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Research

ASSOCIATION BETWEEN *ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)* INCIDENCE AND INCREASED D-DIMER IN COVID-19 PATIENTS AT BETHESDA HOSPITAL YOGYAKARTA

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ABSTRACT

Background: *Acute Respiratory Distress Syndrome* (ARDS) is one of the most common complications of COVID-19 infection and is closely related with patient mortality. Increased D-dimer levels are considered one of the most consistent clinical indicators of coagulopathy. Theoretically, this event is based on the emergence of a cytokine storm triggering lung tissue damage, pulmonary microvascular endothelial damage and alveolar edema, leading to hypoxia in the body.

Objective: To determine the association between ARDS incidence and the increase in D-dimer levels in COVID-19 patients at Bethesda Hospital Yogyakarta.

Method: This research was conducted in retrospective cohort design. The data utilized in this study came from the medical records of male and female COVID-19 patients between 19 and 60 years old, who were diagnosed with ARDS by doctors at Bethesda Yogyakarta Hospital. The medical records were collected between June 1, 2021, and September 30, 2021. The data analysis included univariate (descriptive statistics) and bivariate (Chi-Square, Mann-Whitney, Spearman Rank) analyses.

Result: There was a significant relationship between COVID-19 ARDS patients and the increased levels of D-dimer in patients undergoing hospitalization at Bethesda Hospital Yogyakarta (p<0,001, OR=4,589, 95%CI=2,104-10,007). Additionally, there was a significant difference in D-dimer levels between ARDS and non-ARDS patients. The severity of ARDS, duration of hospitalization, gender, and age did not have a significant association with the increase in D-dimer levels (p>0,05).

Conclusion: There was a significant relationship between the incidence of ARDS and elevation of D-dimer levels in COVID-19 patients at Bethesda Hospital Yogyakarta.

Keywords: ARDS, coagulopathy, COVID-19, D-dimer levels

INTRODUCTION

Coronavirus Disease (COVID-19) is a viral infectious disease, caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) which late 2019 – mid-2022 has become a global pandemic.[1] In pathophysiology, SARS-CoV-2 binds to the host cell receptor Angiotensin Converting Enzyme-2 (ACE2), which initiates the activation of the body's defense mechanisms, extending to the humoral level. Increasing virulence factors will trigger immune system dysregulation and tissue damage. The clinical manifestations of COVID-19 disease generally vary and have a spectrum of symptoms consisting of asymptomatic, mild, moderate, severe, and critical.

The existence of tissue damage is directly proportional to the increase in the spectrum of COVID-19 symptoms, one of which is the occurrence of ARDS which is a complication of COVID-19 and can lead to death. The global mortality data of COVID-19 patients accompanied by conditions ARDS is 39%. In Asia, China had the highest mortality estimate among COVID-19 patients with ARDS of 69%. In Europe, the highest mortality rate among COVID-19 patients with ARDS was reported in Poland 73%, Spain 40%, and France 19%.[2,3]

ARDS due to COVID-19 is characterized by a cytokine storm event that causes diffuse inflammation in lung tissue, increased vascular permeability, non-cardiogenic edema, and decreased aeration of lung tissue, triggering respiratory failure.[3] The diagnosis was determined through the criteria of Berlin 2011, namely (1) the occurrence of acute hypoxemia respiratory failure, (2) the onset of symptoms < 1 week, and (3) bilateral opacity. The hypoxia state, endothelial impact, and continuous inflammatory response will increase the state of procoagulants which can cause vascular microthrombosis (coagulopathy). An increase in D-dimer levels ≥ 0.5 µg/mL

is the most consistent indicator of hemostasis for describing the state of coagulopathy in COVID-19.[4,5] By determining whether there is an association between ARDS incidence and the increase in D-dimer levels in COVID-19 patients at Bethesda Hospital Yogyakarta, it is hoped that patient management will improve.

METHODS

The research received ethical clearance from the Ethical Committee of Bethesda Hospital Yogyakarta No. 26/KEPK-RSB/III/23, which was issued on March 27, 2023. The population in this study was adult patients at Bethesda Hospital Yogyakarta due to ARDS COVID-19 from June 1, 2021 - September 30, 2021. The data in this study came from the medical records of male and female COVID-19 patients aged between 19 and 60 years, who were diagnosed with ARDS by doctors at Bethesda Yogyakarta Hospital. The medical records were collected between June 1, 2021, and September 30, 2021. The author selected this period since it was the peak of reported COVID-19 cases in Yogyakarta.

The inclusion criteria of the study were male or female patients 19 - 60 years old, who were diagnosed with COVID-19 by doctors at Bethesda Hospital Yogyakarta based on PCR examination. The exclusion criteria consisted of patients who were pregnant, had a history of cancer, and post-surgery. This study used a *retrospective cohort* research design, the case group consisted of ARDS COVID-19 patients and the control group were non ARDS COVID-19 patients.

The data collected from medical record data consisted of gender, age, length of hospital stay, D-dimer levels, and characteristics of COVID-19 ARDS patients according to the Berlin 2011 criteria. The data were then analyzed by univariate and bivariate (*Chi-square, Mann-Whitney,* and *Spearman Rank)* tests.

RESULTS

Based on the research that has been conducted, of the 401 available medical record data, as many as 125 people met the inclusion criteria and 276 people were in the exclusion criteria. Among the 276 people included in the exclusion criteria of the study, 261 people were > 60 years, 10 people were pregnant, 3 people had a history of cancer, and 2 people had a history of postoperative disease.

Univariate Analysis

The characteristics of the subjects of this study were divided into two categories, COVID-19 ARDS patients and non-ARDS patients to observe the level of D-dimer level. Based on the results obtained, there were 79 people in the category of COVID-19 ARDS patients and 46 people in the category of non-ARDS COVID-19. These results showed that non-ARDS patients could also experience increased D-dimer levels.

Based on the results of univariate analysis, COVID-19 ARDS patients were dominated by men with a population aged 46-60 years old. The purpose of separating the age of the patients was to find which range has the most ARDS COVID-19 cases and to find the relationship between them. The average length of hospitalization and D-dimer levels of COVID-19 ARDS patients were ≥ 7 days with D-dimer levels ≥ 0.5 µg/mL (increased). Non-ARDS COVID-19 patients were dominated by women with a population aged 36-60 years.

The average length of stay of non-ARDS COVID-19 patients was < 7 days, where most of the results of the D-dimer level examination were < 0.5 µg/mL (normal). Diabetes mellitus, cardiovascular disease, and hypertension were the most common comorbid diseases experienced by ARDS COVID-19 and non-ARDS COVID-19 patients.

Patient characteristics of ARDS according to the 2011 Berlin diagnostic criteria, which consisted of: (1) onset of ARDS symptoms < 7 days (2) the presence of a bilateral opacity picture on radiological examination (3) the ratio of $PaO_2/FiO2$ < 300 mmHg. The characteristics of 79 COVID-19 ARDS patients are shown in Figure 1.

Table 1. Basic Characteristics of Research Subjects

Characteristics Subject	D-dimer level ≥ 0.5 µg/mL		D-dimer level < 0.5 µg/mL	
	Sum (N)	Percentage (%)	Sum (N)	Percentage (%)
ARDS Patients	59	47.2	20	16.0
Non-ARDS Patients	18	14.4	28	22.4

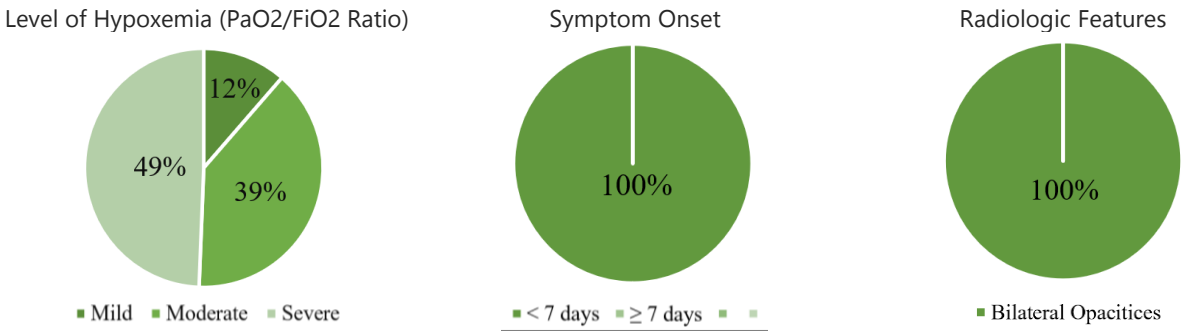

Figure 1. Characteristics of COVID-19 ARDS Patients According to the 2011 Berlin Criteria

Table 2. Other Characteristics of Research Subjects

Characteristic	ARDS Patients		Non-ARDS Patients	
	Sum (N)	Percentage (%)	Sum (N)	Percentage (%)
Gender				
Male	42	33.6	21	16.8
Female	37	29,6	25	20
Age (years)	50.3 ± 10.2		48.4 ± 9.3	
19-25	5	4.0	2	1.6
26-35	2	1.6	2	1.6
36-45	8	6.4	12	9.6
46-55	39	31.2	17	13.6
56-60	25	20	13	10.4
Length of Hospitalization	8.0 ± 5.5		6.4 ± 4.5	
< 7 days	36	28.8	27	21.6
≥ 7 days	43	24.4	19	15.2
Comorbid Diseases				
1. Hypertension	19	24.0	4	8.7
2. Diabetes Mellitus	33	41.7	10	21.7
3. Cardiovascular Diseases	27	34.1	3	6.5
4. Chronic Kidney Disease	11	13.9	1	2.1
5. Corneal Lung Disease	3	3.8	0	0
6. Cerebrovascular Disease	7	8.9	5	10.9
7. Other	4	5.0	1	2.1
8. None	21	26.6	22	47.8

Bivariate Analysis

The main hypothesis of the study was tested through bivariate analysis to see if there was a relationship between the incidence of ARDS COVID-19 and the increase in D-dimer. Bivariate analysis was carried out using *the Chi-Square test*. The results of the analysis showed that there was a significant relationship between the condition of ARDS COVID-19 and the increase in D-dimers (p<0.001, OR=4.589, 95%CI = 2.104-10.007). The results were completed through a comparative analysis of D-dimer levels of ARDS and non-ARDS patients in table 4 using *Mann-Whitney test* after a data normality test was carried out first. The results showed a significant difference in D-dimer levels between ARDS and non-ARDS patients (p<0.001).

Bivariate analysis of the characteristics of the study subjects was carried out to determine whether there was a relationship between the characteristics of the study subjects and the increase in D-dimers of ARDS COVID-19 patients. The severity of ARDS, length of stay, gender, and age of the patient were analyzed.

Based on the results of the Chi-Square test analysis in table 5, it was found that there was no significant relationship between the severity of ARDS and the increase in D-dimer levels of COVID-19 ARDS patients with a significance value of p=0.351 (p<0.05).

Based on the results of the data normality test and correlation analysis of *Spearman Rank test* in table 6, the values of p=0.646 and a correlation coefficient of 1,000 indicated that the length of hospitalization of ARDS patients did not correlate with the increase of D-dimer. Based on the results in table 7 of the analysis of *the Chi-Square* test on both variables, it was found that there was no relationship between the gender of ARDS patients and the increase in D-dimer levels with a value of p=0.220 (p<0.05).

Based on the results of the data normality test and correlation analysis of *the Spearman Rank* test in table 8, the values of p=0.152 (p<0.05) with a correlation coefficient = 1,000 (perfect) it can be concluded that the age of ARDS patients did not correlate with the increase in D-dimer.

Table 3. Association of COVID-19 ARDS to D-dimer elevation

Patient Categories	D-dimer Rate				P	OR	95% CI
	Increase ≥ 0.5 µg/mL		Normal < 0.5 µg/mL				
	Sum (N)	Percentage (%)	Sum (N)	Percentage (%)			
ARDS	59	47,2	20	14,4	<0.001	4,589	2,104 - 10,007
Non-ARDS	18	16,0	28	22,4			

Table 4. Comparison of D-dimer Levels of ARDS and Non-ARDS Patients

Patient Categories	Number of Patients	D-dimer *Mean Rank*	P
ARDS	79	75,44	<0.001
Non-ARDS	46	41,63	

Table 5. The Relationship of ARDS Severity to Patient's D-Dimer Levels

Severity of ARDS	D-dimer Rate				P
	Increase ≥ 0.5 µg/mL		Normal < 0.5 µg/mL		
	Sum (N)	Percentage (%)	Sum (N)	Percentage (%)	
Mild (200 – 300) mmHg	4	5,1	3	3,8	0,351
Moderate (100 – 200) mmHg	22	27,8	9	11,4	
Severe ≤ 100 mmHg	33	41,7	8	10,1	

Table 6. Correlation of Length of Hospitalization of ARDS Patients to Increase in D-Dimer

Variable	D-dimer Value
Length of Hospitalization	r = 1,000 P = 0,646

Table 7. Sex Relationship to Increase in D-Dimer Levels in ARDS Patients

Gender	D-dimer Rate				P	OR	95% CI
	Increase (≥ 0.5 µg/mL)		Normal (<0.5 µg/mL)				
	Sum (N)	Percentage (%)	Sum (N)	Percentage (%)			
Male	29	69,0	13	31,0	0,220	0,521	0,182 – 1,489
Female	30	81,1	7	18,9			

Table 8. Relationship of Patient Age to Increase in D-Dimer Levels in ARDS

Variable	D-dimer Rate
Patient Age	r = 1,000 P = 0,152

DISCUSSION

This study shows that the condition of ARDS COVID-19 was associated with an increase in D-dimer levels in patients who were examined for the first time while hospitalized (p<0.001; OR=4,589; 95%CI=2,104-10,007). These results are similar to a study conducted by Seghal et al., 2021, which found that there was a significant relationship between the condition of ARDS COVID-19 and several coagulation parameters, one of which was the D-dimer level (p=0.002; OR= 0.166; 95%CI=0.054-0.51).[6] Another study by Nandini et al., 2022 on 91 patients admitted to H. Adam Malik Hospital Medan, also found that there was a significant relationship between symptom severity, increased D-dimer levels, and incidence ARDS, with a value of p=0.0001 (p<0.05).[7] Similar results were also presented in a study conducted by Autschbach et., 2021 on 105 ARDS COVID-19 patients undergoing therapy *Extracorporeal Membrane Oxygenation* (ECMO) at RWTH University Hospital, Aachen, Germany.

The results obtained were that the D-dimer level of COVID-19 ARDS patients increased significantly compared to the D-dimer level of non-ARDS COVID-19 patients with a value of p=0.011 (p<0.05).[8] The results are also complemented by a comparative analysis of D-dimer levels of ARDS and non-ARDS patients. Based on the results of the test analysis *Mann-Whitney* in table 4, the value is obtained *p-value* <0.001 which means that there is a significant difference in D-dimer levels between ARDS and non-ARDS patients. The D-dimer level of ARDS patients was higher (mean 75.44) compared to the D-dimer level of non-ARDS patients (mean 41.63). Similar results were also found by Walanndow et al., 2021 and Mubarak et al., 2022 that the higher the severity of COVID-19 symptoms, the higher the value of D-dimer levels will also increase (p<0.001).[9,10]

In theory, ARDS is one of the complications that appear in COVID-19 infection, which is characterized by the destruction of epithelial cells, and the alveolar endothelium which causes excessive fluid accumulation in the interstitial and alveolar layers.[3,6-8] The underlying pathophysiology of ARDS COVID-19 is the occurrence of hyperinflammation that appears within < 7 days. The continuous occurrence of SARS-CoV-2 infection is directly proportional to the increase in virulence levels, especially in severe symptomatic infections, such as in ARDS.[5-7] This causes dysregulation of the immune system so that the body's defense mechanism against pathogens becomes worse. Immune system dysregulation is characterized by the presence of cytokine storms.

The state of hypoxia, the onset of endothelial effects, and the continuous inflammatory response increase the state of procoagulant (hypercoagulation) so that a hyaline membrane rich in fibrin content is formed.[6] An increase in excessive procoagulant activity is directly proportional to the increase in the process of fibrinolysis inhibition, triggering the occurrence of vascular micro thrombosis, interfering with the hemostasis process, resulting in coagulopathy.[11] The impact of such hyperinflammation is the buildup of fibrin in the blood vessels, which is seen as a D-dimer.

This study also found that there was no significant relationship between the severity of ARDS (PaO2/FiO2 ratio) and D-dimer levels of COVID-19 ARDS patients p=0.351 (p<0.05). These results are supported by Robba et al., 2023 and Estensorro et al., 2022 that the increase in D-

dimer levels in COVID-19 ARDS patients is not caused by an increase in the severity of ARDS (decrease in the PiO2/FiO2 ratio), but is caused by the *immunothrombosis* mechanism that is the pathophysiology of respiratory failure and an increase *in dead space* fraction (Vd/Vt) in COVID-19 ARDS and determines the severity of COVID-19 ARDS.[12-15] Different results by Wang et al., 2021 found that elevated levels of D-dimer correlated with the severity of COVID-19 ARDS.[16]

This study also found other results that there was no relationship between the length of hospitalization of ARDS patients and the increase in D-dimer levels, with a value of p=0.646 (p<0.05) and a correlation coefficient = 1.000 (perfect). According to Zhou et al., 2020, the longer the patient's hospital stay is directly proportional to the increase in the patient's D-dimer level (> 1 µg/mL), especially in the non-survivor group, with the median onset of ARDS symptoms after the 10th day of COVID-19 onset (p<0.0001).[17] Based on the results found, there was an increase in D-dimer levels that continued to increase until the 22nd day, especially on days 16 to 19 (23.8 µg/mL – 42.2 µg/mL).

According to Yao et al., 2020, D-dimer levels in patients with mild symptoms and patients with severe-surviving symptoms *(survivors*), showed an increase in D-dimer levels as the hospital stayed, but only fluctuated.[18] The results of this study also found the prevalence of COVID-19 ARDS and non-ARDS COVID-19 patients based on the category of length of hospitalization. Based on the results of the study, it was found that most ARDS patients underwent hospitalization ≥ 7 days (43/79) people, while most non-ARDS patients underwent hospitalization < 7 days (27/46) people. According to research by Zhou et al., 2020, the progression of COVID-19 symptoms toward ARDS COVID-19 appears within 8-15 days (> 7 days) after the onset of COVID-19 symptoms.[17]

An increase in D-dimer levels from the normal limit has a relationship with the mortality rate of a COVID-19 patient, one of which is due to the factor of length of hospitalization (p < 0.001; HR, 51.5; 95% CI, 12.9-206.7), so pharmacological management is necessary to reduce the level of D-dimer.[19] According to the recommendation of the Indonesian Doctors Association (IDI) regarding the administration of prophylactic anticoagulants to hospitalized COVID-19 patients, the recommended prophylactic anticoagulants are *low molecular weight heparin* (LMWH) or *unfractionated heparin* (UFH). The administration *of low molecular weight heparin* (LMWH) is given at a dose of 40 mg once a day subcutaneously for adult patients and a dose of 1 mg/kgbb/12 hours subcutaneously for children.

The administration *of unfractionated heparin* (UFH) is given at a dose of 5000 units subcutaneously, 2 times a day. The D-dimer level examination is carried out to assess the prognosis of coagulopathy before and after anticoagulant therapy and to assess the thromboprophylaxis dose that can be given based on the D-dimer level examined. Anti-inflammatory, anti-viral, statins, immunomodulators, convalescent plasma, *mesenchymal stem cells* (MSCs), and losartan (ARBs) are also options for the management of ARDS COVID-19.[20,21]

This study obtained the results that there was no relationship between the sex of ARDS patients and the increase in D-dimer levels with a value of p=0.220 (p<0.05). From the results of the analysis, the comparison of male and female ARDS patients who experienced increased D-dimer was 29 people and 30 people. This is not by the existing theory that in the case of COVID-19 it tends to be dominated by 24-year-old men. In the case of COVID-19, gender can be a risk factor that can be studied to see the characteristics and *outcomes of* the disease. From the development of existing COVID-19 cases, the *COVID-19 case fatality rate* (CFR) for men and women, has a difference in ratio of 2.8%:1.7%, meaning that men have a better relationship with a poor prognosis for COVID-19 disease, but it is not an independent prognosis factor.[22,23]

Increased D-dimer levels in COVID-19 patients are more experienced by man than women.[9] Factors that cause differences in *outcomes* between the two sexes include biological factors, unhealthy lifestyles, and patient comorbidities.[21] The hormone estrogen in women has a role in helping the immune system fight pathogens by activating the anti-inflammatory response, namely Th2, and inhibiting pro-inflammatory responses such as IL-6, IL-8, and TNF-α.[21] In terms of prevalence, unhealthy lifestyle behaviors such as smoking and consuming alcohol are more common among men than women. Smoking and consuming alcohol can trigger the occurrence of free radicals, thereby triggering pro-inflammation and expression of ACE-2 receptors.[22]

Another result found in this study was that the age of ARDS patients was not correlated with an increase in D-dimer, p=0.152 (p<0.05), and a correlation coefficient = 1,000 (perfect). In this study, ARDS COVID-19 patients were dominated by males with a population aged 46-60 years. According to Wu et al., 2020 and Gujksi et al., 2021, found that there was a relationship between increasing age and the incidence of ARDS.[17,25] Patients ≥ 65 years of age have more correlation with the occurrence of ARDS COVID-19 than patients < 65 years of age (p<0.001) due to a decrease in the ability of the body's immune system, namely a decrease in the expression of the IFN I-β gene, so that the production of T Cells and B Cells also decreases, while at the same time the uninterrupted production of IL-2 will cause a prolongation of the pro-inflammatory mechanism.[17]

The age > 50 years allows the occurrence of excessive expression of ACE-2 as a result of decreased immunity, decreased organ function, the presence of comorbidities, and several other causes such as high social mobilization to do activities outside the home, which can increase susceptibility and the development of COVID-19 disease in a worse direction. This study makes patients > 60 years old an exclusion criterion, to exclude the one of risk factors for the increasing incidence of ARDS COVID-19. Differing from previous studies, this study also found other outcomes of

ARDS COVID-19 patients and whether there is a relationship between the D-dimer levels such as the severity of ARDS COVID-19, length of hospitalization, sex, age, and comorbid. These results can help the clinician manage the ARDS COVID-19 patients from different outcomes.

Comorbidites such as obesity, hypertension, and diabetes can also be factors that trigger permissive states inducing inflammation which may lead to cytokine storm.[22] In this study, it was found that diabetes mellitus, cardiovascular disease, and hypertension are the most common comorbid diseases owned by ARDS patients. According to research conducted by Gutjski et al., 2021 cardiovascular, diabetes mellitus, and COPD, are comorbid diseases that are widely experienced by ARDS patients ($p<0.05$).[25]

Patients with comorbid disease of diabetes mellitus had the highest association with the incidence of ARDS COVID-19 (OR = 1.16; 95% CI: 1.03–1.30; p = 0.01), compared to other comorbid diseases. This study has several limitations, among them, most of the medical record data studied is included in the exclusion criteria for patients > 60 years old, so many data are not studied. Some of the medical record data studied was also incomplete, such as self-identity, anamnesis results, physical examination results, laboratory examination results, and patient diagnosis.

CONCLUSION

There was a significant relationship between the incidence of ARDS and the increase in D-dimer levels of COVID-19 patients hospitalized at Bethesda Hospital Yogyakarta.

RECOMMENDATION

Further research is recommended to evaluate other hemostasis parameters that show hypercoagulability, such as *Prothrombin Time* (PT), platelet count, fibrinogen, aPTT, *von-Willebrand* Factor (vWF), INR, and *fibrin degradation products* (FDP) to complement the results of the D-dimer examination of COVID-19 ARDS patients. Examination of inflammatory markers that indicate exacerbation of COVID-19, such as lymphocyte levels, neutrophils, IL-6, LDH, CRP, and ferritin can also be researched in research Pharmacological therapy of COVID-19 ARDS patients during hospitalization should also be examined whether it can be proven to reduce the patient's D-dimer levels and reduce the length of the patient's hospitalization.

CONFLICT OF INTEREST AND FUNDING RESOURCES

All authors have no conflict of interest. The authors covered all of the necessary costs for the study.

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