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Epidemiological and Clinical Features of Critical and Non-Critical Elderly COVID-19 Patients in Udayana University Academic Hospital: A Retrospective Study

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ABSTRACT

Elderly COVID-19 patients have been associated with worse outcomes and have been presented with the highest mortality rate. However, studies on the clinical features and the differences between critical and non-critical elderly COVID-19 patients in Indonesia and even other countries are still lacking and rare. In this retrospective study, the epidemiological and clinical features of critical and non-critical elderly COVID-19 patients admitted to Udayana University Academic Hospital between April 2020 and March 2021 were analyzed and then compared. Of the 280 medical records analyzed, 60.7% were male and the median age was 65.0 years old. Based on the medical records, 18.2% of elderly patients met our criteria of critical patients. The most common symptoms presented in both category upon admission included fever and coughing. The most common comorbidity found in critical patients was heart disease and hypertension in non-critical patients. Laboratory results differences included leukocytes, neutrophils, lymphocytes, Neutrophil-to-Lymphocyte Ratio, platelets, SGOT, SGPT, and urea. Only 9.9% of critical patients and 6.1% of non-critical patients were given antiviral therapy. In contrast, 68.6% of critical patients and 76% of non-critical patients were given antibiotics. The mortality rate in critical patients was 70.6% and 0.4% in non-critical patients. Based on the results, a multimodal approach in the treatment of elderly COVID-19 patients is very essential. The higher mortality rate in elderly patients should be able to be reduced by giving early and timely antiviral therapy with the addition of effective choice of drugs.

Keywords: Covid-19; epidemiology; elderly patients; geriatric; SARS-CoV-2

Highlights: The novelty of this study is that it is the first study focusing on the clinical profile of elderly COVID-19 patients in Bali. The benefit of this study through its description and comparison is for clinicians to be able to provide a more structured and comprehensive approach towards elderly COVID-19 patients.

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INTRODUCTION

Novel coronavirus disease 2019 (Covid-19) has been a worldwide phenomenon since it was initially found in China in December 2019. It was first declared as a worldwide pandemic by the World Health Organization (WHO) in March 2020.[1] Indonesia reported its first cases in early March 2020 and by late May 2020 the number of cases had undergone significant increase, reaching a total of 21430 cases with 1326 deaths. A study on the epidemiology of COVID-19 in Indonesia, which observed a total of 8211 cases between March 2nd and April 24th 2020, showed that 16% of the patients were from the age group of above 60 years old. Patients from this age group were also presented with the highest mortality rate of 43.6%.[2] Elderly patients have been associated with a higher susceptibility to COVID-19 and worse outcomes due to several reasons such as immunosenescence and comorbidities which usually worsen with aging.

Deterioration of pathophysiological functions in the body systems of elderly patients might also contribute to higher mortality rates.[3] However, studies on the clinical features of elderly Covid -19 patients and the differences between critical and non-critical elderly COVID-19 patients in Indonesia and even other countries are still lacking and rare. Through this descriptive study, we aimed to summarize the clinical features and to provide a comparison between critical and non-critical elderly COVID-19 patients who were admitted to Udayana University Academic Hospital in hope that this could act as a reference for physicians to have a better understanding and to provide better treatment for elderly COVID-19 patients in the future.

MATERIALS AND METHODS

Study Design and Setting

This study was designed as an observational cross-sectional study conducted at Udayana University Academic Hospital which serves as a health facility in Jimbaran, Bali and was the province's main referral site for COVID-19 patients.

Data Collection

Secondary data of all elderly COVID-19 patients admitted to Udayana University Academic Hospital between April 2020 and March 2021 were collected through medical records using the method of total sampling. The inclusion criteria for our study were all elderly COVID-19 patients who were aged 60 to 90 years old. Although there are different ways to classify elderly age range, several studies such as the study by Alterovitz and Mendelsohn[4] in Journal of Aging Studies had used 60 years old as the baseline age for elderly people according to the US census bureau age divisions as well as to previous researches on physical and cognitive aspects of aging. In addition, three other studies which discussed about clinical characteristics of elderly COVID-19 patients in Jakarta, Hunan, and Hainan had also used 60 years old as the baseline age for their population of elderly patients.[5–7]

The patients were then divided into two categories, including critical and non-critical elderly COVID-19 patients. Critical patients were patients who met any of the following criteria, including patients with Acute Respiratory Distress Syndrome (ARDS), shock, and/or sepsis; patients who were admitted to the ICU; and patients who died in a short duration upon admission, whereas non-critical patients consisted of the rest. Patients were excluded if they were not aged 60 to 90 years old and/or were not diagnosed with Covid-19. The collected data only consisted of epidemiological features, clinical manifestations, comorbidities, laboratory results, treatment, and patients' outcome, whereas any data regarding patients' identity were not disclosed due to patients' right to privacy. Patients who decided to opt out of the study were also given the opportunity to contact the authors

and all data were only accessible to the authors. This study had been approved by the Ethical Commission of Udayana University (No. 1010/UN14.2.2.VII.14/LT/2020).

Data Analysis

All statistical analyses were performed using IBM SPSS Statistics 20. All data, except sex and prognosis, were tested using Kolmogorov-Smirnov Z test and continued by either Independent-Samples T test if the asymptotic significance 2-tailed was > 0.05 or Mann-Whitney U test if the asymptotic significance 2-tailed was < 0.05. Sex and prognosis variables were tested using Chi-square test. Continuous variables are described in median (interquartile range, IQR) and categorical variables are presented as n (%).

RESULTS AND DISCUSSION

A total of 280 elderly COVID-19 patients were included in this study and all patients were admitted to Udayana University Academic Hospital, Bali. The median age of all elderly patients were 65.0 years old. This finding correlates with a study in China where COVID-19 had the epidemiological characteristics which commonly affect age group ranging from 30 to 79 years old.[8] Other specific studies on elderly COVID-19 patients also showed similar results where a study in Jakarta by Azwar *et al.*[5] found that the majority of its patients were aged 60 to 69 years old whereas another study in Hunan by Guo *et al.*[6] found that the median age of all its elderly patients was 67 years old.

More than half of the patients in this study were constituted by male patients in both critical and non-critical criterion. The data samples in several other studies from different countries were also predominantly constituted by male patients. A study in a tertiary hospital in North India by Soni *et al.*[9] reported that 57.8% of its patients were males and an even higher percentage were reported from a study in Al Ain Hospital of United Arab Emirates by Ismail *et al.*[10] where 84.6% of its critical patients were also males. Aside from the prevalence of COVID-19 cases among males, it was also found that there was a difference in terms of fatality rate where males showed higher results.[11] There are several mechanisms which may contribute to the possible correlation between male sex and a higher incidence of COVID-19 cases among them. The SARS-CoV-2 is known to infect humans by binding to angiotensin-converting enzyme 2 (ACE2) receptor. After binding to the ACE2 receptor, the virus is then able to enter human tissue through cell surface fusion mediated by transmembrane protease serine 2 (TMPRSS2).[12]

In molecular perspective, ACE2 gene is found to be located on the X chromosome which means there should be alleles that regulates resistance towards Covid-19.[11] In addition, ACE2 was also found to be a constitutive product of Leydig cells which is a factor affecting testosterone secretion in males. To further support this incidence, it was also found that androgen receptor activity had been considered as a factor in the transcription of TMPRSS2 gene, thus implying that the expression of TMPRSS2 modulated by testosterone might contribute to male predominance in COVID-19 cases.[13] Despite several supporting factors which may explain male predominance in COVID-19 cases, there are also several studies which had higher cases among females rather than males.[6,14]

Table 1. Demographics and Clinical Characteristics of Elderly COVID-19 Patients

	All Patients (*n* = 280)	**Critical (*n* = 51)**	**Non-critical (*n* = 229)**	***p* value**
Age, years	65.0 (62.0-72.0)	68.0 (63.0-74.0)	65.0 (62.0-71.0)	0.061
Sex				0.059
Male	170 (60.7)	37 (72.5)	133 (58.1)	
Female	110 (39.3)	14 (27.5)	96 (41.9)	
Symptoms				
Fever	276 (98.6)	51 (100)	225 (98.3)	0.344
Cough	252 (90)	46 (90.2)	206 (90)	0.959
Cold	46 (16.4)	2 (3.9)	44 (19.2)	0.000
Sore Throat	116 (41.4)	17 (33.3)	99 (43.2)	0.187
Cephalgia	78 (27.9)	8 (15.7)	70 (30.6)	0.015
Myalgia	90 (32.1)	10 (19.6)	80 (34.9)	0.020
Diarrhea	15 (5.4)	5 (9.8)	10 (4.4)	0.223
Comorbidities				
Hypertension	132 (47.1)	17 (33.3)	115 (50.2)	0.026
Heart Disease	68 (24.3)	23 (45.1)	45 (19.7)	0.000
Diabetes	72 (25.7)	13 (25.5)	59 (25.8)	0.968
Kidney Disease	12 (4.3)	2 (3.9)	10 (4.4)	0.888
Malignancy	5 (1.8)	1 (2)	4 (1.7)	0.917
HIV	0 (0)	0 (0)	0 (0)	
Autoimmune	0 (0)	0 (0)	0 (0)	

Data are presented in median (IQR) or *n* (%)

The study of critical patients by Ismail *et al.*[10], showed that the most common symptoms presented in its patients were coughing followed by fever. Another study from China by Liu *et al.*[7] which compared the clinical features manifested in elderly patients with young patients also showed that the most common symptoms in both age groups were fever and cough. These clinical features are in accordance with our findings where both non-critical and critical patients were most commonly presented with symptoms of fever followed by coughing. While ACE2 acts as an entry point for Covid-19, it also has a crucial anti-inflammatory role by converting angiotensin II, which is a perpetrator of inflammation, to angiotensin 1-7 in the renin-angiotensin signaling system. The expression of ACE2 declines with aging and in patients with cardiovascular diseases. When SARS-CoV-2 binds to ACE2 receptors in patients, it further reduces the ACE2 cell surface expression. Hence, elderly COVID-19 patients with cardiovascular comorbidities are suspected to have a significantly low level of ACE2 which contributes to the predisposition of a more severe outcome.[15]

A study from Central Sulawesi by Faustine[16] which focused on the severity profile of COVID-19 patients with hypertension concluded that there was no significant correlation between high blood pressure and the severity and mortality of COVID-19 patients. On the other hand, it was stated that cardiovascular comorbidities other than hypertension were associated with the severity of Covid-19.[16] Another study stated that the presence of heart lesion in COVID-19 patients was associated with poor prognosis where these patients were five to ten times more at risk. The cardiac manifestations found were predominated by acute myocardial damage.[17] These findings may provide an explanation to the difference found in terms of the most common comorbidity suffered by the elderly patients in our study where hypertension was more prevalent in non-critical elderly patients whereas heart disease was more prevalent in critical elderly patients. All data on demographics and clinical characteristics are presented in Table 1.

Table 2. Laboratory Results of Elderly COVID-19 Patients

	All Patients (*n* = 280)	**Critical (*n* = 51)**	**Non-critical (*n* = 229)**	***p* value**
Hemoglobin, d/dL	13.2 (12.1-14.1)	13.7 (11.9-14.3)	13.2 (12.1-14.0)	0.967
Hematocrit, %	39.0 (36.1-41.5)	39.1 (35.5-42.4)	38.9 (36.2-41.5)	0.718
Leukocyte count, $x10^3$µL	6.77 (5.1-8.8)	8.1 (6.1-12.4)	6.3 (4.9-8.3)	0.000
Neutrophil count, $x10^3$µL	4.5 (3.2-6.6)	6.9 (4.4-10.5)	4.2 (3.1-5.9)	0.000
Lymphocyte count, $x10^3$µL	1.2 (0.8-1.7)	0.7 (0.5-1.2)	1.35 (0.9-1.9)	0.000
Neutrophil-to-Lymphocyte Ratio	3.4 (2.0-5.7)	10.0 (4.7-16.1)	3.1 (1.9-4.6)	0.000
Platelet count, $x10^3$µL	210.5 (165.0-272.0)	187.0 (163.0-234.0)	219.0 (165.5-276.0)	0.037
Liver function				
SGOT, U/L	33.0 (26.0-50.0)	52.0 (34.3-70.0)	31.0 (25.0-45.0)	0.000
SGPT, U/L	29.0 (21.5-47.0)	44.5 (28.0-67.5)	28.0 (20.0-40.5)	0.000
Kidney function				
Blood urea nitrogen, mg/dL	15.0 (11.0-21.0)	20.0 (15.0-30.5)	14.0 (11.0-19.0)	0.000
Creatinine, mg/dL	0.8 (0.6-1.1)	0.9 (0.7-1.2)	0.8 (0.6-1.0)	0.122
Random blood sugar, mg/dL	114.5 (97.0-152.0)	121.0 (107.0-152.0)	114.0 (96.0-152.0)	0.959

Data are presented in median (IQR) or *n* (%)

Similar to our study, the study by Faustine *et al.*[16] found that most patients' laboratory test showed an increase in neutrophils level but a decrease in lymphocytes level. According to several other studies, majority of the COVID-19 cases also displayed low lymphocytes level, especially in critical patients. The SARS-CoV-2 virus is known to induce the manifestation of cytokine storm during infection which causes an excessive inflammatory reaction. The persistent stimulation in this phenomenon may lead to a reduction in lymphocytes.[18] The higher value of neutrophil and lower value of lymphocyte in critical patients when compared to the lower value of neutrophil and higher value of lymphocyte resulted in a disparity of NLR value where the median NLR in critical patients was significantly higher. The value of NLR was found to be constantly higher in severe COVID-19 patients in several other studies. A study which focused on the predictive values of NLR found that NLR has good specificity and sensitivity, thus makingit a good predictive value on the severity and mortality of COVID-19 patients.[19]

The median platelet level of critical patients was found to be approximately 32 x 10^3/µL lower than non-critical patients in this study. Mild thrombocytopenia had been reported as one of the laboratory findings in 58-95% of severe COVID-19 cases. Viral infections are able to cause thrombocytopenia through various causes. The development of thrombocytopenia in response to viral infections is generally mediated via enhanced platelet clearance. Viruses are also known to interact with megakaryocytes and reduce platelet synthesis.[20]

The correlation between elevated levels of SGOT and SGPT in liver function test and COVID-19 is still a subject of debate and needs further investigation.[21] Direct cytopathic effect may not be the main mechanism for SARS-CoV-2 to induce liver damage since ACE2 receptors are found to be more abundant in cholangiocytes than in hepatocytes.[22] However, other factors such as Covid-19-induced cytokine storm, sepsis, or drug-induced liver injury should be considered as possible mechanisms of Covid-19-related liver injury. In addition, COVID-19 may also worsen underlying chronic liver disease which contributes to a higher mortality outcome.[23] The disparities of kidney function test in median urea between critical and non-critical patients may be due

to the role of COVID-19 in causing kidney damage. The infection of SARS-CoV-2 may contribute to the impairment of kidney through multiple mechanisms. The viral load of SARS-CoV-2 was found to be able to directly induce cytotoxicity of renal resident cell. Symptoms manifested in COVID-19 patients such as fever, vomiting, diarrhea, and shock could also cause kidney hypoperfusion. In addition, the cytokine storm induced by SARS-CoV-2 should also be considered.[24] All data on laboratory results are presented in Table 2.

Table 3. Treatment and Outcomes of Elderly COVID-19 Patients

	All Patients (*n* = 280)	**Critical (*n* = 51)**	**Non-critical (*n* = 229)**	***p* value**
Treatment				
Antiviral Therapy	19 (6.8)	5 (9.8)	14 (6.1)	0.353
Antibiotics	209 (74.6)	35 (68.6)	174 (76)	0.035
Vitamin C	262 (93.6)	43 (84.3)	219 (95.6)	0.038
Anticoagulants	48 (17.1)	14 (27.5)	34 (14.8)	0.066
Prognosis				0.000
Discharge	243 (86.8)	15 (29.4)	228 (99.6)	
Death	37 (13.2)	36 (70.6)	1 (0.4)	

Data are presented in median (IQR) or *n* (%)

A significantly higher overall mortality rate in elderly COVID-19 patients was found in this study and the study conducted by Azwar, et al.[5] in Jakarta when compared to the study by Guo et al.[6] in Hunan, China. The mortality rate in our study and the one in Jakarta was 13.2% and 23% respectively in contrast to the only 2.9% in Hunan.[5,6] There are several factors that we supposed may have contributed to higher mortality rate in Indonesian studies when compared to China. These factors included the lower usage of antiviral therapy and choice of antibiotics administered to patients. Only 6.8% from all the elderly patients in our study were given antiviral therapy with the choice of either Aluvia (Lopinavir-Ritonavir), Favipiravir, or Remdesivir. The administration of antibiotics was much higher with the choice of either Azithromycin, Levofloxacin, or combination of both. In comparison, 93.3% of the elderly patients in Hunan were given antiviral therapy and the most common antibiotic administered was moxifloxacin.[6]

A study by Wu *et al.*[25] found that patients experiencing mild symptoms received earlier initiation of antiviral therapy, thus indicating that early and timely administration of antiviral therapy may contribute to the slowing of COVID-19 progression into a more severe state and may improve the prognosis of patients under care. In a randomized controlled trial, which assessed the clinical efficacy and safety of moxifloxacin compared to levofloxacin plus metronidazole in treating community-acquire pneumonia (CAP), it was found that moxifloxacin monotherapy was more effective in treating CAP with a clinical cure rate of 76.7% compared to 51.5% in the levofloxacin plus metronidazole group. The administration of moxifloxacin also showed lower incidence of adverse events with a more convenient dosing regimen.[26] All data on the treatments and outcomes of patients are presented in Table 3.

STRENGTHS AND LIMITATIONS

The strengths of this study were being the first few studies to focus on the clinical profile of elderly COVID-19 patients and to further compare the characteristics of critical and non-critical patients in Indonesia and even Southeast Asia. The limitations of this study were not including the data of the second wave of COVID-19 in Indonesia, which was predicted to have higher

mortalities, and not further classifying the elderly age group into youngest-old (65-74 years), middle-old (75-84 years), and oldest-old (≥ 85 years) for a more in-depth comparison.

CONCLUSIONS

In conclusion, elderly patients are more susceptible to develop a severe outcome with COVID-19. There is a diverse number of possible factors which affect bodily functions in elderly patients and contribute to the progression of the disease. Hence, a multimodal approach in the treatment of elderly COVID-19 patients is very essential. The higher mortality rate in elderly patients should be able to be reduced by giving early and timely antiviral therapy with the addition of effective choice of drugs.

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ETHICAL CLEARANCE

The research protocol was approved by the Ethical Commission of Udayana University (No. 1010/UN14.2.2.VII.14/LT/2020).

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CONFLICT OF INTEREST

The authors declared that there was no conflict of interests that might bias or fabricate the information and work stated within the paper.

AUTHOR CONTRIBUTION

Study design and data collection: CAWP. Clinical advice and data collection: IKAS. Data analysis and report writing: DJ and RCS. Report writing and manuscript review: IKHA, GVP, IGWP, J, and PKW. Manuscript review and revision: DAFPS and IGNASD.

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