Clinical and laboratory predictors of in-hospital mortality in patients with COVID-19: a cohort study in Wuhan, China

Kun Wang*, Peiyuan Zuo*, Yuwei Liu, Meng Zhang, Xiaofang Zhao, Songpu Xie, Hao Zhang, Xinglin Chen, Chengyun Liu

*Contributed equally

Department of Geriatrics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (K Wang PhD; M Zhang MD; X Zhao MS; S Xie MS; H Zhang MS; Prof C Liu PhD);

The First People's Hospital of Jiangxia District, Wuhan City & Union Jiangnan Hospital, HUST, Wuhan 430200, China. (Prof C Liu PhD)

Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (P Zuo PhD);

Department of Epidemiology and Biostatistics, Empower U, X&Y solutions Inc., Boston, USA (X Chen PhD).

Correspondence to: Prof C Liu PhD, Department of Geriatrics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China chengyunliu@hust.edu.cn

Summary: We developed a clinical model and laboratory model for predicting the in-hospital mortality of COVID-19 patients, the AUCs (95% CI) were 0.88 (0.80, 0.95) and 0.98 (0.92, 0.99) in training cohort, and 0.83 (0.68, 0.93) and 0.88 (0.77, 0.95) in validation cohort, respectively.

ABSTRACT

Background

This study aimed to develop mortality-prediction models for patients with Coronavirus disease 2019 (COVID-19).

Methods

The training cohort were consecutive patients with COVID-19 in the First People's Hospital of Jiangxia District in Wuhan from January 7, 2020 to February 11, 2020. We selected baseline clinical and laboratory data through the stepwise Akaike information criterion and ensemble XGBoost model to build mortality-prediction models. We then validated these models by randomly collecting COVID-19 patients in the Infection department of Union Hospital in Wuhan from January 1, 2020, to February 20, 2020.

Results

296 patients with COVID-19 were enrolled in the training cohort, 19 of whom died during hospitalization and 277 were discharged from the hospital. The clinical model developed with age, history of hypertension and coronary heart disease showed AUC of 0.88 (95% CI, 0.80-0.95); threshold, -2.6551; sensitivity, 92.31%; specificity, 77.44% and negative predictive value (NPV), 99.34%. The laboratory model developed with age, high-sensitivity C-reactive protein (hsCRP), peripheral capillary oxygen saturation (SpO2), neutrophil and lymphocyte count, D-dimer, aspartate aminotransferase (AST) and glomerular filtration rate (GFR) had a significantly stronger discriminatory power than the clinical model (p=0.0157), with AUC of 0.98 (95% CI, 0.92-0.99); threshold, -2.998; sensitivity, 100.00%; specificity, 92.82% and NPV, 100.00%. In the subsequent validation cohort (N=44), the AUCs (95% CI) were 0.83 (0.68, 0.93) and 0.88 (0.75, 0.96) for clinical model and laboratory model, respectively.

Conclusions

We developed two predictive models for the in-hospital mortality of patients with COVID-19 in Wuhan and validated in patients from another center.

Keywords: COVID-19; Predictive model; Mortality.

Introduction

Several cases of "unknown viral pneumonia" have been reported in Wuhan, Hubei Province, China since December 2019. The causative agent was revealed as a novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses. The disease caused by SARS-CoV-2 was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).[1] This infectious disease has rapidly spread from Wuhan to other Chinese regions[2]. Since mid-march 2020, cases have been detected in most countries worldwide and community spread is being detected in a growing number of countries. On March 11, the COVID-19 outbreak was characterized as a pandemic by the WHO external icon. As of March 14, 2020, 23:05, 81,032 and 67,287 people have been diagnosed with COVID-19 in and beyond China, respectively, and 3194 patients died of this disease in mainland China.

Mild acute respiratory infection symptoms, such as fever, dry cough, and fatigue, commonly occur in the early stages of COVID-19, but some patients might rapidly develop acute respiratory distress syndrome, acute respiratory failure, multiple organ failure, and other fatal complications.[3,4] No specific treatment has been fully developed for COVID-19; thus, early identification of patients with poor prognosis may facilitate the provision of proper supportive treatment in advance and reduce mortality.

COVID-19-related deaths are more common in elderly people or patients with increasing counts of neutrophils and D-dimer or decreasing counts of lymphocytes.[5] However, whether these risk factors can predict a fatal outcome is unknown. Current studies on COVID-19 have focused on the epidemiology and clinical features of the patients,[4,6] but information regarding the prediction of its prognosis is scarce. This study aimed to develop a model that precisely predicts the outcome of death for patients with COVID-19.

Methods

Study design and participants

The participants in the training cohort were all the consecutive patients diagnosed with COVID-19 in the First People's Hospital of Jiangxia District in Wuhan, a major hospital in the Jiangxia District. We collected data on patients hospitalized from January 7, 2020, 17:58 to February 11, 2020, 22:01. A total of 296 patients with final outcome (i.e. discharged or dead) were enrolled in this study before February 12, 2020, 14:00. We then randomly collected patients with COVID-19 who had been hospitalized in the Infection department of Union Hospital in Wuhan from January 1, 2020, to February 20, 2020 to form our validation cohort. A flow diagram is showed in Figure 1.

The data of these participants were used to construct two predictive models for in-hospital mortality. The study protocol was approved by the Medical Ethics Committee of the First People's Hospital of Jiangxia District and Union Hospital, and was complied with the Declaration of Helsinki. We verbally informed the patients that their data would be used anonymously for medical studies and obtained their permission. Written informed consent was not gathered, because the data were anonymous and the study was observational.

Variable measurement

Previous medical history, age, cough and fever (the oral temperature>37.5 ℃, the axillary temperature>37℃, or the body temperature fluctuates more than 1℃ in a day) for every subject were obtained by trained nurses. The laboratory data of the first examination after admission of every subject were also collected.

All blood and urinary samples were processed within two hours of collection. Routine blood tests (including white blood cell count [WBC], neutrophil count, lymphocyte count and monocyte count) were measured using BC-3000 auto haematology analyser (Mindray Medical International, Inc.). Blood coagulation including plasma D-dimer, prothrombin time (PT), international normalized ratio (INR), activated partial prothrombin time (APTT), and thrombin time (TT) were measured using the immunoturbidimetry by ACL TOP system (Instrumentation Laboratory, Milan, Italy). HsCRP was detected by immunoturbidimetry in a Japanese automatic biochemical analyzer (Olympus AU2700). Blood Urea nitrogen (BUN), creatinine (Cr), and glomerular filtration rate (GFR) were measured by enzymatic method, Jaffe's kinetic method and the enzymatic equation. Total bilirubin (TBil) was measured by vanadate oxidation method, creatine kinase (CK) was measured by continuous monitoring method, CK-MB was measured by immunosuppression method, Alanine aminotransferase

(ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and blood ammonia were measured by velocity method, albumin (ALB) was measured by bromocresol puple method, globulin (GLO) was measured by colorimetric method on a Beckman-Coulter AU5800 (Beckman-Coulter Co, Brea, CA, USA).

Diagnosis of COVID-19

Meeting any of the following etiological evidence can be defined as COVID-19:

1. Respiratory tract or blood specimens positive for SARS-CoV-2 nucleic acid by real-time fluorescent RT-PCR;

2. Virus in respiratory tract or blood specimens found highly homologous with new SARS-CoV-2 by genetic sequencing.

3. Suspected cases with imaging features of pneumonia (according to the "Diagnosis and treatment plan for pneumonia infected with new coronavirus [trial version 5]" issued by the National Health Commission of China, this standard is limited to Hubei Province).

Statistical analysis

Baseline demographic and clinical characteristics of all participants at time of admission are presented as means (standard deviations) or medians (interquartile ranges) for continuous variables, and as frequencies (percentage) for categorical variables, and presented by training and validation cohort in Table 1 and by in-hospital mortality in Table 2, respectively. Differences among groups were analyzed using χ^2 test, one-way ANOVA and Kruskal-Wallis tests for categorical variables, normally and skewed distributed continuous variables, respectively.

In the model-development phase, we first performed univariate logistic regression analysis of all variables for the in-hospital mortality in the training cohort (supplementary material Table S1). For the variables at a statistically significant level ($p < 0.05$), we carried out variance inflation factor (VIF) test, and excluded the variables causing potential multicollinearity according to the criteria of VIF >5 (supplementary material Table S2). For the remaining variables screened by the above steps, we conducted extreme gradient boosting (XGBoost) model[7, 8] to analysis the contribution (gain) of each variable to the in-hospital mortality (supplementary material Table S3 and Figure S1). At the same time, according to the Akaike information criterion (AIC) [9], we performed backward step-down selection processes by a threshold of $P < 0.05$ for the selection of variables in the predictive model.

After combination of the results of AIC and XGBoost, we selected clinical and laboratory variables to construct predictive models through multivariable logistic regression. We developed a clinical predictive model according to age, history of hypertension and coronary heart disease (CHD), and a laboratory model according to baseline age, peripheral capillary oxygen saturation (SpO2), neutrophil count, lymphocyte count, hsCRP, D-dimer, AST and GFR. We compared the area under the receiver operator characteristic (ROC) curve (AUC) between the two models by "Delong" method [10]. Threshold, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) are also presented in Table 3. We also formulated nomograms for the practical application (Figure 3).

The statistical analyses were 2-tailed and P value < 0.05 was considered statistically significant. Data were analyzed with the use of the statistical packages R (The R Foundation; http://www.r-project.org; version 3.4.3) and Empower (R) (www.empowerstats.com, X&Y solutions, inc. Boston, Massachusetts).

Results

Among the 296 patients with COVID-19 enrolled in the training cohort, 22 (7.28%) died during hospitalization, and 280 (92.72%) were discharged from the hospital (Figure 1). The mean and median hospital stay of the non-survivors were 11.1 ± 5.8 and 11.6 [interquartile range (IQR), 8.6–15.5] days, respectively. The mean and median hospital stay of the survivors were 6.2 ± 5.0 and 4.9 (IQR, 2.6–10.5) days, respectively. The mean and median time interval between symptom onset and admission of the non-survivors were 5.2 ± 3.7 and 5.0 (IQR, 3.0–7.0) days, respectively. And for the survivors were 6.8 ± 4.0 and 5.5 (IQR, 3.0–9.2) days, respectively.

Baseline clinical and laboratory characteristics of study population by training and validation cohort are shown in Table 1. We observed significant differences between the two cohorts in age, outcome, symptoms, and clinical indicators. The patients in validation cohort were remarkably older, with higher rates of diabetes and hypertension, lower SpO2, and worse markers of inflammation, clotting status, and liver and kidney function.

The comparison between the survivors and the non-survivors were shown in Table 2. The mean age of the non-survivor group was remarkably higher than that of the survivor group in both cohorts. Medical history showed that the non-survivor group had a higher proportion of basic disease. No substantial difference was observed in the sex composition and habits of smoking and drinking between survivors and non-survivors. In the training cohort, non-survivors had remarkably lower SpO2 than survivors. Inflammatory cells, namely, WBC and

neutrophil, were considerably higher whereas lymphocyte was remarkably lower in the non-survivor group than in the survivor group. Meanwhile, hsCRP, a marker of inflammation, was also substantially elevated in the non-survivor group. In terms of blood coagulation indexes, the non-survivor group had higher D-dimer and thrombin time and lower activated partial thromboplastin time than the survivor group. Cr, BUN, ALT, AST, LDH, and blood ammonia were remarkably higher whereas GFR and serum ALB were significantly lower in the non-survivor group.

In the model-development phase, the clinical model developed according to age, history of hypertension and coronary heart disease showed good discriminatory power with AUC of 0.88 (95% CI, 0.80-0.95), threshold of -2.6551, sensitivity of 92.31%, specificity of 77.44%, positive predictive value (PPV) of 21.43% and negative predictive value (NPV) of 99.34% (Table 3). The laboratory model developed with age, SpO2, neutrophil count, lymphocyte count, hsCRP, D-dimer, AST and GFR had a significantly stronger discriminatory power than the clinical model ($p = 0.0157$) with AUC of 0.98 (95% CI, 0.92-0.99), threshold of -2.9998, sensitivity of 100.00%, specificity of 89.23%, PPV of 48.15% and NPV of 100.00%.

In the model validation phase, we observed good discriminatory powers with the AUCs of 0.83 (95% CI, 0.68–0.93) and 0.88 (95% CI, 0.75–0.96), threshold of -1.7976 and -3.8238, sensitivity of 64.29 % and 100.00 %, specificity of 93.33% and 70.00%, PPV of 81.82% and 60.87 %, NPV of 100.00% NPVs of 84.85% and 100.00% for clinical model and laboratory model, respectively. (Table 4)

The ROC of the two models in training and validation cohort were plotted in Figure 2. The nomogram of these models was drawn to provide quantitative and convenient tools in predicting the risk of in-hospital mortality of COVID-19 patients by clinical and laboratory characteristics at time of admission. (Figure 3).

Discussion

This training cohort included 296 patients with COVID-19 in Wuhan with a total in-hospital mortality of 6.4%. We established a clinical model and a laboratory model to predict patient death by readily available clinical features at time of admission. Both models exhibited relatively good discriminatory power the and the external verification was also satisfactory. We believe that this is the first study to establish models for predicting the mortality of patients with COVID-19.

The clinical model based on age, history of hypertension, and coronary heart disease had achieved good predictive power. Elderly people are at higher risks for chronic diseases and

more susceptible to infection. Age might be the risk factor for worse outcomes in patients with COVID-19 partially because age-related immune dysfunctions result from low-grade chronic inflammation according to our speculation.[5,11] In addition, elderly patients may possess other risk factors, such as comorbidities and sarcopenia. Hypertension is one of the most common diseases in the elderly. History of hypertension is an important risk indicator in the MuLBSTA score, which is a viral pneumonia death warning model developed by Chinese scholars.[12] Our results are consistent with the above research. In addition, angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV-2,[13] is directly involved in the process of acute lung injury after virus infection because of its important regulatory role in the renin–angiotensin–aldosterone system. However, an abnormal expression and dysregulation of ACE2 may occur in hypertensive individuals,[14] which may be the reason for the poor prognosis of patients with hypertension complicated with COVID-19. The heart of a patient with CHD history and infected with SARS-CoV-2 has to work harder to ensure that sufficient blood oxygen is provided throughout the body. The problem of increased heart burden will become more prominent. Reasonable precautions must be taken to prevent these patients from the viral infection.

XGBoost showed that hsCRP was the most important predictor for the mortality of patients with COVID-19, followed by age, SpO2, AST, neutrophil count, D-dimer, GFR and lymphocyte count. This finding is consistent with our clinical observation.

A low SpO2 level suggests that the patients might have a serious illness at the time of admission. We found that most of the patients with COVID-19 had mild acute respiratory infection symptoms initially; however, the conditions of some patients would rapidly exacerbate and result in multiple organ failure or even death. We suspected this exacerbation was primarily due to the "cytokine storm" and consequent immunologic abnormality. Cytokine storm is an important cause of death in severe acute respiratory syndrome (SARS), Middle East respiratory syndrome coronavirus, and influenza A virus subtype H1N1 infection.[15-17] Cytokine storm also seems to be a remarkable mechanism in the present outbreak of COVID-19 and contributed to the death of several patients, especially young patients. A recent study showed that patients requiring ICU admission had higher concentrations of granulocyte colony-stimulating factor, interferon-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and tumor necrosis factor alpha than those who did not require ICU admission, suggesting that cytokine storm is associated with disease severity.[4] A remarkable finding of our study was that the

increasing level of hsCRP and neutrophil counts had prominent power in predicting fatal outcomes in patients with COVID-19. Neutrophil chemotaxis and transmigration are essential components for host defense during infections, but excessive neutrophil infiltration contributes to deleterious inflammatory processes,[18] which might deeply interact with cytokine storm during virus invasion.

The substantially depressed total lymphocytes in the non-survivor group indicated that SARS-CoV-2 might act on T lymphocytes, and high replication of the virus leads to the depletion of T lymphocytes, which suppresses the body's immunity.[19] In addition, patients with severe illness are more likely to be co-infected with bacteria because of depressed immune function, which is another possible reason for the increased level of neutrophils and hsCRP. Further studies are necessary to elucidate the cytokine storm and immunologic abnormality in SARS-CoV-2 infection.

We found that coagulation indicators might play a role in identifying severe cases as well. We observed that D-dimer was negatively associated with in-hospital mortality. According to previous research on SARS, inflammatory response may modify coagulation pathways and genes, which results in disseminated infarct and hemorrhage that can be seen in the lungs in the autopsy of patients with SARS.[20] Wang et al. showed that 58% of patients with COVID-19 patients have prolonged prothrombin time.[5] Tang et al. investigated the non-survivors with COVID-19 and revealed that these non-survivors had remarkably higher D-dimer and fibrin degradation product levels and longer prothrombin time compared with survivors upon admission. They suggested that common coagulation activation and secondary hyperfibrinolysis occur in the late stages of COVID-19 patients [21].

Liver function was an important predictor for the mortality of patients with COVID-19. A recent research indicated that SARS-CoV-2 may directly bind to ACE2-positive cholangiocytes; thus, liver abnormalities in patients with COVID-19 may be due to cholangiocyte dysfunction and other causes, such as drug-induced and systemic inflammatory response-induced liver injuries [22]. More research are needed, because most of our patients had evidence of liver dysfunction prior to therapy. Multiple-organ dysfunction, including kidney dysfunction, indicates poor survival outcome. In our study, GFR was remarkably lower in the non-survivor group than in the survivor group. A research of critically ill patients with COVID-19 in Wuhan showed that 29% had acute kidney injury [23]. Therefore, we suggest that special care of kidney dysfunction should be included in the treatment of patients with COVID-19 during hospitalization.

At present, this novel infection has no specific treatment, and the use of IgG and systemic corticosteroid remains controversial; therefore, the early identification of patients with poor prognosis and early active intervention (e.g., early respiratory support [22], continuous renal replacement therapy, and immune adsorption) to avoid disease development are the key to treatment. However, early identification remains a difficult task for doctors as the symptoms of COVID-19 are not typical.

The clinical model could help doctors to initially identify high-risk patients in settings with limited medical resources, such as patients who are isolated at home. We observed relatively high sensitivity (92.31%) and NPV (99.34%), which means a lower likelihood of missing high-risk individuals; a relatively low PPV (21.43%), which means a higher likelihood of misjudging individuals with actually low-risk. Therefore, the clinical model is suitable for the initial screening. The laboratory model showed better discriminatory power than the clinical model with an AUC value of 0.98, sensitivity and NPV of 100.00%. Baseline data for the model can be obtained in the patient's first routine examination after admission and can help doctors surmise the prognosis at an early stage and guide subsequent treatments; hence, the patients who are prone to develop the disease at critical level can get close attention and high-level treatments in advance. This model can also be used as a reference for transferring patients from community hospitals or square cabin hospitals (the temporary hospital for the placement and observation of mildly ill patients and suspected cases) to higher-level hospitals.

In the model validation phase, we also observed good discriminatory powers with the AUCs of 0.83 and 0.88 for clinical model and laboratory model, respectively. Interestingly, high specificity and PPV were demonstrated in clinical models in the validation cohort, as opposed to the training cohort. We hypothesized that the probable reason was that there were more deaths in patients with a history of hypertensive or coronary artery disease in the validation cohort. More external validation is needed to demonstrate the robustness of the model, and we currently recommend that clinical models with limited information only be used for preliminary screening of high-risk populations.

By comparing the training and validation populations in Table 1, we had observed significant differences between the two groups in age, symptoms, and examination index (SpO_2, inflammatory cells, coagulation function, liver and kidney function). Our model has been validated and performed good discriminatory powers in heterogeneous populations with different levels of hospital, different death ratio and different physical condition, suggesting that the models may be applicable to different settings

Our study has several limitations. First, our research were carried out among patients with COVID-19 in Wuhan; therefore, further verification is needed in populations in other areas. Second, the record of data may be affected by prehospital medication and the time interval between admission and onset. Third, our analyses did not include data such as body mass index and viral load, which are potential risk factors to predict the severity of infection. However, our predictive models still showed good discriminatory power after verification in heterogeneous population. Fourth, we did not collect treatment-related data (such as mechanical ventilation) which may be critical to patient's prognosis. However, all hospitals in China carried out treatment in accordance with the guidelines issued by the National health commission of China[25]. In our current study, we established two predictive models based on data from the first examination upon admission as baseline data. Future studies should include repeated measures data to test whether longitudinal changes in clinical index have a stronger ability to predict prognosis.

In this study, we built a clinical model and a laboratory model to predict the in-hospital mortality of patients with COVID-19, which exhibited relatively satisfactory discriminatory powers in external verification. Our models may help to achieve early intervention in high-risk patients and rational allocation of medical resources.

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Contributors

WK and LC conceived and designed the study. WK, ZP, CX analyzed the data, and wrote the first draft of the manuscript. WK, LY, ZM, ZX, XS and ZH recruited patients, gathered data and participated in manuscript revision. LC provided study oversight and participated in manuscript revision. All authors had access to study data and approved the decision to submit the manuscript.

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Declaration of interests

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Figure legends

Figure 1 Flow chart of the cohort study

Figure 2 ROC curves for in-hospital mortality of patients with COVID-19 for the training cohort (A) and validation cohort(B) .

ROC curves of in-hospital mortality from logistic regression models of patients with clinical data (red) and laboratory data (black) using Bootstrap resampling (times = 500).

ROC = receiver operator characteristic. AUC = area under the curve.

Figure 3 Nomogram to predict the in-hospital mortality of patients with COVID-19 for clinical model (A) and laboratory model (B).

SpO2=peripheral capillary oxygen saturation. AST=aspartate aminotransferase. GFR= glomerular filtration rate.

Table 1: Baseline clinical and laboratory characteristics of study population by training and validation cohort.

	Training cohort (n=296)	**Validation cohort** (n=44)	**p-value**
Age, years	47.32 ± 14.95	55.2 ± 16.8	0.001
Sex			
Male	140 (47.3%)	24 (54.5%)	0.369
Female	156 (52.7%)	20 (45.5%)	
Outcome			<0.001
Survive	277 (93.58%)	30 (68.2%)	
Non-survive	19 (6.4%)	14 (31.8%)	
Clinical symptoms			
Fever			0.006
no	77 (26.5%)	3 (7.1%)	
yes	213 (73.5%)	39 (92.9%)	
Cough			<0.001
no	97 (33.0%)	29 (65.9%)	
yes	197 (67.0%)	15 (34.1%)	
Chronic Disease			
Hypertension			0.065
no	254 (85.8%)	33 (75.0%)	
yes	42 (14.2%)	11 (25.0%)	
Diabetes			0.045
no	266 (89.9%)	35 (79.5%)	
yes	30 (10.1%)	9 (20.5%)	
Coronary heart disease			0.229
no	286 (96.6%)	41 (93.2%)	
yes	10 (3.4%)	3 (6.8%)	
Cerebrovascular disease			0.329
no	289 (97.6%)	42 (95.5%)	
yes	7 (2.4%)	2 (4.5%)	
Cancer			0.117
no	295 (99.7%)	43 (97.7%)	
yes	1 (0.3%)	1 (2.3%)	
Habits			
Smoking			0.138
no	284 (96.0%)	40 (90.9%)	
yes	12 (4.0%)	4 (9.1%)	
Drinking			0.033
no	279 (94.3%)	41 (93.2%)	
yes	17 (5.7%)	3 (6.8%)	
Laboratory texting			
SpO2, %	97.0 (95.0-99.0)	96.1 (93.8-97.9)	0.020
WBC, 10^9/L	4.7 (3.5-6.5)	6.1 (3.7-7.9)	0.007
Neutrophil, 10^9/L	3.1 (2.1-4.6)	4.8 (2.3-6.4)	0.005
Lymphocyte, 10^9/L	1.0 (0.7-1.4)	0.9 (0.6-1.2)	0.041
hsCRP, mg/L	12.7 (2.5-32.3)	63.6 (19.8-88.5)	<0.001
ESR, mm/h	30.0 (18.0-42.5)	42.0 (26.0-71.8)	<0.001
APTT, sec	30.7 ± 4.0	38.9 ± 5.1	<0.001
PT, sec	13.3 ± 1.9	13.5 ± 1.0	0.093
D-dimer, ug/mL	0.2 (0.1-0.4)	0.8 (0.4-1.4)	<0.001
GFR, ml/min	102.2 ± 24.4	92.1 ± 20.5	<0.001

Cr, umol/L	63.2 (50.9-75.6)	71.8 (59.3-85.6)	0.019
BUN, mmol/L	4.0 (3.1-5.1)	4.4 (3.2-5.6)	0.201
AST, U/L	24.8 (20.0-34.1)	34.5 (25.5-54.5)	<0.001
ALT, U/L	18.2 (12.6-26.2)	27.5 (22.5-40.2)	<0.001
LDH, U/L	214.1 (177.0-267.8)	379.0 (265.0-454.0)	<0.001

Data are n (%), mean ± SD or median (interquartile range).

SpO2=peripheral capillary oxygen saturation. WBC=White blood cell count. hsCRP=high sensitivity C reactive protein. ESR=erythrocyte sedimentation rate. APTT= activated partial thromboplastin time. PT= prothrombin time. GFR=Glomerular filtration rate. Cr=Creatinine. BUN=Blood urea nitrogen. AST=aspartate aminotransferase. ALT=alanine aminotransferase. LDH=lactate dehydrogenase.

Table 2: Baseline clinical and laboratory characteristics of study population by in-hospital mortality.

	Training cohort (n=296)			Validation cohort (n=44)		
	Survivors (277)	**Non-survivors (n=19)**	**p-value**	**Survivors (n=30)**	**Non-survivors (n=14)**	**p-value**
Age, years	46.0 ± 14.4	65.6 ± 12.6	<0.001	48.8 ± 14.2	69.0 ± 13.4	<0.001
Sex						
Male	129 (46.6%)	11 (57.9%)	0.339	14 (46.7%)	10 (71.4%)	0.124
Female	148 (53.4%)	8 (42.1%)		16 (53.3%)	4 (28.6%)	
Signs and Symptoms						
Fever			0.056			0.226
no	68 (25.1%)	9 (47.4%)		3 (10.0%)	0 (0.0%)	
yes	203 (74.9%)	10 (52.6%)		27 (90.0%)	12 (100.0%)	
Cough			0.252			0.226
no	93 (33.8%)	4 (21.1%)		18 (60.0%)	11 (78.6%)	
yes	182 (66.2%)	15 (78.9%)		12 (40.0%)	3 (21.4%)	
Basic Disease						
Hypertension			<0.001			0.709
no	244 (88.1%)	10 (52.6%)		23 (76.7%)	10 (71.4%)	
yes	33 (11.9%)	9 (47.4%)		7 (23.3%)	4 (28.6%)	
Diabetes			0.001			0.362
no	253 (91.3%)	13 (68.4%)		25 (83.3%)	10 (71.4%)	
yes	24 (8.7%)	6 (31.6%)		5 (16.7%)	4 (28.6%)	
COPD			0.012			-
no	276 (99.6%)	18 (94.7%)		-	-	
yes	1 (0.4%)	1 (5.3%)		-	-	
Coronary heart disease			<0.001			0.009
no	272 (98.2%)	14 (73.7%)		30 (100.0%)	11 (78.6%)	
yes	5 (1.8%)	5 (26.3%)		0 (0.0%)	3 (21.4%)	
Chronic kidney disease			0.211			-
no	273 (98.6%)	18 (94.7%)		-	-	
yes	4 (1.4%)	1 (5.3%)		-	-	
Cerebrovascular disease			<0.001			0.572
no	273 (98.6%)	16 (84.2%)		29 (96.7%)	13 (92.9%)	
yes	4 (1.4%)	3 (15.8%)		1 (3.3%)	1 (7.1%)	
Cancer			0.793			0.490
no	276 (99.6%)	19 (100.0%)		29 (96.7%)	14 (100.0%)	

yes	1 (0.4%)	0 (0.0%)		1 (3.3%)	0 (0.0%)	
Habits						
Smoking			0.556			0.759
no	266 (96.0%)	18 (94.7%)		27 (90.0%)	13 (92.9%)	
yes	11 (4.0%)	1 (5.3%)		3 (10.0%)	1 (7.1%)	
Drinking			0.926			0.572
no	261 (94.2%)	18 (94.7%)		29 (96.7%)	12 (85.7%)	
yes	16 (5.8%)	1 (5.3%)		1 (3.3%)	2 (14.3%)	
Laboratory texting						
SpO2, %	97.0 (96.0-99.0)	92.5 (80.5-94.8)	<0.001	97.2 (95.4-98.1)	94.0 (91.3-96.0)	0.013
Systolic pressure, mmHg	124.8 ± 16.8	124.7 ± 24.3	0.509	-	-	-
Diastolic pressure, mmHg	78.8 ± 12.5	68.1 ± 15.7	0.003	-	-	-
WBC, 10^9/L	4.7 (3.4-6.4)	7.8 (4.7-11.9)	<0.001	5.3 (3.2-7.3)	6.8 (5.9-9.1)	0.029
Neutrophil, 10^9/L	3.0 (2.0-4.4)	6.4 (3.2-10.0)	<0.001	3.4 (2.0-5.0)	5.8 (5.0-8.4)	<0.001
Lymphocyte, 10^9/L	1.0 (0.7-1.4)	0.7 (0.5-1.0)	0.003	0.9 (0.7-1.2)	0.6 (0.5-0.8)	0.048
Monocyte, 10^9/L	0.5 (0.3-0.6)	0.3 (0.3-0.6)	0.273	-	-	-
hsCRP, mg/L	11.4 (2.2-27.9)	88.6 (59.7-118.0)	<0.001	39.9 (11.9-68.1)	98.0 (85.5-117.8)	<0.001
ESR, mm/h	30.9 ± 14.5	36.9 ± 13.1	0.192	41.0 ± 25.2	60.9 ± 29.5	0.036
APTT, sec	30.8 ± 4.1	29.3 ± 3.0	0.107	38.8 ± 4.3	39.3 ± 6.6	0.743
PT, sec	13.3 ± 1.9	13.7 ± 1.9	0.372	13.2 ± 0.8	14.1 ± 1.2	0.007
TT, sec	16.3 ± 2.1	18.8 ± 9.7	<0.001	-	-	-
FIB, g/L	3.9 ± 1.0	4.2 ± 1.5	0.099	-	-	-
D-dimer, ug/mL	0.2 (0.1-0.3)	0.5 (0.4-1.4)	<0.001	0.6 (0.3-1.1)	1.1 (0.9-1.6)	0.025
GFR, ml/min	104.0 ± 22.5	74.0 ± 34.7	<0.001	99.6 ± 16.6	76.1 ± 19.2	<0.001
Cr, umol/L	62.5 (50.9-74.6)	81.4 (61.4-110.2)	<0.001	66.9 (56.0-74.8)	80.3 (66.4-96.9)	0.004
BUN, mmol/L	3.9 (3.1-5.0)	6.2 (4.9-8.2)	<0.001	3.9 (3.2-5.1)	6.4 (4.9-8.0)	0.001
AST, U/L	24.4 (19.3-32.1)	43.4 (34.3-60.1)	<0.001	30.0 (23.2-52.2)	41.0 (34.5-56.8)	0.104
ALT, U/L	18.1 (12.3-25.9)	20.2 (16.2-51.9)	0.006	26.5 (19.5-38.0)	30.5 (23.0-50.5)	0.879
LDH, U/L	213.0 (175.5-256.0)	478.6 (363.5-637.2)	<0.001	327.0 (207.0-410.0)	466.5 (363.5-543.0)	0.015
Total bilirubin, umol/L	8.2 (5.5-11.8)	10.2 (5.9-17.0)	0.159	-	-	-
ALB, g/L	40.4 ± 4.1	34.4 ± 4.5	<0.001	-	-	-
CLO, g/L	26.5 ± 5.2	30.1 ± 4.2	0.003	-	-	-
A/G	1.6 ± 0.4	1.2 ± 0.3	<0.001	-	-	-
Blood ammonia, umol/L	25.0 (14.9-35.7)	31.7 (26.3-44.2)	0.066	-	-	-
CK, U/L	57.0 (35.0-91.0)	114.0 (69.0-196.0)	<0.001	-	-	-

CK-MB, U/L	13.5 (11.4-17.1)	17.5 (16.7-28.1)	<0.001	-	-	-

Data are n (%), mean ± SD or median (interquartile range).

SpO2=peripheral capillary oxygen saturation. WBC=White blood cell count. hsCRP=high sensitivity C reactive protein. ESR=erythrocyte sedimentation rate. APTT= activated partial thromboplastin time. PT= prothrombin time. TT=thrombin time. FIB= plasma fibrinogen. GFR=Glomerular filtration rate. Cr=Creatinine. BUN=Blood urea nitrogen. AST=aspartate aminotransferase. ALT=alanine aminotransferase. LDH=lactate dehydrogenase. ALB=albumin. GLO=globulin. CK=creatine kinase.

- Data not collected in the validation cohort.

Table 3: Multivariable logistic regression models of in-hospital mortality in the training cohort.

	Clinical model		Laboratory model	
	Estimate	p value	Estimate	p value
Baseline predictors				
Age, years	1.11 (1.05, 1.17)	0.0005	1.10 (0.97, 1.24)	0.1391
History of hypertension	1.82 (0.50, 6.63)	0.3670	..	..
History of CHD	3.04 (0.45, 20.74)	0.2569	..	..
SpO2, %	..	..	0.71 (0.57, 0.88)	0.0020
Neutrophil count, $10^{\wedge 9}$/L	..	..	1.37 (1.04, 1.81)	0.0248
Lymphocyte count, $10^{\wedge 9}$/L	..	..	0.51 (0.04, 7.12)	0.6204
hsCRP, mg/L	..	..	1.04 (1.01, 1.08)	0.0054
D-dimer, ug/mL	..	..	0.56 (0.24, 1.31)	0.1813
AST, U/L	..	..	1.05 (1.00, 1.10)	0.0547
GFR, ml/min	..	..	1.05 (1.00, 1.10)	0.0447
Model characteristics				
AUC*	0.88 (0.80, 0.95)	..	0.98 (0.92, 0.99)	..
Threshold	-2.6551		-2.9998	
AIC	80.23	..	32.95	..
Sensitivity, %	92.31	..	100.00	..
Specificity, %	77.44	..	92.82	..
Positive predictive value, %	21.43	..	48.15	..
Negative predictive value, %	99.34	..	100.00	..
Laboratory model vs clinical model				
Comparison of AUC*	..	..	..	0.0157

Baseline predictors are OR, unless otherwise stated, with 95% CIs in parentheses when appropriate. Prameters were selected by Stepwise (AIC) and contribution (gain) of each variable to the in-hospital death according to the ensemble XGBoost model. Sensitivity, specificity, positive predictive value, and negative predictive value were based on a predicted probability of 0.50. CHD=coronary heart disease. NA=not applicable. AIC= Akaike information criterion. AUC=area under the curve.

*Bootstrap resampling (times = 500).

Table 4: Accuray of the clinical model and laboratory model in the training and validation cohort.

Model characteristics	Training cohort (n=296)		Validation cohort (n=44)	
	Clinical model	**Laboratory model**	**Clinical model**	**Laboratory model**
AUC*	0.88 (0.80, 0.95)	0.98 (0.92, 0.99)	0.83 (0.68, 0.93)	0.88 (0.75, 0.96)
Threshold	-2.6551	-2.9998	-1.7976	-3.8238
AIC	80.23	32.95	42.20	37.62
Sensitivity, %	92.31	100.00	64.29	100.00
Specificity, %	77.44	92.82	93.33	70.00
Positive predictive value, %	21.43	48.15	81.82	60.87
Negative predictive value, %	99.34	100.00	84.85	100.00

AUC=area under the curve. AIC= Akaike information criterion.

*Bootstrap resampling (times = 500).

Figure 1

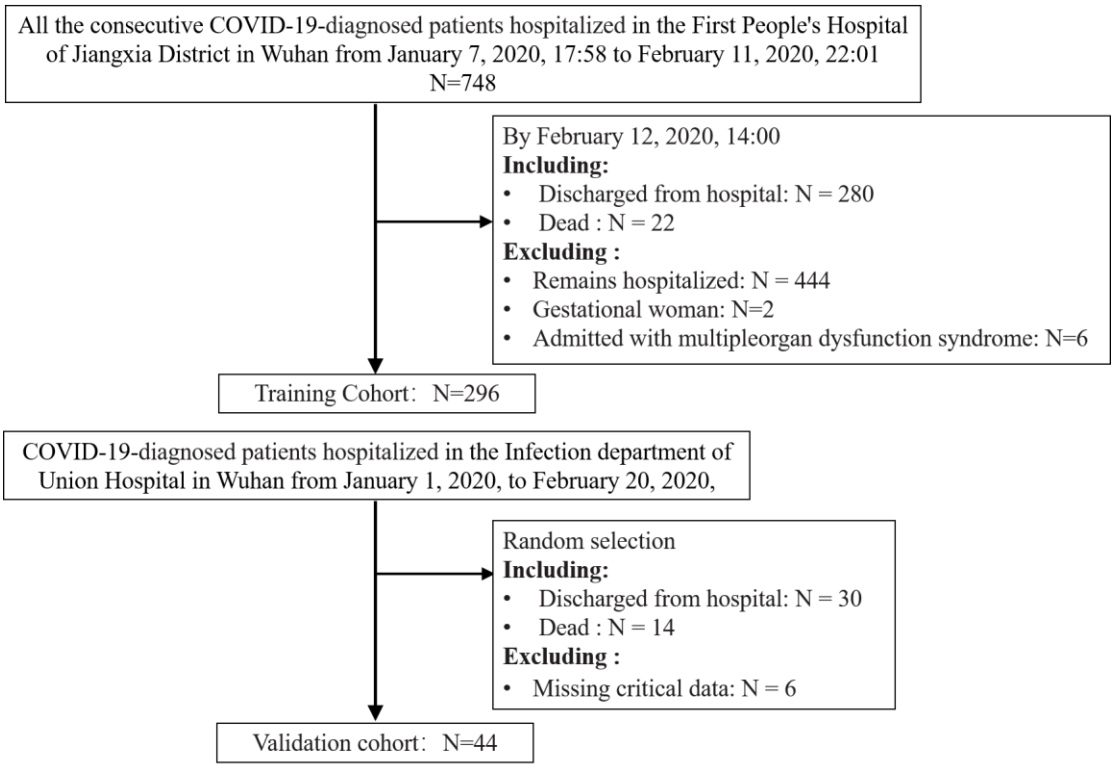

All the consecutive COVID-19-diagnosed patients hospitalized in the First People's Hospital of Jiangxia District in Wuhan from January 7, 2020, 17:58 to February 11, 2020, 22:01
N=748
By February 12, 2020, 14:00
Including:
• Discharged from hospital: N = 280
• Dead : N = 22
Excluding :
• Remains hospitalized: N = 444
• Gestational woman: N=2
• Admitted with multipleorgan dysfunction syndrome: N=6
Training Cohort: N=296
COVID-19-diagnosed patients hospitalized in the Infection department of Union Hospital in Wuhan from January 1, 2020, to February 20, 2020,
Random selection
Including:
• Discharged from hospital: N = 30
• Dead : N = 14
Excluding :
• Missing critical data: N = 6
Validation cohort: N=44

Figure 2

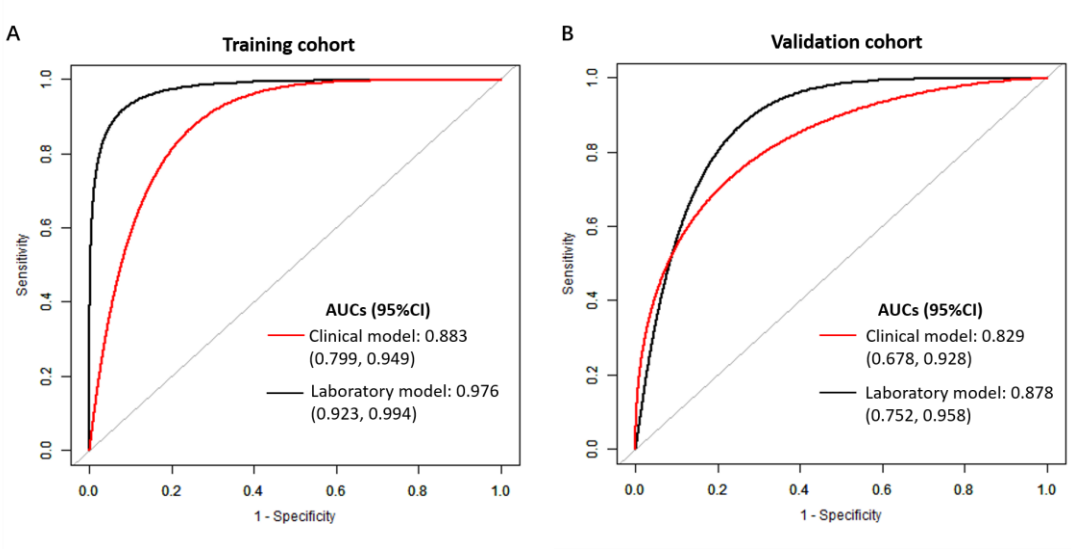

A
Training cohort
Sensitivity
1 - Specificity
AUCs (95%CI)
Clinical model: 0.883
(0.799, 0.949)
Laboratory model: 0.976
(0.923, 0.994)
B
Validation cohort
Sensitivity
1 - Specificity
AUCs (95%CI)
Clinical model: 0.829
(0.678, 0.928)
Laboratory model: 0.878
(0.752, 0.958)

Figure 3A

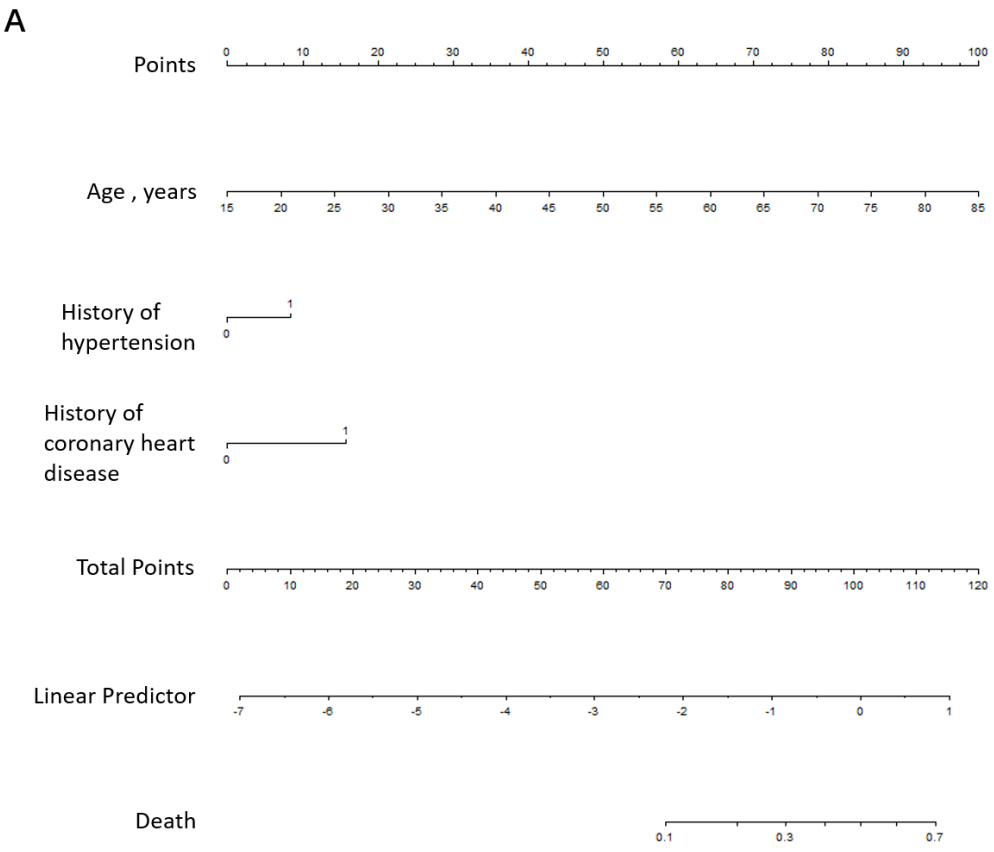
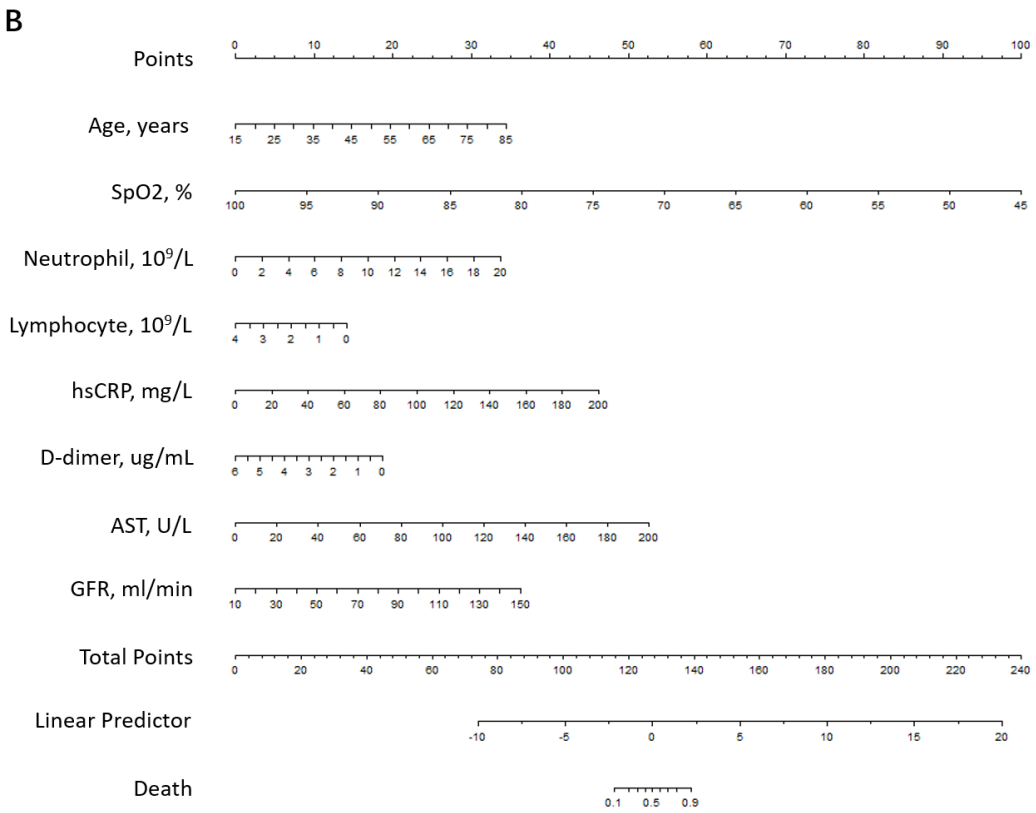

A
Points
0 10 20 30 40 50 60 70 80 90 100
Age , years
15 20 25 30 35 40 45 50 55 60 65 70 75 80 85
History of hypertension
0 1
History of coronary heart disease
0 1
Total Points
0 10 20 30 40 50 60 70 80 90 100 110 120
Linear Predictor
-7 -6 -5 -4 -3 -2 -1 0 1
Death
0.1 0.3 0.7

Figure 3B


B
Points
0 10 20 30 40 50 60 70 80 90 100
Age, years
15 25 35 45 55 65 75 85
SpO2, %
100 95 90 85 80 75 70 65 60 55 50 45
Neutrophil, 10^9/L
0 2 4 6 8 10 12 14 16 18 20
Lymphocyte, 10^9/L
4 3 2 1 0
hsCRP, mg/L
0 20 40 60 80 100 120 140 160 180 200
D-dimer, ug/mL
6 5 4 3 2 1 0
AST, U/L
0 20 40 60 80 100 120 140 160 180 200
GFR, ml/min
10 30 50 70 90 110 130 150
Total Points
0 20 40 60 80 100 120 140 160 180 200 220 240
Linear Predictor
-10 -5 0 5 10 15 20
Death
0.1 0.5 0.9