Original Article

Risk Factors of Mortality in Probable Covid-19 Cases in RSUP Dr. Kariadi Semarang

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Abstract

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Background : On February 19th, 2021, City of Semarang recorded 164 death cases of probable COVID-19. A study of patients who died from COVID-19 found that the death cases occured mostly in patients with comorbidities, such as hypertension, diabetes, heart disease, renal disease, chronic lung disease, and malignancy. The definitions of probable COVID-19 by WHO is a suspected case with radiological features leading to COVID-19 infection. The purpose of this study was to prove pneumoniae, chronic lung disease, heart disease, hypertension, DM, renal disease, and malignancy as risk factors of mortality in probable COVID-19 patients.

Methods : This study used analytic observational design with cross-sectional study approach. Consecutive sampling technique was used with minimum sample of 57 probable COVID-19 medical records. The collected data was analyzed using the SPSS program with univariate, bivariate, and multivariate analysis.

Results : The majority of probable COVID-19 patients died with a number of 65 subjects (91.5%), while the probable COVID-19 patients that survived are only 6 subjects (8.5%). Risk factors like pneumoniae (p=0.151; PR=0.9; 95%CI[0.78–1.03]), chronic lung disease (p=0.764; PR=1.09; 95%CI[1.02–1.18]), heart disease (p=0.591; PR=1.03; 95%CI[0.88–1.20]), hypertension (p=0.254; PR=1.08; 95%CI[0.95–1.23]), DM (p=0.361 PR=1.06; 95%CI[0.93–1.21]), renal disease (p=0.523; PR=1.10; 95%CI[1.02–1.19]), and malignancy (p=0.523; PR=1.10; 95%CI[1.02–1.19]) have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang.

Conclusion : Pneumoniae, chronic lung disease, heart disease, hypertension, diabetes mellitus, kidney disease, and malignancy have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang.

Keywords : Mortality, probable COVID-19, Risk factors

INTRODUCTION

Indonesia became one of the countries with high COVID-19 cases, while COVID-19 was determined as a nonnatural disaster in the form of disease outbreak by BNPB (Badan Nasional Penanggulangan Bencana). On February 19th, 2021, Semarang City recorded 30.167 confirmed cases, 107 suspect cases, and 24 probable cases with 164 probable COVID-19 deaths.[1] Several studies of patients who died from COVID-19 found that the death cases occured mostly in patients with comorbidities, such as hypertension, diabetes, heart disease, renal disease, chronic lung disease, and malignancy.[2-4] Death due to COVID-19 by WHO is defined as a death resulting from clinically compatible illness in a probable or confirmed COVID-19 case. The definition of probable COVID-19 by WHO is a patient who met the clinical criteria of suspect case and had been contacted with probable or confirmed case, or associated with COVID-19 cluster; a suspect case with chest imaging showed suggestive findings of COVID-19 disease; a person with recent onset of anosmia (loss of smell), or ageusia (lost of taste) with no other identified cause; Death in an adult with respiratory distress who had contacted with probable, confirmed case, or associated with COVID-19 cluster.[5]

The high death rate of probable COVID-19 in Semarang City became the reason this study was conducted. The purpose of this study was to prove pneumoniae, chronic lung disease, heart disease, hypertension, DM, renal disease, and malignancy as risk factors of mortality in probable COVID-19 patients.

METHODS

This research was conducted at RSUP Dr. Kariadi Semarang from March–June 2021 (4 month) with an analytic observational design with cross-sectional study approach. The consecutive sampling technique was used with minimum sample of 57 probable COVID-19 medical records between July 2020 – March 2021 period, obtained from the medical records section of RSUP Dr. Kariadi Semarang. Inclusion criteria was patients with diagnosis of probable COVID-19. Exclusion criteria were patients with confirmed diagnosis of COVID- 19, patients with status other than probable COVID-19, patients without medical records, and incomplete medical record data.

Data analysis was carried out using a computer with SPSS 26 statistical analysis program. Data analysis consisted of univariate, bivariate, and multivariate analysis. Univariate analysis was done to find out and describe each independent variables (risk factors). Analysis bivariate was done using Chi-Square 2x2 test to determined significancy of the dependent variable (probable COVID-19) and independent variables (risk factors). The variable is significant if $P < 0.05$. Significant P value from bivariate analysis was then further tested using multivariate analysis with logistic regression test, and calculating the estimated risk of death namely prevalence ratio (PR) and 95%CI. This research has obtained approval from RSUP Dr. Kariadi Semarang and the KEPK Ethics Committee of the Faculty of Medicine Diponegoro University through letter number 109/ EC/ KEPK/ FK-UNDIP/ IV/ 2021.

RESULTS

Medical record research samples that met the inclusion and exclusion criteria from the medical records section of RSUP Dr. Kariadi Semarang were 71 samples. From the univariate analysis (Table 2), it was found that the majority of probable COVID-19 patients died with a number of 65 subjects (91.5%), while the probable COVID-19 patients that survived were only 6 subjects (8.5%). Meanwhile the comorbid risk factors data showed that the majority of patients with probable COVID-19 had pneumonia as their comorbidity in 39 cases (54.9%), followed by hypertension in 27 cases (38.0%), Diabetes Mellitus in 23 cases (32.4%), heart disease in 16 cases

TABLE 1
Probable COVID-19 Patients

Variables	Frequency	%
Deaths		
Yes	65	91.5
No	6	8.5
Patients died with risk factors		
Pneumoniae	34	52.3
CPOD	3	4.6
Heart Disease	15	23.1
Hipertension	26	40
DM	42	33.8
Kidney Disease	10	7
Malignancy	12	7
Pasien survived with risk factors		
Pneumoniae	5	83.3
CPOD	0	0
Heart Disease	1	16.7
Hipertension	1	16.7
DM	1	16.7
Kidney Disease	0	0
Malignancy	0	0

TABLE 2
Bivariate Analysis

Variables	Mortality			
	Yes		No	
	n	%	n	%
Pneumoniae	334	52.3	5	83,3
COPD	3	4.6	0	0
Heart Disease	15	23.1	1	16.7
Hipertension	26	40.0	1	16.7
DM	22	33.8	1	16.7
Kidney Disease	7	10.8	0	0
Malignancy	7	10.8	0	0

TABLE 3
Estimated Risk

Variables	PR (95% CI)	p
Pneumoniae	0.9 (0.78–1.03)	0.151
COPD	1.09 (1.02–1.18)	0.764
Heart Disease	1.03 (0.88–1.20)	0.591
Hipertension	1.08 (0.95–1.23)	0.254
DM	1.06 (0.93–1.21)	0.361
Kidney Disease	1.10 (1.02–1.19)	0.523
Malignancy	1.10 (1.02–1.19)	0.523

(22.5%), kidney disease and malignancy in 7 cases (9.9%), and chronic lung disease in 3 cases (4.2%). The results of the bivariate analysis (Table 2 & 3) have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang. The risk factors for comorbid pneumoniae and the death of probable COVID-19 patients was (p=0.151; PR=0.9; 95%CI[0.78–1.03]), chronic lung disease (p=0.764; PR=1.09; 95%CI[1.02–1.18]), heart disease (p=0.591; PR=1.03; 95%CI[0.88–1.20]), hypertension (p=0.254; PR=1.08; 95%CI[0.95–1.23]), DM (p=0.361 PR=1.06; 95%CI[0.93–1.21]), renal disease (p=0.523; PR=1.10; 95%CI[1.02–1.19]), and malignancy (p=0.523; PR=1.10; 95%CI[1,02–1,19]). Multivariate logistic regression analysis was not necessary because the results of the bivariate analysis were all insignificant.

DISCUSSION

Medical record research samples that meet the inclusion and exclusion criteria from the medical records section of RSUP Dr. Kariadi Semarang were 71 samples. From the univariate analysis, it was found that the majority of probable COVID-19 patients died with a number of 65 subjects (91.5%), while the probable COVID-19 patients that survived were only 6 subjects (8.5%). This finding was in line with the data on probable COVID-19 cases in Semarang City which had always been dominated by death cases, for example the data on August 1st 2021 was dominated by death cases of 390 patients, while only 155 people survived with probable COVID-19.[1] Based on one of WHO criterias for probable COVID-19 diagnosis, "COVID-19 is a death not otherwise explained in an adult with respiratory distress; a suspect case with chest imaging showed suggestive finding of COVID-19 disease and had a positive antigen test result".[5] The rapid antigen test was not recommended for clinical diagnosis in detecting COVID-19 infection because the number of virus particles (viral load) determines the test results, hence to confirm the diagnosis of COVID-19 infection, an RT-PCR examination must be carried out.[6,7] Therefore, a probable case of COVID-19 is identical to death and has

been treated the same as a confirmed COVID-19 patient because of the same clinical manifestations with confirmed COVID-19 case, although it cannot be confirmed whether the patient is infected with COVID-19.

Relationship of Pneumoniae Risk Factors with Probable COVID-19 Death

From univariate analysis results of probable COVID-19 patients at RSUP Dr. Kariadi Semarang, pneumoniae was found in 54.9% of the 71 patients. A literature examining mortality in COVID-19 pneumoniae patients by Rong Hui *et al*. found 179 patients treated at the Wuhan Pulmonary Hospital, 43 (24%) of them were diagnosed with probable COVID-19 with clinical manifestations of pneumonia.[8] This difference finding was due to the fact that radiological examination results at RSUP Dr. Kariadi Semarang came out faster than the results of the RT-PCR swab examination, which gave the patients at RSUP Dr. Kariadi Semarang the probable COVID-19 status due to clinical manifestations that supported the diagnosis of COVID-19 in the form of pneumonia based on radiological examinations, even though the results of the RT-PCR swab have not been released. Thus, this method caused high number of probable COVID-19 patients with pneumonia in RSUP Dr. Karidi Semarang. However the results of bivariate analysis showed that the risk factors for comorbid pneumonia were insignificantly related in causing death in patients with probable COVID-19 at RSUP Dr. Kariadi Semarang. A study literature conducted at a hospital in Wuhan, China on 41 confirmed COVID-19 patients found that 100% of these patients had pneumonia.[9] Immunodeficiency conditions made it easier for pathogens to enter the human body and caused infection. Pathogens that reached the trachea could come from the oropharynx, inhalation, and insertion of an endotracheal tube. The entry of pathogens stimulated the activation of inflammatory mechanisms so that plasma fluid and capillary blood cells entered the lung membranes (alveoli). The accumulation of plasma fluid in the alveoli had an impact on decreasing air perfusion so that oxygen saturation decreased, making the patient had difficulty breathing. This pathophysiology explained how pneumonia could increase the severity of COVID-19, which could increase mortality rate up to 70%.[10] A journal that examined the causes of death in 208 pneumonia patients generally found that pneumonia deaths were caused by respiratory failure, sepsis/bacteremia, and cardiac arrhythmias.[11] Even though a probable diagnosis of COVID-19 did not necessarily lead to COVID-19 infection, the most common comorbidity in patients with a probable diagnosis of COVID-19 was pneumoniae even though the results of the study did not show significant results. Pneumoniae generally had a risk of causing death and the prognosis could be worsen if the patient is infected with COVID-19.

Relationship of Chronic Lung Disease Risk Factors with Probable COVID-19 Death

From univariate analysis results, chronic lung diseases comorbid were only found in 4.6% of total sample. This was in line with the results of a study on post-mortem diagnosis in patients with probable COVID-19 by Syamsun, *et al* who found that the sum of the comorbid findings of Diabetes Mellitus, kidney disease, and COPD from 33 patients who died with probable COVID-19 status was not more than 6%.[12] From bivariate analysis results, chronic lung disease was proven to be insignificant in causing death in probable COVID-19 patients at RSUP Dr. Kariadi Semarang, while according to Jaber S., *et al*. chronic lung disease increased the severity and mortality rate in COVID-19 patients and increases even more if the patient was a smoker.[13] COPD, which often occurs in smokers, the risk of mortality increases due to an increase in the expression of ACE2 receptor which is the entry point for the SARS-CoV2 virus. This makes it easier for COPD patients to be infected with COVID-19.[14] The contradiction of this study results with previous theory could be cause by the number of probable COVID-19 patients at RSUP Dr. Kariadi Semarang. The data showed very few chronic lung disease cases as comorbid, so it cannot be concluded whether chronic lung disease caused death in probable COVID-19 patients at Dr. Kariadi Semarang.

Relationship of Heart Disease and Hypertension Risk Factors with Probable COVID-19 Death

A study by J.Li, *et al* examined that within the total of 596 COVID-19 patients, 215 patients had cardiovascular disease as comorbid, 176 of them had hypertension.[15] The results of the univariate analysis of heart disease comorbidities in patients with probable COVID-19 at RSUP Dr. Kariadi Semarang was 22.5%. In previous study conducted by James SI, *et al* regarding the comparison of heart disease in positive and probable COVID-19 patients, it was found that out of 56 respondents, 7 patients (12.5%) with probable COVID-19 had heart disease.[16] This finding was in line with the results of this study that heart disease did not dominate the patients with probable COVID-19 at RSUP Dr. Kariadi Semarang. This was because the diagnosis of heart disease was mostly enforced by the results of physical examination and thoracic X-ray more than by an EKG, so heart disease was less detectable. Meanwhile, hypertension comorbidity also did not dominate in probable COVID-19 patiens (38% of the 71 cases of probable COVID-19 at RSUP Dr. Kariadi Semarang). This was in line with the research of Badrul Munir, *et al*. who examined neurological manifestations in 4 hospitalized

patients with probable COVID-19 and found that 25% of probable COVID-19 patients suffered a stroke because they had comorbid risk factors including hypertension.[17]

From the results of the bivariate analysis, heart disease did not cause death in patients with probable COVID-19 at RSUP Dr. Kariadi Semarang significantly, as well as hypertension. This was in line with the results of a study, which found that risk factors for cardiovascular disease were not significant in causing death in COVID-19 patients. The incidence of death in COVID-19 patients with cardiovascular disease comorbid was more due to age and the use of ACE-i drugs that increase ACE-2 receptor expression.[18,19]

Although hypertension comorbidities were not significant in causing death in patients with probable COVID-19, hypertension is generally a life-threatening risk because it can increase the risk the number of serious conditions such as heart attack, stroke, heart failure, peripheral arterial disease, aortic aneurysm, kidney disease, etc.

Relationship of DM Risk Factors with Probable COVID-19 Death

In this study, the results of the univariate analysis of comorbid diabetes mellitus risk factors did not dominate the total results (33.8%), while the results of the bivariate analysis also did not significantly cause death in probable COVID-19 patients at the RSUP Dr. Kariadi Semarang. However, a study said that the incidence of Diabetes Mellitus significantly increased the incidence of death in COVID-19 infection due to uncontrolled hyperglycemia disrupting cytokine production, failure in recognizing pathogens, dysfunction of immune cells (neutrophils, macrophages, and NK cells), and inhibition of antibodies and leukocyte recruitment. These made it easier for a person to be infected with pathogens and cause worsening of the disease, so it can be concluded that diabetics are generally more susceptible to various kinds of infections.[18,20,21] The discrepancy between the results of this study and the theory could be caused by the fact that in this study the term probable COVID-19 was used where the patient was not necessarily infected/confirmed by COVID-19, so further research was needed with research subjects with confirmed COVID-19.

Relatioship of Renal Disease Risk Factor with Probable COVID-19 Death

The risk factors for kidney disease comorbid from the univariate analysis in this study were obtained as much as 10.8%. Meanwhile from bivariate analysis, kidney disease was not significant in causing the death of probable COVID-19 at RSUP Dr. Kariadi Semarang. The COVID-19 virus can directly damage podocytes and proximal tubular cells through attachment to the ACE2 receptor and the activity of serine protease enzyme trans cell membrane, which made the kidney a target organ of the COVID-19 virus.[22] A meta-analysis comparing the incidence of mortality in patients with/without comorbid renal disease showed that COVID-19 patients with Acute Kidney Injury (AKI) significantly had worsened condition and died. This was because the ACE-2 receptors were widely expressed in proximal tubular epithelial cells in podocytes, the entry of blood carrying SARS-CoV2 into the kidneys causing attachment between the virus and ACE-2 receptors in podocyte proximal tubular epithelial cells.[23] Acute Kidney Injury in general can cause hypoperfusion in the kidneys. If it is not treated, there will be damage in tubular epithelial cells accompanied by impaired kidney function.[10] This was in accordance with the panelist literature study that there was no literature showing a significant relationship between probable COVID-19.

Relationship of Malignancy Risk Factors with Probable COVID-19 Death

In patients with probable COVID-19 at RSUP Dr. Kariadi Semarang, malignancy does not dominate in comorbid patients with probable COVID-19 (10.8%). This was in line with a study on risk factors and outcomes of COVID-19 patients with blood malignancies by Jose luis pinana, *et al*. It was found that out of 388 patients with blood malignancies, only 21 (5.4%) patients were found with probable COVID-19 status.[24] From the results of the bivariate analysis of the risk factors for comorbid malignancy in this study, it did not have significant effect on causing death in probable COVID-19 patients at RSUP Dr. Kariadi Semarang. In general, malignancy as a comorbidity increases the risk of death because antitumor therapy / chemotherapy inhibits the process of cell division to prevent tumor growth, as well supressing the immune system. So that chemotherapy causes immunosuppression which facilitates the occurrence of infection.[19] A meta-analysis study reported that from 109 COVID-19 patients with malignancy, 32 of them died. Blood malignancies such as leukemia and lymphoma had higher risk of death than solid tumors (50% vs 26.1%). This was because blood malignancies cause dysregulation of T cells so it worsened patient's condition, making them more susceptible to infection.[19] Although from 7 patients with probable COVID-19 at RSUP Dr. Kariadi Semarang all died, the diagnosis of probable COVID-19 still did not necessarily lead to COVID-19 infection. So it cannot be said that malignancy was correlated in causing death of probable COVID-19 patients at RSUP Dr. Kariadi Semarang and further examination should be done.

Limitation of The Research

This study had several limitations. This study used a sample from only one hospital, namely Dr. Kariadi Semarang, so it could not represent the population of probable COVID-19 patients in the city of Semarang. There were few previous literature studies that discussed the relationship between probable COVID-19 and comorbidities, so that researchers had difficulty comparing the data. Definition of heart disease, kidney disease, and chronic lung disease has broad meaning. Also, other risk factors found during the study were not included as risk factors.

CONCLUSION

Pneumoniae, chronic lung disease, heart disease, hypertension, diabetes mellitus, kidney disease, and malignancy have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang.

Acknowledgment

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