

# Neutrophil to Lymphocyte Ratio Levels in Covid-19 Patients : A Literature Review

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## Abstract

Coronavirus Disease 2019 (COVID-19) declared a global pandemic by World Health Organization (WHO) in March 2020 after spread in many countries. Cases with this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present with various clinical sign and symptoms. Inflammation reported in covid-19 cases and play a major role in progression of covid-19. Neutrophil to Lymphocyte Ratio (NLR) is one of many biomarkers of inflammation which can be obtained from Complete Blood Count by dividing neutrophil and lymphocyte count. This change in NLR levels is an important biomarker to asses covid-19 severity and progression of disease. Previous articles found that NLR in covid-19 patients have a tendency to increased.

Keywords: COVID-19, Neutrophil-Lymphocyte Ratio

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## 1. Introduction

The COVID-19 disease first found at Wuhan, China in December 2019. The disease declared a global pandemic by World Health Organization (WHO) in March 2020 after spread in many countries. The pandemic affected people's lives not only their health but also economy and how peoples interact because of mobility restrictions. There have been 641,915,931 confirmed cases of COVID-19 globally reported as 6<sup>th</sup> December 2022 [13].

Severe acute respiratory syndrome corona virus type 2 (SARS-CoV-2) is a new type of corona virus causing COVID-19 that can infects human. Phylogenetic analysis suggested this virus clustered to the genus Betacoronavirus that includes the SARS-CoV and MERS-CoV which presents many similarities with this virus [1]. SARS-CoV-2 virus can be transmitted between people through airborne and droplet. Infected human presents various clinical signs and symptoms from mild symptoms to severe symptoms. Some of the symptoms are fever, cough, shortness of breath, wheezing, difficulty breathing, chills, myalgia, nausea or vomiting, and Acute Respiratory Distress Syndrome. Severe cases of COVID-19 infection reported causing death [2].

In the respiratory systems, SARS-CoV-2 targets ciliated bronchial epithelial cells and type 2 pneumocytes by attaches its receptor binding domain to the angiotensin converting enzyme 2 receptors. The human body reacts to this infection with innate immune response as a first line of immune defense that release some cytokines such as interferon-gamma, tumor necrosis factor alpha, interleukins 1, 2, 4, 7, 10, 12, 13, and 17. These processes could cause inflammation which reported play a major role in progression and development of COVID-19. Some cases of COVID-19 disease reported have severe to life-threatening disease because of the overactive immune response that more destructive than that SARS-CoV-2 infection itself which result damage to the organs. Uncontrolled and massive cytokine release by the innate immune system could be causes to what is termed as a cytokine storm. Cytokine storm contributes to hyperinflammation in the lungs and results in acute respiratory distress syndrome (ARDS). Cytokine storm also could cause multi-organ damage in COVID-19 that may lead to multi-organ failure followed by death [3].

NLR has been known as inflammatory biomarker in several patient populations. NLR can be obtained from Complete Blood Count by dividing neutrophil and lymphocyte count. Influx of neutrophils to the lungs occurred as innate immune response to respiratory infection. Previous studies found that release of anti-inflammatory cytokines can lead to lymphocytes apoptosis, resulting in lymphopenia [4].

This literature review aimed to review and explore the NLR levels in COVID-19 patients.

## 2. Discussion

### 2.1. NLR Levels and Inflammation in COVID-19 Cases

Normal NLR values are 1-3 [5]. Previous studies reported that NLR levels have a tendency to increase in COVID-19 patients. Some studies reported that inflammation play a major role in increasing levels of NLR in COVID-19 patients.

Study by Citu et al., 2022 reported that average NLR values significantly increased to  $9.18 \pm 6.7$  in 108 COVID-19 patients. Fois et al., 2020 also found that average NLR values in covid-19 patients in their study are significantly increases to 5,67. Study by Doganci et al., 2020 involving 397 COVID-19 patients also reported that there was a significantly increases of NLR values. They found that average values of NLR in their study was 5.02 and reported higher in non-survivors COVID-19 patients to 11.98. Another study by Y. Zhou et al., 2020 involving 304 patients also found that NLR values have more tendency to increase in COVID-19 patients. They found that NLR values in COVID-19 patients were increasing to 10.8 in average.

The increasing NLR values could be presented in COVID-19 patients because of inflammation that occurred in these patients.

### 2.2. NLR Values as a COVID-19 Prognosis Predictor

The prognosis of COVID-19 is often associated with the severity of symptoms. Inflammation that occurs in COVID-19 cases plays a major role in progression and development of COVID-19. Inflammation can be measured by using variety of biochemical and hematological markers. NLR is one of circulatory biomarker of inflammation that is cost effective and could be calculated easily by dividing neutrophil and lymphocyte count. Previous article researches reported that NLR values associated with the prognosis of many infectious diseases including COVID-19. As a biomarker of inflammation process that occurs in COVID-19 patients, NLR could be used to predict the prognosis of COVID-19 cases.

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Doganci et al., 2020 found in their study that NLR of non-survivors COVID-19 patients were significantly higher. They found there were 1.16-fold increases in risk of in-hospital death per unit increase in NLR. In a study by Fois et al., 2020 found that there was a significant difference between survivors and non-survivors COVID-19 patients. Non-survivors had significantly higher values of neutrophils and lower values of lymphocytes.

A retrospective cohort study by Liu et al., 2020 involving 245 COVID-19 patients reported that higher levels of NLR significantly associated with COVID-19 patient mortality. They suggested NLR could be an independent risk factor for the in-hospital mortality. A study by Tatum et al., 2020 was using Kaplan-Meier survival analysis and Cox regression models to found the effect of NLR on survival of COVID-19 patients. They used NLR at days 2 and 5 obtained from blood cell counts. The Cox regression analysis in this study revealed NLR on day 2 and 5 to be an independent predictor of in-hospital mortality.

A study in Romania by Citu et al., 2022 reported that NLR can be used as prognostic possibility for COVID-19 mortality with sensitivity 70% and sensibility 67%. This study was using Kaplan-Meier curve univariate cox regression and binominal logistic regression to find the association of inflammatory index and mortality. The mean survival time for COVID-19 patients above the NLR cutoff values was 18.2 days. In comparison, the mean survival time for COVID-19 patients with below NLR cutoff values was 28.3 days. The differences in survival time for patients above cutoff values compared to those below cutoff values were statistically significant ( $p < 0.001$ ). The univariate Cox regression analysis in this study found that NLR was independent predictors of in-hospital mortality. This study found that NLR had a high value as mortality predictors among COVID-19 patients. Yang et al., 2020 found that NLR related to the severity of SARS-Cov-2 infection and may indicate the outcome.

### 3. Conclusion

There has been a consensus regarding the increase of NLR levels in COVID-19 patients due to inflammation processes. The increase of NLR could lead to a more severe COVID-19 also could be as a predictor of COVID-19 mortality.

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