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Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19

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IMPORTANCE Early identification of patients with novel coronavirus disease 2019 (COVID-19) who may develop critical illness is of great importance and may aid in delivering proper treatment and optimizing use of resources.

OBJECTIVE To develop and validate a clinical score at hospital admission for predicting which patients with COVID-19 will develop critical illness based on a nationwide cohort in China.

DESIGN, SETTING, AND PARTICIPANTS Collaborating with the National Health Commission of China, we established a retrospective cohort of patients with COVID-19 from 575 hospitals in 31 provincial administrative regions as of January 31, 2020. Epidemiological, clinical, laboratory, and imaging variables ascertained at hospital admission were screened using Least Absolute Shrinkage and Selection Operator (LASSO) and logistic regression to construct a predictive risk score (COVID-GRAM). The score provides an estimate of the risk that a hospitalized patient with COVID-19 will develop critical illness. Accuracy of the score was measured by the area under the receiver operating characteristic curve (AUC). Data from 4 additional cohorts in China hospitalized with COVID-19 were used to validate the score. Data were analyzed between February 20, 2020 and March 17, 2020.

MAIN OUTCOMES AND MEASURES Among patients with COVID-19 admitted to the hospital, critical illness was defined as the composite measure of admission to the intensive care unit, invasive ventilation, or death.

RESULTS The development cohort included 1590 patients. the mean (SD) age of patients in the cohort was 48.9 (15.7) years; 904 (57.3%) were men. The validation cohort included 710 patients with a mean (SD) age of 48.2 (15.2) years, and 382 (53.8%) were men and 172 (24.2%). From 72 potential predictors, 10 variables were independent predictive factors and were included in the risk score: chest radiographic abnormality (OR, 3.39; 95% CI, 2.14-5.38), age (OR, 1.03; 95% CI, 1.01-1.05), hemoptysis (OR, 4.53; 95% CI, 1.36-15.15), dyspnea (OR, 1.88; 95% CI, 1.18-3.01), unconsciousness (OR, 4.71; 95% CI, 1.39-15.98), number of comorbidities (OR, 1.60; 95% CI, 1.27-2.00), cancer history (OR, 4.07; 95% CI, 1.23-13.43), neutrophil-to-lymphocyte ratio (OR, 1.06; 95% CI, 1.02-1.10), lactate dehydrogenase (OR, 1.002; 95% CI, 1.001-1.004) and direct bilirubin (OR, 1.15; 95% CI, 1.06-1.24). The mean AUC in the development cohort was 0.88 (95% CI, 0.85-0.91) and the AUC in the validation cohort was 0.88 (95% CI, 0.84-0.93). The score has been translated into an online risk calculator that is freely available to the public (http://118.126.104.170/)

CONCLUSIONS AND RELEVANCE In this study, a risk score based on characteristics of COVID-19 patients at the time of admission to the hospital was developed that may help predict a patient's risk of developing critical illness.

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+ Supplemental content

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The outbreak of the novel coronavirus disease 2019 (COVID-19) began in Wuhan, China in December 2019. Since then, it has rapidly spread around the world. As of April 16, 2020, the WHO reported a total of 1 995 983 COVID-19 cases globally, with average mortality of 6.57%.

The clinical spectrum of COVID-19 pneumonia ranges from mild to critically ill cases. Patients with mild disease present with symptoms of fever and cough, followed by sputum production and fatigue. Sepsis, respiratory failure, acute respiratory distress syndrome, heart failure, and septic shock are commonly observed in critically ill patients.[1]

According to the largest current report from the Chinese Center for Disease Control and Prevention with 72 314 cases, 58 574 patients (81%) were classified as mild, 10 124 (14%) were classified as severe, and 3616 (5%) were considered critical illness. The average case-fatality rate was 2.3%, but mortality was as high as 49% in patients with critical illness.[2] Among 201 patients in Wuhan, Wu et al[3] reported that risk factors associated with development of acute respiratory distress syndrome and death included older age, neutrophilia, organ dysfunction, coagulopathy, and elevated D-dimer levels.

Early detection of patients who are likely to develop critical illness is of great importance and may aid in delivering proper care and optimizing use of limited resources. We aimed to construct a risk prediction score based on a nationwide cohort of Chinese patients with COVID-19 to help identify patients at the time of hospital admission who are likely to develop critical illness.

Methods

Data Sources and Processing

This study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University; written informed consent was waived owing to the use of deidentified retrospective data. On behalf of the National Clinical Research Center for Respiratory Disease and collaborating with the National Health Commission of the People's Republic of China, we established a retrospective cohort to study COVID-19 cases throughout China. We obtained medical records from laboratory-confirmed hospitalized cases with COVID-19 reported to the China National Health Commission between November 21, 2019 and January 31, 2020, as previously described.[4] The National Health Commission of China requested that all 1855 hospitals in China that were designated to care for COVID-19 patients submit the clinical records of all hospitalized COVID-19 cases without selection to the database by January 31, 2020. For the development cohort, we used data from the 575 hospitals that contributed clinical data by the deadline.

COVID-19 diagnoses were confirmed by positive high-throughput sequencing or real-time reverse-transcription polymerase-chain-reaction (RT-PCR) assay for nasal and pharyngeal swab specimens. A team of experienced respiratory clinicians reviewed, abstracted and cross-checked the data. Each record was checked independently by 2 clinicians. We included all patients with data on clinical status at hospitalization (laboratory findings, clinical symptoms and signs, severity, and discharge status).

Key Points

Question What epidemiological and clinical characteristics are associated with the development of critical illness among patients with novel coronavirus disease 2019 (COVID-19)? Can these characteristics be used to predict which patients admitted to the hospital with COVID-19 will need admission to an intensive care unit, mechanical ventilation, or will die?

Findings In this study with a development cohort of 1590 patients and a validation cohort of 710 patients, a risk score was developed and validated to predict development of critical illness. We identified 10 independent predictors and developed a risk score (COVID-GRAM) that predicts development of critical illness. The risk score predictors included: chest radiography abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin.

Meaning The COVID risk score may help identify patients with COVID-19 who may subsequently develop critical illness.

Potential Predictive Variables

Potential predictive variables included the following patient characteristics at hospital admission: clinical signs and symptoms, imaging results, laboratory findings, demographic variables, and medical history. Demographic variables collected for the study included age, sex, smoking status, exposure to Wuhan (including Wuhan residency, travel history to Wuhan, or contact with people from Wuhan), residency in Hubei province, and time between onset of symptoms to admission. Medical history included number of comorbidities, chronic obstructive pulmonary disease, diabetes, hypertension, coronary artery disease, cerebrovascular disease, hepatitis B, cancer, chronic renal disease, immunodeficiency disease, and pregnancy. Clinical signs and symptoms included categorical and continuous variables: first body temperature, respiratory rate, heart rate, cardiac arrhythmia, systolic blood pressure, diastolic blood pressure, symptoms rating, fever, conjunctival congestion, nasal congestion, headache, cough, expectoration, sore throat, fatigue, hemoptysis, dyspnea, nausea and vomiting, diarrhea, arthralgia and myalgia, rigor, throat blockage, tonsillar enlargement, enlarged lymph nodes, skin rash, and unconsciousness. Imaging results included chest radiography (CXR) abnormality, the severity of CXR abnormality, chest computed tomographic (CT) imaging abnormality, and the severity of CT abnormality. Laboratory findings included partial arterial oxygen pressure, oxygen saturation, white blood cell, lymphocyte, and platelet counts, neutrophil to lymphocyte ratio, and levels of hemoglobin, C-reactive protein, procalcitonin, lactate dehydrogenase, aspartate transaminase, direct bilirubin, indirect bilirubin, total bilirubin, creatine kinase, creatinine, hypersensitive troponin I, albumin, serum sodium, serum potassium, serum chlorine, D-dimer levels, prothrombin time, and activated partial thromboplastin time.

Outcomes

We defined the severity of COVID-19 (severe vs nonsevere) based on the American Thoracic Society guidelines for community-acquired pneumonia given the extensive acceptance of this guideline.[5] We defined critical COVID-19 illness as a composite of admission to the intensive care unit (ICU), invasive ventilation, or death. We adopted this composite end point because admission to ICU, invasive ventilation, and death are serious outcomes of COVID-19 that have been adopted in previous studies to assess the severity of other serious infectious diseases.[5,6]

Variable Selection and Score Construction

All 1590 patients hospitalized with COVID-19 in the development cohort were included for variable selection and risk score development. As described herein, 72 variables were entered into the selection process. Least Absolute Shrinkage and Selection Operator (LASSO) regression was applied to minimize the potential collinearity of variables measured from the same patient and over-fitting of variables. Imputation for missing variables was considered if missing values were less than 20%. We used predictive mean matching to impute numeric features, logistic regression to impute binary variables, and Bayesian polytomous regression to impute factor features. We used L1-penalized least absolute shrinkage and selection regression for multivariable analyses, augmented with 10-fold cross validation for internal validation. This is a logistic regression model that penalizes the absolute size of the coefficients of a regression model based on the value of λ. With larger penalties, the estimates of weaker factors shrink toward zero, so that only the strongest predictors remain in the model. The most predictive covariates were selected by the minimum (λ min). The R package "glmnet" statistical software (R Foundation) was used to perform the LASSO regression. Subsequently, variables identified by LASSO regression analysis were entered into logistic regression models and those that were consistently statistically significant were used to construct the risk score (COVID-GRAM),[7] which was then used to construct a web-based risk calculator (http://118.126.104.170/). Data were analyzed between February 20, 2020 and March 17, 2020.

Assessment of Accuracy

The accuracy of COVID risk score was assessed using the area under the receiver-operator characteristic curve (AUC). We also used the AUC to compare the accuracy of the COVID-GRAM with CURB-6 models,[8] which have been used in classification of the severity of community-acquired pneumonia. For internal validation of the accuracy estimates and to reduce overfit bias, we used 200 bootstrap resamples. Statistical analysis was performed with R software (version 3.6.2, R Foundation), and *P* < .05 was considered statistically significant.

Score Validation

To validate the generalizability of COVID risk score, we used data from hospitals that were not included in the development cohort including 710 patients. Data for the validation cohort were pooled from 4 sources: (1) a multicenter cohort of hospitals from 10 cities in Hubei province that missed the deadline for data submission, but subsequently submitted data on cases admitted before the January 31, 2020; (2) Daye Hospital (near Wuhan); (3) The First People's Hospital of Foshan (Guangdong province), and Nanhai People's Hospital of Foshan (Guangdong province). The later 3 hospitals reported up-to-date data as of February 28, 2020.

The variables required for calculating the COVID risk score from the validation cohort were collected and cross-checked by 2 experienced physicians (C.Z.S. and C.A.L.) and the risk score was calculated as described herein for the development cohort.

Results

Characteristics of the Development Cohort

In the development cohort, we collected data from 1590 patients from 575 hospitals in 31 provincial administrative regions between November 21, 2019 and January 31, 2020. At hospital admission, 24 of 1590 patients (1.5%) were considered to be severe and the rest (1566 [98.5%]) were considered to be mild according to the American Thoracic Society guideline.[5] A total of 131 patients eventually developed critical illness (8.2%). The overall mortality was 3.2% and 1334 patients (83.9%) had a history of exposure to Wuhan.

Overall, the mean (SD) age of patients in the cohort was 48.9 (15.7) years; 904 patients (57.3%) were men and 399 (25.1%) had at least 1 coexisting condition, including hypertension (269 [16.9%]), diabetes (130 [8.2%]), and cardiovascular disease (59 [3.7%]) as the top 3 comorbidities (**Table 1**). Fever (1351 [88.0%]), dry cough (1052 [70.2%]), fatigue (584 [42.8%]), productive cough (513 [36.0%]), and shortness of breath (331 [23.7%]) were the most common symptoms. Most patients (1130 [71.1%]) had abnormal chest CT findings. Laboratory findings of the development cohort are presented in **Table 2**.

Predictor Selection

Seventy-two variables measured at hospital admission (Table 1 and Table 2) were included in the LASSO regression. After LASSO regression selection (eFigure 1 in the Supplement), 19 variables remained significant predictors of critical illness, including clinical features and blood test results, CXR abnormality, age, exposure to Wuhan, first and highest body temperature, respiratory rate, systolic blood pressure, hemoptysis, dyspnea, skin rash, unconsciousness, number of comorbidities, chronic obstructive pulmonary disease (COPD), cancer, oxygen saturation levels, neutrophils, neutrophil to lymphocyte ratio, lactate dehydrogenase, direct bilirubin, and creatinine levels.

Inclusion of these 19 variables in a logistic regression model resulted in 10 variables that were independently statistically significant predictors of critical illness and were included in risk score. These variables included CXR abnormality (OR, 3.39; 95% CI, 2.14-5.38; *P* < .001), age (OR, 1.03; 95% CI, 1.01-1.05; *P* = .002), hemoptysis (OR, 4.53; 95% CI, 1.36-15.15; *P* = .01), dyspnea (OR, 1.88; 95% CI, 1.18-3.01; *P* = .01), unconsciousness (OR, 4.71; 95% CI, 1.39-15.98; *P* = .01), number of

Table 1. Demographics and Clinical Characteristics Among Patients In the Development Cohort Who Did or Did Not Develop Critical Illness[a]

		Critical illness	
Characteristic	Total, mean (SD) [range]	No	Yes
No.	1590	1459	131
Age, mean (SD), y	48.9 (15.7) [1-95]	47.8 (15.2)	61.6 (14.8)
Incubation period, mean (SD), d	5.0 (4.1) [0-24]	4.9 (4.1)	5.7 (4.2)
Admission measures, mean (SD)			
Temperature, °C	37.3 (0.9) [35.5-40.3]	37.4 (0.9)	37.1 (0.9)
Respiratory rate, breaths/min	21.2 (12.0) [12-65]	21.1 (12.4)	23.1 (5.9)
Heart rate, beats/min	88.7 (14.6) [17-205]	88.6 (14.4)	89.7 (16.0)
Blood pressure, mm Hg			
Systolic	126.1 (16.4) [74-187]	125.5 (15.6)	131.4 (22.5)
Diastolic	79.5 (25.6) [40-160]	79 (11.3)	84.7 (76.1)
Male, No./No. (%)	904/1578 (57.3)	816/1447 (56.4)	88/131 (67.2)
Smoking status, No./No. (%)			
Never	1479/1590 (93.0)	1366/1459 (93.6)	113/131 (86.3)
Former/current	111/1590 (7)	93/1459 (6.4)	18/131 (13.7)
Symptoms, No./No. (%)			
Degree of symptoms			
0	73/1590 (4.6)	67/1459 (4.6)	6/131 (4.6)
1	176/1590 (11.1)	170/1459 (11.7)	6/131 (4.6)
2	353/1590 (22.2)	330/1459 (22.6)	23/131 (17.6)
3	409/1590 (25.7)	378/1459 (25.9)	31/131 (23.7)
4	287/1590 (18.1)	258/1459 (17.7)	29/131 (22.1)
5	158/1590 (9.9)	141/1459 (9.7)	17/131 (13.0)
6	76/1590 (4.8)	68/1459 (4.7)	8/131 (6.1)
7	36/1590 (2.3)	29/1459 (2.0)	7/131 (5.3)
8	14/1590 (0.9)	11/1459 (0.8)	3/131 (2.3)
9	7/1590 (0.4)	6/1459 (0.4)	1/131 (0.8)
10	1/1590 (0.1)	1/1459 (0.1)	0/131 (0)
Fever	1351/1536 (88.0)	1237/1409 (87.8)	114/127 (89.8)
Congestion			
Conjunctival	10/1345 (0.7)	10/1235 (0.8)	0/110 (0)
Nasal	73/1299 (5.6)	64/1191 (5.4)	9/108 (8.3)
Headache	205/1328 (15.4)	190/1221 (15.6)	15/107 (14)
Dry cough	1052/1498 (70.2)	959/1372 (69.9)	93/126 (73.8)
Sore throat	194/1317 (14.7)	181/1207 (15.0)	13/110 (11.8)
Productive cough	513/1424 (36.0)	461/1302 (35.4)	52/122 (42.6)
Fatigue	584/1365 (42.8)	539/1250 (43.1)	45/115 (39.1)
Hemoptysis	16/1315 (1.2)	10/1201 (0.8)	6/114 (5.3)
Shortness of breath	331/1394 (23.7)	257/1275 (20.2)	74/119 (62.2)
Nausea/vomiting	80/1371 (5.8)	73/1256 (5.8)	7/115 (6.1)
Diarrhea	57/1359 (4.2)	52/1244 (4.2)	5/115 (4.3)
Myalgia/arthralgia	234/1338 (17.5)	215/1229 (17.5)	19/109 (17.4)
Chills	163/1333 (12.2)	151/1222 (12.4)	12/111 (10.8)
Signs			
Throat congestion	21/1286 (1.6)	21/1178 (1.8)	0/108 (0)
Tonsil swelling	31/1376 (2.3)	30/1261 (2.4)	1/115 (0.9)
Enlargement of lymph nodes	2/1375 (0.1)	1/1261 (0.1)	1/114 (0.9)
Rash	3/1378 (0.2)	3/1264 (0.2)	0/114 (0)
Unconsciousness	20/1421 (1.4)	10/1303 (0.8)	10/118 (8.5)

(continued)

Table 1. Demographics and Clinical Characteristics Among Patients In the Development Cohort Who Did or Did Not Develop Critical Illness[a] (continued)

Characteristic	Total, mean (SD) [range]	Critical illness	
		No	Yes
Comorbidities, No./No. (%)			
Any	399/1590 (25.1)	322/1459 (22.1)	77/131 (58.8)
No. of comorbidities			
0	1191/1590 (74.9)	1137/1459 (77.9)	54/131 (41.2)
1	269/1590 (16.9)	229/1459 (15.7)	40/131 (30.5)
2	88/1590 (5.5)	68/1459 (4.7)	20/131 (15.3)
3	34/1590 (2.1)	20/1459 (1.4)	14/131 (10.7)
4	5/1590 (0.3)	4/1459 (0.3)	1/131 (0.8)
5	3/1590 (0.2)	1/1459 (0.1)	2/131 (1.5)
COPD	24/1590 (1.5)	12/1459 (0.8)	12/131 (9.2)
Diabetes	130/1590 (8.2)	99/1459 (6.8)	31/131 (23.7)
Hypertension	269/1590 (16.9)	216/1459 (14.8)	53/131 (40.5)
Cardiovascular disease	59/1590 (3.7)	46/1459 (3.2)	13/131 (9.9)
Cerebrovascular disease	30/1590 (1.9)	20/1459 (1.4)	10/131 (7.6)
Hepatitis B infection	28/1590 (1.8)	25/1459 (1.7)	3/131 (2.3)
Malignancy	18/1590 (1.1)	11/1459 (0.8)	7/131 (5.3)
Chronic kidney disease	21/1590 (1.3)	15/1459 (1.0)	6/131 (4.6)
Immunodeficiency	3/1590 (0.2)	2/1459 (0.1)	1/131 (0.8)
Abnormal chest radiography	243/1590 (15.3)	184/1459 (12.6)	59/131 (45.0)
Severity of abnormality			
0	1347/1590 (84.7)	1275/1459 (87.4)	72/131 (55.0)
1	138/1590 (8.7)	104/1459 (7.1)	34/131 (26.0)
2	69/1590 (4.3)	59/1459 (4.0)	10/131 (7.6)
3	36/1590 (2.3)	21/1459 (1.4)	15/131 (11.5)
Abnormal chest CT	1130/1590 (71.1)	1035/1459 (70.9)	95/131 (72.5)
Severity of abnormality			
0	460/1590 (28.9)	424/1459 (29.1)	36/131 (27.5)
1	492/1590 (30.9)	466/1459 (31.9)	26/131 (19.8)
2	291/1590 (18.3)	258/1459 (17.7)	33/131 (25.2)
3	248/1590 (15.6)	224/1459 (15.4)	24/131 (18.3)
4	99/1590 (6.2)	87/1459 (6.0)	12/131 (9.2)
Residency in Hubei Province, yes	647/1590 (40.7)	552/1459 (37.8)	95/131 (72.5)
Exposure to Wuhan, yes	1334/1590 (83.9)	1213/1459 (83.1)	121/131 (92.4)

Abbreviation: COPD, chronic obstructive pulmonary disease; CT, computed tomography.

[a] Data are mean (SD), No./No. (%), where No. is the total number of patients with available data.

comorbidities (OR, 1.60; 95% CI, 1.27-2.00; *P* < .001), cancer history (OR, 4.07; 95% CI, 1.23-13.43; *P* = .02), neutrophil-to-lymphocyte ratio (OR, 1.06; 95% CI, 1.02-1.10; *P* = .003), lactate dehydrogenase (OR, 1.002; 95% CI, 1.001-1.004, *P* < .001), and direct bilirubin (OR, 1.15; 95% CI, 1.06-1.24; *P* = .001) (**Table 3**).

Construction of the Risk Score and Web-Based Calculator

The COVID risk score was constructed based on the coefficients from the logistic model. We used the following formulas for the logistic model to calculate the probability and 95% confidence intervals[9]: probability = $\exp(\Sigma \beta \times X)/[1+\exp(\Sigma \beta \times X)]$, lower limit of 95% CI = $\exp[\Sigma Xn \times \beta n - \Sigma z \times SE(\beta)]/\{1+\exp[\Sigma Xn \times \beta n - \Sigma z \times SE(\beta)]\}$, upper limit of 95% CI = $\exp[\Sigma Xn \times \beta n + \Sigma z \times SE(\beta)]/\{1+\exp[\Sigma Xn \times \beta n + \Sigma z \times SE(\beta)]\}$.

An online calculator based on COVID-GRAM was developed to allow clinicians to enter the values of the 10 variables required for the risk score with automatic calculation of the likelihood (with 95% CIs) that a hospitalized patient with COVID-19 will develop critical illness (http://118.126.104.170/) (**Figure**)

The Performance of COVID Risk Score

By internal bootstrap validation, the mean AUC based on data from the development cohort was 0.88 (95% CI, 0.85-0.91) (eFigure 2 in the Supplement). The AUC of COVID risk score for patients in the epicenter at Hubei was 0.87 (95% CI, 0.83-0.91) and outside Hubei was 0.82 (95% CI, 0.73-0.90). The predictive value of COVID-GRAM was higher than the CURB-6 model, which had an AUC of 0.75 (95% CI, 0.70-0.80) for correct prediction of development of critical illness (*P* < .001).

Table 2. Laboratory Findings Among Patients Who Did or Did Not Develop Critical Illness

Variable	Total, mean (SD) [range]	Critical illness, mean (SD) No	Critical illness, mean (SD) Yes
No.	1590	1459	131
Total urine volume, mL/d	794.6 (901.6) [0-3810]	622.1 (855.4)	1155.1 (907.8)
Pao$_2$ (with oxygen inhalation), mm Hg	84.3 (36.2) [10.2-242.0]	86.5 (36.0)	67.2 (33.3)
FiO$_2$, %	27.5 (16.6) [21.0-99.7]	26.6 (14.7)	33.2 (25.2)
Pao$_2$ (without oxygen inhalation), mm Hg	92.7 (13.5) [6.12-254.0]	93.6 (12.5)	85.8 (18.2)
Neutrophil cell count, ×10^9/L	4.14 (2.2) [0.69-24.0]	3.9 (1.9)	6.4 (3.6)
Lymphocyte count, ×10^9/L	1.4 (3.1) [0-45.0]	1.5 (3.3)	0.7 (0.4)
Platelet count, ×10^9/L	179.5 (70.7) [0.1-602.0]	180.1 (70.4)	173.4 (73.7)
Hemoglobin, g/L	123.5 (43.9) [3.33-414.0]	124.2 (43.9)	115.5 (43.5)
C-reactive protein, mg/L	34.8 (49.2) [0-624.0]	30.6 (43.8)	84.5 (76.3)
Procalcitonin, ng/mL	0.7 (9.8) [0-252.7]	0.8 (10.3)	0.6 (1.4)
Lactate dehydrogenase, U/L	314.3 (693.7) [1.0-1411.0]	273.6 (135.2)	723.6 (2239.5)
Aminotransferase, U/L			
Aspartate	49.7 (451.9) [5.1-203.0]	34.1 (20.9)	205.1 (1493.4)
Alanine	43.1 (242.5) [2.0-435.0]	34.4 (37.2)	130.1 (795.9)
Bilirubin, mmol/L			
Direct	4 (2.7) [0-22.3]	3.7 (2.3)	6.5 (4.1)
Indirect	7.4 (4.5) [0-41.2]	7.2 (4.3)	8.9 (5.3)
Total	11.8 (14.2) [0.1-97.0]	11.4 (14.7)	15.2 (8.4)
Creatine kinase, U/L	135.5 (246.7) [0.05-1013.0]	123 (125.3)	258.9 (702.8)
Creatinine, μmol/L	76 (71.4) [4.05-1441.0]	71.8 (54.2)	118.7 (158.4)
Hypersensitive troponin I, pg/mL	76.3 (586.4) [0-8622.0]	42.7 (439.0)	288.1 (1124.2)
Albumin, g/L	38.7 (9.1) [0-135.0]	39.3 (8.9)	32.6 (8.9)
Sodium, mmol/L	140.5 (50.4) [124.4-151.0]	139.7 (41.2)	148.7 (103.1)
Potassium, mmol/L	4.4 (6.4) [2.3-6.7]	4.4 (6.7)	4.1 (0.8)
Chlorine, mmol/L	103.8 (28.2) [89.8-119.0]	103.7 (29.5)	105 (4.8)
D-dimer level, mg/L	25.5 (138.2) [0-2660.0]	26.3 (144.8)	19.1 (70.1)
Prothrombin time, s	17.4 (48.2) [0-183.0]	17.6 (50.2)	15.9 (24.1)
Activated partial thromboplastin time, s	42.5 (143.7) [3.0-499.0]	43.3 (150.6)	34.8 (50.9)
Neutrophil-lymphocyte ratio	5.1 (5.6) [0.06-78.2]	4.4 (3.8)	12.7 (12.4)

Abbreviations: FiO$_2$, fraction of inspired oxygen; Pao$_2$, partial pressure of oxygen.

Table 3. Multivariable Logistic Regression Model for Predicting Development of Critical Illness in 1590 Patients Hospitalized With COVID-19 in Wuhan

Variables	Odds ratio (95% CI)	*P* value
X-ray abnormality (yes vs no)	3.39 (2.14-5.38)	<.001
Age, per y	1.03 (1.01-1.05)	.002
Hemoptysis (yes vs no)	4.53 (1.36-15.15)	.01
Dyspnea (yes vs no)	1.88 (1.18-3.01)	.01
Unconsciousness (yes vs no)	4.71 (1.39-15.98)	.01
No. of comorbidities	1.60 (1.27-2.00)	<.001
Cancer history (yes vs no)	4.07 (1.23-13.43)	.02
Neutrophil to lymphocyte ratio	1.06 (1.02-1.10)	.003
Lactate dehydrogenase, U/L	1.002 (1.001-1.004)	<.001
Direct bilirubin, μmol/L	1.15 (1.06-1.24)	.001
Constant	0.001	

Abbreviation: COVID-19, coronavirus disease 2019.

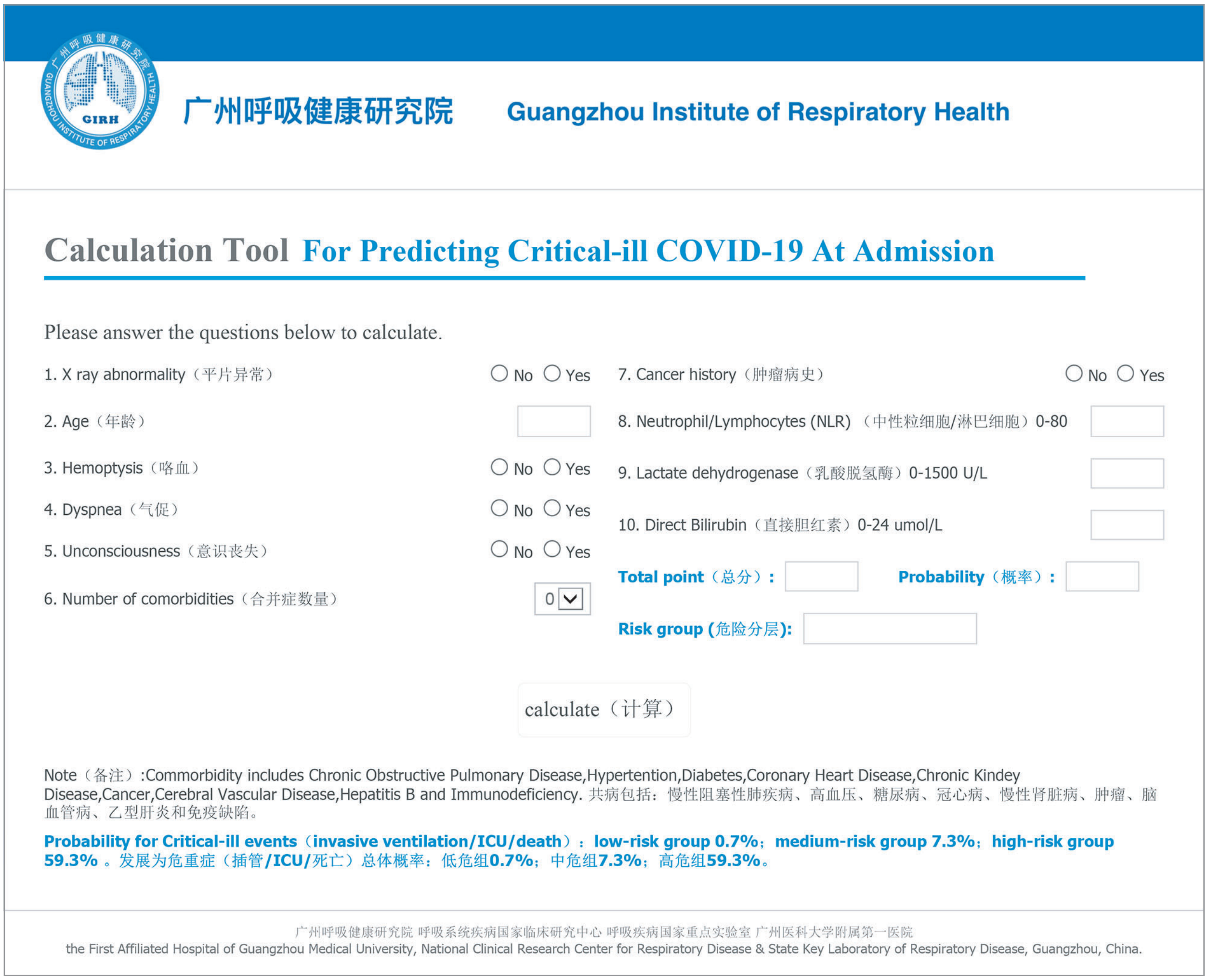
Validation of COVID-GRAM

The validation cohort included 710 patients with a mean (SD) age of 48.2 (15.2) years, 382 (53.8%) were men and 172 (24.2%) had at least 1 coexisting condition. Critical illness eventually developed in 87 (12.3%) of these patients and 8 (1.1%) died. Variables used in COVID risk score for the validation cohort are shown in **Table 4**; eTable 1 in the Supplement. The accuracy of COVID risk score in the validation cohort was similar to that of the development cohort with an AUC in the validation cohort of 0.88 (95% CI, 0.84-0.93) (eFigures 3 and 4 and eTable 2 in the Supplement).

Discussion

In this study, we developed and validated a clinical risk score and a web-based risk calculator to predict the development of critical illness among hospitalized COVID-19 infected patients. The performance of this risk score was satisfactory with accuracy based on AUCs in both the development and validation cohorts of 0.88. The web-based calculator can be used by clinicians to estimate an individual hospitalized patient's risk of developing critical illness. The 10 variables required for calculation of the risk of develop-

Figure. The Online Web-Based Calculator[a] for Predicting Critical Illness Among Patients With COVID-19



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Calculation Tool For Predicting Critical-ill COVID-19 At Admission

Please answer the questions below to calculate.

1. X ray abnormality（平片异常） ○ No ○ Yes
2. Age（年龄） ☐
3. Hemoptysis（咯血） ○ No ○ Yes
4. Dyspnea（气促） ○ No ○ Yes
5. Unconsciousness（意识丧失） ○ No ○ Yes
6. Number of comorbidities（合并症数量） 0
7. Cancer history（肿瘤病史） ○ No ○ Yes
8. Neutrophil/Lymphocytes (NLR) （中性粒细胞/淋巴细胞）0-80 ☐
9. Lactate dehydrogenase（乳酸脱氢酶）0-1500 U/L ☐
10. Direct Bilirubin（直接胆红素）0-24 umol/L ☐

Total point（总分）： ☐ **Probability（概率）：** ☐

Risk group (危险分层): ☐

Note（备注）:Commorbidity includes Chronic Obstructive Pulmonary Disease,Hypertention,Diabetes,Coronary Heart Disease,Chronic Kindey Disease,Cancer,Cerebral Vascular Disease,Hepatitis B and Immunodeficiency. 共病包括：慢性阻塞性肺疾病、高血压、糖尿病、冠心病、慢性肾脏病、肿瘤、脑血管病、乙型肝炎和免疫缺陷。

Probability for Critical-ill events（invasive ventilation/ICU/death）：low-risk group 0.7%；medium-risk group 7.3%；high-risk group 59.3% 。发展为危重症（插管/ICU/死亡）总体概率：低危组0.7%；中危组7.3%；高危组59.3%。

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[a] Guangzhou Institute of Respiratory Health is responsible for the web-based calculator (http://118.126.104.170/).

ing critical illness are generally readily available at hospital admission, and the web-based calculator is easy to use. If the patient's estimated risk for critical illness is low, the clinician may choose to monitor, whereas high-risk estimates might support aggressive treatment or admission to the ICU. We deliberately did not categorize risk into low-, moderate-, and high-risk groups, as we believe that clinicians are better informed by calculating the risk estimate for each individual patient and making decisions based on local or regional conditions. For example, in areas with good access to clinical and supportive care, patient outcomes might be optimized by deciding to provide more aggressive care to moderate risk patients. In contrast, in areas with high case volume and/or limited resources, the decision might be to provide less aggressive care to moderate-risk patients to maximize availability of ICU beds and ventilators.

Chest radiography abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin were included in the COVID risk score. Previous studies have found several of these variables to be risk factors for severe illness related to COVID-19. Wu et al[3] found that older age and more comorbidities were associated with a higher risk of developing ARDS in patients infected with COVID-19. A previous study[10] from our group found that patients with COVID-19 with cancer had higher risk of severe events compared with patients without cancer (39% vs 18%). Zhou and colleagues[1] found lower lymphocyte count, higher lactate dehydrogenase, and more imaging abnormalities in patients who died from COVID-19 disease.

Limitations

Potential limitations of this study include a modest sample size for constructing the risk score and a relatively small sample for validation. The data for score development and validation are entirely from China, which could potentially limit the generalizability of the risk score in other areas of the world. Additional validation studies of the COVID risk score from areas outside China should be completed.

Table 4. Demographics and Clinical Characteristics of Patients in Validation Cohorts

Characteristic	No./No. (%) Validation cohort, total	Critical illness No	Critical illness Yes
No.	729	642	87
Age, mean (SD) [range], y	48.2 (15.2) [4-88]	46.2 (14.3)	63.1 (13.1)
Neutrophil-lymphocyte ratio	5.8 (8.7) [0.08-109.2]	4.3 (3.8)	17.1 (20.0)
Lactate dehydrogenase, mean (SD) [range], U/L	288.3 (151.2) [106-1390]	264.1 (119.6)	479.5 (223.8)
Direct bilirubin, mean (SD) [range], umol/L	9.7 (9.6) [0-79]	9.1 (9.5)	14.1 (9.8)
Abnormal chest radiograph	355/723 (49.1)	277/639 (43.3)	78/84 (92.9)
Hemoptysis	8/724 (1.1)	7/642 (1.0)	1/82 (1.2)
Shortness of breath	118/724 (16.3)	70/642 (10.9)	48/82 (58.5)
Unconsciousness	6/724 (0.8)	0/642 (0)	6/82 (0.7)
Comorbidities			
0	550/722 (76.2)	521/642 (81.2)	29/80 (36.3)
1	103/722 (14.3)	83/642 (12.9)	20/80 (25.0)
2	56/722 (7.8)	33/642 (5.1)	23/80 (28.8)
3	10/722 (1.4)	3/642 (0.4)	7/80 (8.8)
4	3/722 (0.4)	2/642 (0.3)	1/80 (1.3)
Malignant disease	9/723 (1.2)	9/642 (1.4)	0/81 (0)

Conclusions

In this study, we developed a risk score and web-based calculator to estimate the risk of developing critical illness among patients with COVID-19 based on 10 variables commonly measured on admission to the hospital. Estimating the risk of critical illness could help identify patients who are and are not likely to develop critical illness, thus supporting appropriate treatment and optimizing the use of medical resources.

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