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**ORIGINAL RESEARCH** **CORONA EXPERIENCE**

# Comparison of total lymphocytes, neutrophils to lymphocytes ratio, and C-reactive protein in vaccinated and non-vaccinated severe COVID-19 patients

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## Abstract

**Background & objective:** SARS-CoV-2 virus caused acute respiratory illness called COVID-19 with rising case mortality rates. One of the preventive measures to arrest the spread of a contagious disease is the use of vaccines. We assessed the effectiveness of the inactivated vaccine (Coronavac) through three inflammatory parameters e.g., total lymphocyte count, neutrophil-lymphocyte ratio, and C-reactive protein (CRP), in severe COVID-19 patients.

**Methodology:** This study was an observational study with a retrospective cross-sectional design. The study was conducted in the Intensive Care Unit (ICU) of Hasan Sadikin Hospital Bandung, from January 2021 to December 2021. The data of total lymphocyte count, neutrophil-lymphocyte ratio, and C-reactive protein, was collected retrospectively from the medical record documents of 54 patients of COVID-19. The assessment was performed on severe COVID-19 subjects on the 7th day of illness. Data normality test was done using the Shapiro Wilk test. Study data were not normally distributed, and statistical analyses were performed using the Mann-Whitney test for numerical data and the Chi-Square test for categorical data.

**Results:** There were significant differences in inflammation parameters, e.g., total lymphocyte count, neutrophil-lymphocyte ratio, and CRP, between the two groups ($P < 0.0001$) and the subject outcome between two groups ($P < 0.0001$). Total lymphocyte count in severe vaccinated COVID-19 patients was higher than in non-vaccinated patients, while neutrophil-lymphocyte ratio and CRP were lower in vaccinated subjects. Mortality was also lower in the vaccinated patients compared to unvaccinated patients.

**Conclusion:** The inactivated vaccine (Coronavac) effectively reduces the mortality rate of severe COVID-19 patients based on inflammatory parameters including total lymphocyte count, neutrophil-lymphocyte ratio, and C-reactive protein.

**Abbreviations:** ACE: Angiotensin Converting Enzyme; ARB: Angiotensin Receptor Blocker; ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; CFR: Case Fatality Rate; COVID-19: Coronaviruses Disease 2019; CRP: C-Reactive Protein; IL: Interleukin; NLR: Neutrophil Lymphocyte Ratio; SPSS: Statistical Product Service Solution; TLC: Total Lymphocyte Count; TNF: Tumor Necrosis Factor; VEGF: Vascular Endothelial Growth Factor

**Key words:** COVID-19; C-Reactive Protein; Inactivated Vaccine; Neutrophil-Lymphocyte Ratio; Lymphocyte Counr; Vaccine

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# 1. Introduction

In March 11, 2020, WHO declared Coronavirus Disease-19 (COVID-19) as a pandemic.[1] As of August 22, 2021, the number of confirmed cases of COVID-19 in Indonesia, was 3,979,456 cases with a death toll of 126,372 instances or a CFR of 3.2%.[2]

The virus SARS-CoV-2 binds to alveolar epithelial cells and triggers the release of various cytokines such as interleukin 6 (IL-6), IL-10, tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), and other proinflammatory cytokines that can cause inflammation of cytokine storm. IL-6 is a cytokine that plays an essential role in B cell differentiation and antibody production.[3,4] Severe COVID-19 usually occurs about one week after the onset of symptoms.

A study related to laboratory results of COVID-19 patients showed an increase in neutrophils (> $0.7x10^3$/µL), lymphopenia (< $0.8x10^3$/µL), and an increase in CRP (> 4.75 mg/dL) which were the most important predictors of mortality in patients COVID-19. Hematologic abnormalities in COVID-19 patients are expected, including lymphopenia, CD4+ and CD8+ decline, thrombocytopenia, and leukopenia. Decreased lymphocytes and increased neutrophils are common in COVID-19 patients. The two values are compared by the neutrophil-lymphocyte ratio (NLR), which can be assessed from routine blood tests by dividing the absolute neutrophil count and absolute lymphocyte count. NLR can help identify high-risk COVID-19 patients where this marker can be used as an independent risk factor for death from COVID-19 in hospitalized patients. An increase in neutrophils indicates the intensity of the inflammatory response, while a decrease in lymphocytes indicates a damaged immune system.

Lymphopenia correlates with the severity of COVID-19 infection and has predictive value for clinical conditions. A retrospective cohort study involving 191 patients evaluating risk factors for death showed that the lymphocyte count in patients with improved COVID-19 was higher than in patients with worsening, with a lymphocyte ratio of $1.1\times10^9$/L versus $0.6\times10^9$/L ($P < 0.0001$). In COVID-19 patients who experienced improvement, it was found that the highest number of neutrophils and the lowest lymphocytes occurred on the 7th day after the onset of the disease and subsequently experienced improvement during hospitalization. Meanwhile, in patients who experience worsening, there is a high NLR and severe lymphopenia that persists until the patient dies.[5,6]

The inflammatory response can stimulate neutrophil production and accelerate lymphocyte apoptosis.[7] Recent studies have shown that high values of inflammatory cytokines, chemokines, and NLRs in COVID-19 patients correlate with disease severity. This proves the involvement of cytokine storm in the seriousness of COVID-19.[7] Another study showed that the NLR 3,328 had an excellent predictive value in predicting mortality in COVID-19 patients with a sensitivity of 100% and a specificity of 84%. The NLR value can also predict disease progression during hospitalization and is associated with length of stay in the hospital.

In COVID-19 patients, a series of inflammatory processes occur. Some evidence suggests that worsening in COVID-19 patients is closely related to dysregulation and excessive cytokine release. A study in Wuhan showed that patients who died from complications of COVID-19 had high CRP values. Elevated CRP is associated with the overproduction of inflammatory cytokines in severe COVID-19 patients. Cytokines play a role in fighting microbes, but if the immune system becomes hyperactive, it can damage lung tissue.[8,9] Other studies have shown that CRP is an independent risk factor in predicting the severity of COVID-19. When combined with CRP, the NLR value will increase the sensitivity to 77.5% and specificity 98%.[10] Another study showed that CRP levels were positively correlated with lung lesions and disease severity. CRP values > 40 mg/L at the time of hospital admission can indicate disease severity and increase the risk of death.[11]

Various efforts have been made by the government to break the chain of transmission of COVID-19 including vaccination program for all Indonesians.[2] One type of vaccine that has gone through phase 3 clinical trials is the vaccine - Coronavac.[4,12] In patients who have received the Coronavac, as many as two doses will produce antibodies that bind to the SARS-CoV-2 virus spike protein and reduce the risk of infection by 65.3% by reducing the occurrence of cytokine storms which can be assessed through total lymphocyte examination, NLR and CRP in COVID-19 patients. Based on the above background, we compared total lymphocyte count, NLR, and CRP values in vaccinated and unvaccinated severe COVID-19 patients. This research is expected to provide additional information to health workers and the public regarding the effect of the inactivated vaccine (Coronavac) in the era of the COVID-19 pandemic.

# 2. Methodology

This study was an unpaired comparative numerical, analytical observational study with a retrospective cross-sectional design. The data was collected retrospectively from the medical record documents of severe COVID-19 patients treated from January to December 2021 at Hasan Sadikin Hospital Bandung. Informed consent was not required for the study. This research was approved

 

**Box 1: Operational definitions**

| Variable | Operational definition |
|---|---|
| Inactivated Vaccination (Coronavac) | A COVID-19 vaccine containing the inactivated intact SARS CoV-2 virus and using aluminum hydroxide as an adjuvant. 2 doses (each dose 0.5 mL) were administered intramuscularly with an interval of 14 days between doses. |
| 1st sick day | On the first day, the patient experiences one or more symptoms of cough, fever, sore throat, and loss of smell. |
| 7th sick day | The 7th day from the time the patient feels the symptoms of the 1st sick day |
| Total Lymphocyte Count (TLC) | Absolute lymphocyte values obtained from blood examination on the 7$^{th}$ day of illness in the COVID ICU |
| Neutrophil-Lymphocyte Ratio (NLR) | The ratio of neutrophils to blood lymphocytes based on a complete blood count using automated hematologic analysis at Hasan Sadikin Hospital, which was obtained from the results of the differential division of the leukocyte count from the formula: NLR = neutrophils/lymphocytes with ratio units and obtained from a blood examination on the 7th day of illness in COVID ICU. |

by the Research Ethics Committee of Hasan Sadikin Hospital (No. LB.02.01/X.6.5/345/2021).

Convenient sampling technique was employed. The sample size was determined based on the sample size formula for unpaired numerical categorical analytical study and the minimum number of total samples was 48, with 24 samples in the vaccinated group and 24 in the unvaccinated group. The research data included age, sex, body mass index, comorbidities, and laboratory test values (TLC, NLR, and CRP) were taken on the 7$^{th}$ day of illness. The inclusion criteria in this study were: patients aged > 18 y, patients who had received two doses of COVID-19 vaccination with an interval of 14 days between the first and second doses or had never received the vaccine. COVID-19, and patients infected with COVID-19 within ≥ 28 days to ≤ 6 months after receiving the second vaccination dose. While the exclusion criteria in this study were: patients sick for more than 7 days on admission to ICU, and postoperative COVID-19 patients treated in the ICU. The drop-out criteria in this study were patients with incomplete medical record data.

Operational definitions are presented in Box 1.

Numerical data such as age, body mass index, TLC, NLR, and CRP are presented with median and range. Categorical data such as gender and comorbidities were coded and are presented as frequency and percentage.

**Table 1: Comparison of the characteristics of research subjects in the vaccinated and non-vaccinated groups**

| Variable | Severe COVID-19 Patients | | p-value |
|---|---|---|---|
| | Vaccinated Group (n = 24) | Non-vaccinated Group (n = 24) | |
| **Age (y)** | 55 (26-73) | 58 (35-69) | **0.464** |
| **Gender** | | | |
| -Male | 21 (87.5) | 16 (66.7) | **0.086** |
| -Female | 3 (12.5) | 8 (33.3) | |
| **Comorbids** | | | |
| -Hypertension | 12 (50.0) | 13 (54.2) | **0.773** |
| -Diabetes Mellitus | 15 (62.5) | 20 (83.3) | **0.104** |
| -Other comorbid | 13 (54.2) | 14 (58.3) | **0.771** |
| -None | 3 (12.5) | 1 (4.2) | **0.609** |
| **BMI (kg/m$^2$)** | 24.15 (19.50-41.83) | 25.39 (21.11-37.71) | **0.216** |

*Data given as Median (min-max) or n (%); P significance < 0.05; BMI: Body Mass Index*

 

**Table 2: Comparison of TLC, NLR and CRP values in the vaccinated and non-vaccinated groups**

| Variable | Vaccinated Group (n = 24) | Non-vaccinated Group (n = 24) | p-value |
|---|---|---|---|
| **TLC (/μL)** | 1205 (560 -2800) | 405 (160-780) | **0.0001**** |
| **NLR** | 3.58 (0.58-17.83) | 22.06 (2.51-48.90) | **0.0001**** |
| **CRP (mg/dL)** | 2.82 (0.32-20.22) | 18.79 (10.27-123.80) | **0.0001**** |
| Died | 4 (16.7%) | 15 (62.5%) | **0.001*** |

*Values of TLC, NLR and CRP are given as Median (Range); Sgnificance level < 0.05.*
*CRP: C-Reactive Protein; NLR: neutrophil lymphocyte ratio; TLC: total lymphocyte count*

Shapiro-Wilk test was used for the normality test. The significance test compares numerical data from 2

unpaired groups using Mann-Whitney Test. Statistical analysis for categorical data was tested by the chi-square test and Fisher's Exact test. The significance criterion used is the P = 0.05. The data obtained were recorded in a special form and processed through the Statistical Product Service Solution (SPSS) version 25.0 for Windows program.

# 3. Results

The study was conducted on 48 patients, divided into two groups: the vaccinated group and unvaccinated group, with 24 patients in each.

The median age was 57.50 y, with a higher percentage of male gender. The most common comorbidities were DM and hypertension. The median value of BMI was 24.95 kg/m$^2$.

The comparative median ages, the gender ratio, the most common comorbids in both groups are given in Table 1. The homogeneity test results in both study groups was based on age. There was no significant difference between gender, comorbidities, and BMI ($P \leq 0.05$; Table 1).

TLC was higher in the vaccinated group than in the unvaccinated group, and the NLR and CRP were lower than in the unvaccinated group, the differences being statistically significant ($P < 0.05$) as shown in Table 2.

The mortality was significantly less in the vaccinated group than the unvaccinated group ($P < 0.05$; Table 2).

# 4. Discussion

The results of this study indicate that the characteristics of the research subjects in the vaccinated and unvaccinated groups, regarding age, sex, BMI, and comorbidities (hypertension, diabetes mellitus, other comorbidities) had no significant differences ($P > 0.05$).

The severe COVID-19 was more frequent in the males. Preliminary evidence suggests that that men are generally, at greater risk for this disease. A study from China found that 58% of the patients were male.[13,14] In a previous study, it was found that plasma ACE-2 concentrations in men were higher than in women, reflecting higher tissue expression of this receptor for exposure to COVID-19 infection. This might be the reason men are more susceptible to COVID-19 compared to the women.[13,14] Men also carry a more significant burden of non-communicable diseases (e.g., stroke, heart disease, most of the cancers, and DM) which are risk factors for death in patients infected with COVID-19.[13,15] Postmenopausal women have a higher risk of suffering from COVID-19 than young ladies; this is due to the decreased amount of beta-estradiol, the primary estrogen in postmenopausal women.[13,14]

The incidence of severe COVID-19 in our study was higher in middle-aged (45-59 y) and elderly (60-74 y). At this age, the body's immune factors decrease progressively with a decrease in total B cells and T cells compared to the young people. Older adults generally have low-level chronic inflammations resulting from a combination of decreased immunity, persistent exposure to antigens, and increased proinflammatory cytokines

from senescent T cells and macrophages. The results are in agreement to that of an earlier study conducted at the Cipto Mangunkusumo National Hospital Jakarta in 2020, in which the majority of the patients was aged between 60-69 y (68%).[15]

BMI results revealed no significant difference ($P > 0.05$) between the two groups in our tudy. Previous research suggests that obesity increases the risk of severity of COVID-19, wherein the obese individuals have some changes in respiratory physiology, including decreased functional residual capacity and expiratory reserve volume, hypoxemia, and ventilation/perfusion abnormalities. In addition, obesity is characterized by an increased inflammatory state associated with a dysfunctional microadipose environment. Adipose cells are responsible for the secretion of proinflammatory adipokines, such as TNF- factor and IL-6. This can

 

damage the immune system, both in terms of innate and adaptive immune responses, as well as the lung parenchyma and bronchi. Hence, individuals with obesity are very susceptible to experiencing severe degrees of COVID-19 to death.[16]

Comorbidities in the vaccinated group were not significantly different from the unvaccinated group ($P > 0.05$). The most common comorbidities of confirmed severe cases and cases of death in this study were similar to the overall national data, e.g., hypertension and diabetes mellitus.[18] A multicenter study in China also revealed that hypertension and type 2 DM were the most common comorbidities in elderly patients with COVID-19.[15]A retrospective analysis of COVID-19 patients showed that the number of ACE-2 receptors in individuals with hypertension and type 2 diabetes was higher than in individuals without hypertension and type 2 diabetes. A pro-inflammatory condition characterized by an excessive cytokine response to infection makes COVID-19 patients fall to a severe or even critical degree and may even cause death.

A recent study reported that the number of receptors and ACE-2 regulation was substantially increased in patients with comorbid diabetes and hypertension who were treated with ACE inhibitors and angiotensin II receptor blockers (ARBs).[17] Increased expression of ACE-2 will facilitate COVID-19 infection and increase the risk of disease progression to become more severe.[17] DM, with an inflammatory response to infection causes the release of inflammatory mediators, especially TNF-α which can increase systemic insulin resistance and cell damage. As a result, patients with comorbid DM are more susceptible to infection with SARS-CoV-2.[18]

The median TLC value in the vaccinated group was significantly higher than the unvaccinated ($P < 0.05$). Recognition of antigens through vaccination will trigger a natural immune response and induce the release of pro-inflammatory cytokines that will stimulate an adaptive immune response. These antigens are processed into peptides and present to the adaptive immune response, namely T and B lymphocyte cells. T lymphocytes will activate specific B lymphocytes and memory to produce specific antibodies against the SARS-CoV-2 virus. Infected with COVID-19, the antibodies that have been formed will neutralize the SARS-CoV-2 virus antigen (Spike protein). In conditions where rapid viral replication occurs, which can trigger a robust immune response, the number of antibodies that have already been formed can be matched so that even if the individual falls to a severe degree, the number of exhausted T lymphocytes will decrease and prevent the cytokine storm from becoming severe.[19]

In unvaccinated ones, the number of new specific antibodies will be formed after the individual is infected with the SARS-CoV-2 virus. Here the speed of virus replication far exceeds the speed of formation of specific antibodies with the SARS-CoV-2 virus infecting T lymphocyte cells, so that the number of B lymphocytes activated by T lymphocytes to produce specific antibodies against the SARS-CoV-2 virus decreased in number accompanied by apoptosis of infected lymphocyte cells causing the lymphocyte levels to decrease greatly. This triggers a strong immune response leading to a cytokine storm, organ damage, ARDS, and death.[20,21,22]

The median NLR value in the vaccinated group was significantly lower than the unvaccinated group ($P < 0.05$). A study in China reported that NLR > 3.3 was independently associated with severe COVID-19.[10] In our study, patients of both groups suffered from severe COVID-19, which showed an average NLR > 3.3. Still, the NLR value in the vaccinated group was lower than the non-vaccinated group. COVID-19 infection will trigger a natural immune system response where the number of neutrophils will increase accompanied by apoptosis and lymphocyte cell exhaustion causing a decrease in the number of lymphocytes so that the NLR ratio also increased in the uninfected group.[6,20,21] In the vaccinated group, the antibodies formed will neutralize the SARS-CoV-2 virus antigen (Spike protein) so that viral replication can be balanced by the number of antibodies that have been developed, so that the number of lymphocytes undergoing apoptosis and reduced fatigue (the number of lymphocytes remained high) so that even though the patient drifted into severe degrees, the NLR value remained low.[22,23]

The Median CRP value in the group that received vaccination was significantly lower than the group that did not receive vaccination ($P < 0.05$). A previous study reported that CRP values > 4 mg/dL at the time of hospital admission could be used as an indicator of the severity of the disease. Both study groups were severe COVID-19, with an average CRP value of > 4 mg/dL.[11] In patients with severe COVID-19, a pathological host immune response occurred, especially in the lungs, characterized by cytokine storms. IL-6 plays a central role in the pathogenesis and correlates with an increase in CRP, a marker of IL-6 activation. the occurrence of cytokine storms and tissue damage leads to lower CRP production.[23] Other studies have reported reduced cytokine storms, inflammation, and viral load in the vaccinated population.[24]

In non-vaccinated individuals, viral replication cannot be suppressed because specific antibodies that have not yet formed cause hyperinflammation. Cytokine storm that occurs due to excessive inflammatory response results in increased CRP production and causes damage to target organs, especially the lungs, causing ARDS and death.[18,9,21]

 

In our study the number of deaths in the vaccinated group was significantly less than the non-vaccinated group ($P < 0.05$). Vaccination produced an immune response in the form of antibodies from the vaccine to neutralize the SARS-CoV-2 virus, thereby suppressing viral replication and preventing an excessive inflammatory response, thereby suppressing the occurrence of cytokine storms and tissue damage.[21,22] In the elderly, the reaction caused by the vaccine to produce antibodies is weaker than at a young age. This is indicated by the low number of antibodies in the elderly so that the elderly are more at risk of suffering from severe COVID-19 and death.[13,15]

# 6. Conclusion

We conclude that the inactivated vaccine (Coronavac) effectively reduces the mortality rate of severe COVID-19 patients based on inflammatory parameters (total lymphocyte count, neutrophil-lymphocyte ratio, and C-reactive protein). Total lymphocyte counts were higher in vaccinated severe COVID-19 patients. Meanwhile, the neutrophil-lymphocyte ratio and C-reactive protein values were lower in vaccinated severe COVID-19 patients than non-vaccinated ones. As a result, the mortality rate was lower in the vaccinated group than in the non-vaccinated group.

# 5. Limitations

The limitation of this study was that there was no antibody titer examination in the vaccinated group, so the number of antibodies formed in suppressing the occurrence of cytokine storms and tissue damage in severe COVID-19 patients was unknown.

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## 8. Author's Contribution

RWS, AZR and KAP designed the study, collected data, performed data analysis and wrote the manuscript. All authors have read and approved the final manuscript.

## 9. Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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