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ORIGINAL RESEARCH CORONA EXPERIENCE

The impact of hypoalbuminemia and its correlation with D-dimer and IL-6 on severity and 14-day mortality in COVID-19 patients

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ABSTRACT

Background & Objective: COVID-19 took the world by storm, but it also allowed the healthcare professionals to conduct big studies regarding various molecular and biochemical changes produced by the disease. We analyzed the impact of hypoalbuminemia on the severity and 14-day mortality in COVID-19 patients.

Methodology: It was an analytical observational, prospective cohort study design. Clinical and laboratory data collection was carried out in the COVID-19 isolation room of Dr. Soetomo Hospital, between July and October 2020. Serum albumin, D-dimer, and interleukin 6 (IL-6) levels were measured on the day of admission. Statistical analysis using Kolmogorov-Smirnov, Mann-Whitney test, regression test, ROC curve, and 14-day risk of mortality were tested using Univariate Cox Regression and Multivariate Cox Regression tests. The Kaplan Meier test was used to analyze life expectancy.

Results: Of the 119 study subjects, 71 (59.7%) were categorized as severe, and 48 (40.3%) as not severe. Out of the total, 36 (30.25%) patients expired within 14 days of admission, and 83 (69.75%) survived. Regression analysis showed the effect of age on albumin ($P < 0.001$), albumin on D-dimer ($P = 0.003$), albumin on disease severity ($P < 0.001$), and albumin on 14-day mortality ($P < 0.001$). Albumin was not significantly associated with IL-6 ($P = 0.126$). The value of albumin as a predictor of severity was 3.28 g/dL, with a sensitivity of 74.6% and a specificity of 77.1%.

Conclusion: The state of hypoalbuminemia affects the disease severity and mortality of COVID-19; albumin is significantly associated with D-dimer. Poor prognosis is expected if the albumin value < 3.28 in geriatric and obese patients with a high 14-days mortality.

Abbreviations: CRP - C-reactive protein; IL-6 - Interleukin 6; PCR - Polymerase Chain Reaction; PPV+ - Positive Predictive Value; NPV− - Negative Prediction Value; ROC - Receiver Operating Characteristic test; TNF – Tumor Necrosis Factor

Key words: Albumin; COVID-19; D-dimer; Hypoalbuminemia; IL-6; Severity; Mortality.

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1. INTRODUCTION

The COVID-19 pandemic (SARS-CoV-2) has caused more than 100 million infections and 3.2 million deaths.[1] Recent studies illustrate that COVID-19 disease resembles many clinical phenotypes of SARS in its severity and mortality.[2–5] In addition, COVID-19 is much more contagious and more easily transmitted between humans,[6–8] and causes injury to many organs, including the heart, kidneys and liver.

The human liver synthesizes various proteins; one of the most important ones is albumin. It has a half-life in the body of about 20 days and decreases by 10-15% after the age of 50 y.[9] Albumin has many physiological functions, such as providing oncotic pressure, binding and transporting substances, and maintaining acid-base balance.[10] Serum albumin levels have been shown to have a significant association with mortality in a study population and could be considered a strong predictor of mortality in hospitalized patients with COVID-19.[11] A significant decrease in albumin levels is characteristic of severe COVID-19, but these changes in albumin levels are not directly proportional to the severity of the hepatocellular injury.[12] This suggests that other mechanisms may explain the hypoalbuminemia commonly seen in COVID-19.

One possible mechanism is intensive systemic inflammation.[13] During critical conditions, mediators decrease albumin synthesis to prioritize other acute-phase proteins. In addition, these mediators increase vascular permeability, allowing albumin to escape into the extravascular space.[14] Hypoalbuminemia induced by COVID-19 infection due to cytokine symptoms or "cytokine storm" is associated with a poor prognosis in the patients' condition.

Another study conducted by Ramadori et al. suggested two main mechanisms leading to decreased serum albumin concentrations in patients with severe COVID-19 infection. Firstly, reduction of albumin synthesis due to reduced food intake, and secondly, inhibition of specific mRNA synthesis in the hepatocellular nucleus, which is induced by direct interaction of cells with acute-phase cytokines.[15,16]

Recently, Violi et al. described an association between hypoalbuminemia and hypercoagulability, mediated by elevated plasma D-dimer levels, in a cohort of 73 COVID-19 patients.[16] The authors found that patients with serum albumin < 35 g/L exhibited significantly higher D-dimer concentrations than patients with 35 g/L albumins and, more importantly, had a higher likelihood of intensive care.

Hypoalbuminemia might be associated with hypercoagulability, and severe clinical conditions in COVID-19.[17] Increase in serum albumin in albumin-treated patients decreases D-dimer level, suggesting that hypoalbuminemia and coagulopathy in patients with severe COVID-19 may have a direct correlation.[16,18] Albumin level is increased after recovery and it could be used as a biomarker to predict the progression of COVID-19 disease.[19]

The acute-phase proteins, IL-6 and C-reactive protein (CRP), are systemic reactions of the body to local and system immunological stresses that are renewed in the presence of tissue damage or infection and increase markedly in response to infection and correlate with disease severity and recovery room tissue damage.[16,20,21] Prognostic levels of interleukin 6 (IL-6) and CRP have also been studied in many diseases, including sepsis and SARS-CoV-2.[22–24] We investigated the correlation of hypoalbuminemia with D-dimer and IL-6 and its impact on the severity of COVID-19 disease.

2. METHODOLOGY

This analytic observational study with a prospective cohort design was conducted at Dr. Soetomo. General Hospital Surabaya, Indonesia. Data collection was carried out between July 01, 2020 to October 31, 2020, from confirmed cases of COVID-19 based on polymerase chain reaction (PCR) tests. Serum albumin, D-dimer, and IL-6 levels were taken on the day of admission. In addition, for confounding factors that could have influenced our assessment, we excluded patients with a known history of comorbidity with other chronic diseases. The classification and clinical criteria of COVID-19 were determined according to the "Life Guide for Clinical Management of COVID-19" issued by the World Health Organization (WHO). Mildly symptomatic patients were included in the non-severe group, and severe and critical patients were included in the severe group. Mild cases were defined as those with mild symptoms and no manifestation of viral pneumonia or signs of hypoxia. Moderate cases were defined as patients with symptoms such as fever, cough, shortness of breath, or rapid breathing, SpO_2 > 90% on room air, but no signs of severe pneumonia. Severe cases were defined as patients with pneumonia symptoms such as fever, cough, shortness of breath, and rapid shallow breathing, with any of the following signs; respiratory rate > 30x/min, severe respiratory distress, or SpO_2 < 90% on room air. Critical cases were defined as patients with ARDS and sepsis or septic shock.[6] The patient underwent treatment according to the COVID-19 Clinical Practice Guidelines applicable at our hospital. Mild and moderate patients were included in the non-severe group, and severe and critical patients were included in the severe group. Patients were followed up until they expired or were discharged from the hospital.

Table 1: Demographic characteristics of study subjects according to severity level

Variable N(119)		Severe (n = 71)	Non-Severe (n = 48)	P-value [a]
Age (y)		**53.00 (45.0-60.00)**	**46.50 (32.25-54.00)**	**0.004**
Weight (kg)		70.00 (60.00-80.00)	68.00 (60.00-75.00)	0.087
BMI (kg/m^2)		**27.06 (23.44-29.38)**	**24.98 (22.69-28.67)**	**0.046**
Onset-admission time (days)		7.00 (5.00-10.00)	7.00 (5.00-8.00)	0.790
Initial SOFA score		**4.00 (3.00-5.00)**	**1.00 (0.00-2.00)**	**< 0.001**
HbA1C (%)		6.50 (6.00-9.60)	7.20 (6.70-9.70)	0.374
Initial blood sugar (mg/dL)		**175.00 (122.00-267.00)**	**123.50 (104.50-190.25)**	**0.001**
Initial AST (U/L)		63.00 (41.75-95.75)	51.00 (34.50-91.75)	0.328
Initial ALT (U/L)		56.00 (39.00-94.00)	53.00 (30.50-83.75)	0.309
Onset-to-hosp discharge time (days)		**23.00 (14.00-30.00)**	**24.00 (18.00-28.75)**	**< 0.001**
Time of First Secondary Infection (days)		6.00 (3.00-9.00)	7.00 (4.00-11.00)	0.290
Variable		**Percentage of non-survivors**	**Percentage of survivors**	**P-value [b]**
Sex	Men	**52 (73.2)**	**26 (54.2)**	**0.049**
	Women	**19 (26.8)**	**22 (45.8)**	
Referral from other hospitals	With referral	**53 (74.6)**	**20 (41.7)**	**< 0.001**
	Without referral	**18 (25.4)**	**28 (58.3)**	
Comorbidity				
Diabetes		33 (46.5)	15 (31.3)	0.128
Hypertension		25 (35.2)	9 (18.8)	0.064
Cardiac Problem [c]		7 (9.9)	1 (2.1)	0.141
Lung Problem [d]		4 (5.6)	2 (4.2)	1.000
Overweight		32 (45.1)	14 (29.2)	0.088
Obesity		13 (18.3)	9 (18.8)	1.000
Ward	Intensive Care	**49 (69.0)**	**8 (16.7)**	**< 0.001**
	Non-intensive care	**22 (31.0)**	**40 (83.3)**	
Secondary Infection		21 (29.6)	11 (22.9)	0.528
14 Day Mortality		**36 (50.7)**	**0 (0.0)**	**< 0.001**

Notes: *Data presented as Median (Q1-Q3) or n (%)*

[a] *: Mann-Whitney Test, significantly different if P < 0.05*

[b] *: Uji Chi Square Test, significantly different if P < 0.05*

[c] *: Cardiac Problem: Old Myocardium Infarction, Heart Failure, History of Arrhythmia*

[d] *: Pulmonary Problem: Asthma, Chronic Obstructive Pulmonary Disease, History of Tuberculosis (inactive case).*

AST: Aspartate Transferase; ALT: Alanine Transferase.

Statistical analysis

Statistical analysis was performed with SPSS statistical software version 25 (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.). Normality test was carried out using the Kolmogorov-Smirnov test. The Mann-Whitney test was used if the data were not normally distributed ($P < 0.05$). The Student's T-test was used if the data were normally distributed ($P > 0.05$). The variables are expressed as mean ± standard deviation or median (range). A categorical data difference test on two

Table 2: Demographic characteristics of research subjects based on 14 days mortality rate

Variable (n=119)		Non-Survivor (n = 36)	Survivor (n = 83)	P-value a
Age (y)		**55 (45-65)**	**51 (40-55)**	**0.004**
Weight (kg)		70 (60-83.75)	68 (60-75)	0.087
BMI (kg/m^2)		**27.94 (23.55-33.30)**	**25.39 (23.11-28.00)**	**0.046**
Onset-admission time (days)		7 (4-10)	7 (5-9)	0.790
Initial SOFA score		**4.5 (4-6)**	**3 (1-4)**	**< 0.001**
HbA1C (%)		7.4 (6.25-9.72)	6.9 (6-9.6)	0.374
Initial blood sugar (mg/dL)		**203 (137.75-279.25)**	**132 (111-190)**	**0.001**
Initial AST (U/L)		59.00 (37.00-108.00)	62.00 (36.00-88.00)	0.695
Initial ALT (U/L)		52.00 (32.00-94.00)	57.00 (36.00-87.00)	0.798
Onset-to-hosp discharge time (days)		**14 (10-17)**	**27 (20-33)**	**< 0.001**
Time of First Secondary infection (days)		4.50 (3.00-9.25)	7.00 (3.25-10.50)	0.518
		Percentage of non-survivors	**Percentage of survivors**	**P-value [b]**
Gender	Men	25 (69.4)	53 (63.9)	0.676
	Women	11 (30.6)	30 (36.1)	
Referral from other hospitals		25 (69.4)	48 (57.8)	0.306
Comorbidity				
Diabetes		**21 (58.3)**	**27 (32.5)**	**0.014**
Hypertension		**17 (47.2)**	**17 (20.5)**	**0.004**
Cardiac Problem [c]		5 (13.9)	3 (3.6)	0.054
Lung Problem [d]		3 (8.3)	3 (3.6)	0.365
Overweight		12 (33.3)	34 (41.0)	0.540
Obesity		**12 (33.3)**	**10 (12.0)**	**0.010**
Ward	Intensive Care	21 (58.3)	36 (43.4)	0.164
	Non-Intensive care	15 (41.7)	47 (56.6)	
Secondary Infection		12 (33.3)	20 (24.1)	0.369
Severity	Severe	**36 (100)**	**35 (42.2)**	**< 0.001**
	Non-Severe	**0 (0)**	**48 (57.8)**	

***Notes**: Data presented as Median (Q1-Q3) or n (%)*

a : Mann-Whitney Test, significantly different if P < 0.05

b : Uji Chi Square Test, significantly different if P < 0.05

c : Cardiac Problem: Old Myocardium Infarction, Heart Failure, History of Arrhythmia

d : Pulmonary Problem: Asthma, Chronic Obstructive Pulmonary Disease, History of Tuberculosis (inactive case).

AST: Aspartate Transferase; ALT: Alanine Transferase.

independent groups was carried out using the chi-square test, and categorical variables are expressed as absolute sums and proportions.

To assess cause-and-effect relationships, linear regression tests, or logistic regression tests were used. The Receiver Operating Characteristic (ROC) test was used to determine the severity or mortality. The cut-off value was determined based on the highest sensitivity and specificity in the ROC test. Assessment of positive ratio, negative dispute ratio, positive predictive value (PPV), negative prediction value (NPV) was based on ROC cut-off value. The risk of 14-days mortality was tested using the Univariate Cox Regression test and the

Table 3: Variable regression analysis

Independent Variables	Dependent Variables	Coefficient	p-value
Age (y)	Albumin (g/dL)	-0.011	<0.001 [a]
Albumin (g/dL)	D-dimer (ng/ml)	-6109.916	0.003 [a]
Albumin (g/dL)	**IL-6 (pg/ml)**	**-259.945**	**0.126 [a]**
Albumin (g/dL)	CRP (mg/L)	-10.048	0.004 [a]
Albumin (g/dL)	Severity [c]	-4.680	<0.001 [b]
Albumin (g/dL)	14-Day Mortality [d]	-3.467	<0.001 [b]

Notes:
a : Linear Regression, Significant if P < 0.05
b : Logistic Regression, Significant if P < 0.05;
c : value 0: non-severe; 1: severe
d : value 0: survivor; 1: non-survivor

Multivariate Cox Regression test. The life expectancy was examined by Kaplan-Meier test.

3. RESULTS

A total of 142 patients were enrolled in this study; 19 patients dropped out because they were not confirmed positive on PCR examination, and 4 patients dropped out because they refused treatment and asked to be discharged from the hospital.

Of the 119 study subjects, 71 (59.7%) were categorized as severe, and 48 (40.3%) were not severe (Table 1). There were significant differences in mean age (P = 0.004), BMI (P = 0.046), baseline SOFA score (P < 0.001), baseline blood sugar (0.001), and length of stay (P < 0.05). Furthermore, patients with severe conditions were more males than females (P = 0.049); more patients were referred than those who presented on their own (P < 0.001); more hospitalizations than non-intensive (P < 0.001), and more of them could not survive within 14 days (P < 0.01).

There were 36 (30.25%) non-survivors and 83 (69.75%) survivors within 14 days of admission (Table 2). The variables that were significantly different were age (P = 0.004), BMI (P = 0.046), initial SOFA score (P < 0.001), and baseline blood sugar (P = 0.001). The patients' baseline AST and ALT were similar (P = 0.695 vs. P = 0.798). Significant time from onset of symptoms to discharge from hospitalization; 14 (10-17) days vs. 27 (20-33) days (P < 0.001). The time to first secondary infection during hospitalization in non-survivor vs. survivors was similar; 4.50 (3.00-9.25) days vs. 7.00 (3.25-10.50) days (P = 0.518) after admission. Secondary infection occurred in 12 (33.3%) survivors and 20 (24.1%) survivors, but the difference was not statistically different (P = 0.369).

Regression analysis showed a significant effect that age had on albumin (Coeff -0.011) (P < 0.001), albumin on D-dimer (Coeff -6109,916) (P = 0.003), albumin on CRP (Coeff -10.048) (P = 0.004), albumin to severity (Coeff -4.680) (P < 0.001), and albumin to 14-day mortality (Coeff -3.467) (P < 0.001). The older the patient, the lower baseline albumin was found (Figure 1: A). Higher

Table 4: Cross-tabulation of albumin day 0-1 against severity and death 14 days

Cut Off Albumin 3.28 g/dL	To predict severity								
AUC 0.820	**Sens %**	**Spec %**	**LR+**	**LR-**	**PPV %**	**NPV %**	**Accuracy %**	**Relative Risk (95% CI)**	**P-value**
	74.65	77.08	3.26	0.33	82.81	67.27	75.63	2.530 (1.705-3.756)	< 0.001
Albumin < 3.28 g/dL	**To predict 14-day mortality**								
	77.78	56.63	1.79	0.39	43.75	85.45	63.03	3.008 (1.496-6.046)	0.001

Notes: *a: Chi-Square Test, significant if P < 0.05*
Se: Sensitivity; Sp: Specificity; LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio, PPV: Positive Predictive Value; NPV: Negative Predictive Value.

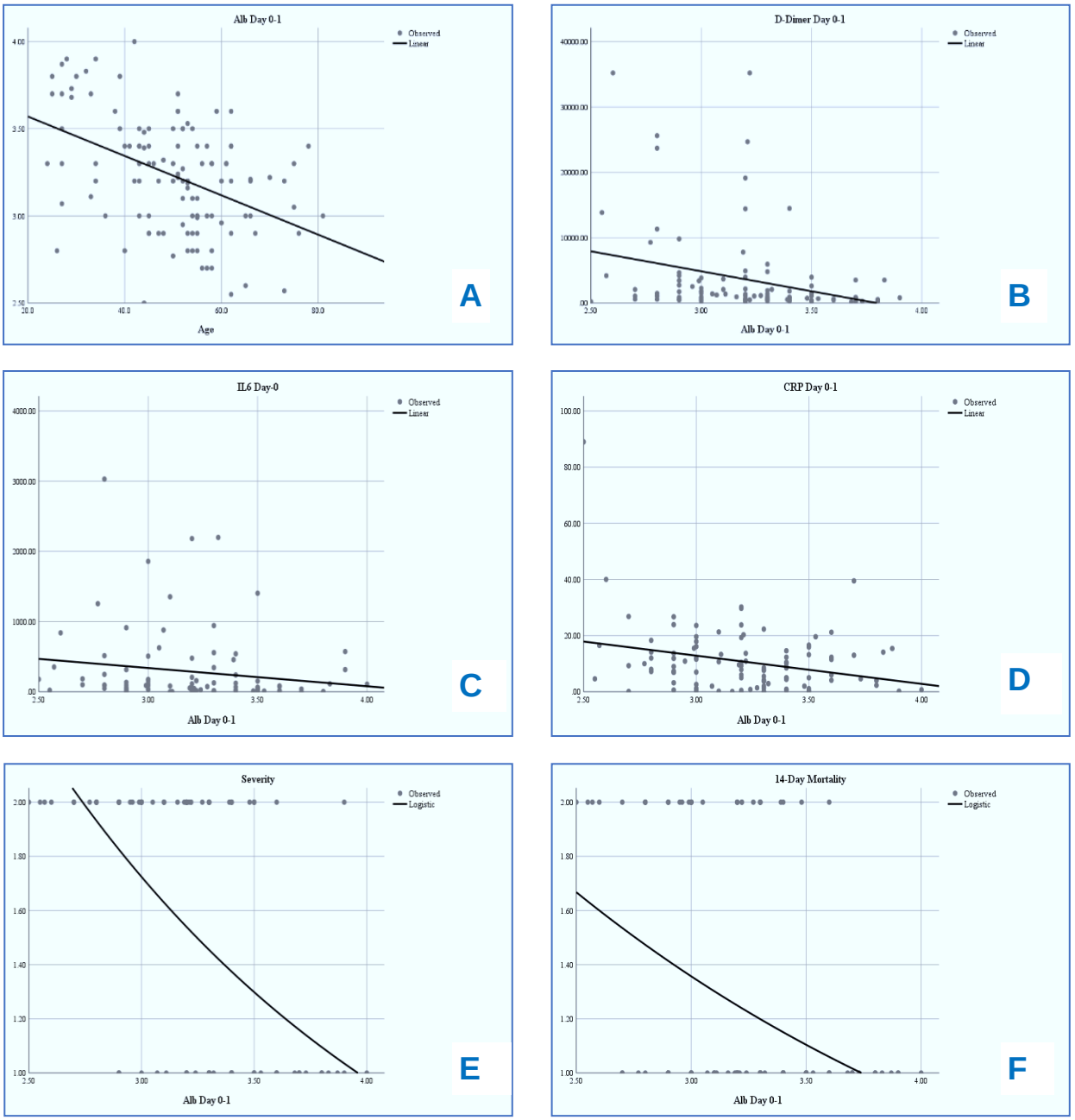


Figure 1: Scatterplot of the regression of albumin-related factors

Notes:

A: Scatter plot of linear regression of age to initial albumin. B: Scatter plot of linear regression of initial albumin to initial D-dimer. C: Scatter plot of linear regression of initial albumin to initial IL-6. D: Scatter plot of linear regression of initial albumin to initial CRP. E: Scatter plot of logistic regression of albumin to severity (1: non-severe; 2: severe). F: Scatter plot of logistic regression of albumin to 14-Day mortality (1: survivor; 2: non-survivor).

albumin on admission, D-dimer, and CRP were found to be lower (Figure 1: B & D). This means that the higher the baseline Albumin level, the lower the severity and 14-day mortality (Figure 1: E & F). Hypertension (HTN), obesity, diabetes mellitus (DM), geriatric age, and albumin less than 3.28 g/dL are the single significant prognostic factors for 14-day mortality which can be seen in Table 6. Patients with HTN were

Initial albumin ROC analysis for predicting COVID-19 severity showed that the optimal point was 3.28 g/dL

Table 5: Hazard ratio analysis for predicting 14-Day mortality

Variables	Univariate Analysis			Multivariate Analysis		
	Coefficient	HR (95% CI)	P [a]	Coefficient	HR (95% CI)	P [a]
Hypertension	0.914	2.495 (1.296-4.801)	0.006	0.626	1.871 (0.913-3.835)	0.087
Obesity	0.925	2.523 (1.260-5.053)	0.009	0.933	2.542 (1.248-5.178)	0.010
Diabetes Mellitus	0.826	2.285 (1.178-4.434)	0.015	**0.585**	**1.794 (0.877-3.670)**	**0.109**
Age > 65 y	1.170	3.222 (1.467-7.080)	0.002	0.838	2.312 (1.013-5.275)	0.046
Albumin < 3.28 (g/dL)	1.202	3.328 (1.517-7.303)	0.003	1.123	3.075 (1.378-6.859)	0.006

Notes: *[a]: Cox Regression Analysis, P-value < 0.05 considered as significant*

with a sensitivity of 74.6% and specificity of 77.1%, AUC of 0.820 (95% CI 0.744-0.897, P < 0.001) (Figure 2). Cross-tabulation using an albumin cut-off of 3.28 g/dL to predict severe illness and 14-days mortality is shown in Table 5. In predicting severity, albumin less than 3.28 g/dL resulted in a sensitivity of 74.65%, a specificity of 77.08 %, positive probability ratio (LR+) 3.26, negative likelihood ratio (LR-) 0.33, positive predictive value (PPV) 82.81%, negative predictive value (NPV) 67.27%, accuracy 75.63% (P < 0.001). In predicting 14-days mortality, albumin less than 3.28 g/dL resulted in sensitivity 77.78%, specificity 56.63% LR + 1.79, LR-0.39, PPV 43.75%, NPV 85.45% Accuracy 63.03% (P < 0.001).

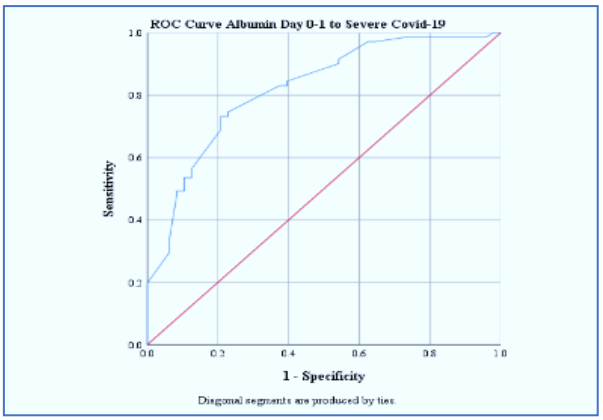
Hypertension (HT), obesity, diabetes mellitus (DM), geriatric age, and albumin less than 3.28 g/dL are the single significant prognostic factors for 14-day mortality which can be seen in table 6. Patients with hypertension were 2.495 (1.296- 4.801) times (P = 0.006) than normal people. Obese people had a HR of 2.523 (1.260-5.053) times that of normal people (P = 0,009). People with DM had HR 2.285 (1.178-4.434) times that of normal people (P = 0,015); People with age < 65 y had HR 3.222 (1.467-7.080) times compared to people with age > 65 y (P = 0.002). People with baseline albumin < 3.28 g/dL had a HR of 3.328 (1.517-7.303) compared with people with baseline albumin > 3.28 g/dL (P = 0.003).

Table 6: Survival time in 14-Days mortality

Variable	Survival time (days) of non-survivor	P-value [a]
Hypertension	10.636 ± 0.887	0.004
Obesity	10.309 ± 1.075	0.006
Diabetes mellitus	11.076 ± 0.730	0.011
Age > 65 y	9.167 ± 1.513	0.002
Albumin < 3.28 (g/dL)	11.177 ± 0.626	0.001

Notes: a : Kaplan-Meier Test; P-value < 0.05 considered as significant; Data shows Mean ± S)

The multivariate analysis in Table 6 shows that obesity,



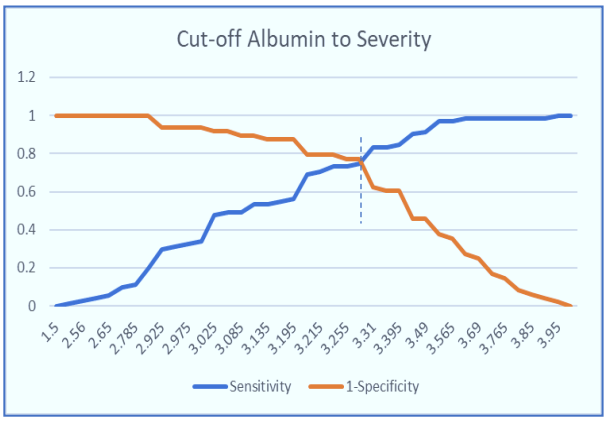


Figure 2: ROC Analysis of Albumin Day 0-1 to predict the Severe Covid-19

Notes: Receiver Operating Characteristic (ROC) Analysis shows AUC of 0.820 (95% CI 0.744-0.897, p<0.001) to predict severe Covid-19. The highest sensitivity and specificity were on the point of 3.28 g/dL, which produce a sensitivity of 74.6 % and a specificity of 77.1 %.

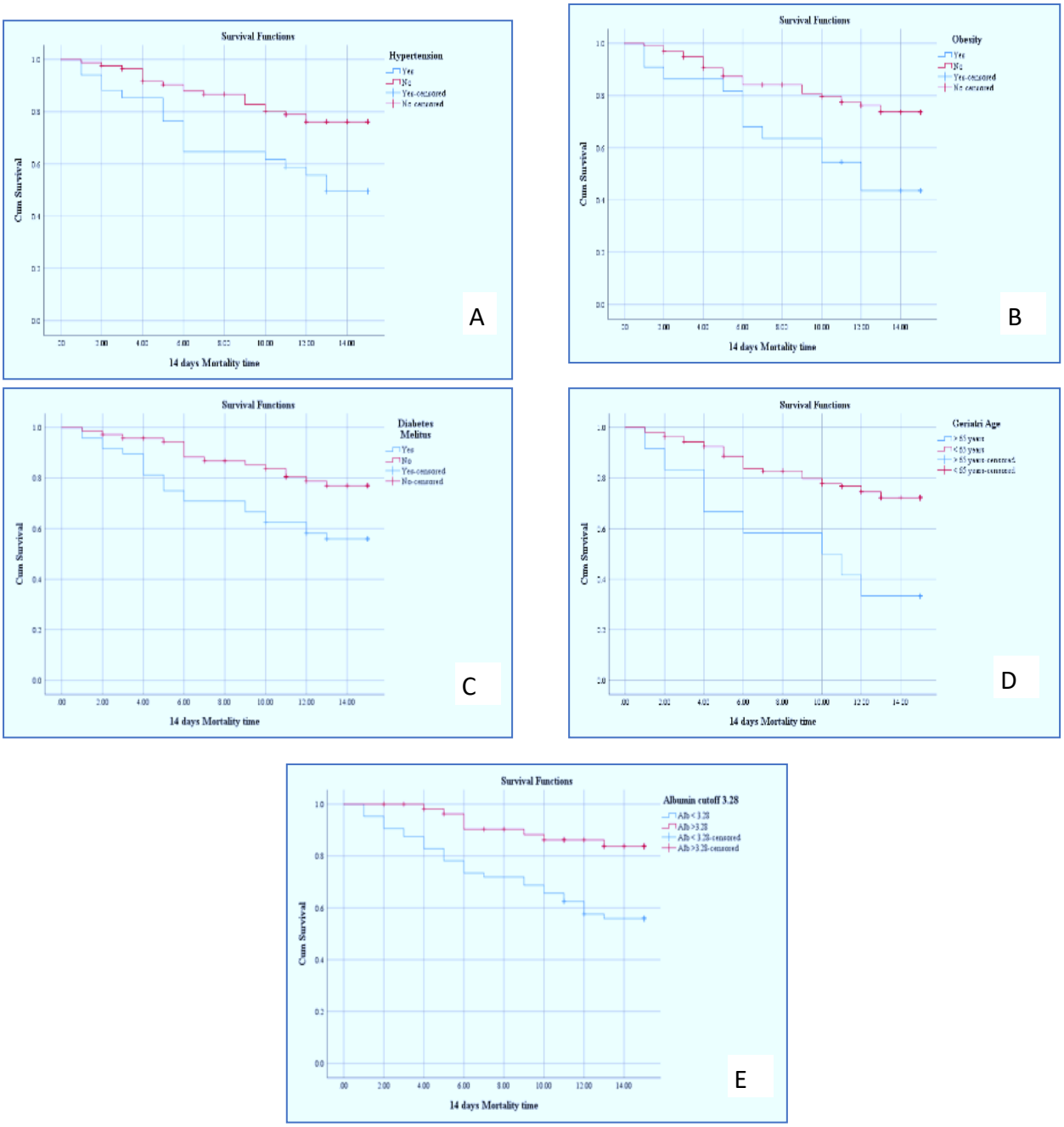


Figure 3: Survival Plots
Notes: 14-days survival plot with a factor of; A. Hypertension co-morbidity, B. Obesity, C. Diabetes mellitus, D. Geriatric (age > 65 y, E. Hypoalbuminemia (albumin < 3.28g/dl)

obesity, DM, age over 65 y, and albumin < 3.28 g/dL is shown in table 7. Nonsurvivable patients who have HTN, obesity, DM, age over 65 y, and albumin <3.28 g/dL had a survival time of 10,636 ± 0.887 days (P = 0.004), 10,309 ± 1.075 days (P = 0.006), 11.076 ± 0.730 days (P = 0.011), 9.167 ± 1.513 days (P = 0.002), 11,177 ± 0.626 days (P = 0.001) respectively. The life plot of the life analysis is depicted in Figure 3.

4. DISCUSSION

This study analyzed 119 COVID-19 patients, stratified into 2 severity groups, 71 (59.7%) categorized as severe and 48 (40.3%) as non-severe. The mean age was 55 y for the severe group (IQR 45.0-60.00) and 46.5 y (IQR 32.25-54.00) for the non-severe group.

Hypoalbuminemia in severe COVID-19 has been repeatedly discussed in the literature;[12–15] however, its predictive value has not been explored extensively. This study found that lower albumin levels at admission could predict a worse outcome from COVID-19, regardless of other known indicators such as age or comorbidities.

The study used the albumin level limit of 3.28 g/dL based on the ROC value, with a sensitivity of 74.6% and a specificity of 77.1%. The results of the study found that hypoalbuminemia is common in COVID-19 patients, especially those with severe disease. In addition, from the analysis we performed on the cross-tabulation, in predicting severity, albumin level < 3.28 g/dL had a positive likelihood ratio (LR+) 3.26, a negative likelihood ratio (LR-) 0.33, a positive predictive value (PPV).) 82.81%, and negative predictive value (NPV) of 67.27%, with an accuracy of 75.63%. In predicting 14 days mortality, albumin levels less than 3.28 g/dL resulted in LR+ 1.79, LR- 0.39, PPV 43.75%, and an NPV 85.45%, with an accuracy of 63.03%.

In a study conducted by Chen et al., they found that the mortality rate of patients with hypoalbuminemia was significantly higher than that of patients with normal albumin (23.85% vs. 0.9%). The proportion of patients with normal standard pulmonary CT, normal CRP and normal lymphocytes at discharge was higher in patients with normal serum albumin levels. They also found that COVID-19 patients with hypoalbuminemia were 2.121 times more likely to have severe disease and 1.479 times more likely to be hospitalized than patients with normal albumin, suggesting that patients with hypoalbuminemia are sick, have a poorer prognosis, and require a more extended period of treatment.[24]

Regression analysis showed significant results, regarding effect of patient's age on albumin; the older the patient, the lower the initial albumin level found (Figure 1: A). Regarding the effect of albumin on D-dimer, the higher the albumin on admission, D-dimer and CRP were higher (Figure 1: B & D). The effect of albumin on the severity and 14-day mortality was also significant. The higher the albumin, the lower the severity and 14-day mortality (Figure 1: E & F).

This study also showed a statistically significant relationship between albumin and D-dimer with severity based on days of hospitalization, indicating that the longer the hospitalization, the higher the albumin value and the higher the grade (Table 2).

The results of this study differ with the results of previous studies.[25] A study by Kheir et al. concluded decreased albumin levels with favorable outcomes in hospitalized COVID-19 patients.[26]

There are several explanations for the inverse relationship between hypoalbuminemia and severe disease. As an anti-inflammatory and antioxidant protein, albumin protects against cytokine storms and prevents multi-organ damage. In addition, albumin contains anticoagulant properties and inhibits coagulation and platelet activation associated with oxidative stress.

These results are also consistent with other studies regarding the correlation of D-dimers with outcomes in critically ill patients.[27–29] Other studies found that higher D-dimer values at hospital admission were significantly associated with in-hospital mortality. In COVID-19 patients,[30] The most common reasons cited in the literature for increased D-dimer include viremia and cytokine storm syndrome, which elevated pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF-α) is insufficiently controlled by anti-inflammatory factors that overwhelm the coagulation cascade.

A study by Vatansever and Becker stated that the baseline levels of IL-6 were closely related to the severity of COVID-19, and elevated IL-6 was significantly associated with clinical manifestations of the severe type.[31] Another study concluded that serum IL-6 and CRP levels could effectively assess disease severity and predict outcomes in COVID-19.[32]

Our study concluded that IL-6 levels showed significantly lower levels than albumin and D-dimer levels and were ineffective at days 3-4, and CRP was not substantial at days 8-10 and 14-15. This may be due to the reduced number of samples obtained due to drop-out criteria and limited resources. A study supported this statement that repeated measurements of IL-6 can assist physicians in identifying critically ill COVID-19 patients with the highest risk of poor prognosis.[33]

The presence of HTN, obesity, DM, geriatric old age, and albumin less than 3.28 g/dL were the single significant prognostic factors for 14-day mortality, as shown in Table 6. Hypertensive patients with a hazard ratio (HR) of 2,495 times that of ordinary people. Obese patients have HR 2.523 times, DM has HR 2.285 times, age > 65 y have had HR 3.222 times, and initial albumin < 3.28 g/dL has HR 3.328 times. The multivariate analysis in Table 6 shows that obesity, geriatric old age, and albumin < 3.28 g/dL co-exist in causing death at day 14; This is presumably because the prevalence of hypoalbuminemia affects about nine out of ten geriatric patients through physiological changes and nutritional problems.[25]

The presence of HTN, obesity, DM, geriatric age, and albumin less than 3.28 g/dL were the single significant prognostic factors for 14-day mortality, as shown in Table 6; HTN 2.495 times, obesity 2.523 times, DM 2.285 times, age > 65 y 3.222 times, and albumin < 3.28 3,328 times. While the multivariate analysis in Table 6

shows that obesity, geriatric age, and albumin < 3.28 g/dL play a role together, which can cause death within 14 days; This is presumably because the prevalence of hypoalbuminemia affects about nine out of ten geriatric patients through physiological changes and nutritional problems.[25]

Furthermore, regarding obesity, this condition does not always mean optimal nutritional status. In fact, in the recent years, the term sarcopenic obesity has become increasingly relevant. Although there are still some concerns regarding its definition and diagnostic method, sarcopenia can be defined as a pathological condition characterized by a general loss of skeletal muscle mass and function. The prevalence of sarcopenic obesity is estimated at 2% for patients aged 60-69 y and increases to 10% for subjects aged over 80 y. However, few studies have dealt with sarcopenic obesity and its effects in subjects under 65 y of age. The pathogenesis is complex and multifactorial, with age, insulin resistance, and inflammatory mediators playing relevant roles. Therefore, SARS-CoV-2 infection in individuals with sarcopenic obesity or hypoalbuminemia may have a poorer prognosis by exacerbating this inflammatory state.[3]

5. CONCLUSION

The state of hypoalbuminemia affects the severity and mortality of COVID-19 patients and is inversely related to increased D-dimer and IL-6. In addition, it has a poor prognosis if albumin is < 3.28 g/dL in geriatric patients and those suffering from obesity with a high mortality rate within 14 days.

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7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

AUH: Concept, Study design, Provision of study materials, Data collection, Manuscript writing

HH: Concept, Study design, Manuscript writing

BPS: Concept, Study design, Manuscript writing

MGSW: Provision of study materials, Data collection, Manuscript writing

11. REFERENCES

1. Liu J, Liao X, Qian S, Yuan J, Wang F, Liu Y, et al. Community Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, Shenzhen, China, 2020. Emerg Infect Dis. 2020 Jun;26(6):1320-1323. [PubMed] DOI: 10.3201/eid2606.200239
2. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020 Mar 5;382(10):929-936. [PubMed] DOI: 10.1056/NEJMoa2001191
3. Gorham J, Moreau A, Corazza F, Peluso L, Ponthieux F, Talamonti M, et al. Interleukine-6 in critically ill COVID-19 patients: A retrospective analysis. PLoS One. 2020 Dec 31;15(12):e0244628. [PubMed] DOI: 10.1371/journal.pone.0244628
4. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nat Med. 2004 Dec;10(12 Suppl):S88-97. [PubMed] DOI: 10.1038/nm1143
5. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med. 2020 May;8(5):433-434. [PubMed] DOI: 10.1016/S2213-2600(20)30127-2
6. Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz. 2020 May;45(3):230-232. [PubMed] DOI: 10.1007/s00059-020-04909-z
7. Moman RN, Gupta N, Varacallo M. Physiology, Albumin. 2022 Dec 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. [PubMed]
8. Fasano M, Curry S, Terreno E, Galliano M, Fanali G, Narciso P, et al. The extraordinary ligand binding properties of human serum albumin. IUBMB Life. 2005 Dec;57(12):787-96. [PubMed] DOI: 10.1080/15216540500404093
9. Gom I, Fukushima H, Shiraki M, Miwa Y, Ando T, Takai K, et al. Relationship between serum albumin level and aging in community-dwelling self-supported elderly population. J Nutr Sci Vitaminol (Tokyo). 2007 Feb;53(1):37-42. [PubMed] DOI: 10.3177/jnsv.53.37
10. Yin M, Si L, Qin W, Li C, Zhang J, Yang H, et al. Predictive Value of Serum Albumin Level for the Prognosis of Severe Sepsis Without Exogenous Human Albumin Administration: A Prospective Cohort Study. J Intensive Care Med. 2018 Dec;33(12):687-694. [PubMed] DOI: 10.1177/0885066616685300
11. Abdeen Y, Kaako A, Ahmad Amin Z, Muhanna A, Josefine Froessl L, Alnabulsi M, et al. The Prognostic Effect of Serum Albumin Level on Outcomes of Hospitalized COVID-19 Patients. Crit Care Res Pract. 2021 Jun 9;2021:9963274. [PubMed] DOI: 10.1155/2021/9963274
12. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int. 2020 Sep;40(9):2095-2103. [PubMed] DOI: 10.1111/liv.14455
13. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020 Jul 28;71(15):762-768. [PubMed] DOI: 10.1093/cid/ciaa248

14. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and Clinical Significance. JPEN J Parenter Enteral Nutr. 2019 Feb;43(2):181-193. [PubMed] DOI: 10.1002/jpen.1451
15. Ramadori G. Hypoalbuminemia: an underestimated, vital characteristic of hospitalized COVID-19 positive patients? Hepatoma Res. 2020;6:28. DOI: 10.20517/2394-5079.2020.43
16. Utariani A, Rahardjo E, Perdanakusuma DS. Effects of Albumin Infusion on Serum Levels of Albumin, Proinflammatory Cytokines (TNF-α, IL-1, and IL-6), CRP, and MMP-8; Tissue Expression of EGRF, ERK1, ERK2, TGF-β, Collagen, and MMP-8; and Wound Healing in Sprague Dawley Rats. Int J Inflam. 2020 May 20;2020:3254017. [PubMed] DOI: 10.1155/2020/3254017
17. Violi F, Ceccarelli G, Cangemi R, Alessandri F, D'Ettorre G, Oliva A, et al. Hypoalbuminemia, Coagulopathy, and Vascular Disease in COVID-19. Circ Res. 2020 Jul 17;127(3):400-401. [PubMed] DOI: 10.1161/CIRCRESAHA.120.317173
18. Aloisio E, Serafini L, Chibireva M, Dolci A, Panteghini M. Hypoalbuminemia and elevated D-dimer in COVID-19 patients: a call for result harmonization. Clin Chem Lab Med. 2020 Oct 25;58(11):e255-e256. [PubMed] DOI: 10.1515/cclm-2020-1038
19. Violi F, Ceccarelli G, Loffredo L, Alessandri F, Cipollone F, D'ardes D, et al. Albumin Supplementation Dampens Hypercoagulability in COVID-19: A Preliminary Report. Thromb Haemost. 2021 Jan;121(1):102-105. [PubMed] DOI: 10.1055/s-0040-1721486
20. Xu Y, Yang H, Wang J, Li X, Xue C, Niu C, et al. Serum Albumin Levels are a Predictor of COVID-19 Patient Prognosis: Evidence from a Single Cohort in Chongqing, China. Int J Gen Med. 2021 Jun 24;14:2785-2797. [PubMed] DOI: 10.2147/IJGM.S312521
21. Gradel KO, Thomsen RW, Lundbye-Christensen S, Nielsen H, Schønheyder HC. Baseline C-reactive protein level as a predictor of mortality in bacteraemia patients: a population-based cohort study. Clin Microbiol Infect. 2011;17(4):627-32. [PubMed] DOI: 10.1111/j.1469-0691.2010.03284.x
22. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018 Apr 13;9:754. [PubMed] DOI: 10.3389/fimmu.2018.00754
23. J Juvela S, Kuhmonen J, Siironen J. C-reactive protein as predictor for poor outcome after aneurysmal subarachnoid haemorrhage. Acta Neurochir (Wien). 2012 Mar;154(3):397-404. [PubMed] DOI: 10.1007/s00701-011-1243-7
24. Ho KM, Lee KY, Dobb GJ, Webb SA. C-reactive protein concentration as a predictor of in-hospital mortality after ICU discharge: a prospective cohort study. Intensive Care Med. 2008 Mar;34(3):481-7. [PubMed] DOI: 10.1007/s00134-007-0928-0
25. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127:104370. [PubMed] DOI: 10.1016/j.jcv.2020.104370
26. World Health Organization. Living guidance for clinical management of COVID-19; 2021. Available from: who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2
27. Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. PLoS One. 2021 Mar 16;16(3):e0248358. [PubMed] DOI: 10.1371/journal.pone.0248358
28. Chen C, Zhang Y, Zhao X, Tao M, Yan W, Fu Y. Hypoalbuminemia - An Indicator of the Severity and Prognosis of COVID-19 Patients: A Multicentre Retrospective Analysis. Infect Drug Resist. 2021 Sep 9;14:3699-3710. [PubMed] DOI: 10.2147/IDR.S327090
29. Shorr AF, Thomas SJ, Alkins SA, Fitzpatrick TM, Ling GS. D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ill patients. Chest. 2002 Apr;121(4):1262-8. [PubMed] DOI: 10.1378/chest.121.4.1262
30. Nugroho J, Wardhana A, Maghfirah I, Mulia EPB, Rachmi DA, A'yun MQ, et al. Relationship of D-dimer with severity and mortality in SARS-CoV-2 patients : A meta-analysis. Int J Lab Hematol. 2021;43(1):110-115. [PubMed] DOI: 10.1111/ijlh.13336
31. Vidali S, Morosetti D, Cossu E, Luisi MLE, Pancani S, Semeraro V, et al. D-dimer as an indicator of prognosis in SARS-CoV-2 infection: a systematic review. ERJ Open Res. 2020;6(2):00260-2020. [PubMed] DOI: 10.1183/23120541.00260-2020
32. Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS One. 2021;16(8):e0256744. [PubMed] DOI: 10.1371/journal.pone.0256744
33. Vatansever HS, Becer E. Relationship between IL-6 and COVID-19: to be considered during treatment. Future Virol. 2020 Dec:10.2217/fvl-2020-0168. [PMC] DOI: 10.2217/fvl-2020-0168

