Section: Medicine

Original Research Article

THE SIGNIFICANCE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) AND LYMPHOCYTE-TO-MONOCYTE RATIO (LMR) AS PREDICTIVE INDICATORS IN COVID-19

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Abstract

Background: A prompt clinical diagnosis in Covid 19 is easily made due to recent scientific advances but it is still difficult to prognosticate the patients in early stages. As the disease carries high mortality it is important to predict the outcome and manage accordingly right from the onset. These prognostic markers should also be widely available and cost effective. So we tried to study NLR, LMR in covid 19 with varying severity, its impact on progression and outcome. The aims and objectives are to investigate and compare the NLR and LMR in admitted patients of COVID-19 with varying severity and to correlate NLR and LMR with disease progression, severity, and outcome in covid patients. **Materials and Methods:** Three hundred laboratory-confirmed COVID-19 records were studied in a retrospective observational study at the Department of Medicine, Gandhi Medical College, Bhopal, from June 2021-June 2022. Out of 300, 100 cases were mild, 100 cases were moderate and 100 belonged to severe category based on the WHO criteria of clinical severity of Covid 19. (Mild Disease (n=100), Moderate Disease (n=100), and Severe Disease (n=100)). Detailed history, vital signs, complete blood cell count (CBC) at admission, and inflammatory markers (mainly serum ferritin, erythrocyte sedimentation rate, CRP, serum lactate dehydrogenase, D- Dimer) & high-resolution computed tomography (HRCT)- chest (wherever indicated) were recorded. NLR and LMR in all patients were calculated. The duration of hospital stay and outcome of each patient, along with the type of respiratory support needed by each patient, was also recorded. **Result:** In out study population, COVID-19 infection was more common in patients with 41-50 years (24%), followed by 51-60 years (18.7%) and 31-40 years (18%). There was slight male preponderance (Males were 58.3% whilst females were 41.7%. Mean NLR was significantly higher in severe Covid-19 cases (6.96±3.8) compared to moderate cases (4.48±3.45) and mild cases (3.31±2.44) ($p<0.001$). No significant association was obtained between LMR and disease severity ($p=0.154$). Receptor operating curve analysis found that NLR, LMR, and CRP were significant prognostic markers for the severity of the disease. The area under the curve was highest for NLR (0.846; $p<0.001$) among the significant parameters. The area under the curve for LMR was 0.154, which is considered a poor instrument in predicting the outcome as per the AUC value, suggesting no value as per the AUC. On univariate analysis, NLR was found to have a significant OR (1.387). **Conclusion:** High NLR but not LMR was significantly associated with the disease severity and mortality in COVID-19.

INTRODUCTION

According to the World Health Organization (WHO) dashboard of 23 November 2022, COVID-19 has been confirmed in 651,918,402 people and has caused 6,656,601 deaths across the globe.[1] The coronavirus disease 2019 (COVID-19) virus spread through close contact, most commonly between members of the same family or close friends, through direct touch or the exchange of droplets.[2,3]

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A prompt clinical diagnosis is essential to provide symptomatic therapy, immediate access to the intensive care unit, and patient isolation to stop the spread of the disease.

Polymerase chain reaction (PCR) is the primary test for diagnosing COVID-19. However, several limitations are universally acknowledged, including lengthy turnaround time and hospitals with PCR infrastructure availability.[4] Serum biochemistry and hemogram analysis are less time-consuming, less challenging to measure, more routine, and less expensive to facilitate the diagnosis and prognosis of this condition. However, despite their widespread use, these diagnostic methods cannot reliably confirm a diagnosis of COVID-19; instead, they raise suspicions among medical professionals over the existence of this disease.[5]

White blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and serum C-reactive protein (CRP) levels have been investigated as independent predictors for the prognosis of systematic inflammatory diseases.[6,7]

Historically, NLR was utilized most frequently in treating oncological disorders, autoimmune illnesses, and bacterial infections.[8,9] On the other hand, it was discovered to be an independent factor in patients who had COVID-19 by Yang et al. in 2019. This lends credence to the hypothesis that there is a connection between hyper-inflammation and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[10] An NLR of more than four was observed to predict the admission of COVID-19 patients to the critical care unit in another investigation carried out by Ciccullo and colleagues.[9]

Recent research has shown that an elevated NLR and LMR might be considered independent biomarkers for identifying poor clinical outcomes. Additionally, investigations have shown that a high LMR value is connected with the severity of COVID-19 disease.[11]

In this study, our objectives were to investigate and compare the NLR and LMR in admitted patients of COVID-19 with varying severity and to correlate NLR and LMR with disease progression, severity, and outcome in covid patients.

MATERIALS AND METHODS

A retrospective observational study was performed at the Department of Medicine, Gandhi Medical College, Bhopal, from June 2021-June 2022 on 300 laboratory-confirmed COVID -19 patients over 18 years at Hamidia Hospital, Bhopal, Madhya Pradesh. Patients with hematological disorders, concomitant bacterial Infections, medications that can affect NLR/LMR, such as steroids and cytotoxic drugs, known cases of HIV, and pregnant females were excluded from the present study.

In our study group we excluded patients of varying severity based on WHO criteria as Mild Disease [n=100; symptomatic patients meeting the case definition for COVID-19 without evidence of Viral Pneumonia or Hypoxia], Moderate Disease [n=100; clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SPO2 >/= 90% on room air] and Severe Disease [n=100; clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following RR >30 per min, Severe respiratory distress or, SPO2 <90% on room air].[12]

Detailed history and examination of each patient were noted from case records along with vital signs, investigations including complete blood cell count (CBC) at admission, and inflammatory markers (mainly serum ferritin, erythrocyte sedimentation rate, CRP, serum lactate dehydrogenase, D- Dimer) & high-resolution computed tomography (HRCT)-chest (wherever indicated) were noted. The duration of hospital stay and outcome of each patient, along with the type of respiratory support needed by each patient, was recorded. NLR and LMR in all patients were calculated.

Statistical Analysis

Data were recorded in the Microsoft Excel program, and statistical analysis was performed by the SPSS program for Windows, version 25 (SPSS, Chicago, Illinois). Continuous variables were presented as mean ± SD, and categorical variables were presented as absolute numbers and percentages. Data were checked for normality before statistical analysis. A descriptive analysis was performed to obtain the general characteristic of the study population.

Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were assessed using ANOVA or independent sample t-test. Pearson correlation (r) was performed to establish the correlation between different parameters. Roc curve was prepared to obtain the effectiveness of the various instruments. ROC interpretation was made as follows >0.900: excellent test/ instrument, between 0.800-9.00: Good test/instrument,

Between 0.700-0.800: Fair test/ instrument, between 0.600-0.700: Poor test/ instrument, and <0.600: No value as an instrument. P<0.05 was considered statistically significant.

RESULTS

The majority of the Covid-19 patients had an age between 41-50 years (24%), followed by 51-60 years (18.7%0 and 31-40 years (18%). The majority of the mild Covid-19 patients had an age between 21-30 (29%), whereas moderate severity was more prevalent in the age groups of 41-50 years (24%0 and severe Covid-19 cases had an age between 41-50 years (29%) (p=0.078).

There was slight male preponderance but the difference was statistically insignificant (p=0.149).

Out of 46 deaths in the present study, 45 were among the severe cases. One moderate case progressed to

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severe disease despite the standard of care and eventually died. This highlights that mortality is more common in patients with severe Covid 19 infection at admission.

Table 1: Characteristics of the patients based on the severity of COVID-19

Characteristics	Mild	Moderate	Severe	P value
Age; years	41.90±17.89	46.92±15.81	49.86±14.48	0.002
Duration of stay; days	7.88±3.919	9.65±4.65	11.23±7.194	0.002
HB; g/dl	12.246±2.12	12.466±2.08	11.450±2.24	0.002
WBC; thou/Ul	6347.00±2747.76	8112.00±4102.13	10774.40±6757.75	<0.001
Neutrophil	67.32±12.80	74.73±10.93	80.16±11.54	<0.001
Lymphocyte	27.40±11.55	21.10±9.49	16.12±10.04	<0.001
Monocyte	3.52±1.62	2.570±1.41	2.170±1.27	<0.001
NLR	3.31±2.44	4.84±3.45	6.96±3.82	<0.001
LMR	8.38±3.94	9.15±4.44	8.061±3.86	0.154
Platelet count; lac	2.41±1.8	2.43±0.74	2.24±1.1	0.526
ESR	20.65±9.114	25.93±10.38	30.09±11.174	<0.001
CRP mg/L	14.80±40.36	52.65±62.40	78.92±67.49	<0.001
D Dimer; mcg/mL	272.03±288.48	448.88±315.32	612.49±429.51	<0.001
HBA1c; %	11.91±52.22	6.05±2.50	6.955±1.83	0.396
S Ferritin ng/ml	188.22±208.03	443.46±388.18	607.74±471.37	<0.001
LDH u/l	338.73±155.75	509.85±209.16	673.19±613.80	<0.001
S PCT mcg/l	0.083±0.046	0.147±0.179	0.360±1.08	0.015
Troponin -I ng/ml	0.042±0.026	0.28±1.28	0.282±0.783	0.159
PRO-BNP pg/ml	80.43±151.63	364.26±1223.43	1882.07±4392.47	<0.001
HRCT CHEST; %	15.13±4.84	36.89±13.01	51.56±17.63	<0.001

Table 2: Comparing mean NLR and LMR based on the severity of the disease

Group		NLR	LMR
Mild	Mean	3.31	8.38
	SD	2.44	3.94
Moderate	Mean	4.84	9.15
	SD	3.45	4.44
Severe	Mean	6.96	8.06
	SD	3.82	3.86
P value		<0.001	0.154

Mean NLR was significantly higher in severe Covid-19 cases (6.96±3.8) compared to moderate cases (4.48±3.45) and mild cases (3.31±2.44) ($p<0.001$). No significant association was obtained between LMR and disease severity, as revealed by the insignificant p-value of 0.154.

Table 3: ROC analysis for predicting outcomes in patients

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NLR	.846	.071	<0.001	.707	.985
LMR	.154	.071	0.021	.015	.293
CRP	.462	.098	0.001	.270	.653
D Dimer	.962	.038	.123	.888	1.000
S Ferritin	.923	.052	.158	.821	1.000
S PCT	.808	.077	.304	.656	.959
Troponin -I	.769	.120	.369	.534	1.000
PRO-BNP	.885	.063	.199	.762	1.000
HRCT CHEST	1.000	.000	.095	1.000	1.000
Neutrophil	.846	.071	.248	.707	.985
Lymphocyte	.135	.068	.223	.002	.268
The test result variable(s): TROPONIN -I, LYMPHOCYTE has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

Receptor operating curve analysis found that NLR, LMR, and CRP were significant prognostic markers for the severity of the disease. The area under the curve was highest for NLR (0.846; $p<0.001$) among the significant parameters. The area under the curve for LMR was 0.154, which is considered a poor instrument in predicting the outcome as per the AUC value, suggesting no value as per the AUC.

Table 4: Univariate analysis of NLR and LMR

Parameters	Univariate analysis		
	OR	95% CI	P value
NLR	1.387	1.298–1.478	<0.001

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LMR	1.126	0.982-1.248	0.021

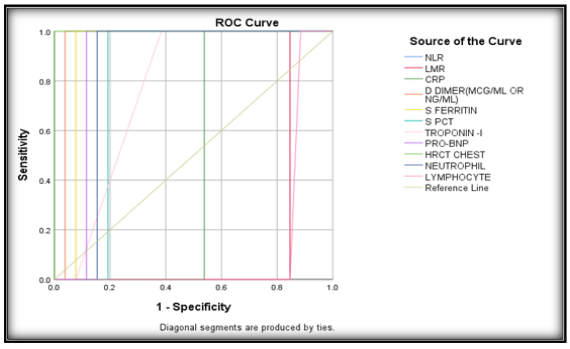
On univariate analysis, NLR was found to have significant OR (1.387); this highlight that NLR is an important prognostic marker for assessing the severity of the Covid-19 disease. LMR was also found to have a significant predictive value per the univariate analysis.

Table 5: Pearson correlation of NLR and LMR with various inflammatory parameters

		NLR	LMR
WBC	Pearson Correlation	.274	-0.018
	P value	<0.001	0.761
Neutrophil	Pearson Correlation	.860	-0.279
	P value	<0.001	<0.001
Lymphocyte	Pearson Correlation	-.865	0.355
	P value	<0.001	<0.001
Monocyte	Pearson Correlation	-.566	-0.344
	P value	<0.001	<0.001
Platelet count	Pearson Correlation	0.003	-0.045
	P value	0.955	0.440
ESR	Pearson Correlation	0.299	-0.087
	P value	<0.001	0.134
CRP	Pearson Correlation	.401	-0.098
	P value	<0.001	0.091
D Dimer	Pearson Correlation	0.122	-0.052
	P value	0.069	0.442
Serum Ferritin	Pearson Correlation	0.307	-0.079
	P value	<0.001	0.205
LDH	Pearson Correlation	0.107	0.097
	P value	0.077	0.107

A significant positive correlation was obtained between NLR and WBC, neutrophil count, ESR, CRP, D-dimer, serum ferritin and LDH which means NLR increases with increasing these parameters and negative correlation was obtained for lymphocytes, monocyte which means NLR increases with decreasing these parameters.

A significant negative correlation was obtained between LMR and WBC, neutrophil count, monocyte, platelet count, ESR, CRP, D-dimer and serum ferritin which means LMR increases with decreasing these parameters and positive correlation was obtained for lymphocytes which means NLR increases with decreasing these parameters.



DISCUSSION

The CBC is a fast, simple, and inexpensive measurement in clinical practice. It provides comprehensive information regarding total and differential WBC counts. A few indicators, such as NLR and LMR, have good predictive ability when employing different cut-offs.[13] NLR and LMR were investigated as potential prognostic markers in Covid-19 patients through a retrospective observational study on 300 patients at Hamidia Hospital in Bhopal.

In the present research, COVID-19 severity grows with age, with older persons at the highest risk possible. Older people are more likely to have health issues that have been present for a longer time, which can place them at an elevated risk for severe effects from COVID-19.[14] Patients who arrived at the hospital showing severe symptoms of covid-19 had a higher risk of mortality. In addition, the mechanisms through which advancing age might predispose a person to a poor prognosis have not yet been fully explained. Several hypotheses have been proposed about why older people might be more susceptible to severe COVID-19 infection. These hypotheses include a weaker immune response, obesity, age-related decline in respiratory function, frailty, and multimorbidity.[15-17]

According to our research findings, the mean length of hospital stay was significantly longer for those with severe clinical profiles compared to the other two categories (p = 0.002). Patients with difficulty breathing, who have an incidence of organ failure, and who have lowered leukocyte counts and increased blood urea nitrogen levels showed longer hospital stays. As a result, it is reasonable to anticipate that patients whose hospital stay was longer due to associated factors would spend more on pharmaceutical and non-pharmacological resources while receiving medical care.[16,18]

In the current study, we could not find any statistically significant differences between males and females concerning the severity of the Covid-19 disease (p-value 0.149). Despite this, it has been evident throughout the pandemic's first two years that

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males, regardless of age, are not only more susceptible to but also have a higher chance of death and more severe illness. According to the clinical classification of severity, men had a greater tendency to acquire more severe cases than women did. Regardless of age, males diagnosed with COVID-19 have an increased likelihood of experiencing adverse outcomes, including death.[19] The ratio of men to women among the patients who have passed away is approximately 2.4 to 1. Even though men and women were equally susceptible, men had a higher mortality rate than women.[19]

In this study, we examined a variety of hematological parameters in patients with COVID-19 with a range of severity levels. We correlated those levels with the level of severity as well as the outcome.

According to our findings, severe cases of covid-19 had significantly higher WBC ($p<0.001$) and neutrophil counts ($p<0.001$) than less severe instances. Except for individuals with bacterial infections or superinfections, neutropenia correlates with a hyperinflammatory state and cytokine storm, which are essential components of the pathogenic mechanism that COVID-19 employs. Neutrophils play an important role in a wide variety of respiratory viruses that are connected with ARDS. This finding tends to correlate with a more severe course and affects a minority of individuals who present with leucocytosis and is accompanied by neutrophilia.[20] Individuals with severe COVID-19 infections had considerably higher levels of leukocytes and neutrophils than patients with less severe COVID-19 infections. In addition, as the COVID-19 disease progressed, severe groups exhibited an increase in both their leukocyte and neutrophil numbers.[21]

We observed considerable lymphopenia in those with severe disease compared to patients with mild to moderate cases of covid-19 illness. ($p<0.001$) Lymphopenia is the most widely recognized hematological aberration in individuals afflicted by COVID-19 infection. This condition manifests itself in up to 85% of severe cases, and the degree to which lymphopenia exists is correlated to the patient's prognosis.[15] In a cohort consisting of 120 COVID-19 patients, 100 influenza patients, and 61 healthy controls, it was found that the COVID-19 and influenza groups had lower lymphocyte counts than the healthy control group.[22]

According to the findings of our research, severe cases had considerably elevated levels of CRP ($p<0.001$), D-dimer ($p<0.001$), serum ferritin ($p<0.001$), LDH ($p<0.001$), and serum PCT ($p = 0.015$). Pro-BNP had a significantly higher abnormality level ($p<0.001$), as did HRCT chest imaging, in severely Covid-19 positive individuals, compared to moderate and mild instances. There is a significant elevation of inflammatory cytokines and biomarkers in the systemic hyperinflammation phase of COVID-19, proposed by Siddiqi and Mehra.[23] These include interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-, tumor necrosis factor-(TNF-), CRP, and ferritin. This stage is characterized by the most severe expression of the cytokine storm, characterized by extreme hyperinflammation that may lead to cardiac collapse and failure of many organs.[23] Koozi et al., found an elevated blood CRP level connected with a 30-day death rate.[24]

In the current investigation, the mean NLR was substantially greater in severe Covid-19 cases than in moderate Covid-19 or mild Covid-19 cases. There was a substantial correlation between NLR and severity, measured by a value of less than 0.001. However, there was no evidence of a significant connection between LMR and the severity of the disease (p-value of 0.154). The fact that NLR had a substantial odds ratio (1.387) suggests that it is an important prognostic marker for determining the severity of the Covid-19 disease. This finding starkly contrasts the pattern in a study that Shivakumar and colleagues carried out. They discovered that most patients had NLR levels that were higher than normal. On the other hand, the incidence was 1.8 times greater among those who survived the research.[25] In a study conducted by Usul et al., it was found that the NLR was considerably higher in severely ill COVID-19 patients compared to the control group. This finding was noticed in the same way as reported in our investigation.[26] Additionally, LMR was shown to be higher among survivors, but the correlation was not statistically significant. Our research revealed that the LMR had decreased in non-survivors, which is consistent with the findings of investigations carried out by Lissoni et al,[27] and Zhang et al.[28]

In their study on 69 non-severe and 24 severe cases diagnosed with COVID-19, Yang et al,[29] reported that age, WBC count, NLR, LMR (lymphocyte-to-monocyte ratio), PLR, CRP, and d-NLR (derived NLR ratio) rates were significantly higher in severe patients than in the other patients. In contrast, the lymphocyte count was significantly lower.

In addition, the researchers concluded that NLR had a positive correlation with the risk of COVID-19 after comparing the crude odds ratio with the adjusted odds ratio that was arrived at after conducting a logistic regression analysis and excluding any potential effects that could have been caused by age or gender. This was done to identify the factors that could influence the progression of the disease. As a result, NLR is a technique that can be recommended for use in clinical practice to evaluate the prognosis and severity of clinical symptoms in COVID-19 patients.

The NLR, LMR, and CRP levels were used as diagnostic indicators to determine the severity of the condition. Among the significant values, NLR had the largest area under the curve (0.846; p 0.001) among the relevant parameters. Although all three ratios can be employed as important screening and prognostic tools since they are easily accessible with a full hemogram, the NLR correlates most substantially with the other two. As a result, the ratio is considered to be of the greatest importance. This

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examination is easily accessible to a large population, even in contexts with limited resources and geographical isolation.

There are a few limitations to this study. This study was a retrospective study at a single tertiary care hospital. Second, even though all of the investigations were carried out at the time of admission, subsequent investigations could not be carried out because of the budgetary and logistical constraints associated with the patients. Hence, pattern of lab results could not be studied. Third, the sample size in most cases was small, so there is a need for additional research with larger samples. Fourth, patients were not followed up after discharge to check for ongoing symptoms or post-COVID sequelae. Additionally, HRCT Chest was not performed in all patients.

CONCLUSION

Patients diagnosed with COVID-19 frequently display abnormalities in their hematological profiles. The levels of NLR and CRP remained higher in severe COVID-19 patients, whereas lymphocytes, monocytes, and hemoglobin levels significantly decreased in severe COVID-19 patients. There is a correlation between the progression of the disease and an increase in CRP and NLR. The NLR, which is a primary metric that is easily accessible, has the potential to provide immediate insights into the early recognition of critical illness and the patients' prognoses. Clinicians can be assisted in devising a personalized treatment approach and in providing immediate intensive care to those in greater need of careful evaluation of laboratory indices performed at the beginning and during the disease. In addition, because our study is retrospective and calls for further data, additional research will be required to analyze these biomarkers and determine the best cut-offs.

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