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A New Coronavirus Estimation Global Score for Predicting Mortality During Hospitalization in Patients with COVID-19

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Abstract

Objective: Coronavirus disease 2019 (COVID-19) exists as a pandemic. Mortality during hospitalization is multifactorial, and there is urgent need for a risk stratification model to predict in-hospital death among COVID-19 patients. Here we aimed to construct a risk score system for early identification of COVID-19 patients at high probability of dying during in-hospital treatment.

Methods: In this retrospective analysis, a total of 821 confirmed COVID-19 patients from 3 centers were assigned to developmental (n = 411, between January 14, 2020 and February 11, 2020) and validation (n = 410, between February 14, 2020 and March 13, 2020) groups. Based on demographic, symptomatic, and laboratory variables, a new Coronavirus estimation global (CORE-G) score for prediction of in-hospital death was established from the developmental group, and its performance was then evaluated in the validation group.

Results: The CORE-G score consisted of 18 variables (5 demographics, 2 symptoms, and 11 laboratory measurements) with a sum of 69.5 points. Goodness-of-fit tests indicated that the model performed well in the developmental group (H = 3.210, P = 0.880), and it was well validated in the validation group (H = 6.948, P = 0.542). The areas under the receiver operating characteristic curves were 0.955 in the developmental group (sensitivity, 94.1%; specificity, 83.4%) and 0.937 in the validation group (sensitivity, 87.2%; specificity, 84.2%). The mortality rate was not significantly different between the developmental (n = 85,20.7%) and validation (n = 94, 22.9%, P = 0.608) groups.

Conclusions: The CORE-G score provides an estimate of the risk of in-hospital death. This is the first step toward the clinical use of the CORE-G score for predicting outcome in COVID-19 patients.

Keywords: Hospital mortality; Coronavirus estimation global score; COVID-19; Goodness-of-fit; Receiver operating characteristics; Risk stratification

Introduction

Coronavirus disease 2019 (COVID-19) is a rapidly changing global public health crisis.[1] Patients with COVID-19 experience pyrexia during their illness in 85% of cases, but only 45% are febrile on early presentation,[2] which implies disease progression in some patients. Epidemiologic studies have reported that people at any age are susceptible, but older patients have a higher incidence of all-cause death.[2,3] The mortality rate increases in the ≥60 years cohort to 8.8% in comparison to 0.46% for patients <60 years old.[4] Furthermore, the case

CLINICAL PERSPECTIVE

WHAT IS NEW?

- Coronavirus disease 2019 (COVID-19) is a pandemic, leading to >300,000 deaths.
- Unfortunately, there is a lack of risk stratification model for predicting in-hospital mortality.

WHAT ARE THE CLINICAL IMPLICATIONS?

- A risk scoring system, Coronavirus estimation global (CORE-G) score, is built from developmental population and tested in another validation group in this study consisting of 821 COVID-19 patients.
- The CORE-G score will be helpful in identifying COVID-19 patients at high risk.

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fatality rate is higher in patients with certain additional comorbidities. Those with cardiovascular issues, diabetes, and hypertension have case fatality rates of 13.2%, 9.2%, and 8.4%,[4] respectively, with a worldwide case fatality rate of ~12%. Routine blood measurements demonstrated that most patients with COVID-19 have normal or decreased leukocytes and lymphocytopenia.[3–6] More recently, there have been reports of a worsening inflammatory storm characterized by progressive elevation of interleukin (IL)-6, IL-10, and tumor necrosis factor-α[7] among patients with severe disease. Mortality during hospitalization obviously has multifactorial etiology. Unfortunately, there is no practical and effective risk model to identify patients with a higher probability of dying from COVID-19. The present study developed a new Coronavirus estimation global (CORE-G) score for predicting in-hospital death using a developmental group and evaluated its performance in a validation group.

Methods

Patient population

Between January 14, 2020, and March 13, 2020, we screened 1019 hospitalized patients with SARS-CoV-2 infections from 3 hospitals (Tongji Hospital, School of Medicine, Huazhong University of Science and Technology, Wuhan, Hubei; Wuhan First Hospital, Wuhan, Hubei; Tianyou Hospital, Wuhan University of Science & Technology, Wuhan, Hubei). Of those patients, 198 patients were excluded: 89 not confirmed by a polymerase chain reaction (PCR)-positive examination (between February 12, 2020 and February 13, 2020), and 109 with incomplete medical records. Finally, 821 patients were included in this retrospective cohort study and assigned to the development group ($n = 411$, between January 14, 2020 and February 11, 2020) or validation group ($n = 410$, between February 14,2020 and March 13, 2020) [Supplementary Figure 1, http://links.lww.com/CD9/A18]. COVID-19 was defined according to the 6th version of interim guidelines by The National Health Commission of China.[8] The study protocol was approved by the Ethic Committees of all 3 hospitals. No informed consent was required for this retrospective cohort analysis.

Data collection

All epidemiologic, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using a standardized data collection form. The raw data were carefully checked by 2 staff members. Any difference in definition was adjudicated by 1 person who was unaware of the study design. Clinical outcomes after discharge from these 3 hospitals were not recorded. Three typical computed tomography (CT) findings (ground glass opacities, consolidation, and bilateral pulmonary infiltration with a reticular pattern or crazy paving pattern) were collected from COVID-19 patients.[9,10]

Laboratory examinations

Routine blood tests on admission included blood cell counts, cytokines, high-sensitivity cardiac troponin I (hs-cTnI), hepatic and renal function, erythrocyte sedimentation rate, high-sensitivity C reactive protein (CRP), D-dimer, and N-terminal-pro brain natriuretic peptide (NT-proBNP). Repeat measurements were done at 48 and 72 hours (second measurement) after admission and 24 hours before discharge (third measurement).

COVID-19 PCR examination

At 3 to 6 hours after admission, routine throat or nose swabs were recommended for all patients. Nasopharyngeal swabs were done for 12 patients in March 2020. The PCR procedure has been described elsewhere.[2,3,11] Briefly, all swabs were delivered to the Chinese Center for Disease Control and Prevention, the Chinese Academy of Medical Science and the Wuhan Institute of Virology, Chinese Academy of Sciences for testing until January 18, 2020. Since then, our 3 hospitals were able to perform real time-PCR. A PCR re-examination was done every 3 days until to discharge.

Criteria for discharge

The discharge criteria for all patients were the absence of a fever for at least 72 hours, substantial improvement in lung CT, significant clinical improvement of symptoms, and negative PCR tests from at least 2 samples taken at least 24 hours apart.[8]

Development of the CORE-G score

Each of the possible explanatory variables in the developmental group was independently evaluated for its association with in-hospital mortality using bivariate logistic regression. Each statistically significant continuous variable was categorized according to its distribution of centiles (<25% centile, 25%–50% centile, >50%–75% centile, >75%–95% centile, and >95% centile, respectively) by means of exploratory analysis. Then each categorized continuous variable was put into a bivariate regression model to evaluate its association with in-hospital death.

Finally, all variables (non-continuous and categorized continuous) that were significantly correlated with the mortality during hospitalization were analyzed in a multiple logistic regression model. The resulting coefficients (Wald statistic) of this analysis were used to assign points to variables after rounding off to the nearest integer. Once the CORE-G score was calculated for each patient, it was used in a multiple logistic regression equation designed to convert this score to a probability of in-hospital mortality.

Evaluation of the CORE-G score

To assess CORE-G score performance, formal goodness-of-fit (Hosmer-Lemeshow) tests were performed on both the developmental and validation datasets to evaluate its calibration.[12] Then the probability interval for mortality was determined. The expected outcomes within each decile of the population were compared with the observed outcomes for each decile. Finally, an H value (compared with the χ^2 distribution $(df = 8)$) to evaluate the overall fit of the model to dataset and the corresponding P value were reported. Area under the receiver operating characteristic (ROC) curve,[13] along with sensitivity, specificity, cutoff scores, and a corresponding P value, were used to evaluate discrimination in both datasets. Based on the cutoff value of CORE-G score, the rate of in-hospital death was compared between low- and high-risk patients.

Statistical analysis

Categorical variables are reported as numbers and percentages and were compared using the χ^2 test or Fisher exact test.

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range (Q1, Q3)). The Student's *t* test or Wilcoxon rank sum scores for non-normally distributed data were used to compare continuous variables. Time-to-first event (in-hospital death) curves were generated using Kaplan-Meier analysis and compared using log-rank tests. Hospital duration (since admission to discharge or death, Y-axis) was plotted then against the CORE-G scores (X-axis) and the locally weighted scatterplot smoothing (LOWESS) function was used to analyze the difference between survivors and deceased patients.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, New York, USA).

Results

Data collection

A total of 81 variables were collected for all patients consisting of 17 demographics, 6 presentations, 3 CT findings [Table 1], 15 laboratory measurements [Table 2], 18 treatment variables [Supplementary Table 1, http://links.lww.com/CD9/A19], and 22 other unnecessary variables for mortality (eg, time arriving at hospital, data not shown). As reflected by the aims of this study, 18 treatment variables (including mechanical device and medications) were excluded from the analysis. Finally, 41 remaining variables were included in the analyses [Tables 1 and 2].

Table 1

Baseline clinical characteristics of patients with COVID-19 in the developmental and validation groups

Variables	Developmental group ($n = 411$)	Validation group ($n = 410$)	*P*
Demographic variables			
Age (years), mean ± SD	60 ± 14	61 ± 15	0.542
≥70 years, *n* (%)	110 (26.8)	117 (28.5)	0.586
Male, *n* (%)	204 (49.6)	233 (56.9)	0.043
Time interval from symptoms to admission (days), mean ± SD	12.5 ± 7.8	13.5 ± 9.7	0.027
Heart rate (beats/min), mean ± SD	92 ± 16	92 ± 17	0.651
Systolic blood pressure (mmHg), mean ± SD	132 ± 18	130 ± 20	0.275
Diastolic blood pressure (mmHg), mean ± SD	81 ± 12	79 ± 11	0.058
Hypertension, *n* (%)	157 (38.2)	155 (37.8)	0.943
Hyperlipidemia, *n* (%)	7 (1.7)	7 (1.7)	1.000
Diabetes, *n* (%)	69 (16.8)	71 (17.3)	0.853
Smoker, *n* (%)	39 (9.5)	44 (10.7)	0.565
COPD, *n* (%)	13 (3.2)	24 (5.9)	0.066
Renal dysfunction, *n* (%)	6 (1.5)	12 (2.9)	0.162
Stroke, *n* (%)	10 (2.4)	7 (1.7)	0.625
Coronary heart disease, *n* (%)	35 (8.5)	36 (8.8)	0.902
Previous PCI, *n* (%)	11 (2.7)	17 (4.1)	0.256
Atrial fibrillation, *n* (%)	3 (0.7)	1 (0.2)	0.624
Cancer, *n* (%)	7 (1.7)	12 (2.9)	0.257
Presentation, *n* (%)			
Fever	311 (75.7)	362 (88.3)	<0.001
Cough	299 (72.7)	295 (72.0)	0.815
Dyspnea	84 (20.4)	127 (31.0)	0.001
Muscle soreness	51 (12.4)	73 (17.8)	0.032
Diarrhea	58 (14.1)	77 (18.8)	0.074
Chest pain	18 (4.4)	15 (3.7)	0.723
Lung CT scan, *n* (%)			
Ground glass opacity	222 (54.0)	190 (46.3)	<0.001
Consolidation	86 (20.9)	102 (24.9)	0.302
Bilateral pulmonary infiltration	210 (51.1)	157 (38.3)	0.001

COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; PCI: Percutaneous coronary intervention; SD: Standard deviation.

Trends of changes in variables

Nearly one-third of the patients had hypertension, and most patients presented with fever, had ground glass opacity on CT scans [Table 1], exhibited a severe inflammatory storm, and frequently had multiple organ dysfunction [Table 2].

Baseline clinical characteristics were comparable between the development and validation groups, except for male sex (49.6% *vs.* 56.0%, $P = 0.043$), the time interval from symptom onset to admission ((12.5 ± 7.8) days *vs.* (13.5 ± 9.7) days, $P = 0.027$), fever (75.7% *vs.* 88.3%, $P < 0.001$), dyspnea (20.4% *vs.* 31.0%, $P = 0.001$), muscle soreness (12.4% *vs.* 17.8%, $P = 0.032$), and CT findings. Routine blood count tests demonstrated fewer lymphocytes and platelets in the validation group. Patients in the validation group had higher plasma concentrations of hs-cTnI (leading to more myocardial injury), NT-proBNP, CRP, and IL-6, but lower values for albumin, estimated glomerular filtration rate (eGFR), and oxygen saturation compared to those in the developmental group [Table 2]. These differences may reflect the progression in disease severity.

Development of new CORE-G score

Table 3 shows the 18 variables significantly associated with mortality during hospitalization, including 5 demographics, 2 symptoms, and 11 laboratory measurements (including pulmonary consolidation on CT scans).

Points assigned for each variable varied from 0.7 to 14.0, with highest scores for NT-proBNP >500 pg/mL (14.0 points), followed by oxygen saturation <90% (12.0 points), IL-6 ≥8 pg/mL (9.0 points), and myocardial injury (5.0 points). Among continuous variables significantly related to mortality, white blood cell (WBC) count $<4 \times 10^9$/L and aspartate aminotransferase (AST) <41 g/L had a point = 0 in multiple regression analysis and therefore were excluded from the Table 3 and Supplementary Table 2, http://links.lww.com/CD9/A19.

Evaluation of the CORE-G score

Once the CORE-G score was calculated from 411 patients in the developmental group, we converted the CORE-G score to the probability of in-hospital mortality. Patients were then assigned to 10 subgroups according to their mortality probability [Table 4], and a goodness-of-fit test was performed. The result showed an H value = 3.210, $df = 8$, and $P = 0.880$. The ROC curve demonstrated that the cutoff score for mortality was 24.4 points, with a sensitivity of 94.1% and a specificity of 83.4% ($P < 0.001$, 95% confidence interval (CI), 0.937–0.973) [Figure 1A]. This was used to categorize patients as low risk (CORE-G score <24.4 points) or high risk (≥24.4 points), and a Kaplan-Meier survival curve revealed a significant difference in in-hospital death (1.8% *vs.* 59.7%, $P < 0.001$) between the 2 groups [Figure 1B].

Table 2

Laboratory measurements of patients with COVID-19 in the developmental and validation groups

Variables	Developmental group ($n = 411$)	Validation group ($n = 410$)	*P*
White blood cells ($\times 10^9$/L), mean ± SD	6.68 ± 3.69	6.99 ± 3.86	0.221
White blood cells classification, *n* (%)			
$<4.0 \times 10^9$/L	57 (13.9)	78 (19.0)	0.048
$>10.0 \times 10^9$/L	44 (10.7)	66 (16.1)	0.024
Lymphocyte ($\times 10^9$/L), mean ± SD	1.31 ± 0.63	0.95 ± 0.51	<0.001
Lymphocyte $< 0.8 \times 10^9$/L, *n* (%)	94 (22.9)	187 (45.6)	<0.001
Platelet ($\times 10^9$/L), mean ± SD	249 ± 104	216 ± 94	<0.001
Platelet $< 100 \times 10^9$/L, *n* (%)	17 (4.1)	28 (6.8)	0.094
Albumin (g/L), mean ± SD	36.68 ± 5.89	34.55 ± 6.41	<0.001
Albumin < 25 g/L, *n* (%)	10 (2.4)	9 (2.2)	1.000
ALT (U/L), median (Q1, Q3)	22.0 (15.0, 35.0)	25.0 (15.0, 43.0)	0.320
AST (U/L), median (Q1, Q3)	23.0 (18.0, 34.0)	35.0 (22.0, 53.0)	0.391
eGFR (mL/(min·m^2)), mean ± SD	88.96 ± 28.58	84.83 ± 29.38	0.041
eGFR < 60 mL/(min·m^2), *n* (%)	61 (14.8)	74 (18.0)	0.222
Serum creatinine (mg/L), median (Q1, Q3)	68.0 (56.0, 86.0)	75.0 (60.0, 94.0)	0.276
Oxygen saturation (%), mean ± SD	94.96 ± 5.87	91.09 ± 9.75	<0.001
Oxygen saturation < 90%, *n* (%)	106 (25.8)	204 (49.8)	<0.001
hs-cTnI (pg/mL), median (Q1, Q3)	3.40 (1.90, 8.25)	6.40 (3.10, 16.20)	0.040
Myocardial injury, *n* (%)	56 (13.6)	97 (23.7)	<0.001
NT-proBNP (pg/mL), median (Q1, Q3)	98 (46, 372)	179 (73, 471)	0.294
NT-proBNP > 300 pg/mL, *n* (%)	73 (17.8)	107 (26.1)	0.004
Erythrocyte sedimentation rate (mm/h), mean ± SD	36.3 ± 30.3	37.9 ± 20.0	0.558
Erythrocyte sedimentation rate > 15 mm/h, *n* (%)	99 (24.1)	251 (61.2)	<0.001
C-reactive protein (mg/L), median (Q1, Q3)	8.00 (1.40, 46.75)	53.70 (10.7, 102.0)	<0.001
C-reactive protein > 10 mg/L, *n* (%)	177 (43.1)	306 (74.6)	<0.001
D-dimer (mg/mL), median (Q1, Q3)	0.69 (0.29, 1.69)	1.07 (0.57, 2.01)	0.245
Interleukin-6 (pg/mL), median (Q1, Q3)	3.98 (1.80, 13.30)	14.17 (3.30, 57.50)	0.026
Interleukin-6 > 7 pg/mL, *n* (%)	111 (27.0)	168 (41.0)	<0.001

ALT: Alanine aminotransferase transaminase; AST: Aspartate transaminase; eGFR: Estimated glomerular filter rate; hs-cTnI: High-sensitivity cardiac troponin; NT-proBNP: N-terminal-pro brain natriuretic peptide; SD: Standard deviation.

Table 3

CORE-G scores of variables that significantly correlated with in-hospital death

Variables	Scores
Demographic variables	10.6
Male sex	3.7
Age ≥ 70 years	1.7
Hypertension	1.3
Smoker	2.3
Cancer	1.6
Presentation	5.3
Fever	2.3
Dyspnea	3.0
Measurements	53.6
White blood cell count $\geq 10 \times 10^9$/L	2.0
Lymphocyte count $< 0.8 \times 10^9$/L	3.0
Platelet count $< 100 \times 10^9$/L	1.3
Pulmonary consolidation on CT scan	1.4
eGFR < 30 mL/(min·m^2)	2.2
Albumin < 25 g/L	3.0
C-reactive protein≥10 mg/L	0.7
IL-6 ≥8 pg/mL	9.0
Myocardial injury (hs-cTnI ≥ 48.0 pg/mL in males or ≥25.0 pg/mL in females)	5.0
Oxygen saturation < 90%	12.0
NT-proBNP ≥500 pg/mL	14.0
Sum of scores	69.5

CORE-G: Coronavirus estimation global; CT: Computed tomography; eGFR: Estimated glomerular filter rate; hs-cTnI: High-sensitivity cardiac troponin; IL: Interleukin; NT-BNP: N-terminal brain natriuretic peptide.

The same process was performed in the validation group. Goodness-of-fit testing yielded an H value of 6.948, $df = 8$, and $P = 0.542$ [Table 4]. The ROC curve demonstrated a sensitivity of 87.2% and a specificity of 84.2% ($P < 0.001$, 95% CI, 0.913–0.962) [Figure 2A]. Finally, patients were classified as low risk (CORE-G score <24.4 points) or high risk (≥24.4 points), and a Kaplan-Meier survival curve revealed a significant difference for in-hospital death (4.3% *vs.* 62.1%, $P < 0.001$) between the 2 groups [Figure 2B].

Correlation of CORE-G scores with hospital duration

When scores and hospital duration were plotted on the *X*- and *Y*-axes, respectively, LOWESS analysis [Figure 3] showed that deceased patients had a shorter hospital duration compared to survivors in the developmental ((11.87 ± 7.00) days *vs.* (17.31 ± 9.20)) days and validation groups ((10.81 ± 7.48) days *vs.* (23.65 ± 8.54)) days (both $P < 0.001$).

Discussion

The present study introduced a new CORE-G score for predicting in-hospital mortality in patients with COVID-19. The major findings are: (1) the mechanisms correlated with the in-hospital mortality among COVID-19 patients are complex and multifactorial, reflected by 18 variables in this CORE-G score and (2) the CORE-G score model closely reflects the true mortality experience in the developmental and validation groups.

Table 4

Goodness-of-fit test for the CORE-G score in the developmental and validation groups

	Developmental group ($n = 411$)				Validation group ($n = 410$)			
	Survivor subgroup ($n = 326$)		Death subgroup ($n = 85$)		Survivor subgroup ($n = 316$)		Death subgroup ($n = 94$)	
Probability of dying	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
0.00–0.10	266	264.2	4	5.8	236	188.1	8	55.9
>0.10–0.20	15	12.9	5	7.1	38	34.7	7	10.3
>0.20–0.30	14	10.5	3	6.5	13	11.6	2	3.4
>0.30–0.40	5	6.7	6	4.3	5	7.7	5	2.3
>0.40–0.50	7	8.3	6	4.7	6	10.8	8	3.2
>0.50–0.60	7	7.3	6	5.7	6	9.2	6	2.8
>0.60–0.70	4	3.1	5	5.9	4	6.9	5	2.1
>0.70–0.80	1	3.9	9	6.1	4	8.5	7	2.5
>0.80–0.90	5	7.5	17	14.5	4	12.3	12	3.7
>0.90–0.99	2	1.6	24	23.4	0	26.2	34	7.8
Indicated CORE-G score	$H = 3.210$, $df = 8$, $P = 0.880$				$H = 6.948$, $df = 8$, $P = 0.542$			

CORE-G: Coronavirus estimation global.

Many variables can predict COVID-19 progression and in-hospital mortality,[2–7] including symptoms,[2] older age,[4] comorbidities,[3,4] abnormal leukocytes and lymphocytopenia,[3–6] and inflammatory cytokine levels.[7] Some cases classified as mild on admission can transform to critical illness within a short period.[8,9] Thus, a practical and effective risk model for identifying the probability of worsening or death is urgently required for COVID-19 patients. Four risk stratification systems[14–17] were recently developed, and data confirmed their individual performances in predicting progression from mild to critical illness or death. However, some studies had high risks of bias and model overfitting, and reporting quality varied substantially, such as different study population sizes and only rare calibration of predictions. Therefore, extensive studies must be performed and models should be adjusted as necessary before these systems can provide accurate estimates of the probability of in-hospital mortality.

The selection of variables and the points assigned for each was weighted with a logistic regression modeling approach,[12,18] which strictly complied with the methodology reported by Le Gall et al.[18] For a given risk model, a goodness-of-fit test and discrimination assessment are critical to evaluate its performance. In the CORE-G scoring system, the H and P values were 3.210 and 0.880, respectively, in the developmental group, which indicated that the model very closely reflected the true mortality. This excellent performance was confirmed in the validation group ($H = 6.948$, $P = 0.542$). Furthermore, discrimination of the CORE-G model was evaluated using an ROC curve. Interestingly, the same cutoff score was calculated for the development and validation groups. The area under the ROC curve confirmed good performance of this model for the probability of in-hospital death of COVID-19 patients. A direct comparison between the CORE-G score and other scoring models is required to clarify the advantages of this model.

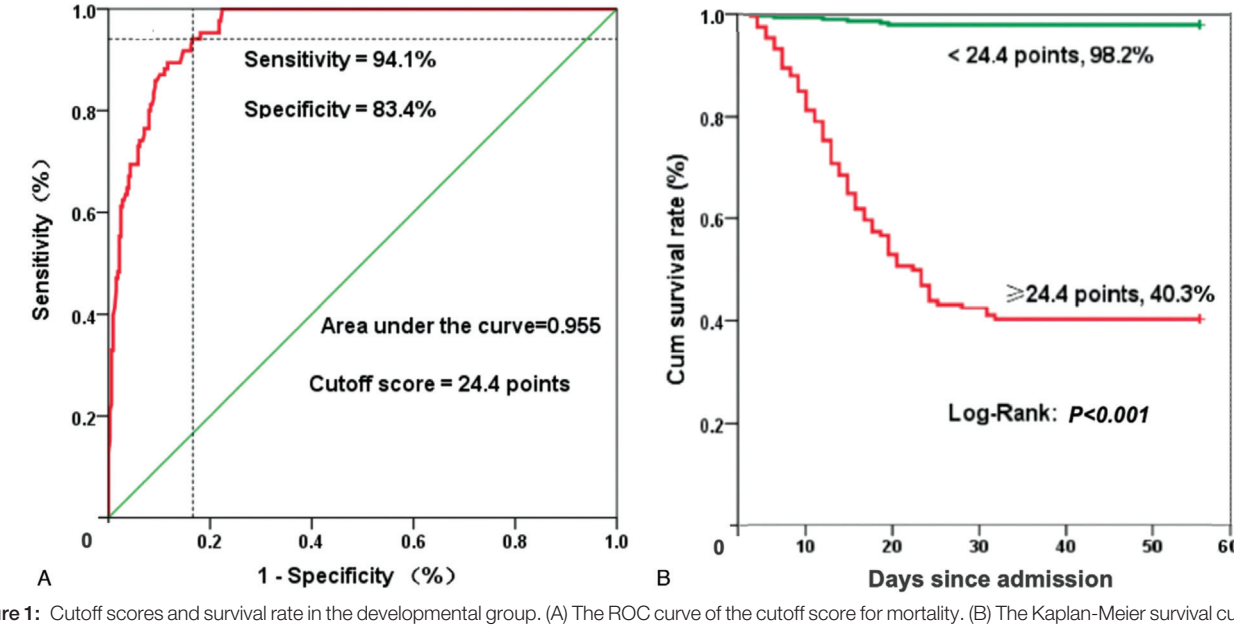

Figure 1: Cutoff scores and survival rate in the developmental group. (A) The ROC curve of the cutoff score for mortality. (B) The Kaplan-Meier survival curve of in-hospital death. ROC: Receiver operating characteristic.

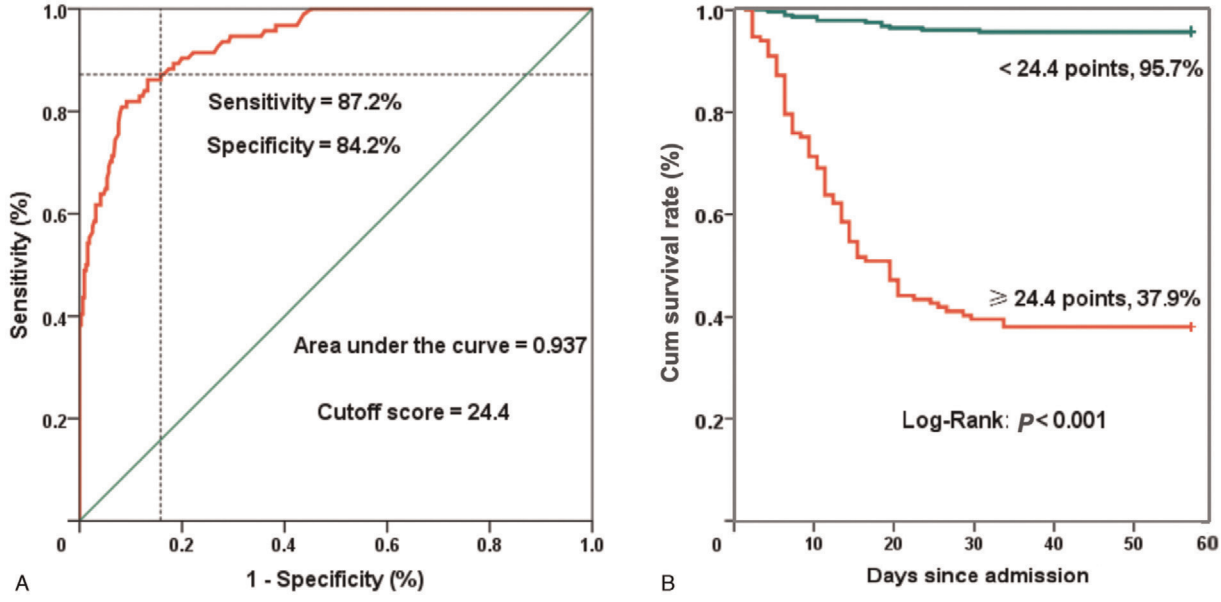

Figure 2: Cutoff scores and survival rate in the validation group. (A) The ROC curve of the cutoff score for mortality. (B) The Kaplan-Meier survival curve of in-hospital death. ROC: Receiver operating characteristic.

Regarding the variables used in our models and previous ones,[14–17] male sex was included in the CORE-G score. The Chinese health authority has announced that the total number of confirmed cases on the Chinese mainland has reached 77,042, and 2445 people had died of the disease as of February 23, 2020. Among the 2445 deceased patients, most were elderly and two-thirds were male, although detailed data has not been reported.[19] While both sexes had the same prevalence of COVID-19 in this study and others,[1–7,9,10] males are at greater risk for worse outcomes and death, independent of age.[20] One study of 425 patients with COVID-19 reported that 56% were males,[21] while another study of 140 patients found that 50.7% were males,[22] similar to our results. We also had more males in the validation group compared to the developmental group, suggesting a trend in sex difference over time during the pandemic. In previous studies, NT-proBNP was not associated with in-hospital mortality.[12–17] This may be due to the fact that NT-proBNP was not routinely measured in most published studies. Inflammatory cytokines, particularly IL-6, were reported to be independent biomarkers of in-hospital death.[2–7,9–13,23] A meta-analysis including 3377 patients and 33 laboratory parameters from 21 published studies demonstrated that among hospitalized patients with respiratory distress, WBC count, lymphocyte count, platelet count, IL-6, and serum ferritin were markers for potential progression to critical illness.[23]

Another striking finding was the ability of the CORE-G score to predict hospital stay duration among survivors and deceased patients. Zhou et al[24] first reported that survivors were discharged from the hospital 3 days later than non-survivors, which was significantly shorter than the 6 and 13 days in the

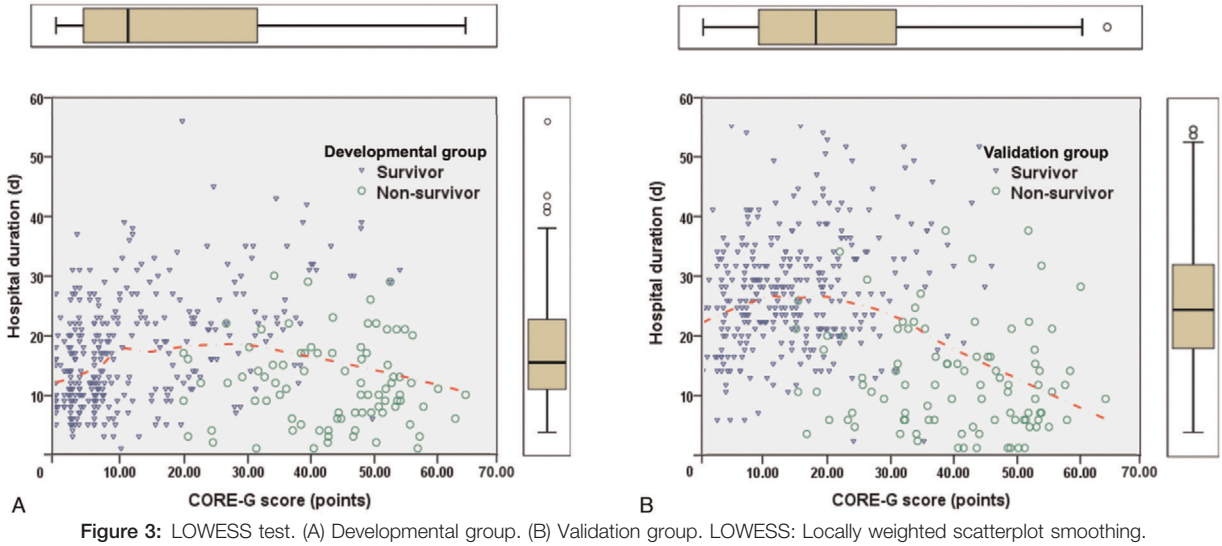

Figure 3: LOWESS test. (A) Developmental group. (B) Validation group. LOWESS: Locally weighted scatterplot smoothing.

developmental and validation groups from our analysis, respectively. On one hand, the agreement between our results and those published by Zhou et al[24] was that critical patients died earlier after admission. On the other hand, recovery of medical resources and gradual adoption of modified treatments over time may explain the significantly longer hospital duration. There is a lack of specific anti-viral treatments recommended for COVID-19. However, mechanical ventilation was recommended for most deceased patients,[8,19] and this rate was particularly higher in the validation group. Nevertheless, the fact that the CORE-G score could enhance the association of scores with hospital duration further supports the strength of this model for predicting in-hospital mortality.

Limitations

The study findings should be considered in the context of several limitations. First, the retrospective design led to 198 patients being excluded from the model, which may have introduced selection bias. Accordingly, further prospective studies with larger sample sizes are warranted. Second, each co-existing cardiovascular disease was individually analyzed in the model, resulting in coronary heart disease being excluded from the scoring system. This may be due to our inclusion of fewer patients with coronary heart disease, as well as diabetes. Third, it is unclear whether uncontrolled hypertension is a risk factor for acquiring COVID-19, or whether controlled blood pressure among hypertensive patients is less of a risk factor.[25] However, our model showed an independent effect of hypertension on mortality among COVID-19 patients. Fourth, the CORE-G score may not be applicable to COVID-19 mutant strains, which is now a serious concern in many countries. Fifth, the inclusion of variables such as IL-6 that are rarely collected during the course of routine clinical care greatly limits the usefulness of the CORE-G score. Finally, the goodness-of-fit and discrimination of the CORE-G model for hospital duration were not evaluated. However, reliable LOWESS tests confirmed the strong correlation of CORE-G score with early death among COVID-19 patients.

Conclusions

The present study introduced the new CORE-G model for predicting in-hospital mortality among COVID-19 patients. Its excellent performance was confirmed in both the developmental and validation groups. This work will serve as the starting point to identify the utility of the CORE-G model in future work.

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Author Contributions

Shaoliang Chen and Hesong Zeng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

None.

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