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# The role of the neutrophil-lymphocyte ratio in predicting poor outcomes in COVID-19 patients

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**The role of the neutrophil-lymphocyte ratio in predicting poor outcomes in COVID-19 patients**

Raymond Farah et al., Neutrophil-lymphocyte ratio in COVID-19

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**ABSTRACT**

**Background:** This study examines how the neutrophil-lymphocyte ratio (NLR) predicts coronavirus disease 2019 (COVID-19) hospitalization, severity, length, and mortality in adult patients.

**Methods:** A study was done using a retrospective, single-center, observational design. A total of 400 patients who were admitted to the Ziv Medical Center (Safed, Israel) from April 2020 to December 2021 with a confirmed diagnosis of COVID-19 through RT-PCR testing were included in the analysis. Two complete blood count laboratory tests were conducted for each patient. The first test was administered upon admission to the hospital, while the second test

was conducted prior to the patient's discharge from the hospital or a few days before their death.

**Results:** Four hundred patients were included in the study, 206 males (51.5%) and 194 females (48.5%). The mean age was 64.5 ± 17.1 years. In the group of cases, there were 102 deaths, and 296 survivors were recorded, with a fatality rate of 25.5%. The median NLR was 6.9 ± 5.8 at the beginning of hospitalization and 15.1 ± 32.9 at the end of hospitalization ($p < 0.001$). The median length of hospital stay was 9.4 ± 8.8 days. NLR in the fatality group was 34.0 ± 49.9 compared to 8.4 ± 20.4 in the survivor group ($p < 0.001$). Comparison between the NLR at the time of admission of the patient and before discharge/death was 6.9 ± 5.8 vs. 15.1 ± 32.9 ($p < 0.001$).

**Conclusions:** The analyses conducted revealed a statistically significant correlation between the NLR and the severity, mortality rates, and the duration of hospitalization. The consideration of NLR should commence during the initial phases of the disease when assessing individuals afflicted with COVID-19.

**Keywords: COVID-19, SARS-CoV-2, severity, neutrophil-lymphocyte ratio (NLR)**

## INTRODUCTION

The etiological agent accountable for the global pandemic, initially detected in Wuhan, China, in 2020, has been identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1, 2]. Although most patients displayed mild to moderate symptoms and achieved a favorable outcome, a minority of individuals diagnosed with coronavirus disease 2019 (COVID-19) demonstrated severe manifestations such as pneumonia, pulmonary edema, coagulation abnormalities including disseminated intravascular coagulation, acute respiratory distress syndrome, septic shock, or multiple organ failures [3–6]. The severity of these instances required patients to be admitted to the intensive care unit and, in certain cases, led to fatalities [7]. The development of a severe manifestation of COVID-19 primarily occurs as a result of hyperinflammatory responses [8–11]. The process of viral replication occurring at an accelerated rate, resulting in cellular harm and the initiation of inflammatory reactions, serves to attract macrophages and monocytes [12, 13]. These immune cells then proceed to generate cytokines and chemokines, which in turn give rise to cytokine storms and heightened immune responses. The inflammatory response can serve as a means to evaluate the extent and intensity of the disease [11, 14]. The inflammatory response can be used as a diagnostic tool to determine the severity and scope of COVID-19. Serum lactate dehydrogenase [15], ferritin

[16], C-reactive protein [17], D-dimer [18], and interleukin-6 are representative examples of inflammatory markers that have demonstrated a robust association with elevated susceptibility to severe COVID-19 [15, 16, 19]. Neutrophils and lymphocytes are integral cellular constituents of the immune system, and their involvement in the pathophysiology of various diseases is of paramount importance [20, 21]. Monitoring the levels of these cells in the bloodstream can yield valuable insights into the health status of patients who are admitted to the hospital. Elevated concentrations of neutrophils in the circulatory system can function as a reliable marker for increased oxidative stress, particularly in populations that are more vulnerable, such as critically ill patients afflicted with COVID-19 [22, 23]. The severity of the disease is exacerbated by the excessive presence of reactive oxygen species, which contribute to lung tissue damage, thrombosis promotion, and impairment of red blood cell functionality [24, 25]. A positive correlation has been observed between reduced concentrations of lymphocytes and increased levels of oxidative stress. This phenomenon can be attributed to the production of different anti-inflammatory cytokines, including interleukins and interferon-gamma, by lymphocytes [26].

The neutrophil-lymphocyte ratio (NLR) is a recognized marker for assessing inflammatory responses. It is calculated by dividing the count of neutrophils by the count of lymphocytes, typically obtained from a peripheral blood sample [27]. Extensive research has established the NLR as a supplementary indicator for critical care-associated disorders and systemic diseases. Studies have shown that a high NLR is an efficient predictor of an unfavorable outcome [28, 29]. To maximize the utilization of resources, it is imperative to proactively identify individuals who are more likely to develop severe illnesses. Early identification of warning signs and red flags associated with severe COVID-19 is of paramount importance in facilitating timely intervention, potentially leading to reduced mortality rates, improved recovery rates, and shortened hospitalization periods. The NLR parameter, derived from blood count analysis, holds potential as a noteworthy indicator for the purposes of diagnosing and managing risk stratification. Consequently, the objective of this study is to assess the predictive significance of the NLR in ascertaining the severity, length of hospital stay, and fatality rates among adult patients admitted to the hospital due to COVID-19 by using retrospective data.

## METHODS

The study was with the Declaration of Helsinki, and ethical approval to proceed with this study was granted by the Hospital Ethical Review Board (HERB) of the Ziv Medical

Center (Safed, Israel; Approval no. 0061-20-16). The requirement for written informed consent from patients was waived because of the study's retrospective nature.

We included 400 patients who were admitted to the hospital with a diagnosis of COVID-19 R between April 2020 and December 2021. Patients in the study had to be 18 years of age or older and were admitted to the hospital with a confirmed COVID-19 diagnosis by testing positive for SARS-CoV-2 using RT-PC. They also had to have a complete blood count (CBC) done within 24 hours of being diagnosed and two CBC lab tests, one when they were admitted to the hospital and the other before they were discharged or a few days before they died. Exclusion criteria included COVID-19 patients who were managed on an outpatient basis or pediatric patients. Clinical information was collected during hospitalization by attending physicians. Patient data, including demographic, clinical, and laboratory data, laboratory examinations, and outcomes were collected from electronic medical records and analyzed. Intrahospital mortality was defined as all-cause mortality during hospitalization.

Venous blood samples were obtained within 24 hours after admission to the Emergency Medicine Department. As an institutional protocol, blood withdrawn from the patients was collected into an EDTA-containing tube for complete blood count evaluation and into a dry tube for biochemical analysis. All the samples collected for analysis were studied within half an hour of the blood withdrawal. White blood count and differential counts were measured. An automatic Coulter analyzer (Beckman Coulter LH 750, Fullerton, CA) was used to count the total number of white blood cells, neutrophils, monocytes, lymphocytes, eosinophils, hemoglobin, platelets, and monocytes.

For categorical variables, summary tables provided the sample size, and absolute and relative frequencies. For continuous variables, summary tables provided the arithmetic mean (M) and standard deviation (SD). Pearson's chi-squared was applied to test the correlations for the categorical parameters. Pearson correlations provided the power of the correlation between the continuous variables. Multiple logistic regression was applied to test the difference between the last status and correlations between the study parameters examined, with adjustments for confounders. A two-sided p-value of 0.05 or less was considered statistically significant. Statistical analysis was performed by using SPSS Statistics, Version 24.0. (SPSS, Inc., Chicago, IL, USA) and Prism software version 8 (GraphPad software, Inc.).

**RESULTS**

A total of 400 patients who were hospitalized with COVID-19 and had a CBC done within 48 hours of diagnosis were included in this study. In total, 206 (51.5%) of the study

participants were males and 194 (48.5%) were females. The mean age was 64.5 ± 17.1 years (range 20–105 years). Full patient characteristics are included in Table 1.

According to CBC analysis, the average total leucocyte count of the study population was 8.4 ± 12.6/μL at the beginning or hospitalization and 11.1 ± 11.5/μL near the end of hospitalization, and the mean platelet count was 207 ± 94/μL.

The mean absolute lymphocyte count (ALC) was 1.6 ± 6.9/μL at the beginning of hospitalization and 2.2 ± 10.4/μL near the end of hospitalization ($p < 0.001$). The mean absolute neutrophil count (ANC) was 5.7 ± 3.6/μL at the beginning of hospitalization and 8.4 ± 6.9/μL near the end of hospitalization ($p < 0.001$). The median NLR was 6.9 ± 5.8 at the beginning of hospitalization and 15.1 ± 32.9 at the end of hospitalization ($p < 0.001$; Table 2).

The median length of hospital stay was 9.4 ± 8.8 (range 1–64 days). There were 102 (25.5%) mortalities during the study period, 296 patients survived the illness (74%), and data were missing for the other 2 patients (Table 3). This analysis showed that there was a significant association between NLR and length of hospital stay and mortality. According to the results, we took the second CBC analysis towards the end of the hospitalization period and made a correlation between NLR and the final status of the patient; this analysis showed that the mean NLR in the fatality group was 34.0 ± 49.9 compared to 8.4 ± 20.4 in the survivor group, which is statistically significant with $p < 0.001$. This supports our hypothesis, which indicates a correlation between higher NLR and severity of COVID-19 infection and mortality (Table 4).

The following table shows a comparison between the NLR at the time of admission of the patient (Time 1) and before discharge/death (Time 2). According to this analysis, at TIME 1 the average of NLR was 6.9 ± 5.8, while at TIME 2 the average NLR was 15.1 ± 32.9, which is statistically significant ($p < 0.001$; Fig. 1).

## DISCUSSION

COVID-19 is a highly contagious illness that poses a significant and ongoing risk to global public health. The phenomenon under discussion has exhibited rapid proliferation across numerous nations globally. While most patients experience a self-limiting and mild illness, those who develop severe or critical cases exhibit a less favorable prognosis [30]. The binding of SARS-CoV-2 to the ACE2 receptors in the alveoli results in the initiation of an inflammatory response, thereby triggering the release of inflammatory factors [31]. This, in turn, activates the immune system, ultimately culminating in the occurrence of a cytokine storm. A multitude of theoretical frameworks have been posited regarding the immune

response of NLR in the context of COVID-19 infection. Neutrophils are integral to the activation of the immune system through the release of reactive oxygen species, which possess the capability to induce damage to cellular DNA [32]. Consequently, this impairment promotes the liberation of viruses from the cells that have been infected. Following this, the viruses that have been released become the focus of immune responses mediated by antibodies. Moreover, neutrophils play a crucial role in the initiation of the production of various cytokines and effector molecules. Nonetheless, it is important to note that while the virus itself activates lymphocytes, systemic inflammation, specifically high levels of interleukin 6, lowers the number of lymphocytes and weakens cellular immunity [33]. Hence, an elevated NLR is suggestive of the extent of inflammation. The findings of our study indicate a statistically significant correlation between disease severity and the mean NLR. Specifically, as the severity of the disease increases, there is a notable increase in the NLR value. Notably, individuals with mild cases of the disease exhibit the lowest NLR values, and they tend to recover from the illness with a shorter duration of hospitalization. Based on our research, the NLR demonstrated reliability in accurately predicting the onset of severe and critical medical conditions at an early stage. Notably, the most substantial discrepancy in average NLR was observed between the group of patients who recovered and those who died from the disease. In support of these findings, a meta-analysis of 20 studies conducted in China demonstrated that the NLR serves as an independent prognostic marker for distinguishing between severe and non-severe cases of COVID-19 [34]. Moreover, the findings of a meta-analysis conducted on individuals diagnosed with COVID-19 indicated that increased levels of NLR upon admission were linked to a significantly elevated risk of mortality, with a relative increase of 174% [35]. Our findings provide further evidence supporting the hypothesis that NLR serves as an economical, reliable, and easily accessible indicator for predicting the severity and fatality of COVID-19. The marker in question is a simple and objective way to show which patients are more likely to get a serious illness and die. Still, it is important to note that even a lower mean NLR can be seen as a worrying rate when applied to different groups, like hospitalized patients. This is because there is a strong link between this NLR level and long-term, low-grade systemic inflammation, which includes diabetes, obesity, heart disease, and kidney and heart disease [36]. Moreover, it is important to highlight that there is a persistent upward trend in the population of individuals who have been vaccinated [37]. It is noteworthy that all currently available vaccines play a pivotal role in eliciting a substantial immune response, thus providing a means to efficiently control the infection [38]. The efficacy of vaccination in mitigating the transmission and impact of the

COVID-19 virus has been well established. The initiation of an immune response through vaccination can lead to 2 main outcomes: the production of antibodies by specialized cells and the formation of memory B and T cells, which are responsible for maintaining durable immunity against pathogens. After the completion of the entire immunization regimen, including the administration of the booster dose, it is expected that there will be a significant increase in the overall count of lymphocytes [39, 40]. This increase can be attributed to the stimulation of the maturation process of memory B and T cells. Therefore, it is possible that the NLR may not possess significant utility as a laboratory indicator in individuals who have undergone COVID-19 vaccination.

This study incorporates certain limitations that need to be acknowledged. Firstly, its scope is confined to a specific population and timeframe, which may influence the generalizability of the results. There is also the possibility of systematic and random errors affecting the data collected and its interpretation. Environmental and genetic variables, which may vary, also contribute to the limitations of this study. The methodology, although carefully selected, may have inherent imperfections impacting the conclusions drawn. The potential interference of other variables, not considered in the study, but which may affect the observed phenomena, should also be taken into account. Lastly, the interpretation of the findings is limited by current scientific knowledge and available technologies, underscoring the need for further research to validate and expand upon these results.

## CONCLUSIONS

The analyses conducted revealed a statistically significant correlation between the NLR and the severity of disease, mortality rate, and duration of hospitalization. The consideration of NLR should commence during the initial phases of the disease when assessing individuals afflicted with COVID-19.

## ARTICLE INFORMATION AND DECLARATIONS

**Data availability statement:** The data that support the findings of this study are available on request from the corresponding author (E.S.).

**Ethics statement:** The institutional review board of the Ziv Medical Center (Safed, Israel) approved the analysis (ethical committee ruling number: 0061-20-16.

**Author contributions:** Conceptualization, R.F., R.K.F., K.D.; methodology, R.F., R.K.F., K.D.; software, N.L.B.; validation, K.D., M.J., L.S.; formal analysis, K.D., N.L.B.; investigation, R.F., R.K.F., M.J.; resources, R.F., R.K.F., M.J.; data curation, K.D., N.L.B,

L.S; writing — original draft preparation, K.D., M.L.B.; writing — review and editing, all authors; visualization, N.L.B.; supervision, R.F., N.L.B., K.D., L.S.; project administration, R.F., R.K.F. All authors have read and agreed to the published version of the manuscript.

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**Conflict of interest:** The authors declare no conflict of interest.

**Supplementary material:** No applicable

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**Table 1.** Baseline characteristics of the study population.

| **Variables** | |
|---|---|
| Age [year] | 64.5 ± 17.1, 20–105 |
| Gender: | |
| Male | 206 (51.5% |
| Female | 194 (48.5%) |

Data are shown as mean ± standard deviation, range, and number (percentage).

**Table 2.** Laboratory parameters for two measurement periods.

| **Variables** | **N** | **Time 1** | **Time 2** | **P** |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Neutrophils | 386 | 5.7 ± 3.6 | 8.4 ± 6.9 | < 0.001 |
| Lymphocytes | 386 | 1.6 ± 6.9 | 2.2 ± 10.4 | < 0.001 |
| **NLR** | **385** | **6.9 ± 5.8** | **15.1 ± 32.9** | **< 0.001** |
| WBC | 386 | 8.4 ± 12.6 | 11.1 ± 11.5 | < 0.001 |
| Hemoglobin [g/dL] | 385 | 12.7 ± 2.1 | 11.6 ± 2.3 | < 0.001 |
| Platelets | 383 | 207 ± 94 | 246 ± 129 | < 0.001 |
| Eosinophils [%] | 386 | 0.48 ± 0.81 | 0.50 ± 0.84 | 0.497 |
| Monocytes [%] | 386 | 5.6 ± 4.0 | 4.9 ± 4.1 | < 0.001 |

NLR — neutrophil-lymphocyte ratio; WBC — white blood count

**Table 3.** Patient outcomes.

| **Variables** | |
|---|---|
| Days in hospital | 9.4 ± 8.8, 1-64 |
| Last status: | |
| Alive | 296 (74.0%) |
| Dead | 102 (25.5%) |
| Missing data | 2 (0.5%) |

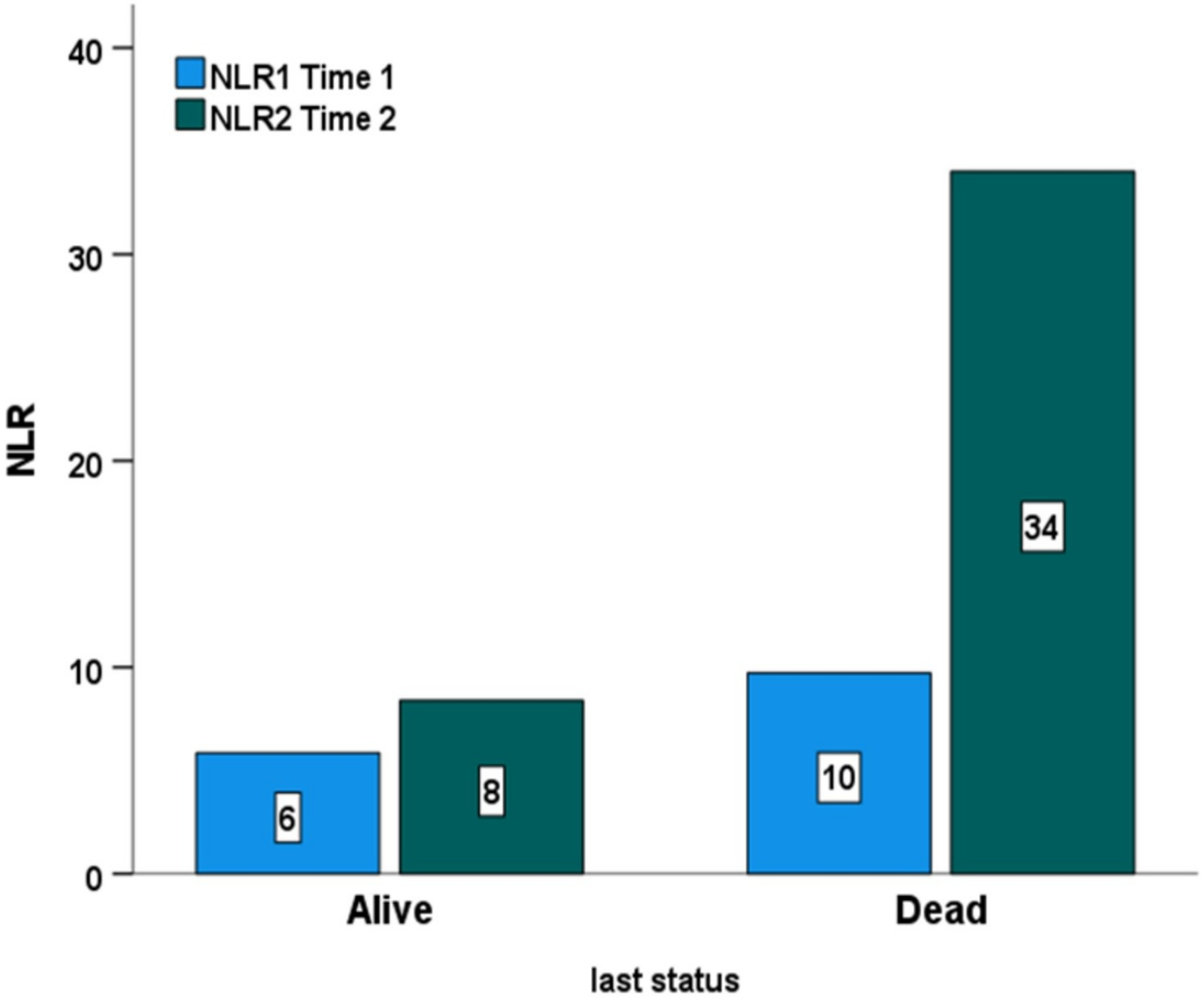
Data are shown as mean ± standard deviation, range, and number (percentage)

**Table 4.** Laboratory parameters according to last patient status.

| **Variables** | **Alive** | **Dead** | **P** |
|---|---|---|---|
| Neutrophils | 6.5 ± 4.5 | 13.6 ± 9.3 | < 0.001 |
| Lymphocytes | 2.6 ± 12.1 | 1.0 ± 1.3 | < 0.001 |
| **NLR** | **8.4 ± 20.4** | **34.0 ± 49.9** | **< 0.001** |
| WBC | 9.6 ± 11.6 | 15.5 ± 1.0 | < 0.001 |
| Hemoglobin [g/dL] | 12.2 ± 2.0 | 10.0 ± 2.5 | < 0.001 |
| Platelets | 269 ± 129 | 183 ± 103 | < 0.001 |
| Eosinophils [%] | 0.57 ± 0.88 | 0.30 ± 0.71 | < 0.001 |
| Monocytes [%] | 5.1 ± 4.4 | 4.1 ± 3.0 | 0.001 |

NLR — neutrophil-lymphocyte ratio; WBC — white blood count

**Figure 1.** Neutrophil-lymphocyte ratio level for 2 measurements with attention to patient status.


NLR1 Time 1
NLR2 Time 2
NLR
40
30
20
10
0
6
8
10
34
Alive
Dead
last status