Prognostic Scoring System for Mortality of Hospitalized COVID-19 Patients in Resource-Limited Settings: A Multicenter Study from COVID-19 Referral Hospitals

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ABSTRACT

Background: *Many studies identified the risk factors and prognostic factors related to in-hospital COVID-19 mortality using sophisticated laboratory tests. Cost and the availability of supporting blood tests may be problematic in resource-limited settings. This multicenter cohort study was conducted to assess the factors associated with mortality of COVID-19 patients aged 18 years and older, based on history taking, physical examination, and simple blood tests to be used in resource-limited settings.* ***Methods:*** *The study was conducted between July 2020 and January 2021 in five COVID-19 referral hospitals in Indonesia. Among 1048 confirmed cases of COVID-19, 160 (15%) died during hospitalization.* ***Results:*** *Multivariate analysis showed eight predictors of in-hospital mortality, namely increased age, chronic kidney disease, chronic obstructive pulmonary disease, fatigue, dyspnea, altered mental status, neutrophil-lymphocyte ratio (NLR) ≥ 5.8, and severe-critical condition. This scoring system had an Area-under-the-curve (AUC) of 84.7%. With cut-off score of 6, the sensitivity was*

76.3% and the specificity was 78.2%. ***Conclusion:*** *The result of this practical prognostic scoring system may be a guide to decision making of physicians and help in the education of family members related to the possible outcome.*

Keywords*: COVID-19, prognostic, predictive score, mortality, resource-limited settings.*

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has become a pandemic, also known as coronavirus disease 2019 (COVID-19) pandemic.[1] To date, most of the available prognostic scoring systems for mortality of COVID-19 patients were based on studies in upper-middle-income countries.[2–5] In reality, countries with the highest COVID-19 case fatality rates mainly were developing countries, including Yemen, Peru, Mexico, Sudan, Syria, Ecuador[6], and Indonesia[6,7], and the risk factors related to COVID-19 mortality in lower-middle-income countries may differ.

The established COVID-19 prognostic scoring system has been found to have a high risk of bias. Risk stratification scoring methods have also been developed by incorporating costly supporting tests.[8] In fact, cost and the availability of supporting blood tests may be problematic in resource-limited settings, especially in Indonesia where the epicenter of the pandemic recently showed signs of shifting to the outside of country's capital city. A physician should preferably try to estimate the prognosis of each patient based on the combination of limited number of nonpatient-burdening and easily measurable variables.[9] Therefore, a feasible prognostication method should be developed to predict mortality of COVID-19 patients based on empirical prognostic research.

Our aim was to identify the prognostic factors as well as to establish and validate a prognostic scoring system for mortality of hospitalized COVID-19 patients using available information on hospital admission. The source of information would be history taking, physical examination and simple blood tests. The prognostic model may help detect high-risk patients as early as possible. The multicenter study included wider range of population groups to increase the generalizability of the study.

METHODS

This study is reported as per TRIPOD Checklist: Prediction Model Development and Validation guidelines.[10] The design of this multicenter study was both retrospective and prospective cohort study to assess the factors associated with in-hospital mortality of COVID-19 patients. The inclusion criteria were all patients aged 18 years old and older hospitalized with confirmed COVID-19 marked by positive Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) test.[11] Patients with incomplete data were excluded. The sample was collected from nasal and/or oropharyngeal swab. Data were taken between July 2020 and January 2021 from five COVID-19 referral hospitals in Indonesia, namely Cipto Mangunkusumo National Hospital as the national referral hospital, Cengkareng District Hospital, Tarakan District Hospital, Jakarta Islamic Hospital Cempaka Putih, and Pasar Minggu District Hospital. The patients were followed from the first day of hospital admission until discharge or in-hospital death.

Ethics Approval

This study was approved by the Faculty of Medicine Universitas Indonesia Ethical Committee (KET-419/UN2.F1/ETIK/PPM.00.02/2020). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Data Collection

We used consecutive sampling technique until it reached the minimum sample size, which was 1000 subjects obtained with the rule of thumb. Data, collected from medical records, included the demographic data (age and sex), chronic medical conditions or comorbidities (hypertension,

diabetes mellitus, cardiovascular diseases, pulmonary tuberculosis, chronic obstructive lung disease [COPD], asthma, chronic kidney disease [CKD], chronic liver disease [CLD], autoimmune disease, immunocompromised condition, and malignancy), clinical symptoms (fever, cough, dyspnea or shortness of breath, fatigue, nausea with/without vomiting, diarrhea, and abdominal pain), level of consciousness, neutrophil-lymphocyte ratio (NLR), and radiological findings (pneumonia based on X-ray reading). Blood analysis and radiological findings were routinely obtained during admission.

Statistical Analysis

The dependent variable in this study was discharge status of confirmed COVID-19. The independent variables include demographic data, chronic medical conditions, clinical symptoms, vital signs, blood analysis, and radiological findings. For the statistical analysis, age was categorized into: (1) 18-49 years old, (2) 50-69 years old or above, (3) ≥70 years old. The subjects were categorized based on their gender into male and female. Chronic medical conditions or comorbidities (hypertension, diabetes mellitus, cardiovascular diseases, pulmonary tuberculosis, COPD, asthma, CKD, CLD, autoimmune disease, immunocompromised condition, and malignancy), clinical symptoms (fever, cough, dyspnea or shortness of breath, fatigue, nausea and/or vomiting, diarrhea, and abdominal pain) were recorded as (1) yes, (2) no. Categories for level of consciousness were: (1) alert (Glasgow Coma Scale 15), (2) altered mental status (Glasgow Coma Scale less than 15). Based on the Indonesian National Guideline on COVID-19, the severity of the COVID-19 was categorized into (1) mild, (2) moderate, (3) severe, or (4) critical. Patients were categorized as mild COVID-19 cases in the presence of symptom(s) such as fever, cough, fatigue, shortness of breath, myalgia, sore throat, headache, diarrhea, nausea/vomiting, and abdominal pain, but without the evidence of pneumonia. Moderate COVID-19 cases had symptoms and evidence of pneumonia without hypoxemia. Patients with severe COVID-19 have the symptoms, evidence of pneumonia, and one of the following criteria: (1) respiratory rate more than 30 breaths per minute, (2) severe respiratory distress, or (3) peripheral oxygen saturation < 90%. Patients were considered to have critical COVID-19 if the patients have respiratory distress syndrome (ARDS) and/or respiratory failure, sepsis, septic shock, or other conditions that require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.[12] Categories for NLR ratio were (1) ≥5.8 and (2) <5.8 [13]. Radiological findings of pneumonia on X-ray was recorded as (1) yes or (2) no. The primary outcome of interest was discharge status during hospitalization: (1) died, (2) discharge from COVID-19 isolation ward.

We performed statistical analysis with SPSS Version 26 (IBM, Armonk, New York, USA). Descriptive analysis was done to explore the characteristics of subjects. Categorical variables were presented as numbers and percentages. The numerical or continuous variables were presented as median (Interquartile Range/IQR). Bivariate and multivariate cox regression analyses were done to determine the mortality risk, using a hazard ratio with a 95% confidence interval (95% CI). All independent variables with a p-value <0.25 in the bivariate analysis were included in the multivariate analysis. A Chi-square test was used in the bivariate analysis to assess the association between the independent variables and mortality of COVID-19 patients. During the model development, patient's demographic, clinical characteristics, signs and symptoms, vital signs, blood analysis, and radiological findings were analyzed for the possible association. Factors with two-sided p-value <0.05 were categorized as significant predictors of mortality. During the model development, patients' demographic, clinical characteristics, sign and symptoms, vital signs, and blood analysis were analyzed for possible association. The final model was established with using the Area-under-the-curve (AUC) value and Hosmer-Lemeshow test. Model calibration was performed to ensure the robustness. Internal validation was performed by bootstrapping technique. We repeated the entire modeling process, including variable selection in 1000 samples drawn with replacement from the original sample. Since we only calculated the

cases with complete data in this study, missing data were analyzed using the missing value analysis to know whether the missing value may affect the results.

RESULTS

A total of 1194 hospitalized patients tested positive for COVID-19 between July 2020 and January 2021 in selected hospitals, of whom 1048 met the inclusion criteria. We excluded 146 subjects due to the incomplete data. Of 1048 patients, 160 (15%) died during hospitalization. The flow of subjects throughout the study can be seen in **Figure 1**. The baseline characteristics of the patients were presented in **Table 1**. Bivariate cox regression analysis was performed (**Table 2**). All independent variables with a p-value <0.25 in the bivariate analysis were included in the multivariate analysis.

In the final model, age 50-69 years old (Hazard Ratio [HR] 1.58, 95% CI 1.07-2.32), age 70 years old and older (HR 2.64, 95% CI 1.56-4.45), CKD (HR 1.61, 95% CI 1.02-2.54), COPD (HR 3.11, 95% CI 1.00-9.86), fatigue (HR 2.12, 95% CI 1.50-3.00), dyspnea (HR 1.55, 95% CI 1.06-2.27), altered mental status (HR 2.46, 95% CI 1.28-4.76), NLR ≥ 5.8 (HR 3.38, 95% CI 2.35-4.85), and severe-critical condition (HR 2.31, 95% CI 1.48-3.60) were included to create the scoring system (**Table 3**). We developed the scoring system with variable score given for the presence of the variables (**Table 4**) with the AUC was 84.7% (95% CI 0.82-0.88) (**Figure 2)**.

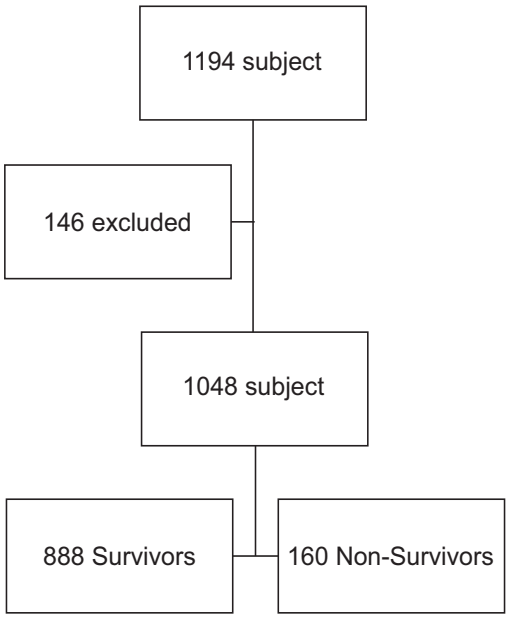

Figure 1. Flowchart of patients.

The optimal cut-off point with the highest combined sensitivity and specificity was a score of ≥ 6, which has a sensitivity of 76.3 % and specificity 78.2% to predict mortality of hospitalized COVID-19 patient. A total score of ≥ 6 had an HR of 1.54 (95% CI 1.41-1.69) compared to a score below 6. Based on internal validation with bootstrapping technique, the result of Hosmer-Lemeshow test was p = 0.784. The result of the missing data compared with the total patients was not statistically significant.

DISCUSSION

Age, as one of the risk factors, is in line with several studies showing that increased age was one of the determining factors for COVID-19 mortality.[8,14] There is an increased risk of having multimorbidity with increasing age. In addition, immunosenescence in older adults may result in impairment of immune response.[15–17]

Several comorbidities are already known to be related to COVID-19 mortality. In this study, we found that CKD and COPD were significant predictors. Previous studies suggested that COVID-19 patient with CKD had nearly twofold higher risk for mortality, compared to patients without CKD, which was similar to our multivariate cox-regression result.[18] CKD patients were hypothesized to have low-grade inflammation causing baseline lymphopenia. Furthermore, abundant reactive oxygen species (ROS) in CKD patients were enhanced by the uremic toxins and angiotensin-mediated activation of Nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, promoting endothelial dysfunction leading to the progression of COVID-19.[19] CKD together with COVID-19 may result in several complications, such as myocarditis, acute myocardial injury, heart failure, and arrhythmias. CKD is one of the major complications of both hypertension and diabetes in the disease course. Contrary to the significance of CKD, the role of hypertension and diabetes mellitus as the predictors of mortality in this study was not statistically significant after

Table 2. Cox regression analysis of variables that were significantly different between survivors and non-survivors.

Variables	Discharge Status		HR (95% CI)	p-value
	Survivor, n (%)	Non-Survivor, n (%)		
Age				
- 18-49 years old	504 (92.8)	39 (7.2)		
- 50-69 years old	342 (77.9)	97 (22.1)	2.81 (1.94-4.08)	<0.001
- ≥ 70 years old	42 (63.6)	24 (36.4)	4.97 (2.99-8.27)	<0.001
Sex				
- Female	502 (88.7)	64 (11.3)		
- Male	386 (80.1)	96 (19.9)	1.65 (1.20-2.27)	<0.001
Hypertension				
- No	546 (88.2)	73 (11.8)		
- Yes	342 (79.7)	87 (20.3)	1.53 (1.12-2.09)	0.01
Diabetes Mellitus				
- No	666 (87.1)	99 (12.9)		
- Yes	222 (78.4)	61 (21.6)	1.48 (1.08-2.04)	0.02
Heart Disease				
- No	761 (86.2)	122 (13.8)		
- Yes	127 (77.0)	38 (23.0)	1.42 (0.99-2.05)	0.06
COPD				
- No	885 (84.9)	157 (15.1)		
- Yes	3 (50.0)	3 (50.0)	4.64 (1.48-14.57)	0.01
Pulmonary tuberculosis				
- No	860 (85.5)	146 (14.5)		
- Yes	28 (66.7)	14 (33.3)	1.85 (1.07-3.21)	0.03
CKD				
- No	839 (85.9)	138 (14.1)		
- Yes	49 (69.0)	22 (31.0)	2.20 (1.40-3.44)	<0.001
Nausea-Vomiting				
- No	564 (87.6)	80 (12.4)		
- Yes	324 (80.2)	80 (19.8)	1.40 (1.03-1.91)	0.03
Fatigue				
- No	501 (91.4)	47 (8.6)		
- Yes	387 (77.4)	113 (22.6)	2.72 (1.94-3.83)	<0.001
Dyspnea				
- No	555 (92.7)	42 (7.3)		
- Yes	353 (74.9)	118 (25.1)	3.32 (2.34-4.73)	<0.001
Altered Mental Status				
- No	884 (85.5)	150 (14.5)		
- Yes	4 (28.6)	10 (71.4)	7.74 (4.07-14.71)	<0.001
NLR ≥ 5.8				
- No	655 (93.6)	45 (6.4)		
- Yes	233 (67.0)	115 (33.0)	5.65 (4.00-7.80)	<0.001
Severe-Critical condition**				
- No	535 (94.9)	29 (2.1)		
- Yes	353 (72.9)	131 (27.1)	4.93 (3.30-7.37)	<0.001

*Variables with p<0.25 were selected for the multivariate analysis, HR: hazard risk, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, NLR: Neutrophil-lymphocyte ratio.
**Severe-Critical condition criteria were based on the COVID-19 severity upon admission, we categorized mild-moderate COVID-19 as no, while severe-critical COVID-19 as yes.

after adjustment.

COPD was also already known to be related to COVID-19 mortality, which was possibly linked to the underlying disruption in the bronchial epithelial cells resulting in increased expression of Angiotensin-converting enzyme-2 (ACE-2). When the spike protein of SARS-CoV-2 binds to the ACE-2, it increases the tissue damage due to an increase in pro-inflammatory effects.[20,21]

Fatigue and dyspnea were other predictors of mortality in our study. The information can

Table 3. Multivariate cox regression analysis of variables that were significantly different between survivors and non-survivors.

	Hazard Ratio	95% CI	p-value
Age ≥ 70 years old	2.64	1.56-4.45	<0.001
Age 50-69 years old	1.58	1.07-2.32	<0.001
CKD	1.61	1.02-2.54	0.04
COPD	3.11	1.00-9.86	0.05
Fatigue	2.12	1.50-3.00	<0.001
Dyspnea	1.55	1.06-2.27	0.02
Altered mental status	2.46	1.28-4.76	0.01
NLR ≥ 5.8	3.38	2.35-4.85	<0.001
Severity: Severe-Critical condition	2.31	1.48-3.60	<0.001

*HR: hazard risk, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, NLR: Neutrophil-lymphocyte ratio.

Table 4. The COVID-19 mortality score for predicting mortality in hospitalized patients.

Components	Category	Points
Age	≥ 70 years old	2
	50-69 years old	1
	18-49 years old	0
CKD	Yes	1
	No	0
COPD	Yes	1
	No	0
Fatigue	Yes	2
	No	0
Dyspnea	Yes	1
	No	0
Altered mental status	Yes	1
	No	0
NLR ≥ 5.8	Yes	3
	No	0
Severity: Severe-Critical condition	Yes	2
	No	0

*COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, NLR: Neutrophil-lymphocyte ratio

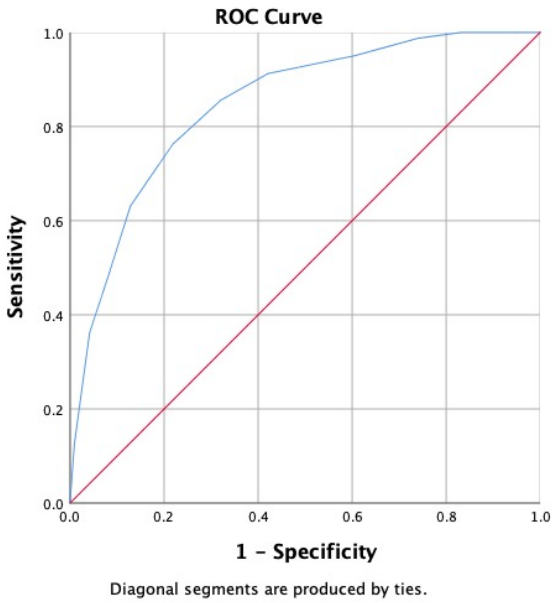

Figure 2. Receiver operating characteristic curve (ROC) for prediction of mortality in hospitalized COVID-19 patients

be easily obtained from history taking. A meta-analysis study done by He et al, presented that dyspnea (Odds Ratio [OR] 6.2, 95% CI 3.6–10.6) and fatigue (OR 2.1, 95% CI 1.3–3.3) were the main difference between mild and severe COVID-19.[22] Previous study also suggested that dyspnea (OR 4.52, 95% CI 3.15, 6.48) and fatigue (OR 1.27, 95% CI 1.09, 1.48) were significantly related to increase in mortality of COVID-19 patients.[23] Not only does the virus affect lungs, but it is also hypothesized that the virus can invade the skeletal muscle leading to fatigue. In addition, SARS-CoV-2 is known to affect the central nervous system, including decreasing neurotransmitters such as dopamine and serotonin.[24]

Overall score of Glasgow Coma Scale (GCS) of less than 15 is also one of the predictors of mortality in our study, a finding that is supported by a previous study.[25] The most common neurological symptom of COVID-19 patients is altered mental status. Several hypotheses stated that it may be related to the severity of the disease itself or due to the direct injury of the brain.[25,26] After adjustment of the comorbidities and severity in our study, altered mental status was still an independent predictor of mortality during hospitalization.

Two meta-analyses showed that NLR was a significant predictor of disease severity and mortality.[27,28] Increase in NLR on admission is known to be independently related to COVID-19 mortality. Prior to COVID-19 pandemic, NLR was known to be a predictor of systemic inflammation in several diseases, including cardiovascular diseases and acute pancreatitis.[27] It is hypothesized that in COVID-19, there was more excessive immune response, consequently decreasing the circulating lymphocyte and increasing the gap between neutrophil and

lymphocytes count. In addition, viral infection may also increase the neutrophil by increasing pro-inflammatory markers, such as interleukin-6 (IL-6).[28] Compared to another inflammatory marker, such as C-reactive protein (CRP), NLR may be a more accessible biomarker in low-middle-income countries.

Severe and critical conditions of COVID-19 patients were also related to mortality. Patients who required oxygen supplementation during hospitalization were associated with respiratory distress, indicating pulmonary inflammation. The immune system tries to eliminate the virus resulting in damage of the epithelial cells of the lungs and can lead to prolonged inflammation.[29] The overdrive immune system also contributes to cytokine storm of which there were a large number of proinflammatory cytokines, especially IL-6, leading to more injury to the lungs.[30] Prolonged inflammation occurs in the lung and other organs, such as blood vessels, heart, and kidney, therefore leading to many complications and increased mortality rate.

The AUC of this prognostic scoring system suggested that the model will be able to predict mortality during hospitalization of COVID-19 patients with 84.7% certainty. A patient with score of 7 or higher had 55% 7-day mortality rate. Moreover, the 14-day mortality rate was higher (73%). Despite having several missing data, the result of the missing data compared with the total patients was not statistically significant.

Due to the growing number of new confirmed case of COVID-19 and potential intensive care bed shortage, we proposed an algorithm for healthcare worker's use. First, physicians may follow local guideline related to patient's criteria for Intensive Care Unit (ICU) transfer. Second, physicians may stratify the mortality risk of each patient using the established prognostic scoring system. Patients with lower mortality risk may be prioritized to be transferred to the ICU. Identifying the population at risk of mortality during hospitalization since their first admission is important to allocate the healthcare resources and educate the family members regarding the prognosis of the patients.

The strength of this scoring system is that it has an AUC of 0.85, which was higher than that of other prognostic scoring system.[8,31] In addition, this prognostic scoring system was based on history taking, physical examination, and easily measurable blood test. Thus, it can be widely applicable in low-middle income countries as these countries are still trying to catch up with the COVID-19 vaccination program. The data in this study were collected from five COVID-19 referral centers in Indonesia. Therefore, there is possibility of inclusion of a wider range of population groups, which may subsequently increase the generalizability of the study. This prognostic scoring system may be used in clinical practice depending on the relevant clinical condition of cases with viral variants spread at certain point of time. An external validation study is still needed to ensure the performance of this scoring system.

CONCLUSION

Components of history taking, physical examination, and simple blood tests can be used to predict the risk for mortality of hospitalized COVID-19 patients. The components include age, underlying CKD, COPD, fatigue, dyspnea, altered mental status, NLR ≥ 5.8, and severe-critical COVID-19. The result of this practical prognostic scoring system may be a guide to decision making of physicians and help in the education of family members related to the possible outcome of the patient.

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CONFLICT OF INTERESTS

All authors declare that there is no conflict of interests.

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