

Age and Gender as The Risk Factors for Mortality Rate in COVID-19 Patients



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ABSTRACT

Background: Coronavirus disease-19 is a disease caused by the SARS-CoV-2 virus. This virus is the newest type of coronavirus identified in humans. A recent study in 2022 in several different age groups found that older age, men, comorbidities such as hypertension, diabetes, and malignancy, were independent risk factors for mortality in COVID-19 inpatients. This study aimed to determine the risk factors for age and gender in the COVID-19 mortality rate.

Method: The design study was a retrospective case control. The research subjects were 6,697 patients from the secondary data medical record from March 2020 to September 2021 at Pasar Minggu Regional General Hospital.

Results: Results obtained 3313 men (49.5%) and 3384 women (50.5%). Men patients have a 1.5 times greater risk of mortality rate [OR 1.5 (1.3-1.7)] compared to women. Elderly patients have a 3 times greater mortality risk than non-elderly people [OR 3.1 (2.6-3.7)]. There was a correlation between the after-treatment condition and age ($p = 0.05$).

Conclusion: This study concludes that the elderly and men are the risk factors for the mortality rate in COVID-19 patients at Pasar Minggu Regional General Hospital.

Keywords: Age, Gender, Covid-19 patients, mortality.

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INTRODUCTION

COVID-19, or Corona virus disease 2019, is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2). This virus is the newest type of coronavirus identified in humans. First reported in Wuhan City, China, on December 31, 2019, then WHO declared COVID-19 a pandemic on March 11, 2020. Globally, WHO data on June 1, 2022, confirmed positive COVID-19 cases in as many as 527,603,107 cases, with death amounting to 6,290,452 with total vaccinations on May 31, 2022, recorded as many as 11,947,644,522 vaccines. In Indonesia, from January 3, 2020, to June 1, 2022, there were 6,055,341 confirmed cases of COVID-19, with a total of 156,594 deaths and a total of 413,361,190 doses of vaccinations were administered.^{1,2}

SARS-CoV-2 attacks the lungs of other organs, such as the brain, heart, and digestive system. It was observed that 75% of hospitalized COVID-19 patients had at least one comorbid COVID-19-related illness or comorbid illness. The most commonly reported comorbidities

were hypertension, diabetes, malignancy, COPD, and heart disease. SARS-CoV-2 also causes hypercoagulability problems such as gangrene, stroke, and other related complications. Individuals with diabetes have higher morbidity and higher ICU hospitalization and admission rates. In addition, data were also obtained that the death rate was higher in patients with heart disease who had elevated troponin levels.³⁻⁵

A recent study in 2022 in several different age groups found that older age, men, alcohol consumption, smoking, hypertension, diabetes, malignancy, chronic renal failure and intracerebral hemorrhage were independent risk factors for hospitalization mortality in COVID-19 patients. It was stated that the risk factors for death from COVID-19 inpatients aged 40-80 years were mainly due to metabolic comorbidities. Malignant disease and intracerebral hemorrhage are major risk factors in patients aged < 40 years. This study found that age and male sex are the main risk factors that increase mortality in patients aged >80 years.^{4,5}

Another meta-analysis study in 2021

also found that older adults are especially vulnerable to COVID-19 infection. Preliminary reports from China show an increase in disease severity and mortality among adults aged 60 years and over, and a similar pattern exists in Europe, with a mortality rate of 10% in adults aged 70 years and over, compared with a mortality rate in young adults of <1%. Older patients also show an increased need for intensive care unit (ICU) care and mechanical ventilation.^{3,5}

The presence of comorbidities is common in elderly patients. Eight out of ten patients had at least one comorbid hypertension and diabetes, while the cardiovascular disease was the most common comorbid. This finding is important as a basis for developing treatment strategies because the presence of comorbidities, such as hypertension or diabetes, can be considered a poor predictor in elderly patients with COVID-19. The purpose of this study was to determine the risk factors for age and gender on the COVID-19 death rate at Pasar Minggu Hospital.^{3,5}

SARS-CoV-2 has a diameter of 60 nm to 140 nm, and spikes range in size from 9 nm to 12 nm, giving it a solar corona-like appearance. The COVID-19 virus has a glycoprotein on the enveloped spike or S protein. Transmembrane serine protease type 2 (TMPRSS2) on the host or host cell promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which mediates virus entry into host cells. ACE2 and TMPRSS2 are expressed in target host cells, particularly type II alveolar epithelial cells. Inside the cell, this virus will duplicate the genetic material and proteins needed to form new virions on the cell surface.⁶⁻⁹

The pathophysiology of COVID-19 is divided into three phases: asymptomatic phase or transmission to host cells, upper respiratory tract invasion or early stage, and lower respiratory tract involvement leading to Acute Respiratory Distress Syndrome (ARDS) or late stage. First, the virus SARS-CoV-2, transmitted by respiratory aerosols, binds to the nasal epithelium in the upper respiratory tract. The main host receptor for viral entry into cells is ACE-2, which is abundant in adult nasal epithelial cells. The virus then undergoes local replication and propagation, along with infection of ciliated cells along the respiratory tract. This stage lasts several days, and the immune response generated during this phase is still limited. Despite having a low viral load at this time, the individual is highly contagious, and the virus can be detected through a swab test. Next is the early stage, where is a greater immune response during this phase involving the release of CXCL 10 motif chemokine ligands (CXCL-10) and interferons (IFN- β and IFN- λ) from virus-infected cells. Then the last stage, about one-fifth of all infected patients progress to this stage of the disease and develop severe symptoms. The virus invades, enters type 2 alveolar epithelial cells via the host ACE-2 receptor, and replicates to produce more viral nucleocapsids. Virus-infested pneumocytes release many different cytokines and inflammatory markers such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumor necrosis factor- α (TNF- α), IFN- and IFN- β , CXCL-10, monocyte chemoattractant protein-1 (MCP-1) and inflammatory

macro protein phage-1 α (MIP-1 α). This is called a cytokine storm which acts as a chemoattractant for neutrophils, CD4 Helper T cells and CD8 cytotoxic T cells. These cells are responsible for fighting off the virus, but they also cause subsequent inflammation and lung injury that leads to extensive alveolar damage and causes ARDS.⁶⁻⁹

The Elderly has a higher risk to mortality rate; this is due to several factors, including decreased innate immune system, decreased adaptive immune system, epigenetic changes, and increased comorbidities. The data from the COVID-19 task force describes an increase of comorbid diseases in the elderly include hypertension, diabetes, heart disease, and kidney disease. About 50.6% of COVID-19 patients have hypertension as their comorbid disease, according to a collaborative report between WHO and China. Patients aged over 60 years with comorbidities have a greater severity and mortality in Indonesia, according to data from the COVID-19 Task Force, Ministry of Health of the Republic of Indonesia of June 2020, the top three comorbidities are hypertension (52.1%), diabetes mellitus (33.6%), and other cardiovascular diseases (20.9%). Those comorbidities lead to hospitalization and mortality, compared with other comorbidities.¹⁰⁻¹³

Regarding the severity of COVID-19, it was found that there was a relationship between the severity of the disease and gender. Although China shows an equal number of cases between men and women, the data show that more men than women suffer from severe illness and death. Similar data were also obtained in several other countries, including Indonesia. Based on research findings, many cases of COVID-19 in Indonesia are men compared to women. Similar findings were also found in several studies where more men were infected with COVID-19 than women. The mortality rate of men is slightly higher than that of women.¹⁴⁻¹⁶

Deterioration in COVID-19 is also associated with comorbidities, including hypertension, cardiovascular disease, and lung disease. The condition is more common in men and is linked to smoking and drinking alcohol. Another explanation is related to differences in the

sex-based immune system. In addition, a study examining factors influencing the adoption of protective behaviors, particularly in the context of a pandemic, found that women were about 50% more likely to practice protective behaviors such as hand washing, use of face masks and avoiding crowds compared to men.¹⁵⁻¹⁷

Women are better at dealing with viral infections; this is thought to be related to the X chromosome and the hormone estrogen, which has an important role in cellular and adaptive immunity mechanisms. Women have more estrogen receptors that protect the body and help the immune system, including T cells, B cells, macrophages, neutrophils, dendritic cells, and NK cells (natural killer cells). Women carry two X chromosome that expresses several genes involved in immunological processes, such as cytokine receptors, genes involved in T-cell and B-cell activity, and transcriptional and translational regulatory factors. While the Y chromosome encodes several inflammatory pathway genes exclusively expressed in men. X-linked parental alleles are an advantage in women regarding the host response to infection, particularly by providing a balance of cellular and adaptive immune responses.^{16,17}

MATERIAL AND METHODS

This study design was a retrospective case control. The secondary data source was inpatients' medical record who meet the study inclusion criteria, age over 15 years and having medical records at Pasar Minggu Regional General Hospital from March 2020 to September 2021. The number of research subjects was 6,697 COVID-19 inpatients. Ethical clearance number 26/KEPK/RSUDPM/VI/2022 was obtained from the Research Ethics Committee of Pasar Minggu Regional General Hospital, Jakarta, Indonesia. The data showed by descriptive and data analysis used Kruskal-Wallis, Chi-square and t-test at a significant level $p < 0.05$.

RESULTS

Of the total 6,697 patients that 3313 (49.5%) were men, and 3384 (50.5%) were women. The highest age group is adult 41.2%, followed by pre-elderly 39.7%. The

median age in men is higher, 49 (15-90), than in women is 43 (15-95) years, as shown in Table 1. The most frequent inpatients stay 7-14 days (49%), while the median inpatient stay is 8 (1-51) days. About 86.4% of inpatients were discharged in healthy condition after treatment; the rest died less than 48 hours (3.9%) and more

than 48 hours (9.7%). The data in Table 2 shows that the younger age discharged in healthy condition after treatment is higher than the elder age ($p < 0.001$).

The table above describes the mortality rate in the elderly, and the number of healthy adults is higher. The odds ratio value is 3.1 (2.6-3.7), which means that elderly COVID-19 patients have three times greater risk of dying compared to adult age. Table 4 shows that the number of women discharged with healthy condition is higher than men, and the number of men who died less than 48 hours and more than 48 hours is higher than women ($p < 0.001$). Table 5 below describes gender risk factors for mortality rate. Men have a 1.5 times greater risk for mortality rate compared to women. Table 6 describes the length of stay in the inpatient elderly is higher than in adults ($p = 0.05$).

Table 1. Patients characteristics.

Characteristics	N	%	Median (Min-Max)
Number of Patients	6,697		
Gender			
Men	3,313	49.5	
Women	3,384	50.5	
Age category			
Teenagers (15-25)	464	6.9	
Adults (26-45)	2,760	41.2	
Pre-elderly (46-65)	2,660	39.7	
Elderly (>65)	813	12.1	
Average age (years)			47 (15-95)
Men age			49 (15-90)
Women age			43 (15-95)
Length of stay			
< 7 days	2,678	40	
7-14 days	3,282	49	
15-21 days	535	7.8	
> 21 days	202	2.8	
Median length of treatment (days)			8 (1-51)
Treatment end status			
Discharged in healthy condition	5,787	86.4	
Died less than 48 hours	258	3.9	
Died more than 48 Hours	652	9.7	

Table 2. After treatment based on age.

Treatment end status	Age (years)	p
Discharged in healthy condition	44 (15-95)	
Died < 48 Hours	58 (24-91)	
Died > 48 Hours	57 (19-89)	< 0.001*

*Kruskal-Wallis test

Table 3. Age risk factors for mortality.

Age category	Died	Healthy	OR
Elderly	233 (29%)	580 (71%)	3.1 (2.6-3.7)
Adult	677 (11%)	5,207 (89%)	

Abbreviation: OR, Odds Ratio

Table 4. After treatment condition based on gender.

Gender	Disharged	Died < 48 hours	Died > 48 hours	p
Men	2,782 (48%)	147 (57%)	384 (59%)	<0.001*
Women	3,005 (52%)	111 (43%)	268 (41%)	

*chi-square test

Table 5. Gender risk factors for mortality rate.

Age category	Died	Healthy	OR
Men	531 (16%)	2,782 (84%)	1.5 (1.3-1.7)
Women	379 (11%)	3,005 (89%)	

Abbreviation: OR, Odds Ratio

DISCUSSION

The COVID-19 pandemic has killed millions of people worldwide and often overwhelms healthcare systems. This study provides detailed clinical data on a large sample of COVID-19 patients at Pasar Minggu Hospital. As with any infectious disease without specific treatment, the host factor is a major determinant of disease severity and the prognosis of COVID-19. Identification of risk factors will optimize patient management and reduce mortality in future respiratory viral pandemics.^{4,5}

Based on patient characteristics, there were more women (50.5%) than men (49.5%) in this study. The data supports the global research reports in 195 countries, which found that out of 70% of the total COVID-19 patients, 40% are women. Another journal stated that among reported cases of COVID-19 infection being treated or working in medical facilities, 72% were women, and 28% were men, with an average age of 41 years. This finding is presumably due to a higher intensity of contact among women. Another study has found COVID-19 morbidity in Europe, that women are more likely to be diagnosed with COVID-19. In Germany, women accounted for 52% of confirmed cases and men 48%. This may be partly due to women disproportionately being exposed to the SARS-CoV-2 virus in the healthcare workforce. Confirmed

Table 6. Length of stay inpatient based on age.

Age	Average length of stay (days)	P
Elderly	8.3 (SD 6.5)	0.05*
Adult	7.8 (SD 6)	

*t-test

cases among health workers indicate that women are infected in higher numbers than men; 68% in Italy, 73% in the United States, 75% in Spain, 72% in Germany 72%.¹⁸⁻²⁰

This study has found that the mortality rate in elderly patients is three times greater than that of non-elderly, with an OR value of 3.1 (2.6-3.7). This evidence in line with a meta-analysis study, found that the mortality rate of the elderly was higher than other ages (16%-25.6%). Several meta-analyses explained that the mortality rate of COVID-19 in the elderly was higher than in other ages, with the percentage range of mortality is 3.1%-5.5%. Comorbidities are common in elderly patients. Eight of ten patients had at least one comorbid hypertension, diabetes, or cardiovascular disease. This finding is important because the presence of comorbidities such as hypertension or diabetes was considered a predictor of adverse outcomes in these patients. Another cause of high mortality in the elderly is the decline of the immune system leads to a decrease in the ability of the innate and adaptive immune systems. Decrease innate immune system characterized by ineffective pathogen recognition, macrophage activation, and reduced natural killer (NK) cell cytotoxicity. Decrease adaptive immune system characterized by thymic atrophy and anergic memory lymphocyte accumulation.^{5,10,11}

In this study, it is also seen that the mortality rate of men is higher, both those who died less than 48 hours (57%) and more than 48 hours of treatment (59%) ($p < 0.001$), with a 1.5 times greater risk compared to women (OR 1.5 (1.3-1.7)). This data is in line with previous research, which stated that men had a higher mortality rate (6.84%) than women. Another study also stated that men dying from COVID-19 were 2.4 times higher than women. Some studies also state that men have a higher mortality rate than women. This may be due to the X

chromosome and sex hormones in women that play a protective role (through innate and adaptive immunity) in susceptibility to viral infections.^{17,18,21}

In this study, the median length of stay was 8 (1-51); this evidence is similar to several European countries, which have shown a median length of stay of 7-8 days. It has been found that the elderly have a longer length of stay than the younger age ($p = 0.05$). This study is in line with previous studies. Namely, there is a significant relationship between old age and an increase in length of stay ($p < 0.001$). This condition is estimated due to younger age having a stronger immune system compared elderly who has an aging process.^{11,17}

CONCLUSION

The elderly and men are at risk factors in increasing COVID-19 mortality among patients at Pasar Minggu Regional General Hospital. Although the number of women infected with COVID-19 is higher than men, the risk and mortality rate of men patients are higher than women. Further study is needed to explore the specific comorbid that increase mortality rate. Since there is no definitive therapy for COVID-19, prevention is the most necessary.

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DISCLOSURE

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AUTHOR CONTRIBUTION

All authors contributed to all aspects of the research and publication.

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