Lymphocyte-to-C-Reactive Protein Ratio and Neutrophil to Lymphocyte Ratio: A Novel Predictor of Adverse Outcomes in COVID-19

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Abstract

Introduction: Systemic inflammation elicited by a cytokine storm is considered a hallmark of coronavirus disease 2019 (COVID-19). This study aims to assess the validity and clinical utility of the lymphocyte-to-C-reactive protein (CRP) ratio (LCR), versus the neutrophil-to-lymphocyte ratio (NLR) for predicting in-hospital outcomes in COVID-19.

Materials and methods: The present study was conducted at RNT Medical College Udaipur. This study was done over a period of one month after getting approval from institutional ethics committee. Written and informed consent from patients were taken. In this study 74 patients admitted in COVID wards medical wards and ICU were taken if they found COVID19 RTPCR positive and COVID19 RTPCR negative patients were excluded.

Results: In our study 74.3% patients were males and 25.7% patients were females, on admission mean of neutrophil count with standard deviation was 72.5(16.3), median of lymphocyte count with interquartile range was 15(8-28.25), median of NLR with interquartile range was 4.6(2.2-10.9), median of LCR with interquartile range was 1.1(0.1-3.75) and mean of spo_2 of patients with standard deviation was 94.6(4.3). 44.6% patients were admitted with NLR >5.5(severe disease), 40.5% patients were admitted with NLR <3.5(mild disease), and 14.9% patients were admitted with NLR 3.5-5.5(moderate disease). 37.8% patients were admitted with spo_2 >97% (normal), 32.4% patients were admitted with spo_2 95-97% (mild seek), 20.3% patients were admitted with spo_2 91-94% (moderate seek), and 9.5% patients admitted with spo_2 <90% (severe seek). In present study mechanical

ventilation required for patients whose NLR was >5.5 on admission and for patients whose LCR was <11 on admission. All mortalities were in severe disease patients whose NLR was >5.5 and low LCR (<11) at admission. Invasive ventilation/mechanical ventilation was required for 2.7% patients. Total 3 (4.1%) patients died out of which 2 (28.57%) were severely seek and 1 (6.7%) were moderately seek and p value for this was 0.004 which was significant. In present study on admission mean NLR with standard deviation was 16.5(5.6) in patients who died, Mann Whitney U value for these was 23.5 and p value was 0.01 which was significant. Median LCR with interquartile range was 0.1(0.1-0.6) in patients who were died, Mann Whitney U value for these was 51.5 and p value was 0.129 which was insignificant. Mean spo_2 of patients with standard deviation was 86.7(6.1) in patients who died, Mann Whitney U value was 17.5 and p value was 0.01 which was significant.

Discussion: In present study mechanical ventilation required for patients whose NLR was >5.5 on admission and for patients whose LCR was <11 on admission. Invasive ventilation/mechanical ventilation was required for high NLR and low LCR on admission. All mortalities were in severe disease patients whose NLR was >5.5 and low LCR (<11) at admission. Mortalities were mostly occurred in patients who was severely seek on admission.

Conclusion: As per present study severity of disease and mortality mostly occurred in patients whose NLR was high and LCR was low at admission so these parameters can be taken for severity, prognosis and outcome for COVID19 disease.

Keywords: LCR, CRP, NLR, COVID19, SD, IQR

Introduction

The coronavirus disease 2019 (COVID-19) is a global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By binding to the angiotensin-converting enzyme 2 (ACE2) receptor, the S1 subset of the surface spike protein elicits the production of angiotensin 1. The ACE then converts angiotensin 1 to angiotensin 2, which in turn binds to the angiotensin receptor, upregulating the levels of endothelin-1 (ET-1). This results in a widespread inflammatory response with the release of pro-inflammatory cytokines and interleukins[1,2]. The large-scale unregulated production of interleukins, particularly interleukin-6 (IL-6), stimulates several downstream pathways, increasing the production of acute-phase reactants like C-reactive protein (CRP), and increases mobilization of neutrophils[3]. This, along with stress-induced neutrophilia, likely explains the relative lymphopenia seen in severe manifestations of the SARS-CoV-2 infection[4-6]. Several studies have sought to demonstrate the clinical utility and feasibility of the neutrophil-to-lymphocyte ratio (NLR) in predicting COVID-19 outcomes[6]. A high NLR value at admission has been proposed as suggestive of COVID-19, while confirmatory tests are pending and a rising NLR has been shown to be associated with worse clinical outcomes in severe COVID-19. While the NLR is well studied, a similar biomarker ratio, the lymphocyte-to-CRP ratio (LCR), has, so far, not been utilized. Typically, the LCR is used as a prognostic marker for several types of cancers, including colon and gastric carcinomas[7-10]. The rationale behind this is that the LCR serves as a good surrogate of the complex host-tumor immunological interactions that result in a systemic inflammatory process, which is believed to contribute towards the pathogenesis and progression of these carcinomas[11]. Since COVID-19 also precipitates a systemic inflammatory response, it follows

that the LCR may also be a good proxy marker in this disease process and may carry prognostic value.

The present study aims to shed light on whether LCR and NLR can be used as reliable predictors for severity, prognosis and outcome in COVID19 patients.

Observations

Table1

Gender	N	%
Female	19	25.7
Male	55	74.3
Total	74	100

In our study 74.3% patients were males and 25.7% patients were females.

Table 2: Biochemical Parameters

	N		
Neutrophil on Admission	74	Mean(SD)	72.5(16.3)
Lymphocyte on Admission	74	Median(IQR)	15(8-28.25)
Neutrophil Lymphocyte ratio on admission(NLR) Median	74	Median (IQR)	4.6(2.2-10.9)
Lymphocyte-CRP Ratio(LCR) on admission	74	Median(IQR)	1.1(0.1-3.75)
Overall mean SPO2 on admission	74	Mean(SD)	94.6(4.3)

In our study on admission mean of neutrophil count with standard deviation was 72.5(16.3), median of lymphocyte count with interquartile range was 15(8-28.25), median of NLR with interquartile range was 4.6(2.2-10.9), median of LCR with interquartile range was 1.1(0.1-3.75) and mean of spo_2 of patients with standard deviation was 94.6(4.3).

Table 3: NLR on admission

	Frequency	Percent
<3.5	30	40.5
3.5-5.5	11	14.9
>5.5	33	44.6
Total	74	100.0

In our study 44.6% patients were admitted with NLR >5.5(severe disease), 40.5% patients were admitted with NLR <3.5(mild disease), and 14.9% patients were admitted with NLR 3.5-5.5(moderate disease).

Table 4:SPO$_2$ for Severity of COVID 19

SPO2	Severity	N	Percent
>97%	Normal	28	37.8
95-97%	Mild	24	32.4
91-94%	Moderate	15	20.3
<90%	Severe	7	9.5
Total		74	100.0

In our study 37.8% patients were admitted with spo_2 >97% (normal), 32.4% patients were admitted with spo_2 95-97% (mild seek), 20.3% patients were admitted with spo_2 91-94% (moderate seek), and 9.5% patients admitted with spo_2 <90% (severe seek).

Table 5: NLR on admission according to COVID 19 Severity

	N	Mean	Std. Deviation	Minimum	Maximum	F statistics	P Value
Normal	28	5.882	7.3783	0.6	38.4		
Mild	24	7.083	5.7670	0.2	20.0		
Moderate	15	9.800	7.8507	1.3	22.2	1.58	0.2
Severe	7	10.614	6.0090	3.5	19.8		
Total	74	7.514	6.9627	0.2	38.4		

Table 6: Outcome status of Patients according to Severity of COVID 19

Severity of COVID 19		Outcome status		Total
		Dead	Alive	
	Normal	0 (0)	28 (39.4)	28 (37.8)
	Mild	0 (0)	24 (33.8)	24 (32.4)
	Moderate	1 (33.3)	14 (19.7)	15 (20.3)
	Severe	2 (66.7)	5 (7)	7 (9.5)
	Total	3 (100)	71 (100)	74 (100)
Chi Value=13.3, Df=3, P=0.004*				
*P <0.05 is significant				

In our study total 3 (4.1%) patients died out of which 2 (28.57%) were severely seek and 1 (6.7%) were moderately seek and p value for this was 0.004 which was significant.

Table 7: Outcome of COVID 19 Patients according to NLR at admission

		Outcome status		Total
		Dead	Alive	
NLR on admission	<3.5	0	30	30
		0.0%	42.3%	40.5%
	3.5-5.5	0	11	11
		0.0%	15.5%	14.9%
	>5.5	3	30	33
		100.0%	42.3%	44.6%
Total		3	71	74
		100.0%	100.0%	100.0%
Chi Square value=3.8,Df=2,P value=0.14				

In present study all mortalities were in severe disease patients whose NLR was >5.5

Table 8

Parameters	Values of Central Tendency	Outcome status		Mann Whitney U Value, P Value
		Dead(N=3)	Alive (N=71)	
NLR at admission	Mean(SD)	16.5(5.6)	7.1(6.7)	23.5, 0.01*
LCR at admission	Median (IQR)	0.1(0.1-0.6)	1.4(0.1-3.8)	51.5, 0.129
SPO2 at admission	Mean (SD)	86.7(6.1)	94.9(3.9)	17.5, 0.01*
*P <0.05 is significant				

In present study on admission mean NLR with standard deviation was 16.5(5.6) in patients who died, Mann Whitney U value for these was 23.5 and p value was 0.01 which was significant. Median LCR with interquartile range was 0.1(0.1-0.6) in patients who were died, Mann Whitney U value for these was 51.5 and p value was 0.129 which was insignificant. Mean spo_2 of patients with standard deviation was 86.7(6.1) in patients who died, Mann Whitney U value was 17.5 and p value was 0.01 which was significant.

Table 9

	COVID 19 Severity	N	Mean Rank	Kruskal wallis Test Chi square value=6.7, Df=3, P=0.08
NLR at admission	Normal	28	30.7	
	Mild	24	37.9	
	Moderate	15	43.1	
	Severe	7	51.07	
	Total	74		

Table 10: Need for Invasive/Mechanical Ventilation

	Frequency	Percent
No	72	97.3
Yes	2	2.7
Total	74	100.0

In our study invasive ventilation/mechanical ventilation was required for 2.7% patients.

Table 11

		Outcome status		
	Grading	Dead (%)	Alive (%)	Total
LCR	Low (<11)	3 (100)	59 (83.1)	62 (83.8)
	High (>11)	0 (0)	12 (16.9)	12 (16.2)
	Total	3 (100)	71 (100)	74 (100)
Chi square value=0.605, Df=1,P=0.4, Risk ratio=1.1(95% CI=0.99-1.11), (Risk of being dead with low LCR is 1.1 times higher than with high LCR)				

In present study LCR was low in patients who died.

Table 12

	COVID 19 Severity	N	Mean Rank	Kruskal wallis Test Chi square value=10.5, Df=3, P=0.01*
LCR at admission	Normal	28	40.75	
	Mild	24	44	
	Moderate	15	27.9	
	Severe	7	20.79	
	Total	74		
*P<0.05 is significant				

Table 13

Need for Mechanical ventilation		Outcome status		Total (%)
		Dead (%)	Alive (%)	
	No	1 (33.3)	71 (100)	72 (97.3)
	Yes	2 (66.7)	0	2 (2.7)

	Total	3 (100)	71 (100)	74 (100)
Chi square value=48.6, DF=1, P= <0.001, Likelihood ratio=14.5, Risk of being dead with respect to being alive by use of Mechanical ventilator is 71.4 times,95% CI=10-500)				

In present study out of 3(4.1%) patients who died, 2(2.7%) patients required mechanical ventilation.

Table 14

NLR Grading		Need for Mechanical Ventilation		Total (%)
		NO (%)	YES (%)	
	<3.5	30 (41.7)	0	30 (40.5)
	3.5-5.5	11 (15.3)	0	11 (14.9)
	>5.5	31 (43.1)	2 (100)	33 (44.6)
	Total	72 (100)	2 (100)	74 (100)
Chi square value=2.55. DF=2, P=0.2				

In present study mechanical ventilation required for patients whose NLR was >5.5 on admission.

Table 15

LCR grading	Grades	Need for Mechanical Ventilation		Total
		No (%)	Yes (%)	
	Low (<11)	60 (83.3)	2 (100)	62 (83.8)
	High (>11)	12 (16.7)	0 (0)	12 (16.2)
	Total	72 (100)	2 (100)	74 (100)
Chi square value=0.398, Df=1,P=0.5				

In present study mechanical ventilation required for patients whose LCR was <11 on admission.

Discussion

In our study more patients were males than females, on admission mean of neutrophil count was high and median of lymphocyte count was low, median of NLR was high and median of LCR was low and mean of spo_2 was 94.6%. 44.6% patients were admitted with NLR >5.5(severe disease), 40.5% patients were admitted with NLR <3.5(mild disease), and 14.9% patients were admitted with NLR 3.5-5.5(moderate disease). 37.8% patients were admitted with spo_2 >97% (normal), 32.4% patients were admitted with spo_2 95-97% (mild seek), 20.3% patients were admitted with spo_2 91-94% (moderate seek), and 9.5% patients admitted with spo_2 <90% (severe seek). In present study mechanical ventilation required for patients whose NLR was >5.5 on admission and for patients whose LCR was <11 on admission.

Invasive ventilation/mechanical ventilation was required for high NLR and low LCR on admission. All mortalities were in severe disease patients whose NLR was >5.5 and low LCR (<11) at admission. Mortalities were mostly occurred in patients who were severely seek on admission.

Conclusion

As per present study severity of disease and mortality mostly occurred in patients whose NLR was high and LCR was low at admission so these parameters can be taken for severity, prognosis and outcome for COVID19 disease.

References

1. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog. 2018;14(8):e1007236. doi: 10.1371/journal.ppat.1007236. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

2. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol. 2009;7(6):439–450. doi: 10.1038/nrmicro2147. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

3. Beniac DR, Andonov A, Grudeski E, Booth TF. Architecture of the SARS coronavirus prefusion spike. Nat Struct Mol Biol. 2006;13(8):751–752. doi: 10.1038/nsmb1123. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846–848. doi: 10.1007/s00134-020-05991-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Millet JK, Whittaker GR. Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein. Proc Natl Acad Sci U S A. 2014;111(42):15214–15219. doi: 10.1073/pnas.1407087111. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

6. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, Luo M. et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81(1):e6–e12. doi: 10.1016/j.jinf.2020.04.002. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

7. Koike Y, Miki C, Okugawa Y, Yokoe T, Toiyama Y, Tanaka K, Inoue Y. et al. Preoperative C-reactive protein as a prognostic and therapeutic marker for colorectal cancer. J Surg Oncol. 2008;98(7):540–544. doi: 10.1002/jso.21154. [PubMed] [CrossRef] [Google Scholar]

8. Okugawa Y, Toiyama Y, Yamamoto A, Shigemori T, Ichikawa T, Yin C, Suzuki A. et al. Lymphocyte-to-C-reactive protein ratio and score are clinically feasible nutrition-inflammation markers of outcome in patients with gastric cancer. Clin Nutr. 2020;39(4):1209–1217. doi: 10.1016/j.clnu.2019.05.009. [PubMed] [CrossRef] [Google Scholar]

9. Okugawa Y, Toiyama Y, Yamamoto A, Shigemori T, Ide S, Kitajima T, Fujikawa H. et al. Lymphocyte-C-reactive protein ratio as promising new marker for predicting surgical and oncological outcomes in colorectal cancer. Ann Surg. 2019 doi: 10.1097/SLA.0000000000003239. [PubMed] [CrossRef] [Google Scholar]

10. Mori K, Toiyama Y, Saigusa S, Fujikawa H, Hiro J, Kobayashi M, Ohi M. et al. Systemic analysis of predictive biomarkers for recurrence in colorectal cancer patients treated with curative surgery. Dig Dis Sci. 2015;60(8):2477–2487. doi: 10.1007/s10620-015-3648-2. [PubMed] [CrossRef] [Google Scholar]

11. Bacha S, Sghaier A, Habibech S, Cheikhrouhou S, Racil H, Chaouch N, Zaouri B. et al. Combined C-reactive protein and Neutrophil to Lymphocyte ratio use predict survival innon-small-cell lung cancer. Tunis Med. 2017;95(12):229–235. [PubMed] [Google Scholar]

12. Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A, Sudo A. The combined use of the neutrophil-lymphocyte ratio and C-reactive protein level as prognostic predictors in adult patients with soft tissue sarcoma. J Surg Oncol. 2013;108(7):481–485. doi: 10.1002/jso.23424. [PubMed] [CrossRef] [Google Scholar]

13. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020 doi: 10.1002/jmv.25819. [PMC free article] [PubMed] [CrossRef] [Google Scholar]