Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score

Dong Ji[1†], Dawei Zhang[1†], Jing Xu[2†], Zhu Chen[1†], Tieniu Yang[3], Peng Zhao[1], Guofeng Chen[1], Gregory Cheng[4], Yudong Wang[4], Jingfeng Bi[1], Lin Tan[2], George Lau[1,4,*], Enqiang Qin[1,*]

[1] The Fifth Medical Center of Chinese PLA General Hospital, Beijing 100039, China

[2] Fuyang Second People's Hospital, Anhui 23600, China

[3] Fuyang Hospital of Anhui Medical University, Anhui 23600, China

[4] Humanity and Health Clinical Trial Center, Humanity & Health Medical Group, Hong Kong SAR, China

[†] These authors contributed equally to this study.

* These authors contributed equally to this study.

Corresponding Author:

Enqiang Qin, The Fifth Medical Center of Chinese PLA General Hospital, 100 West 4th Ring Middle Road, Beijing 100039, China; Tel: 86-10-66933422.

Email: E-mail address: qeq2004@sina.com

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

© The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Summary

This multi-center retrospective study showed underlying comorbidity, older age, higher LDH and lower lymphocyte count were independent high-risk factors associated with COVID-19 progression, and a novel scoring model (CALL score) can predict the progression with optimal sensitivity and specificity.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Abstract

***Background*.** We aimed to clarify the high-risk factors with multivariate analysis and establish a prediction of disease progression, so as to help clinicians to better choose therapeutic strategy.

Methods. All the consecutive patients with COVID-19 admitted to Fuyang second people's hospital or the fifth medical center of Chinese PLA general hospital between January 20 and February 22, 2020, were enrolled and their clinical data were retrospectively collected. Multivariate COX regression was used to identify the risk factors associated with progression, and then were incorporated into the nomogram to establish a novel prediction scoring model. ROC was used to assess the performance of the novel model.

Results. Overall, 208 patients were divided into stable group (n=168, 80.8%) and progressive group (n=40,19.2%) based on whether their conditions worsened during the hospitalization Univariate and multivariate analysis showed that comorbidity, older age, lower lymphocyte 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 0.86 (95%CI 0.81 - 0.91), and had well-fitted calibration curves. A novel scoring model, named as CALL, was established, and its area under ROC was 0.91 (95% CI 0.86 to 0.94). Using a cutoff value of 6 points, the positive and negative predictive values were 50.7% (38.9% - 62.4%) and 98.5% (94.7% - 99.8%), respectively.

***Conclusion*.** Using the CALL score model, clinicians can improve the therapeutic effect and reduce the mortality of COVID-19 with more accurate and reasonable resolutions on medical resources.

Key words. coronavirus; COVID-19; prediction; nomogram

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

The outbreak of coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection has influenced all provinces of China and spread to over 180 countries worldwide since January 2020 [1]. The number 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 asymptomatic carriers [2]. Many countries have made emergency responses and adopted strict measures like locking down cities or regions. The world Health Organization (WHO) had declared COVID-19 a pandemic on March 11, 2020 [3]. The large number of infected persons result in tremendous unmet medical demands and unresolved personal protective equipment shortage in many countries.

With increasing case numbers and clinical experiences, more and more detailed information about COVID-19 pneumonia has been revealed. Huang et al [4] first reported clinical manifestations of 41 patients infected with SARS-CoV-2 and observed that 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 non-severe 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 above studies were single center and univariate analysis-based studies without considering the influence of confounding factors because of small sample sizes.

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

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

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 in view of the designated hospital for new emerging infectious diseases. Both FYSPH in Anhui Province and the fifth medical center of PLAGH in Beijing (center two) were assigned as COVID-19 treatment center on January 20, 2020. Patients presenting with severe COVID-19 were excluded. For this retrospective, non-interventional study, we enrolled all patients with confirmed COVID-19 admitted to either of the two centers since January 20, 2020. COVID-19 was diagnosed based on the WHO interim guidance [7] and guidance for corona virus disease 2019 issued by 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 Center for Diseases Prevention and Control (CDC), 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 one of the followings: hypertension, diabetes, cardiovascular disease, liver disease, asthma, chronic lung disease, HIV infections and malignancy for at least 6 months. Severe COVID-19 was defined as at least one of the followings, respiratory rate ≥ 30 breaths/min, resting oxygen saturation ≤ 93%, PaO_2/FiO_2 ≤ 300 mmHg or requirement of mechanical ventilation. Progression to severe COVID-19 was development of one or more of the above or worsening of lung CT findings during the observation period.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Procedures

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

Data Collection

After admission to the two centers, the presenting history, comorbidity status, epidemiologic history, and vital signs of patients were collected. Comorbidity was defined as having at least one of the followings: hypertension, diabetes, cardiovascular disease, liver disease, asthma, chronic lung disease, HIV infections and malignancy for at least 6 months. The laboratory parameters, including complete blood count, coagulation profile, liver and renal function, lactate dehydrogenase (LDH) and procalcitonin (PCT) were examined at admission. The O_2 saturation was measured by pulse oxygen saturation on room air at rest 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, parainfluenza virus using real-time RT-PCR assays approved by the China Food and Drug Administration. 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 March 18, 2020. The date in source documents were confirmed independently by at least two researchers.

Statistical Analysis

Continuous variables of normal distribution were expressed as mean ± SD and compared using the unpaired, 2-tailed student's t test. Continuous variables of skewed distribution were showed as median [interquartile range

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

(IQR)] and compared with Mann-Whitney test. Categorical variables were presented as numbers (percentage) and compared by the chi-square test. A *p*-value < 0.05 was considered as 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 model for investigating the independent high-risk factors of progression of illness with its hazard ratio (HR) and 95% confidence interval (CI). All the variables at a statistically significant level($p<0.05$) after multivariate COX analysis were candidates for formulation of a nomogram, which is 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 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 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 ≤ 1.0×10^9/L) or WHO's criteria of older people (age > 60 years). The performance of the scoring model was assessed using receiver operating characteristic (ROC) curves. The area under 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 confirmed patients with COVID-19 presented to two centers were enrolled from January 20 through February 22, 2020, the follow-up period ended in March 18, 2020. The average age was 44.0 ± 16.3

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

years, 117 of 208 patients (56.2%) were male, 31 (14.9%) were older than 60 years, 45 (21.6%) had at least one underlying comorbidity, the average hospitalization time was 17.5 ± 8.2 days, and in 40 (19.2%) patients, the clinical conditions deteriorated progressed during the observation period. Clinical characteristics of the stable group and the progressive group were compared. Age, comorbidity, lymphocyte count, D-dimer, LDH were significantly different between these two groups on univariate analysis and log-rank test by Kaplan-Meier analysis (Table 1 and supplementary table and Figure S1).

Independent High-risk Factors Associated with Progression

Further multivariate COX analysis showed that comorbidity (HR 3.9, 95%CI 1.9 -7.9) , age > 60 years (HR 3.0, 95%CI 1.4 - 6.0), lymphocyte count ≤ 1.0 × 10^9/L (HR 3.7, 95% CI 1.8 - 7.8), LDH (250 - 500 U/L) (HR 2.5, 95% CI 1.2 - 5.2) and LDH > 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 of 208 patients were from 0 to 2 points, even for those with progression to severe disease and death, suggesting CURB-65 may not be suitable for COVID-19.

Predictive Nomogram for the Probability of Progression

A predictive nomogram was formulated based on 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 0.86 (95%CI 0.81-0.91). 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 sampling(Figure 2).

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

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 nomogram, named 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 (≤ 1.0 $\times 10^9$/L) as cut off. For LDH, there were 3 levels: <250 U/L, the ULN in our laboratories, >500 U/L, 2x ULN and between 250-500 U/L.

ROC analysis was used to assess the performance of the CALL model, the AUROC was 0.91 (95% CI 0.86 - 0.94). Using a cutoff value of 6 points, the positive predictive values (95% CI) were 50.7% (38.9% - 62.4%) and the negative predictive values (95% CI) were 98.5% (94.7% - 99.8%) for prediction. Using a cutoff value of 9 points, the positive predictive values (95% CI) were 78.3% (56.3% - 92.5%) and negative predictive values (95% CI) were 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 with 4-6 points had less than 10% probabilities of progression were considered low risk (Class A), 7-9 points with 10% - 40% probabilities of progression were intermediate risk (class B), and 10-13 points with over 50% probabilities were high risk (Class C) (supplementary Figure S2).

DISCUSSION

The rapidly increasing number of new COVID-19 cases daily worldwide has put a heavy burden on the medical resources in countries with large outbreaks. Therefore, identifying risk factors at presentation that predict the likelihood of disease progression would help the physicians to 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, lactate dehydrogenase, IL-6, subsets had been shown to be associated with poor prognosis and increased

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

mortalities [4-6,11-13]. Guan et al [14] described the clinical characteristics of 1,099 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 disease. Severe cases had more prominent laboratory abnormalities (i.e., leukopenia, lymphopenia, thrombocytopenia, elevated C-reactive protein levels) as compared with non-severe cases. Zhou et al [15] showed that older age, high SOFA score, and d-dimer greater than 1 μg/L are potential risk factors that could help clinicians to 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 could identify a group of patients with low risk of disease progression. Over 96% of subjects with CALL score of 4-6 points will not progress to severe disease. In our cohorts of 208 patients, 133 (63.9%) had 4-6 points (class A), including patients age > 60 but without comorbidities, these patients could be safely managed at peripheral or district hospitals. On the other hand, some patients age < 60 without comorbidities, might benefit from early transfer to tertiary centers if they had markedly elevated LDH and severe lymphopenia (7 or more points). The CALL scoring system with 4 clinical parameters is also simpler than the 12 parameters MuLBSTA score proposed by Guo L et al [16].

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

In summary, the four clinical parameters in 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

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

that are currently experience large outbreaks. If validated, this may allow efficient utilization of medical resources and increase the therapeutic effect and reduce the mortality of COVID-19.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Note

Acknowledgements. We thank the all medical staffs and patients involved in the study.

Financial support. None.

Potential conflict of Interests. All authors declared there were no conflicts of interest.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

References

1. World Health Organization. Novel coronavirus(2019-nCoV): situation report—40. Accessed February 29, 2020. https://www.who.int/docs/default-source/ coronaviruse/situation-reports/20200229-sitrep-40-covid-19.pdf
2. Hoehl S, Rabenau H, Berger A, Kortenbusch M, Cinatl J, Bojkova D, et al. Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. [published February 18, 2020]. *N Engl J Med*. doi: 10.1056/NEJMc2001899.
3. WHO Virtual press conference on COVID. https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-press-conference-full-and-final-11mar2020.pdf?sfvrsn=cb432bb3_2
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients with 2019 novel coronavirus in Wuhan, China [published January 24, 2020]. *Lancet*. doi:10.1016/S0140-6736(20)30183-5
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. [published January 29, 2020]. *Lancet*. doi:10.1016/S0140-6736(20)30211-7
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. [published February 7, 2020]. *JAMA*. doi: 10.1001/jama.2020.1585
7. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. [Published January 28, 2020]. Accessed January 31, 2020. https://www.who.int/publications-detail/clinical-managementof-severe-acute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected
8. National Health Commission (NHC) of the PRC and National Administration

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

of Traditional Chinese Medicine of the PRC. Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management. Peoples Medical Publishing House. 2020.

9. Barlow G, Nathwani D, Davey P. The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. *Thorax*. 2007, 62(3), 253-259. doi: 10.1136/thx.2006.067371
10. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J.* 2014;35(29):1925-1931.
11. Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. [published February 29, 2020]. *Clin Infect Dis*. doi: 10.1093/cid/ciaa199.
12. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical Course and Outcomes of Critically Ill Patients With SARS-CoV-2 Pneumonia in Wuhan, China: A Single-Centered, Retrospective, Observational Study. [published February 24, 2020]. *Lancet Respir Med*. doi: 10.1016/S2213-2600(20)30079-5.
13. Ji D, Zhang D, Chen Z, Xu Z, Zhao P, Zhang M, et al. Clinical Characteristics Predicting Progression of COVID-19 (2/17/2020). Available at SSRN: https://ssrn.com/abstract=3539674 or http://dx.doi.org/10.2139/ssrn.3539674
14. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. [published February 28, 2020]. *N Engl J Med*. doi: 10.1056/NEJMoa2002032.
15. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. [published March 11, 2020]. *Lancet.* doi: 10.1016/S0140-6736(20)30566-3.
16. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical features predicting mortality risk in patients with viral pneumonia: The MuLBSTA Score. *Front Microbiol*. 2019, 10:2752. doi: 10.3389/fmicb.2019.02752

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Figure legends

Figure 1. **Flow chart for management of patients with COVID-2019 in fever clinics of two centers** NPI, negative pressure isolation ambulance.

Figure 2. Formulated nomogram for 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 of the with bootstrap. (C) Validity of 10-day predictive performance of the with bootstrap.

.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Table 1. Clinical Characteristics of Enrolled Patients on Admission

	Overall (n=208)	Stable group (n=168)	Progressive group (n=40)	*P* value
Age, years	44.0 ±16.3	40.7 ± 14.7	57.7 ± 15.9	<0.001
Male sex (n,%)	117 (56.2)	89 (53.0)	28 (70.0)	0.076
Comorbidity (n,%)	45 (21.6)	20 (11.9)	25 (62.5)	<0.001
Smoke (n,%)	19 (9.1)	13 (7.7)	6 (15.0)	0.216
Lymphocyte, $\times10^9$/L	1.3 (0.7)	1.4 (0.7)	0.9 (0.4)	<0.001
D-dimer, mg/L	0.28 (0.19 - 0.51)	0.24 (0.19 - 0.43)	0.48 (0.31 - 0.75)	<0.001
ALT, U/L	24.0 (14.0 - 37.3)	23.0 (14.0 - 37.0)	26.0 (17.5 - 47.8)	0.192
TBIL, μmol/L	10.2 (7.1 - 15.2)	10.0 (7.0 - 15.1)	10.7 (8.3 - 16.2)	0.430
LDH, U/L	234 (200 - 283)	224 (196 - 262)	304 (246 - 388)	<0.001
PCT, μg/L	0.03 (0.02 - 0.06)	0.03 (0.02 - 0.06)	0.05 (0.02 - 0.09)	0.066
D-dimer, mg/L (n,%)				0.002
≤ 0.55	164 (78.8)	140 (83.3)	24 (60.0)	
> 0.55	44 (21.2)	28 (16.7)	16 (40.0)	
Lymphocyte, $\times10^9$/L (n,%)				<0.001
> 1.0	130 (62.5)	120 (71.4)	10 (25.0)	
≤ 1.0	78 (37.5)	48 (28.6)	30 (75.0)	
Age, years (n,%)				<0.001
≤ 60	177 (85.1)	155 (92.3)	22 (55.0)	
> 60	31 (14.9)	13 (7.7)	18 (45.0)	
LDH, U/L (n,%)				<0.001
≤ 250	125 (60.1)	114 (67.9)	11 (27.5)	
250 - 500	77 (37.0)	53 (31.5)	24 (60.0)	
> 500	6 (2.9)	1 (0.6)	5 (12.5)	

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

CURB-65, points (n, %)				0.081
0	140 (67.3)	119 (70.8)	21 (52.5)	
1	56 (26.9)	40 (23.8)	16 (40.0)	
2	12 (5.8)	9 (5.4)	3 (7.5)	
Hospitalization (days)	17.5 ± 8.2	16.4 ± 7.3	22.2 ± 9.9	<0.001
Death (n,%)	2 (1.0%)	0	2 (5.0)	0.044

Continuous variables of normal distribution were expressed as mean ± SD and compared using the unpaired, 2-tailed student's t test, continuous variables of skewed distribution were showed as median [interquartile range, IQR] and compared with Mann-Whitney test, categorical variables were presented as numbers (percentage) and compared by the chi-square test. Comorbidities[†] included hypertension, diabetes, cardiovascular disease, chronic lung disease and HIV infections.

Abbreviations: ALT, alanine aminotransferase; TBIL, total bilirubin; LDH, lactate dehydrogenase.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Table 2. Univariate and Multivariate COX Proportional Hazards Regression Analysis of Progression of Illness in Training Cohort

	Univariate COX analysis		Multivariate COX analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
D-dimer (mg/L)				
≤ 0.55	1	—	1	—
> 0.55	2.8 (1.5 - 5.2)	0.002	1.0 (0.5 - 2.1)	0.983
Comorbidity				
Without	1	—	1	—
With	7.8 (4.1 -14.8)	< 0.001	3.9 (1.9 - 7.9)	< 0.001
Age (years)				
≤ 60	1	—	1	—
> 60	6.4 (3.4 - 12.0)	< 0.001	3.0 (1.4 - 6.0)	0.006
Lymphocyte ($\times 10^9$/L)				
> 1.0	1	—	1	—
≤ 1.0	5.8 (2.8 - 11.9)	< 0.001	3.7 (1.8 - 7.8)	0.001
LDH (U/L)				
≤ 250	1	—	1	—
250-500	4.2 (2.1 - 8.5)	< 0.001	2.5 (1.2 - 5.2)	0.014
> 500	13.6 (4.3 - 42.9)	< 0.001	9.8 (2.8 - 33.8)	< 0.001

HR was calculated comparing with comorbidity vs without comorbidity, lymphocyte ≤ 1.0×10^9/L vs > 1.0×10^9/L, age≤ 60 (years) vs >60, LDH≤ 250 U/L vs LDH 250-500 U/L or> 500 U/L.

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

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Table 3. The Calculator of CALL Points

	points
Comorbidity	
Without	1
With	4
Age (years)	
≤ 60	1
> 60	3
Lymphocyte ($\times 10^9$/L)	
> 1.0	1
≤ 1.0	3
LDH (U/L)	
≤ 250	1
250 - 500	2
> 500	3

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

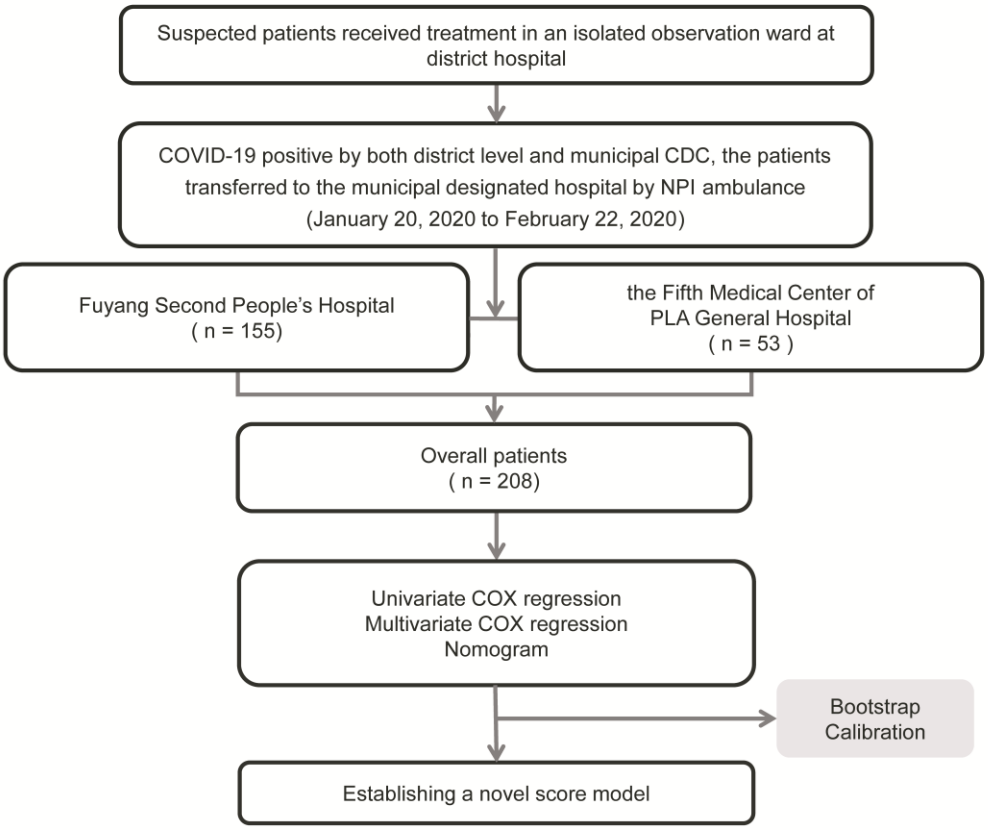
Table 4. Accuracy of the CALL Model for Estimating the Risk of Progression of Illness

Variable	Enrolled patients (n = 208)
AUROC	**0.91 (0.86 - 0.94)**
Cutoff value (95% CI)	**6**
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	0.06 (0.02 - 0.20)
Cutoff value (95% CI)	**9**
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	0.57 (0.40 - 0.80)

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

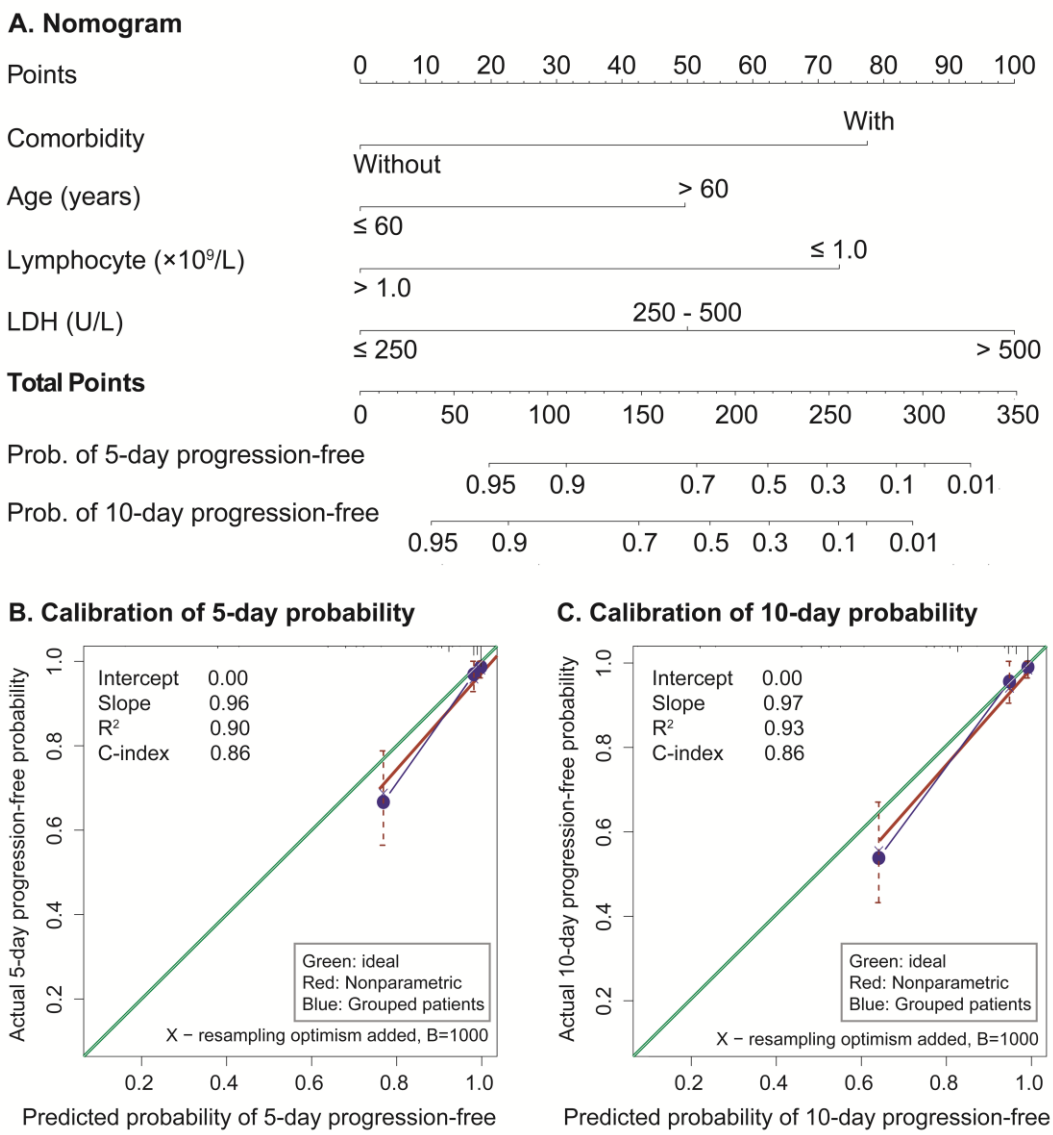
Figure 1



Accepted

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020

Figure 2



Acc

Downloaded from https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa414/5818317 by guest on 30 April 2020