Original Article

Relationship Between D-Dimer, Albumin Levels, and Outcome of COVID-19 Patients at Dr. M. Djamil General Hospital, Padang

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Abstract

Background: Several studies have found an increase in D-dimer levels in patients who died from a severe clinical condition. COVID-19 exhibits multi-organ dysfunction through several markers, including decreased albumin levels. There were some studies that were interested in understanding how D-dimer and albumin levels relate to the outcomes of COVID-19 patients. The aim of this study was to investigate the relationship between D-dimer, albumin levels, and patient outcomes.

Method: This was a cross-sectional study of all COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang, from January 1st, 2021 to December 31st, 2021.

Results: The majority of patients (40.71%) were in the group of 18 and 49 years old; more than half of the subjects (56.16%) were female; and obesity was the most common comorbidity (40.9%). The majority of the subjects (42.79%) had moderate clinical COVID-19. Higher D-dimer levels had a statistically significant independent relationship with unfavorable outcomes (P=0.0001). Lower albumin levels had a statistically significant independent relationship with unfavorable outcomes (P=0.0001). Higher D-dimer and lower albumin each contributed 12.6% to patient outcome. Increasing D-dimer levels per 1 ng/mL would increase the probability of an unfavorable outcome by 0.120 times, and on the other hand, increasing albumin levels per 1 g/dL would increase the probability of survival by 2.143 times.

Conclusion: Higher D-dimer levels independently had a relationship with an unfavorable outcome. Higher albumin levels were independently related to a favorable outcome.

Keywords: albumin, D-dimer, COVID-19, outcome, relationship

INTRODUCTION

The clinical presentation of COVID-19 varies from asymptomatic to critical for each individual.[1] Most patients have mild symptoms and a good prognosis, but it is estimated that 5-20% of symptoms worsen and require intensive care, particularly in elderly patients with comorbidities. Severe to critical symptoms have been reported in 20-26% of COVID-19 cases, necessitating adequate oxygenation and mechanical ventilation, with a poor prognosis and varying mortality rates. Clinicians must

identify clinical severity early to prevent disease progression, a poor prognosis, and death.[1]

Cytokine Release Syndrome (CRS) or cytokine storm contributes to the pathogenesis of acute respiratory distress syndrome (ARDS), coagulation dysfunction, and multi-organ dysfunction in COVID-19, increasing morbidity and mortality.[2] Hypercoagulopathy has been reported in the early stages of COVID-19; it is critical to detect it in patients, particularly those with risk factors for this increase.[3] Tang et al reported that the most common complications in COVID-19 patients who died were coagulopathy and thrombosis.[4]

Tang et al also observed a consistent relationship between D-dimer and prothrombin time at 28 days of death in COVID-19 patients in another study. Oxygen delivery barriers are caused by disseminated intravascular coagulation (DIC) events and multi-organ dysfunction caused by excessive thrombus deposition in the microvascular. Tang et al found that DIC occurred in 71.4% of patients who died.[5]

Early detection to assess the risk of disease progression is important because it affects therapy strategy and death prevention. Several studies found that D-dimer levels were higher in patients with severe clinical disease who died compared to non-survivors and survivors. The assessment of coagulopathy markers is a priority for COVID-19 patients at the start of treatment.[1,3] Increased D-dimer as a coagulopathy marker reflects hypercoagulopathy and thrombosis and can help clinicians decide whether to use anticoagulants in COVID-19 patients.[1,2,5]

Varikasuvu et al reported an association between D-dimer levels and COVID-19 progressivity in their study. High D-dimer levels are linked to an increased risk of coagulopathy and thrombosis in patients. Clinically significant Plasminogen Activator Inhibitor-1 (PAI-1) levels are elevated in COVID-19 patients, which can disrupt the fibrinolytic system and lead to thrombus formation. It can cause vasoconstriction due to hypoxemia via reduced blood flow and vascular occlusion, endothelial dysfunction, and inflammation, particularly in patients with co-morbidities such as hypertension, diabetes, and the elderly.[1,4]

Khodeir et al observed multi-organ dysfunction in COVID-19 through several markers that reflect this condition, including increased aspartate aminotransferase (AST), creatinine, and decreased albumin levels. Decreased albumin levels, with a mean of 3.0 g/dL, were strongly associated with disease progression in severe and critical cases.[3]

According to Violi et al, there was a strong correlation between hypoalbuminemia and hypercoagulopathy, as evidenced by an increase in serum D-dimer levels.[6] According to Aloisio et al, a serum albumin level of ≤3.5 g/dL was highly significant for a fourfold increase in D-dimer levels (upper value of 500 ng/mL) compared to a serum albumin level of >3.5 g/dL. As a causal relationship, this represents the harmonization of decreased albumin levels and increased D-dimer.[7]

Albumin has the ability to downregulate Angiotensine Converting Enzyme-2 (ACE2), which is important for modulating COVID-19 infection. According to Hariyanto et al, when albumin levels were low, ACE2 receptors were activated, and COVID-19 infectivity increased.[8]

Mahardhika et al also found increased D-dimer levels as coagulopathy markers and the inflammatory marker C-reactive protein (CRP) in patients with clinically asymptomatic conditions, which was unusual.[9] The challenge is determining how to detect worsening conditions early in the management of COVID-19 patients. Effective markers can assist in the screening, treatment, and prevention of serious complications.[8]

The authors were interested in examining how D-dimer and albumin levels were related to the outcomes of COVID-19 patients treated at Dr.M. Djamil General Hospital, Padang, based on the background and the limited research on the relationship between D-dimer, albumin levels, and patient outcomes.

METHOD

This was a cross-sectional retrospective study. The study was conducted from January to November 2022 at Dr. M. Djamil General Hospital, Padang. All COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang were tested for D-dimer and albumin levels between January 1, 2021, and December 31, 2021.

The COVID-19 patients treated in the isolation room who were examined for D-dimer and albumin levels; had complete medical record data; and were 18 years old and over, were eligible for the study. COVID-19 patients are divided based on their clinical level of severity, including mild, moderate, severe, and critical.

The COVID-19 patients who had previously received albumin therapy both orally and intravenously, confirmed COVID-19 patients >72 hours, patients with comorbid autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus (SLE), rheumatic heart disease, primary Sjogren's, fibrous bone dysplasia, juvenile idiopathic arthritis (JIA), and uveitis in JIA), chronic inflammation (Erdheim-chester disease, Behcet's syndrome, systemic sclerosis, large cell arteritis), hormonal disorders, thyroid disease, post-organ transplantation, kwarshiorkor malnutrition and nephrotic syndrome were all excluded from the study.

RESULTS

This study included all COVID-19 patients who were treated in the COVID-19 isolation room from January 1, 2021, to December 31, 2021, and met the inclusion and exclusion criteria. A total of 479 COVID-19 patients were selected to be analyzed from the 543 COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. Table 1 shows the characteristics of COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang.

Tabel 1. The COVID-19 Patients Characteristics Treated at RSUP Dr. M. Djamil, Padang (N=479)

The Characteristics of Patients	N	%
Age (year)		
18–49 year	195	40.71
50–59 year	120	25.05
60–69 year	101	21.09
≥70 year	63	13.15
Gender		
Male	210	43.84
Female	269	56.16
Comorbid		
Obesity	196	40.90
Hypertension	54	11.27
Diabetes melitus	47	9.81
Cardiovascular Disease	23	4.80
Chronic Kidney Disease	16	3.34
Malignancy	15	3.10
Chronic Pulmonary Disease	11	2.29
Cerebrovascular Disease	19	3.97
Chronic Liver Disease	13	2.71
Clinical Severity		
Mild	24	5.01
Moderate	205	42.79
Severe	106	22.13
Critical	144	30.06

Table 1 shows that majority of patients (40.71%) with COVID-19 were aged 18-49 years, and most of them (56.16%) were female. Obesity was the most common comorbid condition for 196 (40.9%) patients, followed by 54 (11.27%) patients with hypertension, 47 (9.81%) patients with diabetes, and 11 (2.29%) patients with chronic pulmonary disease. The majority of the subjects, 205 (42.79%) patients, had moderate clinical severity of COVID-19, and a small proportion had mild clinical severity (5.01%).

Table 2 shows that the following COVID-19 patient characteristics have a statistically significant relationship with the outcome of COVID-19 patients: age group 18-49 years, age group 60-69 years, age ≥70 years, comorbid of cerebrovascular disease, chronic liver disease, mild clinical severity, moderate clinical severity, and critical clinical severity.

Table 2. The characteristicss of COVID-19 patients in each outcome group treated at Dr. M. Djamil General Hospital, Padang

The Characteristics of Patients	The Outcome		P
	Alive (n=350)	Died (n=129)	
Age (year)			
18–49 year	168	27	0.0001*[a]
50–59 year	85	35	1.000
60–69 year	63	38	0.006*[a]
≥70 year	34	29	0.0001*[a]
Gender			
Male	146	64	1.000
Female	204	65	1.000
Comorbid			
Obesity	147	96	0.428
Hypertension	39	15	0.882
DM	34	13	0.906
CVD	16	7	0.698
CKD	12	4	0.859
Malignancy	10	5	0.570
COPD	7	4	0.476
CVA	9	10	0.010*[a]
CLD	7	6	0.113
Clinical Severity			
Mild	24	0	0.002*[a]
Moderate	187	18	0.0001*[a]
Severe	85	21	1.000
Critical	54	90	0.0001*[a]

Note: DM=Diabetes melitus; CVD=Cardiovascular Disease; CKD=Chronic Kidney Disease; COPD=Chronic Obstructive Pulmonary Disease; CVA=Cerebrovascular Disease; CLA=Chronic Liver Disease; *P<0.05 significant; [a]Pearson Chi-Square Test

Table 3 shows that D-dimer levels have a significant relationship with patient outcomes, with value of P=0.0001.

Table 3. The association between D-dimer levels and clinical outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang

D-dimer level (ng/mL)	Clinical Outcomes		R^2	OR	P	P adjusted
	Alive (n=350)	Died (n=129)				
≤500	71 (20.28%)	3 (2.32%)	0.126*[b]	0.120	0.0001*[c]	0.044*
>500	279 (79.71%)	126 (97.67%)				

Note: *P<0.05 significant; [b]Negerkerkle R Square; [c]Wald Test

Table 4. The association between albumin levels and clinical outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang

Abumin level (g/dL)	Clinical Outcomes		R^2	OR	P	P adjusted
	Alive (n=350)	Died (n=129)				
≤3.5	131 (37.42%)	79 (61.24%)	0.126*[b]	2.143	0.0001*[c]	0.0001*
>3.5	219 (62.57%)	50 (38.70%)				

Note: *P<0.05 significant; [b]Negerkerkle R Square; [c]Wald Test

D-dimer levels >500 ng/mL were statistically correlated with mortality outcomes and D-dimer levels ≤500 ng/mL had a statistically significant correlation with survival outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang.

D-dimer levels, statistically, contributed 12.6% to the outcome of COVID-19 patients. There was a negative effect, with each 1 ng/mL increase in D-dimer levels decreasing the patient's outcome probability by 0.120 times.

Albumin levels had a significant relationship with patient outcomes, as shown in Table 4, with value of P=0.0001. Albumin levels >3.5 g/dL had a statistically significant correlation with survival outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang and albumin levels ≤3.5 g/dL were statistically correlated with mortality.

Albumin levels contributed 12.6% to the outcome of COVID-19 patients, according to statistics. There was a positive effect, with each 1 g/dL increase in albumin levels escalating the patient's chances of survival by 2.143 times.

DISCUSSION

This study found that the most common age range was 18-49 years (40.71%)and this finding is consistent with the study by Klaiber et al in England, who found that the age range of 18-39 years (42.5%) had the highest incidence of COVID-19.[10] According to a report published in South Korea by Yu et al, the age group 20-39 years also had the highest incidence of COVID-19 (37%).[11] Nabilah also reported in an epidemiological study that the age range of 46 years had the highest incidence of COVID-19 in Semarang.[12]

The incidence of COVID-19 is closely related to age under 50 years; this is based on low adherence to poor preventive behavior and low adherence to social distancing, the habit of washing hands, wearing masks, and social interaction, all of which cause high transmission in young adults.[12,13]

These findings contradict the findings of Novelli et al in Italy, who reported that the majority of COVID-19 patients were over the age of 70. Age 70 is associated with high comorbidities and old

age, namely immunosuppression, which can reduce the immune system, resulting in high virulence and worsening the patient's clinical condition.[14]

The majority of COVID-19 patients were females according to this study. This is consistent with the findings of Fortunato et al, who reported that the incidence of COVID-19 is higher in women than in men.[15] The female gender of the East Asian race is said to have higher ACE2 receptor expression, increasing the likelihood of COVID-19 infection. Surendra et al in Jakarta reported different findings, saying that most COVID-19 patients were male.[16]

Novelli et al also reported the same result. Men (72.4%) were the most common COVID-19 patients in Italy. In contrast, men are more susceptible to COVID-19 infection due to innate immunity, steroid hormones, and sex hormone-related factors. Compared to men, the X chromosome in women reduces viral load thereby reducing inflammation.[14] Men are also associated with a poor lifestyle compared to women.[14,15]

This study obtained that obesity was the most common comorbidity in COVID-19 patients, followed by hypertension (11.27%), diabetes mellitus (9.81%), and a small proportion of chronic lung disease (2.29%). Tsang et al reported similar finding that obesity, diabetes mellitus, and hypertension were the most common comorbidities in COVID-19 patients. Comorbidities will increase morbidity and mortality in COVID-19 patients, particularly those over 60. Obesity, in combination with diabetes and hypertension, will worsen the outcome in COVID-19 patients.[17]

Novelli et al in Italy found that hypertension (53.3%) was the most common comorbidity, followed by obesity (21.2%), and diabetes (19.0%) among COVID-19 patients.[14] According to a reported study from China, the most common comorbidities were hypertension and diabetes mellitus, associated with older age.[16] Obesity can indirectly increase the expression of ACE2, which is produced by ACE2-expressing adipose cells. The abnormal cytokines and complement production cause an acute decrease in inflammation. This raises the likelihood of coagulopathy and contributes to COVID-19 mortality.[18]

The severity of COVID-19 is related to hypertension. The immune system is dysregulated in COVID-19 due to hypertension. Monocytes and other immune cells will produce more IL-6 and increase CD8+ T cells, which will produce tumor necrosis factor (TNF). This causes an increase in cytokine production.[14,17] Diabetes mellitus is said to be more vulnerable due to hyperglycemia, which decreases viral clearance, impairs T cell function, and increases inflammation.[14]

According to this study, the majority of patients had moderate clinical severity (42.79%). This is consistent with the findings of Varikasuvu et al, who discovered that the clinical severity in the majority of COVID-19 patients was mild to moderate; however, 20-26% of cases will be severe or critical.[1]

We found that the agerange of 18-49 years was significantly related to survival outcomes, with value of P=0.0001. This is consistent with a study by Gold et al in Georgia, which found that the age range of 18-49 years had a high survival rate (95.5%).[19] Tsang et al discovered that age played a significant role in increasing the case fatality rate (CFR) among COVID-19 patients by 3.4% as they got older.[17] This study found that the age ranges of 60-69 and ≥70 years were significantly related to the outcome of COVID-19 patients, with patients who died accounting for more than half of the survivors.

This report is consistent with a research conducted by Gold et al in Georgia in 2020, which stated that the mortality rate of COVID-19 patients in this age group was higher (35.6%).[19] This is consistentwith the findings of Tsang et al who discovered that the age range of 20-29 years had a CFR of 0-0.2%, the age range of 30-39 years had a CFR of 0.2-0.3%, and then continued to increase until age ≥80 years that had a CFR of 14.8-20.2%. In these COVID-19 patients, the risk of death is related to age and comorbidities.[17]

The Italian Institute of Health report also found that ages 60 and 80 were strongly related to the outcome of patients who died.[20] A high number of comorbidities are associated with old age, and in elderly patients, it is associated with immunosuppressive conditions that can weaken the immune system, resulting in high virulence and aggravating the patient's clinical condition. Aging is also linked to an inflammatory response.[14]

Except for cerebrovascular disease, which had a significant value of P<0.05, and chronic liver disease after adjustment, the results of this study revealed no significant relationship between comorbidities and the outcome of COVID-19 patients at Dr. M. Djamil General Hospital, Padang. This is consistent with the findings of Shang et al, who found that while comorbidities were not significantly related to the outcome of COVID-19 patients, age did play a significant role.[21]

Cerebrovascular disease is linked to an increased riskof severe COVID-19 and death, with odds ratios of 2.24 and 12.27, respectively. This results in disability, and SARS-CoV-2 can cause direct nerve damage or vascular problems such as stroke, as well as increased proinflammatory cytokines, which damage the vascular endothelium and increase blood coagulability.[22] The underlying mechanism is thrombus formation, cell damage, the endothelial barrier, the inflammatory response, or directly SARS-CoV-2 can damage endothelial cells via ACE2 receptors, resulting in vascular endothelial barrier damage and vascular rupture, particularly in the brain.[23]

According to Alwafi et al, chronic liver diseaseincreased the odds ratio for death in COVID-19 patientsby 1.92 times.[24] Chronic liver disease, according to Zhou et al, had no significant relationship with COVID-19 outcome.[25] Novelli et al in Italy reported that comorbidities such as hypertension, chronic kidney disease, malignancy, and

cardiovascular disease were strongly associated with the outcome of COVID-19 patients. Chronic kidney disease is associated with ongoing inflammation, which can aggravate COVID-19. Cancer is linked to immunocompromised states.[14]

Tsang et al also stated that age and comorbidities play a significant role in the outcome of COVID-19 patients, with cardiovascular disease being the leading cause of death. According to the Institute of Health in Italy, co-morbidities such as diabetes mellitus, hypertension, and cardiovascular disease played an important role in the clinical severity of COVID-19 patients, which had an impact on increasing COVID-19 patient mortality.[17]

In a study of 32,583 COVID-19 patients in Mexico, Marin et al discovered that obesity, followed by diabetes mellitus and hypertension, had a tendency for progression and mortality.[26] Obesity increases ACE2 expression via adipose cells. The abnormal cytokines and complement production cause an acute decrease in inflammation. This raises the likelihood of coagulopathy and contributes to COVID-19 mortality.[18]

According to the findings of this study, mild, moderate, and critical clinical severity have a significant relationship with the outcome of COVID-19 patients who do not have severe clinical severity. Clinical severity, from mild to moderate, is significantly associated with survival outcomes. The majority of those in this study were between the ages of 18 and 49. According to several studies, there were not many comorbidities that would have an impact on the severity of the clinical degree of COVID-19 patients at that age. The outcome of death due to old age is significantly related to critical clinical severity.

These findings are consistent with the findings of Varikasuvu et al, who found that the majority of COVID-19 patients with mild symptoms had a favorable prognosis; however, patients with severe and critical COVID-19 symptoms had a high mortality rate ($P<0.05$).[1] Comorbidities are also associated with old age, which will increase morbidity and mortality in COVID-19 patients, particularly those over 60 years old. Obesity, in combination with diabetes and hypertension, will worsen the outcome in COVID-19 patients.[14,17]

We found that our study is consistent with the findings of Marin et al in America, who found that D-dimer levels of 31,000 ng/mL at admission had a significant relationship with the high mortality rate of COVID-19 patients in hospitals.[26] Guadiana-Romualdo et al reported on 2,663 subjects in Spain that a D-dimer levels of 3,945 ng/mL at admission had a significant association with high mortality in COVID-19 patients ($P=0.001$).[27]

Caricchio et al reported that COVID-19 patients who experienced a cytokine storm had a mean D-dimer level of >500 ng/mL, while COVID-19 patients who did not experience a cytokine storm had a D-dimer level of >4,930 ng/ml.[28] In severe and critical COVID-19 patients, high serum levels of pro-inflammatory cytokines cause a cytokine storm. This will damage the vascular endothelium and activate the

coagulation cascade, but with SARS-CoV-2 immunity, it will result in coagulopathy. A rise in D-dimer levels in COVID-19 indicates coagulopathy. This is extremely complicated.[5,29]

There are at least two mechanisms: coagulation activation caused by SARS-CoV-2 infection and endothelial cell damage. By binding to ACE2, SARS-CoV-2 infects macrophages and endothelial cells. Tissue factor (TF) is then expressed by immune cells, causing cytokine overproduction and stimulating coagulation and endothelial cell damage.[29] Blood clots and fibrin deposition in blood vessels contribute to the obstruction of oxygen delivery to organs, resulting in multi-organ dysfunction and death complications in COVID-19 patients.[30]

According to Varikasuvu et al, the initial D-dimer level can predict the clinical severity of COVID-19 with a sensitivity of 55% and a specificity of 56%, and it can predict death with a sensitivity of 64% and a specificity of 66%.[1] In contrast to Mahardhika et al, who reported an increase in D-dimer and CRP levels in patients with clinically asymptomatic conditions, which was an unusual condition, this was due to age and comorbid factors in patients, which could also increase D-dimer levels.[9]

The most common complications in deceased COVID-19 patients are coagulopathy and thrombosis.[4] Tang et al found that DIC and multi-organ dysfunction occurred in 71.4% of patients who died.[4,5] Varikasuvu et al reported that there was a relationship between D-dimer and COVID-19 progressivity.[1]

High D-dimer levels are linked to an increased risk of coagulopathy and thrombosis in patients. Plasminogen Activator Inhibitor-1 (PAI-1) levels are elevated in COVID-19 patients, which can disrupt the fibrinolytic system and lead to thrombus formation. This can cause vasoconstriction due to hypoxemia via reduced blood flow and vascular occlusion, endothelial dysfunction, and inflammation, particularly in patients with co-morbidities such as hypertension, diabetes, and advanced age.[1,4]

We found that our study is consistent with the findings of Aloisio et al, who found that serum albumin levels of ≤3.5 g/dL were significantly higher for increasing D-dimer levels four times the upper limit value (upper value ≤500 ng/ml) than serum albumin levels of ≥3.5 g/dL. According to this study, there was a causal relationship between decreased albumin levels and increased D-dimer that affected patients in the severe and critical clinical group.[7] Caricchio et al studied albumin level in COVID-19 patients who experienced cytokine storms. COVID-19 patients with cytokine storms had albumin level of 2.7 g/dL, while the predicted value that caused a cytokine storm was 2.8 g/dL.[28]

An inflammatory mechanism can explain the decrease in the rate of albumin synthesis in COVID-19 patients. Inflammation inhibits albumin synthesis, particularly albumin mRNA, which is reduced by up to 90% during inflammation. Because albumin is a negative acute-phase protein, its synthetic potential is drastically reduced. Cytokines

are proteins that are produced during inflammation that degrade amino acids to increase the synthesis of acute-phase proteins that are required for the inflammatory process. Because albumin is not required for inflammation, these cytokines release amino acids from albumin synthesis.[31,32] Hariyanto et al also discovered that albumin could downregulate ACE2, which was critical for modulating COVID-19 infection. When albumin levels are low, ACE2 receptors are activated, and COVID-19 infectivity increases.[8]

Inflammation can impair hepatic albumin synthesis.[31,32] Hypoalbuminemia, or low albumin level, is thought to play an important role in the poor outcome of COVID-19 patients because it can cause pulmonary capillary leakage.[33] According to Khodeir et al, decreased albumin levels were strongly associated with disease progression in severe and critical cases, with a mean value of 3.0 g/dL, affecting the liver in both the survivor and non-survivor groups.[3]

According to Zerbato et al, the threshold for predicting a high risk of death within 90 days for COVID-19 patients is 3.23 g/dL in 15% of COVID-19 patients. The patient's need for mechanical ventilation was also linked to hypoalbumin at 3.17 g/dL.[34]

This study had limitations, including the use of a retrospective study with a cross-sectional design and data from patient medical records, as well as an uneven distribution of patients.

CONCLUSION

Higher D-dimer levels independently had a relationship with unfavorable outcome and higher albumin levels were independently related to a favorable outcome.

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