Exploration of prognostic factors for critical COVID-19 patients：a nomogram analysis

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Abstract

To discuss influencing factors on critical COVID-19 patient's prognosis, construct a basic model and predict their mortality risks. Retrospectively analyzed the general condition and respective laboratory biomarkers of critical patients with duration≥24 h from Feb. 10th, 2020 to Mar. 30th, 2020 to separate them into a survival group and death group based on their clinical features. Multiple logistic regression analysis was performed to assess risk factors for critical COVID-19 patient's and a nomogram was constructed based on screened risk factors. A receiver operating curve (ROC) was created to evaluate the accuracy of the nomogram. Multi-factor Logistic recovery analysis results show: Age, Peripheral blood leucocyte count,Lymphocyte percentage, Thrombocyte count and Hyper C-reactive protein are single danger factors of critical COVID-19 patient's mortality risk (p□0.05). ROC curve indicates Nomogram predictive model AUC is 0.958 (95%CI: 0.923-0.993), which has high predictive value. Findings from this study suggest advanced age, high peripheral blood leucocyte count, high hyper C-reactive protein, low lymphocyte percentage and low thrombocyte count are risk factors of critical COVID-19 patient's death.The Nomogram model is helpful for timely intervention to reduce the incidence of critical COVID-19 patients.

Introduction

2019 novel coronavirus, 2019-nCoV, also known as SARS-CoV-2, can cause serious pneumonia. Although its toxicity is weaker than SARS-CoV, it's more susceptible and more transmissible to crow[1]. Up to 6 o'clock in Apr. 27th CEST, there are 2,810,325 global confirmed cases, 193,825 fatality counts (WHO). Its 6.9% death rate has seriously influenced the general public's safety[2,3]. Wuhan, China's heaviest impacted area by 2019-nCoV, received 50340 COVID-19 patients and 3869 patients with critical clinical syndrome had dead[4]. According to the National Health Commission census, up to Apr. 27th, Wuhan has cleared all sever 2019-nCoV cases (NHC published). With this exhilarating news, we need to understand the importance of patients by estimating correct clinical condition development and establishing rational treatment plans.

Incorporating with "Preventing forward" idea proposed by life-threatening specialists in Wuhan, critical 2019-nCoV death risk estimation model was built. Many scholars found that paying close attention to change in laboratory blood routine, hs-CRP, D-dime, combined with patient's age and medical complication, have distinct instructive value for critical COVID-19 patient prognosis[5-7]. Prediction about critical COVID-19 patient prognosis model was built, which there was not any relative research done in China. In order to find the difference of laboratory indicators between 2019-nCoV patient prognosis, and statistical significance of indicator changes before and after treatment, this research collected 102 2019-nCoV cases of patient clinical characteristics and relative blood examination indicators from Wuhan Tongji Hospital Guanggu District. The report is down below.

Results

General Situation .102 COVID-19 critical patients with that conformed to the including and excluding criteria, were separated into survival group(50) and death group (52)based upon their prognosis. In these 102 patients, there were 63 males, 39 females, 49 cases with hypertension, 21 cases with diabetes, 16 cases with coronary heart disease, 9 cases had smoking habits. As indicated in table 1, in general data, age, gender, coronary heart disease history were considered statistically significant (p□0.5); Peripheral white blood cell count (WBC), Lymphocyte percentage (L%), Platelet count (PLT), Hypersensitive C reactive protein (hs-CRP), Glomerular filtration rate (eGFR), D-dimer (D-D), and Troponin I (TnI) were statistically significant (p□0.001).

Items	Survival group □n=50□	Death group □n=52□	$t/Z/c^2$	P
Age□Years□	65.00(14.50)	74.50(12.75)	-4.68	□0.001
Gender□M/F□	24/26	39/13	7.87	0.005
Hypertension□Y/N□	20/30	29/23	2.54	0.111
Diabetes□Y/N□	11/39	10/42	0.12	0.730
Coronary Heart Disease□Y/N□	3/47	13/39	6.96	0.008
Smoking Habit□Y/N□	3/47	6/46	0.41	0.524
Body temperature□°C□	38(1.63)	37(1.50)	-2.49	0.013
WBC□*10^9/L□	5.68(2.83)	8.06(7.22)	-4.55	□0.001
L%□%□	1.26(0.49)	0.75(0.39)	5.83	□0.001
PLT□*10^9/L□	240(129.75)	144.50(121.25)	-4.90	□0.001
Hs-CRP□mg/L□	18.4(59.90)	113.30(93.20)	-6.51	□0.001
eGFR□ml/min□	92.55(15.30)	66.20(38.05)	-4.17	□0.001
D-Dimer□ug/mL□	0.80(1.43)	19.09(18.97)	-6.35	□0.001
TnI□ug/L□	2.55(4.73)	40.75(652.83)	-6.77	□0.001

Table 1. Comparability of clinical data and laboratory indicators between the death group and survival group

Continuous variables with normal distribution are expressed as the mean ± standard deviation (SD), non-normal variables are expressed as the median (interquartile range(IQR)), and categorical data are expressed as number and percentage. Independent sample Student's t-test was used to compare the means of two continuous normally distributed variables. The means of two non-normally distributed variables were compared with by Mann-Whitney U test. The frequencies of categorical variables were compared by χ2 test.

Critical COVID-19 patient mortality risk logistic Regression analysis . As indicated in table 2, personal characteristics of logistic regression analysis (Model 1) of age, gender, smoking habits, body temperature concluded that age, gender, and body temperature were dangerous factors affecting critical COVID-19 patient mortality risk;Complication logistic of regression analysis (Model 2) of hypertension, diabetes, and coronary heart disease concluded that coronary heart disease was a dangerous factor affecting critical COVID-19 patient mortality risk; Clinical indicators of logistic regression analysis (Model 3) of Peripheral white blood cell count (WBC), Lymphocyte percentage (L%), Platelet count (PLT), Hypersensitive C reactive protein (hs-CRP), Glomerular filtration rate (eGFR), D-dimer (D-D), and Troponin I (TnI) concluded that WBC, L%, PLT, hs-CRP, eGFR were dangerous factors affecting critical COVID-19 patient mortality risk. Integration indicators of logistic regression analysis (Model 4) of age, gender,

smoking habits, body temperature, hypertension, diabetes, and coronary heart disease, WBC, L%, PLT, hs-CRP, eGFR, D-D, TnI, concluded that age, WBC, L% PLT, and hs-CRP were dangerous factors affecting critical COVID-19 patient mortality risk.

Items	OR（95%CI）	*P*
Model 1		
Age	1.106（1.048-1.168）	<0.001
Gender	3.885（1.409-10.717）	0.009
Body Temperature	0.513（0.317-0.832）	0.007
Model 2		
Coronary Heart Disease	5.222（1.388-19.651）	0.015
Model 3		
WBC	1.326（1.032-1.702）	0.027
L%	0.064（0.007-0.598）	0.016
PLT	0.989（0.978-1.000）	0.041
hs-CRP	1.030（1.010-1.051）	0.003
eGFR	0.953（0.919-0.987）	0.008
Model 4		
Age	1.135（1.045-1.232）	0.003
WBC	1.313（1.027-1.678）	0.030
L%	0.048（0.005-0.485）	0.010
PLT	0.986（0.974-0.998）	0.023
hs-CRP	1.028（1.008-1.049）	0.006

Table2. Multivariate Logistic regression analysis on death risk of critically COVID-19 patients

Model 1: Logistic regression analysis of age, gender, smoking habits, body temperature;Model 2: Logistic regression analysis of hypertension, diabetes, and coronary heart disease;Model 3: Logistic regression analysis of Peripheral white blood cell count (WBC), Lymphocyte percentage (L%), Platelet count (PLT), Hypersensitive C reactive protein (hs-CRP), Glomerular filtration rate (eGFR), D-dimer (D-D), and Troponin I (TnI);Model 4: Logistic regression analysis of all items above.

Building and Verification of Critical COVID-19 Patient Mortality Risk Estimation Nomogram. Critical COVID-19 patient mortality risk important risk factor concluded from Model 4 were input into R software. Estimation nomogram of critical COVID-19 patient mortality risk was built. Each item in the model corresponded to a score, the sum of each item score became a total score. The dot on the critical COVID-19 patient mortality risk axis corresponds to the patient mortality risk. In the nomogram, total score went from 179 to 270, its corresponding mortality risk went from 0.05 to 0.95. The higher the score, the higher the mortality risk. The detail is in Figure 1. In addition, the area under ROC curve in Table 3 was utilized to decide accuracy for different test indexs on survival result prediction. The results showed the area under the curve was the largest. Age, L%, PLT, hs-CRP had predictive value to prognosis. In all test indexes, hs-CRP had the largest area under the curve, which was the closest to the prediction model.

Items	AUC（95%CI）	P
Age	0.764（0.669-0.859）	<0.001
Body Temperature	0.769（0.675-0.863）	0.018
L%	0.209（0.118-0.300）	<0.001
PLT	0.216（0.125-0.306）	<0.001
Hs-CRP	0.879（0.815-0.944）	<0.001
Prediction Model	0.958（0.923-0.993）	<0.001

Table 3. ROC curves of critically pneumonia patients

C-index for this nomogram is 0.958 (95% CI; 0.923-0.993), indicating a good differential ability. Calibration curve (Figure 2) shows consistency between prediction probability and actual probability, which indicates the accuracy this nomogram had in estimating critical COVID-19 mortality risk.

Discussion

The new coronavirus pneumonia (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. As of May 4, 2020, there have been 3.5 million confirmed cases of COVID-19 in the world, and the number of deaths had reached 250,000 [8]. The investigation found that only 80% of confirmed cases showed only mild illness, but an admission survey of 166 British hospitals showed that about 33% of diagnosed patients required hospitalization and 45% of patients in intensive care died from the disease [9]. According to the survey, COVID-19 is significantly associated with age, gender and potential comorbidity, with the highest mortality rate among elderly men[10]. According to the general data and relevant clinical indicators of critically ill coronavirus pneumonia patients , it is very important to explore relevant risk factors. The prognosis can be evaluated to achieve individualized prediction of clinical events. This is of great practical significance to guide the clinical development of targeted treatment strategies and improve the prognostic level of critically .,m COVID-19 patients [11]. In this study, the nomogram model was used to integrate data, and the results of multivariate Logistic regression analysis were quantified, graphed, and visualized to explore the prognostic factors affecting critically ill patients.

Model 1 shows that older men with normal body temperature is the personal characteristic of the death group. Chen and other studies analyzed the epidemiology and clinical characteristics of 99 patients with COVID-19[12]. They also pointed out that COVID-19 infection appeared in clusters, which is more likely to affect elderly men with comorbidities. The X chromosome and sex hormones play a key role in innate and adaptive immunity, which may be the reason why women are less infected than men[13]. At the same time, severe COVID-19 can be regarded as a hyperinflammatory disease characterized by the activation of a large number of immune cells. The immune relaxation regulation observed in the elderly may drive the severe onset of COVID-19[14]. Body temperature as a routine test item, the increase in body temperature represents the development of the disease, but the body temperature should not be the only measure, and the development of the disease at normal body temperature cannot be ignored.

Detailed analysis of the patient's comorbidity Model 2 found that coronary heart disease is a risk factor for the risk of death in patients with severe new coronavirus pneumonia. The pathogen of COVID-19 is SARS-CoV-2, which is a new type of coronavirus and infects cells with ACE2 as the receptor[15]. Changes in ACE2 levels in the body can affect the pathogenicity of SARS-CoV-2. The level of ACE2 in patients with coronary heart disease is significantly higher than that in patients with non-coronary heart disease. The high expression of ACE2 enhances the ability of SARS-CoV-2 to infect the body. More SARS-CoV-2 infection may lead to aggravation of the patient's condition.

Model 3 analysis of clinical detection indicators found that high peripheral blood white blood cell count, high-sensitivity C-reactive protein, low lymphocyte percentage, low platelet count, and low glomerular filtration are the risk of death from severe new coronavirus pneumonia factor. In patients with COVID19 infection, peripheral blood leukocytes are more normal or reduced, and lymphocyte count decreases are more common, and may decrease progressively as the disease worsens[16]. Among the patients diagnosed with COVID-19, admission characteristics are associated with increased hospital mortality, including low platelet count, peripheral blood leukocytes, lymphocyte percentage, and decreased glomerular filtration rate [17-18].Wang Yun, Zhao Changcheng, etc. Compared the blood test indexes of 80 patients diagnosed with new coronary pneumonia with the blood indexes of healthy medical examinees , significantly , the figure of COVID-19 patients is lower than that of healthy people ($p<0.05$)[19]. The cause of lymphocyte reduction may be related to the fact that 2019-nCoV will directly or indirectly kill lymphocytes or inhibit lymphocyte production, which ill lead to hypoimmunity in patients [20]. With the development of the disease, the development of the disease makes the pro-inflammatory immune response surge, resulting in the increase of cytokines produced by T cells and phagocytic cells, and the increase of C-reactive protein and peripheral blood leukocytes. Clinical indicators.The results of this study show that the phenomenon of platelet decline in the late course of COVID-19 patients is consistent with the phenomenon of platelet decline in the late stage of other viral infections[21]. Statistics from the Institute of Hematology, Chinese Academy of Medical Sciences show that 80% of acute thrombocytopenic purpura occurs after viral infectious diseases, that is, “thrombocytopenia associated with viral infection”. Studies with Gawaz et al. have shown that sepsis In hypertensive patients, the accumulation of platelets at the site of inflammation may cause microcirculation disturbances, which may lead to organ dysfunction or failure[22]. The obvious decrease in the number of platelets may be related to the immune mechanism, that is, the specific antibodies produced by the virus may cross-react with certain components on the platelet membrane through molecular simulation mechanism to destroy the platelets, or antigen antibodies form immune complexes and deposit on the platelets On megakaryocytes, platelets and megakaryocytes are eliminated as target tissues, and the virus changes the antigenicity of platelets so that the body's immune system removes them as foreign bodies. Therefore, platelet decline should also be used as a clinical indicator of the deterioration of the condition during hospitalization.

Model 4 analysis of all indicators integrated in this study showed that age ($p=0.03$), peripheral blood white blood cell count ($p=0.030$), lymphocyte percentage ($p=0.010$), platelet count ($p=0.023$) and ultra Sensitive C-reactive protein ($p=0.006$) is an independent risk factor for the risk of death in patients with

severe new coronavirus pneumonia. Then, based on the above independent risk factors, the first personalized nomogram model for predicting the death of critically ill new coronavirus pneumonia was established. The nomogram model C-index is 0.958 (95%CI: 0.923-0.993), indicating that it has a good discriminating ability. The calibration curve (see Figure 2) shows that the predicted probability and the actual probability are consistent with good accuracy and differentiation, indicating that the nomographic model can accurately predict the risk of death of patients with severe new coronavirus pneumonia, focusing on patients with relevant risk factors Careful individualized diagnosis and treatment can improve the cure rate of critically ill patients, and provide a reference for the prospective clinical research in the later period.

This study is a retrospective study with limited sample size. Although this study and previous reports have found that there are statistically significant differences between multiple clinical or laboratory tests between the poor prognosis group and patients, but many of them are not independent of each other. For example, the decline of peripheral blood leukocytes will affect the percentage of lymphocytes. The calculation of glomerular filtration rate is closely related to age, so there are many confounding factors. Using these indicators in isolation to predict the clinical outcome of patients with COVID-19, the accuracy will be greatly reduced. At the same time, although the study on patients with coronary heart disease has a positive result, the sample size is relatively small. For patients with coronary heart disease, follow-up studies that require a larger sample size will be observed and summarized.

Materials And Methods

Object of Study. This was a case-control study. Regression study method was used to include 102 critical 2019-nCoV patients received in Wuhan Tongji Hospital Guanggu District from Feb. 2020 to Mar. 2020. Separate them into survival group and death group according to COVID-19 patient's prognosis. This study had been approved by the Hospital Ethics Committee and exempted from patient's informed consent, all methods were carried out in accordance with approved guidelines, and written informed consent was obtained.

Inclusion Criteria. Critical type group and death group both had clear epidemiological contact history and COVID-19 clinical syndrome and/or lung imaging characteristics. One of the etiological evidences was also acquired[4]: (1) respiratory tract specimen or blood sample quantitative real-time PCR tested COVID-19 nucleic acid positive; (2) respiratory tract or blood sample virus DNA sequence was consanguine to known COVID-19 virus2.

Indicator Observation. Peripheral white blood cell count (WBC), Lymphocyte percentage (L%), Platelet count (PLT), Hypersensitive C reactive protein (hs-CRP), Creatinine (CR), Glomerular filtration rate (eGFR), Lactic Dehydrogenase (LDH), D-dimer (D-D), and Procalcitonin (PCT), Troponin I (TnI).

Statistical Methods. SPSS19.0 software and R6.1 software was used for statistical analysis, Kolmogorov-Smirnov test was used to measure data normality. If the data satisfied normal distribution, average ± SD was used to show, the T-test was used to find differences between two populations; Abnormal distribution was shown by median (IQR), risk-sum test was used for interquartile comparison (Mann-Whitney U test). Chi-square test was used for enumeration data interval comparison. After single factor analysis, statistically significant variables (p 0.05) were screened to binary logistic regression analysis. Variables screened were used to build critical COVID-19 patient mortality risk estimation nomogram using Nomogram function in R software rms pack. Harrell's C-statistic was used to calculate C-index and verified nomogram discrimination. Calibration curve was used to verify nomogram conformity. C-index and calibration curve were used to calculate Bootstraps (1,000 multiple sampling), significance level α=0.05.

Declaration

Date Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author Contributions

L.L.W. and C.L. designed the research. R.F. and Y.L. reviewed the literatures. L.L. W.and Z.Q.W. collected the data. R.F. and Y.L. analyzed the data. L.L.W. and C.L. wrote the paper. All authors critically reviewed the manuscript for important intellectual content and approved the final version

Additional Information

Conflicts of Interest: The authors declare no competing interests.

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Figures

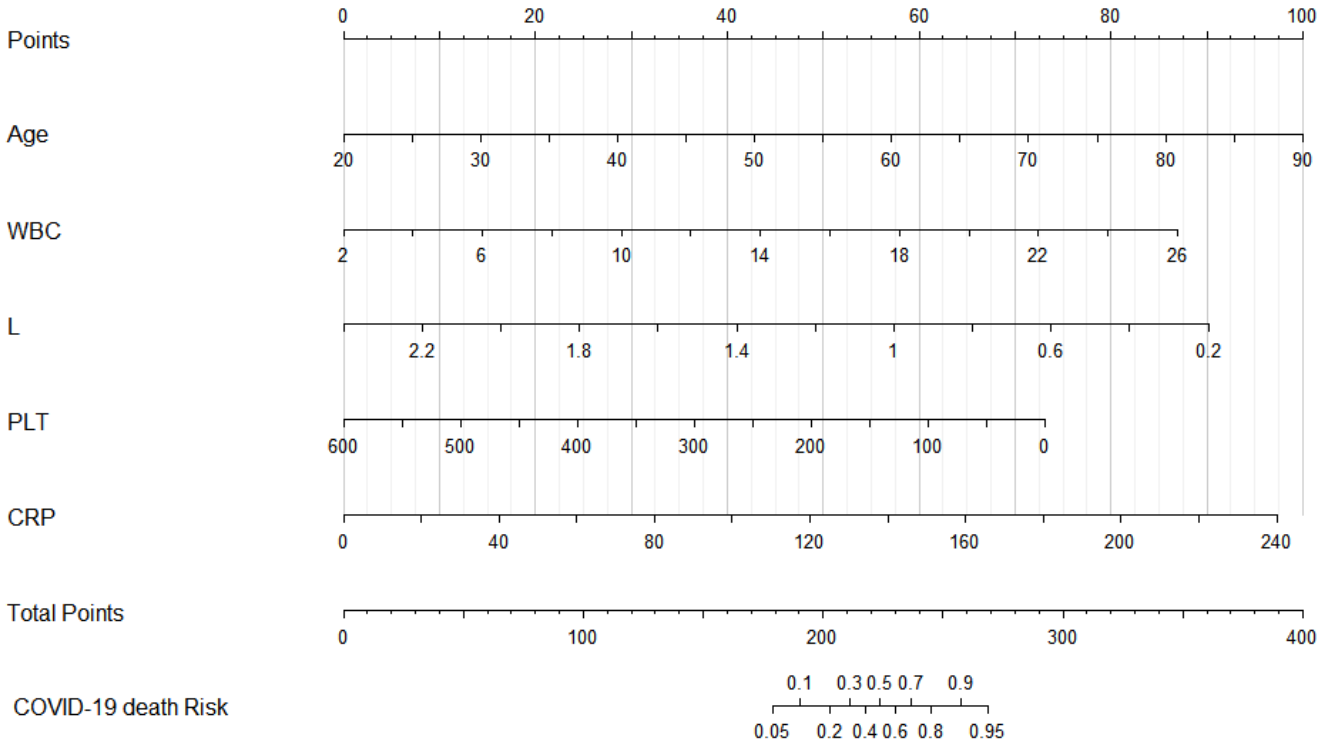

Figure 1

Building and Verification of Critical COVID-19 Patient Mortality Risk Estimation Nomogram. Critical COVID-19 patient mortality risk important risk factor concluded from Model 4 were input into R software. Estimation nomogram of critical COVID-19 patient mortality risk was built. Each item in the model corresponded to a score, the sum of each item score became a total score. The dot on the critical COVID-19 patient mortality risk axis corresponds to the patient mortality risk. In the nomogram, total score went from 179 to 270, its corresponding mortality risk went from 0.05 to 0.95. The higher the score, the higher the mortality risk. The detail is in Figure 1. In addition, the area under ROC curve in Table 3 was utilized to decide accuracy for different test indexs on survival result prediction. The results showed the area under the curve was the largest. Age, L%, PLT, hs-CRP had predictive value to prognosis. In all test indexes, hs-CRP had the largest area under the curve, which was the closest to the prediction model.

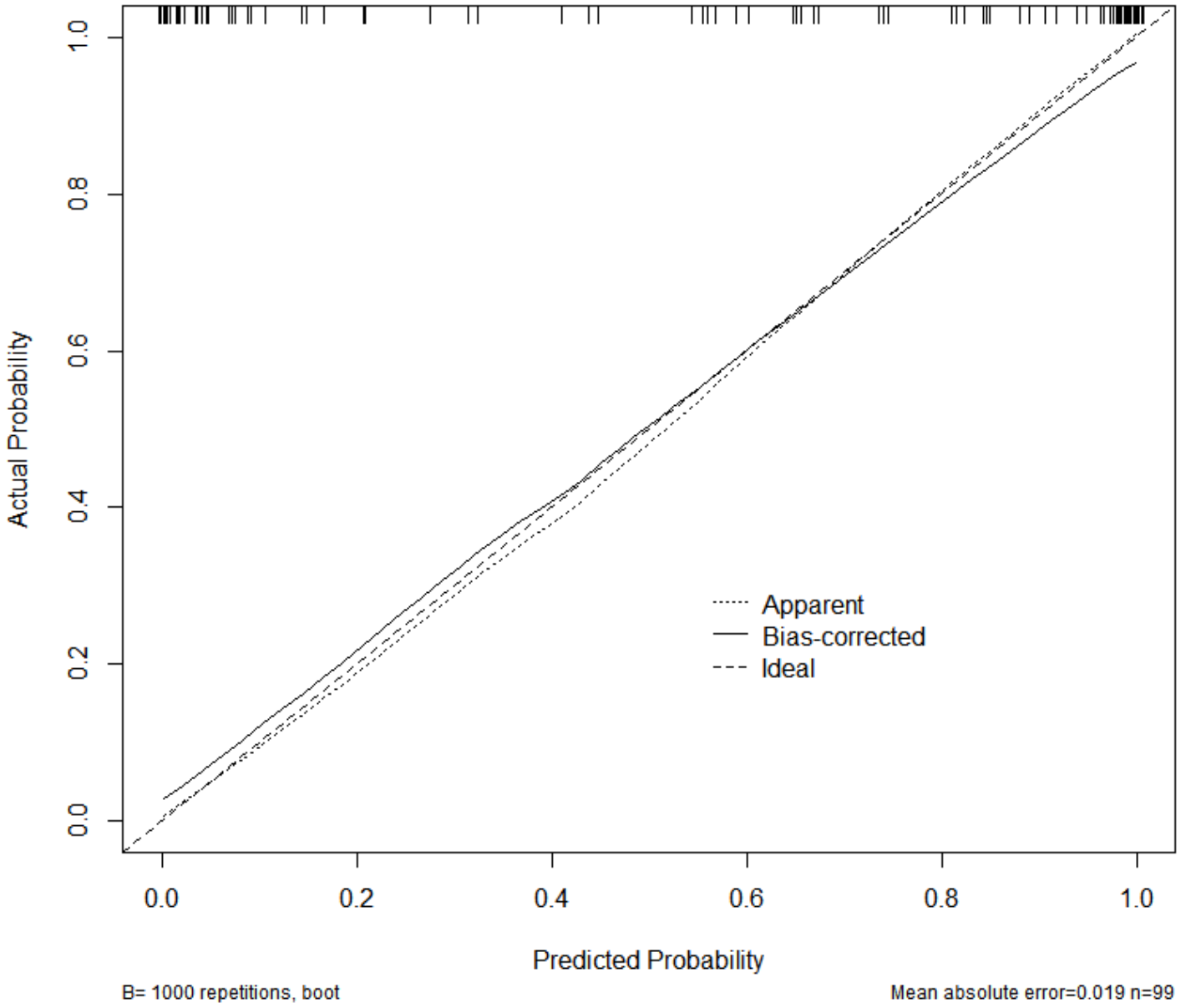

Figure 2

C-index for this nomogram is 0.958 (95% CI; 0.923-0.993), indicating a good differential ability. Calibration curve (Figure 2) shows consistency between prediction probability and actual probability, which indicates the accuracy this nomogram had in estimating critical COVID-19 mortality risk.