Original Article

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Soetomo COVID-19 Prognostic Score: A Multi-Parametric Model for Early Prediction of Disease Severity of COVID-19 in Tertiery -Resource Hospital

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Abstract:

Objective: Coronavirus disease 2019 (COVID-19) became a global pandemic, with high mortality in severely ill patients. This study aimed to develop a novel scoring system to prognosticate disease severity in COVID-19 patients that is effective and widely available in tertiary medical resource settings.

Material and Methods: Laboratory-confirmed COVID-19 patients were enrolled in this retrospective cohort, divided into severe and non-severe groups. We randomly assigned 70% of the subjects to establish a novel scoring system, while the remaining 30% was used for internal validation. The model was constructed by multivariate logistic regression using the first clinical, laboratory, and radiological finding of statistically analysis of group patients. receiver operating characteristic (ROC) and cross-tabulation were used to evaluate the performance of our score and compare it with other models.

Results: A total of 599 patients were included. The Soetomo COVID-19 prognostic score predictors included age, fever, specific comorbidities (diabetes, hypertension, cardiac disease, lung tuberculosis), respiratory rate, heart rate, SF ratio, whole blood cell (WBC) count, neutrophil lympocyte ratio (NLR), blood urea nitrogen (BUN), and a RALE score. The area under the ROC of the model indicated an excellent discriminatory ability (training datasets 0.715 [95% CI 0.664-

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0.767, p-value<0.001]; testing datasets 0.720 [95% CI 0.638-0.802, p-value<0.001]). Our scoring system was superior to both qSOFA and MEWS regarding predictive value. The sensitivity and specificity were 60.6% and 82.5%, respectively. **Conclusion:** The developed scoring system accurately predicted a significant proportion of severe disease in COVID-19 patients.

Keywords: COVID-19, human and health, prognostic model, scoring system

Introduction

The coronavirus disease 2019 (COVID-19), quickly became a serious threat worldwide following its appearance in 2020. The World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic in March 2020. In early 2021, over 98.2 million confirmed cases and over 2.1 million deaths were recorded as the global cumulative COVID-19 impact[1]. On January 26, 2021, Indonesia surpassed 1 million confirmed cases after reporting 13,094 new cases in that month. The number of new cases and confirmed COVID-19 deaths continued to rise in the following months[2].

Most patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection presented with mild symptoms such as fever and cough. However, 14% of the patients experienced severe pneumonia, and 5% rapidly progressed to critical illness, including acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation disorders. COVID-19 patients with severe and critical manifestations had poor prognoses and high mortality[3,4]. The differences in clinical characteristics, comorbidities, and healthcare resources significantly affected the clinical progression and management of COVID-19 in low and middle-income countries. In Indonesia, the prevalence of COVID-19 patients immediately admitted to the intensive care unit (ICU) was 3%, while 2% of the patients were recorded to require immediate endotracheal intubation. Despite that, the proportion of immediate ICU admission of the total number of deceased patients was only 16%[5]. Many people had difficulties accessing equal healthcare services due to low resources and a poor health system[6].

Even though the COVID-19 patients with the most incredible case-fatality rates in the European population had cardiac illnesses (25.7%), diabetes (15.5%), and malignancies (9.9%), the European Surveillance System has noticed this through the use of population data[7]. Moreover, while earlier systematic reviews evaluated several clinical indicators or comorbidities on their own, they didn't include age or gender-adjusted analyses or patient setting stratifications. A meta-analysis of pooled age-adjusted estimates from available cohort studies was done to identify which comorbidities should place patients in the high-risk group for adverse COVID-19 outcomes because death from COVID-19 is substantially highly associated older age with comorbidities. Additionally, the most recent scientific research about the dangers of COVID-19 should be regularly evaluated when new SARS-CoV-2 variants appear. For instance, the WHO designated the most recent version Omicron (B1.1.529), as a variant of concern on November 26, 2021[8], which caused severe pneumonia in young patients even without high-risk factors[9].

A SARS-CoV-2 infection may exacerbate poorly managed chronic comorbidities and worsen the patient's clinical progression. Hence, there is an urgent need to manage limited resources to maximize healthcare services and resolve unmet medical demands. The critical predictive factors to prognosticate COVID-19 severity remain unclear.

In this study, we developed a novel scoring system to predict severe clinical progression in COVID-19 patients in tertiary teaching hospitals based on data collected on the first day of admission. This scoring system is the first prognostic model using parameters widely available in the hospital with limited resources. In a situation with tertiary medical resources, the study sought to create a novel scoring system to prognosticate illness severity of COVID-19. The authors hope this further studies research can expand to more patients are needed and produce methods that can be applied to almost the same case model's research.

Material and Methods

Study population

We included 599 hospitalized adult patients with laboratory-confirmed diagnoses of COVID-19 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, between March 2, 2020, and August 20, 2020. 70% of the cases (439 subjects) were randomly assigned to the training dataset, and 30% (160 subjects) were in the testing dataset. The study collected data from medical records, electronic laboratory information system, and radiology installations in the same hospital. The Ethics Committee of Dr. Soetomo General Academic Hospital approved the study. Informed consent was not required as the study design was retrospective and did not involve patient privacy.

The diagnosis of COVID-19 was based on the prevention and control guideline of COVID-19 by the Indonesian Ministry of Health[10]. The laboratory-confirmed diagnosis followed a positive result from a reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay using a nasopharyngeal or oropharyngeal swab and sputum specimen. The study participants were classified into two groups based on the severity: patients with severe disease and those with non-severe disease. Severe disease was defined as COVID-19 patients with one or more of the following conditions: respiratory distress with RR >30/min; blood oxygen saturation <93%; acute respiratory distress syndrome (ARDS); respiratory failure requiring mechanical ventilation; sepsis; septic shock; or other organ failures needing intensive care in the ICU. Participants with none of these conditions were classified into the non-severe group. The exclusion criteria were patients with severe disease in the first examination[6].

Data collection

The data used in this study were the first in-hospital results. Clinical indicators were collected, including age 40 years until more than 65 years (40 to ≥65), gender, presenting symptoms (fever, cough, expectoration, rhinorrhea, nasal congestion, anosmia, headache, fatigue, dyspnea, diarrhea, nausea or vomiting, abdominal pain), pre-existing comorbidities (diabetes, hypertension, cardiac disease, COPD, asthma, lung tuberculosis, CKD, cancer), vital signs (temperature, RR, HR, systole, diastole, MAP, GCS), and the ratio of oxygen saturation to a fraction of inspired oxygen (SF ratio). The following laboratory results were extracted; hemoglobin (Hb), white blood cell count (WBC), the ratio of neutrophils to lymphocytes (NLR), platelet count (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (Alb), blood urea nitrogen (BUN), creatinine (Cr), the ratio of arterial oxygen partial pressure to a fraction of inspired oxygen (PF ratio), serum sodium (Na), serum potassium (K), and serum chloride (Cl). Based on the clinical judgment and limited resources of a Computed Tomography (CT) scan, a chest X-ray was employed to evaluate the severity of pneumonia The Radiographic Assessment of Lung Edema score proposed by Warren et al. was used to quantify the extent of consolidation[11]. A score of 0-4 was assigned to each lung (0=no involvement; 1≤25% involvement; 2=25–50% involvement; 3=50–75% involvement; 4≥75% involvement). The scores for each lung were summed to produce the final chest X-ray severity score. The score was analyzed

retrospectively and independently by three radiologists blinded to the diagnosis and other clinical data.

Statistical analysis

Continuous variables are expressed as means with standard deviations. Categorical variables are expressed as the number of frequencies in each group. The training datasets were initially analyzed to establish the novel scoring system as a model for prognosticating disease severity. Interclass correlation coefficient (ICC) analysis was performed to assess the reliability of the RALE score observed by three independent radiologists. We used the independent T-test to evaluate continuous data, and the chi-square test was used for categorical data. Variables associated with severe disease in univariate analysis were further analyzed using multivariate logistic regression with a backward stepwise selection method to identify independent risk factors. We selected the components of our multi-parametric model by the regression results and the authors' consideration. ROC curve analysis was performed to select continuous parameters to derive cut-off values for convenient use of the model. The odds ratio in the multivariate analysis estimated point allocation for each predictor. We determined the optimal cut-off point of the developed scoring system by cross-tabulation in the training datasets.

The authors conducted internal validation by calculating the novel score in the testing datasets to further assess the discrimination ability for predicting disease severity. Statistical performance was measured by the area under the receiver operating characteristic curve (AUC), sensitivity, and specificity. In addition, we also calculated quick Sepsis Related Organ Failure Assessment (qSOFA) scores and Modified Early Warning Scores (MEWS) as model comparisons based on the training datasets, testing datasets, and all datasets. Patients presenting with systolic blood pressure ≤100 mmHg, respiratory rate ≥22/min, and altered mental status scored one point. Patients with infection may have a poor prognosis if they presented with a qSOFA score of ≥2[12]. The systole, heart rate, respiratory rate, temperature, and AVPU score parameters are given 0–3 points in MEWS. A previous study reported that a score of 5 or more on the MEWS scale was associated with an increased risk of clinical deterioration and death[13]. The predictive values of our scoring system, qSOFA, and MEWS were compared by assessing the AUC, sensitivity, and specificity of all three.

Results

Baseline characteristics

There were 599 patients out of 801 admissions for laboratory-confirmed COVID-19, meeting our criteria. Of these, we excluded 202 subjects due to presenting with severe illness at the first examination. The baseline characteristics of the study participants in training datasets, testing datasets, and all datasets are presented in Table 1. 439 COVID-19 patients were enrolled in the training datasets, consisting of 165 (62%) patients with severe disease and 274 (38%) patients with non-severe disease. As presented in Table 2, several parameters were associated with disease severity in the univariate analysis. The COVID-19 patients with severe manifestations were more likely to be older and present with clinical symptoms than non-severe cases, such as fever, cough, anosmia, and dyspnea. Specific comorbidities, including diabetes, hypertension, cardiac disease, and lung tuberculosis, were also significantly associated with severe disease progression. Relative to the non-severe group, progression patients to severe manifestations showed higher respiratory rate, heart rate, and systolic blood pressure.

Conversely, severely ill patients tended to have a lower SF ratio. WBC count, NLR, platelet count, AST, BUN, creatinine, and serum potassium level were the biomarkers associated with disease severity. Moreover, a significant

difference in the RALE score between the two groups was observed. As a note, a high degree of reliability in the measurements was found between the RALE scores analyzed by three independent radiologists. The average measurement ICC was 0.937 with a 95% confidence interval from 0.909 to 0.957 (F (86, 172)=15.768, p-value<0.01).

The Soetomo COVID-19 prognostic score

We performed multivariate logistic regression analysis on variables significantly associated with severe clinical progression in the patients with COVID-19. Fever, diabetes, cardiac disease, respiratory rate, SF ratio, and BUN were revealed as independent risk factors of disease severity (Table 3). These parameters were used as predictors in the scoring system, with their odds ratios used as references for determining the score points. However, the authors also incorporated age, hypertension, lung tuberculosis, heart rate, WBC count, NLR, and RALE score into the model, considering these predictors were theoretically related to disease severity. We also combined pre-existing diabetes, hypertension, cardiac disease, and lung tuberculosis into a compound comorbidity variable. We selected a cut-off value for continuous parameters to simplify the operability of the scoring system according to the ROC analysis result for each predictor (Table 4). Subsequently, the optimal cut-off point for the model was 6, determined by cross-tabulation (Table 5). The need for a high-specificity model led to selection of the cut-off point without while maintaining acceptable sensitivity good sensitivity. Finally, the Soetomo COVID-19 scoring system was finalized with scores ranging from 0 to 12 by calculating each parameter's score. Patients with scores of 0-5 were classified as at low risk of severe disease, while 6-12 were at high risk (Table 6).

Table 1 Baseline characteristics of patients in the training datasets, testing datasets, and all datasets

Variable	Training (n=439)	Testing (n=160)	All (n=599)
Symptoms			
Age (years)	50.32±14.06	51.06±14.98	50.52±14.30
Male	223 (50.8)	83 (51.9)	306 (51.1)
Female	100 (67.3)	33 (32.7)	133 (50.0)
Fever	258 (58.8)	91 (56.9)	349 (58.3)
Cough	313 (71.3)	110 (68.8)	423 (70.6)
Expectoration	108 (24.6)	38 (23.8)	136 (24.4)
Rhinorrhea	40 (9.1)	11 (6.9)	51 (8.5)
Nasal congestion	16 (3.6)	5 (3.1)	21 (3.5)
Anosmia	8 (1.8)	1 (0.6)	9 (1.5)
Pharyngalgia	55 (12.5)	21 (13.1)	76 (12.7)
Headache	25 (5.7)	4 (2.5)	29 (4.8)
Fatigue	96 (21.9)	35 (21.9)	131 (21.9)
Dyspnea	241 (54.9)	91 (56.9)	332 (55.4)
Diarrhea	43 (9.8)	14 (8.8)	57 (9.5)
Nausea or vomiting	115 (26.2)	43 (26.9)	158 (26.4)
Abdominal pain	30 (6.8)	12 (7.5)	42 (7.0)

Table 1 (Continued)

Variable	Training (n=439)	Testing (n=160)	All (n=599)
Comorbidities			
Diabetes	116 (26.4)	42 (26.3)	158 (26.4)
Hypertension	122 (27.8)	48 (30.0)	170 (28.4)
Cardiac disease	23 (5.2)	10 (6.3)	33 (5.5)
COPD	1 (0.2)	0 (0.0)	1 (0.2)
Asthma	1 (0.2)	2 (1.3)	3 (0.5)
Lung tuberculosis	21 (4.8)	2 (1.3)	23 (3.8)
Chronic kidney disease	15 (3.4)	9 (5.6)	24 (4.0)
Cancer	15 (3.4)	1 (0.6)	16 (2.7)
Physical signs			
Body temperature (°C)	36.81±0.55	36.86±0.59	36.82±0.56
RR (breaths/min)	23.23±4.16	23.68±4.64	23.35±4.30
HR (beats/min)	95.96±15.31	97.76±15.88	96.44±15.47
SBP (mmHg)	124.72±18.74	126.84±20.33	125.28±19.18
DBP (mmHg)	77.00±12.46	77.18±10.90	77.05±12.06
MAP (mmHg)	92.87±13.11	93.71±12.78	93.10±13.02
SF ratio	317.21±155.69	348.16±139.67	325.34±152.14
GCS	14.93±0.42	14.93±0.36	14.93±0.40
Laboratory workup			
Hb (g/L)	12.78±2.38	12.58±2.77	12.72±2.49
WBCs ($x10^9$/L)	10.40±7.43	10.73±6.90	10.49±7.29
NLR	7.92±7.68	10.04±14.60	8.49±10.03
PLTs ($x10^9$/L)	257.58±113.12	264.54±121.92	259.43±115.46
AST (U/L)	77.86±89.35	72.53±64.54	76.44±83.45
ALT (U/L)	62.75±68.34	60.53±60.39	62.16±66.27
Alb (g/dL)	3.47±4.04	3.18±0.39	3.39±3.47
BUN (mmol/L)	21.22±24.38	24.50±28.34	22.10±25.52
Cr (μmol/L)	1.63±2.89	1.82±2.87	1.68±2.89
Na (mEq/L)	139.07±61.15	136.71±7.53	138.44±52.45
K (mEq/L)	4.02±0.85	4.06±0.82	4.03±0.84
Cl (mEq/L)	99.05±8.72	100.01±10.42	99.30±9.20
Radiologic workup			
RALE score	4.12±2.66	4.20±2.70	4.15±2.66
Severe cases	165 (37.6)	71 (44.4)	236 (39.4)
ARDS	144 (32.8)	56 (35.0)	200 (33.4)
Mortality	144 (32.8)	59 (36.9)	203 (33.9)
ICU admission	58 (13.2)	21 (13.1)	79 (13.2)

Note: Data presented as means±standard deviation (S.D.) or n (%)
COPD=chronic obstructive pulmonary disease, RR=respiratory rate, HR=heart rate, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, SF ratio=the ratio of oxygen saturation to fraction of inspired oxygen, GCS=Glasgow coma scale, Hb=hemoglobin, WBC=white blood cell count, NLR=neutrophil-lymphocyte ratio, PLT=platelet count, AST=aspartate aminotransferase, ALT=alanine aminotransferase, Alb=albumin, BUN=blood urea nitrogen, Cr=creatinine, Na=serum sodium, K=serum potassium Cl=serum chloride, RALE score, the radiographic assessment of lung edema score, ARDS=acute respiratory distress syndrome

Table 2 Univariate analysis results in the training dataset

Variable	Non-severe disease (n=274)	Severe disease (n=165)	p-value
Symptoms			
Age (years)	47.19±14.41	55.53±11.76	<0.001
Male	134 (48.9)	89 (53.9)	0.307
Female	80 (60.15)	53 (39.85)	0.295
Fever	144 (52.6)	114 (59.1)	0.001
Cough	181 (66.1)	132 (80)	0.002
Expectoration	68 (24.8)	40 (24.2)	0.892
Rhinorrhea	21 (7.7)	19 (11.5)	0.174
Nasal congestion	8 (2.9)	8 (4.8)	0.300
Anosmia	8 (2.9)	0 (0)	0.027
Pharyngalgia	32 (11.7)	23 (13.9)	0.488
Headache	16 (5.8)	9 (5.5)	0.866
Fatigue	56 (20.4)	40 (24.2)	0.350
Dyspnea	120 (43.8)	121 (73.3)	<0.001
Diarrhea	27 (9.9)	16 (9.7)	0.957
Nausea or vomiting	67 (24.5)	48 (29.1)	0.284
Abdominal pain	20 (7.3)	10 (6.1)	0.630
Comorbidities			
Diabetes	56 (20.5)	60 (36.4)	<0.001
Hypertension	66 (24.1)	56 (33.9)	0.026
Cardiac disease	9 (3.3)	14 (8.5)	0.018
COPD	0 (0)	1 (0.6)	0.197
Asthma	1 (0.4)	0 (0)	0.437
Lung tuberculosis	6 (2.2)	15 (9.1)	0.001
Chronic kidney disease	7 (2.6)	8 (4.8)	0.200
Cancer	6 (2.2)	9 (5.5)	0.068
Physical signs			
Body temperature (°C)	36.77±0.53	36.87±0.57	0.056
RR (breaths/min)	21.78±3.21	25.64±4.45	<0.001
HR (beats/min)	92.18±12.73	102.24±17.11	<0.001
SBP (mmHg)	123.05±16.24	127.48±22.07	0.016
DBP (mmHg)	77.03±12.67	76.95±12.14	0.946
MAP (mmHg)	92.32±12.40	93.78±14.21	0.260
SF ratio	380.56±124.88	212.52±144.94	<0.001
GCS	14.93±0.40	14.93±0.46	0.981
Laboratory workup			
Hb (g/L)	12.85±2.35	12.64±2.45	0.376
WBC (x10^9/L)	9.48±5.24	11.94±9.91	0.001
NLR	6.81±7.35	9.79±7.88	<0.001
PLT (x10^9/L)	265.85±112.96	243.71±112.363	0.048
AST (U/L)	65.10±70.01	98.53±111.09	<0.001
ALT (U/L)	62.47±70.88	63.21±64.19	0.914
Alb (g/dL)	3.69±5.14	3.09±0.34	0.135

Table 2 (continued)

Variable	Non-severe disease (n=274)	Severe disease (n=165)	p-value
BUN (mmol/L)	16.69±17.87	28.49±30.91	<0.001
Cr (µmol/L)	1.38±2.45	2.02±3.46	0.029
Na (mEq/L)	141.29±77.73	135.51±7.34	0.343
K (mEq/L)	3.94±0.82	4.14±0.90	0.023
Cl (mEq/L)	99.66±9.43	98.06±7.32	0.065
Radiologic workup			
RALE score	3.66±2.56	4.9±2.64	<0.001

Note: Data presented as means±standard deviation (S.D.) or N (%)
COPD=chronic obstructive pulmonary disease, RR=respiratory rate, HR=heart rate, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, SF ratio=the ratio of oxygen saturation to fraction of inspired oxygen, GCS=Glasgow coma scale, Hb=hemoglobin, WBC=white blood cell count, NLR=neutrophil-lymphocyte ratio, PLT=platelet count, AST=aspartate aminotransferase, ALT= alanine aminotransferase Alb=albumin, BUN=blood urea nitrogen, Cr=creatinine, Na=serum sodium, K=serum potassium, Cl=serum chloride, RALE score=the radiographic assessment of lung edema score

Table 3 The logistic regression analysis for predicting disease severity

Parameter	p-value	OR (95% CI)
Age	0.076	1.027 (0.997-1.058)
Fever	0.044	2.144 (1.020-4.505)
Cough	0.782	1.132 (0.470-2.729)
Dyspnea	0.467	1.317 (0.628-2.762)
Diabetes	0.027	2.316 (1.099-4.880)
Hypertension	0.447	0.736 (0.335-1.620)
Cardiac disease	0.037	4.899 (1.104-21.727)
Lung tuberculosis	0.309	2.138 (0.494-9.245)
RR	0.016	1.139 (1.025-1.266)
HR	0.352	1.012 (0.987-1.039)
SBP	0.716	0.997 (0.978-1.015)
SF ratio	<0.001	0.994 (0.991-0.996)
WBC	0.066	1.052 (0.997-1.111)
NLR	0.161	0.971 (0.931-1.012)
PLT	0.626	0.999 (0/996-1.003)
AST	0.917	1.000 (0.996-1.004)
BUN	0.042	1.022(1.001-1.043)
Cr	0.429	0.937 (0.798-1.100)
K	0.611	1.116 (0.731-1.705)
RALE score	0.593	0.963 (0.840-1.105)

OR=odd ratio, RR=respiratory rate, HR=heart rate, SBP=systolic blood pressure, SF ratio=the ratio of oxygen saturation to fraction of inspired oxygen, WBC=white blood cell count, NLR=neutrophil-lymphocyte ratio, PLT=platelet count, AST=aspartate aminotransferase, ALT= alanine aminotransferase Alb=albumin, BUN=blood urea nitrogen, Cr=creatinine, Na=serum sodium, K=serum potassium, Cl=serum chloride, RALE score=the radiographic assessment of lung edema score

Table 4 Cut-off points of selected continuous parameters

Parameters	AUC	Cut-off point	95% CI	Sensitivity (%)	Specificity (%)
Age	0.642	≥65	0.580–0.703	20.7	87.8
Respiratory rate	0.779	≥23	0.725–0.832	78.4	64.6
Heart rate	0.688	≥95	0.642–0.751	65.5	66.1
SF ratio	0.807	≤310	0.764–0.851	76.0	71.3
WBC count	0.590	≥10,000	0.524–0.656	47.4	66.7
NLR	0.639	≥6.2	0.577–0.702	56.9	64.6
BUN	0.655	≥20	0.593–0.718	40.5	76.2
RALE score	0.631	≥5	0.566–0.697	62.1	59.3

AUC=area under curve, CI=confidence interval, SF ratio=the ratio of oxygen saturation to fraction of inspired oxygen, GCS=Glasgow coma scale, Hb=hemoglobin, WBC=white blood cell count, NLR=neutrophil-lymphocyte ratio, BUN=blood urea nitrogen, RALE score=the radiographic assessment of lung edema score

Table 5 Predictive value of each cut-off point in the scoring system

Total score	Sensitivity (%)	Specificity (%)
≥1	100.0	10.9
≥2	99.4	23.4
≥3	96.4	38.3
≥4	89.7	53.6
≥5	77.0	69.7
≥6	60.6	81.8
≥7	35.8	90.9
≥8	21.8	96.7
≥9	7.3	99.3
≥10	1.2	100.0
≥11	0.0	100.0
≥12	0.0	100.0

Internal validation and performance comparison

Internal validation was conducted to investigate further the predictive value of the Soetomo COVID-19 prognostic scoring system. We randomly assigned about 30% of the total population (160 patients) to the testing datasets, while the remainder (439 patients) were in the training datasets. ROC curves for the scoring system in the training datasets, testing datasets, and all datasets are presented in Figures 1a, 1b, and 1c, respectively. We also compared the model's performances with the qSOFA and modified early warning score (MEWS) by measuring AUCs, sensitivities, and specificities. The sensitivities and specificities were derived by cross-tabulation for each dataset. As seen in Table 7, our novel scoring system was superior to both the qSOFA and MEWS.

Table 6 The Soetomo COVID-19 prognostic score

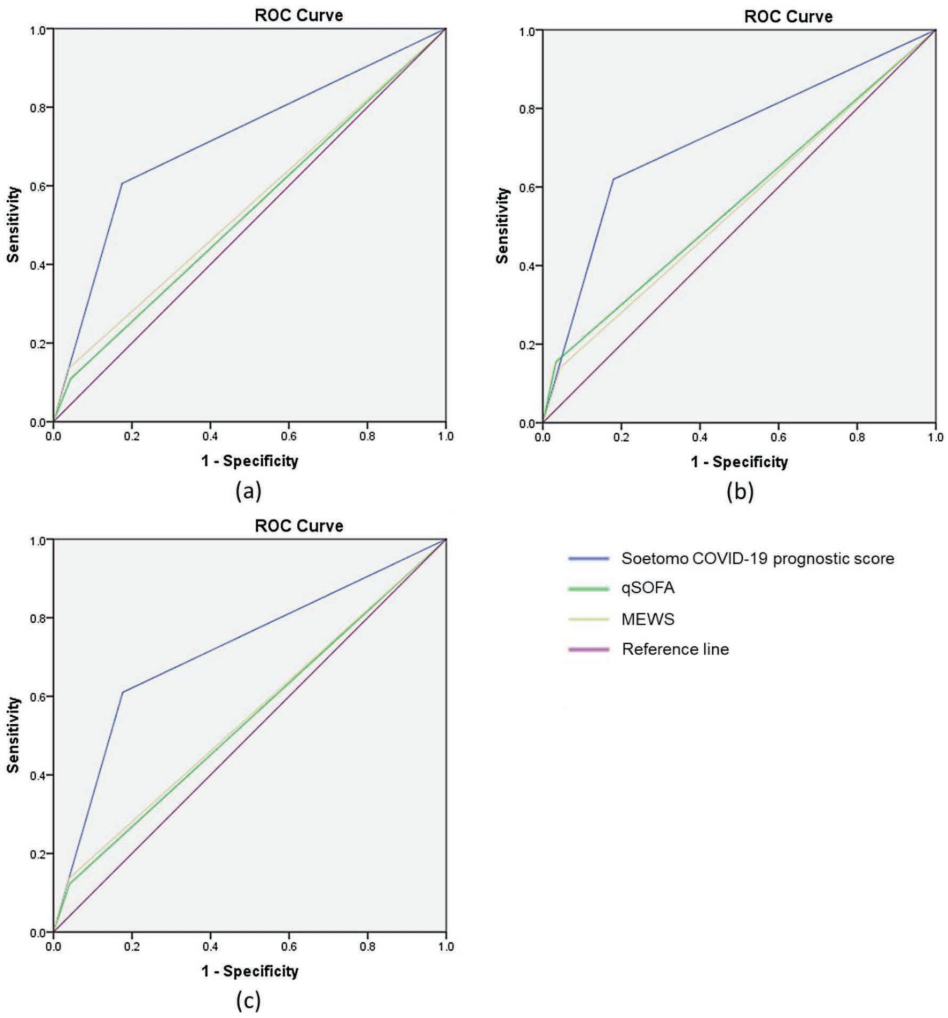
Parameters	Assessment	Score
Age	≥65 years old	1
Fever	Present	2
At least one of the following comorbidities: – Diabetes – Hypertension – Cardiac disease – Pulmonary tuberculosis	Present	1
Respiratory rate	≥23 breaths/min	1
Heart rate	≥95 beats/min	1
SF ratio	≤310	1
WBC count	≥10,000/μL	1
NLR	≥6.2	1
BUN	≥20 mg/dL	1
RALE score	≥5	1
Interpretation 0–5 : Low risk of severe COVID-19 6–12 : High risk of severe COVID-19		

SF ratio=the ratio of oxygen saturation to a fraction of inspired oxygen, WBC=white blood cell count, NLR=neutrophils–lymphocytes ratio, BUN=blood urea nitrogen, RALE score, the radiographic assessment of lung edema score

Table 7 Performances of Soetomo COVID-19 prognostic score and comparison models

	Severe disease progression	Training datasets	Testing datasets	All datasets
Soetomo COVID-19 prognostic score	Sensitivity (%)	60.6	62.0	61.0
	Specificity (%)	82.5	82.0	82.4
	AUC (95% CI)	0.715 (0.664–0.767)	0.720 (0.638–0.802)	0.717 (0.673–0.761)
	p-value	<0.001	<.001	<0.001
qSOFA	Sensitivity (%)	10.9	15.5	12.3
	Specificity (%)	95.6	96.6	95.9
	AUC (95% CI)	0.533 (0.476–0.589)	0.561 (0.470–0.651)	0.541 (0.493–0.589)
	p-value	0.252	0.188	0.091
MEWS	Sensitivity (%)	13.3	14.1	13.6
	Specificity (%)	96.4	95.5	96.1
	AUC (95% CI)	0.548 (0.492–0.605)	0.548 (0.457–0.639)	0.549 (0.501–0.596)
	p-value	0.089	0.298	0.045

qSOFA=quick sepsis related organ failure assessment, MEWS=modified early warning scores, AUC=area under curve



qSOFA=quick sepsis related organ failure assessment, MEWS=modified early warning scores, ROC=receiver operating characteristic

Figure 1 Illustration of ROC Curves, comparing Suetomo COVID-19 prognostic score (cut-off at 6) qSOFA, and MEWS

Discussion

Our study found that older age was associated with severe clinical progression. Advanced age (≥65) has been previously demonstrated as a predictive factor of COVID-19 severity[14,15]. In elderly patients, dysfunction of B-cells and T-cells and altered cytokine production might attenuate the immune response to a new pathogen[16]. Hence, we preferred to include age as one of the scoring components despite its being rejected in the logistic regression analysis. Patients with fever on hospital admission were also reported at higher risk of severe illness in another retrospective study[17]. Our study also found that fever was significantly associated with severe outcomesin hospitalized COVID-19 patients. Cytokine storms that may play a significant role in severe illness are characterized by a fever of one, multi-organ failure, and hyperferritinemia[18].

The Soetomo COVID-19 prognostic score also includes certain pre-existing diseases, including diabetes, hypertension, cardiac disease, and lung tuberculosis. We incorporated all comorbidities associated with severe COVID-19, although they did not show independent associations. This consideration was due to the high prevalence of these diseases in Indonesia[19] and our belief they might contribute to clinical to disease severity. A meta-analysis concluded that the risk of severe clinical in COVID-19 was increased two-fold in diabetic patients compared to non-diabetic patients[20]. Cardiovascular and metabolic disease patients may have a greater risk of clinical deterioration in COVID-19. In an earlier study, the severe COVID-19 group showed a higher incidence of pre-existing hypertension, cardio-cerebrovascular disease, and diabetes compared with the non-severe group of about two-fold, three-fold, and two-fold, respectively[21,22]. The possible underlying mechanism was suggested a being that a SARS-CoV2 attack over the endothelium aggravated chronic systemic endothelial dysfunction in patients with cardiovascular and metabolic diseases[23]. Moreover, a previous study demonstrated that patients with a pre-existing lung tuberculosis infection were likelier to develop severe manifestations of SARS-CoV-2 co-infection[24]. TB patients also had a two-fold increased mortality risk and tended not to recover[25].

We considered selecting three bedside parameters: respiratory rate, heart rate, and SF ratio. These components represent quick assessment of ventilation status, hemodynamic status, and oxygenation. In a pilot study, elevated respiratory rate and heart rate were described as predictors for the early detection of sepsis[26], whereas in other studies the SF ratio demonstrated good prognostic values in ARDS, sepsis, and septic shock[27,28]. A prior studies found that the SF ratio was correlated with the PF ratio in patients with ARDS[29]. This indicates that the SF ratio could be a good substitution for the PF ratio since many limited-resource hospital laboratories do not have an arterial blood gas measurement facility.

The biomarkers in our novel scoring system are white blood cell count, NLR, and BUN. Higher WBC and lower lymphocyte counts have been significantly associated with disease severity in patients with SARS-CoV-2 infection[15,30,31]. A previously published meta-analysis also reported that NLR had good predictive values for severe clinical progression and mortality, which enabled early detection of potentially severe cases and and effective COVID-19 triaging[32,33] a novel coronavirus and the primary causative agent of COVID-19. BUN elevation was reported to have a good performance in predicting in-hospital COVID-19 mortality[34]. Increased urea reabsorption and significant protein catabolism may occur early in severe manifestations. In other studies a chest CT scan was considered a first-line radiologic investigation for COVID-19[35] because of its high accuracy[36]. Unfortunately, the availability of this imaging modality is often limited in referral hospitals. An earlier study suggested that the RALE score, based on chest X-rays, can predict clinical outcomes in patients with COVID-19[37,38]. Chest radiography is widely available. Hence, it provides an alternative strategy in limited medical resource settings.

Since our data was primarily obtained from the first in-hospital results, this scoring system is appropriate for the initial risk stratification of COVID-19 in-patients. The Soetomo COVID-19 prognostic score cannot be used dynamically for clinical and treatment evaluation. High-risk patients should be monitored more intensively and prioritized for transfer into a high-care unit.

Our study included a relatively large sample size. The predictors of our scoring system are standard, routine, and easily accessible in most limited-resource hospitals. Furthermore, it is the first prognostic model developed based on the clinical characteristics of the Indonesian population. This finding is essential since another cohort study reported that people of South Asian ethnicity were more likely to present with severe disease in SARS-COV-2 infection[39].

Study limitations

Nevertheless, several limitations of this study should be taken into account. The sources of potential bias were the retrospective cohort design. Our study was conducted in a single center, a quaternary referral hospital, in the east Indonesian region. With complicated cases being transferred to our center, the percentage of patients with severe illness was relatively high. The fact that the times between symptoms onset and first hospital admission were highly varied may become an uncontrollable confounder. Bias might also be present because the authors did not collect treatment information during hospitalization. Differences in clinical outcomes between ethnicities were observed in prior reports[40]. Therefore, our model may be different from a model based on the global population. The first two months of data collection was a tremendous strain due to unprepared resources, limited understanding and the significant surge of new patients, resulting in the late submission of this paper. While this novel score suits current practice, further validation in a large prospective cohort study is still required.

Conclusion

The study confirmed that the developed scoring system accurately predicted a significant proportion of severe disease in COVID-19 patients. This research was conducted at the start of the pandemic, so there were deficiencies that could serve as input for further research. Although these limitations, the study suggests that the quaternary referral hospital in the east of Indonesia was the site of our study's sole location. Considerably more work will need to be done to validate the study's findings in a large prospective cohort study in the Indonesian population.

Conflict of interest

There are no conflicts of interest to declare.

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