

ORIGINAL ARTICLE

Clinical Characteristics of Hospitalized Individuals Dying with COVID-19 in Ulin Regional Hospital Banjarmasin

Haryati*, Mohamad Isa, Ali Assagaf, Ira Nurrasyidah, Erna Kusumawardhani

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Lambung Mangkurat University/Ulin Regional Hospital, Banjarmasin, Indonesia.

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ABSTRACT

Background: Corona Virus Disease (COVID-19) has become a global pandemic and has spread to more than 200 countries including Indonesia. South Kalimantan is one of the provinces in Indonesia that has a high COVID-19 mortality rate (case fatality rate 4.1%). Information about characteristic of mortality patients with SARS-CoV-2 infection in Indonesia was limited. The objective of this study to describe clinical characteristics of COVID-19-confirmed deaths at Ulin Regional Hospital Banjarmasin, as a referral hospital in South Kalimantan

Methods: Medical records of 108 hospitalized patients dying with COVID-19 between March until August 2020 were collected. The recorded information included gender, age, onset and severity of disease, comorbidities, symptoms, signs, and laboratory findings

Results: The 108 confirmed cases of COVID-19 deaths were mostly male (73.1%) aged <65 years old (85.2%). About 84% of the cases had at least one comorbidity or more, like hypertension (44.4%), obesity (38%), and diabetes mellitus (32.4%). Common early symptoms were fever (91.7%) and shortness of breath (89.8%). Laboratory findings included lymphocytopenia and eosinophilopenia (80.6% and 72.2%), increased neutrophil lymphocyte ratio (NLR; 86.1%), decreased absolute lymphocyte count (ALC; 72.2%), and hyponatremia (55.6%). Elevated C-reactive protein (CRP; 92.6%), lactate dehydrogenase (LDH; 91.7%), serum glutamic oxaloacetic transaminases (SGOT; 82.4%), and creatinine levels (57.4%). The majority of non survivors were severe-critical stage with severe acute respiratory distress syndrome (ARDS).

Conclusion: In this depictive study, patients with comorbidities and severe-critical stage are at risk of death. Laboratory abnormalities were common in non survivors. Shortness of breath may indicate poor prognosis of COVID-19.

INTRODUCTION

World Health Organization (WHO) has determined that Corona Virus Disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-Cov)-2 has become a global pandemic.^{1,2} Currently, COVID-19 has spread to more than 200 countries including Indonesia.³ Clinical manifestations of COVID-19 patients have a broad spectrum, ranging from symptomless (asymptomatic), mild symptoms, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, sepsis, to shock

sepsis. According to the data of countries affected by COVID-19 pandemic, 40% of the cases experienced mild illness, 40% experienced moderate diseases including pneumonia, 15% experienced severe diseases (clinically or >50% lung involvement in imaging), and 5% experienced critical conditions.^{4,5}

Until September 24, 2020, Indonesia recorded 257,388 confirmed cases of COVID-19 and 9,997 of which died with a case fatality rate (CFR) of 3.9%.⁶ Nearly a third of COVID-19 infections were in the 31-45 years old age group (29.3%). However, the highest

*Corresponding author: Haryati. Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Lambung Mangkurat University/Ulin Regional Hospital. Jl. Veteran Sungai Bilu No.128, Melayu, Banjarmasin. Indonesia. e-mail address: haryatiharsono@yahoo.com

mortality rate occurs in elderly and is dominated by male.⁷

South Kalimantan is one of the provinces in Indonesia that has a high COVID-19 mortality rate (CFR 4.1%).⁸ Some studies abroad mention that age and comorbidity (hypertension, diabetes, heart disease, and so forth) are the most important risk factors associated with death from COVID-19.^{9,10} The most common organ damage caused by COVID-19 is the lungs, followed by the heart, kidneys, liver, and hematology.^{7,9,11,12} Patients who died at the age of ≥ 65 years old had a higher number of comorbidities than the age of <65 years old. However, non-respiratory complications such as acute renal failure, cardiac injury, and superinfection are actually higher in young adult patients.¹⁰ Some laboratory variables such as lymphocytes, neutrophils, platelets, amyloid serum A (SAA), procalcitonin (PCT), cardiac thromboxine I (cTnI), D-dimer, lactate dehydrogenase (LDH), and lactate serum can be used as indicators of disease progressiveness.^{9,11} Some of these clinical phenomena illustrate that pathogenesis of COVID-19 disease is highly complex. Meanwhile, in Indonesia, research about the characteristics of COVID-19 patients who died is still limited.

From March to August 2020 Ulin Regional Hospital Banjarmasin as a COVID-19 referral hospital in South Kalimantan has treated a number of COVID-19 patients. In this study, 108 patients were analyzed to describe the characteristics of COVID-19 confirmed patients at Ulin Regional Hospital Banjarmasin from March to August 2020 with the aim of identifying an overview of risk factors associated with mortality in COVID-19 patients. It is hoped that the results of this study can assist in the stratification of the risk of patients with SARS-CoV2 infection, thus further intervention can be given on time to avoid disease progression, as well as to improve the outcome of the patients infected with COVID-19 and reduce the mortality rate from COVID-19 in the future.

METHODS

This research was a retrospective study using epidemiological, clinical, and laboratories data extracted from the medical records of COVID-19 confirmed patients who died at Ulin Regional Hospital

Banjarmasin in the period of March until August 2020. A confirmed diagnosis of COVID-19 is defined as someone who is declared positively infected with COVID-19 virus as evidenced by laboratory examination of reverse transcriptase-polymerase chain reaction (RT-PCR). This research had been approved by the Research Ethics Committee of Ulin Regional Hospital Banjarmasin.

The sample selection technique in this study used total sampling and obtained the number of research subjects as many as 108 patients. The inclusion criteria in this study were the medical records of all COVID-19 confirmed patients who died in the period of March until August 2020, and the exclusion criteria were incomplete medical records of patients according to the specified variables. The variables examined in this study were the initial data of patients upon hospital admission consisting of epidemiological data namely gender, age, onset of disease (from the beginning of complaints to hospital admission, and from the beginning of rising complaints until the patient dies), and the severity of the disease at the beginning of hospital admission (asymptomatic, mild degree, moderate [pneumonia(+), $\text{SaO}_2 \geq 93\%$ room air], severe [$\text{SaO}_2 < 93\%$ room air], critical [ARDS, $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg]) and comorbidities. Clinical descriptions of COVID-19 patients were clinical symptoms and laboratory analysis including complete blood count (haemoglobin (Hb), leukocytes, platelets, neutrophil count, eosinophils, and lymphocyte count), liver function, renal function, electrolyte serum, C-reactive protein (CRP), LDH, and other viral infection status (neutrophil lymphocyte ratio [NLR] and absolute lymphocyte count [ALC]). The onset date of the disease, the initial date of hospital admission, the initial diagnosis of COVID-19, and death were accurately recorded. The data was then collected using a computer program according to a standard form that had been designed before and then tabulated. The results were displayed in the form of a table.

RESULTS

Based on 108 confirmed cases of COVID-19 who died at Ulin Regional Hospital Banjarmasin in the period of March until August 2020, it obtained clinical characteristics data presented in Table 1.

Table 1. Clinical characteristics of patients dying with COVID-19

Variables	Frequency	Percentage (%)		
Gender			Laboratory	
Men	79	73.1%	Haemoglobin	
Women	29	26.9%	>18.0 g/dl	0 0.0%
Age Group			12.0 – 18.0 g/dl	84 77.8%
≥65 years old	16	14.8%	<12.0 g/dl	24 22.2%
<65 years old	38	85.2%	Leukocyte	
55-64 years old	30	35.2%	>10.5 x 10E3/ul	47 43.5%
45-54 years old	18	27.8%	4.0 – 10.5 x 10E3/ul	55 50.9%
35-44 years old	6	16.7%	<4.0 x 10E3/ul	6 5.6%
25-34 years old	0	5.6%	Platelets	
18-24 years old	16	0.0%	>450 x 10E3/ul	12 11.1%
Onset Disease until Hospital Admission			150 – 450 x 10E3/ul	82 75.9%
<7 days	57	52.8%	<150 x 10E3/ul	14 13.0%
7-14 days	44	40.7%	Neutrophils	
15-21 days	2	1.9%	<50%	2 1.9%
>21 days	4	3.7%	50 – 81%	54 50.0%
Onset Disease until Patient's Death			>81%	52 48.1%
<7 days	13	12.0%	Lymphocyte	
7-14 days	49	45.4%	<20%	87 80.6%
15-21 days	25	23.1%	20 – 40%	18 16.7%
>21 days	20	18.5%	>40%	3 2.8%
Degree of Disease Severity			Eosinophil	
Asymptomatic	0	0.0%	<1%	78 72.2%
Mild	0	0.0%	1-3%	28 25.9%
Moderate	3	2.8%	>3%	2 1.9%
Severe	10	9.3%	NLR	
Critical	95	88.0%	<3.13	15 13.9%
Mild ARDS	19	17.6%	≥3.13	93 86.1%
Moderate ARDS	31	28.7%	ALC	
Severe ARDS	45	41.7%	>1500	30 27.8%
Comorbidity			≤1500	78 72.2%
Hypertension	48	44.4%	Liver Function	
Diabetes Mellitus	35	32.4%	SGOT	
Cardiovascular Disease	22	20.4%	5 – 34 U/L	19 17.6%
Cerebrovascular Disease	3	2.8%	>34 U/L	89 82.4%
Chronic Kidney Disease	13	12.0%	SGPT	
Chronic Lung Disease	11	10.2%	0 – 55 U/L	66 61.1%
Chronic Liver Disease	4	3.7%	>55 U/L	42 38.9%
Malignancy	4	3.7%	Renal Function	
Obesity	41	38.0%	Ureum	
Number of Comorbidities			0 – 50 mg/dl	58 53.7%
0	16	14.8%	>50 mg/dl	50 46.3%
1	35	32.4%	Creatinin	
2	33	30.6%	<1.25 mg/dl	46 42.6%
≥3	24	22.2%	≥1.25 mg/dl	62 57.4%
Early Symptom			CRP	
Fever/Fever History	99	91.7%	< 6.00 mg/dl	8 7.4%
Shortness of Breath	97	89.8%	≥6.00 mg/dl	100 92.6%
Cough	82	75.9%	LDH	
Sore Throat	17	15.7%	<122	5 4.6%
Colds	4	3.7%	122 – 220 U/L	4 3.7%
Haemoptysis	2	1.9%	>220 U/L	99 91.7%
Anosmia	2	1.9%	Natrium	
Nausea/Vomiting	39	36.1%	>145 Meq/L	4 3.7%
Diarrhea	16	14.8%	136-145 Meq/L	44 40.7%
Myalgia/ Artralgia	1	0.9%	<136 Meq/L	60 55.6%
Fatigue	29	26.9%	Potassium	
Headaches	3	2.8%	>5.1 Meq/L	9 8.3%
Subfebris	16	14.8%	3.5-5.1 Meq/L	84 77.8%
			<3.5 Meq/L	15 13.9%
			Clorida	
			>107 Meq/L	40 37.0%
			98-107 Meq/L	55 50.9%
			<98 Meq/L	13 12.0%

Data on the table showed 73.1% of the cases were male and 85.2% of the cases aged <65 years old with the most age range being 55-64 years old (35.2%). A total of 52.8% of the cases experienced COVID-19 symptoms <7 days before being hospitalized at Ulin Regional Hospital Banjarmasin. Most patients had the number of days from onset to death in the range of 7-14 days (45.4%). The majority of the cases had critical degree of severity (88%) and 41.7% of the cases had severe ARDS. About 84% of the cases had comorbidity of at least one or more. The most common comorbidities were hypertension (44.4%), obesity (38%), and diabetes mellitus (32.4%). The most common early clinical symptoms were fever (91.7%), shortness of breath (89.8%), and cough (75.9%).

Laboratory results showed the majority of the cases had haemoglobin, leukocyte, platelet, and neutrophil values within the normal range, while lymphocytes and eosinophils tended to decrease by <20% and <1% (80.6% and 72.2%). Elevated CRP (≥ 6.00 mg/dl) in 92.6% of the cases and LDH (>220 U/L) in 91.7% of the cases. There were an increase in NLR results (≥ 3.13) in 86.1% of the cases and a decreased ALC (≤ 1500) in 72.2% of the cases. Liver function tests showed an increase in serum glutamic oxaloacetic transaminases (SGOT) in 82.4% of the cases, while serum glutamic pyruvic transaminases (SGPT) at 61.1% of the cases was within normal limits. Renal function tests showed normal ureum levels in 53.7% of the cases, but there was an increase in creatinine levels (>1.25 mg/dl) in 57.4% of the cases. Electrolyte test results showed the absence of hyponatremia (<136 Meq/L) in 55.6% of the cases, while potassium and chloride levels of most patients were within normal limits.

DISCUSSION

A number of cases of COVID-19 deaths at Ulin Hospital Banjarmasin are dominated by male, aged <65 years old with one or more comorbidities and severity of critical illness (ARDS). The number of deaths in men is greater than women at 2.7:1. This study is comparable to some studies which also mention that mortality in men is higher than in women.^{4,7,11,13} It is estimated due to the association of male with the prevalence of active

smokers, the absence of comorbidity (hypertension and diabetes mellitus) resulting in increased expression of angiotensin converting enzyme (ACE)-2 receptors is higher in men than in women.^{7,13,14} In addition, women are thought to be able to fight the virus better due to the protection of the X chromosome and sex hormone (estrogen) which plays an important role in innate and adaptive immunity.^{7,15}

Age and comorbidity are the most influential risk factors in COVID-19 mortality.^{13,15,16} Some studies show that the age group that has high mortality in COVID-19 is ≥ 65 years old.¹⁵⁻¹⁷ This is associated with several things including decreased physiological immunity and the absence of comorbidities that contribute to a decrease in the body's functional reserves, thus reducing the capacity and the ability to fight infections.^{10,16,17} Nevertheless, in this study, the most mortality occurred at <65 years old (55-64 years old) with most cases having only one comorbidity (32.4%). This is expected because the distribution of COVID-19 patients treated at Ulin Hospital Banjarmasin is dominated by patients <65 years old. Palmeri L., *et al.* mentioned that COVID-19 patients with young adulthood have less comorbidity than the elderly. However, they are more likely to die with complications that develop during treatment. In addition to the onset of symptoms up to hospital admission in patients <65 years old longer than the elderly, this suggests that delayed hospital referrals lead to less optimal care and increase the risk of disease progression and complications.¹⁰

Certain comorbidities are associated with strong ACE-2 receptor expression and higher release of proprotein convertase which increases the entry of the virus into the host cell. Comorbidity causes COVID-19 patients to be substantially associated with morbidity and significant mortality.¹⁸ The most common comorbidities found in COVID-19 cases are hypertension, diabetes mellitus, and cardiovascular disease, in which all three diseases are associated with high mortality rates in COVID-19 patients.^{4,11,16,17} In this study, obesity was ranked as the 3rd most common comorbidity in addition to hypertension and diabetes mellitus. It had been previously known that the age group with the highest mortality rate in this study was <65 years old (85.2%). According to the research by Steinberg E., *et al.*, it mentioned that obesity is an

independent risk factor for severity and poor outcome in young adult patients with COVID-19.¹⁹ Hajifathalian K., *et al.* in his study also mentioned that obesity in the case of COVID-19 is strongly related to intensive care (ICU) and death.²⁰

In general, the incubation period of COVID-19 is 3-14 days (median 5 days) with frequent symptoms being fever, cough, and fatigue.^{7,14} In this study, the initial symptoms of COVID-19 patients who died were fever/history of fever, cough, and shortness of breath with the majority of patients (54.4%) had experienced these symptoms within <7 days before finally being hospitalized. According to its pathophysiology, symptoms of shortness of breath in COVID-19 generally appear in the second attack which is about 4-7 days after the virus spreads through the bloodstream to the tissue expressing ACE-2 such as the lungs, heart, and gastrointestinal tract.^{7,14} Shortness of breath can also be a marker that pulmonary function has begun to be impaired until pneumonia and ARDS emerge. In addition, the absence of symptoms of shortness of breath is also associated with a poor prognosis.^{21,22}

Viral infections can cause inflammation of the human body. Various inflammatory mediators produced during cytokine storms can cause systemic immune damage and even multi-organ failure.^{9,14} In this study, haemoglobin, platelets, leukocytes, and neutrophils in early screening of COVID-19 patients tended to be normal with increased NLR and decreased lymphocytes, eosinophils, and ALC. The results of this study are comparable to several other studies showing that the characteristics of haemoglobin levels in COVID-19 patients tend to be normal, with normal or decreased platelet and leukocyte values (lymphopenia) accompanied by an increase in NLR and a decrease in ALC.^{9,23-25} A large number of clinical studies have reported the incidence of lymphopenia in COVID-19 patients which can be considered a meaningful sign for COVID-19 infection, where patients with pneumonia have lower lymphocytes compared to patients without pneumonia. In addition, there was also a sharp decrease in ALC, especially in cases of severe and critical degrees. Another interesting finding related to COVID-19 infections reported by some studies is eosinopenia, as in the results of this study. Recent findings suggest that eosinophils have important antiviral properties where

granular proteins derived from eosinophils (eosinophil-derived neurotoxins and eosinophil cationic proteins) exhibit antiviral activity against single-chain ribonucleic acid (RNA) viruses. In addition, eosinophils are capable of producing nitric oxide and can induce the proliferation and activation of CD8⁺ T cells in response to exposure to viruses. The research of Zhang J. J., *et al.* of 140 hospitalized patients suggests that eosinopenia with lymphopenia can be a potential indicator for COVID-19 as a diagnostic and prognostic value. Du, *et al.* also reported that eosinopenia can be indicated as poor prognostic value in COVID-19 patients.²⁶ On the other hand, this study also found as much as 43.5% of the cases of increased number of leukocytes that are suspected of other infections including bacterial infections. Zheng Z., *et al.* in his research stated that the increase in the number of leukocytes at the beginning of COVID-19 patient screening may be related to the absence of other infections and may worsen the prognosis of COVID-19.¹⁵

In this study, there was an increase in the levels of SGOT, creatinine, LDH, and CRP similar to some other studies.^{9,10,16} Increased levels of SGOT and creatinine indicate the presence of renal and liver dysfunction. This phenomenon can occur in part because of the direct effects of SARS CoV-2 infection that causes cytokine storms. Aside from lungs and blood vessels, ACE-2 expression is also obtained in the kidneys, heart, liver, and other organs, thus SARS-CoV-2 can attack and damage those organs which then gives rise to immune cells to produce pro-inflammatory cytokines, cytokine storms that ultimately lead to tissue injury and failure of target organs.¹⁸ Bloom, *et al.* in his study mentioned that COVID-19 patients with increased SGOT require more intubation action. In addition, increased SGOT was also associated with hepatitis and myositis/heart damage infections.²⁷ Research conducted by Cheng, *et al.* showed that patients who experienced an increase in serum creatinine at the beginning of hospitalization had a greater likelihood of being treated in an intensive care unit (ICU) and required mechanical ventilation, thus it can be said that kidney abnormalities at the beginning of hospitalization represent a higher risk of worsening.²⁸

In addition to kidney and liver damage, the increase in LDH and CRP in COVID-19 patients also

represents an overview of lung damage and respiratory distress due to inflammatory processes, thus it can be used to predict respiratory failure (ARDS).²⁹ The increase in CRP is said to have a correlation with an increase in the area of pulmonary lesions, while an increase in LDH may indicate an increase in inflammatory processes and lung damage rates in critically ill COVID-19 patients.³⁰⁻³² A study showed significantly higher LDH levels in ICU patients compared to non-ICU patients.³²

Some studies have shown that the majority of COVID-19 cases have electrolyte abnormalities correlated with a high risk of intensive care needs, mechanical ventilation and encephalopathy events with high mortality rates and longer treatment days.^{33,34} Comparable to some other studies, most cases found that most cases had hyponatremia (55.6%). Tezcan, *et al.* mentions that hyponatremia is the most common electrolyte abnormality compared to other electrolyte abnormalities. In addition, hyponatremia can also be used as an independent predictor of poor prognosis in COVID-19 patients.³⁴

One of the clinical picture in COVID-19 is the development of lung injuries that have the potential to cause ARDS. Pneumonia and ARDS usually develop late in the course of infection between 5-10 days from the onset of clinical symptoms.³⁵ ARDS is one of the leading causes of death in COVID-19 patients. The cause of ARDS in COVID-19 cases is cytokine storms, which are uncontrolled systemic inflammatory responses due to the release of large amounts of proinflammatory cytokines.^{13,26} In this study, 88% of COVID-19 patients who died were in critical condition and were dominated by severe ARDS conditions.

In this study, the sample used was quite a lot with complete data but had limitations because it did not exclude some cases of COVID-19 that had previously undergone treatment in other health facilities, thus there was a possibility of treatment of patients that could affect the results of the initial examination when the patient was hospitalized at Ulin Regional Hospital Banjarmasin.

CONCLUSION

COVID-19 deaths at Ulin Regional Hospital Banjarmasin from March to August 2020 were dominated by severe-critical degree cases consisting mostly of male, aged <65 years old with one or more comorbidities. Hypertension, diabetes mellitus, and

obesity were the most commonly found comorbidities with early symptoms of fever, cough, and shortness of breath. Laboratory results in most cases showed haemoglobin, platelets, leukocytes, and neutrophils tended to be normal with increased NLR, as well as decreased lymphocytes, eosinophils, and ALC. Natrium levels tended to decrease and there was an increase in SGOT, creatinine, CRP, and LDH.

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