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Research Article

Neutrophil Lymphocyte Ratio

Estimation of neutrophil to lymphocyte ratio (NLR) in COVID-19 Patients in a Tertiary Care Center & determining its significance as a prognostic marker

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Introduction: The rapid spread and serious harm of COVID-19 makes it urgent to continuously improve and enrich its clinical diagnosis and treatment research. Using a simple test like NLR for assessing the risk of mortality and early identification of severe cases will help in preventing life-threatening complications in COVID-19 patients. **Objectives:** To study trends of NLR counts in COVID 19 patients and the correlation between NLR and COVID-19 severity. **Methods:** A total of 137 random subjects whose blood samples were collected on the day of admission, on the 3rd day and on the 6th day of admission were included in the study. NLR was calculated as simply neutrophils /lymphocytes and trends were studied. **Results:** An average of all three NLR counts for the patients revealed an overall decreasing trend in cases of survivors, whereas an overall upward trend was noted in the non-survivors. All of the patients admitted to the COVID ICU, that is those who had severe disease, showed a high NLR value of >3, in at least one of the three tests. **Conclusion:** The NLR was the most promising predictive factor for critical illness incidence of COVID-19 pneumonia. Early application of NLR will be beneficial for patient management and relief of medical resource shortage.

Keywords: NLR, COVID-19, Prognostic Marker, NLR Trends

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Introduction

In Wuhan, China, unknown etiology pneumonia's several cases were witnessed in December 2019[1]. A new beta-coronavirus from the throat swab sample of a patient was discovered through high-throughput sequencing by the "Chinese CDC (Center for Disease Control and Prevention)" on January 7th2020 [2].WHO ("World Health Organization") named this disease as "novel coronavirus disease-2019(COVID-19)".The rapid spread and serious harm of COVID-19 make it urgent to continuously improve and enrich its clinical diagnosis and treatment research. The latest research provides more precise data, highlighting key laboratory findings as well as also explaining the risk factors associated with mortality[3]. Various infectious diseases cause inflammation, and its significant role in the progression of various viral pneumonia including COVID-19 is supported by the emerging evidence [4]. The poor adaptive immune response is contributed by the serious inflammatory response, thus, resulting in immune response imbalance. Therefore, circulating biomarkers that can represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients [5]. Indicators of systematic inflammatory response include a lymphocyte-to-monocyte ratio (LMR), PLR (platelet-to-lymphocyte ratio), d-NLR (derived NLR ratio, neutrophil count divided by the WBC count result minus neutrophil count), neutrophil (N)-to-lymphocyte (L) ratio (NLR), and peripheral WBC (white blood cell) count which is being widely investigated as useful predictors for the prognosis of patients with viral pneumonia [6]. Using a simple test like NLR for assessing the risk of mortality and early identification of severe cases could help in preventing life-threatening complications and mortality. The present study will be based in a tertiary care hospital and will include the patients suffering from severe COVID-19 infection that is the patients who are admitted in the COVID –ICU, who have a saturation of less than 94% on room air. We aim to study trends of NLR counts in patients of COVID 19 and correlate the NLR with the severity of cases of COVID -19. We will attempt to determine the effectiveness of NLR on the clinical outcomes in patients of COVID-19, by collecting the data from laboratory-confirmed cases.

Materials and Methods

Study design: Retrospective, descriptive study

Study setting: Central Clinical Laboratory, Department of Pathology, Medical College, Tertiary Health Care Centre.

Duration of the study: June 2020 to June 2021.

Study participants: Sample Size – 137

Data collection procedure: A total of 137 random subjects who were admitted to the COVID ICU were included after they satisfied the eligibility criteria. The first blood sample was collected from the patients within 24 hours of their admission to the hospital, before the administration of antibiotics. Follow up samples were collected from the patients on the 3rd day (1st follow-up) and the 6th day (2nd follow-up) following the admission.

CBCs (Complete Blood Counts) were performed on the Ethylenediamine tetraacetic acid **(**EDTA) samples collected from the patient.CBCs were analyzed on the Beckman Coulter automated cell count analyzer with EDTA samples obtained from peripheral venipuncture of the patients.

NLR was calculated as simply neutrophils /lymphocytes and the trends were studied.

In case a patient was discharged or succumbed before all three tests, the trends were based on the two counts.

In case, the patient had just one NLR and was discharged or succumbed before the first follow up test, that patient was excluded from the study, as studying the trend was not possible.

Inclusion Criteria: All the known COVID-19 positive patients admitted in the hospital ICU were detected through RT-PCR.

Exclusion Criteria:

- COVID-19 negative patients.
- Patients on whom RT-PCR for COVID-19 was not performed.

Results

A total of 137 patients that were admitted to the COVID ICU (those who had saturation levels less than 94% on room air) were included in the study. The outcome was decided based on whether the patient was discharged or succumbed to the disease. Out of the 137 patients, 103 were males (75.2%) and 34 were females (24.8%). The average age was 55.8 years, the range being

22-85 years. There were 53 patients (38.68 %) above the age group of 60 years, 66 patients (48.17%) in the age group of 40-60 years and 18 patients (13.13%) whose ages were less than 40 years. The study had 70 patients (51.1 %) who were discharged and 67 (48.9%) patients who succumbed either due to COVID-19 or due to its complications. Out of the 67 patients who succumbed, 42 patients (62.69%) were in the age group of above 60 years, 21 patients (31.34%) were in the age group 40-60 years and 4 patients (5.97%) were less than 40 years of age. There were a total of 9 patients for whom just two counts of NLR (one on the day of admission and the other one on the 3rd day of admission) could be obtained. Out of these 9, 7 patients succumbed to the disease before their 2nd follow-up (on the 6th day of admission), whereas the other 2 patients, recovered and were discharged.

The NLR studies revealed 4 trends:

- Increasing trend (NLR count on admission <NLR count of first follow-up <NLR count of second follow–up).
- Decreasing trend (NLR count on admission > NLR count of first follow-up>NLR count of second follow–up).
- Increasing then decreasing (NLR count on admission <NLR count of first follow-up>NLR count of second follow–up).
- Decreasing then increasing (NLR count on admission >NLR count of first follow-up <NLR count of second follow–up).

Table 1: The number of patients in each of the trends:

Outcome of the patient	NLR Trends	Increasing trend	Decreasing trend	Increasing then decreasing	Decreasing then increasing	Total
Succumbed		36 (53.73%)	06 (8.955%)	06 (8.955%)	19 (28.36%)	67
Discharged		10 (14.29%)	39 (55.71%)	14 (20%)	07 (10%)	70
Total		46	45	20	26	137

An average of all three NLR counts for the patients revealed a decreasing trend in cases of survivors, whereas an overall upward trend was noted in the non-survivors.

Table 2: Average NLR counts:

Average NLR counts	The outcome of the patients	
	Succumbed	Discharged
NLR counts on admission (NLR1)	6.86	6.76
NLR counts during first follow-up (3rd day) (NLR2)	9.56	7.84
NLR counts during second follow-up (6th day) (NLR3)	11.85	6.80

The average NLR counts during each test were higher in the patients who succumbed as compared to the patients who were discharged.

Table 3: NLR values in patients who succumbed and got discharged:

High NLRseen in	Succumbed	Discharged	Total
NLR1 only	04 (2.92%)	15 (10.95%)	19 (13.87%)
NLR2 only	05 (3.65%)	13 (9.49%)	18 (13.14%)
NLR3 only	08 (5.84%)	04 (2.92%)	12 (8.76%)
NLR1 & NLR2	07 (5.11%)	22 (16.06%)	29 (21.17%)
NLR2 & NLR3	13 (9.49%)	03 (2.19%)	16 (11.68%)
NLR1 & NLR3	12 (8.76%)	02 (1.46%)	14 (10.22%)
NLR1,NLR2,NLR3	18 (13.14%)	11(8.03%)	29 (21.17%)
Total	67 (48.9%)	70 (51.1%)	137 (100%)

Our study reveals an increased NLR > 3, in at least one of the tests in all of the patients suffering from a severe infection of COVID-19.

According to the best of our knowledge, our study is the 1ststudy that compares the NLR trends in patients of COVID-19.

Table 4: Study of NLR trends:

NLR trend	DECREASING TRENDS		INCREASING TRENDS		Total
	Decreasing	Increasing then decreasing	Increasing	Decreasing then increasing	
Succumbed	06	06	36	19	67
Discharged	39	14	10	07	70
Total	Succumbed – 12 patients out of 67 patients (17.91%)		Succumbed – 55 patients out of 67 patients (82.09%)		137
	Discharged –53 patients out of 70 patients (75.71%)		Discharged - 17 patients out of 70 patients (24.28%)		

A study of trends of NLR revealed an interesting finding. Decreasing trends or overall decreasing trends (Increasing then decreasing) were observed in a larger number of survivors as compared to non-survivors. Also increasing our overall increasing trends (decreasing then increasing) were common in the non-survivors.

Discussion

NLR, a well-known marker of systemic inflammation and infection, has been studied as a predictor of bacterial infection, including pneumonia [7-9]. The results of our investigation are following the report published by Wang et al, who found that during the severe phase, several patients of COVID-19 reported decreasing lymphocyte count and increasing neutrophil count [10]. which indicated potential critical conditions as well as a serious disturbance in the internal environment of patients with severe infection.

Mo P et al investigated 155 patients with COVID-19 and found that refractory patients had a higher level of neutrophils in comparison with general patients. [11]

For systemic inflammation, NLR has been proposed as a novel biomarker, taking into consideration the levels of both neutrophils and lymphocytes. A large number of neutrophils raise the NLR. Decreasing the lymphocyte counts raises the NLR. Inflammation response may lead to an increase in neutrophils as well as to an acceleration of apoptosis of lymphocytes. Immunologic abnormalities and dysregulated immune cell responses are both thought to be significant contributors to the virus-induced illness severity.[12]Dysregulated immune cell responses cause an excessive inflammatory response, and maybe even death. Amongst the most significant contributing variables associated with the severity as well as outcomes of the MERS-CoV disease is the hematological change in leukocyte populations. [13]Leukocytosis characterized by increased neutrophils and monocytes was primarily observed in several MERS-CoV patients, and all the deceased patients showed rapid drops of lymphocyte counts [14, 15]. Studies showed that higher levels of inflammatory cytokines, chemokines and NLR in infected patients correlated with the severity of the disease, suggesting the involvement of cytokine storm in disease severity [16, 17]. These findings are consistent with our results. Systemic inflammation is closely associated with NLR, which has a quick and simple operation and predicts prognosis in various pathological conditions.[18, 19]

A new study has discovered that NLR has a greater prognostic value in community-acquired pneumonia (CAP) than conventional infection indicators, Such as neutrophil count, WBC count, and CRP. [20, 21]. It has also been seen that CD8+ and NK T-cell numbers are dramatically reduced in patients infected with SARS-CoV-2. In COVID-19 patients, with the increased expression of NKG2A, the CD8+ and NK T-cell functions were already exhausted. [22]

In a study of 61 COVID-19 patients with 17 patients under the category of severe disease, conducted by Liu J et al, it was showed that NLR was the most significant factor affecting the severe illness incidence and that it had significant predictive value. [23]. A study conducted on 245 patients by Liu Y et al concluded that patients with increased NLR had a higher risk for mortality during hospitalization. [24]

In a study of the immune responses in 452 COVID-19 patients by Qin C et al, it was found that an increase in NLR and lymphopenia were common among COVID-19 patients and were more evident in severe cases. [16]. In a study of 75 COVID-19 patients by Fu J et al, it was seen that the dynamic change of neutrophil to lymphocyte ratio (NLR) can discriminate severe COVID-19 cases from mild/moderate ones on consequent days after admission. [25]

This study has many noteworthy limitations. As mentioned previously, the data from a single clinical research facility was used to produce the findings of this report. Secondly, it was retrospective and relied on data collected from case records. Therefore, we may have missed important information in some patients. Our research was hampered by differences in the definitions used for disease severity amongst other studies, the bias of which, we in part, mitigated through subgroup analysis. For more accurate and precise results, and wider generalizability of the findings, multicentric and larger sample size clinical studies are required to validate our results.

Neutrophils are a crucial part of the human immune system. Immune cells chemotactically gather rapidly near the infection site to both defend the body against infection and help regulate the immune system.[26] In the event of decreased neutrophil counts, the immune system is impaired, and therefore the body is more susceptible to infection. [27]The main effector cells of the human immune response are the lymphocytes. The

Number of lymphocytes in the body is closely related to the body's immunity and defence system against pathogenic microorganisms and is negatively correlated with the degree of inflammation.[28] NLR encompasses two types of leukocyte subtypes, reflecting the balance of the body's neutrophil and lymphocyte count levels and the degree of systemic inflammation. More accurately, it reflects the balance between the severity of the inflammation and the body's immunity status, [29]. and is thus considered an important marker of systemic inflammatory response. This information leads us to conclude that there may be considerable systemic inflammation during COVID-19 infection and that NLR could play an important role in the prediction of the severity of infection.

The outbreak of COVID-19 is caused by the SARS-CoV-2 virus infection. The spectrum of disease spans from sickness with no symptoms to a serious illness and death. It has been established via clinical observation that certain individuals with mild illness can rapidly progress to severe disease with a high death rate. It is not understood exactly what causes the pathogenic process. Researchers suggest that the development of ARDS and the subsequent multi-organ failure is connected to the release of large quantities of cytokines as a result of the "cytokine release storm" and could be the reason for the sudden aggravation of the condition [12]. The concept of an inflammatory factor storm was first proposed in 1993.[30]. In 2003, when the SARS-CoV virus infection caused ARDS and multiple-organ failure, resulting in an exceedingly high rate of mortality, the underlying pathology of inflammatory factor storm gradually attracted the attention of the medical community.[31]. SARS-CoVand SARS-CoV-2 are extremely closely related viruses. Both these viruses belong to the β-CoV coronavirus family, [32]. and in terms of genetic characteristics both possess sequence similarity of 79.5%,[33]. and with regards to clinical manifestations, it is easy to progress to ARDS and multiple-organ dysfunction in infections caused by these viruses. Therefore, based on the close similarities between the two viruses, when clinical conditions of patients of COVID-19 change from mild to critical, this may be related to the inflammatory storm. In a study by Li et al, it was found that higher plasma levels of inflammatory markers like TNFα, MIP1A, MCP1, IP10, GSCF, IL10, IL7, and IL2 were seen in the patients with COVID-19 pneumonia admitted to ICU.[34]. This is due to an apparent inflammatory response in the patient's body.

In the early stage, there is no severity in COVID-19 pneumonia, however, on days 7–14 of the disease progression, the situation of critical patients deteriorates and they enter into an acute respiratory failure and severe pneumonia state. Mostly, the patients of COVID-19 infection who had a critical course of an illness or passed away were of old age and had other comorbidities.[35].The human immune response is created by lymphocytes triggered by viral infections.[36]Further, cellular immunity is suppressed by systemic infections. The novel coronavirus may mainly act on lymphocytes, especially T lymphocytes.[37]In COVID-19 patients, there is a decrease in NK cells, B cells, CD8+ T cells, CD4+ T cells, and total lymphocytes, and severe cases had lower levels of these cells than mild cases.[36,38]. Thus, NLR is increased by the CoV-induced inflammation-related lymphopenia.

In patients with different cardiovascular illnesses, the NLR, an inflammatory marker, which is measured by the neutrophils count/lymphocytes count ratio, can be used to predict the probability of mortality [39, 40]. Moreover; NLR has been identified in a meta-analysis as a prognostic biomarker for patients with sepsis [41].NLR is an independent risk factor for severe disease for patients of COVID-19 [42–44]. NLR elevation may be due to dysregulated expression of inflammatory cytokines, an aberrant increase of pathological low-density neutrophils and the upregulation of genes involved in the lymphocyte cell death pathway, caused by the mechanism of SARS-CoV- 2 infection [45].

Conclusion

The NLR was the most promising predictive factor for critical illness incidence of COVID-19 pneumonia. The early application of NLR will be beneficial to patient classification, management and relief of medical resource shortage.

Studying the trends of NLR may also help in predicting the risk for mortality in severely ill patients.

What does this study add to existing knowledge?

A high NLR count was seen in the patients admitted to the COVID ICU (that is had a severe disease). Decreasing trends or overall decreasing trends (increasing then decreasing) were observed in a larger number of survivors as compared to non-survivors. Also increasing or overall increasing trends (decreasing then increasing) were common in the non-survivors. Thus, the study of the NLR trends can help in predicting the outcome of severe patients.

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