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Survival Analysis and Risk Factors for COVID-19 Patients at Koja Hospital

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ABSTRACT

The COVID-19 pandemic is impacting global health, and no specific drug has been proven effective in curing SARS-CoV-2 infection to date. This study aimed to analyze the survival characteristics of COVID-19 patients in Koja Hospital. This research method is analytically observational with a cross-sectional design. The study population was 1080 people, and the research sample amounted to 284 patients. The sampling technique used a purposive sampling method with a retrospective approach from the medical records of confirmed COVID-19 inpatients for the period May – October 2020. Analysis uses SPSS software version 26. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Kaplan Meier, Log Rank, and Cox Regression were used for the probability of survival analysis and mortality risk ratio in COVID-19 patients. The case fatality rate (CFR) of 284 COVID-19 patients was 20.4%. The mean age of the patients was 49 years (IQR 37 – 57). The most common comorbidity was hypertension (34%). The average probability of survival of COVID-19 patients was above 60%. In addition to gender, predictors including age, comorbidities, type of intensive care, and use of antivirals had significant differences and affected the chances of survival of COVID-19 patients. Patients given oseltamivir monotherapy had the highest survival rate of about 80% after undergoing treatment for about 38 days ($p = 0.000$). The mortality risk ratio of COVID-19 patients with comorbid diabetes mellitus was 8.7 times higher than that of those without comorbidities ([95% CI 1,02 – 75.82], $p < 0.048$). Patients with intensive care had an 11.43 times increased mortality risk ratio compared to usual care ([95% CI 6,34 – 20,62], $p < 0.000$). The conclusion of this study is intensive care and a history of diabetes mellitus are associated with the risk of death. There needs to be an increase in COVID-19 control measures, especially in populations prone to comorbid diabetes with severe and critical degrees.

Keywords: COVID-19; Survival analysis; Mortality risk factor; Antiviral

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INTRODUCTION

The novel coronavirus respiratory disease (2019-nCoV infection), better known as coronavirus disease 2019 (COVID-19), became a pandemic phenomenon in early 2020. The disease is caused by the SARS-COV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) virus, which is potentially fatal and has a major impact on the world's public health problems.(1) The World Health Organisation (WHO) reports that more than 90% of COVID-19 deaths are experienced by adult patients aged over 60 years.[2] Based on epidemiological study data published in several European countries, the risk of death in SARS-CoV-2 patients aged >65 years is 15-100 times higher than <65 years. (3) Ahmad et al. also reported increased disease severity and likelihood of intensive care admission in older patients. (4) Several factors may be associated with increased disease severity and comorbidities such as diabetes, cardiovascular disease (including hypertension), and respiratory tract disease. (5–7)

Meta-analysis studies show that the most common comorbidities in COVID-19 patients are hypertension (17%), diabetes mellitus (8%), and cardiovascular disease (5%).(8) A study in Surabaya reported that men, old age, diabetes comorbidities, and hypertension were risk factors for death in COVID-19.(9) The survival probability of males was reported to be higher than females at 49% and 33%, respectively. COVID-19 patients with comorbidities have a lower probability of survival and the increased risk of death may be due to comorbid hypertension.(10)

Good management and treatment of COVID-19 infection is key in preventing mortality and increasing disease severity.(11,12) Antiviral administration is a hope to prevent disease movement, especially in high-risk populations. Based on a study by Afriani et al, antiviral therapy can increase survival and be a factor in preventing disease movement.(13) The use of antiviral drugs in COVID-19 continues to develop until specific drugs are found that are effective and safe. Drugs used in the therapy regimen include antiviral agents for other pre-existing viruses and supportive drugs.(3,14) National Institutes of Health (NIH) [11] and the initial edition of the COVID-19 management guidelines (12), recommended pharmacological therapy for SARS CoV-2 infection includes chloroquine phosphate/hydroxychloroquine and a choice of antiviral agents consisting of oseltamivir, favipiravir, lopinavir + ritonavir or remdisivir

The use of antiviral drugs in COVID-19 therapy is one hope for preventing disease progression, but its impact on increasing survival is still unclear. Evaluation of the survival of COVID-19 patients needs to be evaluated further. Survival analysis is a method for assessing a patient's probability of survival based on factors that influence survival.(17) Identification of factors that drive the progression of COVID-19 severity and their association with survival rates may help in early prediction in high-risk patients. (18) Age, gender, degree of disease and comorbidities are factors that may lead to increased mortality of COVID-19 patients.(5,15,16) Therefore, survival analysis of COVID-19 patients is interesting to study so that it can provide guidance on disease treatment, especially at Koja Hospital. RSUD Koja

Jakarta is the main regional referral hospital serving COVID-19 patients. Based on data until the end of May 2020, the Case Fatality Rate (CFR) of severe/critical conditions of COVID-19 was reported at 37.74% in the ICU treatment room and 5.58% for mild-moderate conditions in the non-ICU treatment room. This study aims to analyze the probability of survival and factors associated with mortality and severity of COVID-19 infection.

METHODS

This study used an analytical observational method with a cross-sectional design through retrospective medical record searches. Based on the general aim of the study, researchers sought to analyze the probability of survival and factors associated with mortality of COVID-19 patients. The target population is COVID-19 patients at the Koja Jakarta Regional Hospital for the period May – October 2020. The consideration for choosing a location represents the main referral health facility in the Jakarta city area. The total population was 1080 samples. There were 284 patients sampled by purposive sampling. The number of samples was calculated using the Krejcie Morgan algorithm and selected based on the completeness and uniformity of the required data according to the inclusion criteria. Inclusion criteria are inpatient adult COVID-19 patients >18 years old, moderate and severe/critical degrees. Exclusion criteria are patients who do not use antivirals, as well as with incomplete diagnoses and medical record data.

The determination of the sample taken is based on the proportion of the ward (severity of the disease) and the calculation of CFR / mortality status. The complete sampling proportion can be seen in the following table 1.

Table 1. Proportion of Research Sampling

	Population			**Sample**		
Room	Total Patients	Death	CFR (%)	Sample Quantity	Death	Survive
Intensive Care Unit (ICU)	113	111	98,2%	30	29	1
Non intensive (non ICU)	967	111	11,5%	254	29	225
TOTAL	**1080**	**222**	**20,6%**	**284**	**58**	**226**

This research instrument uses a case report form. Data were analyzed to determine the frequency distribution and proportion of variables, survival probability, and mortality risk ratio assessment. Categorical variables were expressed as numbers (%). Numerical variables were expressed as median values and presented as interquartile range (IQR). Chi-Square/Fisher Exact cross-tabulation statistical analysis was used to test for significant associations between sociodemographics, clinical profile, and antiviral drug profile on patient mortality status. Data on the probability of survival of COVID-19

patients including; (1) sociodemographics, (2) comorbidities (3) hospitalisation room, and (4) antiviral drug regimen were analysed using the Kaplan Meier method and log-rank test. Cox Regression analysis was used to determine the risk ratio of the independent variables for death in COVID-19 patients. Data analysis was performed using the SPSS 26.

RESULTS

Statistical analysis of patient characteristics

Table 2. The Sociodemographic characteristics, clinical profile, and antiviral drug profile

Variable	n **284**	Death **58**	Survive **226**	p-*value*
Sociodemographics				
Gender				0,187
Male	134 (47%)	32 (55%)	102 (45%)	
Female	150 (53%)	26 (45%)	124 (55%)	
Age; IQR (Q_1 – Q_3)	49 (37 - 57)	54 (43-62)	46 (35-56)	
Age Category (years)				0,026
Adolescent 18-25 years old	25 (9%)	1 (2%)	24 (11%)	
Adults 26-45 years old	98 (34%)	16 (27%)	82 (35%)	
Elderly 46-65 years	135 (48%)	32 (55%)	103 (46%)	
Seniors >65 years old	26 (9%)	9 (16%)	17 (8%)	
Clinical Profile				
Comorbidities				
No comorbidities	51 (18%)	1 (2%)	50 (22%)	0.001
Hypertension	53 (19%)	11 (19%)	42 (19%)	
Diabetes mellitus (DM)	33 (11%)	9 (15%)	24 (11%)	
Hypertension and DM	43 (15%)	15 (26%)	28 (12%)	
Other comorbidities	104 (37%)	22 (38%)	82 (36%)	
Get intensive care				0.000
Yes (ICU)	30 (11%)	29 (50%)	1 (0.4%)	
No (Non ICU)	254 (89%)	29 (50%)	225 (99.6%)	
Length of Stay; IQR (Q_1 – Q_3)	10 (7-13)	5 (3-8)	11 (9-14)	
LOS category (days)				0.000
≤ 7 days	79 (28%)	39 (67%)	40 (18%)	
8 – 14 days	151 (53%)	16 (28%)	135 (60%)	
≥ 15 days	54 (19%)	3 (5%)	51 (22%)	
Antiviral regimen				
Combination : oseltamivir + chloroquine/hydroxychloroquine	143 (50%)	40 (69%)	103 (46%)	0.000
Oseltamivir (monotherapy)	122 (43%)	11 (19%)	111 (49%)	
Other antiviruses	19 (17%)	7 (12%)	12 (5%)	

Note : n = number of patients; IQR = *Interquartil range*; Q_1 = Kuartil 1; Q_3 = kuartil 3

Table 2 shows that there are differences in COVID-19 patients in terms of age, comorbidities, intensive care, length of treatment, and antiviral use between patients who were discharged and died.

Survival Analysis of COVID-19 Patients

The movement of disease severity to mortality in COVID-19 can be influenced by several factors. Survival analysis based on factors that affect mortality aims to determine differences in the probability of patient survival. Differences in the distribution of survival time of COVID-19 patients in hospitals can be analyzed with the log-rank test as follows:

Table 3. The Survival Factors *Log-rank* Test

Variables	*Log-rank*	*df*	P-*value*
Age	5,471	1	**0,019**
Gender	0,864	1	0,353
Comorbidities	14,191	4	**0,007**
Treatment room	201,350	1	**0,000**
Antiviral drug regimen	6,413	2	**0.011**

Table 3 shows that there are differences in the survival time of COVID-19 patients based on predictors of age, comorbidities, treatment room, and the use of antiviral drug regimens. However, the survival time of COVID-19 patients based on predictors of the gender of COVID-19 patients is not different. As for estimating the cumulative probability of hospital discharge/survival by each independent variable/predictor, we can use the Kapplan Meier survival curve in Figure 1.

Based on Figure 1, it can be seen that the survival probability of COVID-19 patients at Koja Hospital is still moderate, which is above 70% (0.7 - 1), with an estimated average survival time of around 33 days. The survival curve of patients aged 18-25 years tends to be constant at the beginning of hospital admission until >30 days, so the probability of survival is still high. The average survival duration of 46 to 65 years old is 31 days, while that of >65 years old is 24 days. The survival probability of female patients is higher than that of males. The probability of hospital discharge for COVID-19 patients with comorbidities of hypertension and diabetes is the lowest, with an average survival duration of 23 days. The survival probability of patients with intensive care (ICU) is smaller than that of non-intensive care (non-ICU) with an average duration of care of 6 days (ICU) and 38 days (non-ICU), respectively. The probability of survival in the group given oseltamivir antiviral therapy monotherapy was higher than the other two antiviral groups.

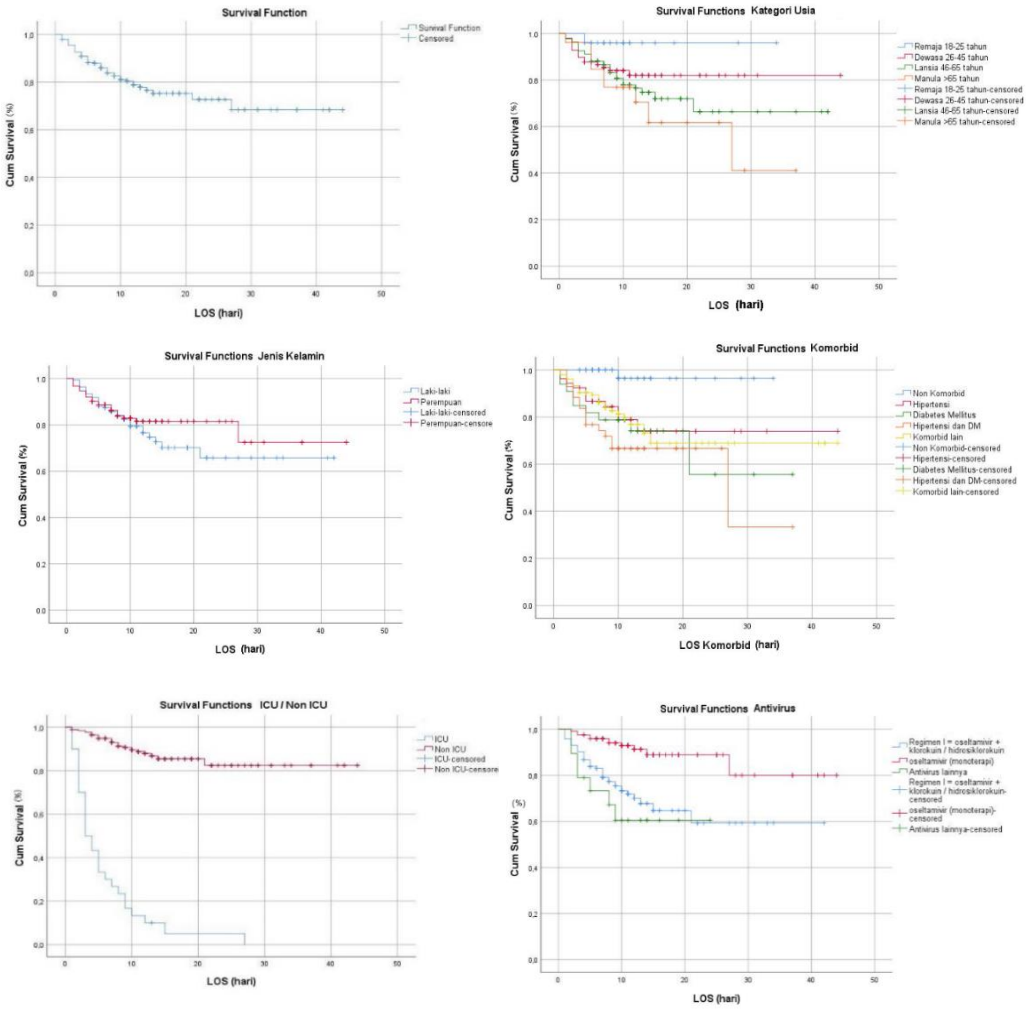

Figure 1. *Kaplan-Meier* curve.

This research instrument uses a case report form. Data were analyzed to determine the frequency distribution and proportion of variables, survival probability, and mortality risk ratio assessment. Categorical variables were expressed as numbers (%). Numerical variables were expressed as median values and presented as interquartile range (IQR). Chi-Square/Fisher Exact cross-tabulation statistical analysis was used to test for significant associations between sociodemographics, clinical profile, and antiviral drug profile on patient mortality status. Data on the probability of survival of COVID-19 patients, including (1) sociodemographics, (2) comorbidities, (3) hospitalization room, and (4) antiviral drug regimen, were analyzed using the Kaplan Meier method and log-rank test. Cox Regression analysis was used to determine the risk ratio of the independent variables for death in COVID-19 patients. Data analysis was performed using the SPSS 26.

Mortality Risk Analysis of COVID-19 Patients

In mortality risk analysis, candidate variable data were analyzed to obtain the best model that could estimate the effect of independent variables after controlling for covariates.[19] Variable data from bivariate analysis that can be continued in multivariate analysis are comorbidities, intensive care rooms,

and antiviral use. Table 4 shows that patients with diabetes mellitus had an increased risk of mortality by 8.7 times ([95% CI 1.02 - 75.82], p < 0.048). When compared with the non-intensive care group (non-ICU), patients with intensive care type (ICU) had an increased risk/danger of mortality of 11.43 times ([95% CI 6.34 - 20.62], p < 0.000. The variable group age and antiviral use did not have a relationship with the survival of COVID-19 patients. Although the antiviral use variable group was statistically significant (p<0.05), the confidence interval value does not meet the requirement of ≥1.[19]

Table 4. Multivariate Analysis of Cox Regression (Proportional Hazard)

Variables	n *event*	Population	Average survival time (days)	Sign.	*Hazard ratio (95% CI)*
Usia					
Category 1 = Adolescent 18 - 25 years	1	25	32,75	0.413	*reff*
Category 2 = Adult 26 - 45 years	16	98	36,86	0.644	1,63 (0,20 - 13,04)
Category 3 = Elderly 46 - 65 years	32	135	31,12	0.815	1,28 (0,16 - 10,38)
Category 3 = Seniors >65 years	9	26	23,93	0.404	2,54 (0,28 - 22,76)
Comorbidities					
Non-comorbid	1	51	33,14	0.406	*reff*
Hypertension	11	53	34,34	0.061	7,66 (0,91 - 64,38)
Diabetes Mellitus	9	33	25,69	**0.048**	8,77 (1,02 – 75,82)
Hypertension & DM	15	43	22,98	0.072	7,17 (0,84 – 61,25)
Other comorbidities	22	104	32,97	0.054	7,56 (0,96 – 59,33)
Room					
ICU	29	30	6	**0.000**	11,43 (6,34 - 20,62)
Non ICU	29	254	38,02		*reff*
Antiviral					
Oseltamivir + chloroquine/hydroxychloroquine	40 (28.0%)	143	28,476	0.002	*reff*
Oseltamivir (monotherapy)	11 (9.0%)	122	38,533	0.001	0.286 (0,135 – 0,606)
Other antiviral	7 (36.8%)	19	16,417	0.770	1,140 (0,475 - 2,736)

* n *event* = number of COVID-19 patient deaths

DISCUSSION

Among the 284 COVID-19 patients admitted to Koja Hospital during the period from 1 May to 31 October 2020, 58 patients (20.4%) died, and 226 patients (79.6%) survived hospital discharge. The age of patients in this study ranged from 18 to 89 years old, and more than half of the patients were female (53%). These results are similar to those in Vietnam,[20] patients aged up to 88 years (range 22 -54 years), and females (48.9%) accounted for the majority of gender among hospitalized. There is a shift from the severity of the disease to the need for intensive care. This was similarly reported in an Australian study (7). More than one-fifth of the patients in the study had severe/critical conditions in intensive care (ICU). The mean duration of hospitalization among patients was 10 (IQR: 7-13) days. The mean length of stay in some Indonesian studies was 10 - 14 days.[21–23] A study in Sichuan province [24] reported a mortality rate of 38% for severe cases with a median length of ICU stay until death of 7 days. The distribution of the use of oseltamivir antiviral drugs was mostly clinically cured (111 [91%] of 122 patients) in Koja Hospital.

The results of the Kaplan Meier survival analysis and Log-rank test on variables that significantly affect the survival of COVID-19 patients consist of age, comorbidities, type of intensive care, and antiviral use. Gender is not a survival factor and has no significant relationship with prevention behavior.([25] This study shows that the survival probability of gender was found to have no difference. This study is in line with survival analysis research conducted in Sichuan, China. The study states that there is no difference in the probability of survival based on gender.[24] This is different according to Dwiyanti et al, a higher risk of death occurs in male patients, has symptoms of shortness of breath, has a history of comorbidities, and high severity.[26]

Older COVID-19 patients (≥65 years old) had a 2.54 times risk of death compared to adolescent (18-25 years old), but this was not statistically significant (p>0.05; p=0.404) (Table 4). Susceptibility to death can occur in all age groups. The older a person is, the greater the risk of mortality. According to a meta-analysis study that included 37 studies, the elderly group had an increased hazard ratio of death by 1.31.[27] This is supported by data from research on risk factors for case fatality in Australia, that increasing age is the characteristic most strongly associated with the severity of the disease. The risk of severe cases is almost ten times greater in patients aged >80 years, and in patients aged 60-79 years, it is around three times higher when compared to those aged 30-39 years.[7] The aging process is closely related to changes in physiological function and body immunity. As a person ages, a person's immune capacity will decrease, resulting in an increased risk of death from certain diseases.[28]

COVID-19 patients treated with comorbidities have a higher risk of death than those without comorbidities.[27,7] The results of the Cox Regression multivariate analysis show that comorbidities diabetes mellitus have a risk of 8.77 times experiencing death compared to do not have comorbidities (p<0.05;p=0.048). Patients with comorbidities will have a weaker immune system than without comorbidities.[28] Patients with comorbidities are more at risk of complications or organ system failure

due to disease, which can increase the risk of mortality. This is supported by meta-analysis studies that show up to 50% of deaths are caused by comorbidities.[5] Comorbidities will worsen the condition because of their lower immune system, this can be even worse if comorbidities are not well controlled.[5]

COVID-19 patients who were treated in intensive care had an 11.43 times risk of death compared to those not treated in intensive care for various medical considerations. The data was statistically significant ($p<0.05$; $p=0.000$). The estimated average survival time for intensive care (ICU) is six days, while 38 days in non-intensive care. Patients treated in the ICU have a greater risk of death. The adjusted hazard ratio (aHR) of ICU or death when compared with those aged 30-39 years was 4.45 times in the 70-79 year age group, 8.43 times in the age group 80-89 years, and 16.19 times in the elderly group >90 years.[7]

Patients receiving oseltamivir monotherapy in this study had a median survival rate of about 80% after approximately 38 days of treatment. Patients who received oseltamivir + chloroquine/hydroxychloroquine combination therapy had an average survival rate of about 60% after about 28 days of treatment. This study's results align with the results of a study reported by Ramatillah, et al.,[23] Patients who received Oseltamivir + Chloroquine combination therapy had an average survival rate of approximately 17% after about 23 days. In patients who used oseltamivir alone, the patient survival rate was higher (18%), with an estimated survival time of approximately 27 days.[23] Oseltamivir has a higher survival rate than oseltamivir + chloroquine. Oseltamivir antiviral monotherapy had a 0.286 times lower risk of death compared to the combination of oseltamivir + chloroquine/hydroxychloroquine. This research data is comparable to the survival cohort study conducted by Liu, J et all. Oseltamivir administration has the benefit of reducing disease severity and mortality in severe patients (HR 0.21, 95% CI 0.10- 0.43; $p < 0.001$).[29] The results of the multivariate Cox regression analysis showed that it was statistically significant ($p<0.05$; $p=0.000$), but the confidence interval value did not meet the requirement of ≥1 (HR 0.286, 95% CI 0.135 – 0.606). This indicates that the use of the antiviral oseltamivir monotherapy is not associated with mortality using the combination of oseltamivir + chloroquine/hydroxychloroquine. The estimated average survival time for oseltamivir monotherapy is 38 days, while it is 28 days for the combination of oseltamivir + chloroquine/hydroxychloroquine. In research conducted by Yang et al., the average length of stay for non-survivor patients after receiving intensive care in the hospital was 7 to 14 days. Elderly patients >65 years with comorbidities and ARDS tend to have an increased risk of death. The severity of COVID-19 pneumonia can place high pressure on management for health facilities that do not have adequate resources.[30] An observational study in Italy conducted by Desai et al. showed that the median survival rate for those aged 65 to 80 years who received early treatment was 44 days. In this age range, there was a significant association between the overall survival analysis and the use of antiviral drug regimens when administered on time. Multivariate regression models showed that older age and symptoms of dyspnea were associated with a high risk of mortality.[31]

CCONCLUSIONS AND RECOMMENDATIONS

In general, the probability of survival for COVID-19 patients is quite good (>60%). However, predictors including age, comorbidities, type of intensive care, and antiviral use affect the chances of patient survival. For future researchers to monitor and evaluate drug use and antiviral effectiveness in COVID-19 patients with comorbid hypertension or diabetes mellitus. In addition, further research is needed regarding the survival analysis of other antivirals according to the development of science so that appropriate, effective, and safe therapy can be obtained.

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