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Factor Influencing Mortality in Moderate - Severe Covid-19 Patients In Tertiary Hospital, Indonesia

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ABSTRACT

Introduction: Covid-19 is highly contagious respiratory tract infection caused by infection of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This infection has a case fatality rate in those with moderate – severe case up to 30%. This study aims to analyse factor influencing mortality in moderate to severe Covid-19.

Method: This study was conducted using retrospective cohort study on moderate - severe Covid-19 patients who were treated in tertiary hospital in Medan, Indonesia, in March 2020-June 2022.

Results: From 180 moderate – severe Covid-19 inpatients, up to 37,8% died. Factor that influences the mortality is the presence of comorbidity (P=0,001), such as hypertension and chronic kidney disease (CKD), high levels of neutrophil-lymphocyte Ratio (NLR), procalcitonin, c-reactive protein (CRP), D-dimer, and low levels of albumin with P values 0,016, 0,036, 0,001, 0,001, 0,001, 0,003, and 0,006 consecutively.

Conclusion: It can be concluded that the demographic factors that are significantly related to the death of Covid-19 patients are the presence of comorbidities such as hypertension and CKD.

Keywords

Covid-19, Comorbidity, Mortality

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INTRODUCTION

Covid-19 is a disease caused by corona virus, namely SARS-CoV-2. This disease is thought to have originated in bats and spread to humans through unknown media and was first discovered in the city of Wuhan, China.[1] The SARS-CoV-2 infection was initially identified during a spike of pneumonia cases at the end of December 2019 in the city of Wuhan, China. This infection spread rapidly and on March 11, 2020, was declared as pandemic by World Health Organization (WHO).[2] In June 2021, Covid-19 has infected up to 226 million people around the world with case fatality rate up to 2%. In Indonesia, mortality has been up to 2,7%, with up to 8.000 people infected within a single day in June 2021.[3] in North Sumatra, up to 185 people were infected per day, and about half of it (86 person) was from Medan City.[4] Covid-19 have a wide variety of symptoms and up to 80% of patients were asymptomatic. This disease has a low mortality rate globally, but in moderate-severe Covid-19, mortality rate rises a lot up to 30 – 60%.[1,2]

Previously, various studies reported that factors influencing mortality in Covid-19 included older age (>65 years), male, the presence of comorbidity like hypertension, chronic kidney disease (CKD), type 2 diabetes (DMT2), cardiovascular disease (CVD), asthma, and chronic pulmonary obstructive disease (COPD). The laboratory parameter that has been reported are neutrophil-lymphocyte ratio (NLR), c-reactive protein (CRP), procalcitonin, D-dimer, and albumin.

We conducted a retrospective cohort study of moderate - severe Covid-19 patients in tertiary hospital in North Sumatra, Medan, Indonesia to determine factor influencing mortality.

METHOD

This is an analytic study with a cross-sectional research design that aims to analyse demographic factors, laboratory parameters, and comorbidities in influencing mortality in patients with moderate - severe Covid-19 at Haji Adam Malik General Hospital Medan. Sampling was carried out using nonprobability sampling, namely consecutive sampling in January 2022 – March 2022 using medical record data from Covid-19 inpatients who were treated from March 2020 to July 2021. The data used was secondary data from medical records. Total of 180 moderate – severe Covid-19 inpatient with minimum age of 18 years old and survive in hospital for minimum 24 hours were included in this study. The patients died within the first 24 hours and did not complete the treatment were excluded from this study. The diagnose of Covid – 19 was made based on Real Time – Polymerase Chain Reaction (RT-PCR) swab. Univariate, Bivariate, and multivariate analysis was done using SPSS 25.0 software and were considered statistically significant if $P < 0,05$.

RESULT

In this study, samples were collected from patients with Covid-19 who were treated at the Haji Adam Malik General Hospital Medan from March 2020 - July 2021, 1,416 patients were obtained. Consecutive sampling was conducted on 260 adult Covid-19 patients and found 180 patients who met the criteria. In this study, 151 samples (83.89%) were less than 65 years old. The number of men and women in this study was almost the same (49.44% vs 50.56%).

Based on the results of the bivariate analysis that was show in table 1, we found that several factors in influencing mortality based on the patient data were the age group, the presence of comorbidities, and the presence of comorbidities such as hypertension and chronic kidney disease.

When compared between age groups, statistical tests showed a significant relationship between age groups and mortality (p=0.003), with the highest mortality occurring at the age of 45-64 years, as many as 37 people (54.4%).

In this study, 133 patients (73.89%) had comorbidities, of which 51 (28.33%) had more than one comorbid. There is a relationship between the presence comorbidities with mortality in Covid-19 patients ($p = 0.001$). However, there is no significant relationship between the number of comorbidities and mortality (p=0.475). However, the percentage of deaths in patients with comorbid more than one disease was only slightly higher (49.02%). The most common comorbid were hypertension, type 2 DM, and CKD and we found a significant relationship between comorbid hypertension and CKD on mortality of Covid-19 patients in this study ($p = 0.024$ and $p = 0.008$).

In this study, analysis of the data was carried out to determine the cut-off values for the NLR, CRP, and procalcitonin levels in influencing the mortality of Covid-19 patients. From the analysis, we found that the NLR value with a cut-off value of 6.54, CRP levels with a cut-off of 1.15 mg/L, and procalcitonin levels 0.195 ng/mL were the best. In the laboratory parameters, we found 100 patients (55.56%) had NLR less than 6.54 and 80 patients (44.44%) had a high NLR. Albumin levels higher than 3.5 g/dL was found in 68 patients (37.78%) and about 112 patients (62.22%) have a low albumin level (<3,5g/dL).

In this study, bivariate tests were also carried out from each laboratory result such as NLR values, albumin levels, D-dimer levels, CRP levels, and procalcitonin levels on mortality from Covid-19 patients. By using a cut off NLR ≥6.54, we found a higher mortality rate than those with NLR <6.54 (75% vs 25%, $p = 0.001$). Of the 112 patients with albumin levels <3.5g/dL, the risk of death was also found to be higher (45.54% vs 25%, p=0.006).

Using the cut off D-dimer ≥500, we found a higher mortality rate in patients who had a D-dimer ≥500 than in those who did not (77.9% vs. 22.1%, p=0.003). If the D-dimer value is divided by categories <500, 500 - <1000, 1000 - <2000 and ≥2000, as seen from table 2, the highest mortality rate is in the group of patients

who have a D-dimer value ≥2000 (39.7%). This is supported by statistical tests that there is a significant relationship between the level of D-dimer value and mortality (p = 0.001).

Table 1. Samples characteristic

		Survival				
	Total	Alive (n=112)	%	Death (n=68)	%	p
Age group (years)						
18-24	15	12	10,7	3	4,4	0.003*
25-44	66	50	44,6	16	23,5	
45-64	70	33	29,5	37	54,4	
≥65	29	17	15,2	12	17,6	
Sex						
Woman	91	62	55,4	29	42,6	0.098
Man	89	50	44,6	39	57,4	
Comorbidity						
No	47	39	34,8	8	11,8	0.001*
Yes	133	73	65,2	60	88,2	
Number of Comorbid						
1	82	47	64,4	35	58,3	0.475
>1	51	26	35,6	25	41,7	
Type of Comorbid						
DM, n (%)			49 (27.2)			
No	131	85	75,9	46	67,6	0.228
Yes	49	27	24,1	22	32,8	
Hypertension, n (%)			66 (36.6)			
No	114	78	69,6	36	52,9	0.024*
Yes	66	34	30,4	32	47,1	
CKD, n (%)			18 (10)			
No	162	106	94,6	56	82,4	0.008*
Yes	18	6	5,4	12	17,6	
CVD, n (%)			15 (8.3)			
No	165	105	93,8	60	88,2	0.194
Yes	15	7	6,2	8	11,8	
Asthma, n (%)			1 (0.6)			
No	179	112	100	67	98,4	0.378
Yes	1	0	0,0	1	0,6	
COPD, n (%)			9 (5)			
No	171	106	94,60	65	95,6	1
Yes	9	6	5,40	3	4,4	
HIV, n (%)			2 (1.1)			
No	178	112	100	66	97,1	0.141
Yes	2	0	0,0	2	2,9	
Malignancy, n (%)			9 (5)			
No	171	108	96,4	63	92,6	0.301
Yes	9	4	3,6	5	7,4	
Pregnant, n (%)			12 (6,66)			
No	168	102	91,1	66	97,1	0.137
Yes	12	10	8,9	2	2,9	
Tuberculosis, n (%)			2 (1,1)			
No	178	112	100	66	97,1	0.141
Yes	2	0	0,0	2	2,90	

*P < 0,05 is significant

In the analysis of CRP levels on mortality, an analysis was also carried out to assess the best threshold for CRP levels and obtained a CRP value of 1.15mg/L having a sensitivity value of 63.2% and a specificity of 67.9%. In table 4, 96 patients had CRP values <1.15mg/L, while 84 patients had CRP values 1.15mg/L. The mortality percentage in the CRP 1.15mg/L group was 63.2% (p=0.001).

An analysis of the value of procalcitonin levels with cut off value of procalcitonin of 0.195ng/mL have a sensitivity value of 70.6% and a specificity of 63.4%. The mortality rate of procalcitonin ≥0.195ng/mL was reported to be higher at 70.6% (p = 0.001).

Table 2. Laboratory Parameters

Laboratories Parameters	Total	Survival				p
		alive (n=112)	%	death (n=68)	%	
NLR						
<6,54	100	82	73,20	18	26,50	0.001*
≥6,54	80	30	26,80	50	73,50	
Albumin (mg/dL)						
< 3.5	112	61	54,50	51	75,00	0.006*
≥ 3.5	68	51	45,50	17	25,00	
D-dimer (ng/mL)						
<500	64	49	43,80	15	22,10	0.003*
≥500	116	63	56,20	53	77,90	
D-dimer (ng/mL)						
<500	64	49	43,80	15	22,10	0.001*
500 - <1000	42	25	22,30	17	25	
1000 - <2000	30	21	18,80	9	13,20	
≥2000	44	17	15,20	27	39,70	
CRP (mg/L)						
< 1,15	96	71	63,40	25	36,80	0.001*
≥ 1,15	84	41	36,60	43	63,20	
Procalcitonin (ng/mL)						0.001*
<0,195	91	71	63,40	20	29,40	
≥0,195	89	41	36,60	48	70,60	

*p<0,05 is significant

Table 3. Multivariate Analysis of factor influencing mortality

Step	Variable	P	OR 95% CI	95% CI
Step 7	Sex	0.035	0.833	1.061 - 4.991
	Comorbidity	0.014	1.242	1.284 - 9.334
	NLR (≥6,54)	0.000	1.973	3.256 - 15.893
	CRP (≥1,15)	0.003	1.131	1.46 - 6.573
	Procalcitonin (≥0,195)	0.01	1.004	1.273 - 5.847

In the research data, multivariate analysis was performed using logistic regression method. Based on the test results, it was found that the factors influencing mortality the most were NLR (p = 0.001; OR: 1.973) followed by CRP levels (p = 0.003; OR: 1.131), procalcitonin (p = 0.01; OR: 1,004), and the presence of comorbidities (p = 0.014; OR: 1.242).

DISCUSSION

The mortality rate in this study was quite high, which is 37.8%. This mortality rate is very high even if we compared to global data, but in this study the analysis was carried out on patients with moderate - critical degrees of Covid-19 and did not include patients with asymptomatic and mild degrees, while global data included patients with mild degrees of Covid-19. A meta-analysis of 29 studies of hospitalized Covid-19 patients showed a high number of Covid-19 patients experiencing complications from their illness, reaching 36% and the mortality rate in hospitalized Covid-19 patients being 15%.[5] The high mortality rate in this study may be due to unwillingness, low knowledge, and patient usually become denial when the Covid-19 diagnosis was made, so the majority of patients often getting late in receiving treatment.

Other study has concluded that, people with older age are prone to develop infection due to decline in immunity, vulnerable to adverse drug reaction, and tend to have multiple comorbidities. In this study, statistical

analysis shows a significant relationship between age group on mortality, with the highest mortality occurred at the age of 45-64 years as many as 37 people (52.86%). The results of this study are in accordance with a meta-analysis of 20 studies which reported that the mortality rate was higher in older age. The high mortality rate at this age is more associated with the presence of comorbidities. Old age with comorbidities has a greater risk of death than those with one risk factor alone.[6]

Comorbidity play a certain role in Covid-19 infection. Hypertension and diabetes were the most common comorbidities in patients with Covid-19 in previous study. Previous studies have shown that people with Covid-19 with diabetes tend to have more severe infection activity and have a higher mortality. This is thought to occur because of an increase in angiotensin converting enzym-2 (ACE-2) receptors in patients with type 2 diabetes mellitus which results in a stronger inflammatory response, causing alveolar-capillary barrier dysfunction.1 In this study, 133 patients (73.89%) had comorbidities, of which 51 (28.33%) had more than one comorbid. The results of the multivariate analysis showed that comorbidity was one of the most influential factors in increasing the risk of death from Covid-19. Like a previous study, the most common comorbidity in this study were hypertension and diabetes. However, we found that only hypertension has a significant relationship with mortality (p=0,024) and, we did not find a significant relationship between diabetes and mortality (p=0.228). A previous meta-analysis reported that of 15 studies examining diabetes and death from Covid-19, it was found that 8 studies reported a significant association, and 7 studies reported no association. However, almost all studies reported increased mortality in Covid-19 patients who were diabetic compared to those without.[7]

CKD was also one of the top three comorbidity that affect mortality in this study, but there are still few data showing the relationship between CKD and the severity of Covid-19 infection. However, based on available data, patients with CKD tend to suffer from a more severe infection severity compared to those who do not suffer from CKD. This is thought to occur because patients with CKD generally have a high prevalence of hypertension, cardiovascular disease, and type 2 diabetes mellitus.[1]

Neutrophils are one of the vital immune cells in the human body. When pathogenic microorganisms invade the body, immune cells tend to rapidly assemble chemotactically to the site of infection and play a role in host defence and immune regulation. When the body's neutrophil levels are reduced, the immune system is compromised, and the risk of infection is significantly increased. Lymphocytes are the main effector cells of the human immune response. The number of lymphocytes in the body is closely related to the immune system and the body's defence against pathogenic microorganisms and is negatively correlated with the degree of inflammation. The NLR includes two types of leukocyte subtypes, which reflect the body's neutrophil balance and lymphocyte count level. and the degree of systemic inflammation.[9] More precisely, it reflects a balance between the severity of inflammation and immune status thus considered an important marker of the systemic inflammatory response. The results of this study are in line with other studies which also reported that there was a significant relationship between the increase in NLR and mortality with the cut off NLR used 2.69.[10] In this study, a multivariate analysis was carried out whose results showed that NLR was the most influential factor in the mortality of Covid-19 patients.

Albumin is often used as an indicator of nutrition in critically ill patients. Poor nutritional status, exposure to hepatotoxins and the resulting inflammatory state can inhibit the synthesis of albumin.[11] In Covid-19, several studies have linked hypoalbuminemia with a more severe degree of Covid-19, but the mechanism of hypoalbuminemia in Covid-19 is still not fully elucidated. The incidence of hypoalbuminemia in patients with Covid-19 is thought to occur because of systemic inflammation that arises and causes disruption of capillary permeability, resulting in extravasation of albumin into the interstitial tissue. The effect of albumin on patients with Covid-19 shows that albumin has a modulating effect on inflammation and oxidative stress.[12] In this study, the risk of death was also found to be higher than those with normal albumin levels (45.54% vs 25%, p=0,006).

Following the Covid-19 pandemic, increased D-dimer and thrombotic complications have been widely reported in patients with Covid-19. Guan et al. reported that a D-dimer of more than 0.5 g/ml was found in

260 of 560 patients (46%). Several studies were conducted to study the relationship between baseline D-dimer measurements and disease severity and outcome. A study conducted by Zhang et. Al. in China of 343 patients concluded that D-dimer >2000 could be a useful early marker for predicting in-hospital mortality in patients.[13] This study reported that 62.4% of patients had D-dimer values >500 with a mean D-dimer value of 1447.71. Of the 180 patients, 23.8% had D-dimer 2000, 16.7% had D-dimer 1000-<2000, 21.1% had D-dimer 500-<1000 and 37.2% had D-dimer < 500. In line with previous theory and research, this study also found a significant relationship between an increase in D-dimer and (mortality) due to Covid-19 (p=0.003).

In a previous study of 298 patients with Covid-19, patients who died had baseline CRPs that were 10-fold higher than survivors (100.0vs.9.7 mg/L, P < 0.001), and CRP concentrations were associated with death, with an area under the curve (AUC) of 0.896.[14] In this study, the average CRP value was 2.04. From the results of the study, an analysis of the ROC curve was performed, and it was found that the CRP cut off was 1.15. From the study, 86 patients had CRP values higher than 1.15. The percentage of mortality in the CRP 1.15 group was 41.50%.

A meta-analysis also showed that increased PCT scores were associated with a 5x increase in the risk of dying from COVID-19.[15] In this study, the average procalcitonin value was 2.44. Out of 180 patients, 33.89% of patients experienced an increase in PCT (≥0.5). In line with previous studies, this study also showed a significant relationship between procalcitonin and mortality in this study (p=0.001). The results of the multivariate analysis also showed that the procalcitonin value was one of the influential factors in increasing the risk of death from COVID-19.

CONCLUSION

It can be concluded that the demographic factors that are significantly related to the death of Covid-19 patients are the presence of comorbidities such as hypertension and CKD. Meanwhile, laboratory parameters that significantly affected mortality were levels of Neutrophil Lymphocyte Ratio above 6.54, hypoalbuminemia, increased levels of D-dimer, increased levels of CRP, and increased levels of procalcitonin.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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