Host Determinants on Death of Covid-19 Patients

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ARTICLE INFO	ABSTRACT
Keywords: Determinant, Host, Death, Patient, Covid-19	The 2019 corona virus infection (COVID-19) pandemic is a problem that is being faced in more than 200 countries in the world. The number of deaths from COVID-19 also increased to 33,673 in the world. The number of positive cases of COVID-19 worldwide has reached 1,936,700 people. Comorbid hypertension and diabetes mellitus, male gender, and active smoking are risk factors for SARS-Cov-2 infection. The purpose of this study was to determine the host determinants (age, sex and comorbidities) in the death of Covid-19 patients in the hospital. Wahidin Sudirohusoso, Makassar City. This study uses a quantitative approach with a case control research design using secondary data sources from medical record data. Data analysis was carried out by univariate, bivariate, and multivariate analysis. The population in this study were all Covid-19 patients diagnosed and receiving treatment at RSUP Dr. Wahidin Sudirohusodo. The minimum required sample size for each case-control group is 68, with a ratio of 1:1. The results of the OR calculation showed that respondents aged 46 years had 5,958 times more deaths due to Covid-19 compared to the age group <46 years (95% CI 2,817-12,6042,817-12,604). The results of the Chi Square test show that there is no significant relationship between gender and the death of Covid-19 patients (P Value 0.195), so that respondents with male sex do not necessarily experience death from Covid-19 compared to female sex. The results of the OR calculation show that respondents who have comorbidities are 38,400 times more likely to die from Covid-19 than respondents who do not have comorbidities (95% CI 38,400 (12,319-119,694)). The variable that was significantly related to the death of Covid-19 patients was comorbidity with an OR of 3.648, meaning that Covid-19 patients with comorbidities had 3. There is a significant relationship between age and comorbidities with the death of Covid-19 patients and there is no significant relationship between gender and the death of Covid-19 patients. The results of the multivariate analysis showed that the variable that was significantly related to the death of Covid-19 patients was comorbid with an OR of 3.648. The active role of health workers is to carry out the socialization of Covid-19 prevention, so that it is hoped that the community will be able to take preventive measures and can reduce the death rate due to Covid-19.
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1. INTRODUCTION

The world was shocked by the outbreak of a new pneumonia that started in Wuhan, Hubei Province in early 2020, which then spread rapidly to more than 190 countries. This outbreak was named Coronavirus Disease 2019 (Covid-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).

Coronavirus is part of a large family of viruses that cause disease in animals or humans. When humans contract the virus, they show signs of respiratory tract infections ranging from the flu to more

serious ones. Coronavirus is a new type that was discovered by humans since it first appeared in Wuhan, China in December 2019, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV2). So, this disease is called Coronavirus Disease-2019 (COVID-19).

The 2019 corona virus infection (COVID-19) pandemic is a problem that is being faced by more than 200 countries in the world. As of 31 March 2020, 719,758 cases were confirmed worldwide. Deaths from COVID-19 have also increased, namely 33,673 worldwide. On April 14 2020, the number of positive cases of COVID-19 worldwide has reached 1,936,700 people. Several countries such as the United States, Spain and Italy are still the 3 countries with the highest number of infection cases. In Spain, the addition of cases in the last day even reached 2,442 patients. These three countries also have the most deaths from COVID-19. The first Covid-19 was reported in Indonesia on March 2 2020 with a total of two cases. Data for March 31, 2020 showed that there were 1,528 confirmed cases and 136 deaths. 3 The Task Force for the Acceleration of Handling COVID-19 announced that the total number of positive cases of corona in Indonesia had risen to 4,839 patients. 3,954 positive patients for Covid-19 in Indonesia are still undergoing treatment and isolation. This number is equivalent to 81.7% of the total positive cases of the corona virus in the country. Corona patients who have successfully recovered also increased to 426 people. However, this number is still below the total death rate for Covid-19 patients in Indonesia, which has increased again to 459 people (Ministry of Health, 2020). 4

As of June 24 2021, there were 2,053,995 positive cases of COVID-19. The number of recovered cases was 1,826,504 people and the number of cases that died was 55,949 people (Ministry of Health, 2021). 5 In addition, the total number of deaths due to corona virus infection at the global level has touched 3,889,723 people. While the total number of COVID-19 patients who have successfully recovered in the world has reached 459,015 people (WHO, 2021). 6 Many factors influence Covid-19 deaths such as gender, age, comorbidities (diabetes and strokes).7

Comorbid hypertension and diabetes mellitus, male sex, is a risk factor for SARS-Cov-2 infection. A more male sex distribution is thought to be associated with a higher prevalence of active smokers. In smokers, hypertension, and diabetes mellitus, it is suspected that there is an increase in ACE2 receptor expression. Even though it is realized that the corona virus can infect anyone, some groups of people have a higher level of risk of being exposed to the corona virus so that it can lead to death.

2. METHOD

This study uses a quantitative approach with a case control research design using secondary data sources from medical record data. Wahidin Sudirohusodo in 2022. The population in this study were all Covid-19 patients diagnosed and receiving treatment at Dr. Wahidin Sudirohusodo. The sample is part of the population selected by the sampling method so that it is considered to be representative of the population. The sample consisted of the case group, namely Covid-19 patients who died and the control group, namely Covid-19 patients who recovered or improved. The required minimum sample size for each case-control group is 68, with a ratio of 1:1. Data analysis was carried out using univariate, bivariate and multivariate analysis using the SPSS program computerized system to determine the determinants of age, sex and comorbidity in the death of Covid-19 patients.

3. RESULTS AND DISCUSSION

The distribution of respondents based on the research variables obtained from the respondents is presented in the form of a frequency distribution as shown in the following table.

Univariate analysis

Table 1. Characteristics of Covid-19 Patients

Characteristics	Case		Control	
	n	%	n	%
Age				
≥46 Years	52	76.5	24	35,3
< 46 years	16	23.5	44	64,7

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Gender				
Man	37	54,4	28	41,2
woman	31	45,6	40	58,8
Comorbidity				
Yes	64	94,1	20	29,4
Not	4	5,9	48	70,6
Hypertension				
Yes	20	29,4	15	22,1
Not	48	70,6	53	77.9
Diabetes mellitus				
Yes	16	23.5	8	11,8
Not	52	76.5	60	88.8

Source: Media Record Data of Wahidin Sudirohusodo Hospital in 2022

Table 1 shows the frequency distribution based on the age of Covid-19 patients, which is based on age category, for old age (≥46 years) as many as 52 people (76.5%) % and young people (<46 years) as many as 16 people (23.5 %). In the control group, the frequency distribution was based on the age of Covid-19 patients, which was based on age category, for old age (≥46 years) as many as 24 people (35.3%) and young people (<46 years) as many as 44 (64.7%)).

The results of data analysis showed that there were 37 male Covid-19 patients (54.4%) and 31 female patients (45.6%). In the control group, there were 28 male (41.2%) Covid-19 patients and 40 female (58.8%) patients.

There were 64 Covid-19 patients who had co-morbidities (comorbidities).people (94.1%) more than those who did not have co-morbidities (comorbidities) as many as 4 people (5.9%). In the control group, the results showed that there were 20 fewer Covid-19 patients (29.4%) who had comorbidities than those who did not have comorbidities (48 people (70.6%).

The data obtained showed that Covid-19 patients who had comorbid hypertension were 20 people (29.4%) while those who did not have comorbid hypertension were 48 people (70.6%). In the control group, the data obtained showed that there were 15 Covid-19 patients who had comorbid hypertension (22.1%), while those who did not have comorbid hypertension were 53 people (77.9%).

Covid-19 patients with comorbid Diabetes Mellitus can be seen that the results of data analysis showed Covid-19 patients with comorbid Diabetes Mellitus were 16 people (23.5%) and those who did not have comorbid Diabetes Mellitus were 52 people (76.5%). In the control group, the results of data analysis showed that there were 8 Covid-19 patients with Diabetes Mellitus comorbidities (11.8%), and 60 people who did not have Diabetes Mellitus comorbidities (88.8%).

Bivariate Analysis

Bivariate analysis is an analysis carried out to determine the effect of the independent variables on the dependent.

Table 2. Determinants of Age on Death of Covid-19 Patients

Age	Case		Control		OR 95% CI	P Value
	n	%	n	%		
≥46 Years	52	76.5	24	35,3		
< 46 Years	16	23.5	44	64,7	5,958	0.000
Total	68	100	68	100	(2,817-12,604)	

Source: Media Record Data of Wahidin Sudirohusodo Hospital in 2022

Table 2 shows that there were more respondents who were aged ≥ 46 years with the final status of death (76.5%) than those who recovered (35.5%). The results of the Chi Square test showed that there was a significant relationship between age and the death of Covid-19 patients (P Value 0.000). The OR calculation results show that respondents aged ≥ 46 years are 5.958 times more likely to die from Covid-19 compared to the age group <46 years (95% CI 2.817-12.6042.817-12.604).

Table 3. Determinants of Gender in the Mortality of Covid-19 Patients

Gender	Case		Control		OR 95% CI	P Value
	n	%	n	%		
Man	37	54,4	28	41.8	1.705	
Woman	31	45,6	40	58,8	(0.865-	0.170
Total	68	100	68	100	3.362)	

Source: Media Record Data of Wahidin Sudirohusodo Hospital in 2022

Table 3 shows that there were more male respondents with final death status (54.4%) than those who recovered (41.8%). The results of the Chi Square test showed that there was no significant relationship between gender and the death of Covid-19 patients (P Value 0.195). So that respondents with male gender do not necessarily experience death from Covid-19 compared to female gender.

Table 4. Determinants of Comorbidity on Death in Covid-19 Patients

Comorbidity	Case		Control		OR 95% CI	P Value
	n	%	n	%		
Yes	64	94,1	20	29,4	38,400	
Not	4	5,9	48	70,6	(12,319-	0.000
Total	68	100	68	100	119,694)	

Source: Media Record Data of Wahidin Sudirohusodo Hospital in 2022

Table 4 shows more respondents who had comorbidities with final death status (94.1%) than those who recovered (29.4%). The results of the Chi Square test showed that there was a significant relationship between age and the death of Covid-19 patients (P Value 0.000). OR calculation results

Multivariate Analysis

Multivariate analysis with logistic regression test. Selection of candidate variables is done through analysis of each dependent variable and independent variable. Variables that can be included in the multivariate analysis are variables that have a p value <0.25. All variables in this study are included as multivariate candidate variables. Complete candidate variables can be seen in the table below.

Table 5. Multivariate Candidate Variables

Variable	p-value
Age	0.000
Gender	0.170
Comorbidity	0.000

Source: Media Record Data of Wahidin Sudirohusodo Hospital in 2022

Based on the condition that the p value is <0.25, what can become a multivariate variable is age and comorbidities.

Table 6. First Multivariate Modeling

Variable	OR	p-value	Exp B	95% CI
Age	0.092	0.872	1,096	0.357-3.370
Gender	0.50	0.51	0.951	0.378-2.392
Comorbidity	3,603	0.000	36,692	9,701-138,787

Source: Media Record Data of Wahidin Sudirohusodo Hospital in 2022

The table above shows that the independent variables with a p value > 0.05 are age and gender variables. Variables with a p value > 0.05 were excluded from the multivariate model and then gradually starting from the highest p value. After the age and sex variables are removed, the results are obtained in the 2nd (two) modeling table as follows:

Table 7. Second Multivariate Modeling

Variable	OR	p-value	Exp B	95%CI
Comorbidity	3,648	0.000	38,400	12,319-119,694

Source: Media Record Data of Wahidin Sudirohusodo Hospital in 2022

After the second modeling analysis (two), there was no change in the OR value > 10%. So the second modeling table is the final model where there is one independent variable that has a p value <0.05. And it can be seen that the variable that is significantly related to the death of Covid-19 patients is comorbidity with OR 3,648 meaning that Covid-19 patients with comorbidities have died 3,648 times compared to those without comorbidities (95% CI: 12,319-119,694).

Discussion
Age

Older people are at risk of experiencing Covid-19 because they tend to have long-term health problems that can put them at risk. The immune system tends to weaken with age, making it more difficult for older people to fight off infections. Lung tissue becomes less elastic over time, making respiratory illnesses like Covid-19 a particular concern for older people. Inflammation in the elderly can be more intense, causing organ damage. 9

The results showed that there was a significant relationship between age and death in Covid-19 patients (P Value 0.000). The OR calculation results show that respondents aged ≥ 46 years are 5.958 times more likely to die from Covid-19 compared to the age group <46 years (95% CI 2.817-12.6042.817-12.604), this study is in line with several other studies which explain that Age is a risk factor for the death of Covid-19 patients. Overall, participants aged 75 years were at a 13-fold (95% CI 9.13–17.85) risk of death compared with those who were <65 years. 10

Another study conducted by Biswas, M., et al showed that patients aged 50 years had a significantly 15.4-fold increased risk of death compared to patients aged <50 years (RR 15.44: 95% CI 13.02-18.31; p < 0.00001). 11 Death from Covid-19 has a close relationship with old age, both men and women, with co-morbidities. 12

Gender

Another study on gender showed that there was no significant relationship between gender and the death of Covid-19 patients (P Value 0.195). So that respondents with male gender do not necessarily experience death from Covid-19 compared to female gender. The OR calculation results show that respondents have a 5.958 times the risk of dying from Covid-19 (95% CI 1.705 (0.865-3.362)). Another research that is in line is that there was no significant relationship between age and gender on the incidence of COVID-19 where the p-value was 0.924 > 0.05. This study concludes that there is no correlation between age and gender on the incidence of COVID-19.

There is a theory explaining that infected men are more likely to enter the Intensive Care Unit (ICU) and experience mortality than women because in the male immune system they have an adaptive innate immune system and also differences in the number of X chromosomes.

Comorbidity

Co-morbidities such as DM are risk factors that cause COVID-19 patients to experience high levels of morbidity and mortality. One of the results of the study showed that there were 42 people with COVID-19 who had DM comorbidities per 1000 cases with a mortality rate of up to 10%.

The results showed that there was a significant relationship between age and death in Covid-19 patients (P Value 0.000). The OR calculation results show that respondents who have comorbidities are 38,400 times more likely to die from Covid-19 than respondents who do not have comorbidities (95% CI 38,400 (12,319-119,694)).

A study that is in line with the results of this study is a study that reported cases in the United States, Europe, and Asia, which found that the mortality rate for COVID-19 patients was higher in patients with comorbidities, especially DM (25% and 20% vs. 13% ;p <0.02). 17 The severity of COVID-19 patients can also be caused by several other comorbid factors such as hypertension, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cerebrovascular disease. 18 Other studies have explained that there is a significant effect of DM comorbidities on the mortality rate of COVID-19 patients, so that mortality in COVID-19 patients with DM comorbidities is higher than COVID-19 patients without DM comorbidities. 19

There are other research results which explain that the mortality rate (88.6%) is significantly higher in comorbid cases of COVID-19 patients (p<0.001), and COVID-19 patients who do not have comorbidities have a 5,073 times greater chance of recovery than patients with co-morbidities. There is a relationship between co-morbidities and the severity of hospitalization and the final outcome of COVID-19 patients. 20

The most worrying clinical thing in Covid 19 patients is the presence of comorbidities in patients. Comorbidities can lead to poorer health, more complex clinical management, and increased health care costs. 21 In a study conducted by Wei-jie et al (2020), patients with confirmed COVID-19 with clinical comorbidities were in a worse condition than those without comorbidities. In patients with a greater number of comorbidities, it is also associated with poorer health examination results

Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder that affects insulin action in glucose absorption. This disease is also an international health threat, the severity of which has increased in the last twenty years. 23 Diabetes is one of the main risk factors for COVID-19. Diabetics are susceptible to infection due to hyperglycemia, impaired immune function, vascular complications and co-morbidities such as hypertension, dyslipidemia and cardiovascular disease. The severity and mortality from COVID-19 were significantly higher in patients with diabetes than in non-diabetics. As a result of decreased immune function, people with diabetes are one of the factors that trigger COVID-19 during this pandemic

The results of the study show that the incidence of diabetes mellitus in Covid-19 patients is not too many, but the cause of death is quite high because it is accompanied by other co-morbidities. Parveen et al's research shows that diabetes in people with Covid-19 causes general health conditions to get worse. 25 This is the same as what was found by Hussain et al, which showed that diabetes is one of the important factors that influence the severity and mortality of Covid-19 patients. 19.26 Another study by Kumar et al also explained that diabetes was significantly associated with the risk of death from COVID-19 with an odds ratio of 1.90 (95% CI: 1.37-2.64; p<0.01). It also states that diabetes is associated with more severe COVID-19 severity, including risk of ARDS,

Hypertension

Covid-19 patients with comorbid hypertension are more susceptible to COVID-19 infection because it causes an increase in ACE-2 receptor expression. The vascular system, electrolyte balance and blood pressure are regulated by ACE-2. SARS-CoV-2 which uses the ACE2 receptor results in reduced effectiveness of ACE-2 which inhibits the formation of angiotensin thereby disrupting blood pressure homeostasis and causing vasoconstriction of blood vessels and worsening the condition of high blood pressure. In SARS CoV-2 infection, angiotensin II in the lung tissue increases so that vascular permeability also increases which can result in pulmonary edema characterized by pneumonia and

shortness of breath. This can lead to continuous Acute Respiratory Distress Syndrome (ARDS) which is at risk of death. In patients with comorbid hypertension,

The results showed that there were not too many Covid-19 patients with hypertension status. However, what causes the death rate to be quite high in Covid-19 patients is because it is accompanied by other comorbidities suffered by patients. In research that knows the magnitude of the relationship between hypertension and death, it is necessary to pay attention to other variables which are confounding variables that can interfere with the relationship between hypertension comorbidities and death. Several studies have shown comorbid kidney failure, heart failure, diabetes mellitus, malignancy and immune disorders, clinical symptoms of shortness of breath, and pneumonia. Old age is a risk factor for death from COVID-19, which can interfere with the relationship between comorbid hypertension and death. In comorbid patients, there is increased expression of ACE2 and impaired ACE2,

The results of another study found that COVID-19 cases with comorbid hypertension had a 2.2 times the risk of dying compared to COVID-19 cases without comorbid hypertension (HR 2.2 Pv <0.001 95% CI 1.66-3.87). 30 The meta-analysis study by Pranata et all showed that hypertension increased the risk 2.2 times for COVID-19 death. 13.17 This is in line with the meta-analysis study by Lippi et all.

Angiotensin-Converting Enzyme 2 (ACE2) binds to the S-protein of SARSCoV-2 so that the virus can enter cells and replicate. ACE2 receptors are abundant in the cardiovascular system, nasopharynx, and lungs. In cases of comorbid hypertension there is increased expression of ACE2 receptors making them more susceptible to COVID-19 infection. The binding of SARS-CoV-2 to ACE2 results in reduced expression of ACE2 on the cell surface, thus blocking the cells' ability to degrade angiotensin II to angiotensin. Disruption of angiotensin production causes a vasodilator effect that is not maximized so that the condition of COVID-19 patients with comorbid hypertension can become more severe. 33

In patients who have comorbid hypertension, it causes dysregulation of the body's immune system, high lymphocyte count, CD8+ T dysfunction so that the body's response to viral infections is ineffective but contributes to increasing cytokine production, causing complications of cytokine storms, microcirculation ischemia resulting in organ failure.

Chronic kidney failure is a disease that can occur in patients with Covid-19 with hypertension and can increase the risk of death. The prevalence of hypertension increases with age. The presence of excessive inflammation and decreased body immunity in elderly cases makes them more susceptible to being infected with COVID-19 and can experience a cytokine storm which can cause severity with a longer treatment time, even death. At an advanced age, there is a decrease in the body's immune response, and it is also susceptible to having several co-morbidities so that elderly cases of COVID-19 are more at risk of becoming severe. Hypertensive comorbidities in the elderly are vulnerable to complications that can exacerbate and increase the risk of death from COVID19. 35

4. CONCLUSION

There is a significant relationship between age and comorbidities and the death of Covid-19 patients and there is no significant relationship between gender and the death of Covid-19 patients. The results of the multivariate analysis showed that the variable that was significantly related to the death of Covid-19 patients was co-morbidity with an OR of 3.648. The active role of health workers in socializing the prevention of Covid-19, so that it is hoped that the community will be able to take preventive measures and can reduce the death rate from Covid-19.

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