Original Article

The Associations Between Severity Of Symptoms, D-Dimer and Incidence of ARDS In COVID-19

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Abstract

Background: Severe acute respiratory injury caused by COVID-19 (ARDS) is a serious emerging complication. ARDS results from a cytokine storm that occurs in the second week of the disease course and acute-onset hypoxemia can be seen with bilateral infiltrates on chest radiograph. This study aimed to relate the severity of symptoms and D-dimer level to the incidence of ARDS in COVID-19 at H. Adam Malik Hospital as the referral center for COVID-19 in North Sumatra.

Method: This was a descriptive study with a retrospective cohort design. The sample of this study was secondary data from medical records of positive RT-PCR COVID-19 patients from November 2020 to April 2021. The inclusion criteria were patients with moderate to critical COVID-19 cases with D-dimer examination taken from the first day of admission. Subjects were then followed up until discharge from the hospital to assess for ARDS episodes which were confirmed by the results of PaO2/FiO2 in arterial blood gases and bilateral infiltrations in chest X-Ray. The exclusion criteria were incomplete medical records.

Results: The association between the severity of symptoms and the incidence of ARDS, 1 of which was found to be moderate, 19 cases were severe and 20 were critical. However, there was a statistically significant correlation between the severity of symptoms and the incidence of ARDS (P=0.0001).

Conclusion: There was a significant correlation between the severity of symptoms and the D-dimer value on the incidence of ARDS.

Keywords: ARDS, COVID-19, D-dimer

INTRODUCTION

ARDS is a condition resulting from the destructions of epithelial, endothelial, and alveolar cells which lead to fluid accumulation in the interstitial and alveolar space.[1,2] Pathologically, the lung parenchyma of patients diagnosed with COVID-19 shows diffuse alveolar damage with fibrin-rich hyaline membranes and several multinucleated giant cells.[3] These

manifestations will interfere with the diffusion process across the alveolar-endothelial membrane and contribute to hypoxemic state of ARDS.[4] Later, after the hyperinflammatory reaction occurs intensively in acute phase, this alveolar damage will form scar and fibrosis that appear to be more severe in COVID-19.[3] Therefore, early treatment or early recognize of the onset of ARDS is necessary to reduce the risk of morbidity and mortality among all degrees of COVID-19.

Cytokine storm is the basic mechanism of ARDS in COVID-19. Cytokine hypersecretion during COVID-19 was influenced by several factors.[5] Demographic characteristics including gender, older age, smoking habits, and comorbidities have been identified as predisposing factors for ARDS.[6] Furthermore, inflammatory markers in laboratory findings might predict the development of ARDS in COVID-19. This study aimed to investigate the association between D-dimer and severity of symptoms in patients diagnosed with COVID-19 at H. Adam Malik General Hospital.

METHOD

This was a descriptive study with a retrospective cohort design conducted in 2020-2021 at the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara. All research procedures have been approved by the Ethics Committee of Faculty of Medicine, Universitas Sumatera Utara.

The sample of this study was secondary data from medical records of positive RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) COVID-19 patients from November 2020 to April 2021 at H. Adam Malik General Hospital Medan as the referral center of COVID-19 in North Sumatera, Indonesia.

The inclusion criteria were patients with moderate to critical COVID-19 cases confirmed by RT-PCR swab for SARS-CoV2. Subsequently, the D-dimer examination was carried out through blood tests taken from the first day of admission. The samples were then followed up until discharge from the hospital to assess for ARDS episodes which were confirmed using Berlin Criteria consisted of PaO_2/FiO_2 <300 mg/mL in arterial blood gases, bilateral infiltrations on chest X-Ray (CXR), and clinical progression within the last 7 days. The exclusion criteria were incomplete medical records.

All collected data were entered and analyzed using a statistical analysis program for Windows. Data were presented in categorical data with a D-dimer cut off value of 500 mg/dL. Chi square test was used to analyze the correlations between D-dimer and severity of symptoms on the incidence of ARDS.

RESULTS

Most subjects recruited in this study were male (36.3%), age >40 years (82.4%), and had smoking history (61.55%). The most common complaints were shortness of breath (42,9%), cough

(21,9%), loss of smell (7,69%), loss of taste (3,3%) and fever (39,6%). Further clinical characteristics were described in Table 1.

Table 1. Clinical characteristics of all subjects recruited in the study

Characteristic	N	%
Gender		
Male	58	63.7
Female	33	36.3
Age		
≥40 years	75	82.4
≤40 years	16	17.6
Smoking History		
Smoker	56	61.5
Never smoker	35	38.5
Clinical symptoms		
Shortness of breath	39	42.9
Cough	29	21.9
Loss of smell	7	7.69
Loss of taste	3	3.3
Fever	36	39.6

The severity of symptoms was categorized based on the latest COVID-19 guideline in December 2020 from The Ministry of Health of the Republic of Indonesia. In this study, 1 subject (1.1%) had moderate symptoms, 19 subjects (20.9%) had severe symptoms and 20 subjects (22%) had critical symptoms. That one subject with moderate symptoms developed ARDS after the second week of hospitalization. All of the 19 subjects with severe symptoms developed ARDS after 2 weeks. On the other hand, all subjects with severe symptoms developed ARDS within the first week of hospital admission. Furthermore, this study showed a significant correlation between severity of symptoms and the incidence of ARDS in COVID-19 patients (P=0.0001).

Table 2. Correlation between severity of symptoms and the incidence of ARDS

Severity Symptoms	ARDS		Non-ARDS		P
	N	%	N	%	
No Symptom	0	0	0	0	0.0001
Early	0	0	0	0	
Moderate	1	1.1	40	44	
Severe	19	20.9	11	12.1	
Critical	20	22.0	0	0	

D-dimer were measured by immunofiltration in the Clinical Pathology Department of H. Adam Malik General Hospital with a cut-off value of 500 mg/dL on the first day of hospital admission. Of all subjects with ARDS, 33 subjects had increased D-dimer and 7 subjects had normal D-dimer. Statistically, there was a significant correlation between D-dimer and the incidence of ARDS in COVID-19 patients.

Table 3. Correlation between D-dimer and the incidence of ARDS

D-dimer	ARDS		Non-ARDS		P
	N	%	N	%	
Increased	33	36.2	20	22.0	0.000
Decreased	7	7.7	31	34.1	

DISCUSSION

COVID-19 is a pandemic viral infection with clinical manifestations that vary according to immune status. The Ministry of Health of the Republic of Indonesia has complied specific guidelines for COVID-19 and described the severity of symptoms in COVID-19. Mild symptoms are described as upper respiratory tract infections without signs of pneumonia or gastrointestinal syndrome. Moderate symptoms are described as pneumonia with symptoms including cough and shortness of breath with oxygen saturations >93%. Severe symptoms

showed the severe pneumonia with oxygen saturation below 93% while critical symptoms are diagnosed when severe symptoms progress to ARDS or sepsis.[1] In this study, there were no subjects with asymptomatic and mild symptoms because there was no indication of hospitalization.

In subjects with severe and critical symptoms, cytokine storm had occurred and disrupted oxygen diffusion process in the alveolar-endothelial compartment. This process manifested as hypoxemia.[7] If the immune status was inadequate to deal with this condition, this process would continuously occur and caused ARDS.[4] This was line with the study of Emanuelerezaghi et al which stated that there was a significant association between severity of symptoms and the incidence of ARDS.[6,8]

D-dimer is a residual product of fibrin and represents the activation of coagulation and fibrinolysis. The coagulation cascade is activated in the hyperinflammatory process.[9] The severe inflammatory process induces damage to the blood vessels around the lungs and activates the coagulation pathway.[10] The severity of inflammation is accompanied by a large amount of fibrin remnants in the blood vessels, where these fibrin remnants are referred to as D-dimers.[9] In the case of COVID-19, ARDS is related to the high risk of thrombosis depicted as elevated D-dimer.[11] He at al pointed out that high D-dimer on the first admission was associated with poor prognosis in COVID-19 patients.[12] This was similar with our study that exhibited significant correlation between D-dimer and the incidence of ARDS in COVID-19. Higher dose of anti-coagulation drug are required in critically-ill patients diagnosed with COVID-19 to prevent life-threatening thrombotic complications.[11]

CONCLUSION

There was a significant association between the severity of symptoms and high level of D-dimer with the incidence of ARDS in COVID-19 patients at H. Adam Malik General Hospital.

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