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RESEARCH ARTICLE

Survival analysis and outcome prediction of COVID-19 patients: a retrospective observational study from tertiary referral hospital in Indonesia

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) pandemic has become a global concern. Recently, Indonesia contributed the third-highest number of new COVID-19 cases in the world. We provide supporting information for COVID-19 management. This retrospective cohort study was conducted at Dr. Soetomo General Hospital. Researchers collected demographics, comorbidity, initial laboratory tests, and complications data of patients. This study performed a comparative, survival, and Receiver Operating Characteristic (ROC) curve analysis. Survival analysis showed a decrease in the probability of survival associated with an increase in the variables of age, diabetes, white blood cell (WBC) count, and neutrophils percentage, and a decrease in lymphocytes percentage during hospitalization. Lymphocyte percentage, neutrophil-lymphocyte ratio (NLR), WBC count, neutrophil percentage, had an accuracy 0.727 (95%CI 0.642-0.812; p<0.001), 0.726 (95%CI 0.641-0.812; p<0.001), 0.706 (95%CI 0.615-0.796; p<0.001), and 0.700 (95%CI 0.612-0.788; p<0.001) respectively, in predicting worse outcome. Our study suggests routine complete blood count tests in the admission of a patient with COVID-19 infections, which can be used to determine the survival and prognosis of hospitalized patients.

Keywords: Comorbidity; covid-19; infectious disease; predictive; survival.

INTRODUCTION

Since the discovery of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019, this virus has continued to spread globally. Until mid-year of 2021, Coronavirus Disease 2019 (COVID-19) has caused a total of more than 177 million cases with 3.9 million deaths. The exponential increase of COVID-19 patients is also found in Indonesia, with 2,033,421 cases and 55,594 deaths as of June 23rd, 2021 (World Health Organization, 2021a). Recently, on July 27th, 2021, Indonesia contributed the third-highest number of new COVID-19 cases in the world (World Health Organization, 2021b). Therefore, several developing countries like Indonesia must increase awareness, and there is a need for information that can support the COVID-19 management in developing countries.

Patients with COVID-19 have a broad clinical spectrum, ranging from asymptomatic to severe pneumonia with respiratory failure. They are often associated with intensive care unit (ICU) admission and high fatality rates (Huang *et al*., 2020). Thus, the identification of factors associated with mortality is critical to reducing mortality rates. A previous study reported comorbidities associated with worsening output (Yang *et al*., 2020; Kamal *et al*., 2021). The presence of comorbidities is also associated with worsened patient outcomes (Atkins *et al*., 2020; Guan *et al*., 2020; Jin *et al*., 2020). However, errors in separate complications and comorbidities have severe implications in clinical, epidemiological research. Most studies did not separate comorbid conditions and complications and reported the two conditions as one result. It is important to note that if complications are considered comorbidities, the effects of exposure and outcome will be masked and will alter the study results (Ording & Sørensen, 2013).

The early identification can provide necessary information for managing COVID-19 patients (Mudatsir *et al*., 2020). Previous study found an association between complete blood counts or coagulation factors and severity of COVID-19 patients (Demelo-Rodríguez *et al*., 2020). Early laboratory examination potential to predict worsen outcomes (Duan *et al*., 2020). However, no studies from a large developing country like Indonesia reported early laboratory examination on predicting survival and mortality.

The existing capacity of Indonesia's healthcare professionals and supply is insufficient to deal with potentially increased demands for managing COVID-19 cases as the instances continue to fluctuate (Mahendradhata *et al*., 2021). Implementing good triage to maintain hospital activity while reducing the risk of mortality requires judgment based on patient prognosis. Our study aims to analyze the factors associated with patient survival and estimate the early laboratory predictive value for predicting COVID-19 mortality. Therefore, these findings may support the creation of clinical management protocols, subsidizing decisions made in the hospital setting.

MATERIALS AND METHODS

Study Design and Participants

This study was a retrospective cohort study of hospitalized patients with COVID-19 enrolled at Dr. Soetomo General Hospital (Surabaya City, East Java Province, Indonesia) as Tertiary Referral Hospital in Indonesia. All confirmed COVID-19 patients were screened, and those who had definite outcomes (dead or discharged) between March 1st, 2020 and June 30th, 2020, were listed. The study was approved by the Research Ethics Commission of Dr. Soetomo General Hospital and was performed following the Helsinki Declaration.

The minimum sample size was calculated using the formula (Dahlan, 2009). Formula for categorical variables are

$$n_1 = n_2 = \left(\frac{Z_\alpha \sqrt{2PQ} + Z_\beta \sqrt{P_1 Q_1 + P_2 Q_2}}{P_1 - P_2} \right)^2$$

and for continuous variables are

$$n_1 = n_2 = 2 \left(\frac{(Z_\alpha + Z_\beta) S}{X_1 - X_2} \right)^2$$

with the n1: sample size group 1; n2: sample size group 2; Zα: alpha standard deviation; Zβ: beta standard deviation; P1: proportion of known group; Q1: 1-P1; P2: proportion of predicted group; Q2: 1-P2; P = (P1+P2)/2; S:combined standard deviation; X1-X2: the minimum difference which considered significant.

Since the data have several categorical and numerical variables, we choose the highest minimum sample size among all variables. The minimum sample size required is 124 samples. From the list, 190 adult inpatients (>18 years old) were selected randomly using a research randomizer (Randomizer.org). Then, 14 pregnant patients, four patients with no Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test record, and 35 patients with preliminary medical tests were excluded, leaving 137 patients included in this study.

Data Collection

The data of demographic, comorbidity, initial laboratory test, treatment, and complications were collected from secondary data from electronic and non-electronic medical records using a standardized data collection form. All data were checked twice on to ensure the data retrieved correctly before being entered into a computerized database – any difference between electronic and non-electronic medical records adjudicated by discussion of all researchers.

Laboratory Procedures

Routine laboratory procedures in this study mainly include complete blood tests, renal and liver function tests, and electrolytes. The complete blood test including white blood cell (WBC), hemoglobin, hematocrit, neutrophil percentage, and lymphocyte percentage was analyzed using Sysmex XM-1000 Automatic Hematology Analyzer. Other parameters like serum creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), potassium, chloride, and sodium level was analyzed using Dimension RXL Automatic Clinical Chemistry Analyzer. All instruments had been calibrated to ensure the validity of the result. Most laboratory tests were conducted on admission before RT-PCR results were available to confirm patients' diagnoses. The treating physician determined the frequency of subsequent examination. The initial values of laboratory tests were collected to analyze early predictive factors. The extreme values were collected to validate complications, which are written in the patient's resume.

Definitions

The diagnosis of COVID-19 was defined according to the Indonesian Ministry of Health COVID-19 prevention and control guidelines (version 5.0) (Menteri Kesehatan Republik Indonesia, 2020). Detection of SARS-CoV-2 infection is done by using real-time RT-PCR methods from nasopharyngeal swab specimens. The confirmatory examination was conducted by the Diagnostic Center of Dr. Soetomo General Hospital, Surabaya. The criteria for discharge were complete isolation for ten days from the date of onset with a minimum of 3 days after an absence of fever and respiratory problems (for mild and moderate patients) or has obtained a negative one time RT-PCR follow-up examination plus a minimum of 3 days after an absence of fever and respiratory problems (for severe and critical patients). Severe cases are defined by Intensive Care Unit (ICU) admission or respiration rate ≥ 30 times/minute or oxygen saturation ≤ 93%. Our study cannot use PaO2/FiO2 in identifying severe cases, because this parameter is rarely examined in all patients. Hypertension is defined as elevated blood pressure (above 140 mmHg for systolic or 90 mmHg for diastolic). Obesity using criteria of body mass index (BMI) more than 25.0 kg/m2 (World Health Organization, 2000; Kanazawa *et al*., 2002). Diabetes is established based on the assessment of the doctor in charge based on the patient's history and laboratory examination. Other complications were established based on Dr. Soetomo General Hospital Clinical Practice Guidance.

Statistical Analysis

Continuous was presented as median and interquartile range (IQR), while categorical variables were presented as count (n) and percentage (%). The Mann-Whitney U test and Chi-square test were used to compare differences between survivors and non-survivors. We performed univariable binary logistic regression to explore the risk factors associated with in-hospital death. Variables with significant univariate odds ratio (OR) will continue to multivariate logistic analysis (to measure the adjusted OR), survival analysis, and Receiver Operating Characteristic (ROC) curve analysis. Survival analysis was conducted using the Kaplan-Meier survival curve to measure survival probability during hospitalization, which also shows the Log Rank p-value. The cox proportional hazard regression model was done to determine hazard ratio (HR). ROC curves were conducted to measure the area under the curve (AUC) value, sensitivity, and specificity of a predictive variable. Statistically significant was considered using two-sided α less than 0.05. Statistical analysis was done using the IBM SPSS software (version 13).

RESULTS

Patients Characteristic and Comparative Test

The patient's baseline characteristics and the results of the comparative test are presented in Table 1. The mortality rate of patients in this study reached 43%, almost the same as the overall percentage of COVID-19 confirmed patients hospitalized at Dr. Soetomo General Hospital until June 2020, which is 41%. Severe cases dominated inpatients who were treated in Dr. Soetomo General Hospital (69%). Severe cases affected mortality significantly, where severe cases were found to dominate in the group of non-survivor (88%) than the group of survivors (55%).

A total of 137 patients who met the criteria for participating had a median age of 55 (IQR 45.5-62) years. The non-survivor group had a median age of 58 (IQR 48-68) years, significantly older than survivors (Median 53.5 (IQR 42-60.25) years). There are no significant difference of mortality between male and female groups. Of the 137 patients, 48 people (35%) had a history of hypertension, 24 people (18%) had a history of obesity, and 45 people (59%) had a history of diabetes. Initial laboratory tests were obtained from routine laboratories performed on patients on admission to the

Table 1. Baseline characteristic of the study cohort

Variable	Total (137)	Survivor (78)	Non-Survivor (59)	*p*-value
Age (year)	55.00 (45.50-62.00)	53.50 (42.00-60.25)	58.00 (48.00-68.00)	0.003*
Sex			0.403	
Male	71 (52%)	38 (49%)	33 (56%)	
Female	66 (48%)	40 (51%)	26 (44%)	
Severe Case	95 (69%)	43 (55%)	52 (88%)	<0.001*
Hypertension	48 (35%)	26 (33%)	22 (37%)	0.631
Obesity	24 (18%)	13 (17%)	11 (19%)	0.763
Diabetes	45 (33%)	19 (24%)	26 (44%)	0.015*
Day of Hospitalization	10.00 (4.00-16.00)	15.00 (11.00-19.00)	4.00 (2.00-8.00)	<0.001*
Day Onset to Hospitalize**	4.00 (3.00-7.00)	4.00 (3.00-7.00)	3.00 (2.00-6.00)	0.047
Day Onset to Diagnosis**	5.00 (3.00-8.00)	7.00 (4.00-9.00)	4.00 (2.00-6.75)	0.003*
Day Onset to Discharge**	16.00 (8.00-22.50)	21.00 (17.00-27.00)	07.00 (5.00-12.00)	<0.001*
Early Laboratory Test				
White Blood Cell Count (10^3/uL)	8.50 (6.15-11.78)	7.15 (5.59-9.23)	10.26 (7.89-13.34)	<0.001*
Platelet Count (10^3/uL)	250.00 (181.5-316.00)	249.50 (184.50-301.50)	260.00 (173.00-328.00)	0.907
Hemoglobin Concentration (g/dL)	13.10 (11.90-14.30)	13.40 (12.18-14.53)	12.80 (11.30-14.00)	0.061
Hematocrit Concentration (%)	38.80 (35.50-42.25)	39.95 (36.00-42.65)	37.80 (33.30-41.20)	0.076
Neutrophil Percentage (%)	78.80 (69.55-85.60)	73.40 (67.73-82-83)	83.20 (76.40-88.30)	<0.001*
Lymphocyte Percentage (%)	13.20 (8.45-20.70)	15.55 (11.40-23.13)	10.97 (6.60-14.40)	<0.001*
Serum Creatinine Levels (mg/dL)	1.00 (0.70-1.25)	0.87 (0.70-1.10)	1.10 (0.80-2.20)	0.005*
Blood Urea Nitrogen Levels (mg/dL)	16.00 (10.00-23.50)	15.00 (10.00-21.00)	19.00 (10.00-42.00)	0.023*
Aspartate Aminotransferase (U/L)	53.00 (35.00-84.00)	48.00 (28.75-74.00)	64 (44.00-98.00)	0.004*
Alanine Aminotransferase (U/L)	43.00 (31.00-74.00)	39.50 (28.75-84.75)	44.00 (34.00-71.00)	0.568
Potassium (mmol/)	4.00 (3.50-4.60)	3.90 (3.50-4.50)	4.00 (3.50-4.90)	0.102
Chloride (mmol/)	99.00 (96.00-103.00)	100.00 (97.00-103.00)	98.00 (95.00-104.00)	0.185
Sodium (mmol/)	136.00 (132.50-140.00)	136.00 (133.00-139.00)	137.00 (132.00-140.00)	0.967
Treatment***				
Hydroxychloroquine	66 (48%)	48 (62%)	18 (31%)	0.000*
Quinolones	84 (61%)	40 (51%)	44 (75%)	0.006*
Cephalosporins	8 (6%)	7 (9%)	1 (2%)	0.137
Azithromycin	4 (3%)	3 (4%)	1 (2%)	0.634
Other antibiotics	15 (11%)	5 (6%)	10 (17%)	0.050
Lopinavir/Ritonavir	19 (14%)	8 (10%)	11 (19%)	0.160
Oseltamivir	1 (1%)	1 (1%)	0 (0%)	1.000
Methisoprinol	61 (45%)	42 (54%)	19 (32%)	0.012*

**p*-value<0.05; **missing value 6%; ***other supportive and symptomatic treatment provided as appropriate.

hospital. From the 13 variables, only six variables (WBC count, neutrophil percentage, creatinine, BUN, AST, and lymphocyte) had a significant comparative test value. There are higher number of patients in survivors group receive the hydroxychloroquine and methisoprinol than non-survivor group. Opposite with the use of quinolones which are higher in non-survivor group.

Each patient has different complications. As shown in Table 2, damage can occur in almost all organs. The three most common complications experienced by the subjects were hypoalbuminemia, transaminitis, and hyperglycemia. In almost all complications, complications were more common in a non-survivor group than survivors. There is a relationship between the number of organs damaged and mortality. By using several parameters for each organ, (respiratory failure for the lungs, hypertension for cardiovascular, thrombocytopenia for coagulation, hyperglycemia for the pancreas, AST or ALT for the liver, and BUN or creatinine for the kidneys), this study found that when more organs were affected, more likely patients lead to poor outcome. Table 3 shows the leading causes of mortality of COVID-19 patients treated at Dr. Soetomo General Hospital which was dominated by the incidence of type 1 respiratory failure.

Logistic Regression

Our bivariate logistic regression showed in Table 4. Each addition of one year's age would increase 1.046 (95% CI (1.016-1.077)) mortality risk. Diabetes, increase of WBC, increase of neutrophils, and increase of BUN increase the risk of mortality, while increase of lymphocyte showed converse relation with mortality risk. The multivariate analysis fulfills several assumptions, with a significant Omnibus Tests (<0.001) and non significant Hosmer and Lemeshow test (p>0.634) which indicate the model formed was fit for multivariate analysis. The overall percentage of the research model reached 70.8%. The independent variable in this multivariate analysis model can explain 30.2% of the dependent variable, calculated based on the Nagelkerke R Square. The multivariate analysis also proved a strong influence of the age variable, where in the multivariate analysis increase of age significantly (p=0.041) increased the risk of mortality in COVID-19 patients (OR 1.034, 95% CI (1.001-1.068)).

Table 2. Multiorgan complication

Variable	Total (137)	Survivor (78)	Non-Survivor (59)	*p*-value
LUNG				
Respiratory Distress**	70 (51%)	17 (22%)	53 (90%)	<0.001*
CARDIOVASCULAR				
Hypertension**	34 (25%)	17 (22%)	17 (29%)	0.346
BLOOD & COAGULATION				
Thrombocytopenia**	20 (15%)	9 (12%)	11 (19%)	0.243
Leukocytosis	50 (36%)	16 (21%)	34 (58%)	<0.001*
Anemia	47 (34%)	20 (24%)	27 (46%)	0.014*
PANCREAS				
Hyperglycemia**	77 (56%)	34 (44%))	43 (73%)	0.001*
LIVER				
Transaminitis**	103 (75%)	50 (64%)	53 (90%)	0.001*
Hypoalbuminemia**	106 (77%)	50 (64%)	56 (95%)	<0.001*
RENAL				
High BUN**	48 (35%)	19 (24%)	29 (49%)	0.003*
High Creatinine**	30 (22%)	2 (3%)	21 (36%)	0.001*
Hypokalemia	45 (33%)	24 (31%)	21 (36%)	0.552
Hypochloremia	51 (37%)	21 (27%)	30 (51%)	0.004*
Hyponatremia	63 (46%)	34 (44%)	29 (49%)	0.518
SEPSIS				
Sepsis	29 (21%)	2 (3%)	27 (46%)	<0.001*
MULTI ORGAN**				
0	8 (6%)	8 (10%)	0 (0%)	<0.001*
1	17 (12%)	17 (22%)	0 (0%)	
2	36 (26%)	26 (33%)	10 (17%)	
3	31 (23%)	17 (22%)	14 (24%)	
4	32 (23%)	7 (9%)	25 (42%)	
>4	13 (9%)	3 (4%)	10 (17%)	

Anemia = hemoglobin lower than 11 g/dL for female or 13 g/dL for male; High BUN = blood urea nitrogen higher than 18 mg/dL; High Creatinine = serum creatinine higher than 1.3 mg/dL; Hyperglycemia = blood glucose higher than 126 mg/dL; Hypoalbuminemia = albumin serum lower than 3.4 g/dL; Hypochloremia = serum chloride concentration below 98 mmol/l; Hypokalemia = serum potassium concentration below 3.5 mmol/l; Hyponatremia = serum sodium concentration below 136 mmol/l; Leukocytosis = white blood cells count higher than $10x10^3$/uL; Thrombocytopenia = blood platelets lower than $150'10^3$/uL; Transaminitis = AST or ALT higher than 35 U/L for female or 50 U/L for male; **p*-value<0.05; **counting for six organ dysfunction (lung. cardiovascular. blood & coagulation. pancreas. liver. renal).

Table 3. Main mortality cause

Main Mortality Cause	Non-Survivor (59)
Type 1 respiratory failure	42 (71%)
Sepsis	8 (14%)
Multiorgan failure	4 (7%)
Cardiovascular event	4 (7%)
Type 2 respiratory failure	1 (2%)

Survival Analysis

As seen in Figure 1, patients with old age, diabetes, high WBC count, high neutrophil percentage, low lymphocyte percentage, and high BUN level seem more vulnerable with lower survival during hospitalization. However, this decline is not significant (Log Rank p-value=0,123) compared for age ≤59 years versus > 59 years, but significant in comparison for another predictive factor. Table 5 shows that diabetes has the largest hazard ratio value, 1.870 (95% CI 1.117-3.128), which means that patients with diabetes

Table 4. Logistic regression model for the risk of mortality

Variable	Univariate OR	*p*-value	Multivariate OR	*p*-value
Age	1.046 (1.016–1.077)	0.002*	1.034 (1.001–1.068)	0.041*
Diabetes	2.447 (1.180–5.072)	0.016*	1.870 (0.810–4.318)	0.142
WBC	1.156 (1.058–1.264)	0.001*	1.101 (0.997–1.215)	0.057
Neutrophil	1.084 (1.040–1.130)	<0.001*	0.950 (0.839–1.076)	0.421
Lymphocyte	0.891 (0.843–0.943)	<0.001*	0.868 (0.740–1.017)	0.081
Creatinine	1.111 (0.973–1.269)	0.119	–	–
BUN	1.014 (1.000–1.028)	0.043*	1.005 (0.992-1.018)	0.471
AST	1.001 (0.997–1.006)	0.481	–	–

AST = Aspartate Aminotransferase; BUN = Blood Urea Nitrogen; OR = Odds Ratio; WBC = White Blood Cells; **p*-value<0.05.

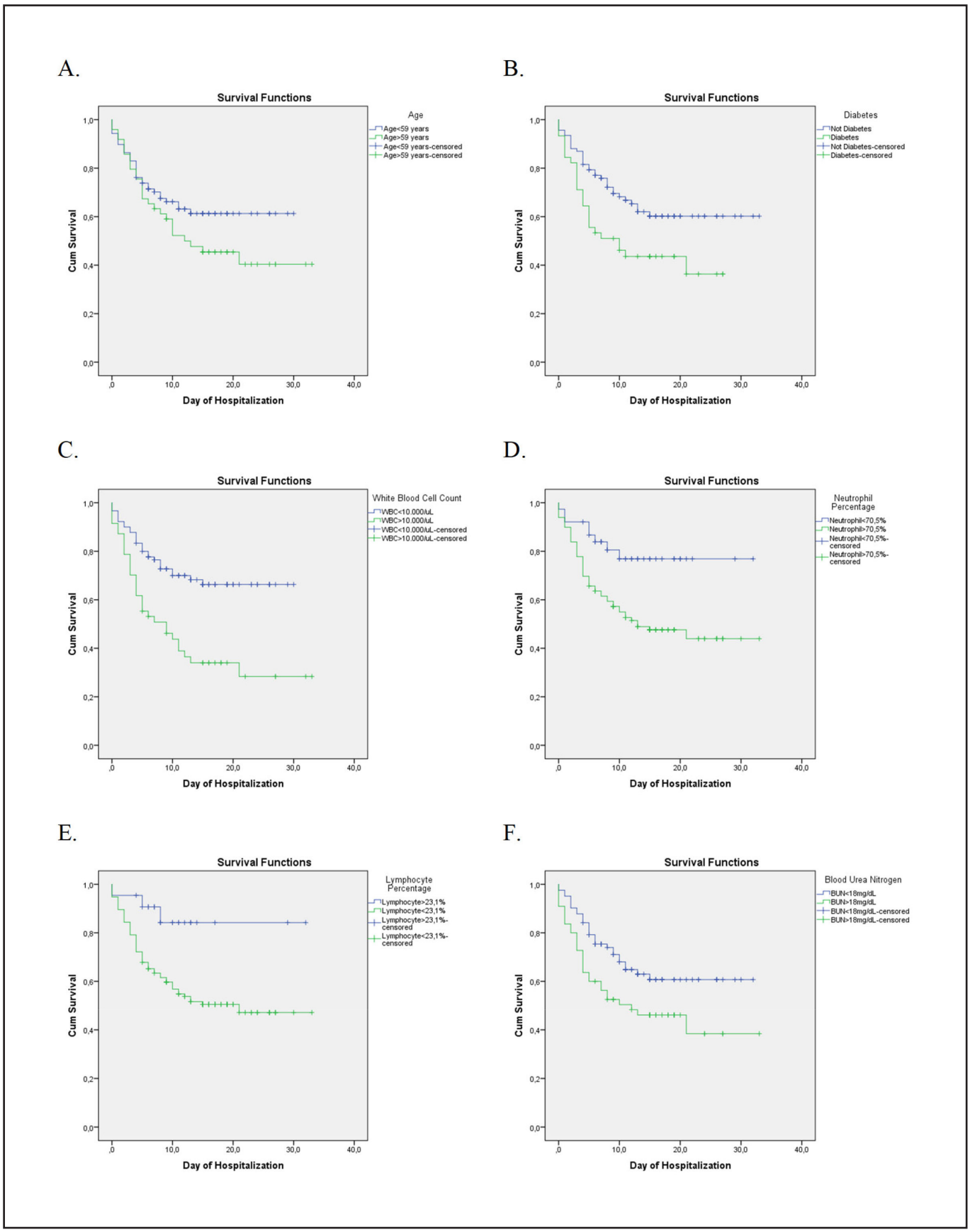

Figure 1. Kaplan-Meier survival curve of (A) Age (B) Diabetes (C) White blood cell count (D) Neutrophil percentage (E) Lymphocyte percentage (F) Blood urea nitrogen for COVID-19 patients survival.

Table 5. Kaplan-Meier and COX regression analysis of predictive variables

Variable	K-M Survival Analysis	Univariate COX Analysis		Multivariate COX Analysis	
	log-rank test *p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (year)		1.030 (1.007–1.053)	0.010*	1.019 (0.996–1.043)	0.104
>59 vs ≤59	0.123	1.482 (0.887–2.475)	0.133		
Diabetes	0.014*	1.870 (1.117–3.128)	0.017*	1.595 (0.922–2.758)	0.095
WBC (n/uL)		1.079 (1.033–1.126)	0.001*	1.056 (0.998–1.117)	0.059
>10 vs ≤10	<0.001*	2.587 (1.550–4.317)	<0.001*		
Neutrophil (%)		1.055 (1.023–1.087)	0.001*	0.945 (0.861–1.037)	0.234
>70.5 vs ≤70.5	0.006*	2.686 (1.274–5.662)	0.009*		
Lymphocyte (%)		0.924 (0.887–0.963)	<0.001*	0.884 (0.784–0.998)	0.047*
<23.1 vs >23.1	0.015*	3.732 (1.167–11.933)	0.026*		
BUN (mg/dL)		1.006 (1.001–1.012)	0.019*	1.004 (0.998–1.010)	0.173
>18 vs <18	0.023*	1.774 (1.064–2.957)	0.028*		

BUN = Blood Urea Nitrogen; HR = Hazard Ratio; K-M = Kaplan-Meier; WBC = White Blood Cells; *p-value<0.05.

increase the risk of mortality during treatment by 87% compared to patients without diabetes. It is important to underline, the increase in lymphocytes provides a protective factor in COVID-19 patients. The increase in lymphocytes significantly reduced mortality risk by 0.924 (95% CI 0.887-0.963) times.

ROC Analysis

Variable with AUC value above 70% is shown in Figure 2 and Table 6. Older age, higher number of WBC, neutrophils, and BUN, the greater the probability of mortality while the smaller number of lymphocytes percentage, the greater the probability of mortality. The lymphocyte variable has an AUC value of 0.727 (95% CI (0.642-0.812)) which has a medium accuracy value category (0.7-0.8). With a cut-off value of 12.70, this variable has a sensitivity and specificity of 69.5% and 70.5%, respectively. Then the variables with the moderate accuracy (0.7-0.8) sequentially were neutrophil-lymphocyte ratio (NLR), WBC count, and neutrophil percentage.

DISCUSSION

The increasing number of COVID-19 cases has burdened medical healthcare systems. Identifying the factors of mortality is essential to improve healthcare systems by being an early warning system. The mortality rate of COVID-19 patients which hospitalized in Dr Soetomo General Hospital even surpass the mortality rate of patients in Emergency Unit (4%) of Dr Soetomo General Hospital before the COVID-19 pandemic (Wahyuhadi, 2019). This may be explained by its function as Tertiary Referral Hospital which manage most of severe COVID-19 cases. The setting when the start of pandemic, may also influence the referral system. This was supported by the data that showed the shorter day of hospitalization in the non-survivor group compared to the survivor group.

In this study, we identified risk factors for COVID-19 patients' mortality: age, diabetes, WBC count, neutrophil percentage, lymphocyte percentage, BUN, and AST. Some of these factors also have influenced the patient's survival and can be predictors with moderate accuracy. Similar to other studies, our study reports an increased risk of mortality in older patients with COVID-19 (Jin *et al*., 2020; Wu *et al*., 2020). Older patients are related to several complications such as dementia, depression, atrial fibrillation, or chronic kidney damage that worsen the condition of patients (Atkins *et al*., 2020; Chen *et al*., 2021). In addition, immunopathology like

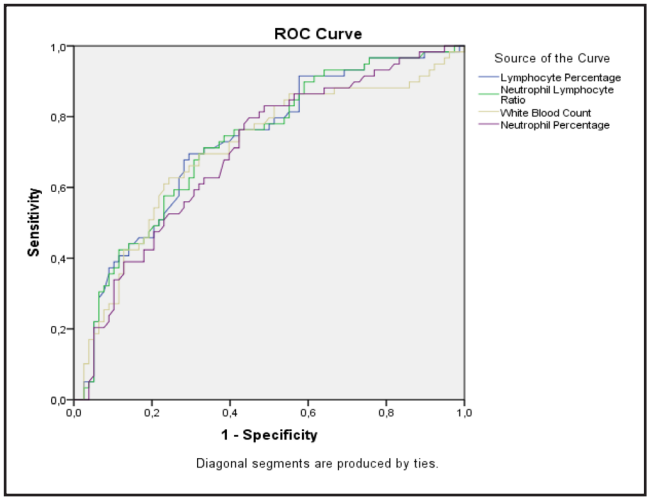

Figure 2. Receiver operating characteristic curve of predictor variables for risk mortality classification of COVID-19.

Table 6. Area under the curve, sensitivity, and specificity of predictive variables

Variable	AUC (95% CI)	*p*-value	Sensitivity	Specificity	Cut-off value	PPV	NPV
Lymphocyte	0.727 (0.642–0.812)	<0.001*	69.5%	70.5%	12.70	64.06%	75.34%
NLR	0.726 (0.641–0.812)	<0.001*	71.2%	66.7%	6.115	61.76%	75.36%
WBC	0.706 (0.615–0.796)	<0.001*	62.7%	75.6%	9.245	66.07%	72.84%
Neutrophil	0.700 (0.612–0.788)	<0.001*	79.7%	55.1%	75.70	57.32%	78.18%

AUC = Area Under the Curve; NLR = Neutrophil-Lymphocyte Ratio; NPV = Negative Predictive Value; PPV = Positive Predictive Value; WBC = White Blood Cells; *p-value<0.05.

immunosenescence decreased function of cellular immunity, and humoral immunity in older patients often worsen inflammation and organ dysfunction (Chen *et al*., 2021).

Previous studies have reported that diabetic patients with COVID-19 have higher severity than non-diabetic patients (Akbari *et al*., 2020). We confirmed that diabetic patients also have low survival on hospitalization. The dysfunction of pro-inflammatory cytokine response, mainly mediated by interleukin-6 (IL-6), decline of the compensatory function of visceral organs (Maddaloni & Buzzetti, 2020). The higher IL-6 profile in diabetic patients also induces cytokine-induced lung damage which account for more severe pulmonary destruction (Zhu *et al*., 2021).

Interestingly, this study did not find any significance in hypertension and obesity as a risk factor for mortality in COVID-19 patients. Our different results can be explained because we do not divide patients with controlled and uncontrolled hypertension. The previous study showed a difference between patients with hypertension but do not receive previous therapy compared to patients with hypertension but have received previous therapy (Gao *et al*., 2020). For obesity, most of the studies reported used the different obesity criteria (BMI > 30), while this study used (BMI > 25) Asian obesity criteria (World Health Organization, 2000; Kanazawa *et al*., 2002).

The findings from this study, consistent with several studies, indicated that patients with higher WBC count, higher neutrophil, and lower lymphocytes had higher odds of COVID-19 mortality (Ji *et al*., 2020; Savrun *et al*., 2021). The lymphopenia in COVID-19 patients reflects the low cluster of differentiation (CD)3 and CD4 cell counts (Chen *et al*., 2020). Increased neutrophils reflected an increase in pro-inflammatory cells and decreased regulatory T cells, which have a role in controlling inflammation to worsen the condition (Qin *et al*., 2020; Khosroshahi & Rezaei, 2021). ROC curve analysis reveals moderate accuracy of this parameter on predicting mortality of COVID-19 patients. This routine examination is also commonly available at an affordable price, so it is recommended for prognostic purposes in developing countries. Thus, this finding supports the use of this parameter for predicting the mortality of COVID-19 patients (Ma *et al*., 2020).

Lower hemoglobin and hematocrit levels are associated with more severe outcomes (Wang *et al.*, 2020). Low hemoglobin levels in the blood reflect the possibility of malnutrition, coagulation disorders, or impaired oxygen delivery (Ghahramani *et al*., 2020). Regarding platelet count, more severe COVID-19 presentation has been reported associated with low platelet count (Ghahramani *et al*., 2020). Thrombocytopenia may be caused by endothelial damage which causes platelet activation and aggregation or pulmonary thrombosis (Lippi *et al*., 2020). However, our study did not find a significant relationship between hemoglobin, hematocrit, platelet count, and patient mortality.

Our findings also show a significant relation of AST with mortality but the nonsignificant result for ALT, which is similar to another study (Li *et al*., 2020). ALT was considered as more specific to hepatocyte cell destruction than AST. The increase of AST level was also associated with muscle injury, especially for striated muscle and myocardium, hence the single elevation of AST may represent the manifestations of systemic illness (Otto-Ślusarczyk *et al*., 2016; Wagner *et al*., 2021).

Multi-organ complication may be associated with worsen outcome in COVID-19 patients. The hyperglycemia may be caused by pre-existing diabetes melitus, new-onset diabetes, stress hyperglycemia, or the usage of corticosteroids for severe cases (Gerganova *et al*., 2022). Additionally, SARS-CoV-2 may also destroy pancreatic cells by direct viral infection. In the acute state, the glucotoxicity and systemic inflammation will contribute to global insulin-resistance syndrome that worsen the patient condition (Gerganova *et al*., 2022).

Moreover, most of non-survivor groups were experiencing transaminitis and hypoalbuminemia. The liver injury may be caused by direct viral effects on hepatocyte, the host's immune response induce negative acute phase reactant (Alqahtani & Schattenberg, 2020). The capillary leakage which is triggered by systemic inflammation may lose the albumin into the interstitial space (Wagner *et al*., 2021). With the negative balance of albumin synthesis and degradation, this could lead into hypoalbuminemia (Viana-Llamas *et al*., 2021). The nutritional status assessment during hospitalization is also required since the hypoalbuminemia may also be caused by malnutrition.

Until now, there are still few studies that focus on analysis of survival for COVID-19 mortality from developing countries in Southeast Asia. Our strength is that we are able to provide comorbidities and complications separately, which have the potential to obscure the main findings. Therefore, our result can be used as a reference, especially in the southeast Asia region. Several other limitations exist in our study. First, due to the limited sample size of this study, our logistic model only included one factor as an independent variable, and it left out crucial critical predictors like age. Second, our study could not include radiological imaging and oxygen supplementation for determining the patient's severity. Third, not all laboratory tests are complete immediately after admission. Finally, the investigators could not separate patients with controlled or uncontrolled hypertension or diabetes. This limitation is due to the absence of complete data in the medical record.

CONCLUSION

In summary, we identified several factors associated with patient survival (diabetes, WBC, neutrophil, lymphocyte, and BUN) and identified several moderate accuracy early predictors (NLR, WBC, neutrophil, and lymphocyte). Our study suggests routine complete blood count tests in the admission of patients with COVID-19 infections that can be used to determine the prognosis of hospitalized patients at an affordable price, which is suitable for developing countries. Further research on the impact of previous control on hypertension or hyperglycemia on mortality of COVID-19 patients is warranted to corroborate the current evidence.

Conflict of Interest

The authors declare that they have no conflict of interest.

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