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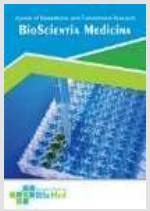

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Differences in Average Albumin Levels in Coronavirus Disease 2019 (COVID-19) Survivor and Non-Survivor Patients: A Single Center Observational Study at Dr. M. Djamil General Hospital, Padang, Indonesia

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A B S T R A C T

Background: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection triggers a systemic inflammatory response that can lead to a decrease in serum albumin levels. A more severe inflammatory response in non-survivor COVID-19 patients may correlate with a more significant decrease in albumin levels. This study aims to analyze differences in mean albumin levels in COVID-19 survivors and non-survivors. **Methods:** This cross-sectional analytical study involved 40 COVID-19 survivors and non-survivors treated at Dr. M. Djamil General Hospital Padang from July 2021 to September 2021. Serum albumin levels were checked using an automated clinical chemistry tool. Data analysis was carried out using the Mann-Whitney non-parametric test, with a significance level of $p < 0.05$. **Results:** The mean age of the study subjects was 49.4 (16.3) years, with the majority of cases occurring in men (67.5%). The median albumin levels in all COVID-19 patients, COVID-19 survivors, and COVID-19 non-survivors were 3.2 (2.20–5.00) g/dL, respectively; 4.1 (3.0–5.0) g/dL; and 2.9 (2.20–3.70) g/dL ($p = 0.001$). **Conclusion:** There is a significant difference in mean albumin levels between COVID-19 survivors and non-survivors. Lower albumin levels were found in non-survivor patients. Albumin can be a potential biomarker for predicting clinical outcomes of COVID-19 patients.

1. Introduction

The COVID-19 pandemic, triggered by the highly contagious SARS-CoV-2 virus, has drastically changed the global health landscape. This virus presents a wide range of clinical manifestations, ranging from asymptomatic infection to life-threatening severe acute respiratory distress syndrome (ARDS). Although the majority of infected individuals experience mild to moderate symptoms, a significant proportion progress to severe and critical illness, demanding intensive medical intervention. Behind the diverse clinical manifestations of COVID-19, there is a complex pathophysiology involving an intense systemic inflammatory response. This response is characterized by excessive release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). These cytokines, which should act as a biological alarm to activate the body's immune system, in the case of COVID-19 actually experience an uncontrolled increase, creating what is known as a cytokine storm. This cytokine storm is a frightening threat, because it

can trigger extensive multi-organ damage. The lungs, as the main organ attacked by SARS-CoV-2, suffer severe damage due to excessive inflammation. In addition, the heart, kidneys and liver are also not spared from the raging cytokine storm, causing life-threatening organ dysfunction.[1-3]

Amid the chaos caused by the cytokine storm, there is one molecule that is often forgotten but has a crucial role in the battle against COVID-19: albumin. Albumin, the most abundant plasma protein, is synthesized by the liver and has a variety of important physiological functions. One of its main functions is to maintain plasma oncotic pressure, which plays a role in maintaining fluid balance between blood vessels and surrounding tissues. In addition, albumin also functions as a transporter for various endogenous and exogenous molecules, including hormones, fatty acids, drugs, and bilirubin. Moreover, albumin has powerful antioxidant and anti-inflammatory properties. Albumin can neutralize free radicals that damage cells and tissues, as well as inhibit leukocyte activation and the release of pro-inflammatory cytokines. However, in acute and chronic inflammatory conditions, such as those occurring in COVID-19, serum albumin levels often decrease. This decrease is caused by several factors, including increased capillary permeability which causes leakage of albumin into tissues, decreased albumin synthesis by the liver due to damage caused by viruses and inflammatory responses, and increased albumin catabolism due to increased body energy needs.[4,5]

Decreased albumin levels in COVID-19 patients have been highlighted in several studies, which show a correlation between low albumin levels and an increased risk of mortality, need for mechanical ventilation, and length of hospital stay. These findings underscore the potential of albumin as a prognostic biomarker that can help doctors predict the clinical outcomes of COVID-19 patients. However, most previous studies focused on patients with severe or critical disease, leaving questions about the role of albumin in patients with milder severity. Research evaluating differences in albumin levels between COVID-19 patients who recover (survivors) and those who do not recover (non-survivors) is still limited.[6-8] This study aims to fill this gap in knowledge by analyzing differences in mean serum albumin levels in COVID-19 survivors and non-survivors treated at Dr. M. Djamil General Hospital Padang. By understanding these differences, we can gain deeper insight into the role of albumin in the pathogenesis of COVID-19 and its potential as a prognostic biomarker that can aid in clinical decision-making. It is hoped that this research will make a valuable contribution to our efforts to understand and overcome the COVID-19 pandemic. By further uncovering the role of albumin in the battle against this virus, we can open the door to the development of new, more effective, and personalized therapeutic strategies to improve the clinical outcomes of COVID-19 patients.

2. Methods

This research is an observational study with a cross-sectional design, an observational approach that aims to observe and analyze the relationship between variables in a population at a certain point in time. In the context of this study, that time point is when the COVID-19 patient was admitted to the hospital. A cross-sectional design was chosen because of its efficiency in data collection and its ability to identify differences between the groups studied. The population of this study was all COVID-19 patients treated at Dr. M. Djamil General Hospital Padang during the period July 2021 to September 2021. The research sample consisted of 40 patients who met the predetermined inclusion and exclusion criteria. Strict inclusion criteria were applied to ensure sample homogeneity and minimize bias. Patients who met the inclusion criteria were: Age ≥ 18 years: This criterion was applied to ensure that research subjects had reached adulthood and had adequate physiological maturity; Confirmatory diagnosis of COVID-19 based on rRT-PCR: This criterion ensures that the study subject is indeed infected with SARS-CoV-2 so that the observed differences in albumin levels can be attributed to infection with this virus; Survivor or non-

survivor status: This criterion divides the sample into two clear groups, namely patients who recovered after hospital treatment (survivors) and patients who died during hospital treatment due to complications of COVID-19 (non-survivors). Exclusion criteria were also applied to avoid potential bias that could influence the study results. Patients who had a history of chronic liver disease, chronic kidney disease, autoimmune disease, or were pregnant or breastfeeding were excluded from this study. This is done because these conditions can affect serum albumin levels independently of SARS-CoV-2 infection.

Demographic data (age, gender) and clinical data (survivor/non-survivor status) were obtained from patient medical records retrospectively. Serum albumin levels, which are the main variable in this study, were checked on blood samples taken when the patient was admitted to the hospital. The examination is carried out using automatic clinical chemistry equipment that has been calibrated and standardized, thereby ensuring the accuracy and precision of the measurement results. Data analysis was carried out using SPSS statistical software version 25.0. The first step in data analysis is to carry out a normality test using the Shapiro-Wilk test. This test aims to determine whether the distribution of numerical data (albumin levels) follows a normal distribution or not. If the data is normally distributed, the data will be presented in the form of mean ± standard deviation (SD). However, if the data is not normally distributed, the data will be presented in the median (interquartile range) form. The interquartile range provides information about the distribution of data around the median, which is the value that divides the data into two equal parts. Differences in mean albumin levels between COVID-19 survivors and non-survivors were analyzed using the Mann-Whitney non-parametric test. This test was chosen because it is suitable for comparing two independent groups with data that is not normally distributed. The significance level was set at $p < 0.05$, which means that differences are considered statistically significant if the probability of the difference occurring by chance is less than 5%.

3. Results

Table 1 presents the demographic and clinical characteristics of the study subjects. A total of 40 COVID-19 patients were involved in this study, with 27 (67.5%) male and 13 (32.5%) female. The mean patient age was 49 years with a standard deviation of 16 years, indicating considerable age variation in the study sample. The research subjects were divided into two groups of equal size, namely 20 (50%) survivor patients and 20 (50%) non-survivor patients. This balanced distribution allows a robust comparative analysis between the two groups to identify significant differences in albumin levels.

Table 1. Characteristics of respondents.

Variable	Frequency (%)	Mean (SD)
Gender		
Male	27 (67,5)	
Female	13 (32,5)	
Age (years)		49 (16)
COVID-19 survivor		
Survivor	20 (50)	
Non-survivor	20 (50)	

Table 2 presents the results of the analysis of albumin levels in COVID-19 survivors and non-survivors. There was a significant difference between the two groups, where survivor patients showed a higher median albumin level, namely 4.10 g/dL (interquartile range 3.0-5.0 g/dL), compared to non-survivor patients who had a median albumin level of 2.90 g/dL (interquartile range 2.20-3.70 g/dL). This difference has a p-value of <0.001, indicating very strong statistical significance. This indicates that

lower albumin levels at hospital admission may be a potential predictor of poor clinical outcomes in COVID-19 patients. These findings support the initial research hypothesis that albumin can act as a prognostic biomarker in COVID-19 patients.

Table 2. Albumin levels in COVID-19 survivor and non-survivor patients.

Group	Median (min-max)	p-value
Survivor	4,10 (3,0 – 5,0)	<0,001
Non-survivor	2,90 (2,20 – 3,70)	
Total	3,20 (2,20 – 5,00)	

4. Discussion

The results of this study clearly show significant differences in mean albumin levels between COVID-19 patients who successfully recovered (survivors) and those who did not (non-survivors). Non-survivor patients consistently show lower albumin levels compared with survivor patients. This finding is not new, but is in line with evidence that has been collected in several previous studies. Albumin, as the most abundant plasma protein, is often underestimated and considered only as a space-filling molecule in the blood. However, this and previous studies have revealed the important role of albumin in maintaining the body's physiological balance and response to infection. Albumin has a variety of crucial physiological functions. One of its main functions is to maintain plasma oncotic pressure, which plays an important role in maintaining fluid balance between blood vessels and surrounding tissues. Oncotic pressure is the force that draws fluid back into the blood vessels, preventing edema or fluid buildup in the tissue. Apart from that, albumin also functions as a transporter for various important molecules in the body, such as hormones, fatty acids, drugs and bilirubin. The hormones transported by albumin play a role in the regulation of various body functions, including growth, metabolism, and stress response. Fatty acids are an important source of energy for body cells, while drugs bound to albumin can be distributed throughout the body and reach their target action. Bilirubin, a byproduct of the breakdown of red blood cells, is also transported by albumin for excretion by the liver. One important role of albumin that is often overlooked is its strong antioxidant properties. Albumin has the unique ability to bind and neutralize free radicals, reactive molecules that can damage cells and tissues. Free radicals form naturally in the body as a result of normal metabolism, but excessive production of free radicals can cause oxidative stress. Oxidative stress is a condition where there is an imbalance between the production of free radicals and the body's ability to neutralize them. This condition can damage various cellular components, including DNA, proteins, and lipids. This damage can trigger various diseases, including cardiovascular disease, cancer, neurodegenerative diseases, and chronic inflammatory diseases.[9-11]

Albumin acts as an antioxidant by several mechanisms. One of the main mechanisms is through the thiol group (-SH) on the cysteine residue. This thiol group can donate electrons to neutralize free radicals, turning them into more stable and harmless molecules. Apart from that, albumin can also bind and neutralize metal ions, such as iron and copper, which can trigger the formation of free radicals. Research has shown that albumin can protect cells and tissues from oxidative damage caused by various factors, including radiation, toxic chemicals, and infections. In the context of COVID-19, oxidative stress has been identified as one of the main pathogenic mechanisms. SARS-CoV-2 infection can trigger excessive production of free radicals, either directly through viral activity or indirectly through the inflammatory response it causes. Albumin, with its antioxidant properties, can help protect cells and tissues from oxidative damage caused by SARS-CoV-2 infection. This can help reduce

the severity of the disease and increase the chances of recovery for COVID-19 patients. In addition to its antioxidant properties, albumin also has significant anti-inflammatory properties. Albumin can inhibit the activation of leukocytes, white blood cells that play an important role in inflammatory responses. Activated leukocytes can release pro-inflammatory cytokines, such as IL-6, TNF-α, and IFN-γ, which trigger and amplify the inflammatory response. The inflammatory response is the body's defense mechanism against infection and injury. However, excessive or uncontrolled inflammatory responses can cause severe tissue damage and contribute to the development of various diseases. In the context of COVID-19, cytokine storm is an extreme example of an excessive inflammatory response, which can cause multi-organ damage and increase the risk of mortality.[12-14]

Albumin can inhibit leukocyte activation through several mechanisms. One of the main mechanisms is through the binding and neutralization of adhesion molecules, such as ICAM-1 and VCAM-1, which are expressed on the surface of endothelial cells. These adhesion molecules play an important role in the migration of leukocytes from the bloodstream to infected or injured tissue. By inhibiting the expression and function of adhesion molecules, albumin can prevent leukocytes from reaching their target tissues and releasing pro-inflammatory cytokines. In addition, albumin can also bind and neutralize pro-inflammatory cytokines directly, thereby reducing their inflammatory effects. Albumin can also increase the production of anti-inflammatory cytokines, such as IL-10, which helps reduce inflammation and promote tissue healing. Studies have shown that albumin can reduce inflammation in various disease models, including sepsis, arthritis, and inflammatory bowel disease. In the context of COVID-19, intravenous administration of albumin has been associated with reduced levels of pro-inflammatory cytokines and improved clinical outcomes in patients with severe disease.[15-17]

Albumin's antioxidant and anti-inflammatory properties make it a potential candidate as an adjuvant therapy in COVID-19 patients. Intravenous administration of albumin can help reduce oxidative stress and inflammation, thereby improving organ function, reducing the severity of disease, and increasing the chances of recovery. Several clinical trials are ongoing to evaluate the effectiveness and safety of intravenous albumin administration in COVID-19 patients. Preliminary results show that intravenous administration of albumin can increase serum albumin levels, reduce pro-inflammatory cytokine levels, and improve lung function in patients with ARDS due to COVID-19. However, further research is still needed to confirm these findings and determine the optimal dose and most effective time of administration of albumin. Additionally, research is also needed to identify subgroups of COVID-19 patients most likely to benefit from albumin therapy. Albumin, with strong antioxidant and anti-inflammatory properties, has great potential as an adjuvant therapy in COVID-19 patients. Intravenous administration of albumin can help reduce oxidative stress and inflammation, improve organ function, and improve clinical outcomes. Although further research is still needed, albumin offers new hope in the treatment of COVID-19 and could be a powerful weapon in the battle against this global pandemic.[16-18]

SARS-CoV-2 infection triggers an intense systemic inflammatory response, characterized by excessive release of pro-inflammatory cytokines. This cytokine storm can cause multi-organ damage and contribute to the development of severe and critical disease. At the same time, this inflammatory response can also lead to a decrease in serum albumin levels. Decreased albumin levels in COVID-19 patients can occur through several mechanisms. First, increased capillary permeability due to endothelial damage by viruses and pro-inflammatory cytokines can cause albumin leakage into tissues. Second, albumin synthesis by the liver can be impaired due to virus-induced liver damage and inflammatory responses. Third, albumin catabolism can increase due to the

body's increased energy needs to fight infection and repair tissue damage.[15-17]

Decreased albumin levels in COVID-19 patients can worsen the patient's condition in several ways. First, a decrease in plasma oncotic pressure can cause edema or fluid accumulation in tissues, including the lungs. Pulmonary edema can interfere with gas exchange and cause difficulty breathing. Second, decreased albumin transport capacity can disrupt the distribution of hormones, fatty acids, drugs, and bilirubin, which can affect the function of various organs. Third, decreased antioxidant and anti-inflammatory activity of albumin may exacerbate systemic inflammatory responses and increase the risk of multi-organ damage. Thus, a decrease in albumin levels in COVID-19 patients can create a deadly vicious circle. The systemic inflammatory response triggered by SARS-CoV-2 infection causes a decrease in albumin levels, which in turn exacerbates the inflammatory response and increases the risk of complications. This vicious circle may explain why patients with low albumin levels have a higher risk of mortality.[19,20]

This study has several limitations that need to be noted. First, the cross-sectional study design does not allow to determine the causal relationship between albumin levels and mortality in COVID-19 patients. That is, we cannot be certain whether decreased albumin levels directly cause an increased risk of mortality, or whether both are a manifestation of the severity of the underlying disease. Second, the number of research samples is relatively small, so generalization of research results needs to be done with caution. Third, this study did not evaluate other factors that might influence albumin levels, such as nutritional status and comorbidities. These factors can be confounding variables that influence the relationship between albumin levels and mortality. Nonetheless, this study provides valuable additional evidence that serum albumin levels may be a potential biomarker for predicting the prognosis of COVID-19 patients. Further studies with prospective designs and larger sample sizes are needed to confirm these findings and evaluate the potential of albumin as a therapeutic target in COVID-19 patients. Prospective studies could involve monitoring albumin levels periodically in COVID-19 patients from the onset of infection until recovery or death. Thus, we can observe changes in albumin levels as the disease progresses and evaluate their impact on clinical outcomes. In addition, prospective studies can also allow us to control for confounding variables, such as nutritional status and comorbidities, so as to obtain more accurate estimates of the relationship between albumin levels and mortality. If further research can confirm albumin's role as a powerful prognostic biomarker, then albumin could be used as a tool to identify COVID-19 patients at high risk of complications and death. Thus, early intervention can be carried out to prevent or reduce the risk of these complications. In addition, further research is also needed to evaluate the potential of albumin as a therapeutic target in COVID-19 patients. Some possible therapeutic strategies that can be considered are the administration of exogenous albumin, nutritional supplementation to increase albumin synthesis, and the use of drugs that can reduce albumin catabolism or increase its antioxidant and anti-inflammatory activity.

The results of this study and evidence from previous studies suggest that albumin plays an important role in the pathogenesis of COVID-19 and may be a valuable prognostic biomarker. Decreased albumin levels in COVID-19 patients may worsen the systemic inflammatory response and increase the risk of complications, including death. Therefore, monitoring albumin levels in COVID-19 patients can help doctors identify high-risk patients and provide appropriate early intervention. Further research is needed to further uncover the mechanisms underlying the relationship between albumin levels and mortality in COVID-19 patients. By understanding these mechanisms, we can develop new, more effective, and personalized therapeutic strategies to improve the clinical outcomes of COVID-19 patients. Albumin, which has been considered a simple plasma protein,

turns out to have great potential to be the key to overcoming the COVID-19 pandemic.[17-20]

5. Conclusion

The results of this study show that there is a significant difference in mean albumin levels between COVID-19 survivors and non-survivors. Lower albumin levels were found in non-survivor patients. Albumin can be a potential biomarker for predicting clinical outcomes of COVID-19 patients.

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