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Diabetes Mellitus, Hypertension and Heart Disease as Main Comorbid Factors in COVID-19 Patient Mortality

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Abstract

Problem: *COVID-19 patients with comorbid or comorbid diseases have a higher death rate compared to patients without congenital diseases. This is supported by research which shows that 88% of deaths in SARS-CoV-2 positive patients are caused by a history of comorbidities. Diabetes, hypertension, and heart disease are the most common comorbidities found in patients with confirmed COVID-19.*

Purposes: *The purpose of this study was to determine the main comorbid factors that cause COVID-19 death in Indonesia.*

Methods*: This study used a retrospective cohort design. The population in this research was secondary data on Medical Records of 'Aisyiyah General Hospital of Ponorogo from March-December 2021, with a sample size were 874 patients' data.*

Result: *The results of the multivariate analysis showed that the risk factors for comorbidities or comorbidities had an effect on the final status of patients with confirmed cases of COVID-19, where the variables that had a significant effect on the death of COVID-19 included Diabetes mellitus (OR=1.36), Hypertension (OR = 1.78) and heart disease (OR = 1.4).*

Conclusion: *Comorbidities that are the main cause of death in COVID-19 cases are diabetes mellitus (18.5%), hypertension (39.6%), and heart disease (31.7%). COVID-19 mostly occurs in male patients and the elderly. The pathophysiological mechanism of comorbid diabetes mellitus, the risk of hypertension, and complex heart disease are one of the causes of increased mortality in COVID-19 patients.*

Keywords: *COVID-19, Diabetes Mellitus, Hypertension, Heart Disease, Death*

INTRODUCTION

The COVID-19 pandemic that has attacked various countries since the end of 2019 cannot be completely controlled and stopped. It was reported for the first time that it occurred in Wuhan, Hubei Province, China. Due to the rapid spread of this disease to various countries, the World Health Organization (WHO) declared this coronavirus a pandemic on March 11, 2020. The cause of the spread of COVID-19 is the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2 which attacks anyone). with varying symptoms and severity (Ejaz et al., 2020).

COVID-19 patients with comorbid or comorbid diseases have a higher death rate compared to patients without congenital diseases (Parveen et al., 2020). This is supported by research which shows that 88% of deaths in SARS-CoV-2 positive patients are caused by a history of comorbidities(Grippo et al., 2020). During treatment, patients with co-morbidities will experience an increased risk of death due to COVID-19 infection(Satria et al., 2020). Diabetes, hypertension, and heart disease are the most commonly found comorbidities, besides that potential risk factors for COVID-19 patients can be shown by comorbidities in the case of patients undergoing ICU care(Ejaz et al., 2020). The difference between this study and previous research lies in the comorbid factor variables which include: hypertension, diabetes mellitus, and heart disease. Based on the description above, researchers are interested in researching to know the main comorbid factors that cause COVID-19 death in Indonesia.

METHODS

The design of this study used a retrospective cohort design, with a secondary data collection method from the Medical Records of 'Aisyiyah Ponorogo Public Hospital from March to December 2021. The dependent variable in this study was the final status of COVID-19 patients, namely alive and dead. While the dependent variable consisted of gender, age, history of diabetes mellitus, hypertension and heart disease. The population of this study were COVID-19 patients who were hospitalized at 'Aisyiyah General Hospital Ponorogo from March to December 2021. The sample size for this study was 874 hospitalized COVID-19 patients.

RESULTS

The results of the descriptive analysis related to the characteristics of the respondents can be shown in the following table:

Table 1. Characteristics of Respondents

Variable	Category	Frequency	Percentage (%)
Gender	Male	453	51.8
	Female	421	48.2
Age	0-25y	34	3.9
	26-45y	139	15.9
	46-65y	477	54.6
	>65y	224	25.6
Diabetes mellitus	Have a history of DM	162	18.5
	Has no history of DM	712	81.5
Hypertension	Have a history of hypertension	346	39.6
	Has no history of hypertension	528	60.4
Heart disease	Have a history of heart	277	31.7
	No history of heart	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	Have a history of DM	64	39.5	98	60.5	162	1.51	0.022	1.060-2.149
	Has no history of DM	215	30.2	497	69.8	712		Ref	
Hypertension	Have a History of Hypertension	142	41.0	204	59.0	346	1.99	0.000	1.487-2.653

Variable	Category	Final Status				Total	OR	P-values	95% CI
		Die		Life					
		N	%	N	%				
	Do not have a history of hypertension	137	25.9	391	74.1	528		Ref	
Heart disease	Have a history of heart	105	37.9	172	62.1	277	1.48	0.010	1.10-2.00
	Has no history of heart	174	37.9	423	70.9	597			

Based on Table 2, it is known that patients aged 46-65 years will have the potential to die 0.168 times greater than patients who are > 65 years old, and male patients will have the potential to die 0.840 times greater than female patients. Patients with comorbid DM, HT, and heart disease will potentially experience death with 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, so there was a relationship between age and the patient's final status; the p-value of DM comorbidities was 0.022 so that there was a relationship between comorbidities and the patient's final status; the p-value of comorbid hypertension is 0.00 or <0.05 so that there is a relationship between comorbidities and the patient's final status; The p-value of comorbid heart disease is 0.010 so that there is a relationship between co-morbidities and the patient's 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. Selection is done by removing variables starting with the highest p-value. If the change in OR <10% then the variable is excluded if not then it is 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 patient's final status variable.

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 y		ref			
Diabetes Mellitus	Have a history of DM	0.30	1.36	0.25	0.102	0.94-1.96
	Has no history of DM		ref			
Hypertension	Have a History of Hypertension	0.58	1.78	0.27	0.000	1.32-2.40
	Do not have a history of hypertension		ref			
Heart disease	Have a history of heart	0.34	1,4	0.22	0.031	1.03-1.92
	Has no history of heart		ref			

In the multivariate analysis, it was found that the variables were highly related and significant with the patient's 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 comorbid or

comorbid disease risk factors had an effect on the final status of patients with confirmed cases of COVID-19. In this multivariate analysis, it was found that aged 46-65 years had a 0.37 times risk of dying compared to those aged <45 years, then those with comorbid DM had a 0.3 times risk of dying when compared to those who did not have DM comorbid. Those who have comorbid hypertension have a risk of 0.58 times dying when compared to those who do not have comorbid hypertension. Furthermore, those who have comorbid heart disease have a risk of 0.34 times dying when compared to those who do not have comorbid heart disease.

DISCUSSIONS

Epidemiology can help us understand that agents, environment, and host are the three components that help spread COVID-19. In this case, SARS-CoV-2 acts as the agent, as well as the pathogenicity and virulence of the various strains. Environment specified to the external factors that affect the agent and the exposure such as spit droplets and the surfaces that contaminated by the viruses. Host is anyone who is not infected and their susceptibility characteristics, such as age, gender (the diction used should be consistent), and co-morbidities. Current study shows that the gender (male), age (>60 years), underlying disease (hypertension, diabetes, and cardiovascular disease), secondary ARDS, and other factors suggested the poor prognosis of COVID-19 patient. other relevant(Cheng et al., 2020). To reduce the expansion of COVID-19 we can minimize the interactions between these three components

Age and COVID -19

Based on Table 2, out of 874 patients who were positive for COVID-19, it was found that the age of the patients was in the range of 46-65 years, namely 477 (54.6%) with 153 cases of death (32.1%). This shows that age can be another risk factor for COVID-19 sufferers. 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 inpatient 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% corresponds to the total number of deaths (Casas-Deza et al., 2021). The elderly COVID-19 patients have higher risk of mortality because of the high CFR and symptomatic infection rates. Around 80% and 90% of deaths occur in patients aged > between 70 years and 60 years in Korea and Italy (Kang & Jung, 2020). The death rate for COVID-19 grows exponentially with the age. This occurs especially in patients who suffer from any diseases which related to the age, such as diabetes and hypertension, because this kind of 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). One of the factors that affect the condition of infected patients is age, the higher the age, the worse the condition will be, coupled with co-morbidities or co-morbidities.

Gender and COVID-19

Most of the population (N=874) who tested positive for COVID-19 were male, namely 453 patients (51.8%), with 146 cases of death (32.2%) (Table 3). Gender affects the expression of ACE2, the role of sex hormones, the regulation of the immune system, and behavior (Kelada et al., 2020). In humans, the highest expression of ACE2 was found in the small intestine, testis, kidney, heart, thyroid, and adipose tissue (M. Y. Li et al., 2020). Testosterone acts an important role in coagulation that can affect mortality of male. The prognosis of COVID-19 can be complicated by intravascular thrombosis and endothelial dysfunction. Announced evidence suggests it occurs more frequently in males than females (Kelada et al., 2020). The male patients experience the greater inflammatory reaction, with higher levels of interleukin 10, tumor necrosis factor-α, lactose dehydrogenase, ferritin, and hypersensitive C-reactive protein, but with the lower amount of lymphocyte compared to women in accordance with age and comorbidity(Qin et al., 2020). The abnormal release of inflammatory cytokines (IL-2, IL-6, IL-8, IL-10) and proteins (LDH, ferritin, high-sensitivity CRP [hs-CRP]) will impair the epithelial cell barrier after the viral invasion on the lung took place. Alveolar causes edema and hypoxia leads to ARDS(Kelada et al., 2020). Some particular behaviors also have the effect in the death risk of COVID-19 patients. They are such as smoking and drinking alcohol; WHO reports that 40% of men worldwide smoking compared to 9% of women(Kelada et al., 2020), therefore men are at higher risk of this case. In addition, it is evaluated that women are more likely to lead hygiene and prevention life style[13].

One research found a correlation between disease severity and smoking habit. Smokers contributed more of severe COVID-19 patients compared to non-severe patients (16.9% and 11.8%, respectively)(Guan et al., 2020). However, it should be noted that in this study gender was not considered. Bagone et al. observed the relationship between cigarette smoke and increased heme oxygenase-1 (HO-1) induction of lung fibroblasts in rats. HO-1 indicated to contained anti-viral and cytoprotective properties(Hooper, 2020). Men are reported of having higher risk of being infected by COVID-19 than women, this is due to chromosomal and hormonal factors. Women are at lower risk than men by having the X chromosome and sex hormones such as progesterone which provide the advantages in innate and adaptive immunity. Due to the demands of work, men usually leave the house more often than women, so they are susceptible to this disease.

Main Comorbidity Factors

This study found several co-morbidities/comorbidities in positive cases of COVID-19. The results of this study also provide information that co-morbidities/comorbidities affect the final status of COVID-19 patients in Indonesia. The most reported comorbid/comorbid diseases are as follows: hypertension 346 (39.6%), heart 277 (31.7%), and diabetes mellitus (DM) 162 (18.5%). The findings of these cases are one of the factors that affected the patient's final status, even to the worst, namely the death of the patient. Based on data for 2020, it is known that hypertension is the most common comorbid in cases of COVID-19 patients in Indonesia, with the percentage of 52.1% (Hooper, 2020). This is supported by a meta-analysis whose results show that hypertension is the most common comorbid, with the percentage of 21.1% (Yang et al., 2020). The second position is occupied by Diabetes Mellitus 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%) (X. Li et al., n.d.). 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 be suffered from COVID-19 with Diabetes Mellitus, with 64 cases of death (39.5%). Diabetes Mellitus is a comorbid that frequently found in COVID-19 patients with the highest mortality rate. It suggests that COVID-19 patients with Diabetes Mellitus are related to the patient's final status which affects the patient's condition and severity. Based on the results of this study, it is known that there is a significant effect of DM disease on the final status of COVID-19 patients with a significant value of 0.102 (OR: 1.36; CI 0.94-1.96) (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). Retrospective observational study method by applying the Administrative Hospital Episode Statistics dataset with logistic regression indicated that metastatic carcinoma increased OR 1.14 (95% CI 1.10-1.19) (Gray et al., 2021). The high level of blood sugar and the metabolism disorders of carbohydrate, lipid and protein is a result of insufficiency of insulin function into multiple etiologies of chronic metabolic disorders or well known as diabetes mellitus. The deficiency of insulin production by Langerhans beta cells of the pancreatic gland or unresponsive body's cells to insulin causes insulin function insufficiency (Kementerian Kesehatan RI., 2020). The mechanism of immunity and angiotensin-converting enzyme 2 (ACE2) is the pathophysiology that forms the basis of the relationship between DM and COVID-19. DM sufferers will be more susceptible to infection so sufferers experience impaired immune responses and longer viral clearance mechanisms. The increased risk of a cytokine storm arises from a proinflammatory condition in DM sufferers, which leads to shock, Acute Respiratory Distress Syndrome (ARDS), and worsening of COVID-19 symptoms and death. This is indicated by higher levels of D-dimer in COVID-19 patients with DM compared to patients without DM.

Hypertension and COVID-19

Based on the data above, out of 874 patients who tested positive for COVID-19, 346 cases (39.6%) were found to be infected with COVID-19 with comorbid hypertension, with 142 cases of death (41.0%). Where Diabetes Mellitus is the most reported comorbid found in patients who have been confirmed COVID-19 and cases of death in COVID-19 patients with comorbidities. In addition, hypertension is a co-morbid that is highly related to influencing the condition and severity of COVID-19 patients, even to death. Where this is related to ACE 2 disorders in COVID-19 patients with hypertension. The results of this study showed that

hypertension caused a significant effect on the final status of COVID-19 patients with a significant value of 0.000 (OR: 1.78; CI 1.32-2.40). This is in accordance with the 2020 study by Ejaz, et al which explained that hypertension is generally the most common type of co-morbidity and is often found in patients infected with COVID-19. COVID-19 infection and the high case fatality rate (CFR) are associated with uncontrolled blood pressure. During the pandemic fears in China, the number of hypertensive COVID-19 was reported to reach 23% with the CFR of 6% and kept growing. Hypertension or high blood pressure is a condition when the systolic blood pressure increases of more than 140 mmHg as well as diastolic blood pressure increases of more than 90 mmHg in two times 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 loads resulting in stronger heart muscle contractions resulting in greater blood flow through the arteries, the elasticity of the arteries decreases and blood pressure (Parasher, 2021). ACE-2 inhibitors and angiotensin receptor blockers (ARBs) are repeatedly used for medicinal purposes for the patients who suffer from hypertension. The expression of ACE-2 receptors will increase along the amount of inhibitor used, 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). Infection is more prone to occur when the expression of lung receptor cells is higher, and possibly the severe lung injury and an increased chance of respiratory failure will occur. The Renin-Angiotensin-Aldosterone System (RAAS) acts as in increasing the risk of death in COVID-19 patients with hypertension. Hypertension can be immediately 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

Based on the data, there were 277 cases (39.6%) of patients infected with COVID-19 with comorbid heart disease, with cases of death in 105 (37.9%) respondents. Where comorbid Heart Disease is comorbid that is commonly found in patients who confirmed COVID-19 and cases of death in COVID-19 patients with comorbidities. Based on the results of this study, it is known that there is a significant effect of heart disease on the final status of COVID-19 patients with a significant value of 0.031 (OR: 1.4; CI 1.03-1.92). This is in line with previous research, where the cardiovascular disease has a relationship with the mortality rate in patients infected with COVID-19. Research that 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) (Xiao et al., 2021). Method used: Observational analytic study with a retrospective study design, 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. Cardiovascular sufferers infected with COVID-19 have a more dangerous 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, especially in a diseased heart, this makes work heart harder to get blood and deliver oxygen throughout the body. A diseased heart has problems pumping efficiently and burdens the body's system as a whole. Management and prevention that can be carried out by COVID-19 patients with comorbid conditions to reduce the risk of morbidity and mortality, namely by monitoring the condition of the body with routine control to the doctor, maintaining a healthy lifestyle, and managing a 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) and regular exercise adapted to comorbid conditions and avoiding stress.

CONCLUSIONS

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%). COVID-19 mostly occurs in male patients and the elderly. DM sufferers will be more susceptible to infection so sufferers experience impaired immune responses and longer viral clearance mechanisms. In hypertensive patients, the heart will pump a greater load 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 responding to viruses. Cardiovascular patients who are infected with COVID-19 have a more dangerous 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. So cardiovascular disease has a relationship with the risk of death in patients infected with COVID-19.

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