CORRELATION BETWEEN NEUTROPHIL LYMPHOCYTES RATIO (NLR) AND SEVERITY, PROGRESSION & OUTCOME OF COVID-19 DISEASE

**Dr. Ronak Kankrecha[4]*, Dr. Gaurav Chhabra[1], Dr. SK Luhadia[1],
Dr. Rishi Kumar Sharma[1], Dr. Shubhakaran Sharma[1], Dr. Atul Luhadia[1],
Dr. Amit Gupta[2], Dr. Divax Oza[3], Dr. Viren Patel[4], Dr. Harsh Sharma[5]**

1. Professors, Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
2. Consultant, Pulmonary Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
3. Senior Resident, Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
4. Final year post graduate, Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.
5. First year post graduate, Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.

*Corresponding author: Dr. Ronak Kankrecha
Final Year Post Graduate, Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India.

ABSTRACT
Aim: The aim of the present study was to assess the Correlation between Neutrophil Lymphocytes Ratio (NLR) and Severity, Progression & Outcome of Covid-19 disease.
Methods: The Prospective, Cross-Sectional, Analytical study was conducted at OPD/IPD patients of Geetanjali Medical College and Hospital, Udaipur. Patients with COVID-19 RTPCR positive of OPD/IPD at Geetanjali Medical College and Hospital, Udaipur were included. For the study, 103 patients of Covid-19 Positive were considered.
Results: The study was carried out in 103 COVID patients. Out of total patients, 56 i.e. 54.37% were of age group 50-69 and 28(27.18%) of age 30-49 years.15.53% patients were of age more and 70 years and only 2.91% patients were observed under age of 30 years. Out of 103 patients, 71(68.93%) were males and 32(31.07%) were females. Regarding place of admission, 59(57.28%) were in ward and 44 (42.72%) were in ICU. Out of 103 patients, 69 (66.99%) patients had moderate CT severity score, 28(27.18%) had mild CT severity score and 6 (5.83%) had severe CT score. Fever, cough, shortness of breath and weakness were found to be the most common symptoms. Sore throat, headache, vomiting, diarrhea, body ache, cold, chest pain, abdomen pain and loss of taste were also seen in some cases.
Conclusion: It was concluded that Neutrophil-Lymphocytes Ratio (NLR) has significant correlation with Clinical profile, Progression of disease and Outcome in Covid-19 and Neutrophil Lymphocytes Ratio (NLR) also had significant correlation with Biochemical markers, Radiological findings and Co-morbidities.
Keywords: NLR, Covid-19, progression, outcome

1. INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a rapidly spreading disease; first cases of Corona virus emerged in China in 2019, following which it was declared a global pandemic in March

2020 by World Health Organization (WHO).[1] COVID-19 presents with a wide range of symptoms. The spectrum of disease is variable, with majority cases being mild and self-limiting. However, the disease can be fatal with development of severe pneumonia progressing to acute respiratory distress syndrome (ARDS) and multi-organ failure.[2]

Inflammation plays a major role in development and progression of COVID-19. People infected with COVID-19 are known to have an immune system that is dysregulated and can cause abnormal immune response.[3] For patients who become septic, timely identification and intervention is necessary to reduce mortality and hospital stay. Circulatory biomarkers which depict inflammation can be used to assess the disease severity and a possible predictor of progression of disease. One such biomarker is Neutrophil to Lymphocyte Ratio (NLR) which can be easily obtained from a simple blood test i.e. Complete Blood Count (CBC) with differential count by dividing the absolute neutrophil count and absolute lymphocyte count. NLR has historically been used as a predictor of morbidity and mortality in patients with cancer,[4] cardiac disease[5] and sepsis[6] amongst other conditions. NLR is a cheap and a readily available indicator of inflammation in patients suffering from COVID-19 and can predict prognosis of patients who are in sepsis.

Corona virus presentations are classified as mild in the majority of cases with no or mild pneumonia symptoms, moderate in the case of sepsis, severe pneumonia, and MODS, and severe in the case of sepsis, severe pneumonia, and MODS.[7,8] Fever, exhaustion, dry cough, muscular discomfort, and dyspnea were the most commonly reported symptoms at the time of infection's start, whereas headache, dizziness, stomach pain, diarrhoea, nausea, and vomiting were the least common.[9] Hypertension, diabetes, cardiovascular illnesses, and cerebrovascular disorders are the most common co morbidities associated with Corona virus infection in the elderly population.[9,10] The WHO recommends collecting samples from both the upper and lower respiratory tracts (nasal and oropharyngeal swabs) (expectorated sputum, endotracheal aspirate, and bronchoalveolar lavage). At 4 degrees Celsius, samples should be kept. These saliva and mucus samples are tested using reverse transcription polymerase chain reaction (RT-PCR), which amplifies genetic material collected from the samples and detects and preserves CoV material.[11,12] Lymphocytopenia is the most common laboratory finding in COVID-19 disease patients, followed by thrombocytopenia and leukopenia. The majority of patients had high levels of C-reactive protein (CRP), while high levels of alanine transaminase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK), and D-dimer were less common.[13] The majority of patients have ground glass opacity, which is accompanied by ill-defined borders, smooth or irregular interlobular septal thickening, air bronchogram, crazy paving pattern, and thickening of surrounding pleura on a computed tomography scan (CT-Scan).[14] There have been no definitive antivirals introduced in recent intervals to treat novel corona virus disease (COVID-19), so supportive care, which includes broad-spectrum antibiotics, antivirals, corticosteroids, oxygen therapy, mechanical ventilation, and convalescent plasma, is a prominent regimen in the current scenario.

The aim of the present study was to assess the Correlation between Neutrophil Lymphocytes Ratio (NLR) and Severity, Progression & Outcome of Covid-19 disease.

2. MATERIALS AND METHODS

The Prospective, Cross-Sectional, Analytical study was conducted at OPD/IPD patients of Geetanjali Medical College and Hospital, Udaipur. Patients with COVID-19 RTPCR positive of OPD/IPD at Geetanjali Medical College and Hospital, Udaipur were included. For the study, 103 patients of Covid-19 Positive were considered.

INCLUSION CRITERIA:

All Adults (>18 years) patients who meet the following criteria:

1.   Positive Reverse transcription-polymerase chain reaction (RT-PCR) of respiratory

samples (nasal/oropharyngeal swab)

2.   Radiological findings of consolidation, ground-glass opacities (GGOs) on high-resolution computed tomography (HRCT).

EXCLUSION CRITERIA:

1.   Patient refusal not to be enrolled in the study.

2.   Patients with bacterial pneumonia (confirmed by sputum bacterial culture).

3.   Patients with interstitial pneumonia (previously diagnosed based on radiological findings).

4.   Patients with all malignancies.

5.   Patients on immunosuppressive drugs (including long-term steroids).

METHODOLOGY:

After obtaining approval from IRRC and IEC & informed consent from the study participants, the study was conducted in Geetanjali Medical College and Hospital.

ETHICAL CLEARANCE:

It was obtained by institutional research and ethical committee.

PROPOSED STATISTICAL ANALYSIS:

The data obtained was entered in MS Excel software and analyzed using Statistical Packages for Social Sciences (SSPS). The descriptive data was expressed in proportions. The categorical variables were expressed as percentage. Discrete / Continues variables was expressed as mean, median, standard deviation. The categorical data was analyzed using chi-square test. The quantitative data was analyzed using appropriate statistical tests such as T-test/ Fisher's exact test. Prediction and Pearson's correlation coefficient, Predictive value, and Likelihood ratio was used. P Value <0.05 was considered significant.

3. RESULTS

Table 1: Patient details

Variables	Number Of Patients	Percentage
Age		
Less than 30	3	2.91%
30-49	28	27.18%
50-69	56	54.37%
More than 70	16	15.53%
Gender		
Male	71	68.93%
Female	32	31.07%
Place Of Admission		
Ward	59	57.28%
ICU	44	42.72%
CT Severity Score		
Mild	28	27.18%
Moderate	69	66.99%
Severe	6	5.83%
COMORBIDITIES		
None	51	49.51%
Diabetes mellitus	29	28.16%
Hypertension	26	25.24%
Cardiac disease	4	3.88%

Thyroid	12	11.65%
Others	11	10.68%
Oxygen Support		
Yes	52	50.49%
No	51	49.51%
Outcome		
Deceased	11	10.68%
Discharged	62	60.19%
Home isolation	30	29.13%

The study was carried out in 103 COVID patients. Out of total patients, 56 i.e. 54.37% were of age group 50-69 and 28(27.18%) of age 30-49 years.15.53% patients were of age more and 70 years and only 2.91% patients were observed under age of 30 years. Out of 103 patients, 71(68.93%) were males and 32(31.07%) were females. Regarding place of admission, 59(57.28%) were in ward and 44 (42.72%) were in ICU. Out of 103 patients, 69 (66.99%) patients had moderate CT severity score, 28(27.18%) had mild CT severity score and 6 (5.83%) had severe CT score. Among 103 patients, 51 (49.51%) patients were seen with no co morbidities and 53 (51.46%) were seen with co morbidities such as Diabetes mellitus (29 out of 53 i.e. 54.72%), hypertension (26 out of 53 i.e. 49.06%), thyroid (12 out of 53 i.e. 22.64%) and cardiac disease (4 out of 53 i.e. 7.55%) respectively.11 out of 53 patients were seen with other type of co morbidities (asthma, COPD, stroke, Kidney diseases. Out of total, 52(50.49%) patients required support out of which 44 were in ICU and had moderate CT severity score. 51(49.51%) had not required oxygen support. Regarding the outcome of patients, it was seen that majority were discharged i.e. 62 (60.19%) and majority of them were from ward and with mild to moderate CT severity score. 30 (29.13%) were stayed under home isolation. 11 (10.68%) died and 6 of them had high CT severity score and 5 had moderate CT severity score.

Table 2: Distribution of patients according to symptoms

SYMPTOMS	NUMBER OF PATIENTS	PERCENTAGE
Fever	69	66.99%
Cough	41	39.81%
Shortness of breath	34	33.01%
Weakness	27	26.21%
Dry cough	13	12.62%
Sore throat	7	6.80%
Headache	6	5.83%
Vomiting	5	4.85%
Diarrhea	5	4.85%
Body ache	4	3.88%
Cold	3	2.91%

Chest pain	3	2.91%
Abdomen pain	2	1.94%
Loss of taste & Smell	2	1.94%
Pain throat	1	0.97%
Loss of appetite	1	0.97%
Nausea	1	0.97%
Hemoptysis	1	0.97%
Dehydration	1	0.97%
Chest congestion	1	0.97%
Asymptomatic	1	0.97%

Fever, cough, shortness of breath and weakness were found to be the most common symptoms. Sore throat, headache, vomiting, diarrhea, body ache, cold, chest pain, abdomen pain and loss of taste were also seen in some cases.

Table 3: Comparison of pre and post parameters

PARAMETERS	PRE (N =103)		POST (N= 103)		T VALUE	P VALUE
	MEAN	SD	MEAN	SD		
Hemoglobin	13.30	1.96	13.44	1.75	-1.291	0.200
TLC	7.84	4.07	9.51	4.86	-4.588	<0.001*
Neutrophils	71.11	12.91	71.01	12.61	0.094	0.926
Lymphocytes	21.86	11.58	21.75	11.68	0.116	0.908
NLR	5.09	4.38	5.06	4.39	0.102	0.919
CRP	66.52	71.21	42.80	61.01	3.372	0.001*
IL-6	64.25	83.72	67.90	188.36	-0.232	0.817
PCT	0.36	1.34	2.23	13.81	-1.371	0.173
D-DIMER	1364.98	2752.81	2660.02	2401.25	-6.545	<0.001*

Significant increase in TLC, D-Dimer and significant decrease in CRP was observed at post-test as compared to pre-test value. ($P<0.001$) whereas insignificant change in values of other parameters such as hemoglobin, NLR, IL-6 and PCT at post-test as compared to pre-test values of these parameters.

Table 4: Difference in NLR according to CT severity score, outcome

CT SEVERITY SCORE	N (n=103)	MEAN NLR	SD	F VALUE	P VALUE
Mild	28	3.03	1.84		

Moderate	69	5.16	4.02	**21.927**	**<0.001**
Severe	6	14.01	5.84		
OUTCOME					
Deceased	11	10.45	4.87	**14.021**	**<0.001***
Discharged	62	5.08	4.39		
Home isolation	30	3.16	1.97		
Co-Morbidities				T VALUE	P VALUE
Diabetes mellitus	Yes	29	5.6	4.67	0.728	0.496
	No	74	4.9	4.28		
Hypertension	Yes	26	6.55	**4.94**	**1.992**	**0.049***
	No	77	4.60	4.09		
Cardiac disease	Yes	4	5.36	2.55	0.059	0.953
	No	99	5.08	9.45		
Thyroid dysfunction	Yes	12	5.56	4.54	0.392	0.696
	No	91	5.03	4.38		

Mean NLR was found to be more in patients with severe CT score followed by moderate and mild CT score. There was significant increase in NLR with the increase in CT severity score. Mean NLR was found to be more in deceased patients as compared with discharged patients and those in home isolation. There was significant difference in NLR with the outcome of patients. Mean NLR was found to be significantly more in hypertensive patients as compared to Normotensive patients whereas insignificant difference in NLR was seen among patients with Diabetes, cardiac disease and thyroid dysfunction as compared to patients without these co morbidities.

Table 5: Association of outcome and radiological findings

Outcome	CT SEVERITY SCORE			Chi-square value	p-value
	Mild	**Moderate**	**Severe**		
Deceased	0.00 %	54.54 %	45.46%	**127.099**	**<0.001**
Discharged	0.00 %	98.38 %	01.61 %		
Home Isolation	93.33 %	06.67 %	0.00 %		

With the high or low CT score significant effect on outcome was found. Thus, significant association was observed between CT severity score and outcome in patients.

Table 6: Correlation of NLR with various parameters

Correlation of NLR with		Correlation Coefficient (r)	p value
CT Severity Score		**0.475**	**<0.001***
Age		**0.214**	**0.030***
	Hemoglobin	-0.031	0.757
	TLC	**0.563**	**<0.001***

Biochemical Parameters	CRP (Quantitative)	0.495	<0.001*
	D-DIMER	0.317	0.001*
	IL-6	0.305	0.002*
	PCT	0.313	0.001*

Significant positive correlation of NLR was observed with CT severity score, age and biochemical parameters i.e. with the increase in age, CT severity score and biochemical parameters such as TLC, CRP, D-Dimer, IL-6 and PCT there was significant increase in NLR.

4. DISCUSSION

A pandemic COVID-19 had a considerable impact on the sociopolitical environment and healthcare delivery systems. It is a disease that has spread extensively and quickly around the world. There are many different clinical manifestations, ranging from asymptomatic carriers to patients needing assisted ventilation support and ICU stays with higher mortality. Most common symptoms are fever, cough, shortness of breath or difficulty breathing, sore throat etc. COVID-19 infection causes systemic inflammation. Neutrophil-Lymphocytes Ratio (NLR) is an inflammatory biomarker that can be used as an indicator of the systemic inflammatory process. These biomarkers were determined by dividing the absolute neutrophil and absolute lymphocyte counts. Even though majority patients have self-limiting and mild illness, patients who develop severe or critical cases have a grave prognosis. It had been observed very early after the beginning of COVID-19 pandemic that the neutrophil-to-lymphocyte ratio (NLR) is much higher in severe or critically ill patients as compared to those with milder disease. NLR has been shown to be a reliable indicator to determine disease severity in COVID-19.[15,16]

Age-related disorders and vulnerability to infectious diseases are both correlated with the multiple biochemical changes in the immune system that is associated with ageing. Age-related changes affect the human immune system, which subsequently impairs defenses against respiratory infections. The lungs, heart, and digestive system are among the tissues that SARS-CoV-2 frequently affects because they express high levels of angiotensin-converting enzyme-2 (ACE-2). In this study, 54.37% were from age group of 50-69 followed by 27.18% in 30-49 years This finding was similar with the finding of study conducted by Kong M et al.[17] Mean age of patients was found to be 54.51 years which was similar with the study of Liu L et al[18] and Kong M et al.[17] In this study, 68.93% were male patients and 31.07% were female i.e. proportion of male patients was more in the study which was similar with the findings of Xu J B et al.[19] and Liu L et al.[18] Our patients were predominantly males which is keeping with other studies as COVID-19 is known to have a predilection for male gender.[20]

In this study, 72.82% patients had moderate-severe CT score and 27.18% had mild CT score which was similar with the finding of Liu L et al.[18] but contradict with the finding of Kong M et al[17] because according to Indian government guidelines of COVID-19, patients who had mild symptoms were isolated at home and could be treated at home with oral medications. Amongst the symptomatic individuals, the most common clinical symptoms were fever, respiratory symptoms, and myalgias which are comparable to those described by the WHO interim guidance. Our study has shown that mean NLR value significantly increases as disease severity progresses with lowest NLR recorded in asymptomatic and mild disease. This is in line with a Cochrane Meta-analysis Review of twenty Chinese studies which

established that NLR is an independent prognostic marker to differentiate severe vs nonsevere COVID-19 disease.[21]

Mean hemoglobin of patients in this study was found to be 13.30 g/dl which was similar with the findings of Kong M et al.[17], Liu L et al.[18], Liu J et al.[22] There was no significant correlation of NLR with hemoglobin. In this study, mean NLR was found to be more in patients with severe CT score followed by moderate and mild CT score and there was significant increase in NLR with the increase in CT severity score which was found to be similar with the results of Kong M et al. Simadibrata DM et al[23] and Liu L et al.[18] As NLR is an inflammatory marker hence with increased inflammation in lungs, it leads to increase in NLR.

In this study, significant positive correlation of NLR was observed with CT severity score, age and biochemical parameters i.e. with the increase in age, CT severity score and biochemical parameters such as TLC, CRP, D-Dimer, IL-6 and PCT there was significant increase in NLR which was similar with the findings of Kong M et al.[17], Liu J et al.[22], Simadibrata DM et al[23], Liu L et al[18] and Imran MM et al.[24]

5. CONCLUSION

It was concluded that Neutrophil-Lymphocytes Ratio (NLR) has significant correlation with Clinical profile, Progression of disease and Outcome in Covid-19 and Neutrophil Lymphocytes Ratio (NLR) also had significant correlation with Biochemical markers, Radiological findings and Co-morbidities.

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