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Neutrophil to Lymphocyte Ratio (NLR) as a Prognostic Factor of Disease Severity in Novel Corona Virus-Infected Critical Patients in Dedicated Covid Hospital Government Bundelkhand Medical College Sagar MP: A Retrospective Cross-Sectional Study

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Abstract

Background: Since December 2019, NCIP, or novel coronavirus infected pneumonia, has spread to 195 countries and territories.The condition of some COVID19 patients rapidly deteriorates. Identifying the prognostic predictors of mortality could help determine the severity of the disease and make the best treatment decisions. Researchers have developed a simple way to measure the body's inflammatory response by using the neutrophil to lymphocyte ratio (NLR) in patients in intensive care.

Aims and objectives: To explore whether NLR as a prognostic factor for assessing disease severity and fatal outcome in patients with severe coronavirus disease 2019 (COVID-19).

Materials and Methods: Retrospectively, three hundred and fifty-nine RT PCR confirmed patients with COVID-19 were studied from May 2020 to September 2020. Complete blood counts details were collected from the records of Central Pathology. The NLR was calculated at the time of admission and analyzed for any association with the severity and prognosis of the disease.

Results: A significant association between NLR and disease severity in critically ill COVID-19 patients was obtained ($p<0.05$). Ninety-two patients who died had a median age of 68 years, significantly older than survivors 52 years ($p=0.004$), and male sex was more predominant in non-survivors($P=0.004$). The total leucocyte count was higher in non-survivors and males in 60-70 years. Patients having values >3.5 had an association with a more severe form of the disease [NLR=24.0 (13.56-48.82), $P<0.001$], longer duration of stay in ICU [15 (10-21), $P<0.001$], and greater mortality [78 (61.42%)].

Conclusions: This study establishes NLR as an independent prognostic marker to differentiate severe versus non-severe disease in COVID-19 patients. Also, it can be used as a valuable indicator of poor prognosis at the initial moment of hospitalization.

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1. INTRODUCTION

The etiology of severe pneumonia was identified using bronchoalveolar lavage fluid samples obtained from a patient in Wuhan. The disease caused by SARSCoV2, which the World Health Organization (WHO) has dubbed coronavirus disease 2019 (COVID-19), has been shown in studies to induce symptoms such as fever, dry cough, dyspnea, fatigue, and lymphopenia in infected individuals. Viral pneumonia infections can result in severe acute respiratory syndrome (SARS) and, in extreme cases, death.[1]

There were 13 876, 411 confirmed cases, and 593,087 deaths in 216 countries as of July 18, 2020. Ninety-two countries documented community transmission, 75 countries, including India, reported infection clusters, and 27 countries reported sporadic infections. Case definitions, management, and control approaches have all been refined due to increased data availability, which was not the case during the epidemic's early phases.[2]The majority of patients first reported having traveled from Wuhan, China. Thailand, Singapore, South Korea, Japan, the United States, and France all reported cases of COVID-19 following that.[2] In the initial phase, most patients (78 percent) involved males between the ages of 30 and 69. (51 percent). COVID-19 case fatality rates varied between 2.3 and 9% in China and Italy. COVID-19 incubated for a median of five days and had a basic reproductive number of 2.2.[2]

In India, where suspicions about COVID-19 have driven large-scale containment initiatives at the national, state, and local levels, over 1.3 billion individuals are at risk of infection with SARS-CoV-2. On January 30, 2020, an Indian national removed from China was identified as the country's first known COVID-19 case. Andhra Pradesh and Tamil Nadu are two southern Indian states having a combined population of 127.8 million or nearly 10% of the country's total population. Despite their poverty, Andhra Pradesh and Tamil Nadu have the greatest health care workforces and public health expenditures per capita in India. They are well-known for their competent health care systems.[1,3]

After one week, most people infected with the novel coronavirus experienced mild to moderate illness, with severe illness frequently resulting in dyspnea. Acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy, and septic shock were frequent consequences for individuals undergoing critical illness. When critical illness risk factors were detected early, it was possible to provide adequate supportive treatment and expedite admission to the intensive care unit (ICU). Patients with mild to severe disease require general isolation but do not require ICU care unless the condition develops.[3]As a result, early prognosis prediction could help reduce mortality and alleviate medical resource shortages.

COVID-19 is responsible for an increasing number of fatalities. COVID-19, on the other hand, is neither vaccinated nor explicitly treated. The most frequently used treatments include empirical antibiotics, antiviral medicine, and systemic corticosteroids; nevertheless, these may have only a minimal effect on a fatal outcome.

There is emerging evidence that the condition of some COVID-19 patients deteriorates fast. Identifying prognostic markers of death in COVID-19 patients may thus be beneficial in assessing the disease's severity and making the optimal treatment decisions. 3 The neutrophil to lymphocyte ratio (NLR) has been proposed as a simple indicator of systemic inflammatory response in critically ill individuals. Additionally, it has been associated with non-infectious illnesses such as acute myocardial infarction, stroke, and several cancers as a prognostic

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factor. NLR is also an independent predictor of both short- and long-term death in critically unwell patients.[4]
NLR is a valuable systemic inflammatory marker in predicting clinical risk and outcome in various illnesses.[3]To our knowledge, no adequate investigation has been conducted into the use of NLR to predict death in COVID-19 patients. The purpose of this retrospective study was to determine whether NLR is a predictive factor for disease severity and fatal outcome in individuals with severe COVID19.

2. MATERIALS AND METHODS

The present retrospective study was performed on469 patients with severe COVID-19 illness admitted between May 2020 and September 2020 at Dedicated Covid Hospital in Bundelkhand Medical College, Sagar.
All patients aged more than 18 years and having neutrophil and lymphocyte counts results within 24 hours after admission were included in this study. Patients who missed the neutrophil and lymphocyte records or chronic hematological disorder were excluded.
The main objective of the present study is to explore whether NLR as a prognostic factor for the assessment of disease severity and fatal outcome in patients with severe coronavirus disease 2019 (COVID-19). Individuals with an arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio of less than 300 mm Hg, respiratory frequency greater than 30 breaths/min, or lung infiltrates greater than 50% on room air at sea level were defined as severe patients.

Data were collected from patients who were cured and discharged or who died without a cure. Confirmation of COVID-19 was diagnosed according to the Indian Council of Medical Research (ICMR). Before starting the study, approval from the Research Ethics Committee of Bundelkhand Medical College Sagar was obtained.
Throat swab samples were collected for extracting 2019-nCoV RNA from patients suspected of having the 2019-nCoV infection. The reverse transcription-polymerase chain reaction assay was performed at the Virology Lab at the Department of Microbiology. These diagnostic criteria are based on the recommendations of the ICMR.
Routine blood examinations, i.e., complete blood count done for all critical patients at admission, were collected from records. The NLR was calculated from the complete blood counts of these patients and analyzed for any association with the severity and prognosis of the disease.

Statistical Analysis

IBM SPSS ver. 25 software was used to do the data analysis. The tables were prepared using cross-tabulation and frequency distribution. Graphs were created using the PRISM program. The mean and standard deviation were used to convey quantitative data, whereas the number and percentage express categorical data. The means were compared using one-way ANOVA. The percentages were compared using the Chi-Square test. The odds ratio was calculated using multiple regression analysis. The degree of significance was set to 5%.

3. RESULTS

A total of 359 patients were admitted to the intensive care unit after being diagnosed with COVID19. COVID19 claimed the lives of 92 of these patients. Non-survivors were much

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older than survivors (52 years), with a median age of 68 years. Male sex was more prevalent in non-survivors than in survivors.

In the laboratory examinations, the total leucocyte count was higher in non-survivors and males in the age group of 60-70 years. Patients with NLR >3.5 were associated with a more severe form of the disease, a longer duration of stay in ICU, and greater mortality. In this study, we found an association between NLR and the clinical outcomes in patients of COVID-19.

Table 1: Showing baseline characteristics of survivors and non-survivors

Variables	**Survivors (n=267)**	**Non-survivors (n=92)**	**P-value**
Age (years)	52	68	0.004
Male, n (%)	46 (17.22)	69 (75)	0.012
WBC, 10 × 9/L	6.05 (4.70-7.80)	4.22 (10.68-17.58)	0.001
NLR	4.10 (2.42-7.88)	48.26 (26.68-71.46)	<0.001

Figure 1: Distribution of patients according to their NLR level and survival status

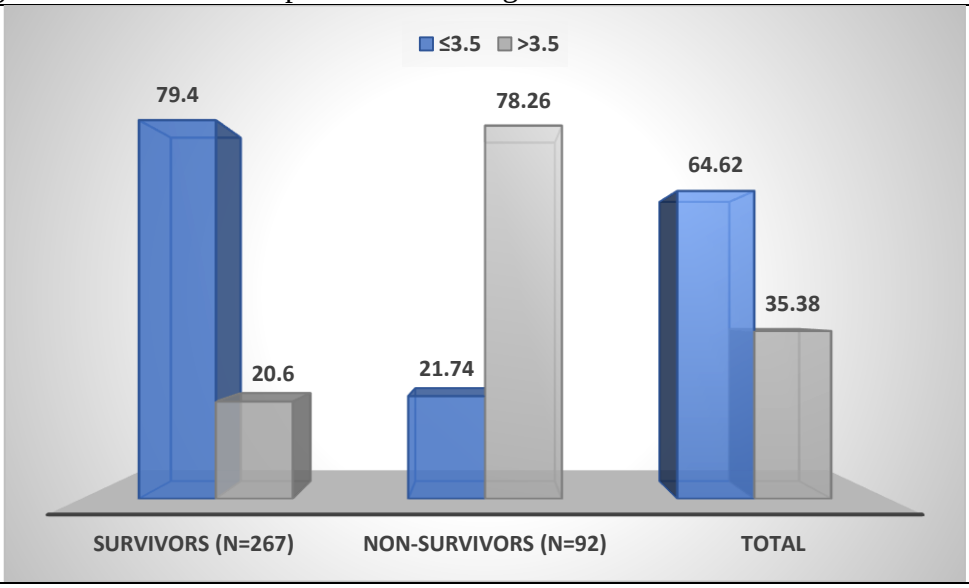

Table 2: Comparing clinical characteristics between low and high NLR

Variables	**Low NLR (≤3.5)**	**High NLR (>3.5)**	**P-value**
NLR	3.46 (2.02-6.12)	24.0 (13.56-48.82)	<0.001
Number of deaths, n (%)	14 (6.03)	78 (61.42)	<0.001
Length of stay	13 (7-17)	15 (10-21)	<0.001
Age, years	60 (46-70)	62 (55-74)	0.002
Male, n (%)	14 (6.03)	78(61.42)	<0.001
WBC, 10 × 9/L	5.4 (4.2-7.0)	11.2 (7.6-14.9)	<0.001

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Table 3: Showing odds ratio for NLR taking cut off of 3.5 as a predictor of in-hospital mortality

Variable	OR	95% CI	P-value
NLR >3.5	32.422	2.662-412.182	0.002

4. DISCUSSION

Although COVID-19 pneumonia is not life-threatening in its early stages, critical patients developed severe pneumonia and abrupt respiratory failure after 7–14 days.COVID-19-infected patients were primarily old and had comorbidities when they became seriously ill or died. The study's sick severely patients were all over the age of 50. The disease's progression was linked to a decrease in lymphocyte count. It is unknown why lymphopenia is related to severe illness. COVID-19 may act on T lymphocytes, and T lymphocyte destruction significantly contributes to the patient's condition deterioration. Additionally, critically ill patients frequently have a high leukocyte count because damaged cells induce innate inflammation in the lungs, which is primarily driven by pro-inflammatory macrophages and granulocytes. The NLR was a widely used marker for determining the severity of bacterial infections and the prognosis of patients with pneumonia and tumours.[3, 4]

The MuLBSTA score, which consists of six markers, has previously been shown to early warning of viral pneumonia mortality. This score is influenced by age, smoking history, hypertension, bacterial co-infection, lymphopenia, and multilobular infiltration. The CURB-65 score was widely used to assess 30-day mortality in individuals with community-acquired pneumonia. The purpose of this study was to determine whether NLR is a predictive factor for disease severity and death outcome in individuals with severe COVID19.[2,3,4]

The primary conclusion of this study is that there is a strong correlation between NLR and clinical outcomes in patients with COVID-19. NLR has various advantages over other markers of systemic inflammation in the hospital clinical routine, including its ease of measurement and low cost.[5]As a caution, two more accurate COVID-19-specific prognosis scores were recently described.

In this investigation, we chose a cut-off level of 3.5 for the NLR. According to our data, a high NLR is a significant predictor of hospital mortality in patients with COVID-19. NLR is a highly predictive marker for systemic inflammation and infection that exceeds absolute leukocyte, lymphocyte, and neutrophil counts. Additionally, it is an effective biomarker for predicting bacterial illness, particularly pneumonia.[6]Additionally, NLR has been demonstrated to help predict outcomes in individuals with cardiovascular disease and solid tumour malignancy.[7]

Additionally, mounting clinical evidence supports the utility of NLR as a predictor and prognostic indicator for severe COVID-19.[6,8,9]

In a prior study, 61 patients with COVID-19 infection were included in the derivation cohort, and 54 patients were included in the validation cohort. The predictive factor for critical illness was determined using LASSO regression analysis. A nomogram based on non-specific laboratory signs was devised to forecast the possibility of severe disease. The neutrophil-to-lymphocyte ratio (NLR) was demonstrated to be an independent risk factor for critical illness in individuals with COVID-19 infection in this investigation. The calibration curves were well-fitting, and the decision and clinical impact curves demonstrated that the NLR provided a significant standardized net benefit. In the derivation cohort, the NLR had an area under the receiver operating characteristic of 0.849 (95 percent confidence interval [CI] 0.707 to 0.991). The validation cohort had an area under the receiver operating factor of 0.867 (95

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percent CI 0.747 to 0.944). As part of the trial, a COVID-19 pneumonia management protocol was established. The author found that NLR is a predicting factor for patients infected with COVID-19 who are likely to develop a severe illness at an early stage. Patients over the age of 50 with an NLR of 3.13 are at an increased risk of developing severe disease and should have immediate access to an intensive care unit if necessary.[3]

Elderly males with chronic comorbidities associated with weakened immune functioning are more prone to contract COVID-19. Atypical signs and symptoms and many comorbid diseases are common in elderly patients, resulting in delayed diagnosis and treatment, as well as mortality. Indeed, these patients face a greater risk of COVID19 infection, hospitalization, intensive care unit admission, and in-hospital death than young people.[6]

Physicians may find it time-consuming and challenging to conduct a comprehensive assessment of these elderly patients. Nonetheless, NLR is a biomarker that combines two WBC subsets that suggest the existence of two antagonistic immunological pathways. It denotes a conveniently available objective metric that can be computed from differential WBC counts, is more stable for measurement than individual WBC counts, and is less affected by factors that affect individual cell counts.[10]

The NLR is beneficial for physicians since it helps them understand the severity of COVID19. Therefore, a high-calculated NLR may aid in identifying outcome risk, the necessity for close clinical monitoring, and the requirement for immediate effective therapy.[9]Samaras et al. proposed a targeted approach for high-risk patients.[11]Our findings could potentially aid in the early detection of older patients at a higher risk of COVID19-related problems.

NLR is a low-cost marker compared to cytokines, as blood counts are often utilized in clinical practice. As a result, NLR is a useful systemic inflammation marker for COVID-19 infection screening and maybe an early predictor of a poor outcome. Increased neutrophils indicate a more severe inflammatory response, but decreased lymphocytes indicate a more severe immunological imbalance in COVID-19.[8]

The prognostic effect of NLR on disease severity was reported in thirteen studies, including 1579 people. Sensitivity (SEN), specificity (SPE), and area under the curve (AUC) were, respectively, 0.78 (95 percent confidence interval 0.73–0.83), 0.78 (95 percent confidence range 0.73–0.83), and 0.85 (95 percent confidence interval 0.81–0.88). The prognostic effect of NLR on death was demonstrated in eleven studies involving 2967 participants. The total SEN, SPE, and AUC values were 0.83 (95% confidence interval [CI] 0.75–0.89), 0.83 (95% CI 0.74–0.89), 0.90 (95% CI 0.87–0.92), and 0.90 (95% CI 0.87–0.92). The author concluded that NLR was associated with favorable prognoses for disease severity and mortality in patients infected with COVID-19. NLR evaluation can assist doctors in identifying potentially severe cases early, commencing effective care promptly, thereby reducing COVID-19 overall mortality.[12]

Previous coronavirus research revealed that lymphocyte depletion might be related to the virus's immune evasion mechanism. Nowadays, it has been hypothesized that lymphocyte loss may be associated with either direct virus infection of lymphocytes or antiviral myelosuppression.[13]

We adopted a cut-off of 3.5 in the current study and discovered that patients with NLR >3.5 had a more severe form of the disease, required a longer stay in the intensive care unit, and had a higher mortality rate. The amount of NLR upon admission may be an independent predictor of COVID-19 prognosis, not only for death but also for disease severity. Additionally, patients who did not have extra risk factors had a better predictive value. NLR has the potential to assist physicians in rapidly identifying high-risk patients and intervening

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appropriately, hence reducing the rates of severe disease and mortality. 14 According to a Chinese study to define the NLR cut-off value for disease progression, NLR>3.3 is independently associated with more severe COVID-19 (HR: 2.46, 95 percent CI 1.98–4.56). Additionally, NLR>3.3 was associated with a shorter survival duration than NLR 3.3 (6.3 days vs. 13.5 days for NLR >3.3). 15 Another Chinese study, conducted at Hubei Provincial Hospital of Integrated Chinese and Western Medicine, included 32 mild and 31 severe cases and established an adequate cut-off of NLR >4.7 as an independent risk factor for severe COVID-19. Following that, an Italian study discovered that severe patients are also older and have a higher NLR than non-severe patients, hinting that NLR may be a useful indicator for early COVID-19 patient screening.[17]

Additionally, various chronic disorders may affect the circulating leukocyte count and thus the NLR. Qin et al. discovered that 44% of COVID-19-infected persons had at least one comorbidity, with hypertension, diabetes, cardiovascular disease, or chronic obstructive pulmonary disease most prevalent. On the other hand, a low NLR has been associated with a decreased risk of hospitalization in individuals with chronic illnesses such as renal disease and diabetes.

Because patients with chronic diseases can progress from mild to severe, NLR levels should be monitored beginning with hospitalization, as elevated NLR levels exacerbate symptoms and thus the mortality rate of COVID-19 patients, and timely intervention should be implemented to reduce rates of severe disease and mortality.[1]

This study has several important flaws that should be taken into account. There was a selection bias in the subjects because of the study's retrospective nature and the inability to demonstrate a direct link between NLR and death. As a result, we must conduct a prospective multicenter trial to verify our findings. Second, we could not look at the causes of specific deaths because our primary objective was overall inpatient mortality. We don't know what causes the association between NLR and mortality in the elderly. Comorbidities and medications that lower the neutrophil or lymphocyte count can also affect the NLR. This may be associated with death, but further study is needed to identify the specific pathways. Even though we only examined NLR at the time of admission, future NLR exams may reveal a pattern. NLR may have more mortality-specific if it is associated with repeated NLR. Even though our study only identified a correlation, this does not mean that our findings have any clinical significance. More research is required to find out if NLR has any connection to cause-specific mortality in the elderly.

5. CONCLUSIONS

In critically ill COVID19 patients, a high NLR was linked to poor outcomes. In COVID19 patients, NLR was an independent risk factor for all-cause in-hospital mortality. As a result, the NLR at admission could be used to proxy for illness severity. However, more external validation is required before the NLR may be used in clinical decision-making.

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