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Age and Comorbidities as The Main Factors of Mortality in Covid-19 Patients

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**Abstract**

Background: The high mortality rate in COVID-19 patients is associated with demographic factors and comorbid conditions. This is supported by research which shows that a history of comorbidities causes 88% of deaths in SARS-CoV-2 positive patients. Consequently, it is important to identify factors associated with poor outcomes among COVID-19 patients.

Objective: The purpose of this study was to determine the main factors that cause COVID-19 mortality in Indonesia.

Methods: The research design used a retrospective cohort. The population of this study was all Covid-19 patients treated at the 'Aisyah Ponorogo General Hospital' from March to December 2021, totalling 881. The data was arranged based on the completeness of the medical records, and seven respondents had to be excluded due to incomplete data. Therefore, the total number of samples used was 874 patients. Data was analyzed using logistic regression.

Result: The multivariate analysis showed that patients aged 46-65 years had a 1.45 times greater potential to die than patients who were 0-25 years old. The risk factors for comorbidities had an effect on the mortality of patients with confirmed cases of COVID-19. The variables that had a significant effect on the mortality of COVID-19 included Diabetes mellitus (OR=1.36), Hypertension (OR = 1.78) and heart disease (OR = 1.4).

Conclusion: The most common causes of mortality in Covid-19 patients are age and comorbidities diseases, there are diabetes mellitus, hypertension and heart disease

Keywords: age; comorbidities; mortality; COVID-19

INTRODUCTION

The World Health Organization classified the COVID-19 epidemic as a pandemic on March 11th, 2020 (WHO, 2020). As of September 9th 2020, the Indonesian government had reported 8336 fatalities and 203,342 verified cases of COVID-19 (WHO, 2022). According to data from China, older individuals are more likely than younger individuals to experience severe COVID-19-related illness and death, especially if they have major underlying medical conditions (Clark et al., 2020). Although most COVID-19 cases recorded in China were minor

(81%), about 80% of fatalities involved adults under 60 (CDC COVID-19 Response Team, 2020). In the United States, the fatality rates for COVID-19 patients ranged from 3% to 11% for those 65 and older and 10% to 27% for those under 85, according to the first early description of results (Djharuddin et al., 2021). The mortality of COVID-19 was 4.3%, and severe cases (treated in the ICU) were older people (Chen et al., 2020), more likely to have underlying comorbidities, dyspnea and anorexia (Li et al., 2020). Based on data compiled by the Indonesian COVID-19 Handling Task Force as of



October 13th, 2020, from the total confirmed positive cases of COVID-19, 1488 patients were recorded as having co-morbidities. The highest percentage of co-morbidities includes hypertension at 50.5%, followed by Diabetes Mellitus at 34.5% and heart disease at 19.6%. While from the 1488 cases of patients who died, it was found that 13.2% had hypertension, 11.6% had Diabetes Mellitus, and 7.7% had heart disease (Indonesian Health Ministry, 2020). In general, the co-morbidities that can increase the risk of death in COVID-19 patients include Hypertension, Diabetes Mellitus, COPD, CVD, liver disease, obesity, renal disease, malignancy, Asthma, pneumonia, HIV, heart disease, hematologic, CVA (Ejaz et al., 2020) (Rozaliyani et al., 2020)(Satria et al., 2020)(Bajgain et al., 2021). However, information regarding the demographic characteristics and comorbid disease features that impact mortality rates in relation to COVID-19 patients has still not been investigated. In this study, we will determine the main factors that cause the mortality of COVID-19 patients in Indonesia.

METHOD

We retrospectively reviewed the medical records of all in-patients diagnosed with COVID-19 at the 'Aisyiah Ponorogo General Hospital. The study design used a retrospective cohort. The population of this study was all COVID-19 patients treated from March to December 2021, which totaled 881. The data was then sorted based on the completeness of the medical records and seven respondents were excluded due to incomplete data. The final number of samples used was 874 patients. The Research Ethics Commission of RSU 'Aisyiah approved this research by Decree No. RSUA/01.a/170/EC/A/II/2021. Data was analyzed using logistic regression.

RESULTS

The results of the descriptive analysis related to the characteristics of the respondents can be seen in the following table.

Table 1. Characteristics of Respondents

| Variable | Category | Frequency | Percentage (%) |
|-------------------|-----------------------------|-----------|----------------|
| Gender | Male | 453 | 51.8 |
| | Female | 421 | 48.2 |
| Age (years) | 0-25 | 34 | 3.9 |
| | 26-45 | 139 | 15.9 |
| | 46-65 | 477 | 54.6 |
| | >65 | 224 | 25.6 |
| Diabetes mellitus | History of DM | 162 | 18.5 |
| | No history of DM | 712 | 81.5 |
| Hypertension | History of hypertension | 346 | 39.6 |
| | No history of hypertension | 528 | 60.4 |
| Heart disease | History of heart disease | 277 | 31.7 |
| | No history of heart disease | 597 | 68.3 |
| Final Status | Die | 279 | 31.9 |
| | Life | 595 | 68.1 |

Table 2. Relationship between age, gender, diabetes mellitus, hypertension, and heart disease on the final status of COVID-19 patients

| Variable | Category | Final Status | | | | Total | OR | P-values | 95% CI |
|-------------------|-----------------------------|--------------|------|------|------|-------|------|----------|-------------|
| | | Die | | Life | | | | | |
| | | N | % | N | % | | | | |
| Age (years) | 26-45 | 28 | 20.1 | 111 | 79.9 | 139 | 0.97 | 0.954 | 0.384-2.463 |
| | 46-65 | 153 | 32.1 | 324 | 67.9 | 477 | 1.92 | 0.168 | 0.775-4.275 |
| | >65 | 91 | 40.6 | 133 | 59.4 | 224 | 2.64 | 0.029 | 1.102-6.318 |
| | 0-25 | 7 | 20.6 | 27 | 79.4 | 34 | | Ref | |
| Gender | Male | 146 | 32.2 | 307 | 67.8 | 453 | 1.03 | 0.840 | 0.774-1.369 |
| | Female | 133 | 31.6 | 288 | 68.4 | 421 | | Ref | |
| Diabetes mellitus | History of DM | 64 | 39.5 | 98 | 60.5 | 162 | 1.51 | 0.022 | 1.060-2.149 |
| | No history of DM | 215 | 30.2 | 497 | 69.8 | 712 | | Ref | |
| Hypertension | History of hypertension | 142 | 41.0 | 204 | 59.0 | 346 | 1.99 | 0.000 | 1.487-2.653 |
| | No history of hypertension | 137 | 25.9 | 391 | 74.1 | 528 | | Ref | |
| Heart disease | History of heart disease | 105 | 37.9 | 172 | 62.1 | 277 | 1.48 | 0.010 | 1.10-2.00 |
| | No history of heart disease | 174 | 37.9 | 423 | 70.9 | 597 | | | |

Based on the data presented in Table 2, it can be seen that patients aged 46-65 years have an increased potential to die that is 0.168 times greater than patients who are > 65 years old, and male patients have a 0.840 percent higher chance to die than female patients. Patients with comorbid DM, HT, and heart disease have the potential to experience death within a range of 0.00-0.022 times greater than patients without comorbidities. From the results of the chi-square test, it was found that the p-value was 0.02, indicating there was a relationship between age and the patient's final status; the p-value of DM comorbidities was 0.022 indicating there was a relationship between comorbidities and the patients' final status; the p-value of comorbid hypertension is 0.00 or <0.05 so that there is a relationship between co-morbidities and the patients' final status; The p-value of

comorbid heart disease is 0.010 indicating there is a relationship between co-morbidities and the patients' final status.

Based on the results of bivariate analysis between the main independent variables and potentially confounding variables, it shows that the p-value is > 0.05. The selection was carried out for multivariate analysis. The selection was completed by removing variables starting with the highest p-value. If the change in OR was <10% then the variable was excluded, if not then it was included in the confounding variable. Furthermore, multivariate analysis was carried out to determine the relationship between the surviving variables and potential confounding variables together with the patient's final status variable (die or life).

Table 3. Relationship between age, gender, diabetes mellitus, hypertension, and heart disease on the final status of COVID-19 patients

| Variable | Category | B | OR | SE | P-value | 95% CI |
|-------------------|-----------------------------|-------|------|------|---------|-----------|
| Age (years) | 26-45 | -0.07 | 0.93 | 0.44 | 0.890 | 0.36-2.40 |
| | 46-65 | 0.37 | 1.45 | 0.64 | 0.402 | 0.60-3.45 |
| | >65 | 0.70 | 2.02 | 0.91 | 0.123 | 0.83-4.92 |
| | 0-25 | | Ref | | | |
| Diabetes Mellitus | History of DM | 0.30 | 1.36 | 0.25 | 0.102 | 0.94-1.96 |
| | No history of DM | | ref | | | |
| Hypertension | History of hypertension | 0.58 | 1.78 | 0.27 | 0.000 | 1.32-2.40 |
| | No history of hypertension | | Ref | | | |
| Heart disease | History of heart disease | 0.34 | 1,4 | 0.22 | 0.031 | 1.03-1.92 |
| | No history of heart disease | | Ref | | | |

Through the multivariate analysis, it was found that the variables were highly related and had significant impact on the patients' final status, namely the age group 46-65 years (OR=1.45), Diabetes mellitus (OR=1.36), Hypertension (OR=1.78) and heart disease (OR=1.4). From these results it was found that co-morbidities or comorbid disease risk factors had an effect on the final status of patients with confirmed cases of COVID-19. In the multivariate analysis, it was found that patients aged 46-65 years had a 0.37 times risk of dying compared to those aged <45 years, and those with comorbid DM had a 0.3 times risk of dying when compared to those who did not have comorbid DM. Those who had comorbid hypertension had a risk of 0.58 times dying when compared to those who did not have comorbid hypertension. Furthermore, patients who had a comorbid heart disease had a 0.34 times higher risk of dying when compared to those who did not have a comorbid heart disease.

Based on the data in Table 2, it can be seen that patients aged 46-65 years had the potential to die 1.45 times greater than patients who were 0-25 years old. Patients with comorbid Diabetes mellitus, Hypertension, and heart disease were more likely to experience death than patients without comorbidities. Based on the results of bivariate analysis, between the main independent variables and confounding variables, it showed that the p-value is > 0.05. The selection was carried out for multivariate analysis. Selection was completed by removing variables starting with the highest p-value. If the change in OR <10% then the variable was excluded, if not then it was included in the confounding variable. Furthermore, multivariate

analysis was carried out to see the relationship between the survival variables and potentially confounding variables together with the patients' final status variable.

Through the multivariate analysis, it was found that the variables were highly related and had a significant impact on the patients' final status, namely the age group 46-65 years (OR=1.45), Diabetes mellitus (OR=1.36), Hypertension (OR=1.78) and heart disease (OR=1.4). From these results it was found that co-morbidities or comorbid disease risk factors had an effect on the final status of patients with confirmed cases of COVID-19. In the multivariate analysis, it was found that patients aged 46-65 years had a 1.45 times higher risk of dying compared to those aged 0-25 years, and those with comorbid Diabetes mellitus had a 1.36 times risk of dying when compared to those who did not have Diabetes mellitus comorbid. Those who have comorbid hypertension had a risk of 1.78 times higher of dying when compared to those who did not have comorbid hypertension. Furthermore, those who had comorbid heart disease have a risk of 1.4 times dying when compared to those who did not have comorbid heart disease.

DISCUSSION

In this study, we have reported that the clinical characteristics of the patients indicated that age and underlying diseases were the most significant risk factors for death. With regard to underlying diseases, the most common disease was hypertension, followed by heart disease and diabetes mellitus. From these results, it was found that co-morbidities or comorbid disease risk factors

had an effect on the final status of patients who had COVID-19. In this multivariate analysis, it was found that aged 46-65 years had a 1.45 times higher risk of dying compared to those aged 0-25 years, and those with comorbid Diabetes mellitus had a 1.36 times greater risk of dying when compared to those who did not have Diabetes mellitus comorbid. Those who have comorbid hypertension had a risk of 1.78 times dying when compared to those who did not have comorbid hypertension. Furthermore, those who had comorbid heart disease had a risk of 1.4 times dying when compared to those who did not have comorbid heart disease (Table 2).

Age and COVID -19

Based on the data from Table 2, out of 874 patients who were positive for COVID-19, it was found that the average age of patients was 46-65 years, namely 477 (54.6%) with 153 cases of death (32.1%). In Indonesia, 40% of COVID-19 patients who died were aged over 60 years, and 56% were in the age range of 50-59 years (Matla Ilpaj & Nurwati, 2020). This demonstrates that age can be another risk factor for COVID-19 patients. 40% of COVID-19 patients who died were aged over 60 years, and 56% were in the age range of 50-59 years (Matla Ilpaj & Nurwati, 2020). The in-patient population is predominantly over 50 years old (42.7% of the population) and 11.4% is over 75 years old, but this age accounts for 84.4% of the total number of deaths (Casas-Deza et al., 2021). Among COVID-19 patients, elderly patients have higher mortality rates due to high Case Fatality Rate (CFR) and symptomatic infection rates. Between 80% and 90% of deaths occurred in patients aged between 70 years and 60 years in Korea and Italy (Kang & Jung, 2020). (Kang & Jung, 2020). In a retrospective cohort study from China, hospitalized patients were predominantly men with a median age of 56 years, and there was a 28% mortality rate (Zhou et al., 2020). The death rate for COVID-19 increases exponentially with age. This occurs especially in patients who have age-related diseases, such as diabetes and hypertension, because these diseases are a manifestation of aging as a result of decreased cellular function. The pseudo-programmed aging hyperfunction theory explains age-dependent COVID-19 susceptibility (Blagosklonny, 2020). Age is one of the factors that affects the condition of infected patients, the older the patient, the worse the condition will be, particularly when coupled with co-morbidities. When imposing contact or job restrictions during

the COVID-19 pandemic, it is important to precisely define risk groups relating to the severity of the illness. This study demonstrates that mortality and hospitalization rates rise with age and that there is no specific age cut-off for a significant increase in risk.

Main Comorbidity Factors

This study found several co-morbidities in patients with COVID-19. The results of this study also provide information that co-morbidities affect the final status of COVID-19 patients in Indonesia. Co-morbid diseases in the form of hypertension 346 (39.6%), heart disease 277 (31.7%), and Diabetes Mellitus (DM) 162 (18.5%). The findings relating to these cases showed co-morbidities are one of the factors that influence a patient's final status. Based on data from 2020, it is known that hypertension is the most common comorbid case in cases of COVID-19 patients in Indonesia (52.1%) (Hooper, 2020). This is supported by a meta-analysis which showed that hypertension is the most common comorbid, namely 21.1% (Yang et al., 2020). Diabetes Mellitus is the second most comorbid in COVID-19 patients in Indonesia with cases of 33.6% (Hooper, 2020). In addition, the results of research in Wuhan China, found many patients who died from respiratory failure (92%) and had comorbidities, namely hypertension (64%), DM (40%), heart problems (32%) (Li et al., 2020). Hypertension is the main comorbid found in several countries.

Diabetes Mellitus (DM) and COVID-19

Based on the data in Table 3, out of 874 patients who tested positive for COVID-19, 162 cases (18.5%) were found to have comorbid Diabetes Mellitus, with 64 cases resulting in death (39.5%). Diabetes Mellitus is comorbid that is often found in COVID-19 patients with the highest mortality rate. It can be concluded that there is a relationship between COVID-19 patients who have comorbid Diabetes Mellitus and the patient's final status, condition and severity. Based on the results of this study, it has been found that DM has a significant effect on the final status of COVID-19 patients, with a value of 0.102 (OR: 1.36; CI 0.94-1.96) (see Table 2). In research conducted in Wuhan, China, Odds Ratio (OR) was obtained by logistic regression with an OR of 1.68 (95% CI 0.80-3.52). In a retrospective observational study using the Administrative Hospital Episode Statistics dataset with logistic regression, metastatic carcinoma increased OR 1.14

(95% CI 1.10-1.19) (Gray et al., 2021). High blood sugar levels are accompanied by disturbances in carbohydrate, lipid and protein metabolism as a result of insufficiency of insulin function into multiple etiologies of chronic metabolic disorders or what is often known as diabetes mellitus. Disturbance or deficiency of insulin production by Langerhans beta cells of the pancreatic gland or lack of responsiveness of the body's cells to insulin causes insulin function insufficiency (Kementerian Kesehatan RI., 2020). The mechanism of immunity and angiotensin-converting enzyme-2 (ACE-2) is the pathophysiology that forms the basis of the relationship between DM and COVID-19. The increased risk of a cytokine storm arises from a proinflammatory condition in patients with DM, which leads to shock, Acute Respiratory Distress Syndrome (ARDS), and worsening of COVID-19 symptoms leading to death. This is indicated by higher D-dimer levels in COVID-19 patients with DM than those without DM. DM sufferers will be more susceptible to infection, so their experience impaired immune responses and longer viral clearance mechanisms.

Hypertension and COVID-19

Based on the data above, out of 874 patients who tested positive for COVID-19, 346 cases (39.6%) were infected with COVID-19 with comorbid hypertension, with death resulting in 142 cases (41.0%). Whereas comorbid Diabetes Mellitus was the most common comorbid found in patients with confirmed COVID-19 that resulted in death hypertension was the comorbid that most influences the condition and severity of COVID-19 patients. This is related to ACE 2 Angiotensin Converting Enzyme type 2 (ACE-2) disorders in COVID-19 patients with hypertension. Based on the results of this study, hypertension has a significant effect on the final status of COVID-19 patients, with a substantial value of 0.000 (OR: 1.78; CI 1.32-2.40). This reflects the results of the 2020 study by Eja et al., which found that hypertension is generally the most common type of comorbidity found in patients infected who have COVID-19. Uncontrolled blood pressure is associated with COVID-19 infection and a high case fatality rate (CFR). In China, 23% of hypertensive COVID-19 cases were reported with a CFR of 6%, and the number continued to increase due to pandemic fears. Hypertension or high blood

pressure is an increase in systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mmHg in two measurements with an interval of five minutes in calm conditions. The pathophysiology of hypertension is influenced by genetics, age, smoking habits, diet, and activation of the sympathetic nervous system (SNS), vasodilation of blood vessels, and the renin-angiotensin-aldosterone system (Perhimpunan Dokter Hipertensi Indonesia, 2021). When the heart pumps greater amounts resulting in more muscular heart muscle contractions and greater blood flow through the arteries, the elasticity of the arteries decreases and increased blood pressure (Parasher, 2021). For patients suffering from hypertension, ACE-2 inhibitors and angiotensin receptor blockers (ARBs) are often used for medicinal purposes. If this inhibitor is used in high amounts, it can increase the expression of ACE-2 receptors, thereby causing an increased susceptibility to SARS-CoV-2 infection. Angiotensin Converting Enzyme type 2 (ACE-2) was identified as a target receptor for SARS-CoV-2 (Cevik et al., 2020). ACE-2 is a specific functional receptor for SARS-CoV-2 and is the starting point for COVID-19 infection (Ni et al., 2020) (Parasher, 2021). The disease is more prone to occur when the expression of lung receptor cells is higher, and the possibility of severe lung damage and an increased chance of respiratory failure can occur. The Renin-Angiotensin-Aldosterone System (RAAS) increases the risk of death in COVID-19 patients with hypertension. Hypertension can be prevented and controlled by screening and early detection of correct and regular blood pressure measurements so that it can reduce the severity of infection, especially COVID-19 (Perhimpunan Dokter Hipertensi Indonesia, 2021).

Heart Disease and COVID-19

There were 277 cases (39.6%) of patients infected with COVID-19 who had comorbid heart disease, with 105 cases resulting in death (37.9%) (Table 1). Comorbid Heart Disease is commonly found in patients with confirmed COVID-19 and issues of death in COVID-19 patients with comorbidities. Based on the results of this study, it was found that heart disease had a significant effect on the final status of COVID-19 patients, with a substantial value of 0.031 (OR: 1.4; CI 1.03-1.92). This is in line with previous research, where cardiovascular disease

was shown to be connected with the risk of death in patients infected with COVID-19. Prior Research which has been carried out includes a retrospective observational study conducted at Hankou Hospital in Wuhan, China. The odds ratio (OR) was obtained by logistic regression with an OR of 2.02 (95% CI 0.90-4.54) (Bajgain et al., 2021). Dying of COVID-19 with cardiovascular comorbidities of 10.6% (OR 4.319) was the highest risk factor for COVID-19 death in this study (Satria et al., 2020). Disturbances in the function of the heart and blood vessels cause cardiovascular disease. Diseases that often occur in the cardiovascular system are coronary heart disease and stroke. In patients with cardiovascular disease, the immune system tends to be weak in responding to viruses (Mishra et al., 2021). Cardiovascular sufferers infected with COVID-19 have a higher risk of serious illness or death because the pathophysiological process of ACE-2 receptors in the cardiovascular system is the entry point for the COVID-19 virus and increases the risk of cardiovascular disorders in sufferers of COVID-19, especially in a diseased heart which must work harder to produce blood and deliver oxygen throughout the body (Nishiga et al., 2020). A diseased heart has problems pumping efficiently and burdens the body's system as a whole. There is anagement and prevention that can be carried out for COVID-19 patients with comorbid conditions in orderto reduce the risk of morbidity and mortality, namely by monitoring the state of the body by the doctor, maintaining a healthy lifestyle, and managing diet according to comorbid conditions, complying with health protocols by implementing 5M (wearing masks, keeping distance, washing hands, keeping the environment clean, reducing mobility and interaction), avoiding stress and undertaking regular exercise adapted to comorbid conditions.

CONCLUSION

The co-morbidities that are the main cause of death in cases of COVID-19 are diabetes mellitus (18.5%), hypertension (39.6%), and heart disease (31.7%). Male patients and the elderly are more vunrable to COVID-19. DM sufferers will be more susceptible to infection, as sufferers experience impaired immune responses and longer viral clearance mechanisms. In hypertensive patients, the heart will pump a greater amount which results in stronger contractions of the heart muscle resulting in greater blood flow through the arteries, reducing arterial elasticity and

increasing blood pressure. In patients with cardiovascular disease, the immune system tends to be weak in response to viruses. Cardiovascular patients who are infected with COVID-19 have a higher risk because the pathophysiological process of ACE-2 receptors in the cardiovascular system is the entry point for the COVID-19 virus and increases the risk of cardiovascular disorders in sufferers of COVID-19. Therefore, cardiovascular disease has a significant relationship with risk of death in patients infected with COVID-19.

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