats/min, respiratory distress, oxygen saturation mean \leq 93% in resting state, arterial blood oxygen (ABO) partial pressure \leq 300 mmHg], and iv) critical [if respiratory failure following mechanical ventilation, shock, intensive care unit admission for combined organ failure].

Initially after screening all Covid-19 patient underwent sample taking process of upper respiratory tract (throat and nasopharyngeal swab), these specimens were preserved in a virus transport medium and then sent to National Institute of Health (NIH) Pakistan laboratory and PCR samples were sent to laboratory of POF Hospital, Wah Cantt Pakistan. Confirmed cases were followed after admission to critical illness. Vital signs, symptoms, blood routine, chest radiograph, laboratory tests, C-reactive protein were collected at the time of onset. Laboratory indexes and imaging analysis were reexamined in critical patients. NLR and LCR were measured. Data was analyzed using SPSS v 23. Analysis of data include mean \pm SD calculation for continues data, frequency and percentage calculation for categorical data. Linear regression was performed to predict disease severity using NLR and LCR in Covid-19 patients. ROC curve analysis was performed for NLR and LCR accuracy determination for Covid-19 severity. A probability p-value \leq 0.05 as statistically significant findings.

Results

A total of 123 Covid-19 patients were enrolled in the study. The patients mean age was 53.83 ± 16.2 years. Among 123 Covid-19 patients, 80 (65%) were males and 43 (35%) females. Out of all patients, 73 (59.3%) were non diabetic, while 50 (40.7%) were diabetic. Mean days from symptoms to onset of presentation were 5.7 ± 3.5 days. Mean total leukocyte count was 8198.29 ± 42.8 per microliter. Mean absolute neutrophil count was 6286.07 ± 40.3 per microliter. Mean absolute lymphocyte count was 1702.02 ± 89.17 per microliter. Mean C-reactive protein was 59.7 ± 6.5 mg/dl. There were 49 (39.8%) hypertensives, while 74 (60.2%) were non-hypertensive. Among all the patients, 10 (8.1%) had respiratory disorder, while 113 (91.9%) did not showed respiratory diseases. Ischemic heart disease (IHD) was reported in 21 (17.1%) patients, while 102 (82.9%) did not showed IHD. Malignancy was found in 4 (3.3%) patients. In our study, there were 14

(11.4%) smokers, while 109 (88.6%) nonsmokers. Mean CURB-65 scores were 2.1 ± 1.2 points. In our study, majority of patients had moderate diseases severity 42 (34.1%) following critical with ARDS, severe 22 (17.9%), mild 20 (16.3%), critical with septic shock 4 (3.3%), asymptomatic and critical with sepsis 2 (1.6%). In our study, 46 (37.4%) patients were still admitted after 14 days of admission, while 63 (51.2%) were treated, discharged and 14 (11.4%) were expired (Table 1). In our study, we found high NLR in severe Covid-19 patients as compared to mild and moderate (13.91 ± 3.8 vs 4.2 ± 1.9 , $p=0.05$). However, patients with severe Covid-19 are more likely to have low LCR as compared to those who had mild and moderate disease (75.17 ± 3.2 vs 45.90 ± 7.1 , $p=0.01$). NLR and LCR showed insignificant difference with CURB-65 scores ($p=0.473$ and $p=0.069$, respectively). Outcome after 14 days of admission also showed insignificant difference in NLR and LCR ($p=0.458$ and $p=0.128$ respectively, Table 2).

Table 1: Frequency distribution of disease severity and outcome after 14 days of admission, n=123

Severity of disease	Frequency	Percentage
Asymptomatic	2	1.6%
Mild	20	16.3%
Moderate	42	34.1%
Severe	22	17.9%
Critical with ARDS	31	25.2%
Critical with sepsis	2	1.6%
Critical with septic shock	4	3.3%
Outcome after 14 days		
Treated and discharged	63	51.2%
Still admitted	46	37.4%
Expired	14	11.4%

Table 2: Comparison of NLR and LCR ratios with severe Covid-19, CURB-65 scores and outcome after 14 days of admission, n=123

Severe Covid-19		Frequency	Mean	SD	p-value
NLR ratio	No	64	4.2033	1.9	.05
	Yes	59	13.9178	3.8	
LCR ratio	No	64	447.9030	7.1	.01
	Yes	59	75.174	3.2	
CURB-65 scores					
NLR ratio	<3 scores	103	8.0655	1.9	.473
	≥ 3 scores	20	12.97	6.7	
LCR ratio	<3 scores	103	312.9212	65.2	.069
	≥ 3 scores	20	43.509	11.9	
Outcome after 14 days of admission					
NLR ratio	Expired	13	14.3069	3.7	.458
	Survived	110	8.2197	2.1	
LCR ratio	Expired	13	26.996	5.8	.128
	Survived	110	297.728	63.4	

Table 3: Regression analysis to predict disease severity, CURB 65 scores and mortality, n=123

Severe Covid-19					
	Mean±SD	Pearson's Correlation	R-square	Beta coefficient (95% CI)	p-value
NLR ratio	8.86±2.78	0.175	0.115	0.143	.001
LCR ratio	269.1±65.3	-0.309	-	-0.293	.01
CURB-65 scores					
NLR ratio	8.86±2.7	0.65	0.29	0.48	.634
LCR ratio	269.1±65.8	-1.6	-	-0.159	.08
Outcome after 14 days of admission					
NLR ratio	8.68±2.6	-0.68	0.22	-0.53	.562
LCR ratio	257.1±63.1	0.138	-	0.132	.149

NLR and LCR ratios significantly predict disease severity ($p=0.001$ and $p=0.01$, respectively), while they do not predict CURB-65 scores and outcome of patients after 14 days of admission ($p \geq 0.05$, Table 3). Age and gender had insignificant impact on disease severity with respect to NLR and LCR ($p = 0.983$ & $p = 0.218$). ROC curve showed 78% accuracy in NLR and 17% LCR for predicting disease severity (Figure 1).

Discussion

NLR and LCR are most common established systemic inflammatory markers used, worldwide.¹³ Evidence from latest studies reported that severe Covid-19 patients showed dysregulation of immune response leading towards viral hyper inflammation development. Hyper inflammation needs to be screened using inflammatory markers like NLR and LCR for mortality reduction.¹⁴ In present study, we found high NLR and low LCR values for predicting disease severity ($p = 0.05$, & $p = 0.01$). Waqas et al reported that mean NLR was significantly high among patients who underwent mortality during

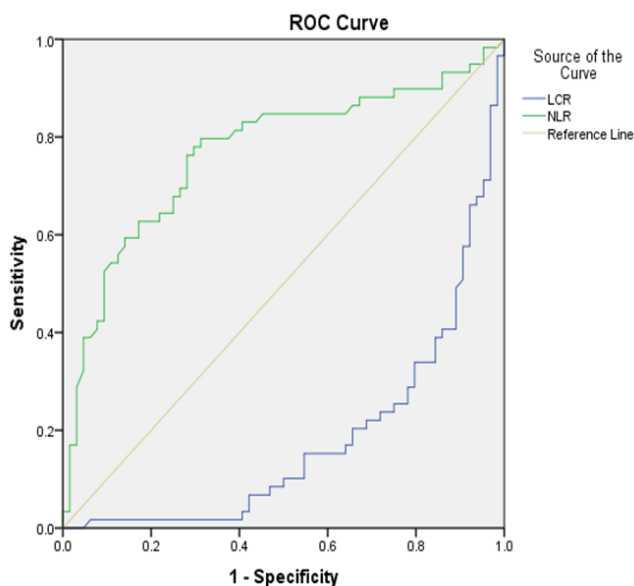


Figure 1: ROC curve analysis of NLR and LCR

hospitalization with Covid-19 ($p = 0.001$). However, LCR showed inverse relation with disease severity ($p = 0.04$).¹⁵ Yan et al reported that NLR values of survival individuals were significantly lower than non-survival ($p = 0.001$). They mentioned that NLR value ≥ 11.75 were statistically correlated with mortality.¹⁶ Liu *et al.*, reported that NLR in highest tertile are 15.04 times more at risk of mortality as compared to patients at lower tertile (OR = 15.04; C.I 95%, $p = 0.03$). NLR stands as an independent risk factor for in-hospital mortality among COVID-19 patients, particularly notable in male patients.¹⁷ Mo et al reported similar findings of increasing NLR in severe Covid-19 patients (SMD = 2.4, 95% C.I, $p = 0.01$) and decreasing LCR (SMD = -0.9, C.I 95%, $p = 0.02$).¹⁸ In present study, CURB-65 showed positive correlation with NLR and negative correlation with LCR. Oktariani *et al.*, reported that CURB scores are effective in measuring 14 days outcome in Covid-19 hospitalized patients.¹⁹ Lagunas-Rangel reported that patients with CURB-65 ≥ 3 scores showed high NLR value and low LCR.²⁰ Qu et al reported that patients with severe Covid-19 showed high neutrophil count, high CRUB scores and low lymphocyte count as compared to non-severe patients.²¹ In our study, ROC curve showed 78% accuracy in NLR for predicting disease severity. Murillo-Zamora *et al.*, reported that greater area under receiver operating curve is associated with high NLR and high CURB scores for critically ill patients of Covid-19 patients.²² Another similar study reported that adjusted odd of reduction in LCR, increase in NLR, need for high level care, ventilator support are common predictors of in hospital mortality.²³

In hospital complications could be predicted early and help in effective and timely allocation of available resources. There is need to actively monitor high NLR and decreasing LCR in critically ill patients of Covid-19. In this pandemic situation, there is need of finite health care resources or validated tools like NLR or LCR in health care system

for early triage and guiding prognosis of patients with severe Covid-19.

Conclusion

Neutrophil to lymphocyte and lymphocyte to C-reactive protein ratios are effective prognostic biomarkers of measuring severity of disease in Covid-19 patients. High neutrophil to lymphocyte and low lymphocyte to C-reactive protein ratios significantly predict disease severity, however, could not significantly predict CURB-65 scores and outcome after 14 days in Covid-19 patients. Study was conducted at single center and due to limited resources, it was not possible to take laboratory sample on daily basis that limits generalizability of our study. Our study is unique study in our setup where majority of population is affected with health and financial issue due to Covid-19.

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