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Original Research Article

Neutrophil Lymphocyte Ratio (NLR) as a Predictor of Disease Severity and Mortality in Geriatric Patients with COVID-19

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Abstract

Introduction: COVID-19 pandemic affected 44,696,984 people in India Geriatric (age 60 years and above) population is increasing globally. Older adults have been affected badly with COVID-19 Neutrophil lymphocyte ratio (NLR) is used in several diseases as an inflammatory marker in predicting prognosis. According to a recent study patients with severe COVID-19 are reported to have higher Neutrophil lymphocyte ratio (NLR). In this study we aimed to assess the accuracy of Neutrophil lymphocyte ratio (NLR) as a predictor of disease severity and mortality in geriatric patients with COVID-19.

Materials and Methods: 200 geriatric inpatients infected with COVID-19 were included in the study. Neutrophil lymphocyte ratio (NLR) at admission was recorded. Neutrophil lymphocyte ratio (NLR) cutoff was taken 3.5. Patients were categorized into mild, moderate, severe and critical cases according to criteria given by Maharashtra Task Force. Relationship between Neutrophil lymphocyte ratio (NLR) and disease outcome was assessed. A p value < 0.05 was taken as statistically significant.

Results: The mean age of study sample was 69.00 ±7.09 years. A significant association was found between Neutrophil lymphocyte ratio (NLR) and disease severity (p -0.048) as well as mortality (p-0.041).

Keywords: Neutrophil to Lymphocyte Ratio (NLR), Severity, Mortality, Geriatric, COVID-19.

Introduction

COVID-19 pandemic affected 44,682,206 people in India.[1] Geriatric (age 60 years and above) population is increasing globally and in India too. Elderly people are more susceptible to COVID-19 associated mortality and morbidity. In older adults, immune-senescence and co-morbidities are more likely to accelerate virus induced

cytokine storm, resulting in unfavourable outcomes[2]. Geriatric COVID-19 patients with chronic co-morbidities have an increased risk of complications, for ex: acute respiratory distress syndrome, acute kidney injury and acute cardiac injury which causes high mortality rate.[3]

Several parameters like C Reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), Ferritin, Interleukin -6 (IL-6) and Procalcitonin can be used evaluate inflammatory response of disease.[4]

The neutrophil to lymphocyte ratio (NLR),is a easily calculated score from a routine blood investigation, obtained by dividing absolute neutrophil count by absolute lymphocyte count. Several studies have reported its value in indicating a patient's overall inflammatory status. In addition to viral disorders, NLR can be used in many other conditions like cancer, acute coronary syndrome, intra cerebral haemorrhage, polymyositis, and dermatomyositis. [5] According to a recent study higher NLR have been found in patients with severe COVID-19.[6] However, further studies in the domain of COVID-19 are needed regarding this. [5]

Since the beginning of the COVID, researchers and clinicians have been looking into the role of NLR as a biomarker of severity and its use in COVID-19 prognostication. NLR has been shown to predict death, the progression of severe illness, the risk of invasive ventilation, the risk of severe illness in mechanically ventilated patients, length of being in intubated state, and being admitted under Intensive Care Unit.[7]

To the best of our knowledge, till date, very few studies has been published in literature which focused on the geriatric population. In the present study, our aim was to assess the NL ratio as severity and mortality predictor in geriatric patients with COVID-19.

Materials and Methods

This was a cross sectional study carried out at Tertiary Care centre (Dedicated COVID-19 Hospital) from December 2020 to November 2022. 200 Geriatric patients with diagnosis of COVID-19 were included in the study. Patients were followed from admission to their outcome (Discharge/ death). Patients were classified according to disease severity as asymptomatic ,mild, moderate, severe, critical as per Maharashtra Task Force guidelines.[8]

Asymptomatic: Covid nucleic acid test positive. No clinical symptoms and signs and with normal chest X ray.

Mild: Symptoms of upper respiratory tract infection (for example fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing,) or digestive symptoms (eg. nausea, vomiting, abdominal pain, diarrhoea)

Moderate: Pneumonia (frequent fever, cough) with no obvious saturation drop, chest CT with lesions

Severe: Pneumonia with hypoxemia ($SpO_2 <$ 92%).

Critical: Patients with one of the following (Acute Respiratory Distress syndrome (ARDS), shock, encephalopathy, Myocardial injury, heart failure, coagulation dysfunction and acute kidney injury).[8]

Patients with raised NLR were grouped into survivor and non-survivor group to see mortality prediction. NLR was calculation was done by dividing number of neutrophils by number of lymphocytes.

ANOVA Test: Appropriate test for analysing continuous variables when there are 3 or more groups to be compared.[9]

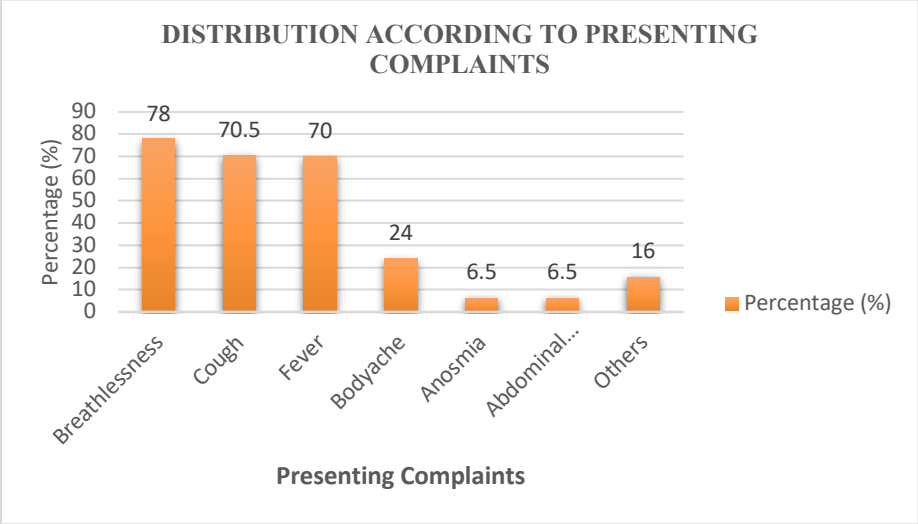
Statistical Analysis

Initial data was captured in the customised proforma and then transferred to Microsoft Excel for analysis. Statistical Software SPSS

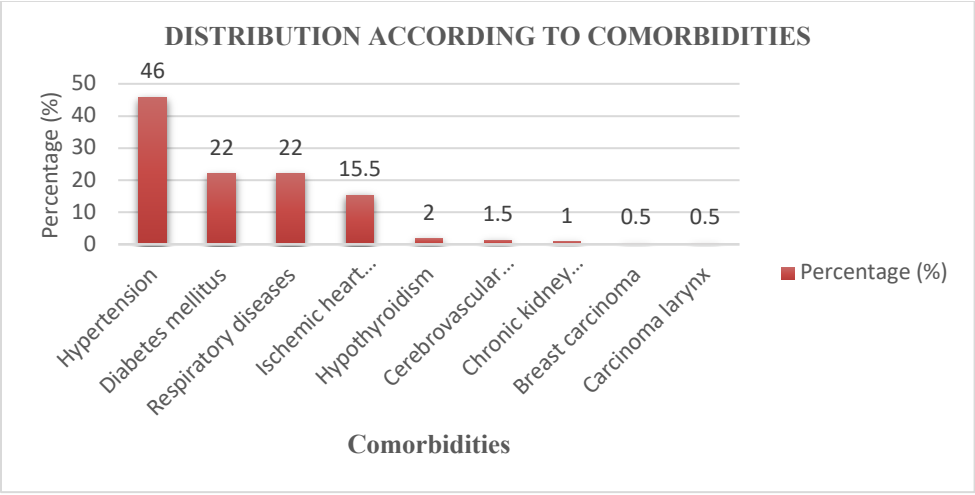
Version 27.0.0.0 was used for calculating P values. Continuous variables like age and NLR were being reported as mean values with standard deviation. Frequency and percentages were calculated for categorical variables including disease severity categories, symptoms and co-morbidities. Confidence interval of 95% was taken. Games-Howell test and ANOVA were used to check whether there are inter categorical differences in mean values. To detect between group variance of mean NLR amongst patient outcome groups i.e. those who recovered or those who died ,F statistic was calculated. A p value of < 0.05 was taken as statistically significant.

Results

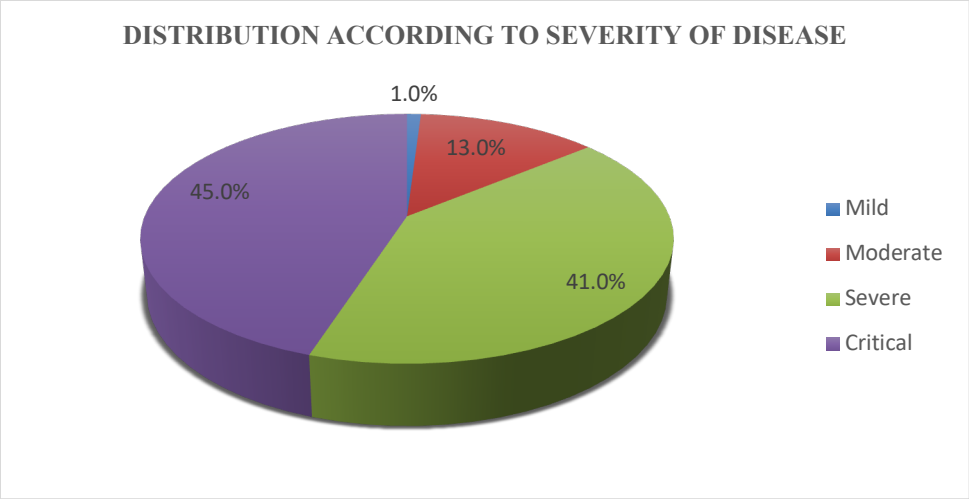
The mean age of study participants was 69.19 ± 7.40 years. 56.5% patients of total patients were male and 43.5% were females.



Graph 1: Bar diagram shows the distribution according to presenting complaints.



Graph 2: Bar diagram shows the distribution according to comorbidities.



Graph 3: Pie diagram shows the distribution according to severity of disease.

Out of 200 patients raised NLR found in 178 patients. Out of which 84 recovered and 94 died.

Table I represents the descriptive statistics of NLR across all four categories of disease severity. Mean NLR was observed to be in increasing trend from 3.95 in mild patients to 6.62 in moderate, 9.29 in severe and 13.75 in critical patients. There is significant positive association between NLR and disease severity (p -0.048) in our study.

Games-Howell test was applied for further exploration of the difference in mean NLR across various categories of disease severity. The results are shown in Table II. The difference in mean NLR has been found to be statistically significant in Critical- mild and mild –severe groups only.

The comparison of mean NLR of patients who recovered from COVID-19 with those who died is presented in Table III. ANOVA was conducted to see statistical differences between both groups. It was quite noticeable that patients who died had a significantly raised NLR compared to those who recovered. NLR is significantly associated with mortality (p-0.041).

Table 1: Variability of NLR across all Categories of Disease Severity ANOVA.

		Disease Severity			
		Mild	**Moderate**	**Severe**	**Critical**
	Mean	3.95	6.62	9.29	13.75
	(95% Confidence Interval)	(3.85,4.04)	(5.5,7.74)	(7.41,11.16)	(10.71,16.8)
NLR	Minimum	3.9	3.7	3.60	3.60
	Maximum	4.0	12.0	47.0	96.0
	Std Dev	0.071	2.62	8.16	14.07
	n	02	21	73	82

*p-value 0.048

Table 2: Games-Howell Post Hoc Comparisons - Severity

		95% CI for Mean Difference			
Comparison	**Mean Difference**	**Lower**	**Upper**	**SE**	**p-value**
Critical - Mild	9.808	5.727	13.888	1.556	* < .001
Critical Moderate	5.121	-1.623	11.866	2.533	0.194
Critical - Severe	4.468	-0.281	9.217	1.825	0.073

Mild - Moderate	-4.686	-10.284	0.911	2.000	0.122
Mild - Severe	-5.340	-7.857	-2.822	0.957	*< .001
Moderate - Severe	-0.653	-6.682	5.376	2.216	0.991

Note: * p-value significant at 0.05 level

Table 3: Association between NLR and mortality ANOVA

	Mean NLR	Minimum	Maximum	F-Statistic, p-value
Recovered	9.34	3.60	47.0	4.235, 0.041
Died	12.87	3.60	96.0	

Discussion

COVID-19 is known to have worse outcome in Geriatric patients, especially those with comorbidities.[11] NLR has been found to be a reliable indicator to determine disease severity in COVID-19.[11,12]

Several theories about how polymorphs and lymphocytes response to COVID 19 infection have been put forth. Apart from stimulating the immune system , neutrophils, also create reactive oxygen species that can cause DNA damage in cells and release of viruses, which are further destroyed by antibodies. A variety of cytokines and effector chemicals are also produced by neutrophils. While viral infection itself primarily causes a lymphocyte response, systemic inflammation, particularly high Interleukin 6, paradoxically lowers the lymphocyte count causing decrease in cellular immunity. The outcome of both of these factors result in an elevated NLR .[12]

Many researchers have been studying the difference of baseline leukocyte counts between the clinical stages in COVID-19 patients.[6] According to the data provided by these studies, patients with severe COVID-19 infections typically had greater neutrophil counts but lower lymphocyte counts than non-severe patients; as a result, the NLR tended to be higher in such patients. [14] However, similar data in elderly has been found to be lacking. Therefore, the purpose of the current study was to evaluate the relationship between NLR and disease severity and mortality in geriatric patients with COVID-19. We have found a considerable difference in NLR levels between discharged and deceased patients with levels in the latter group being much higher. NLR was significantly higher in severe diseases. According to several meta-analyses reports patients with severe COVID-19 infection had a greater NLR than those with non-severe COVID-19 infection.

The mean age in our study was 69.19 ± 7.40 years. In Kaleem Ullah Toori et al [10] study, the mean age of the patients was 40 years, which is much lower than that seen in our study because we have included only geriatric patients.. There were (56.5%) males in our study. Most of the patients were males In Kaleem Ullah Toori et al study [10].

The patients in our study were mostly critical 45%, as compared to Kaleem Ullah Toori et al [10] study where most of the patients are asymptomatic. The difference is because ours was a tertiary care centre and patients were referred from periphery.

In presenting complaints breathlessness was the commonest complaint seen in (78%) patients followed by cough (70.5%) and fever (70%), while anosmia and digestive symptoms were seen in only in 6.5 % of patients in our study. However, according to study by to Kaleem Ullah Toori et al [10]most common presenting symptoms were fever, respiratory symptoms, and myalgias.

Present study has demonstrated that mean NLR values significantly rise as illness severity increases, with mild disease having the lowest NLR values, similar findings have been observed by Kaleem Ullah Toori et al. [10] study where NLR was lowest in asymptomatic and mild disease and progressively increased with disease severity. Similar results have been found in Rathod et al. study [7] where NLR progressively increased from asymptomatic to severe disease. Other study Lian et al.[13] also showed same findings that mean NLR progressively increased from mild to severe disease and significantly associated with disease progression (p- <0.001)

We reviewed the difference in mean NLR between disease severity and found that the highest difference in mean NLR is between the mild, severe and critical patients. In Kaleem Ullah Toori et al [10] study highest difference was observed in mean NLR between the asymptomatic and severe patients.

A link between high NLR and mortality has also been established in our study. Which led us to the result that mean NLR ratio of those who died was 12.87 as compared to 9.34 in those who recovered which was significantly high and shows significant association with mortality (p- 0.04). Similar results found in In Kaleem Ullah Toori et al [10] study where mean NLR ratio of succumbed was 10.5 as compared to 2.34 in recovered and shows significant association with mortality (p- 0.00) . Rathod at el study [7] also shows significant association of NLR with mortality (p- 0.003)

Conclusion

In our study, high NLR has been significantly associated with mortality and disease severity in Geriatric COVID 19 patients. NLR represents a rapid, widely available, cost effective method that can be used in early triage and management of geriatric COVID 19 patients. Since these findings occurs early, it can be specially useful in peripheral areas where tests like D DIMER,LDH, IL-6 etc are not available. As only simple heamogram (DLC- Absolute Neutrophil and lymphocyte count) can help in risk stratification and timely referral. There are some limitations to our study. Being done at a single centre, it has limited external validity. Sample size was relatively small. We suggest multicenter studies with bigger sample size considering findings of our study as preliminary data, to clarify the role of NLR in predicting the disease severity and mortality in Geriatric patients with COVID-19.

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