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Modified COVID-19 Mortality Scoring as a Mortality Prognostic in COVID-19 Patients

Rahmadani Puji Lestari[1], B. Hangga Harinawantara[1], Khoironi Rachmad Damarjati[1], and Purwadi Sujalmo[1]

[1] Universitas Gadjah Mada Academic Hospital
*Correspondence: rahmadanipujilestari@gmail.com

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Abstract

Background: The number of patients infected with COVID-19 was increasing. The COVID-19 clinical presentation varies from asymptomatic, mild, moderate, severe, and critical. Mortality rates increase with morbidity and disease severity. This study aimed to develop a prognostic intrahospital mortality scoring named "Modified COVID-19 Mortality Scoring".

Methods: A retrospective cohort study was conducted on COVID-19 inpatients at the UGM Academic Hospital during November 2020-March 2021. Data were obtained from electronic medical records. Clinical and laboratory parameters were taken at the time of admission.

Results: The study involved 413 patients, including 50 subjects who died from COVID-19 and 363 survivors. The final stage of multivariate analysis resulted in some variables; age≥55 years, history of stroke, qSOFA score≥2, d-dimer≥1500 ng/mL, absolute neutrophil count (ANC)≥5,000 cells/uL, and absolute lymphocyte count (ALC)<1,000 cells /uL affected intrahospital mortality (p<0.050). In the scoring model, the d-dimer≥1500 ng/mL was worth 2 points, and each remaining variable was worth 1 point. The score had a strong predictive ability with an area under the ROC curve, 0.814(95%CI=0.757–0.871). The sensitivity and specificity of the score was 76%, with a cutoff point score of 3, an OR of 10,357 (95%CI=5.179-20,710, p=0.000). Moreover, the probability scores of 3, 4,5,6,7 were 18%, 33%, 53%, 72%, and 85%.

Conclusion: The existence of a scoring system is expected to help identify COVID-19 inpatients who have a higher risk of death so that stricter monitoring and early intervention can be carried out.

Keywords: *COVID-19, Indonesia, intrahospital mortality scoring, prognostic.*

1. Introduction

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus and has become a pandemic since early 2020. It has widespread clinical presentations, with respiratory symptoms being the majority of complaints. [1,2] At the beginning of its existence, about 18,5% of adult patients developed severe diseases characterized by hypoxemic pneumonia with a case fatality rate of 3,4-11%. [3,4] Recently, the appearance of some SARS-CoV-2 variants has been linked to the increasing frequency of severe diseases. Despite causing severe pneumonia, COVID-19 is also related to systemic thrombosis affecting the cardiovascular system and increasing mortality and morbidity of the patients. [5,6]

Indonesia had faced its nightmare of COVID-19 pandemic with the second wave of cases in the middle of 2021 for more than fifty thousand cases per day and more than one thousand deaths per day. [7] A surge of cases will make the health resource-limited. Thus, the patient management

system must be more efficient to suppress the death toll. [8,9] Determining the patient's prognosis early at admission could help the patients' management be more efficient to increase the health system's resilience.[10]

Several prognostic scoring systems have been developed to predict the mortality of COVID-19 patients. Intensivists in Italy developed the Brescia COVID-19 Respiratory Severity Scale (BRCSS), and clinicians in the United States created the quick COVID-19 Severity Index (qCSI) to help in the decision-making of the patients' management.[11,12] Both of them showed good performance in predicting ICU admission. [13] A previously well-known score, the sequential organ failure assessment (SOFA) score, has also been used. The decrease of Serial SOFA score is associated with survival.[14] Chinese researchers have modified it into a COVID-19 mortality score to predict 30-day outcomes in hospitalized patients.[15] Accordingly, none of the prognostic scoring systems above was validated with the Indonesian population.

Although several prognostic systems have been developed, the prognostic parameters being used contain moderate to advanced clinical indicators that could not be applied in all resource settings in Indonesia. A simpler prognostic scoring system must be developed and validated for the Indonesian population and health system settings. It makes us eager to develop a modified COVID-19 mortality scoring that is feasible for the Indonesian clinical setting and helps in the decision-making of the clinicians and patients.

2. Methods

The researchers did an observational analytic retrospective cohort study. The research included 413 patients, 363 alive patients, and 50 passed away patients, aged more than 18 years old, who were admitted to the academic hospital of UGM from November 2020-March 2021. Moreover, the researchers excluded patients whose medical records were incomplete, and the main diagnosis was not COVID-19, like asymptomatic COVID-19 in pregnant women, fracture with COVID-19 coincident, etc.

Data from medical records were baseline characteristics of research subjects, blood laboratory at admission, and history of previous chronic diseases. Examples are such as diabetes mellitus, hypertension, and heart disease. Data of quick-SOFA (qSOFA) scores was obtained at the beginning of hospitalization. qSOFA were given each of 1 point if the conditions of GCS < 15, respiratory rate > 22, and systolic blood pressure < 100. The outcome data sought was intrahospital patient mortality.

The different proportions of categorical data were analyzed using the Chi-square test. Fisher's alternative test was used if there was an expected value of less than five exceeding 20% of the number of cells. The proportions of numerical data were analyzed using the Mann-Whitney U test and then converted into categorical data. The significantly different variables were then included in the multivariate logistic regression analysis using the backward stepwise method with a statistical significance of $p<0.10$. The last step of logistic regression analysis was used to obtain a prognostic model as the basis for determining the parameters of the "Modified COVID-19 Mortality Scoring". The predictive ability of this score was assessed using ROC analysis. As a result, the difference is considered significant if the p-value <0.05.

3. Results

Table 1 showed the baseline characteristics of the patients. The mean age of the study subjects in both groups was 54±14 years, with the mean age in the dead group being higher than the survivors (62.3 ± 10.9 and 52.7 ± 14.5 years; *p*=0.000). Male gender was higher in the non-survivor (54%) and survivors (57.6%) groups, although the result was not significantly different (*p*=0.632). For previous/comorbid diseases, hypertension and heart disease (congestive heart failure, coronary heart disease, valvular heart disease, and arrhythmias) did not differ between the survivors and dead groups (*p*=0.861 and *p*=0.188). The comorbidities that influenced the intrahospital mortality in the bivariate analysis included diabetes mellitus (*p*=0.019), stroke (*p*=0.001), and stage 5 of chronic kidney disease (CKD) (*p*=0.033). Clinical conditions based on the qSOFA score ≥ 2 had a difference in the proportion of intrahospital mortality outcomes in bivariate analysis (*p*=0.023). Several laboratory parameters were also significantly different between the dead and survivor groups, the increase of CRP ≥ 6 mg/L (*p*=0.002), leukocytosis (AL ≥ 11,000 cells/uL) (*p*=0.000), anemia (Hb<11 g/dL) (*p*=0.005), neutrophilia (absolute neutrophil count/ANC ≥ 5,000 cells/uL) (*p*=0.000), and lymphopenia (absolute lymphocyte count/ALC <1,000 cells/uL) (*p*=0.000). There was also an increase in values that exceeded the mean of the two groups in the NLR variables ($\bar{X}$=5.2 ± 6.1, cut off 5.0) and d-dimer ($\bar{X}$=1,436 ± 1,957, cut off point 1,500 ng/mL) which showed a statistically significant difference in the dead group compared to survivors (*p*<0.050). Meanwhile, the amount of albumin was below the mean of both groups ($\bar{X}$=3.7 ± 0.52 g/dL). It affected the difference in the outcome of intrahospital mortality between the two groups (*p*=0.000) (Table 1).

Table 1 Baseline Characteristics

Variable	Non-survivor (n=50)	Survivor (n=363)	*p*-value*
Age (mean, years old)	62.3 ± 10.9	52.7 ± 14.5	0.000
≥ 55	39 (78)	177 (48.8)	0.000
< 55	11 (22)	186 (51.2)	
Sex (n,%)			0.632
Male	27 (54)	209 (57.6)	
Female	23 (46)	154 (42.4)	
Diabetes mellitus (n, %)	16 (32)	65 (17.9)	0.019
Hypertension (n, %)	14 (28)	106 (29.2)	0.861
Stroke (n, %)	7 (14)	8 (2.2)	0.001#
Heart disease (n, %)	7 (14)	30 (8.3)	0.188#
Chronic Kidney Disease stage 5 (n, %)	4 (8)	7 (1.9)	0.033#

CRP (mg/L) (n,%)			0.002
≥ 6	47 (94)	270 (74.4)	
< 6	3 (6)	93 (25.6)	
qSOFAscore (n,%)			0.023#
≥ 2	4 (8)	6 (1.7)	
< 2	46 (92)	357 (98.3)	
Leucocyte count (mean, cell/uL)	11.1 ± 6.6	7.5 ± 3.3	0.000
≥ 11,000	18 (36)	39 (10.7)	0.000
< 11,000	32 (64)	324 (89.3)	
Hemoglobin (mean, g/dL)	12.5 ± 2.5	13.6 ± 2.1	0.005
<11	13 (26)	36 (9.9)	0.001
≥11	37 (74)	327 (90.1)	
Thrombocyte count (mean, cell/uL)	254.6 ± 120.2	264.8 ± 102.8	0.290
<150,000	7 (14)	30 (8.3)	0.188#
≥150,000	43 (86)	333 (91.7)	
Netrophil (mean, sel/uL)	9,174 ± 6,170.8	5,409.1 ± 3,366.7	0.000
≥ 5,000	37 (74)	152 (41.9)	0.000
< 5,000	13 (26)	211 (58.1)	
Lymphocyte (mean, sel/uL)	1,211±728	1,531 ± 681	0.000
<1,000	22 (44)	75 (20.7)	0.000
≥ 1,000	28 (56)	288 (79.3)	
NLR (mean)	11.2 ± 11.7	4.4 ± 4.3	0.000
≥ 5.00	31 (62)	98 (27)	0.000
< 5.00	19 (38)	265 (73)	
Albumin (mean, g/dL)	3.2 ± 0.6	3.8 ± 0.5	0.000
<3.7	38 (76)	142 (39.1)	0.000
≥3.7	12 (24)	221 (60.9)	
INR (mean)	1.1 ± 0.4	1.0 ± 0.2	0.000
<1.2	44 (88)	341 (93.9)	0.004
1.2-1.4	2 (4)	18 (5)	
>1.4	4 (8)	4 (1.1)	

D-dimer (mean, ng/mL)	2,511.3 ± 2,590.0	1,288.9 ± 1,809.1	0.000
≥ 1500	28 (56)	78 (21.5)	0.000
< 1500	22 (44)	285 (78.5)	

The superscript ***** denotes *Chi-square* test for categorical data and *Mann whitney test* for numerical data. While the superscript # showed the useage of Fischer-exact test.

Tabel 2 Final stage of multivariate analysis

Variable	*p-value*	OR	95% CI.	
			Upper range	Lower range
Age≥ 55 years old	0.007	2.868	1.329	6.190
History of stroke	0.012	4.267	1.368	13.309
qSOFA score ≥ 2	0.039	4.422	1.079	18.126
D-dimer ≥1500 ng/mL	0.000	3.473	1.775	6.797
ANC ≥ 5,000 sel/uL	0.006	2.729	1.334	5.585
ALC <1,000 sel/uL	0.005	2.661	1.350	5.244

Table 2 showed six variables which remained statistically significant in the final stage of multivariate analysis. (OR: odds ratio, CI: confidence interval)

Tabel 3 Conversion to a scoring system

Variable	B	S.E.	B/S.E.	(B/S.E.) : 2.065	Scoring simplification
Age≥ 55 y.o.	1.054	0.392	2.685	1.300	1
History of stroke	1.451	0.580	2.500	1.211	1
qSOFA score ≥ 2	1.487	0.720	2.065	1.000	1
D-dimer ≥1500 ng/mL	1.245	0.343	3.634	1.760	2
ANC ≥ 5,000	1.004	0.365	2.748	1.331	1
ALC <1,000	0.979	0.346	2.826	1.369	1

B is the unstandardized regression weight and S.E. is the standard error. Due to the lowest number of B/S.E. is 2.065, all variables are divided by this constant to point the score of each variable.

Variables that had statistical significance in the bivariate analysis were continued to multivariate logistic regression analysis. It was processed with backward stepwise method. In contrast, the variables whose statistical significance of $p<0.10$ were continued to the next stage. In the final stage (table 2), six variables remained statistically significant. The data included their age ≥55 years old (p = 0.007, OR = 2.868), stroke (p = 0.012, OR = 4.267), qSOFA score ≥ 2 (p = 0.039, OR= 4.422), d-dimer ≥ 1500 ng/mL (p=0.000, OR=3.473), ANC ≥ 5,000 cells/uL (p=0.006, OR=2.729), and ALC <1,000 cells/uL (p= 0.005, OR= 2.661).

The next step was to convert it into a scoring system. It was according to table 3 with the final results including the scores for each variable age ≥ 55 years (1 point), stroke (1 point), qSOFA

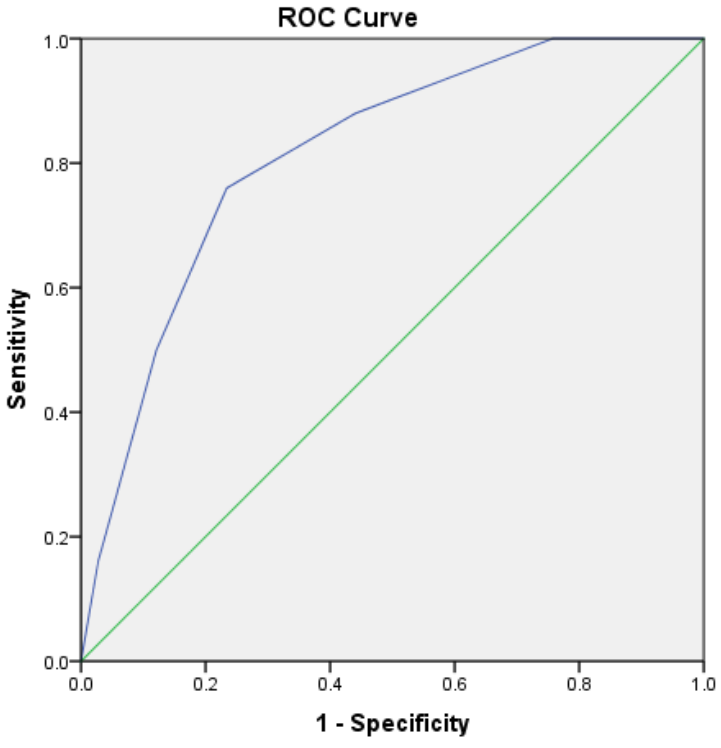
score ≥ 2 (1 point), d-dimer ≥1500 ng /mL (2 points), ANC ≥5,000 cells/uL (1 point), and ALC <1,000 cells/uL (1 point). With this scoring model, the Hosmer-Lemeshow test in logistic regression analysis obtained *p*=0.308. It indicates a good scoring calibration aspect (*p*>0.05). The result means that the score discrimination value is strong. It is because the area under the ROC curve is 0.814 (95% CI=0.757 – 0.871) (figure 1).

Table 4 Sensitivity and specificity based on each score

Score	Probability	Sensitivity	Specificity
0	1.78%	1.000	0.000
1	4.00%	1.000	0.242
2	8.73%	0.880	0.559
3	18.02%	0.760	0.766
4	33.56%	0.500	0.879
5	53.72%	0.160	0.972
6	72.73%	0.000	1.000
7	85.97%	0.000	1.000

The equal sensitivity and specificity best predict in total score of 3.

Figure 1. ROC curve



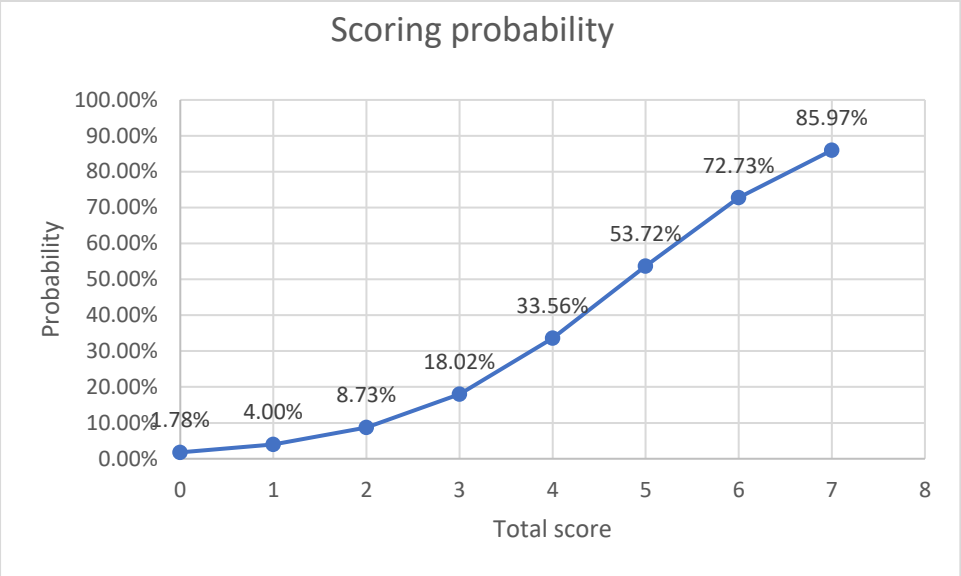
Diagonal segments are produced by ties.

The area under the ROC curve is 0.814 (95% CI=0.757 – 0.871)

Based on table 4, the score of ≥3 has the best sensitivity and specificity (76%). It was chosen as the cutoff point for subjects who had a poor prognosis in the form of intrahospital mortality

with a probability of 18%. As a result, the probability of intrahospital death increases as the "Modified COVID-19 Mortality Scoring" parameter increases (figure 2).

Figure 2. Scoring probability



Higher scoring shows higher probability of mortality

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4. Discussion

The researchers aimed to develop system scoring which combined clinical conditions and simple lab parameters. Furthermore, it was found that each variable of age≥ 55 years old, history of stroke, qSOFA score ≥2, ANC ≥5,000 cells/uL, and ALC <1,000 cells/uL contributed one point in "Modified COVID-19 Mortality Scoring". Moreover, the d-dimer level of 1500 ng/mL gave two points.

Elder age, which affected the mortality due to COVID-19, was similar to a previous study conducted in Indonesia which found the average age of patients who died from COVID 19 was 55 years, with the risk of death increased threefold in patients aged ≥50 years.[16] In a multi-centered study with the largest subjects in Indonesia, the mean age of dead group due to COVID-19 was 58 years, and the percentage increased proportionally to the age: 17% aged 50–59; 22% aged 60–69; and 34% for age ≥70 years.[17]

In this study, various previous medical histories, hypertension and heart disease (CHD, CHF, valvular heart disease, and arrhythmia), DM, and stage 5 CKD did not differ between the survivors and the dead. Only a history of stroke remained statistically significant in the multivariate analysis and contributed one point to the score. It was different from other studies conducted in Indonesia and found that hypertension, diabetes, and CKD increased mortality risk from COVID-19.[17] This difference might be due to a "silent" disease that may have been suffered but hadn't been detected yet, causing bias.

The clinical parameter quick SOFA score (qSOFA) was developed to screen patients with suspected sepsis as a substitute for Sequential [Sepsis-related] Organ Failure Assessment (SOFA) in facilities which did not routinely check SOFA components such as bilirubin, blood gas analysis, and kidney function (urea and creatinine). qSOFA parameters include changes in mental status, systolic blood pressure≤100 mmHg, and

respiratory rate ≥22 breaths/minute. Each parameter was accounted for 1 point with a total range score of 0-3. Research by Liu et al. found that a qSOFA score≥ 1 was associated with mortality in patients with severe COVID-19 symptoms (AUC: 0.742, 95% CI 0.657–0.816) although its use was still inferior to a SOFA score 3 (AUC: 0.890 (95% CI: 0.826–0.955).[18] It is consistent with this study which found that an increase in qSOFA contributed to COVID-19 mortality.

A meta-analysis study showed the effect of lymphopenia on admission to COVID-19 disease progression (OR 4.2; 95%CI: 3.46-5.09) and mortality (OR 3.71; 95%CI, 1.63-8.44). Neutrophilia was also found to have a significant effect on the progression of COVID-19 severity (OR 7.99; 95%CI, 1.77-36.14) and mortality (OR, 7.87; 95%CI: 1.75-35.35).[19] In this research, lymphopenia (ALC <1,000 cells/uL) and neutrophilia (ANC≥ 5,000 cells/Ul) play a role in increasing the risk of COVID-19 mortality. In addition, d-dimer levels ≥1,500 ng/mL also contributed 2 points to the risk of COVID-19 mortality. It is in line with the results of a study that found that an increase in d-dimer levels affected mortality in COVID-19 patients with a ROC curve area of 0.807 (95% CI). 0.728–0.886, p<0.001). Also, it had the most optimal cut-off point was 1,500 ng/mL (sensitivity 70.6%, specificity 78.4%) (20).

Many scoring systems had been developed to predict COVID-19 mortality with clinical settings abroad.[15,21,22] Research by Gue et al., the initial inspiration in this study, used simple parameters of age ≥ 75 years, male gender, and a modified sepsis-induced coagulopathy (mSIC) score consisting of the International Normalized Ratio (INR), platelet count, and qSOFA score. This score looked at the risk of death from COVID-19 in the next discrimination area under the ROC curve was 0.7933 (95% CI 0.745–0.841), and the cutoff point score ≥ 4 had an odds ratio of 7.6 for the next 30 days with a sensitivity of 78.36% and specificity 67.59%.[15] The scores had strong discrimination, but the validity was reduced when applied in Indonesia. It was because of the lower life expectancy, which was less than 75 years, referring to the data from the world bank.[23]. In this study, the age that affected the mortality outcome was ≥55 years old, while gender, INR, and platelet counts did not significantly differ.

At the beginning of admission, another study used age, NLR, d-dimer, and CRP level (ANDC score) data to predict COVID-19 mortality. This scoring result was in good discrimination with an area. It was below the ROC of 0.921 (95% CI 0.835–0.968). Based on the total ANDC score obtained, patients were categorized into three probabilities, that are low risk of death <5% (ANDC score <59), moderate risk (59 ≤ANDC≥ 101), 5-50%, and high risk of death (ANDC>101) more than 50%.[24]. This score was quite good, but the nomogram was not very familiar for some health workers in Indonesia.

Similar study was conducted in Jakarta, Indonesia which found that ages ≥70 years old, previous medical histories of CKD and Chronic Obstructive Pulmonary Disease (COPD), symptoms of fatigue and dyspnea, altered mental status, NLR≥ 5.8 and severe-critical condition were contributed for predicting mortality in hospitalized patients. Total score of 7 or higher had 55% 7-day mortality rate and the 14-day mortality rate was higher (73%).[25]

This study tried to develop a scoring parameter to predict the mortality risk of COVID-19 patients by using clinical conditions at the time of initial admission and simple laboratory clinical findings with a clinical setting in Yogyakarta,

Indonesia. This study did not consider the onset at admission, the history of previous therapy, the comorbidities recently detected during admission, and the changes of laboratory parameters as long as the disease progressed. The CRP parameters used were only qualitative, so it might underestimate the effect of CRP level. The research method was also carried out retrospectively, leading to bias by knowing the outcome of alive/dead patients. The number of patient samples was also small and only involved our center, requiring independent external validation.

5. Conclusion

The "Modified COVID-19 Mortality Scoring" system was expected to predict the outcome of COVID-19 inpatients to know whether they were at a higher risk of death so that stricter and earlier monitoring could be carried out. This is the first clinical scoring system which developed based on local population in Yogyakarta, Indonesia. This scoring system has potential, but further research is still needed to test its validity to be used more widely.

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