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Early prediction model for progression and prognosis of severe patients with coronavirus disease 2019

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Abstract

Coronavirus disease 2019 (COVID-19) has been a rampant worldwide health threat and we aimed to develop a model for early prediction of disease progression.

This retrospective study included 124 adult inpatients with COVID-19 who presented with severe illness at admission and had a definite outcome (recovered or progressed to critical illness) during February 2020. Eighty-four patients were used as training cohort and 40 patients as validation cohort. Logistic regression analysis and receiver operating characteristic curve (ROC) analysis were used to develop and evaluate the prognostic prediction model.

In the training cohort, the mean age was 63.4 ± 1.5 years, and male patients (48, 57%) were predominant. Forty-three (52%) recovered, and 41 (49%) progressed to critical. Decreased lymphocyte count (LC, odds ratio [OR] = 4.40, $P = .026$), elevated lactate dehydrogenase levels (LDH, OR = 4.24, $P = .030$), and high-sensitivity C-reactive protein (hsCRP, OR = 1.01, $P = .025$) at admission were independently associated with higher odds of deteriorated outcome. Accordingly, we developed a predictive model for disease progression based on the levels of the 3 risk factors (LC, LDH, and hsCRP) with a satisfactory performance in ROC analysis (area under the ROC curve [AUC] = 0.88, $P < .001$) and the best cut-off value was 0.526 with the sensitivity and specificity of 75.0% and 90.7%, respectively. Then, the model was internally validated by leave-one-out cross-validation with value of AUC 0.85 ($P < .001$) and externally validated in another validation cohort (26 recovered patients and 14 progressed patients) with AUC 0.84 ($P < .001$).

We identified 3 clinical indicators of risk of progression and developed a severe COVID-19 prognostic prediction model, allowing early identification and intervention of high-risk patients being critically illness.

Abbreviations: AUC = area under the ROC curve, CI = confidence interval, COVID-19 = coronavirus disease 2019, CT = computed tomography, cTnI = cardiac troponin I, ESR = erythrocyte sedimentation rate, FiO_2 = fraction of inspired oxygen, hsCRP = high-sensitivity C-reactive protein, ICU = intensive care unit, IL-6 = interleukin-6, IQR = interquartile range, LDH = lactate dehydrogenase, NT-proBNP = N-terminal brain natriuretic propeptide, PaO_2 = partial pressure arterial oxygen, PCT = procalcitonin, ROC = receiver operating characteristic curve, RT-PCR = real time reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SE = standard error, SpO_2 = percutaneous blood oxygen saturation.

Keywords: Coronavirus disease 2019, disease progression, prediction model

1. Introduction

Coronavirus is an important class of pathogens that can cause diseases ranging from the mild colds to fatal respiratory infections in humans. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly recognized coronavirus, causing coronavirus disease 2019 (COVID-19).[1] COVID-19 is a rampant worldwide health threat, which is prone to transmit in family clusters or cause outbreaks in hospitals. As of November 23, 2020, the global total number of SARS-Cov-2 infections has exceeded 58,000,000, and >1370,000 people have died.[2] The outbreak of COVID-19 has constituted a threatening global public health emergency of great international concern.

The clinical onset symptoms of COVID-19 include fever, dry cough, fatigue, diarrhea, loss of taste and smell, chest tightness, lymphocytopenia, and pneumonia.[3,4] Most patients with COVID-19 present with mild or moderate symptoms; however, patients with severe illness may develop hypoxemia within 1 week after onset of the disease, which may quickly deteriorate to acute respiratory distress syndrome, multiple organ dysfunction syndrome, or even death.[5–7] No vaccine against SARS-CoV-2 or specific antiviral therapy has been proven to be absolutely effective. So far, it has been reported that nearly one-third of patients with COVID-19 are prone to develop critical illness.[3,5] Once the patient progresses to critical illness, the mortality rate will greatly increase.[4] Thus, early identification and more

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effective treatment of those at high risk of progressing to critical illness are of paramount importance to reduce the mortality rate.

Most previous studies have only reported the epidemiological investigations, clinical manifestations, clinical outcomes of SARS-Cov-2 infections, or focused more on non-survivors.[3–8] However, risk factors leading to progression of poor clinical outcomes from severe to critical illness have not been well delineated. In this study, we aimed to evaluate the associated risk factors and develop a prediction model for the early identification of severely ill patients who are at risk of progressing to critically ill and most likely to benefit from initiating intensive care treatment as early as possible.

2. Materials and methods

2.1. Study design and participants

This retrospective study included a consecutive case series of 124 adult inpatients (≥18 years old) from Sino-French Branch of Tongji Hospital (Wuhan, China), which was a designed hospital for treatment of severe or critically ill patients with COVID-19. All 124 patients diagnosed with COVID-19 were initially presented as severe patients at the time of admission, and had a definite outcome (recovered and discharged, or progressed from severe to critical illness) between February 1, 2020 (when the patients were first admitted) and February 28, 2020. Of all the 124 patients, data of 84 patients from 2 wards were first collected as training cohort for model development; and then data of 40 patients from another ward were used as validation cohort.

The clinical classifications of patients with COVID-19 were defined in accordance with the guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) issued by the National Health Commission of China.[9] Patients meeting at least one of following items should be identified as severe cases: respiratory rates ≥30 breaths/min; SpO_2 ≤93% at rest; partial pressure arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio ≤300; pulmonary imaging lesions progressed over 50% within 24 to 48 hours. Patients meeting any of following items should be identified as critically ill cases: shock; respiratory failure requires mechanical ventilation; complications of other organ failure occur; and patients require treatment in intensive care unit (ICU). All the recovered patients had completely remission of symptoms and signs, had substantial improvement of pulmonary and extrapulmonary organ dysfunction, no longer required supportive care, and confirmed viral clearance before discharge. Accordingly, in the training cohort, 84 initial severe patients were categorized based on the clinical outcome of our analysis as recovered group (patients recovered from severe to discharge, n=43) and progressed group (patients progressed from severe to critical illness, n=41), as defined by above recommend standards; and in the validation cohort, 24 patients and 16 patients were categorized as recovered group and progressed group, respectively.

All subjects gave their oral informed consent for inclusion before they participated in the study. The study was approved by the Research Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (No. S130).

2.2. Data collection

Archives arrangement and analysis of all the participants was performed from admission logs and histories in all available electronic medical records. We retrospectively reviewed all clinical electronic medical records, including admission records, progress notes, and nursing records for all patients with COVID-19. Information on demographic characteristics, chronic medical histories, clinical symptoms from onset to transferring to Tongji Hospital, vital signs at admission, laboratory findings, and chest computed tomography (CT) scans were collected. Front-line residents who treat patients collected the admission information of patients. Any missing or uncertain information was collected and confirmed as possible through direct communication with these patients and their families.

2.3. Laboratory procedures

All the patients were laboratory confirmed by local Chinese Center for Disease Control and Prevention prior to admission. Method for laboratory confirmation of SARS-CoV-2 infection was using respiratory or archenteric specimens by real time reverse transcription polymerase chain reaction (RT-PCR) or next-generation sequencing. After hospital admission, throat-swab or archenteric specimens were obtained for SARS-CoV-2 PCR re-measurement. The detail for RT-PCR assay for SARS-Cov-2 has been described previously.[10] Two consecutive tests of SARS-CoV-2 PCR at least 24 hours apart should be negative before discharge.

Laboratory values were obtained by routine tests including hematologic and urine routine tests, serum biochemical indexes (including liver and renal function, lipid, lactate dehydrogenase [LDH], and electrolytes), N-terminal brain natriuretic propeptide (NT-proBNP), Cardiac troponin I (cTnI), coagulation function tests, and inflammation markers (including high-sensitivity C-reactive protein [hsCRP], interleukin-6 [IL-6], serum ferritin, procalcitonin [PCT], and erythrocyte sedimentation rate [ESR]). The frequency of laboratory examinations was determined by illness severity and treatment effect. The baseline laboratory data shown in the Results section were collected once the patients were admitted while the fasting plasma and serum samples for the respective fasting blood glucose and lipids tests were collected the next early morning. The endpoint laboratory data were the last tests before the patients recovered or progressed to critically illness.

2.4. Statistical analysis

Data are presented as mean ± SE or median (interquartile range, IQR) for continuous variables and percentage for categorical variables. Comparisons between the recovered and progressed groups were analyzed using Student's *t* test and Mann–Whitney *U* test for normally distributed and non-normally distributed respectively for continuous variables, and chi-squared test or Fisher exact test for categorical variables. Logistic regression analysis was used to explore the risk factors and to develop a model for prediction of adverse outcome from severe to critical illness. Having considered the total number of patients (n=84) in the training cohort and to avoid overfitting in the model, no >8 variables without colinearity were selected for multivariable analysis on the basis of previous findings,[11–14] clinical implications, and the significant different variables between 2 groups (recovered group and progressed group). Multivariable logistic stepwise backward regression was used to choose the best final predictive model. Receiver operating characteristic curve (ROC) analysis was constructed to assess the predictive performance for adverse outcome according to the value of area under the ROC curve (AUC). Furthermore, we used leave-one-out cross-validation to internally validate the performance of the

logistic predictive model and another validation cohort (n = 40) for external validation. R version 3.0.2 software (R Core Team (2015), R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 20.0 software (SPSS Inc., Chicago, IL) were used for statistical analysis. Statistical significance was defined by a 2 sided P value $<.05$.

3. Results

3.1. Demographics and baseline characteristics of recovered and progressed patients with severe COVID-19

The training cohort included 84 hospitalized patients with confirmed COVID-2019. They were all identified as severe cases at admission. Demographics and baseline characteristics at admission are presented in Table 1. The mean age was 63.4 ± 1.5 years, and 48 (57%) were men. Comorbidities were present in 60 (71%) patients. Hypertension was the most common comorbidity, followed by diabetes and cardiovascular disease. The most common manifestations at onset were fever (68 [81%]), dry cough (65 [77%]), fatigue (34 [41%]), diarrhea (29 [35%]), and myalgia (26 [31%]). Since Tongji Hospital is the designated hospital for the treatment of severe cases with confirmed COVID-2019, patients admitted to the hospital had been often manifested with dyspnea (50 [60%]) and chest tightness (30 [36%]). Less common symptoms were headache, hemoptysis, nausea or vomiting, anorexia, and palpitation.

Of these 84 severe patients, 43 (52%) were recovered and then discharged, and 41 (49%) were progressed to critically ill patients during our follow-up. The mean age of progressed patients was older than recovered patients (67.0 ± 1.9 vs 60.1 ± 2.3 years, $P = .023$), but sex and comorbidities showed no significant differences across groups. Most of the patients in both groups had fever, dry cough, chest tightness, or dyspnea. Compared with progressed patients, the recovered patients were more likely to have fatigue (24 [56%] vs 10 [24%]), myalgia (18 [42%] vs 8 [20%]), headache (9 [21%] vs 2 [5%]), nausea or vomiting (9 [21%] vs 1 [2%]), and palpitation (8 [19%] vs 1 [2%]) ($P < .05$ for each). However, the progressed patients were likely to present a higher heart rate (100 ± 3.7 vs 91 ± 2.3 beats per min) and respiratory rate (24 [IQR, 20–28] vs 22 [IQR, 20–24] breaths per min), and lower percutaneous oxygen saturation (91% [IQR, 85–95] vs 96% [IQR, 93–98]) ($P < .05$ for each) than the recovered patients at hospital admission.

3.2. Baseline laboratory parameters and CT scans of recovered and progressed patients with severe COVID-19

Laboratory findings at hospital admission are summarized in Table 2. Of all the patients in the training cohort, median levels of

Table 1

Demographics and baseline characteristics of severe patients with COVID-19 who recovered and progressed in the training cohort.

Characteristics	Total (n = 84)	Recovered patients (n = 43)	Progressed patients (n = 41)	*P* value
Age, y	63.4 ± 1.5	60.1 ± 2.3	67.0 ± 1.9	.023
Gender				.257
Female	36 (43%)	21 (49%)	15 (37%)	
Male	48 (57%)	22 (51%)	26 (63%)	
Comorbidity				
Hypertension	34 (41%)	18 (42%)	16 (39%)	.791
Diabetes	16 (19%)	7 (16%)	9 (22%)	.508
Cardiovascular disease	12 (14%)	7 (16%)	5 (12%)	.593
Chronic lung disease	9 (11%)	4 (9%)	5 (12%)	.668
Chronic kidney disease	10 (12%)	8 (19%)	2 (5%)	.089
chronic liver disease	3 (4%)	0 (0%)	3 (7%)	.112
Malignancy	2 (2%)	0 (0%)	2 (5%)	.235
Signs and symptoms				
Fever	68 (81%)	33 (77%)	35 (85%)	.314
Cough	65 (77%)	33 (77%)	32 (78%)	.886
Fatigue	34 (41%)	24 (56%)	10 (24%)	.003
Myalgia	26 (31%)	18 (42%)	8 (20%)	.027
Headache	11 (13%)	9 (21%)	2 (5%)	.049
Chest tightness	30 (36%)	19 (44%)	11 (27%)	.097
Dyspnea	50 (60%)	23 (54%)	27 (66%)	.248
Hemoptysis	7 (8%)	5 (12%)	2 (5%)	.434
Diarrhea	29 (35%)	15 (35%)	14 (34%)	.943
Nausea or vomiting	10 (12%)	9 (21%)	1 (2%)	.015
Anorexia	15 (18%)	10 (23%)	5 (12%)	.186
Palpitation	9 (11%)	8 (19%)	1 (2%)	.030
Vital signs at admission				
Systolic pressure, mm Hg	133 ± 2.5	133 ± 3.6	132 ± 3.5	.907
Heart rate, bpm	96 ± 2.2	91 ± 2.3	100 ± 3.7	.042
Respiratory rate, per min	22 (20, 25)	22 (20, 24)	24 (20, 28)	.014
Percutaneous oxygen saturation, %	95 (88, 97)	96 (93, 98)	91 (85, 95)	.001
Days from illness onset to first outpatient visit	5 (0, 11)	8 (0, 14)	4 (1, 9)	.170
Days from illness onset to hospital admission	13 (8, 18)	16 (11, 26)	9 (7, 14)	<.001

Data are presented as mean ± SE or median (interquartile range) for continuous variables and n (%) for categorical variables. *P* values comparing patients who recovered and progressed are from Chi-squared test, Fisher exact test, Student *t* test, or Mann–Whitney *U* test. bpm = beats per min; COVID-19 = coronavirus disease 2019.

lymphocyte count (0.8×10^9/L [IQR, 0.5–1.2], decreased), hemoglobin (125 g/L [IQR, 116–141], decreased), albumin (34 g/L [IQR, 30–38], decreased), LDH (332 U/L [IQR, 246–466], increased), fibrinogen (4.8 g/L [IQR, 3.6–6.4], increased), D-dimer (1.4 μg/mL [IQR, 0.8–5.1], increased), hsCRP (43 mg/L [IQR, 6–110], increased), IL-6 (31 pg/mL [IQR, 4–68], increased), serum ferritin (834 μg/L [IQR, 351–1373], increased), PCT (0.10 ng/mL [IQR, 0.04–0.46], increased), and ESR (36 mm/h [IQR, 23–67], increased) were deviated from normal reference.

Markedly, compared with recovered patients, progressed patients showed significantly decreased level of lymphocyte count ($P < .001$) and increased levels of multiple indicators of inflammation, such as neutrophil count, hsCRP, IL-6, serum ferritin, and PCT ($P < .05$ for each). In the damage functional indicators of liver and heart, the median levels of aspartate aminotransferase, total bilirubin, LDH, hypersensitive cTnI, and NT-proBNP ($P < .05$ for each) were significant elevated in progressed patients. Furthermore, the progressed patients might also have worse coagulation function as indicated as higher levels of D-dimer ($P = .001$) and prothrombin time ($P < .001$), as well as lower levels of platelet count ($P = .006$) and prothrombin activity ($P < .001$). In terms of kidney injury, the progressed patients were more likely to be positive for urinary protein ($P < .001$) and occult ($P < .001$). There were also significantly differences in the levels of blood urea nitrogen ($P = .003$) and serum bicarbonate ($P = .004$) between 2 groups. In addition, a small number of patients underwent lymphocyte subgroup analysis and showed that the number of $CD4^+$ T cells and $CD8^+$ T cells was markedly lower in the progressed cases than recovered cases ($P < .001$, Supplementary table S1, http://links.lww.com/MD/F813).

Interstitial lung abnormalities were observed in chest CT scans of all patients. The typical findings of pulmonary lesions of progressed patients with severe COVID-19 group showed significant deterioration on chest CT images, with rapid progression from initial bilateral ground glass opacity to subsegmental consolidation and even "white lung" (Supplementary Figure S1, http://links.lww.com/MD/F812).

3.3. Development of a model for prediction of disease progression

To establish a predictive model which could be efficiently used for early identification of severe patients who might progress to critically ill patients, we first performed a multivariate logistic regression analysis (Table 3) to find the most associated risk factors in the training cohort. According to the previous literature[11–14] and the different variables between 2 groups, we chose one representative indicator in each aspect of demographics, signs and symptoms, and function of organs, etc. Therefore, 8 significant baseline variables (age, lymphocyte count, LDH, D-dimer, hsCRP, albumin, blood urea nitrogen, and percutaneous oxygen saturation) were initially introduced into the analysis. To optimize the combination and avoid overfitting, stepwise backward selection was performed to determine the best model. Finally, 3 variables remained statistically significant, which showed that disease progression from severe to critical illness was independent associated with decreased lymphocyte count ($<0.8 \times 10^9$/L, odds ratio [OR] = 4.40, 95% confidence interval [CI] 1.20–16.16, $P = .026$), elevated LDH (>350 U/L, OR = 4.24, 95% CI 1.15–15.65, $P = .030$), and hsCRP (OR = 1.01, 95% CI 1.00–1.02, $P = .025$) at admission after adjustment for other variables. Consistently, the levels of these 3 indicators (lymphocyte count, LDH, and hsCRP) were even more significantly different when the patients finally recovered or progress to critical illness ($P < .05$ for each, Fig. 1).

Then, the final best model was determined using logistic regression analysis based on the 3 independent significant variables, resulting a new variable calculated as following: $P_{(\text{index})} = -0.673 + 0.005 \times [\text{LDH, U/L}] - 1.950 \times [\text{lymphocyte count, } 10^9\text{/L}] + 0.007 \times [\text{hsCRP, mg/L}]$. The model was tested to be significant using a likelihood test ($X^2 = 40.76$, $P < .001$).

3.4. Efficiency of the model for prediction of disease progression

The predictive performance of the model was assessed with ROC analysis. As shown in Fig. 2A, the AUC value of the model was 0.88 (95% CI 0.80–0.95, $P < .001$) in the training cohort. When the Youden index reached the maximum, the optimal cutoff point was >0.526. The corresponding sensitivity, specificity, positive predictive value, and negative predictive value were 75.0%, 90.7%, 88.2%, and 79.6%, respectively. That means if the value of $P_{(\text{index})}$ is above 0.526, the severe patient with COVID-19 will be possibly predicted as the one who might progress to critically ill patient.

Furthermore, we used leave-one-out cross-validation to internally validate the efficiency of the predictive model in the training cohort. The resulting AUC was 0.85 (95% CI 0.76–0.93, $P < .001$). In addition, another validation cohort including 40 patients (26 recovered and 14 progressed) with COVID-19 was used to externally validate the discriminatory efficiency of the model. The demographics and baseline characteristics of validation cohort were shown in the Supplementary Table S2, http://links.lww.com/MD/F814 and Supplementary Table S3, http://links.lww.com/MD/F815. ROC analysis showed the AUC was 0.84 (95% CI 0.69–0.95, $P < .0001$) with the corresponding sensitivity and specificity of 85.7% and 80.8%, respectively (Fig. 2B).

4. Discussion

In this retrospective cohort study, we comprehensively delineated the differences in clinical characteristics between patients with severe COVID-19 who recovered after admission and those who progressed to critical illness. In the training cohort (43 recovered patients and 41 progressed patients), compared with the recovered patients, the patients who progressed were more likely to be older in age, and have more severe lymphocytopenia, systematic inflammation, and multiple organ (lung, heart, liver, and kidney) injury and coagulation dysfunction. As further noted in the multivariable logistic regression analysis, decreased lymphocyte count and increased LDH and hsCRP at admission were independently associated with higher odds of poor outcome. Accordingly, we then developed a predictive model based on the 3 baseline variables (lymphocyte count, LDH, and hsCRP) for prediction of severe patients who are at risk of becoming critically ill. The predictive model presented a satisfactory discriminated performance in the ROC analysis (AUC = 0.88, $P < .001$). In addition, the model was internally validated by leave-one-out cross-validation with value of AUC 0.85 ($P < .001$) and externally validated in another validation cohort (26 recovered patients and 14 progressed patients) with AUC 0.84 ($P < .001$).

Table 2

Laboratory findings at hospital admission of severe patients with COVID-19 who recovered and progressed in the training cohort.

	Normal range	Total (n = 84)	Recovered patients (n = 43)	Progressed patients (n = 41)	*P* value
Hematologic					
White blood cell count, $\times 10^9$/L	3.5–9.5	6.5 (4.6, 10.2)	5.1 (4.5, 6.8)	8.2 (5.9, 12.1)	<.001
<4		10 (12%)	6 (14%)	4 (10%)	<.001
4–10		52 (62%)	35 (81%)	17 (42%)	
>10		22 (26%)	2 (5%)	20 (49%)	
Neutrophil count, $\times 10^9$/L	1.8–6.3	4.6 (3.2, 8.7)	3.8 (2.7, 4.6)	7.7 (4.8, 11.1)	<.001
<1.8		3 (4%)	1 (2%)	2 (5%)	<.001
>6.3		26 (31%)	3 (7%)	23 (57%)	
Lymphocyte count, $\times 10^9$/L	1.1–3.2	0.8 (0.5, 1.2)	1.2 (0.7, 1.5)	0.6 (0.4, 0.9)	<.001
<0.8		42 (50%)	12 (28%)	30 (73%)	<0.001
Hemoglobin, g/L	130–175	125 (116, 141)	121 (113, 129)	136 (123, 149)	.001
<110		12 (14%)	8 (19%)	4 (10%)	.352
Platelet count, $\times 10^9$/L	125–350	201 (152, 282)	247 (168, 303)	179 (143, 229)	.006
<100		6 (7%)	2 (5%)	4 (10%)	.427
Biochemical					
Alanine aminotransferase, U/L	≤41	26 (15, 40)	24 (13, 40)	28 (18, 40)	.213
Aspartate aminotransferase, U/L	≤40	29 (20, 45)	23 (19, 35)	35 (27, 46)	.002
>40		24 (29%)	9 (21%)	15 (37%)	.112
Albumin, g/L	35.0–52.0	34 (30, 38)	35 (32, 38)	32 (29, 36)	.019
<32		32 (38%)	11 (26%)	21 (51%)	.016
Total bilirubin, mmol/L	≤26	10 (7, 15)	8 (6, 12)	12 (9, 19)	<.001
Blood urea nitrogen, mmol/L	3.1–8.0	5.5 (4.2, 9.3)	4.7 (3.6, 6.5)	6.2 (5.3, 10.0)	.003
Creatinine, μmol/L	59–104	73 (61, 94)	69 (58, 94)	77 (64, 98)	.455
>133		14 (17%)	8 (19%)	6 (15%)	.625
Serum uric acid, μmol/L	202–417	259 (178, 342)	259 (172, 334)	259 (182, 344)	.694
Serum bicarbonate, mmol/l	22–29	24 (21, 25)	25 (24, 26)	22 (20, 25)	.004
Potassium, mmol/L	3.5–5.1	4.4 (4.0, 4.8)	4.4 (4.0, 4.9)	4.4 (4.0, 4.8)	.823
Sodium, mmol/L	136–145	140 (137, 142)	140 (139, 142)	138 (135, 142)	.157
Triglycerides, mmol/L	<1.7	1.4 (1.0, 2.0)	1.3 (1.0, 1.8)	1.6 (1.2, 2.0)	.373
Total cholesterol, mmol/L	<5.2	3.7 (3.2, 4.2)	3.8 (3.3, 4.3)	3.7 (3.0, 4.0)	.088
Lactate dehydrogenase, U/L	135–225	332 (246, 466)	266 (224, 351)	456 (332, 538)	<.001
>350		41 (49%)	11 (26%)	30 (73%)	<.001
Hypersensitive cardiac troponin I, pg/mL	≤34.2	10.2 (3.9, 29.8)	4.5 (3.2, 11.3)	20.8 (8.6, 120.2)	<.001
>34.2		14/73 (19%)	2/35 (6%)	12/38 (32%)	.007
N-terminal pro-brain natriuretic peptide, pg/mL	<285	250 (111, 1495)	179 (65, 629)	756 (187, 1925)	.003
≥285		37/76 (49%)	12/37 (32%)	25/39 (64%)	.006
Coagulation function					
Prothrombin time, s	11.5–14.5	14.3 (13.5, 14.9)	13.8 (13.2, 14.4)	14.7 (14.0, 16.0)	<.001
Prothrombin activity, %	75–125	86 (80, 97)	94 (86, 101)	81 (68, 90)	<.001
Fibrinogen, g/L	2–4	4.8 (3.6, 6.4)	4.6 (3.6, 5.3)	5.6 (3.2, 7.1)	.348
D-dimer, μg/mL	<0.5	1.4 (0.8, 5.1)	1.1 (0.4, 2.2)	1.8 (1.1, 14.6)	.001
>1.0		40/82 (49%)	8/28 (29%)	32/54 (59%)	.002
Inflammation indicators					
High-sensitivity C-reactive protein, mg/L	<1	43 (6, 110)	11 (2, 64)	78 (37, 211)	<.001
>60		35/83 (42%)	11/43 (26%)	24/40 (60%)	.002
Interleukin 6, pg/mL	<7	31 (4, 68)	7 (2, 38)	62 (30, 118)	<.001
Serum ferritin, μg/L	30–400	834 (351, 1373)	515 (239, 1069)	1307 (800, 2547)	<.001
>800		37/71 (52%)	13/40 (33%)	24/31 (77%)	<.001
Procalcitonin, ng/mL	0.02–0.05	0.10 (0.04, 0.46)	0.06 (0.01, 0.16)	0.12 (0.08, 0.67)	.002
≥0.5		18/75 (24%)	7/36 (19%)	11/39 (28%)	.375
Erythrocyte sedimentation rate, mm/h	0–15	36 (23, 67)	38 (24, 60)	36 (18, 70)	.918
Urine test					
Positive urinary protein	Negative	30/63 (48%)	11/41 (27%)	19/22 (86%)	<.001
Positive urinary occult blood	Negative	39/63 (62%)	18/41 (44%)	21/22 (96%)	<.001

Data are median (IQR) or n/N (%), where N is the total number of patients with available data. *P* values comparing patients who recovered and progressed are from chi-squared test, Fisher exact test, or Mann–Whitney *U* test. COVID-19 = coronavirus disease 2019.

The pathogenesis of human coronavirus is still not completely illustrated. Early previous studies have demonstrated that increases in serum proinflammatory cytokines were associated with extensive lung damage and inflammation in patients infected with SARS-CoV and Middle East respiratory syndrome coronavirus.[15,16] In our analysis, patients who progressed to critical illness were more likely to contract secondary bacterial infections (higher neutrophil count and PCT), or have elevated inflammatory indicators (hsCRP, IL-6, ferritin, and ESR). Furthermore, the elevated hsCRP was an independent predictor

Table 3

Risk factors associated with disease progression from severe to critical illness in patients with COVID-19.

Variables	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)*	*P* value
Age, y	1.04 (1.00–1.04)	.027	–	–
Lymphocyte count, $\times 10^9$/L				
≥0.8	1 (ref)	–	1 (ref)	–
<0 8	7.05 (2.70–18.40)	<.001	4.40 (1.20–16.16)	.026
Lactate dehydrogenase, U/L				
≤350	1 (ref)	–	1 (ref)	–
>350	7.93 (3.00–20.99)	<.001	4.24 (1.15–15.65)	.030
Albumin, g/L	0.88 (0.80–0.98)	.015	–	–
Blood urea nitrogen, mmol/L	1.01 (0.96–1.07)	.644	–	–
D-dimer, μg/mL				
<1.0	1 (ref)	–	–	–
≥1.0	3.64 (1.36–9.72)	–	–	–
High-sensitivity C-reactive protein, mg/L	1.02 (1.01–1.02)	<.001	1.01 (1.00–1.02)	.025
Percutaneous oxygen saturation, %	0.87 (0.79–0.96)	.005	–	–

CI = confidence interval; ref, reference; COVID-19 = coronavirus disease 2019; OR = odds ratio.

* Variables were adjusted for age, albumin, blood urea nitrogen, D-dimer, and percutaneous oxygen saturation in the multivariable logistic regression analysis.

of disease progression from severe to critical illness, indicating that systematic inflammation also plays an important role in the severity and progression of COVID-19. Previous evidence suggested cytokine storm syndrome observed in patients with COVID-19 who died. A recent retrospective, multicenter study reported predictors of fatality included elevated ferritin and IL-6 though an analysis of 150 patients with confirmed COVID-19 in Wuhan, China, suggesting that mortality might be due to virally driven hyperinflammation.[17] Thus, we theorized that the hyperinflammation might initiate before the patient becomes critically ill. At the same time, secondary bacterial infections also deserve attention. It is crucial to identify and treat hyper-inflammation as early as possible to reduce the adverse outcome in patients with COVID-19.

Patients who progressed had more severe lymphocytopenia at admission compared with patients who recovered. In addition, the number of $CD4^+$ and $CD8^+$ T cells was significantly lower in the progressed group than in recovered group, suggesting that a state of cellular immunodeficiency was associated with the severity and disease progression. A recent study has also revealed that the SARS-CoV-2 infection may mainly affect T lymphocytes, especially $CD4^+$ and $CD8^+$ T cells, and IFN-γ production.[18] Defections in T-cell and B-cell function and excessive production of type 2 cytokines might lead to an inadequate control of viral replication and a longer proinflammatory response, potentially resulting in poor outcomes.[19] Further studies are necessary to characterize the lymphocyte response or CD4 and CD8T cells immune response in patients with COVID-19 and to elucidate its associated pathogenesis.

It is also noteworthy that patients who progressed presented with more severe pulmonary and extrapulmonary organ damage at admission. The elevation in LDH levels reflects destruction of tissue/cell. LDH is one of the most important and significant prognostic indicators of severe idiopathic pulmonary fibrosis and myocardial injury,[20] which deserves more of attention.

A few established prognostic models for COVID-19 have been reported in the previous literature, and most of them were used for mortality prediction.[14,21] However, we think it makes more

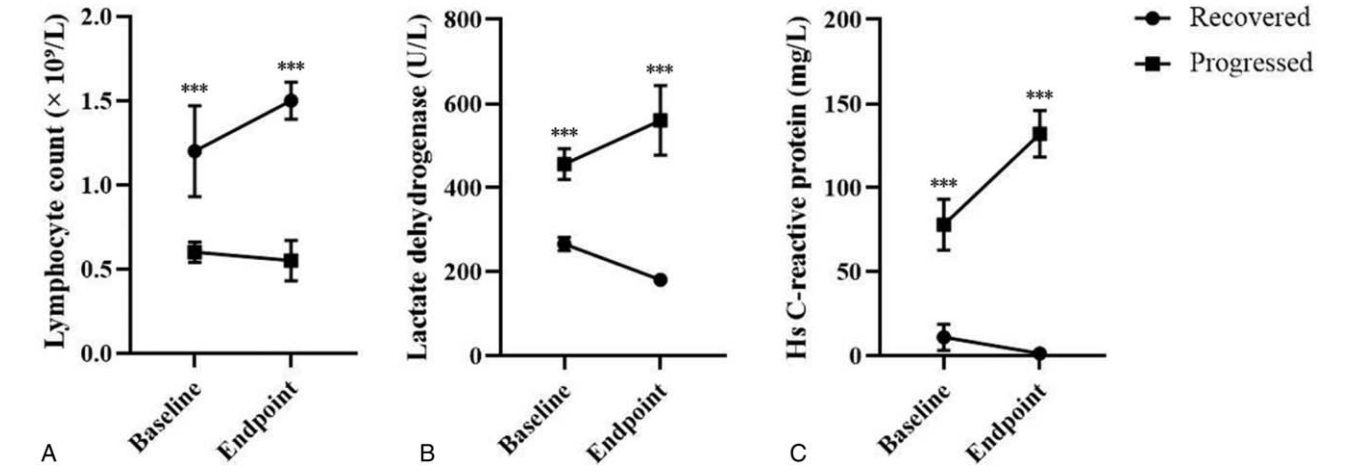

Figure 1. Trends of laboratory indicators changed with the course of disease. A. Lymphocyte count; B. Lactate dehydrogenase; C. High-sensitivity C-reactive protein. Baseline: the data of patients at hospital admission. Endpoint: at the time of the patients finally had a definite outcome (recovered and discharged, or progressed from severe to critical illness) during our observational period. *** *P* value comparing the patients between the recovered group and the progressed group are <.001.

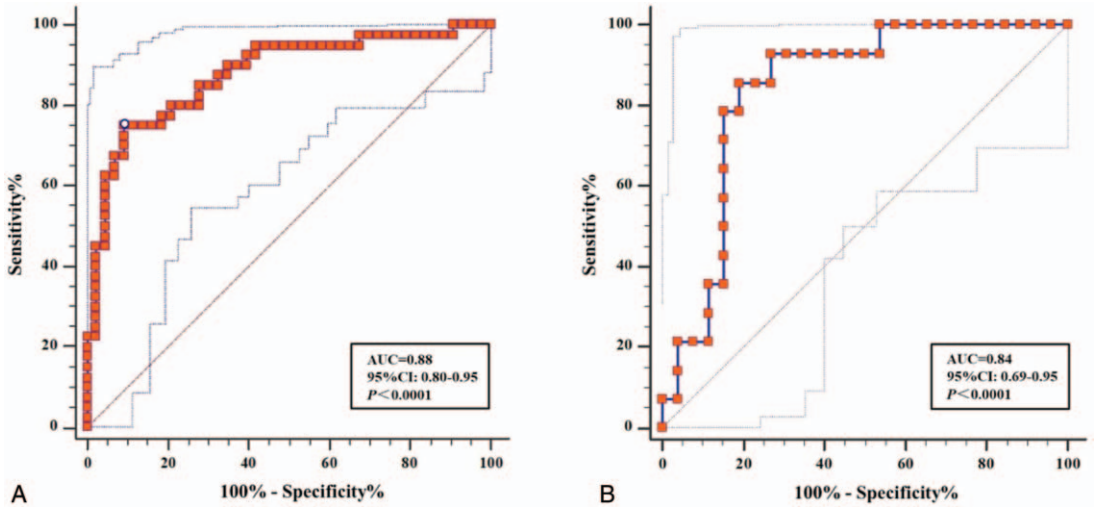

Figure 2. Receiver operating characteristic curve analysis of the model in predicting the cases progression from severe to critical illness in patients with COVID-19 in the training cohort (A) and validation cohort (B). COVID-19 = coronavirus disease 2019.

sense to predict who is at risk of disease progression rather than risk of mortality and provide effective treatment as early as possible, thereby resulting in greater benefits owing to potentially improve the prognosis of patients. There were two studies that developed models to predict progression to a severe or critical illness other than mortality. Allenbach et al[11] used data from single-center prospective cohort study evaluated 152 French patients with severe COVID-19 and found that older age, poorer respiratory presentation, higher CRP-level, and lower lymphocytes count were associated with an increased risk of ICU requirement or death. Gong et al[13] used 7 indicators, including age, CRP, LDH, albumin, direct bilirubin, blood urea nitrogen, and the coefficient of variation of red blood cell distribution width, to construct a model to identify non-severe cases who would progress to severe COVID-19. What separates them from us are that, we used backward stepwise regression to choose the optimal model to avoid overfitting, consisting of the least variables to achieve the best prediction performance. Thus, we used only 3 easily available variables (lymphocyte count, LDH, and hsCRP), after selection and adjustment for model development, proving the model convenient to use in clinical application. Moreover, the model showed a good efficiency in the training dataset. Not only that, it also has good discriminant performance in the internal (leave-one-out cross-validation) and external validation (another independent validation cohort), suggesting that the model had good stability and reliability.

However, there are some important facts to be acknowledged. This model was developed and validated based on the data from a single center in Wuhan; the generalizability to subjects in other settings and countries has not been verified. Moreover, sample size was limited during follow-up, as clinical outcomes had not yet been determined for more patients during the observation period. In addition, although this model consists of the least variables needed to achieve the best prediction performance, some medical centers may not test for the relevant indicators because of diverse practice guidelines and physician's practice patterns. It may be less applicability for these medical centers. Further validation is needed with another larger sample size, multi-centered study and, ideally, involving patients of different ethnic origins to verify the model's efficiency and the value for testing these laboratory indicators in medical centers.

5. Conclusions

This study identified 3 easily available clinical indicators (lymphocyte count, LDH, and hsCRP) for severe COVID-19 prognostic prediction. We also developed and validated a predictive model with excellent discriminant performance for early identification of severe cases who are at high risk of progressing to critically ill. Our model is particularly valuable for risk assessment and hierarchical management of patients, which will be helpful for early intensive intervention prior to disease deterioration in high-risk patients with severe COVID-19.

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