Correlation Between Hypertension and Mortality of Covid-19 Patient at Dr. Soehadi Prijonegoro Hospital

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Abstract. Covid-19 pandemic has been spreading throughout the world for almost 2 years. Hypertension was one of the most common comorbidities among Covid-19 patients. We conducted this study to investigate the correlation between hypertension and mortality in Covid-19 patients. We collected 159 medical records of Covid-19 patients at dr. Soehadi Prijonegoro Hospital, Sragen, Central Java, Indonesia between March 2020 and March 2021, which met the following inclusion criteria: diagnosed as Covid-19 from RT PCR or Antigen test of SARS-CoV-2, age more than 18 years old, inpatient hospitalization and had complete medical record data. We investigated the independent variables i.e. sex, age, length of stay in hospital, antiviral treatment, oxygen saturation and history of hypertension, increased blood pressure upon arrival, and a dependent variable i.e. mortality. We used Chi-square and logistic regression to analyze the correlation between the independent variables with mortality. Using Chi-square analysis we found that there was no significant correlation between sex (p 0.604) and history of hypertension (p 0.378) with mortality. However, there was a significant correlation between mortality and the following variables: length of stay more than 14 days, decreased oxygen saturation (<93%) upon arrival, age more than 60 years, using Favipiravir rather than Remdesivir as antiviral treatment, and increased blood pressure upon arrival (p 0.000; 0.000; 0.004; 0.021; 0.049 accordingly). Logistic regression showed that length of stay of more than 14 days, oxygen saturation of less than 93% upon arrival, age more than 60 years, and hypertension upon arrival were significantly correlated with mortality among Covid-19 patients (p 0,000; 0,000, 0,005 and 0,049 respectively). History of hypertension was not found to be correlated with mortality among Covid-19 patients. However, increased blood pressure upon arrival was significantly correlated with mortality in Covid-19 patients, along with other factors such as age more than 60 years, decreased oxygen saturation upon arrival, and length of stay more than 14 days.

Keywords: Hypertension · Age · Length Of Stay In Hospital · Mortality · COVID-19

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1 Introduction

Coronavirus Disease 2019 or known as COVID-19 has been announced by the World Health Organization (WHO) as a pandemic that attacks almost all countries in the world on March 12, 2020, following the discovery of the initial case in Wuhan, Hubei Province, China at the end of 2019. Initially, this disease was temporarily named as 2019 novel coronavirus (2019-nCoV), and then on February 11, 2020, WHO set a new name, namely Coronavirus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome-2 (SARS-CoV-CoV-2) virus. This virus can be transmitted from human to human and has spread throughout the world. Almost all coronavirus infections are mild, epidemics of the previous two viruses such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) caused more than 10,000 cases in the past 2 decades, with a mortality rate of 10%. SARS-CoV and 37% MERS-CoV [1].

Until now, there are more than 200 countries in the world that are reported to still have active cases. The total number of COVID-19 cases until the end of October 2020 was recorded to have infected more than 250 million people and more than 4 million deaths worldwide. Indonesia is ranked first in Asia with the highest COVID-19 cases with a total of 4 million positive COVID-19 cases and 100 thousand deaths [2]. Most patients infected with the SARS-CoV-2 virus were found to have no symptoms or have mild symptoms such as fever and dry cough, but several other patients were found to have symptoms of pneumonia, severe pneumonia, Acute Respiratory Distress Syndrome (ARDS), sepsis to septic shock. As many as 80% of cases of COVID-19 are classified as mild or moderate, 13.8% of cases are severe, and 6.1% of patients experience worsening to critical conditions [3].

Hypertension is one of the most common chronic diseases found in society, it is estimated that 1.13 billion people in the world suffer from hypertension according to WHO in 2015 [4]. Hypertension is known to be associated with an increase in the worsening of COVID-19 disease, an increased risk of mortality, ARDS, and the need for patients to receive ICU care [5].

2 Method

This study was an observational quantitative study using a cross-sectional data collection method. The data used were secondary data from medical records of patients with confirmed cases of COVID-19 that were hospitalized and registered from May 2020 to July 2021. The data were collected from dr. Soehadi Prijonegoro Hospital, Sragen, Central Java, Indonesia.

The subjects of this study were choosen with the following inclusion criteria: adult and elderly patients over 18 years of age who were diagnosed with COVID-19 using antigen test and RT-PCR, and patients who had completed the hospitalization period with outcomes recovered and death. Meanwhile, the exclusion criteria was incomplete medical record data.

There were 8 independent variables in this study, namely age, gender, hypertensive status of the patient, number of comorbidities, blood pressure upon arrival at the hospital,

length of stay in hospital, the type of antiviral used, oxygen saturation upon arrival at the hospital. There was one dependent variable, namely the patient's outcome after receiving treatment at the hospital.

All analyses were performed using the SPSS Statistics 23.0 software. The bivariate analysis used in this study was the Chi-square test. Multivariate analysis in this study was then conducted using a logistic regression test.

3 Result and Discussion

This research was conducted at dr. Soehadi Prijonegoro Hospital on August 24 to 28, 2021 by examining the medical records of hospitalized patients with confirmed COVID-19. The data taken were medical records of patients from May 2020 to July 2021. The data were taken using a consecutive sampling technique. 159 samples met the inclusion and exclusion criteria.

3.1 Patient Characteristics

From Table 1, it was found that COVID-19 patient data was dominated by women with 86 (54.1%) patients, the average patient age was 55.06 with a standard deviation of 13,477 and among the patient age groups, the highest number of COVID-19 patients were in the <60 years age group, 98 (61.6%) patients. When classified according to the number of comorbidities, there were 48 (30.2%) COVID-19 patients with no comorbidity, 82 (51.6%) patients have 1 comorbidity and 29 (18.2%) patients have more than one comorbidities. From the medical record, 60 (37.7%) of the patients were diagnosed with hypertension. Average length of stay was 13.636 days with 81 (50.9%) patients hospitalized for less than 14 days. Upon arrival at the hospital, 92 (57.9%) patients showed an increase in blood pressure and 85 (53.5%) patients showed decreased oxygen saturation <93%. Among the types of antiviral used, Remdesivir was the most widely used antiviral in 99 (62.3%) COVID-19 patients compared to Favipiravir in 60 (37.7%) patients. The overall outcome of the patients studied showed 110 (69.2%) patients recovered and 49 (30.8%) patients died.

3.2 Bivariate Analysis

Based on the results of the analysis of eight independent variables with one dependent variable above (Table 2), it was found that 5 independent variables had significant correlation with patient outcome, namely patient's age (p 0.004), length of stay (p 0.000), patient's blood pressure upon arrival (p 0.049), type of antiviral used (p 0.021), and oxygen saturation upon arrival (p 0.000). The analysis of the other 3 independent variables showed no significant correlation with the patient's outcome, namely sex (p 0.604), hypertension status (p 0.378), and the number of comorbidities (p 0.060).

Table 1. Characteristics of COVID-19 Patients from dr. Soehadi Prijonegoro Hospital

Characteristics	Frequency (n = 159)	Percentage
Sex		
Male	73	45,9%
Female	86	54,1%
Age		
Mean dan Deviation (55,06 ≠ 13,477)		
<60 years	98	61,6%
>60 years	61	38,4%
Hypertension		
Yes	60	37,7%
No	99	62,3%
Comorbidity		
No Comorbid	48	30,2%
1 Comorbid	82	51,6%
>1 Comorbid	29	18,2%
Length of stay		
Mean (13,636) days		
Median (13) days		
<14 days	81	50,9%
>14 days	78	49,1%
Blood Pressure		
Normal	67	42,1%
Elevated (>140/90 mmhg)	92	57,9%
Antivirus		
Favipiravir	60	37,7%
Remdesivir	99	62,3%
Oxygen saturation		
<93%	85	53,5%
>94%	74	46,5%
Outcome		
Discharge	110	69,2%
Deaths	49	30,8%

Table 2. Chi-square analysis from all variables

Variables	*p*-value	Odds Ratio
Sex	0,604	1,195
Age	**0,004**	**2,743**
Hypertension	0,387	1,375
Comorbidities	0,060	-
Length of stay	**0,000**	**5,383**
Blood Pressure	**0,049**	**2,032**
Antivirus	**0,021**	**2,387**
Oxygen Saturation	**0,000**	**11,603**

Table 3. Logistic regression analysis from significant variables

Variables	*p*-value	Exp(B)	Nagelkerke R Square
Age	0,005	1,089	0,789
Length of stay	0,000	0,783	
Blood Pressure	0,049	4,554	
Antivirus	0,967	1,031	
Oxygen Saturation	0,000	0,846	

3.3 Multivariate Analysis

After the chi-square analysis test was performed, a logistic regression test (Table 3) was carried out on six significant independent variables to find the variable with the most significant influence and highest risk, and 4 variables were found to have the highest influence, namely the patient's age (p 0.005), length of stay (p 0.000), patient's blood pressure upon arrival (p 0.049), and oxygen saturation upon arrival (p 0.000). Based on the results of the logistic regression test, it was found that length of stay and oxygen saturation had a more significant value (p 0.000) than the patient's age (p 0.005) and the patient's blood pressure upon arrival (p 0.049). In the patient's blood pressure variable, the higher the patient's blood pressure, the risk of mortality increases by 4,554 times. In the logistic regression test, it was also found that the Nagelkerke R-value of 0.789 indicates that the five independent variables affected 78.9% of the dependent variable so there are 21.1% of other mortalities caused by factors outside the independent variables.

4 Discussion

Based on the results of the bivariate analysis between hypertension status and patient mortality using chi-square analysis test, the results showed no significant relationship between the patient's hypertension status and patient mortality (p 0.378, OR 1.375, 95% CI 0.677–2.793). In the medical record data of hypertensive patients, drugs such as ACEI or ARB were given to maintain the patient's blood pressure, which might reduce mortality in COVID-19 patients. Hypertensive patients who are infected with COVID-19 are at risk for infection, deterioration of the condition, and experiencing various complications from COVID-19. Hypertension itself makes the RAAS component affect the COVID-19 pathogenesis where the ACE2 receptor acts directly in hypertension and the replication and transmission of the SARS-CoV-2 virus. The balance of the RAAS system determines the effect on several organs such as the heart and kidneys. In addition, the ACE2 receptor puts hypertension medications such as ACEIs or ARBs into question whether these medications would affect a person's susceptibility to COVID-19 virus infection or not. A multicentre study of 1128 COVID-19 patients with hypertension showed that the use of ACEIs or ARBs reduced mortality compared to patients who did not use ACEIs or ARBs. The study then considered continuing the use of ACEIs or ARBs as hypertension treatment as long as the use of these medications did not cause unwanted effects [6].

In a bivariate analysis between the number of comorbidities and mortality of COVID-19 patients, the results were not significant (p 0.060), which means that there was no significant relationship between the number of comorbidities and mortality among COVID-19 patients. The types of comorbidities that could be found in this study were hypertension, type 2 diabetes mellitus, stroke, heart disease, kidney disease, and HIV. The presence of comorbid congenital disease reduced survival time among patients who died and increased length of stay among survivors. The mechanism of the comorbidity itself is still under further research, but can be analysed based on the mechanism of each comorbidity. For example, patients with the cerebrovascular disease are associated with higher risk for worse outcome during COVID-19 infection. In a meta-analysis, it was stated that patients with cerebrovascular disease were 2.5 times more likely to develop severe disease. Diabetes is also associated with ACE2 receptors and dipeptidyl peptidase-4 (DPP-4) which play a role in the mechanism of diabetes and COVID-19. In patients with heart disease, the risk for mortality is increased, which is mediated by myocardial infarction with ACE2 receptors or inflammatory conditions such as myocarditis and arrhythmias [7].

In a bivariate analysis, age showed significant correlation to mortality in COVID-19 patients (p 0.004, OR 2.743, 95% CI 1.372–5.486). Among all COVID-19 patients, elderly patients have a higher mortality rate due to a high case fatality rate (CFR). It was estimated that 80%-90% of deaths occured in patients aged >70 years. Age also prolonged length of stay and viral clearance. In animal studies, SARS-CoV-2 caused more severe pneumonia and viral replication in the lungs of older monkeys compared to young monkeys. In addition, old age also affects the immune system, increasing cytokine levels in the body, resulting in cytokine storm. Inflammatory conditions are the main pathogenesis of COVID-19 cases where inflammation also causes deterioration of the patient's outcome [8].

Bivariate analysis showed significant correlation between length of stay and mortality in COVID-19 patients (p 0.000, OR 5.383, 95% CI 2.486–11656). The pathophysiology of SARS-CoV-2 itself is still under further research, but genetic factors, levels of exposure to the virus, immunosuppression of the virus itself, or hyper-inflammation may worsen disease severity. The increased risk of mortality with increasing age may also be explained by disease severity of COVID-19 infection, especially in ICU settings [9]. Elevated levels of C-reactive protein (CRP) may be associated with the overproduction of pro-inflammatory cytokines in critically-ill COVID-19 patients. High levels of CRP may be a marker to determine which patients would experience disease progression from mild to critical. Patients who died in the hospital showed higher CRP levels than patients who recovered [10]. Other factors can also cause an increase in length of stay such as age, decreased lymphocyte levels in old age, duration of symptoms before hospital admission, blood albumin level, and medications such as immunosuppressants and antibiotics [11].

The results of the bivariate analysis between blood pressure and mortality of COVID-19 patients showed significant correlation (p 0.049, OR 2.032, 95% CI 0.996–4.148). High blood pressure can lead to kidney injury, coupled with an increase in creatinine levels at the time of treatment initiation. Renal dysfunction could lead to a poorer prognosis or even multi-organ dysfunction that can lead to death [12]. The use of blood pressure medication such as ACEIs or ARBs might help to reduce mortality risk from COVID-19 infection. A European study showed that patients who discontinued ACEI or ARB treatment had a higher mortality rate (27.4%) compared to patients who continued treatment (12.5%) and patients who were not treated (17.4%). Potential protective mechanisms of ACEIs or ARBs against COVID-19 infection are reducing pneumonia severity, increasing defenses against hypoxia and vasoconstriction, renoprotective effect, and protection against myocardial injury [13].

From the bivariate analysis, the type of antiviral administered was found to be significantly correlated with mortality among COVID-19 patients (p 0.021, OR 2.387, 95% CI 1.125–5.065). In this study, 60 (37.7%) patients received Remdesivir, and 99 (62.3%) patients received Favipiravir. Favipiravir is a pyrazine analog drug and a potent inhibitor of influenza virus RNA polymerase. Favipiravir was previously used as an effective antiviral against influenza viruses and is efficient against some RNA viruses. Currently, Favipiravir is used in COVID-19 cases based on a study in China that shows Favipiravir can reduce viral clearance compared to patients taking Lopinavir/ Ritonavir. Another study also stated that Favipiravir treatment was shown to increase the recovery rate (from 55.86% to 71.43%) and significantly reduce fever and cough in COVID-19 patients. Some studies suggest that the maximum plasma concentration is reached within 2 h after oral administration and the half-life of the drug is 2–5.5 h; after 7 days, 80–100% will be excreted from the body. Favipiravir is relatively safe and well-tolerated for short-term use but further research is needed for long-term use, [14].

Remdesivir is a nucleoside C-adenosine analogue drug and is a new antiviral against zoonotic viruses from several families. Remdesivir eliminates viral RNA synthesis by inhibiting RNA-dependent RNA polymerase (RdRp). Remdesivir is broad-spectrum antiviral that are active against Coronaviridae (SARS-CoV, MERS-CoV, other bat strains), Filoviridae (Ebolavirus), and Paramyxoviridae (Nipah virus and Hendra virus).

Studies showed that Remdesivir is effective against a variety of viruses including SARS-CoV, MERS-CoV. The use of Remdesivir in an observational study demonstrated ventilator release on day 10 of use. In addition, studies using placebo and remdesivir showed that the combined use of 200 mg on day 1 and 100 mg on day 2–10 showed an increase (decrease untuk improvement?) in respiratory rate on day 10. Remdesivir can last >35 h in the active state. Because remdesivir has some oral bioavailability and could be found in breast milk, breastfeeding mothers should be cautioned about its potential effect on newborns. Thus far, the use of remdesivir is proven to be relatively safe. Further studies are needed to determine the efficacy and efficiency of the drug [14].

In the bivariate analysis, oxygen saturation was found to be significantly correlated to the mortality of COVID-19 patients (p 0.000, OR 11.603, 95% CI 4.547–29.608). Severe hypoxemia is associated with increased pro-inflammatory markers (elevated white blood cells, neutrophil count, D-dimer levels, and CRP levels), acute inflammation of the respiratory system leading to secondary bacterial infection. Prompt oxygenation in this condition may increase the patient's chances for survival [15, 16]. The main cause of death in patients who could not receive ICU treatment was respiratory failure or ARDS (if PEEP did not reach >5 mmHg) compared to patients who died in the ICU whose main cause of death was septic shock followed by ARDS and multiorgan failure [15].

In this study, there are several limitations. Firstly, the research method used was quantitative observational, hence it was not focused only on hypertension as comorbidity. Secondly, we used consecutive sampling methods where the proportion of hypertensive and non-hypertensive patients became unbalanced, affecting the results of the analysis. Thirdly, the history of hypertension in the patient's medical record is based on the patient's past history without sufficient knowledge of patients' current blood pressure condition. Furthermore, we did not distinguish between controlled and uncontrolled hypertension which could affect the analysis results. Patients' other comorbidities may interfere with the results of this study. We did not analyse potential drug interaction among the drugs given to the patient which could affect patients' outcome. It would also be beneficial to analyse patients' laboratory results to investigate the conditions which led to death outcomes.

5 Conclusion

Based on this study, it was concluded that there was no significant correlation between hypertension status and mortality. On the other hand, there was a significant relationship between age, length of stay, blood pressure upon arrival, type of antiviral used, and oxygen saturation with mortality among COVID-19 patients at dr. Soehadi Prijonegoro Hospital. Among the five variables, length of stay and oxygen saturation had the highest significance to mortality.

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