

Serum albumin levels as a marker for multi-organ dysfunction syndrome in coronavirus disease 2019 patients: A prospective observational study

Arie Utariani¹, Susy Melanie¹, Fajar Perdhana¹

Abstract

Objective: Coronavirus disease 2019 (COVID-19) causes a severe impact on patients with comorbidities. Most of them are likely to develop multi-organ dysfunction syndrome (MODS). Serum albumin level is a reliable predictor of severe outcomes in COVID-19 patients. Therefore, this study aimed to investigate the association between serum albumin levels and the risk of developing MODS in COVID-19 patients.

Design: A prospective analytical observational study.

Setting: A single tertiary referral hospital in Surabaya, Indonesia.

Patients and participants: We collected 153 patients from May-June 2021 who were confirmed positive for COVID-19 based on the real-time reverse-transcription polymerase chain reaction (RT-PCR) test aged 19-84 years. Seven patients were excluded due to incomplete data. Therefore, 146 patients were eligible participants.

Interventions: Patients underwent the laboratory test during admission. An eight ml of venous blood plasma specimen was taken. The specimen

was examined at the Clinical Pathology Laboratory, Diagnostic Center in our hospital using the enzyme-linked immunosorbent assay (ELISA) method.

Measurement and results: Of 146 COVID-19 patients ages ranged from 19-84 years old. Almost 83% of patients have developed MODS, and 31.5% of them were non survived. Serum albumin of COVID-19 patients with MODS and non-survivor were lower than those who had good outcomes (2.95 ± 0.39 ; 2.82 ± 0.40 vs 3.07 ± 0.40 ; 3.19 ± 0.47 g/dl). We found a significant difference between serum albumin levels and the incidence of MODS and mortality ($p=0.001$). In multivariate analysis, low serum albumin <3.5 g/dl had a 15 times higher risk of developing MODS in COVID-19 patients ($p=0.011$).

Conclusion: Early hospitalization serum albumin level is an excellent marker for predicting the development of MODS in COVID-19 patients. This first step might help physicians choose an appropriate treatment in the future.

Key words: Albumin, MODS, comorbidity, COVID-19.

¹Department of Anesthesiology and Intensive Therapy, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia

Address for correspondence:

Arie Utariani
Department of Anesthesiology and Intensive Therapy
Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia
Tel: +62 812-3008-875
Email: arieutariani299@gmail.com

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 was first reported in Wuhan City, Central China, and has spread to two domestic cities and several countries in a short time, (1) with a mortality rate of up to 4% in Southeast Asia. (1,2). The severity of COVID-19 is influenced by the comorbidities suffered, such as hypertension, diabetes, obesity, chronic obstructive pulmonary disease (COPD), and others. Approximately 25.1% of severe cases had at least one comorbid, and 8.2% had at least two or more. (3) At the beginning of the ob-

ervation, many signs of a high-level acute inflammation marker were observed in COVID-19 patients who experienced worsening conditions. Still, the factors that caused these serious complications have not been identified yet. (4-6) Initial laboratory examination and history taking are necessary to determine the risk of comorbid severity experienced by COVID-19 patients at admission.

Serum albumin is the main anti-inflammatory agent in our body. (7,8) Albumin also acts as a primary defense that protects cells from oxidative bursts against infection or inflammation. (9-11) Serum albumin level is an indicator that plays a role in predicting worsening prognosis and death in COVID-19 patients. (12,13) Serum albumin level is a new marker that shows systemic inflammation and death that can be calculated using hemogram parameters. A decrease in serum albumin level can cause severe conditions in patients and cause mortality. (13) In some cases, patients with severe COVID-19 have lower albumin levels than non-severe patients. In addition, patients with decreased albumin levels are more likely to have a poor outcome. (14,15) In Indonesia, we hardly find any proven studies which discuss whether serum albumin levels can predict a worsening prognosis in COVID-19 patients, especially for those with comorbidities and at risk of developing multi-organ dysfunction syndrome (MODS). Therefore, we investigated the association of serum albumin levels at initial admission in COVID-19 patients for the occurrence of serious outcomes for developing MODS.

Methods

A prospective analytical observational study was carried out at the Intensive Care Unit of Dr. Soetomo General Hospital, Surabaya, from May to June 2021. The samples in this study were patients who were confirmed positive for COVID-19 through the real-time reverse-transcription polymerase chain reaction (RT-PCR) test, aged 19-84 years. They were willing to participate in the study and provided informed consent at the time of initial admission. Exclusion criteria in this study included incomplete patient's medical records, the patient had died before or less than 24 hours since the blood sample was taken, the patient refused to be treated or received therapy according to the standard procedures, and unwilling to participate or signed the informed consent. This research has received ethical clearance from the Ethical Committee of the Clinical Research Unit in the local hospital with the number 0009/KEPK/VI/2020.

The recruitment of samples in this study began

when the patient was willing and signed the informed consent. The doctor on duty checked the patient's condition and comorbidities, then recorded demographic data and patient history in the medical record. Furthermore, at the beginning of admission, eight ml of venous blood plasma specimen was taken, five ml into the serum separator tube (SST) and three ml into the ethylenediaminetetraacetic acid (EDTA) tube. The blood sample that has been taken would be examined at the Clinical Pathology Laboratory, Diagnostic Center in our hospital using the enzyme-linked immunosorbent assay (ELISA) method. The doctor on duty will monitor the patient's condition and whether the patient developed MODS during the treatment. The assessment of the development of MODS condition was seen through the patient's medical records, which were collected every day after the patient's examination. Patients were categorized as having developed MODS if there were two or more organ system disorders.

Material and tools

This study used human serum albumin, which was taken by taking blood specimens. Other requirements included in this study were a three ml syringe, micropipette, 15 ml centrifuge tube, centrifugation machine, ELISA reader, microplate 96 wells, microscope, glass and cover slide, pH meter, photography equipment and dry incubator, and pipette tip (yellow and blue tips).

Laboratory examination

For a color reaction to occur in ELISA, an antibody labeled with an enzyme was needed, and a substrate with a color indicator known as a chromogen. The enzymes used to label antibodies include 1) Alkaline phosphatase, 2) Horseradish peroxidase, and 3) Beta-galactosidase. In ELISA, the previously detected material must be attached to the solid phase (on the microtiter well). Material (antigen [Ag]-antibody [Ab]) can stick to the microtiter wells because these wells have been coated with polystyrene/polyvinylchloride. The ELISA principle consists of the coating phase, the Ag-Ab reaction phase, and the chemical reaction phase.

ELISA was carried out according to the working instructions on the Insert Kit (quantikine-Rnl). The capturing antibody was coated on the surface of the polycarbonate microplate - in a coating buffer of pH 9.8 and incubated at 4 °C for 24 hours, then washed three times with a washing solution (0.15 Molar sodium chloride + 0.05% Triton x 0.02 g sodium azide in 1 liter of distilled water). To avoid reactions that were not antigen-specific, they were closed using a cover solution (1% bovine serum albumin +

0.02 g sodium azide in phosphate-buffered saline, pH 7.0) as much as 200 µl per well, incubated at room temperature for one hour, washed three times, then added samples (serum/plasma/culture medium) and 100 µl of standard protein per well, and incubated at room temperature for one hour. Then, washed three times and incubated at room temperature for 30 minutes. The reaction was stopped by adding 1 Normality sulfuric acid. The reading of the results (optical density) was carried out with an ELISA reader at a wavelength of 450 nm.

Data analysis

IBM SPSS Statistics version 25 was used for data analysis. Data with a categorical scale would be presented as frequency distribution (n) and percentage (%). Numerical scale data was either expressed as the mean (mean) with a standard deviation (SD) if a variable was normally distributed, or the median with an interquartile range (IQR) value if the variables were not normally distributed. The normality test would be carried out using the Shapiro-Wilks or Kolmogorov-Smirnov test. An independent T-test analyzed the difference test on two numerical variables if the data were normally distributed or the Mann-Whitney U test if the data were not normally distributed. A variable was declared statistically significant if the p-value was 0.05. The relationship between variables would be analyzed using the Pearson chi-square test or the Fisher exact test. We then continued to include variables that had $p > 0.25$ in the previous test to be analyzed using multivariate logistic regression to assess the effect of these variables on the development of MODS in COVID-19 patients. The variables studied included sex, age, sickness duration, dyspnea, arterial oxygen partial pressure (PaO₂) to fractional inspired oxygen (FiO₂) ratio (P/F ratio), body mass index (BMI), Sequential Organ Failure Assessment (SOFA) score, length of stay (LOS), comorbidities, and serum albumin level.

Results

A total of 153 COVID-19 patients were recruited for this study; seven of them were excluded due to the absence of serum albumin. Therefore, 146 COVID-19 patients were eligible participants. A total of 52% of participants in this study were male. The COVID-19 patients in this study were 19-84 years old. The most common age group of patients was 45-64 years (43.2%), with LOS ranging from 1-50 days of treatment. Dyspnea in COVID-19 patients experienced an average of three days. The average serum albumin level in all COVID-19 patients in

this study was 2.99 ± 0.420 g/dl. Of the 146 participants, 121 (82.9%) had MODS with more than two comorbidities. A total of 46 (31.5%) patients died during treatment. The clinical characteristics of patients based on MODS and their mortality are shown in **Tables 1** and **2**.

Table 1 shows that almost all variables have significant differences in the incidence of developing MODS in COVID-19 patients ($p < 0.05$) except for the sex of the patient. Serum albumin levels in COVID-19 patients suffering from MODS were lower than those without comorbidities, 2.95 ± 0.39 vs 3.19 ± 0.47 g/dl, respectively. Serum albumin levels had a significant difference in the incidence of developing MODS and mortality ($p = 0.001$). Fisher exact test was used to determine the correlation between serum albumin level < 3.5 g/dl and BMI. We found no significant correlation between the two variables in this study ($p = 0.208$). In multivariate analysis, BMI and age of COVID-19 patients were also not correlated to the incidence of developing MODS and mortality. The results showed that COVID-19 patients with serum albumin levels < 3.5 g/dl had a significant effect on the incidence of developing MODS with a p-value of 0.009 (**Table 3**). **Table 4** presents the comorbidities experienced by COVID-19 patients. All comorbid variables in this study did not provide a significant relationship to the direct incidence of mortality but could worsen the patient's prognosis. Diabetes and malignancy resulted in a strong significant association with the risk of developing MODS in COVID-19 patients with a p-value of 0.001 and 0.009, respectively.

Discussion

This study showed that serum albumin levels in the non-survivor group were lower than in the survivor group. This was supported by a systematic review study and meta-analysis conducted by Paliogiannis (2021). Of the 67 articles reviewed, all results showed lower serum albumin levels in the severe outcome group, and there was only 1 study that found the lowest albumin levels in the severe outcome group, i.e., 20.3 ± 5.4 g/l. (16,17) Our study found that BMI did not correlate with the incidence of developing MODS and COVID-19 patients with serum albumin levels < 3.5 g/dl. This finding was supported by a study in Japan that BMI and lower albumin levels were not correlated in thin patients. In addition, if the albumin levels were above 3.3 g/dl, the patient's prognosis might be good, even if treated in the emergency room. (18)

This study proved that serum albumin level at the time of initial admission could predict a patient's

likelihood of developing MODS, especially in patients with diabetes and malignancy. Albumin was also considered a reliable indicator for the prognosis of patients with severe COVID-19 infection. (19) In the case of COVID-19 patients, most of them experienced a decrease in serum albumin below normal levels. (11,20) Hypoalbuminemia was commonly seen in patients with comorbidities such as diabetes, hypertension, and chronic heart failure, and these patients were most susceptible to SARS-CoV-2 infection. (21) Low serum albumin in SARS-CoV-2 infection was associated with a higher incidence of serious disease outcomes such as post-viral physical weakness, hypercoagulability, kidney injury, cardiac injury, encephalopathy, and higher mortality. (11)

Johnson et al. (2020) explained that plasma protein elements play a role in maintaining the vascular glycocalyx layer's integrity. The decrease in plasma protein levels indirectly implied the possibility of vascular damage to various organs in addition to plasma oncotic changes. (22) Based on a study conducted by Yao et al. (2021), decreased albumin levels were associated with severe symptoms of COVID-19. Our study showed that COVID-19 patients who had a lower albumin level of <3.5 g/dl had a 15-times higher risk of worsening outcomes in developing MODS than COVID-19 patients who had normal albumin levels. (23) Din et al. (2020) also mentioned that low serum albumin concentrations were associated with the severity of chronic inflammatory disease, inflammatory bowel disease, and diabetes mellitus. (24) Inflammation has been shown to cause the release of serum albumin into the interstitial space due to increased capillary permeability and ultimately caused an increase in the volume of distribution of the albumin. (25)

The low serum albumin on examination can be used as a sign so that health workers can be aware of the selection of safe and appropriate follow-up treatment for COVID-19 patients. In this case, there are many confounding factors such as age and patient comorbidities. Diabetes mellitus was defined as a

chronic low-grade inflammatory state initiated by excess fat tissue. (26) Regardless of the pathogenesis of type 2 diabetes and insulin resistance, an increase in pro-inflammatory macrophages, cytokines, chemokines, and proteases contributed to the development of diabetes-associated neuropathy, nephropathy, retinopathy, and cardiovascular infections. (27) Dysregulation of the innate and humoral immune systems was the cause of the high risk of people with diabetes becoming infected with SARS-CoV-2. (28,29)

This study had several limitations because the serum albumin level examination was only done once at initial admission. It might be potential for this study to be developed by comparing the serum albumin of several samples such as admission and during the treatment period. In addition, this study was monotonically at one of the largest referral hospitals. Most patients treated had moderate to severe symptoms of acute respiratory distress syndrome because the characteristics of patients other than moderate to severe symptoms are not well known. However, as an initial step to determine the best treatment, we believe this study can provide suitable history support, especially albumin as a marker for the incidence of developing MODS in COVID-19 patients.

Conclusion

The low serum albumin level that occurs early in the treatment admission provides a significant association as a determinant marker in severe cases such as the development of MODS in COVID-19 patients. The comorbidities of COVID-19 patients, especially diabetic and malignant cases, also support exacerbated outcomes. For this reason, markers at the initial examination can assist physicians in providing the best treatment options for COVID-19 patients, especially with moderate to severe symptoms. Multicenter follow-up studies are needed to compare the conditions of COVID-19 patients, including the initial treatment period to the post-treatment period.

Table 1. The distribution of clinical characteristics in COVID-19 patients based on the risk of developing MODS

Characteristics	MODS		p
	No (n=25)	Yes (n=121)	
Sex, n (%)			0.078 ^a
- Female	16 (64)	54 (44.6)	
- Male	9 (36)	67 (55.4)	
Age (years), n (%)			0.006 ^{a*}
- 17-44	14 (56)	37 (30.6)	
- 45-64	4 (16)	59 (48.8)	
- ≥65	7 (28)	25 (20.7)	
BMI (kg/m ²), n (%)			0.010 ^{a*}
- <18.5	6 (24)	5 (4.1)	
- 18.5-24.9	6 (24)	52 (43)	
- 25-29.9	9 (36)	48 (39.7)	
- ≥30	4 (16)	16 (13.2)	
P/F ratio (mmHg), n (%)			0.001 ^{a*}
- <100	0 (0)	30 (24.8)	
- 100-199	3 (12)	47 (38.8)	
- 200-299	4 (16)	19 (15.7)	
- 300-399	7 (28)	22 (18.2)	
- ≥400	11 (44)	3 (2.5)	
Sickness complaints (days), median (IQR)	3.00 (1.50-7.00)	7.00 (5.00-8.00)	0.001 ^{b*}
Dyspnea (days), median (IQR)	0 (0-3.50)	4.00 (3.00-5.00)	0.001 ^{b*}
SOFA score, median (IQR)	1.00 (1.00-2.00)	4.00 (3.00-8.00)	0.001 ^{b*}
Albumin (g/dl), mean±SD	3.19±0.47	2.95±0.39	0.001 ^{c*}
LOS (days), median (IQR)	9.00 (6.50-15.00)	13.00 (8.00-20.50)	0.031 ^{b*}
Outcome, n (%)			0.005 ^{a*}
- Survived	23 (92)	77 (63.6)	
- Non-survived	2 (8)	44 (36.4)	

Legend: COVID-19=coronavirus disease 2019; MODS=multi-organ dysfunction syndrome; BMI=body mass index; P/F ratio=arterial oxygen partial pressure to fractional inspired oxygen ratio; IQR=interquartile range; SOFA=Sequential Organ Failure Assessment; SD=standard deviation; LOS=length of stay.

*p-value ≤0.05 was significant; ^aChi-square and/or Fisher exact test were used as appropriate; ^bMann-Whitney U test; ^cT-test.

Table 2. The clinical characteristics based on mortality in COVID-19 patients

Characteristics	Outcome		p
	Survived (n=100)	Non-survived (n=46)	
Sex, n (%)			0.276 ^a
- Female	51 (51)	19 (41.3)	
- Male	49 (49)	27 (58.7)	
Age (years), n (%)			0.547 ^a
- 17-44	34 (34)	17 (37)	
- 45-64	46 (46)	17 (37)	
- ≥65	20 (20)	12 (26)	
BMI (kg/m ²), n (%)			0.021 ^{a*}
- <18.5	7 (7)	4 (8.7)	
- 18.5-24.9	46 (46)	12 (26.1)	
- 25-29.9	31 (31)	26 (56.5)	
- ≥30	16 (16)	4 (8.7)	
P/F ratio (mmHg), n (%)			0.001 ^{a*}
- <100	8 (8)	22 (47.8)	
- 100-199	32 (32)	18 (39.1)	
- 200-299	20 (20)	3 (6.5)	
- 300-399	27 (27)	2 (4.3)	
- ≥400	13 (13)	1 (2.2)	
Sickness complaints (days), median (IQR)	6.50 (3.00-7.00)	7.00 (5.00-9.25)	0.051 ^b
Dyspnea (days), median (IQR)	3.00 (0-5.00)	4.00 (3.00-6.00)	0.008 ^{b*}
SOFA score, median (IQR)	3.00 (1.00-3.00)	8.00 (6.00-9.25)	0.001 ^{c*}
Albumin (g/dl), mean±SD	3.07±0.40	2.82±0.40	0.001 ^{b*}
LOS (days), median (IQR)	17.71 (9.25-22)	7.50 (3.00-12.25)	0.001 ^{b*}
MODS, n (%)			0.005 ^{a*}
- No	23 (23)	2 (4.3)	
- Yes	77 (77)	44 (95.7)	

Legend: COVID-19=coronavirus disease 2019; BMI=body mass index; P/F ratio=arterial oxygen partial pressure to fractional inspired oxygen ratio; IQR=interquartile range; SOFA=Sequential Organ Failure Assessment; SD=standard deviation; LOS=length of stay; MODS=multi-organ dysfunction syndrome.

*p-value ≤0.05 was significant; ^aPearson's chi-square test and/or Fisher exact test were used as appropriate; ^bMann-Whitney U test; ^cT-test.

Table 3. The effect of clinical characteristics on the risk of developing MODS and mortality

	MODS			Mortality		
	p	OR	95% CI (lower-upper)	p	OR	95% CI (lower-upper)
P/F ratio (mmHg)	0.006*	18.362	2.268-148.639	0.472	0.171	0.001-21.150
Dyspnea	0.033*	1.463	1.030-2.076	0.903	0.975	0.653-1.458
Albumin (g/dl)	0.009*	15.795	2.012-124.008	0.899	1.052	0.644-1.719
LOS (days)	0.018*	1.133	1.022-1.256	0.001*	0.771	0.683-0.870
SOFA score	0.186	1.273	0.868-1.820	0.001*	2.621	1.807-3.801

Legend: MODS=multi-organ dysfunction syndrome; P/F ratio=arterial oxygen partial pressure to fractional inspired oxygen ratio; LOS=length of stay; SOFA=Sequential Organ Failure Assessment; OR=odds ratio; CI=confidence interval.

*p-value ≤ 0.05 was significant; multivariate logistic regression was used.

Table 4. Association of comorbidity distribution with MODS and mortality in COVID-19 patients

Comorbidity	Total (n=153)	MODS (n=121)		Non-survived (n=46)	
		n (%)	p	n (%)	p
Diabetes	75	70 (57.9)	0.001*	27 (58.7)	0.230
Thyroid	3	3 (2.5)	0.426	2 (4.3)	0.185
Dyslipidemia	48	43 (35.5)	0.132	17 (37)	0.477
Hematology	61	51 (42.1)	0.843	24 (52.2)	0.084
Hypertension	78	67 (55.4)	0.299	22 (47.8)	0.358
Stroke	15	12 (9.9)	0.755	5 (10.9)	0.872
Deep vein thrombosis	4	3 (2.5)	0.672	2 (4.3)	0.419
Arrhythmia	4	3 (2.5)	0.672	1 (2.2)	0.776
Hipertensive heart disease	57	47 (38.8)	0.914	15 (32.6)	0.280
Coronary artery disease	15	14 (11.6)	0.256	7 (15.2)	0.182
Chronic lung disease	33	28 (23.1)	0.733	9 (19.6)	0.552
Chronic kidney disease	46	41 (33.9)	0.174	19 (41.3)	0.084
Autoimmune	14	10 (8.3)	0.232	4 (8.7)	0.804
Chronic liver disease	24	21 (17.4)	0.511	6 (13)	0.453
Malignancy	18	11 (9.1)	0.009*	4 (8.7)	0.365
Trauma	7	5 (4.1)	0.410	0 (0)	0.066
Secondary infection	3	2 (1.7)	0.451	2 (4.3)	0.185
Pregnancy	11	8 (6.6)	0.353	4 (8.7)	0.718

Legend: MODS=multi-organ dysfunction syndrome; COVID-19=coronavirus disease 2019.

*p-value ≤ 0.05 was significant; Pearson's chi-square test and/or Fisher exact test were used as appropriate.

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