Comorbidities as Risk Factors for Mortality in COVID-19 Acute Respiratory Distress Syndrome Adult Patients: A Single-Center Retrospective Study

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ABSTRACT

Background: Geriatric, obesity, and chronic disease are classified as risk factors for adverse outcomes of coronavirus disease 2019 (COVID-19). Studies regarding the importance of these comorbidities in COVID-19 with severe complications such as acute respiratory distress syndrome (ARDS) are scarce. This study aims to analyze age, obesity, and chronic disease comorbidities as risk factors for 28-days mortality in COVID-19 patients with ARDS.

Methods: A retrospective, single-center study was conducted in Dr. Soetomo General Hospital, Surabaya, Indonesia between July-October 2020. We included all adult inpatients (≥18 years old) of confirmed COVID-19 with ARDS. Demographic, comorbidities, initial PaO2/FiO2 ratio, time of discharge or death were obtained from medical records and compared the ARDS severity between survivors and non-survivors. The univariate and multivariate logistic regression methods were used to identify risk factors associated with in-hospital death.

Result: Among 102 patients of COVID-19 with ARDS, the median age is 52 years. Most of them are within 50 – 59 age categories. The median hospital length of stay (LOS) for survivor is 22 (15.7 – 26) days and 9 (4.25 – 14.4) days for non-survivor. The 28-days mortality rate is 48 (47.1%) patients. Age > 65 years old (HR= 2.7, 95% CI 1.39 – 5.44, p value= 0.004), obesity (HR= 2.2, 95% CI 1.16 – 4.51, p value= 0.016), and chronic hypertension (HR= 1.98, 95% CI 1.11 – 3.52, p value= 0.02) are the independent risk factors for 28-days mortality in COVID-19 with ARDS.

Conclusion: Geriatric, obesity, and chronic hypertension comorbidities are the risk factors for mortality of COVID-19 with ARDS complications.

Keywords: Geriatric; obesity; chronic disease; comorbidities; COVID-19; ARDS

INTRODUCTION

COVID-19 is a pandemic and worldwide healthcare primary problem. (1) It has a wide spectrum of clinical signs and symptoms. Most of them have mild symptoms, but severe cases can be fatal. (2) On May 28, 2020, the World Health Organization (WHO) received 5.593.631 confirmed cases of COVID-19 infection with a mortality rate of 353.334 cases in all countries. (3) As of May 24, 2020, Indonesia had 22.271 active cases with a total of 1.372 death cases and a cure rate of 5.402 cases. (4) The mortality rate in Indonesia is 6.16% and is the highest mortality rate in Southeast Asia. (5) In most cases, COVID-19 infection can have mild symptoms and heal on its own, but some have developed and caused complications such as respiratory failure, pulmonary edema, acute respiratory distress syndrome (ARDS), septic shock, and multiorgan dysfunction. (2) Severe cases can lead to acute respiratory hypoxemia and ARDS. ARDS is a life-threatening complication of COVID-19 in critically ill patients. Patients with severe COVID-19 infection can develop symptoms and signs of respiratory failure, 42% of these patients can develop ARDS and about 61-81% require intensive care in the Intensive Care Unit (ICU). (6) The data on the clinical characteristics and outcomes of patients with severe ARDS complications are rare, but the most important is to reduce mortality.

The COVID-19 pandemic has claimed many victims, especially in patients with confirmed COVID-19 accompanied by comorbidities such as older adults, diabetes, hypertension, chronic heart disease, kidney disease, cerebrovascular disease, respiratory disease, and others. (7) Since the assessed risk of mortality is quite high for a growing population as large as Indonesia and patients with different interventions in each case, therefore, it is necessary to obtain sufficient data evidence. Throughout this study, we assessed critically ill patients admitted to Dr. Soetomo General Hospital with confirmed COVID-19 pneumonia. This study's baseline data on COVID-19 comorbidity and mortality will be highly vital in evaluating who is at higher risk of becoming critically ill and who will most likely benefit from intensive care treatment.

METHODS

A single-center retrospective observational study was conducted in Dr. Soetomo General Hospital in Surabaya, Indonesia. The data were extracted from medical records of confirmed-COVID-19 patients who were admitted to High-care units and ICU of the hospital from July 2020 to October 2020. Adult patients with the age of ≥ 18 years who have confirmed suffering COVID-19 through polymerase chain reaction (PCR) test, the PaO2/FiO2 ratio <300 mmHg was included as inclusion criteria. We excluded the patients who have not been confirmed by PCR test and/or probable cases, pregnant patients, and, early discharge and/or incorporated patients. Identification of baseline characteristics, demographics, and underlying chronic disease was described. ARDS severity is based on the Berlin Definition of ARDS. (8) We obtained the Ethical Clearance of this study by The Clinical Research Unit of Ethical Committee in Health Research, Dr. Soetomo General Hospital, Surabaya Number 0009/KEPK/VI/2020. All participants of this study have signed the informed consent form.

Statistical analysis of this study was performed using the 26th version of the IBM Statistical Package for the Social Sciences (SPSS). The normality test is done by Kolmogorov-Smirnov test. The quantitative variables were presented as a median (interquartile range), categorical variables were presented as frequency (percentage). We compared the continuous variables using the T-test and Mann-Whitney test. Pearson Chi-Square test, Fisher exact test, and Kruskal Wallis test are performed to determine the differences in categorical variables. We used Cox proportional hazards modeling to assess the independent risk factor for 28-days mortality while adjusting for other covariates simultaneously.

RESULT

A total of 102 patients of confirmed-COVID-19 with ARDS complications were treated in ICU and High-care units. Their baseline characteristics are reported in Table 1. The median age of the participants of this study is 52 years old and did not differ significantly across the ARDS severity group. Most of the participants with severe ARDS are male and within the 50-59 age group. There are 27 participants with normal Body Mass Index (BMI), 26 participants with overweight, and 11 obese patients with severe ARDS. Diabetes and chronic hypertension are the most underlying disease in the population. Eighteen participants with severe ARDS were not treated in ICU because of limited resources. The median of the initial PaO2/FiO2 ratio was 79.6 (58 – 137) mmHg. The mortality rate is 48 (47.1%) patients who were classified as severe ARDS which is the highest mortality in both intensive and non-intensive care, totaling 41 patients.

The median age, age group, sex, weight, BMI were not statistically significant among the survivor and non-survivor groups.

Commordibities, geriatric, hypertension, admittance, and ARDS severity are related to 28-days mortality in COVID-19 patients with ARDS according to the Pearson Chi-square test with a p-value of 0.005, 0.011, 0.006, 0.022, and 0.001 respectively (Table 2). The underlying comorbidities and other covariates were analyzed with Cox proportional hazards regression to determine the independent risk factor for 28-days mortality. Table 3 reported that age > 65 years old with Hazard Ratio (HR) of 2.7, 95% Confidence Interval (CI) of 1.39 – 5.44, and a p-value of 0.004. The obesity (HR= 2.2, 95% CI 1.16 – 4.51, p-value= 0.016), and chronic hypertension (HR= 1.98, 95% CI 1.11 – 3.52, p-value= 0.02) are the independent risk factors for 28-days mortality in COVID-19 with ARDS respectively.

DISCUSSION

We report on 102 confirmed-COVID-19 patients with ARDS characterized by acute respiratory hypoxemia. Seven of moderate ARDS and 41 of severe ARDS patients had died at 28 days. Of all those who died, 33 (32.4%) patients required ICU treatment, and 15 (14.7%) died in a High-care unit setting because of the limited resources at that time. We observed that the age groups of COVID-19 patients with ARDS are above 50 years old. COVID-19 patients with ARDS accompanied by geriatric comorbidities had a 2.7 times greater risk of death than non-geriatric patients. Age factor, especially at age > 50 years, there are several physiological changes in the immune system, including cell cytokine signaling function, nitric oxide and peroxide production, and decreased function of neutrophils (CD11b+Gr-1+ cells). Old age is susceptible to secondary infections, bacterial infections to sepsis, so it is closely related to a worse prognosis if you are critically ill. (9, 10) It is proved that the age is related to decreasing function of the immunity system and leads to worse outcomes. (11) According to prior studies, about 70% of COVID-19 infected patients were males. (12-14) Males and adults over the age of 65 are more likely to have ARDS than females or people of a younger age. (15, 16) Furthermore, in this study, males are the most number with severe ARDS and mortality in this study. A greater number of expressions of ACE-2 receptors may be the cause. (17, 18)

Most of the patients in this study had a normal BMI, followed by an overweight BMI, and a small proportion (19 patients) were obese. The median BMI was 25.9, the median weight was 70 kg. This study found no significant difference in body weight and BMI when it was associated with the severity of ARDS. In contrast to studies in the United States, body weight and BMI profiles have differences in almost half of the study participants who are obese (> 50.8%) with BMI 30. (19) In this study, COVID-19 patients with ARDS and obesity had a 2.2 times risk of dying compared to those without obesity. This is also similar in several other studies which state that there is a close correlation between high BMI and the risk of hospitalization, ICU care and mechanical ventilation, and the risk of death (19-21) The risk will increase progressively starting from BMI 25.9. (19) Obesity is a condition with small but prolonged chronic inflammation, it leads the body to produce more proinflammatory cytokines. Obesity is associated with other comorbidities such as diabetes, cardiovascular disease and is strongly related to worse outcomes in severe COVID-19 cases. (13, 20, 21)

Comorbid chronic disease is a risk factor in COVID-19 patients with ARDS. The most common comorbid diseases were diabetes (46 patients) and hypertension (33 patients), and most patients had at least one type of comorbidity. The results of this study are similar to a study that stated that the prevalence of diabetes was high in COVID-19 patients, but differed in terms of mortality. (22)

Diabetics are susceptible and are associated with a high risk of mortality from COVID-19 infection. The causes include an increase in pro-inflammatory cytokines, a decrease in anti-inflammatory cytokines, a decrease in the activity of Natural Killer (NK) Cells due to high blood sugar exposure, disturbances in the glutathione (GSH) system so that Reactive oxygen species (ROS) increases, and decreases the function of macrophages. However, according to this research, diabetes was not significantly associated with the incidence of patient mortality.

Hypertension is reported as a risk factor for worse outcomes in COVID-19 because greater ACE-2 was expressed in the body. (23-25) This study also reports that COVID-19 patients with ARDS who have comorbid hypertension have a 1.9 times risk of death compared to patients without hypertension. Several other studies have shown the same thing, that hypertension increases the risk of death by 7.4 times and most of the non-survivors of COVID-19 are hypertensive patients. (14, 26) Clinical deterioration in COVID-19 patients with hypertension is due to an increase in ACE-2 receptor expression so that COVID-19 patients with hypertension are more susceptible to infection and have a faster clinical deterioration. (17)

Severe ARDS was a complication that occurred in most of the study participants (64 patients) with a median P/F ratio of 79.6, and most of them were treated in intensive care (58 patients), and 48 patients died (47.1%). The average LOS in the hospital in this study was 16 days or with a median of 16.5 days. The most common causes of ARDS, sepsis, and other complications of organ failure in COVID-19 are cytokine storms and severe immune injury. This cytokine storm is closely related to an increase in pro-inflammatory cytokines in the body. The pro-inflammatory cytokines IL1b, IFNγ, IP10, and MCP1, and the anti-inflammatory cytokines IL4 and IL10 were found to be elevated in COVID-19 patients. (12)

COVID-19 patients with severe ARDS have a high mortality rate, recorded 46 patients (45.1%) in intensive care and 18 patients (17.6%) in non-intensive care died. Not all patients with severe ARDS received intensive care, and some died in non-intensive care. This is due to limited space in intensive care. The limitation of this study is that the data collection for COVID-19 patients with ARDS was done through secondary data from medical records, and was carried out retrospectively. This does not represent the trend of the P/F ratio or the existence of a worsening trend in the following days.

CONCLUSION

Comorbidity is indeed a risk factor that exacerbates COVID-19 patients with ARDS. Geriatric factors or adults aged > 65 years, obesity, and chronic hypertension are independent risk factors for the incidence of 28-day mortality in COVID-19 with ARDS. Adult people with a history of these comorbidities can be more vigilant because they are a vulnerable group. Complete Covid-19 vaccination and implementation of Health protocols need to be maintained to reduce the risk of exposure. In addition, it is important to conduct further research covering a larger number of research participants, in a longer period, and involving other teaching hospitals. Furthermore, this study can be used as a reference for the profile of COVID-19 patients with ARDS in Indonesia.

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TABLE 1: Baseline Characteristic of the Participants Based on ARDS Severity

Variables	ARDS Severity			p-value[ab]
	Mild (n=8)	Moderate (n=30)	Severe (n=64)	
Age (years)	52.38 (±13.1)	49.87 (±13.3)	52.56 (±11.3)	0.774[a]
Age Categories (years old), n (%)				0.630[b]
18 – 29	0 (0)	4 (13.3)	2 (3.1)	
30 – 39	1 (12.5)	2 (6.7)	4 (6.3)	
40 – 49	1 (12.5)	7 (23.3)	16 (25)	
50 – 59	5 (62.5)	10 (33.3)	26 (40.6)	
60 – 69	0 (0)	5 (16.7)	11 (17.2)	
≥ 70	1 (12.5)	2 (6.7)	5 (7.8)	
Sex				0.114[b]
Male	3 (37.5)	18 (60)	46 (71.9)	
Female	5 (62.5)	12 (40)	18 (28.1)	
Weight (kg)	62.5 (58.5 – 73.7)	69 (60 – 80)	70 (62.5 – 80)	0.469[a]
BMI	24.7 (22.7 – 27.2)	27.1 (22.4 – 29.7)	25.9 (23.4 – 29.3)	0.657[a]
Normal	5 (62.5)	11 (10.8)	27 (26.4)	0.693[b]
Overweight	2 (25)	12 (11.8)	26 (25.5)	0.691[b]
Obesity	1 (12.5)	7 (6.9)	11 (10.8)	0.698[b]
Comorbidities				0.504[b]
None	3 (2.9)	9 (8.8)	14 (13.7)	
Had at least 1	3 (2.9)	10	27	
Had at least 2	2 (2)	11	23 (22.5)	
Geriatric				0.757[b]
Yes	1 (12.5)	3 (10)	10 (15.6)	
No	7 (87.5)	27 (90)	54 (84.4)	
Diabetes				0.943[b]
Yes	4 (50)	13 (43.3)	29 (45.3)	
No	4 (50)	17 (56.7)	35 (54.7)	
Hypertension				0.897
Yes	2 (25)	10 (33.3)	21 (32.8)	
No	6 (75)	20 (66.7)	43 (67.2)	
Cardiovascular disease				0.734[b]
Yes	0 (0)	2 (6.7)	3 (4.7)	
No	8 (100)	28 (93.3)	61 (95.3)	
Chronic lung disease				0.760[b]
Yes	0 (0)	2 (6.7)	4 (6.3)	
No	8 (100)	28 (93.3)	60 (93.8)	

Chronic kidney disease				0.776b
Yes	0 (0)	1 (3.3)	1 (1.6)	
No	8 (100)	29 (96.7)	63 (98.4)	
Initial PaO2/FiO2 ratio	258.3 (213.7 – 283.3)	147 (118.1 – 173.9)	67.9 (54 – 78.1)	**<0.001a**
Hospital Admittance				**0.035b**
Not referred	5 (62.5)	11 (36.7)	14 (21.9)	
Referred from another hospital	3 (37.5)	19 (63.3)	50 (78.1)	
Admittance				**<0.001b**
ICU	0 (0)	12 (40)	46 (71..9)	
High-care unit	8 (100)	18 (60)	18 (28.1)	
28-days Mortality				**<0.001b**
Survivor	8 (100)	23 (76.7)	23 (35.9)	
Non-survivor	0 (0)	7 (23.3)	41 (64.1)	
Hospital Length of Stay	20.5 (12 – 28)	17 (9 – 22)	14.5 (6 – 24)	0.327a

a : Kruskal-Wallis test, p-value<0.05 was significantly different
b : Pearson Chi-square test, p-value<0.05 was viewed as a significantly different

TABLE 2 : Characteristics of the Participants Based on 28-days Mortality

Variables	28-days Mortality		p-valueab
	Survivor (n=54)	**Non-survivor (n=48)**	
Age (years)	50.13 (±11.14)	53.58 (±12.88)	0.321 a
Age Categories (years old), n (%)			0.142b
18 – 29	4 (7.4)	2 (4.2)	
30 – 39	5 (9.3)	2 (4.2)	
40 – 49	11 (20.4)	13 (27.1)	
50 – 59	25 (46.3)	16 (33.3)	
60 – 69	8 (14.8)	8 (16.7)	
≥ 70	1 (1.9)	7 (14.6)	
Sex			0.147b
Male	32 (59.3)	35 (72.9)	
Female	22 (40.7)	13 (27.1)	
Weight (kg)	69 (60 – 75)	70 (60 – 80)	0.500 a
BMI	25.71 (23.3 – 27.9)	27.1 (23 – 30.7)	0,234 a
Normal	24 (44.4)	19 (39.5)	0.225b
Overweight	23 (42.6)	17 (35.5)	0.459b
Obesity	7 (13)	12 (25)	0.119b
Comorbidities			**0.005b**
None	20 (37)	6 (12.5)	
Had at least 1	24 (44.4)	16 (33.3)	
Had at least 2	10 (18.6)	26 (54.2)	
Geriatric			**0.011b**
Yes	3 (5.6)	11 (22.9)	
No	51 (94.4)	37 (77.1)	
Diabetes			0.181b
Yes	21 (38.9)	25 (52.1)	
No	33 (61.1)	23 (47.9)	
Hypertension			**0.006b**
Yes	11 (20.4)	22 (45.8)	
No	43 (79.6)	26 (54.2)	
Cardiovascular disease			0.746b
Yes	3 (5.6)	2 (4.2)	
No	51 (94.4)	46 (95.8)	
Chronic lung disease			0.321b
Yes	2 (3.7)	4 (8.3)	
No	52 (96.3)	44 (91.7)	
Chronic kidney disease			0.130b
Yes	0 (0)	2 (4.2)	
No	54 (100)	46 (95.8)	
Initial PaO2/FiO2 ratio	113.92 (78.12 – 173.9)	60.5 (54 – 79.9)	**<0.001a**
ARDS Severity			**<0.001b**
Mild	8 (14.8)	0 (0)	
Moderate	23 (42.6)	7 (14.6)	
Severe	23 (42.6)	41 (85.4)	

Hospital Admittance			0.627[b]
Not referred	17 (31.5)	13 (27.1)	
Referred from another hospital	37 (68.5)	35 (72.9)	
Admittance			**<0.022[b]**
ICU	25 (46.3)	33 (68.8)	
High-care unit	29 (53.7)	15 (31.3)	
Hospital Length of Stay	22 (15.75 – 26)	9 (4.25 – 14.5)	**<0.001[a]**

[a] : Mann-Whitney test, p-value<0.05 was significantly different
[b] : Pearson Chi-square test, p-value<0.05 was viewed as a significantly different

TABLE 3: Cox Proportional Hazards Regression of ROX Index Predicting Intubation and 28-Days Mortality

Variable	HR	Corr. Coefficient	95% CI	p-value*
Sex	-	-	-	0.056
Age > 65 years (geriatric)	2.753	1.013	1.392 – 5.446	**0.004**
Overweight	-	-	-	0.752
Obesity	2.291	0.829	1.164 – 4.511	**0.016**
Diabetes	-	-	-	0.388
Hypertension	1.981	0.684	1.115 – 3.520	**0.020**
Chronic kidney disease	-	-	-	0.818
Chronic lung disease	-	-	-	0.249
Cardiovascular disease	-	-	-	0.876

* Cox proportional hazards regression forward likelihood ratio (LR) test