

Prediction for Progression Risk in Patients With COVID-19 Pneumonia: The CALL Score

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Background. We aimed to clarify high-risk factors for coronavirus disease 2019 (COVID-19) with multivariate analysis and establish a predictive model of disease progression to help clinicians better choose a therapeutic strategy.

Methods. All consecutive patients with COVID-19 admitted to Fuyang Second People's Hospital or the Fifth Medical Center of Chinese PLA General Hospital between 20 January and 22 February 2020 were enrolled and their clinical data were retrospectively collected. Multivariate Cox regression was used to identify risk factors associated with progression, which were then incorporated into a nomogram to establish a novel prediction scoring model. ROC was used to assess the performance of the model.

Results. Overall, 208 patients were divided into a stable group ($n = 168$, 80.8%) and a progressive group ($n = 40$, 19.2%) based on whether their conditions worsened during hospitalization. Univariate and multivariate analyses showed that comorbidity, older age, lower lymphocyte count, and higher lactate dehydrogenase at presentation were independent high-risk factors for COVID-19 progression. Incorporating these 4 factors, the nomogram achieved good concordance indexes of .86 (95% confidence interval [CI], .81–.91) and well-fitted calibration curves. A novel scoring model, named as CALL, was established; its area under the ROC was .91 (95% CI, .86–.94). Using a cutoff of 6 points, the positive and negative predictive values were 50.7% (38.9–62.4%) and 98.5% (94.7–99.8%), respectively.

Conclusions. Using the CALL score model, clinicians can improve the therapeutic effect and reduce the mortality of COVID-19 with more accurate and efficient use of medical resources.

Keywords. coronavirus; COVID-19; prediction; nomogram.

The outbreak of coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has influenced over 180 countries worldwide [1]. The numbers of new and severe cases have been increasing rapidly daily due to the easy transmissibility of the virus by patients with only mild illness or by asymptomatic carriers [2]. Many countries have enacted emergency response efforts and adopted strict measures such as locking down cities or regions. The World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 [3]. The large number of infected persons has resulted in tremendous unmet medical demands and an unresolved personal protective equipment shortage in many countries.

With increasing case numbers and clinical experience, more detailed information about COVID-19 pneumonia has been revealed. Huang et al [4] first reported clinical manifestations of 41 patients infected with 2019 novel coronavirus and observed that intensive care unit (ICU) patients had higher plasma levels of cytokines compared with non-ICU patients. Chen et al [5] found that the infection more likely affected older males with comorbidities. Wang et al [6] compared clinical parameters of severe and nonsevere cases in 138 hospitalized patients. Again, patients who required ICU care were significantly older and more likely to have underlying comorbidities, such as hypertension, diabetes, cardiovascular disease, and cerebrovascular disease. However, all of the above studies were single-center and univariate analysis-based studies without consideration of the influence of confounding factors because of their small sample sizes.

Therefore, clarifying the independent high-risk factors with multivariate analysis and establishing an accurate prediction of progression of COVID-19 has become desirable. In the present study, we used Cox proportional regression and a nomogram to provide an evidence-based, factors-weighted, highly accurate risk-estimation model to help clinicians better choose a therapeutic strategy. To our knowledge, this scoring prediction

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model is the first nomogram for progressive risk estimation in patients with COVID-19.

METHODS

Study Population

This study was approved by both the Ethics Committees of Fuyang Second People's Hospital (FYSPH), Anhui (20200303006), and the Fifth Medical Center of Chinese PLA General Hospital (PLAGH), Beijing (2020005D). Written informed consent was waived due to the rapid emergence of this infectious disease. Both FYSPH in Anhui Province (center 1) and the Fifth Medical Center of PLAGH in Beijing (center 2) were assigned as COVID-19 treatment centers on 20 January 2020. Patients presenting with severe COVID-19 were excluded. For this retrospective, noninterventional study, we enrolled all patients with confirmed COVID-19 admitted to either of the 2 centers since 20 January 2020. COVID-19 was diagnosed based on the WHO interim guidance [7] and guidance for COVID-19 issued by the National Health Commission of China [8]. The presence of SARS-CoV-2 in respiratory specimens was confirmed using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay by local district-level and municipal Centers for Disease Prevention and Control (CDCs), as described previously [4]. The exclusion criteria were primary infection by other pathogens, such as bacteria, fungi, other respiratory virus, mycoplasma, or chlamydia. Comorbidity was

defined as having at least 1 of the following: hypertension, diabetes, cardiovascular disease, chronic lung disease, or human immunodeficiency virus (HIV) infection for at least 6 months. Severe COVID-19 was defined by at least one of the following: respiratory rate 30 breaths or more per minute, resting oxygen saturation of 93% or less, arterial partial pressure of oxygen (PaO_2) / oxygen concentration (FiO_2) of 300 mmHg or less, or requirement of mechanical ventilation. Progression to severe COVID-19 was development of 1 or more of the above or worsening of lung computed tomography (CT) findings during the observation period.

Procedures

According to the roadmap of National Health Commission of China, all of the patients with suspected disease received treatment in an isolated observation ward at district hospitals. After the results of COVID-19 were determined to be positive by both district-level and municipal CDCs, the patients were transferred to the nearest municipal designated hospital by negative-pressure-isolation ambulance (Figure 1).

Data Collection

After admission to the 2 centers, the presenting history, comorbidity status, epidemiologic history, and vital signs of patients were collected. Laboratory parameters, including complete blood count, coagulation profile, liver and renal

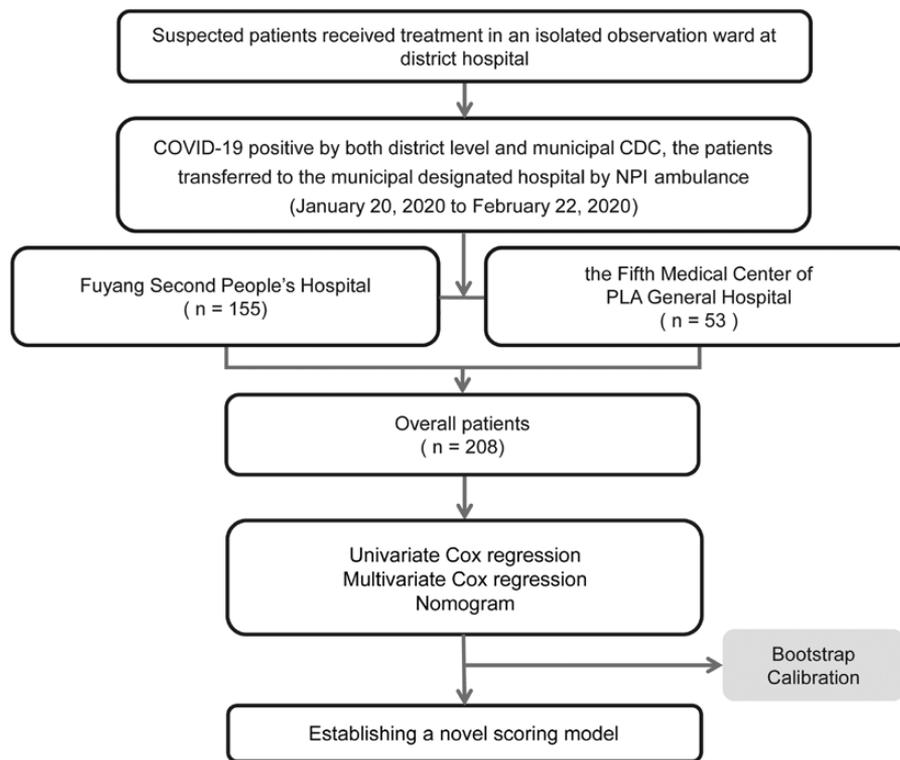


Figure 1. Flow chart for management of patients with COVID-19 in clinics of 2 centers. Abbreviations: CDC, Centers for Disease Prevention and Control; COVID-19, coronavirus disease 2019; NPI, negative-pressure-isolation.

function, lactate dehydrogenase (LDH), and procalcitonin, were examined at admission. Oxygen saturation was measured by pulse oxygen saturation on room air in the resting state and confirmed by blood gas test. Respiratory specimens, including nasal and pharyngeal swabs, or sputum were tested for influenza, avian influenza, respiratory syncytial virus, adenovirus, and parainfluenza virus using real-time RT-PCR assays approved by the China Food and Drug Administration. The Confusion, Urea, Respiratory rate, low Blood pressure, age (CURB)-65 severity score [9] was calculated for each subject. All patients were examined by chest X-ray or CT scan. Clinical outcomes (progression of illness, days to progression, mortality, discharges, and length of hospital stay) were monitored up to 18 March 2020. The dates in source documents were confirmed independently by at least 2 researchers.

Statistical Analysis

Normally distributed continuous variables are expressed as means \pm SDs and were compared using the unpaired, 2-tailed Student's *t* test. Continuous variables with skewed distribution are shown as medians (interquartile range) and compared by using the Mann-Whitney test. Categorical variables are presented as numbers (%) and compared by using the chi-square test. A *P* value $< .05$ was considered significant for all statistical tests. The statistical analyses were performed using R software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

The significance of each variable was assessed by univariate and multivariate Cox proportional hazards models for investigating the independent high-risk factors for progression of illness with its hazard ratio (HR) and 95% confidence interval (CI). All of the variables at a statistically significant level ($P < .05$) after multivariate Cox analysis were candidates for formulation of a nomogram, which was based on proportionally converting each multivariate regression coefficient to a 0- to 100-point scale, by using the rms package of R. The predictive performance of the nomogram was measured by the concordance index (C-index) and calibration with 1000 bootstrap samples to decrease the overfit bias [10].

For convenience of clinical use, a novel scoring model was established; their relevant points were determined by the above multivariate Cox regression to reflect their weights of impact on the progression of illness. High-risk-factor candidates (D-dimer, LDH) were categorized based on their normal ranges, the definition of lymphopenia according to most medical dictionaries (lymphocyte counts $\leq 1.0 \times 10^9/L$) or the WHO's criterion for older age (>60 years). The performance of the scoring model was assessed using receiver operating characteristic (ROC) curves. The area under the ROC (AUROC) and optimal cutoff values were determined and assessed by the sensitivity, specificity, predictive values, and likelihood ratios.

RESULTS

Clinical Characteristics of Patients

Overall, 208 consecutive patients with confirmed COVID-19 who presented to 2 centers were enrolled from 20 January through 22 February 2020, and the follow-up period ended 18 March 2020. The average age was 44.0 ± 16.3 years, 117 of 208 patients (56.2%) were male, 31 (14.9%) were older than 60 years, 45 (21.6%) had at least 1 underlying comorbidity, the average hospitalization time was 17.5 ± 8.2 days, and, in 40 (19.2%) patients, their clinical condition deteriorated during the observation period. The clinical characteristics of the stable and the progressive groups were compared. Age, comorbidity, lymphocyte count, D-dimer, and LDH were significantly different between these 2 groups on univariate analysis and log-rank test by Kaplan-Meier analysis (Table 1; Supplementary Table 1 and Supplementary Figure 1).

Independent High-risk Factors Associated With Progression

Further multivariate Cox analysis showed that comorbidity (HR, 3.9; 95% CI, 1.9–7.9), age older than 60 years (HR, 3.0; 95% CI, 1.4–6.0), lymphocyte count of $1.0 \times 10^9/L$ or less (HR, 3.7; 95% CI, 1.8–7.8), LDH of 250–500 U/L (HR, 2.5; 95% CI, 1.2–5.2), and LDH more than 500 U/L (HR, 9.8; 95% CI, 2.8–33.8) were independent high-risk factors associated with progression of illness (Table 2). CURB-65 scores of 208 patients ranged from 0 to 2 points, even for those with progression to severe disease and death, suggesting that CURB-65 may not be suitable for assessment of COVID-19 progression.

Predictive Nomogram for the Probability of Progression

A predictive nomogram was formulated based on the above independent high-risk factors (categorized) associated with progression, and validated using the bootstrap method internally. The nomogram demonstrated good accuracy in estimating the risk of progression of illness, with a C-index of .86 (95% CI, .81–.91). In addition, calibration plots graphically showed good agreement between estimated and actual progression with a slope of 0.96 ($R^2 = 0.90$) in 5-day prediction and 0.97 ($R^2 = 0.93$) in 10-day prediction after 1000 bootstrap samplings (Figure 2).

Construction and Assessment of a Novel Scoring Model

In order to facilitate clinical use and further assessment, a novel scoring model was established according to the results of the nomogram, referred to as CALL (Comorbidity, Age, Lymphocyte, and LDH), which scores from 4 to 13 points (Table 3). For lymphocyte scores, we chose the definition of lymphopenia ($\leq 1.0 \times 10^9/L$) as a cutoff. For LDH, there were 3 levels: no more than 250 U/L (the upper normal limit in our laboratories), between 250 and 500 U/L, and more than 500 U/L.

ROC analysis was used to assess the performance of the CALL model; the AUROC was .91 (95% CI, .86–.94). Using a cutoff value of 6 points, the positive-predictive value (95% CI)

Table 1. Clinical Characteristics of Enrolled Patients on Admission

	Overall (N = 208)	Stable Group (n = 168)	Progressive Group (n = 40)	P
Age, years	44.0 ± 16.3	40.7 ± 14.7	57.7 ± 15.9	<.001
Male sex, n (%)	117 (56.2)	89 (53.0)	28 (70.0)	.076
Comorbidity, n (%)	45 (21.6)	20 (11.9)	25 (62.5)	<.001
Smokers, n (%)	19 (9.1)	13 (7.7)	6 (15.0)	.216
Lymphocyte count, ×10 ⁹ /L	1.3 ± 0.7	1.4 ± 0.7	0.9 ± 0.4	<.001
D-dimer, mg/L	0.28 (0.19–0.51)	0.24 (0.19–0.43)	0.48 (0.31–0.75)	<.001
ALT, U/L	24.0 (14.0–37.3)	23.0 (14.0–37.0)	26.0 (17.5–47.8)	.192
TBIL, μmol/L	10.2 (7.1–15.2)	10.0 (7.0–15.1)	10.7 (8.3–16.2)	.430
LDH, U/L	234 (200–283)	224 (196–262)	304 (246–388)	<.001
PCT, μg/L	0.03 (0.02–0.06)	0.03 (0.02–0.06)	0.05 (0.02–0.09)	.066
D-dimer, n (%)				.002
≤0.55 mg/L	164 (78.8)	140 (83.3)	24 (60.0)	
>0.55 mg/L	44 (21.2)	28 (16.7)	16 (40.0)	
Lymphocyte, n (%)				<.001
>1.0 × 10 ⁹ /L	130 (62.5)	120 (71.4)	10 (25.0)	
≤1.0 × 10 ⁹ /L	78 (37.5)	48 (28.6)	30 (75.0)	
Age, n (%)				<.001
≤60 years	177 (85.1)	155 (92.3)	22 (55.0)	
>60 years	31 (14.9)	13 (7.7)	18 (45.0)	
LDH, n (%)				<.001
≤250 U/L	125 (60.1)	114 (67.9)	11 (27.5)	
250–500 U/L	77 (37.0)	53 (31.5)	24 (60.0)	
>500 U/L	6 (2.9)	1 (0.6)	5 (12.5)	
CURB-65, n (%)				.081
0 points	140 (67.3)	119 (70.8)	21 (52.5)	
1 point	56 (26.9)	40 (23.8)	16 (40.0)	
2 points	12 (5.8)	9 (5.4)	3 (7.5)	
Hospitalization, days	17.5 ± 8.2	16.4 ± 7.3	22.2 ± 9.9	<.001
Death, n (%)	2 (1.0%)	0	2 (5.0)	.044

Normally distributed continuous variables are expressed as means ± SDs and compared using the unpaired 2-tailed Student's *t* test; continuous variables of skewed distribution are shown as medians (interquartile range) and compared with Mann-Whitney test; categorical variables are presented as n (%) and compared by the chi-square test. Comorbidities included hypertension, diabetes, cardiovascular disease, chronic lung disease, or human immunodeficiency virus infection. CURB-65 was calculated based on the presence or absence of the following criteria: new confusion, urea > 7 mmol/L, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg and age ≥ 65 years. Abbreviations: ALT, alanine aminotransferase; LDH, lactate dehydrogenase; PCT, procalcitonin; TBIL, total bilirubin.

Table 2. Univariate and Multivariate Cox Proportional Hazards Regression Analysis of Progression of Illness in the Study Cohort

	Univariate Cox Analysis		Multivariate Cox Analysis	
	HR (95% CI)	P	HR (95% CI)	P
D-dimer				
≤0.55 mg/L	1		1	
>0.55 mg/L	2.8 (1.5–5.2)	.002	1.0 (.5–2.1)	.983
Comorbidity				
Without	1		1	
With	7.8 (4.1–14.8)	<.001	3.9 (1.9–7.9)	<.001
Age				
≤60 years	1		1	
>60 years	6.4 (3.4–12.0)	<.001	3.0 (1.4–6.0)	.006
Lymphocyte				
>1.0 × 10 ⁹ /L	1		1	
≤1.0 × 10 ⁹ /L	5.8 (2.8–11.9)	<.001	3.7 (1.8–7.8)	.001
LDH				
≤250 U/L	1		1	
250–500 U/L	4.2 (2.1–8.5)	<.001	2.5 (1.2–5.2)	.014
>500 U/L	13.6 (4.3–42.9)	<.001	9.8 (2.8–33.8)	<.001

HRs were calculated comparing with comorbidity and without comorbidity, lymphocyte count ≤1.0 × 10⁹/L versus >1.0 × 10⁹/L, age ≤60 years versus >60 years, LDH ≤250 U/L versus LDH 250–500 U/L or >500 U/L.

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase.

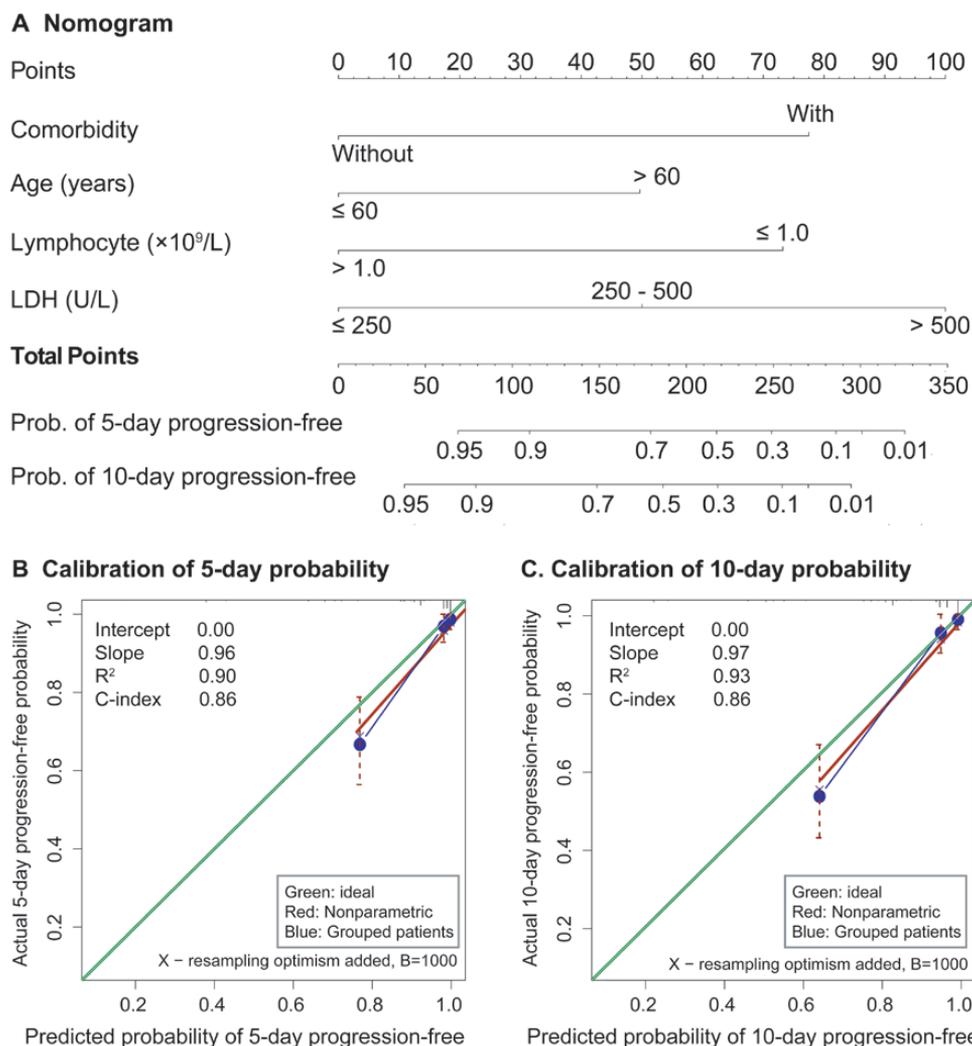


Figure 2. Formulated nomogram for the prediction of progression risk and its performance assessment. *A*, Nomogram to estimate the risk of progression in patients with COVID-19. The value of each variable is given a certain score on a point scale from 0 to 100; to use the nomogram, find the position of each variable on the corresponding axis, draw a line to the points axis for the number of points, add the points from all of the variables, and project the total points to the lower risk lines to determine the 5- or 10-day progression probabilities. *B*, Validity of 5-day predictive performance with the bootstrap method. *C*, Validity of 10-day predictive performance with the bootstrap method. Abbreviation: LDH, lactate dehydrogenase.

was 50.7% (38.9–62.4%) and the negative-predictive value (95% CI) was 98.5% (94.7–99.8%) for prediction. Using a cutoff value of 9 points, the positive-predictive value (95% CI) was 78.3% (56.3–92.5%) and the negative-predictive value (95% CI) was 11.9% (7.6–17.4%) (Table 4).

Furthermore, CALL scores were classified into 3 levels of risk according to their probabilities to progression: those who scored 4–6 points had less than a 10% probability of progression and were considered low risk (class A), 7–9 points with a 10–40% probability of progression were intermediate risk (class B), and 10–13 points with a more than 50% probability were considered high risk (class C) (Supplementary Figure 2).

DISCUSSION

The rapidly increasing number of new COVID-19 cases daily worldwide has put a heavy burden on medical resources in

countries with large outbreaks. Therefore, identifying risk factors at presentation that predict the likelihood of disease progression would help physicians decide which group of patients can be managed safely at district hospitals and who needs early transfer to tertiary centers. Age, comorbidities, lymphopenia, serum ferritin, D-dimer levels, cardiac troponin I, LDH, and interleukin-6 (IL-6) subsets have been shown to be associated with poor prognosis and increased mortality [4–6, 11–13]. Guan et al [14] described the clinical characteristics of 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals through 29 January 2020. Lymphopenia was observed in 82.1% of patients. Oxygen saturation, respiratory rate, blood leukocyte/lymphocyte count, and chest X-ray/CT manifestations predicted poor clinical outcomes. Increasing age and comorbidities were associated with more severe disease. Severe cases had more prominent laboratory abnormalities

Table 3. Calculator of CALL Points

	Points
Comorbidity	
Without	1
With	4
Age	
≤60 years	1
>60 years	3
Lymphocyte	
>1.0 × 10 ⁹ /L	1
≤1.0 × 10 ⁹ /L	3
LDH	
≤250 U/L	1
250–500 U/L	2
>500 U/L	3

Abbreviations: CALL, Comorbidity, Age, Lymphocyte, and LDH; LDH, lactate dehydrogenase.

(ie, leukopenia, lymphopenia, thrombocytopenia, elevated C-reactive protein levels) as compared with nonsevere cases. Zhou et al [15] showed that older age, high Sequential Organ Failure Assessment score, and D-dimer greater than 1 µg/L are potential risk factors that could help clinicians identify patients with poor prognosis at an early stage.

Here, we derived a risk-factors scoring system (CALL) based on patients' age, comorbidities, lymphocyte count, and serum LDH at presentation that could identify a group of patients at low risk of disease progression. Over 96% of subjects with CALL scores of 4–6 points will not progress to severe disease. In our cohort of 208 patients, 133 (63.9%) had scores of 4–6s (class A), including patients older than 60 but without comorbidities; these patients could be safely managed at peripheral or district hospitals. On the other hand, some patients

Table 4. Accuracy of the CALL Model for Estimating the Risk of Progression of Illness

Variable	Enrolled Patients (N = 208)
AUROC (95% CI)	.91 (.86–.94)
Cutoff value of 6 points (95% CI)	
Sensitivity, %	95.0 (83.1–99.4)
Specificity, %	78.0 (70.9–84.0)
Positive-predictive value, %	50.7 (38.9–62.4)
Negative-predictive value, %	98.5 (94.7–99.8)
Positive likelihood ratio	4.31 (3.20–5.80)
Negative likelihood ratio	.06 (.02–.20)
Cutoff value of 9 points (95% CI)	
Sensitivity, %	45.0 (29.3–61.5)
Specificity, %	97.0 (93.2–99.0)
Positive-predictive value, %	78.3 (56.3–92.5)
Negative-predictive value, %	11.9 (7.6–17.4)
Positive likelihood ratio	15.12 (6.00–38.30)
Negative likelihood ratio	.57 (.40–.80)

Abbreviations: AUROC, area under the receiver operating characteristic curve; CALL, Comorbidity, Age, Lymphocyte, and Lactate dehydrogenase; CI, confidence interval.

younger than 60 without comorbidities might benefit from early transfer to tertiary centers if they had markedly elevated LDH and severe lymphopenia (≥7 points). The CALL scoring system with 4 clinical parameters is also simpler than the 12-parameter multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age (MuLBSTA) score proposed by Guo et al [16].

Our study has several limitations. First, the sample size is small; it involved only patients in 2 centers outside Hubei and may not be applicable to the patients in Wuhan or Hubei. Second, a prospective study is needed to confirm the reliability of the CALL model. Finally, adding other specific markers might further improve the sensitivity and specificity.

In summary, the 4 clinical parameters in the CALL model with its high accuracy and easy-to-use features achieved an optimal prediction of progression, and can be easily tested in clinical cohorts in countries or regions that are currently experiencing large outbreaks. If validated, this may allow efficient utilization of medical resources and increase the therapeutic effect and reduce the mortality of COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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