

Original Article

Risk Factors of COVID-19 Mortality in Elderly Patients

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ABSTRACT

Background/Purpose: Older age is thought to have an impact on both the risk of COVID-19 mortality and the severity of the illness. Lower immunity levels and/or age-related chronic medical disorders could be a feasible explanation for this. Unfortunately, there is currently little information available about the clinical traits of older COVID-19 patients. The purpose of this study was to evaluate the risk factors associated with COVID-19 mortality in elderly.

Methods: We included 312 COVID-19 confirmed patients aged 60 years or older who were admitted to the Internal Medicine Ward between July 2021 and December 2022. This was a single-center study and a case control in design, which died participants were classified as case group and survived participants were classified as control group. Patients against medical advice, aged <60 years, and repeated COVID-19 infections were not included.

Results: 149 (47.8%) patients survived and 163 (52.2%) patients died. The majority of individuals (86.2%) had moderate to severe COVID-19 infection, and 95.2% had pneumonia. Variables significantly associated with mortality in bivariate analyses were age ($p = 0.046$), incidence of pneumonia ($p < 0.001$), severity of COVID-19 infection ($p < 0.001$), stages of CKD ($p = 0.003$), hypertension classification ($p = 0.001$), diabetes classification ($p < 0.001$), number of comorbidities ($p < 0.001$), and number of vaccines ($p = 0.001$).

Conclusion: Age > 80 years old, male, diabetes mellitus, stage 2 and 3 of hypertension, and obesity class 2 increased the risk of COVID-19 mortality, while number of COVID-19 vaccinations reducing the COVID-19 death.

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1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19

clinical spectrum ranges from asymptomatic to a clinical disease marked by multiple organ dysfunction syndrome and severe respiratory failure needing mechanical ventilation. According to Mizumoto et al, 17.9% to 33.3% of infected people are having no

symptoms. The mild to moderate clinical symptoms were fever, coughing, and dyspnea. Sore throat, anosmia, anorexia, nausea, malaise, myalgias, and diarrhea are less frequent symptoms. According to Stokes et al., out of 373,883 verified symptomatic COVID-19 cases in the USA, 36% and 34% of patients had myalgia, 34% reported headache, and 70% reported fever, coughing, and shortness of breath. Severe COVID-19 infection is more common in people 60 years of age or older and in patients with underlying medical comorbidities (obesity, cancer, smoking, diabetes, chronic renal disease, diabetes, diabetes, obesity, solid organ transplant patients), and they may exhibit acute respiratory distress syndrome (ARDS) and lead to death. According to CDC's National Vital Statistics System (NVSS) which collects data on all deaths that occurred in the United States between 2020 and 2022, patients with COVID-19 aged 50 to 64 have a 25-fold increased risk of death compared to aged ≤ 30 . It increases 60 fold in aged 65 to 74. The probability of death rises to 340 times in elderly aged over 85.¹⁻³ Numerous studies indicate that older people are more vulnerable to COVID-19 and are more likely to experience negative consequences.⁵⁻¹⁰

The elderly's poor outcomes in COVID-19 infection can be attributed to a number of co-morbidities, frailty, diminishing functional status, and declining cognitive state.¹¹ The aging immune system is primarily caused by immunosenescence and inflammaging, whereby the buildup of senescent immune cells causes the system to deteriorate and an increase in the inflammatory phenotype causes immunological dysfunction. Immune system aging affects cells and soluble immune response mediators, which control disease course, clinical results, and susceptibility to infection.¹⁰ Elderly individuals are therefore more susceptible to latent or novel infection due to age-related immune system alterations and co-morbidities, which increases COVID-19 infection morbidity and mortality. Unfortunately, there is currently little information available about the clinical traits of older COVID-19 patients. The purpose of this study was to evaluate the risk factors associated with COVID-19 mortality in older individuals.

2. METHODS

2.1. Population and Design

Using a total sampling technique, we included 312 COVID-19 confirmed patients aged 60 years or older who were admitted to the Internal Medicine Ward between July 2021 and December 2022. Patients with COVID-19 positive results on the Reverse-Transcriptase Polymerase-Chain-Reaction (RT-PCR) assay using nasopharyngeal swabs were referred to as COVID-19 confirmed patients. The Dr. Soetomo

Hospital's Ethical Committee granted ethical clearance with number 2074/101/4/III/2023.

This was single-center study and a case control in design. The study's deceased participants were designated as the case group; while the study's living participants were designated as the control group. Patients against medical advice, aged < 60 years, and repeated COVID-19 infections were not included.

2.2. Data Collection and Statistical Analysis

Data were taken from medical records regarding age, gender, the occurrence of pneumonia, severity of the COVID-19 infection, mortality, diabetes mellitus (DM) classification, obesity classification, stage of chronic kidney disease (CKD), stage of hypertension, number of COVID-19 vaccinations received, number of comorbidities, and the other comorbidities (coronary heart disease, stroke, chronic lung disease, chronic liver disease, malignant disease, HIV infection, autoimmune disease, and hematological diseases). As a result, we evaluated mortality.

Pneumonia was diagnosed at the beginning of admission, which referred to diagnosis criteria in 4th Edition Indonesian Guideline of COVID-19 Management Protocol. The diagnostic criteria based on clinical symptoms consist of fever, cough, dyspnea/shortness of breath or tachypnea, decrease of consciousness, or respiratory distress with peripheral oxygen saturation $< 93\%$ and radiologic findings on chest x-ray which showed infiltrate on lungs.

We classified obesity based on BMI (Body Mass Index) which refers to Indonesian Health Ministry Classification. BMI 18.5–22.9 kg/m² classified as normal, BMI 23–24.9 kg/m² as overweight, BMI 25–29.9 kg/m² as obesity class 1, BMI ≥ 30 kg/m² as obesity class 2, and BMI ≤ 18.4 kg/m² as underweight. In our study, normal BMI and underweight classified as No Obesity. DM was classified into no history of diabetes, well-controlled diabetes (HbA1c $< 9\%$), and poor-controlled diabetes (HbA1c $\geq 9\%$). Hypertension was classified based on blood pressure. According to 2018 ESC guidelines, SBP of 140–159 mmHg and/or DBP of 90–99 mmHg was classified as stage 1 hypertension, SBP 1 of 160–179 mmHg and/or DBP of 100–109 mmHg was classified as stage 2 hypertension, and SBP of 180 mmHg or greater and/or DBP of 110 mmHg or greater was classified as stage 3 hypertension. According to 2012 KDIGO guidelines, CKD is classified based on glomerular filtration rate. CKD stage 1 (GFR > 90 mL/min per 1.73 m²), CKD stage 2 (GFR 60 to 89 mL/min per 1.73 m²), CKD stage 3 (GFR 30 to 59 mL/min per 1.73 m²), CKD stage 4 (GFR 15 to 29 mL/min per 1.73 m²), and CKD stage 5 (GFR < 15 mL/min per 1.73 m² or treatment by dialysis).

Statistical analysis was carried out with SPSS Version 25.0. The number of occurrences in each group was used to describe the characteristics of patients. For bivariate analysis, we used the Mann-Whitney and Chi-Square tests. The backward likelihood ratio method in logistic regression was used for multivariate analysis, which conducted on variables with p value < 0.25 in bivariate analyses.

3. RESULTS

312 patients between July 2021 and December 2022 fulfilled the study's requirements. Figure 1 showed the diagram used for participant selection. Table 1 showed that there were 163 (52.2%) patients in the case group and 149 (47.8%) patients in the control group. A number of 51.6% of patients were male. The majority of individuals aged 60–70 years old (71.2%), and 86.2% had moderate to severe COVID-19 infection, while 95.2% had pneumonia. A total of 52.2% of participants in this study were not vaccinated. The most common comorbidities were DM (76%), CKD (61.2%), and hypertension (37.2%). It also showed variables which significantly associated with mortality in bivariate analyses, such as age ($p = 0.046$), incidence of pneumonia ($p < 0.001$), severity of COVID-19 infection ($p < 0.001$), stages of CKD ($p = 0.003$), hypertension classification ($p = 0.001$), diabetes classification ($p < 0.001$), number of comorbidities ($p < 0.001$), and number of vaccines ($p = 0.001$).

Table 2 displays the results of multivariate analyses conducted on variables in bivariate analyses which the p value < 0.25, such as age, gender, incidence of pneumonia, severity of COVID-19 infection, obesity classification, stages of CKD, hypertension classification, diabetes classification, HIV infection, number of comorbidities and number of vaccines. Since we used backward likelihood ratio in logistic regression, variables which eliminated from the equation were pneumonia, severity of COVID-19 infection, HIV infection and number of comorbidities. Obesity classification wasn't significant in bivariate

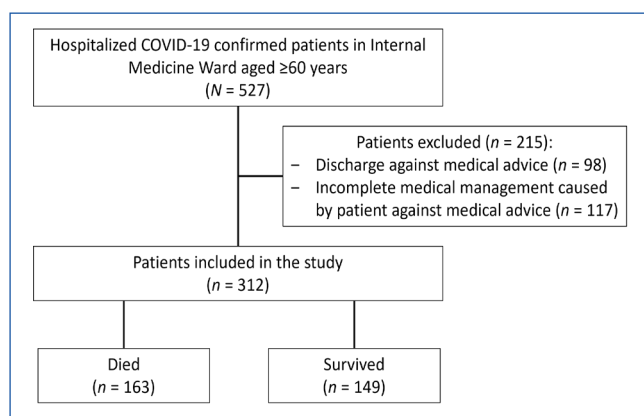
Table 1. Conditions associated with COVID-19 mortality in elderly patients

Variable	Survived (<i>n</i> = 149)	Died (<i>n</i> = 163)	<i>p</i> value
Age (years)			
60–70	111 (74.5)	111 (68.1)	0.046 ^a
71–80	32 (21.5)	33 (20.2)	
>80	6 (4)	19 (11.7)	
Sex			
Man	69 (46.3)	92 (56.4)	0.074 ^a
Woman	80 (53.7)	71 (43.6)	
Pneumonia			
Yes	134 (89.9)	163 (100)	< 0.001 ^a
No	15 (10.1)	0 (0)	
Severity			
Mild	35 (23.5)	8 (4.9)	< 0.001 ^a
Moderate to severe	114 (76.5)	155 (95.1)	
Obesity classification			
No obesity	98 (65.8)	87 (47)	0.063 ^a
Overweight	28 (18.8)	32 (19.6)	
Obesity class 1	17 (11.4)	29 (17.8)	
Obesity class 2	6 (4)	15 (9.2)	
Stages of CKD			
No CKD	75 (50.3)	46 (28.2)	0.003 ^a
CKD stage 1 (GFR > 90)	25 (16.8)	30 (18.4)	
CKD stage 2 (GFR 60–89)	25 (16.8)	37 (22.7)	
CKD stage 3 (GFR 30–59)	10 (6.7)	20 (12.3)	
CKD stage 4 (GFR 15–29)	4 (2.7)	9 (5.5)	
CKD stage 5 (GFR < 15)	10 (6.7)	21 (12.9)	
Hypertension classification			
No hypertension	104 (69.8)	92 (56.4)	0.001 ^a
Hypertension stage 1	32 (21.5)	28 (17.2)	
Hypertension stage 2	8 (5.4)	30 (18.4)	
Hypertension stage 3	5 (3.4)	13 (8)	
Diabetes classification			
No DM	59 (39.6)	16 (9.8)	< 0.001 ^a
DM HbA1c < 9%	75 (50.3)	86 (52.8)	
DM HbA1c ≥ 9%	15 (10.1)	61 (37.4)	
Other comorbidities			
Coronary heart disease	8 (5.4)	12 (7.4)	0.315 ^a
Stroke	12 (8.1)	14 (8.6)	0.864 ^a
Chronic lungs disease	3 (2)	5 (3.1)	0.557 ^b
Chronic liver disease	9 (6)	5 (3.1)	0.205 ^a
Malignant disease	12 (8.1)	11 (6.7)	0.659 ^a
HIV infection	3 (2)	0 (0)	0.069 ^b
Autoimmune disease	1 (0.7)	2 (1.2)	0.616 ^b
Haematological diseases	2 (1.3)	3 (1.8)	0.727 ^b
Number of comorbidities			
0	13 (8.7)	1 (0.6)	< 0.001 ^b
1	37 (24.8)	13 (8)	
2	53 (35.6)	52 (31.9)	
3	34 (22.8)	64 (39.3)	
4	12 (8.1)	27 (16.6)	
5	0 (0)	5 (3.1)	
6	0 (0)	1 (0.6)	
Number of vaccines			
0	64 (43)	99 (60.7)	0.001 ^a
1	8 (5.4)	13 (8.0)	
2	52 (34.9)	42 (25.8)	
3	25 (16.8)	9 (5.5)	

^a p value for Chi-square. ^b p value for Mann-Whitney test.

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; GFR, glomerular filtration rate.

Figure 1. Flowchart of patient selection



analyses but significant when adjusted with other variables in multivariate analyses ($p = 0.005$). In our study, patients aged >80 years old had OR of 6.069 (95% CI = 1.929–19.095) compared to age 60–70 years old in risk of COVID-19 mortality. Female gender had protective factor in COVID-19 mortality over male (OR = 0.375, 95% CI = 0.254–0.552). Linear increasing risk of COVID-19 mortality was seen in classification of DM ($p < 0.001$). Increasing risk of COVID-19 death were also seen in hypertension stage 2 (OR = 4.448, 95% CI = 1.634–12.328) and 3 (OR = 5.808, 95% CI = 1.669–20.208), and obesity class 2 (OR = 7.587, 95% CI = 2.279–25.263). Number of vaccinations has significant protective factor to reduce COVID-19 death (OR = 0.534, 95% CI = 0.415–0.687).

4. DISCUSSION

Age is thought to be a crucial factor for the clinical outcomes, course, severity and prognosis of the COVID-19 infection.¹¹ In our bivariate analyses, age has significant association with mortality ($p = 0.046$). According to a study in China 2020 which recruiting 105 elderly patients aged above 60 years old, it was found that ≥ 75 years old group compared to 60–74 years old group, the incidence of sepsis, severe Acute Respiratory Distress Syndrome, Acute Kidney Injury, and invasive mechanical ventilation needs were more common in older group ($p < 0.05$).⁹

Table 2. Multivariate analyses

Variables in the equation	df	p value	OR (95% CI)
Age (years)			
60–70	Ref	0.009	
71–80	1	0.757	1.115 (0.562–2.212)
>80	1	0.002	6.069 (1.929–19.095)
Sex			
Man	Ref		
Woman	1	< 0.001	0.375 (0.254–0.552)
Classification of DM			
No DM	Ref	< 0.001	
DM HbA1c < 9%	1	< 0.001	5.054 (2.677–9.544)
DM HbA1c $\geq$ 9%	1	< 0.001	19.042 (8.111–44.702)
Classification of Hypertension			
Absent	Ref	0.002	
Hypertension stage 1	1	0.544	1.250 (0.609–2.564)
Hypertension stage 2	1	0.004	4.448 (1.634–12.328)
Hypertension stage 3	1	0.006	5.808 (1.669–20.208)
Classification of obesity			
No obesity	Ref	0.005	
Overweight	1	0.862	1.065 (0.525–2.16)
Obesity class 1	1	0.067	2.152 (0.947–4.889)
Obesity class 2	1	0.001	7.587 (2.279–25.263)
Number of vaccinations	1	< 0.001	0.534 (0.415–0.687)

Abbreviations: CI, confidence interval; df, degree of freedom; DM, diabetes mellitus; HbA1c, hemoglobin A1c; OR, odds ratio; Ref, reference.

This may due to aging process, which is linked to an increase in immune-mediated inflammation and related inflammatory disorders. The immune system undergoes numerous biochemical alterations with aging, rendering elderly individuals more vulnerable to infections.¹²

In this study, male was a risk factor for COVID-19 mortality in elderly. Several previous studies stated that men were having a more severe COVID-19 infection rather than women.^{14,15} A meta-analysis recruiting 57 researches showed that men have a higher COVID-19 incidence than women.¹⁶ These might due to higher level of Angiotensin-converting enzyme 2 receptor in men.¹⁷ Women had a better innate immune response because smoking habits, alcohol consumption, and pre-existing comorbidities were found greater in men.¹⁵

DM, CKD, and hypertension were the three most prevalent comorbidities in our study. The three comorbidities each had a substantial independent association with COVID-19 mortality. In previous study conducted in China, the most frequent comorbidities were hypertension, DM, and cardiac disease.⁹ The elderly patients with comorbid conditions were more likely to progress to severe illness, so the management of chronic disease is vital in elderly patients with COVID-19.^{4,15,16} According to this study, DM showed a significant correlation in bivariate analyses and supported by linear increasing risk for COVID-19 mortality in multivariate analysis. A nationwide study in Poland, 2020, reported that diabetes was an independent risk factor of in-hospital death due to COVID-19 infection.²⁰ In our study, compared to no hypertension, hypertension stage 2 and 3 were also showed an increasing risk to COVID-19 death. Two meta-analyses revealed that patients of all ages had an increased chance of critical COVID-19, ICU needs, and mortality outcomes when they had coexisting conditions of diabetes and hypertension.^{21,22} Diabetic and hypertension patients will have decreased resistance to viral infections. Patients with long-term diabetes and hypertension are more susceptible to developing critical illness in COVID-19 because these conditions can deteriorate cardiac function and damage vascular structure.²³ A study reported an association between higher blood pressure and a reduced antibody response to an inactivated viral vaccine ($p = 0.01$).²⁴ Obesity class 2 increase to COVID death compared with no obesity (OR = 7.587, 95% CI = 2.279–25.263). This is accordance to another study, which showed that obesity (BMI ≥ 30) was linked to a worse prognosis and a more severe illness.²⁵ The biological pathways that could be responsible for the severe COVID-19 in obese people include inflammation and widely expressed ACE2 in adipose tissue.²⁶

The amount of COVID-19 immunizations had become an independent protective factor in our study. A

significant correlation was found in the bivariate analysis between the number of vaccines received and the COVID-19 mortality. This finding was further supported by the multivariate analysis, which showed that the more vaccines the participants received, the stronger their protection against COVID-19 mortality (OR = 0.534, 95% CI = 0.415–0.687). According to a previous study, for every 10% increase in vaccine coverage, the death rate may decrease by 7.6%.¹⁹ Subsequent studies conducted after the vaccine's release revealed that people who had not gotten all recommended vaccines had significantly higher rates of COVID-19 infection, hospitalization, and death than those who had.²⁰ Theoretically, a successful COVID-19 immunization can reduce the severity of an illness linked to a SARS-CoV-2 infection. Not simply the production of antibodies, but also the development of immunological memory and the stimulation of T-cells, should contribute to the vaccination's protective effects.²¹ This finding supported that vaccines remain crucial, especially for the older population, despite the possibility that immunosenescence in older adults will lessen the effectiveness and response to COVID-19 vaccines.

In our study we have several limitations. First, this research does not differentiate between frailty status and cognitive status in the elderly population. Second, this study does not distinguish whether there is an acute organ damage condition such as acute renal failure, acute coronary syndrome, acute stroke, hyperglycemic crisis, or hypertensive crisis to be a confounder of mortality. Third, we didn't distinguish the variants of SARS-CoV-2 because lack of whole genome sequencing facility. Fourth, we didn't specify the COVID-19 vaccines type, because vaccine during the pandemic era in our country depends on government supplies, which rely on the availability of COVID-19 vaccine at that time, so it varies greatly. A single individual can receive multiple COVID-19 vaccine platforms.

5. CONCLUSION

Since there has been limited research on COVID-19 infection in the elderly, this study attempts to fill in the gaps by referencing relevant risk factors for COVID-19 death among aged population. The study revealed that several risk factors were nearly the same in the general population: age, gender, DM, hypertension, obesity and the number of COVID-19 vaccinations the individuals had received. Managing blood pressure, blood sugar, and body mass index in the elderly was essential to the COVID-19 survival. The older population still benefits from COVID-19 immunization for reducing COVID-19 mortality.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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