Development and Validation of a Nomogram for Assessing Survival in Patients with COVID-19 Pneumonia

Yi-Min Dong[1], Jia Sun[2, 3], Yi-Xin Li[4], Qian Chen[5], Qing-Quan Liu[6], Zhou Sun[7], Ran Pang[8], Fei Chen[9], Bing-Yang Xu[10], Anne Manyande[11], Taane G Clark[12], Jin-Ping Li[13], Ilkay Erdogan Orhan[14], Yu-Ke Tian[2, 3], Tao Wang[15#], Wei Wu[1#], Da-Wei Ye[16#]

1. Department of Orthopedics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

2. Anesthesiology Institute, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

3. Department of Anesthesiology and Pain Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

4. Cancer Center, Tongji Hospital, Tongji Medical college, Huazhong University of Science and Technology, Wuhan, China.

5. Department of Pharmacy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

6. Department of Nephrology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

7. Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

8. Department of Infectious Disease, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

9. Department of Oncology, The Central Hospital of Xiaogan, Wuhan University of Science and Technology, Xiaogan, China

10. Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Key Laboratory of Organ Transplantation, Ministry of Education, NHC Key Laboratory of Organ Transplantation, Key Laboratory of Organ Transplantation, Chinese Academy of Medical Sciences, Wuhan, China.

11. School of Human and Social Sciences, University of West London, London, UK

12. Faculty of Infectious and Tropical Diseases and Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK.

13. Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden

14. Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, Ankara, Turkey.

15. Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

16. Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Shanxi Medical University; Shanxi Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Taiyuan, China.

 # Corresponding author:

Tao Wang, Wei Wu and Da-Wei Ye, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China. E-mail: wt7636@126.com, 15127417@qq.com or dy0711@gmail.com.

Summary

A nomogram consisting of hypertension, neutrophil-lymphocyte-ratio and NT-proBNP is an effective tool for predicting in-hospital survival probability of patients with COVID-19. This nomogram could be used to optimize the clinical management of COVID-19.

Abstract

Background: The outbreak of coronavirus disease (COVID-19) in 2019 has spread worldwide and continues to cause great threat to peoples' health as well as put pressure on the accessibility of medical systems. Early prediction of survival of hospitalized patients will help the clinical management of COVID-19, but such a prediction model which is reliable and valid is still lacking.

Methods: We retrospectively enrolled 628 confirmed cases of COVID-19 using positive RT-PCR tests for SARS-CoV-2 in Tongji Hospital in Wuhan, China. These patients were randomly grouped into a training cohort (60%) and a validation cohort (40%). In the training cohort, least absolute shrinkage and selection operator (LASSO) regression analysis and multivariate Cox regression analysis were utilized to identify prognostic factors for in-hospital survival of patients with COVID-19. A nomogram based on the three variables was built for clinical use. Areas under the ROC curves (AUC), concordance index (C-index) and calibration curve were used to evaluate the efficiency of the nomogram in both the training and validation cohorts.

Results: Hypertension, higher neutrophil-to-lymphocyte ratio and increased NT-proBNP value were found to be significantly associated with poorer prognosis in hospitalized patients with COVID-19. The three predictors were further used to build a prediction nomogram. The C-index of the nomogram in the training and validation cohorts was 0.901 and 0.892, respectively. The AUC in the training cohort was 0.922 for 14- day and 0.919 for 21-day probability of in-hospital survival, while in the validation cohort was 0.922 and 0.881, respectively. Moreover, the calibration curve for 14- day and 21-day survival also showed high coherence between the predicted and actual probability of survival.

Conclusion: We managed to build a predictive model and constructed a nomogram for predicting in-hospital survival of patients with COVID-19. This model represents good performance and might be utilized clinically in the management of COVID-19.

Keywords:

Coronavirus; COVID-19; nomogram; prediction; survival

Introduction

In December, 2019, an unknown pneumonia emerged in Wuhan, China, which turned out to be the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses [1]. Since its emergence, COVID-19 has spread across China and globally, with high morbidity and mortality [2]. With the progression of this pandemic, public health is greatly threatened and healthcare systems worldwide are under great pressure. Progress in vaccine development has brought hope of potentially preventing the disease [3]. However, effective drugs are still lacking for clinical treatment. Prediction of patients' outcomes as early as admission will help to identify those at high risk of poor outcome, and active supportive treatments may be given to these patients to improve their prognosis. Considering this, a predictive model with reliable efficacy is of great importance for the clinical management of COVID-19.

Recently, a number of models or factors have been proposed to predict the severity or survival of patients confirmed with COVID-19. For example, one study reported that severe cases of COVID-19 tend to have a higher neutrophil-lymphocyte-ratio (NLR) [4], while another study suggested that monitoring platelet-to-lymphocyte ratio (PLR) has beneficial effects on the management of patients with COVID-19 [5]. Increased N terminal pro B type natriuretic peptide (NT-proBNP) has also been found to be correlated with greater disease severity of COVID-19 [6]. However, most of these studies only studied the predictive value of indicators for disease severity and their prognostic value for outcomes of COVID-19 have been less explored. In addition, sample sizes in these studies are usually relatively small. The predictive value of these factors or models remains to be validated and their clinical practicability to be tested.

Nomograms are graphical mathematical models that have been used to predict prognosis by estimating clinical events and integrating significant prognostic factors in numerous diseases [7-9]. In this study, by enrolling an adequate number of patients from the first epicenter, Wuhan, China, we aimed to develop an easy-to-use and effective prognostic model for

evaluating the incidence of severe COVID-19 infection, and to compare existing clinical predictive models of patients with confirmed COVID-19 infection.

Methods

Study Participants

Patients of this retrospective study were enrolled during the period between January and March 2020, from Tongji Hospital. All the patients recruited were confirmed with COVID-19 by positive RT-PCR tests for SARS-COV-2 from throat-swab specimens and had a definite outcome of either hospital discharge or death. Those who were still receiving treatment at the time of data collection were not included due to unknown outcome. This study was approved by the Ethics Committee of Tongji Hospital. The ethics committee of the hospital waived the written informed consent from patients with COVID-19. Diagnosis of COVID-19 was made according to the interim guidance of the World Health Organization [10].

Data Collection

Laboratory confirmation of SARS-CoV-2 infection was conducted in Tongji Hospital. Methods for laboratory confirmation of SARS-CoV-2 infection have been described previously [11]. Throat-swab specimens were obtained from all patients after admission for SARS-CoV-2 detection. Those who tested positive by real-time RT-PCR were considered confirmed cases. Baseline population characteristics (age and gender), clinical data (signs and symptoms on admission, comorbidities and laboratory findings upon admission), treatment and outcomes data were collected in detail from electronic medical records of these patients. Laboratory tests included blood assays (e.g. leukocytes, lymphocytes, neutrophils), inflammatory indicators (procalcitonin, C-reactive protein, erythrocyte sedimentation rate, interleukin-6), coagulation profile, liver and renal function and cardiac enzymes. In order to minimize sampling bias, data were obtained by communicating effectively with medical workers and double checking with them. After enrollment, all patients were randomly grouped into a training cohort and validation cohort. The predictive model and nomogram

were constructed in the training cohort based on symptoms, comorbidities and results of the first laboratory tests after admission, and then validated in the validation cohort.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR), while categorical variables were presented as frequencies and percentages (%). To compare the difference between groups, we used chi-squared test for categorical variables and Wilcoxon rank-sum tests for continuous variables. NLR and PLR were calculated based on results of patients' first blood assay results after admission. Survival time was defined as time from hospital admission to date of death or discharge. In the training cohort, potential prognostic factors were screened out using LASSO regression, and factors selected in LASSO regression [12-15] were further analyzed in multivariate Cox proportional hazard model to identify significantly the prognostic factors associated with survival of COVID-19. Subsequently, factors with prognostic significance in the multivariate Cox regression analysis were utilized to build an in-hospital survival-prediction model and a nomogram was used to visualize the model. A receiver operating characteristic curve (ROC), under the ROC curve (AUC) and Harrell's concordance index (C-index) were used to assess discrimination of the model, while the calibration plot was used to graphically evaluate the calibration of the nomogram in both training and validation cohorts. The value of the C-index ranges from 0.5 to 1.0, with 0.5 indicating random chance and 1.0 demonstrating perfect discrimination. The performance of the model was also augmented with 10-fold cross validation in the validation cohort. All analyses were conducted using R software (version 3.6.3), and P values less than 0.05 were considered statistically significant in each statistical analysis.

Results

Symptoms and Comorbidities of enrolled patients with COVID-19

Table 1 shows the details of baseline characteristics of those patients enrolled. Of the total patients in this study, the median age was 61years (IQR: 53-70 years) and 300 patients (47.8%) were male. Most patients in the overall cohort had fever (83.0%) and cough (66.9%), while 216 (34.4%) patients had shortness of breath. Headache (24.9%), sore throat (22.5%) and diarrhea (22.3%) were less common. Hypertension (167 [26.6%]) was the most common coexisting disease followed by diabetes (14.2%), while coronary heart disease, chronic kidney disease, chronic obstructive pulmonary disease and cancer were present in 14.2%, 6.4%, 2.5%, 1.9%, and 1.6% of total patients, respectively. We randomly allocated 390 patients (60%) to the training cohort and 238 (40%) to the validation cohort. There was no significant difference in most characteristics between the two cohorts (all P value > 0.05) (Table 1).

Laboratory findings after admission

In the overall cohort, abnormal laboratory findings included decreased lymphocyte count (49.8%), increased neutrophil (22.9%) and leukocyte (23.6%) count as well as prolonged activated partial thromboplastin time (24.6%) and prothrombin time (28.9%). 67.5% of patients had increased D-Deimer. Elevated level of inflammatory biomarkers such as lactose dehydrogenase, C-reactive protein and Interleukin were present in over half of the patients (Table 1). Similar findings were also observed in the training and validation cohorts.

Treatment and outcome

Antiviral therapy (70.2%) was the most common therapy for hospitalized patients with COVID-19 followed by oxygen therapy (68.7%). Antiviral drugs included lopinavir-ritonavir, oseltamivir and remdesivir. Oxygen therapy was mainly oxygen inhalation (65.1%) and mechanical ventilation (3.6%). Antibiotics, glucocorticoids and intravenous immunoglobulin were administered to 63.1%, 27.1% and 23.6% of patients, respectively. There were 121 deaths in the total cohort and 507 patients were discharged after treatment.

Prognostic factors of in-hospital survival of patients with COVID-19.

Data regarding age, gender, symptoms (including fever, cough, shortness of breath, headache, sore throat, diarrhea nausea and vomiting), chronic medical illnesses (including kidney disease, cancer, hypertension, diabetes, chronic obstructive pulmonary disease and coronary heart disease) and laboratory findings (including NLR, PLR, hemoglobin, activated partial thromboplastin time, prothrombin time, D-Dimer, albumin, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, lactose dehydrogenase, C-reactive protein, N-terminal pro-B-type natriuretic peptide, procalcitonin and interleukin-6) were considered potential prognostic factors affecting in-hospital survival and were included in LASSO regression. The results showed that age, cancer, hypertension, coronary heart disease, NLR, NT-proBNP, albumin, C-reactive protein and creatinine obtained from the training cohort were associated with in-hospital survival when the optimal lambda was 0.028 (Figure S1). These factors were subsequently included in the multivariate Cox regression analyses (Table 2), and the results revealed that hypertension, NLR and NT-proBNP were independent prognostic factors affecting in-hospital survival of COVID-19. Patients with hypertension, higher NLR and increased NT-proBNP tended to have poorer prognosis, while the prognosis of patients without hypertension, lower NLR and NT-proBNP value was relatively better.

Nomogram construction and validation

The three independent prognostic factors (hypertension, NLR and NT-proBNP) were incorporated to establish a predictive model for predicting of 14- and 21-day probability of in-hospital survival (Figure1). A final Cox regression analysis including only the three predictors was conducted to demonstrate the fitted coefficients and hazard ratio of each predictor in the model (Table 3). This model was visualized using a nomogram, the usage of which is illustrated with an assumptive patient with hypertension, NLR of 4.0 and NT-proBNP of 1000 pg/mL upon admission (vertical red lines). Points for hypertension, NLR and NT-proBNP were 0, 22 and 36, respectively. The total point added up to 58 for this patient, which represents approximately 0.75 and 0.62 of 14-day and 21-day probability of in-

hospital survival. Performance of this nomogram was assessed by C-index, AUC and calibration plots. The C-index of the predictive model was 0.901 in the training cohort and 0.892 in the validation cohort. Subsequently, we drew the ROC curves for 14- day and 21-day survival in both the training and validation cohorts with the AUC value indicated (Figure 2). In the training cohort, AUC for predicting 14- and 21- day survival was 0.922 and 0.919, and was 0.922 and 0.881 in the validation cohort, indicating high discrimination of the model (Table 4). The calibration plots also showed excellent agreement between the predicted probability of survival and actual observation, which indicates good calibration of the model (Figure 3). To further evaluate the generalizability of model performance, we conducted 10-fold cross-validation for the model in the training cohort. The mean (standard deviation) of the C-index was 0.899 (0.0004) in cross-validations, and the AUC value was 0.920 (0.001) and 0.921 (0.001) for 14-day and 21-day survival prediction, respectively, which indicates stable and favorable performance of the model.

Comparison of the NLR, PLR, NT-proBNP and our model.

Previous studies have reported the predictive value of NLR, PLR, NT-proBNP for COVID-19 severity, but their association with outcomes of COVID-19 has rarely been reported. We also compared the performance of our model incorporating hypertension, NLR and NT-proBNP to that of single PLR, NLR and NT-proBNP in predicting survival. The results showed that the prognostic value of PLR for survival was limited (Table 4). NLR exhibited higher C-index and AUC for 14- and 21- day survival compared with PLR or NT-proBNP. However, it did not perform better than our new model in both the training and validation cohorts according to the AUC and C-index (Table 4), suggesting that the new model is superior to the other three separate models in predicting survival in patients with COVID-19.

Discussion

COVID-19 is an acute infectious disease caused by a new coronavirus (SARS-CoV-2), which has spread quickly and brought a huge burden on human health and health care systems [16]. A previous study reported that 26% of patients received intensive care, and the in-hospital mortality was 4.3% [17]. Half a year has passed since it first emerged, and the number of patients is still increasing rapidly globally, with no specific treatment method currently available.

There is a growing body of evidence suggesting that several clinical indicators can be used to predict the severity and outcomes of patients with COVID-19. In our study, we used LASSO regression and multivariate Cox regression analysis to identify significant factors associated with in-hospital survival of COVID-19. Consequently, hypertension, NLR and NT-proBNP were identified and used to develop the prognostic nomogram in our study. This nomogram demonstrated good discrimination and calibration in predicting the 14- day and 21- day probability of survival of patients with COVID-19, as assessed by the C-index, AUC value and calibration plots, indicating good performance and high value for clinical use.

In this study, hypertension (26.6%) is associated with poor prognosis of COVID-19. Previous clinical studies have shown that COVID-19 patients with pre-existing hypertension are more likely to incur disproportionately worse outcome [17-19]. Our study also suggested that patients with hypertension are more likely to suffer poorer prognosis compared to those without. Besides, patients with hypertension are older, and old age is known to be a risk factor for unfavorable outcome of adult in-patients with COVID-19 [19]. These patients might also have other unfavorable conditions that render them at a higher risk of poor prognosis, and great importance should, therefore, be attached to such patients in order to improve their health and survival outcomes.

We also found that increased NLR and NT-proBNP levels were significantly associated with poor outcome of COVID-19 patients. Increased NLR indicates elevated neutrophil count or decreased lymphocyte count, or both. Decreased lymphocyte count, or lymphopenia, has been reported to be predictive of poor outcome [20]. Lymphocytes are crucial in the defense against viral infection, and decreased lymphocytes indicate either vast viral load or

compromised immune function in infected patients, leading to poor conditions and outcomes. NT-proBNP is a biomarker for heart failure that is released from cardiomyocytes in response to ventricular wall stretch caused by high intra-ventricular pressure [21]. In COVID-19 cases, enlarged pulmonary artery diameter, which indicates pulmonary hypertension, was found to be associated with death from COVID-19 [22]. In the condition of pulmonary hypertension, right ventricular pressure is also increased, correspondingly triggering release of NT-proBNP, which in combination with the pulmonary artery diameter can serve as a prognostic factor of survival of COVID-19. Significantly increased NT-proBNP levels are indicative of compromised heart function or heart failure, which renders patients with COVID-19 more prone to unfavorable prognosis [23].

Previously published studies have reported that NLR or NT-proBNP can be a predictor of severe COVID-19 cases. For example, a study based on 61 patients demonstrated that NLR could be an early predictor of severe disease [24], with higher AUC, sensitivity and specificity compared to MuLBSTA and CURB-6 models that have been widely used to evaluate mortality due to pneumonia [25-27]. Another study with 245 patients illustrated that NLR is an independent prognostic factor of survival in COVID-19 patients, especially for male patients [28]. NT-proBNP has been used to assess prognosis in a variety of diseases, such as heart failure and acute respiratory distress syndrome (ARDS) [29, 30]. Recently, one study with a sample of 54 patients indicated that higher NT-proBNP value is associated with poor outcomes of severe patients with COVID-19, suggesting that NT-proBNP is a prognostic factor in patients with severe COVID-19 [31].

However, the sample sizes of these studies are relatively small and their findings have not been validated possibly due to lack of adequate patients, which might decrease the clinical practicability of their findings. In addition, studies which predict in-hospital survival of COVID-19 are still limited. In this study, we confirmed that NLR and NT-proBNP were significant prognostic factors associated with outcomes of patients with COVID-19 and were used to construct a predictive nomogram for clinical use.

As this pandemic progresses to global proportion, the situation in many cities worldwide resembles or is even worse than that in Wuhan at the early stages of the COVID-19 crisis, characterized by increasing number of infections, overburdened healthcare systems and

shortage of medical supplies. Hospitals and medical workers in these healthcare settings are facing similar challenges to those experienced in Wuhan. Given this situation, our prediction model based on patients from one of the major hospitals at the center of the first epidemic is of great value for clinical reference and use. It might help clinicians to identify early patients at greater risk of death and give intensive and active treatment to reduce mortality.

The study had some limitations. First, this is a retrospective, single center study and may have some inevitable biases. The outcomes of in-hospital patients with different conditions (such as medical force, supplies and number of infections) might differ. Patients in this study were enrolled during the peak of COVID-19 explosion when there was shortage of medical resources and inadequate experience of treating such a disease. In some areas with low epidemic and medical burden, patients with comparable conditions may have better outcomes than those treated in overburdened centers. In such case, combining survival prediction with the nomogram with actual clinical situations is recommended. Second, NT-proBNP is not a routine laboratory test and might not be available in some community hospitals, which potentially reduces the practicability of the nomogram in areas with limited medical resources. Despite these limitations, we managed to build a predictive model of in-hospital survival of patients with COVID-19 with high accuracy. We hope that this prediction model might help clinical practice in the management of COVID-19 and improve patients' outcomes.

Conclusion

A prognostic model and nomogram for predicting in-hospital survival of COVID-19 was built and demonstrated good discrimination and calibration. It allowed prediction of outcomes as early as at the time of admission and could help the clinical management of COVID-19.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Table 1 Demographic and clinical features, treatment and outcomes of patients in the training and validation cohorts.

Table 2 Multivariate cox analysis of potential prognostic factors identified by LASSO regression in the training cohort.

Table 3 Coefficients, hazard ratio and 95% confidence interval of the three predictors in the final model.

Table 4 C-index and AUC of 7-day and 14- day overall survival in each of the PLR, NLR, NT-proBNP, PLR+NLR and gender+ NLR+ NT-proBNP models.

Figure 1 The final nomogram consisting of NLR, hypertension and NT-proBNP is displayed. The usage of the nomogram is illustrated in an assumptive patient with hypertension, NLR of 4.0 and NT-proBNP of 1000 pg/mL upon admission (vertical red lines). According to the nomogram, points for hypertension, NLR and NT-proBNP were 0, 22 and 36, respectively. The total point added up to 58 for this patient, which represented approximately 0.75 and 0.62 of 14-day and 21-day in-hospital survival probability (indicated in the nomogram).

Figure 2 ROC curve and AUC of the nomogram in the training and validation cohort. A and B indicate the ROC curve and AUC of the nomogram in predicting 14-day and 21-day survival in the training cohort, while C and D illustrate 14-day and 21-day survival prediction in the validation cohort.

Figure 3 The calibration plot of the nomogram in the training and validation cohort. The calibration plot for predicting 14-day (A) and 21-day (B) survival in the training cohort and for predicting 14-day (C) and 21 day (D) survival in the validation cohort. Actual rate of survival is shown on the y-axis, and the nomogram- predicted probability of survival is shown on the x-axis.

Table 1 Demographic and clinical features, treatment and outcomes of patients in the training and validation cohorts.

Characteristic No. (%)	**All patients (n = 628)**	**Training Cohort (n=390)**	**Validation Cohort (n=238)**	**P-value [d]**
Age, (median (IQR [a]))	63 (53, 70)	63 (53, 70)	63 (53, 71)	0.515
Male	300 (47.8 %)	182 (46.7 %)	118 (49.6 %)	0.531
Symptoms				
Fever	521 (83.0 %)	327 (83.8 %)	194 (81.5 %)	0.519
Cough	420 (66.9 %)	265 (67.9 %)	155 (65.1 %)	0.521
Breath shortness	216 (34.4 %)	132 (33.8 %)	84 (35.3 %)	0.776
Headache	71 (24.9 %)	41 (25.2 %)	30 (24.6 %)	1.000
Sore throat	64 (22.5 %)	39 (23.9 %)	25 (20.5 %)	0.586
Diarrhea	140 (22.3 %)	81 (20.8 %)	59 (24.8 %)	0.282
Nausea and vomiting	70 (24.6 %)	37 (22.7 %)	33 (27.0 %)	0.481
Comorbidities				
Chronic kidney disease	7 (2.5 %)	5 (3.1 %)	2 (1.6 %)	0.701
Cancer [b]	10 (1.6 %)	4 (1.0 %)	6 (2.5 %)	0.261
Hypertension	167 (26.6 %)	111 (28.5 %)	56 (23.5 %)	0.206
Diabetes	89 (14.2 %)	54 (13.8 %)	35 (14.7 %)	0.856
COPD [c]	12 (1.9 %)	8 (2.1 %)	4 (1.7 %)	0.977
Coronary heart disease	40 (6.4 %)	15 (3.8 %)	25 (10.5 %)	0.002
Laboratory findings to admission				
Leukocyte> $3.5*10^9$/L	148 (23.6 %)	94 (24.1 %)	54 (22.7 %)	0.062
Neutrophil> $6.3*10^9$/L	144 (22.9 %)	89 (22.8 %)	55 (23.1 %)	0.941
Lymphocyte< $1.1*10^9$/L	313 (49.8 %)	193 (49.5 %)	120 (50.4 %)	0.157
Platete< 125*10^9/L	54 (8.6 %)	33 (8.5 %)	21 (8.8 %)	0.728
Hemoglobin< 130 g/L	368 (58.6 %)	226 (57.9 %)	142 (59.7 %)	0.850
Activated partial thromboplastin time > 42 s	144 (24.6 %)	91 (25.1 %)	53 (23.8 %)	0.907
Prothrombin time > 14.5 s	181 (28.9 %)	117 (30.0 %)	64 (27.0 %)	0.477
D-Deimer≥0.5 μg/mL	405 (67.5 %)	253 (68.0 %)	152 (66.7 %)	0.802
Albumin< 30 g/dL	312 (49.8 %)	192 (49.4 %)	120 (50.6 %)	0.412
Alanine aminotransferase> 41 U/L	124 (19.7 %)	81 (20.8 %)	43 (18.1 %)	0.470
Aspartate aminotransferase> 40 U/L	140 (22.3 %)	85 (21.8 %)	55 (23.1 %)	0.776
Blood urea nitrogen< 3.6 mmol/L	92 (14.6 %)	54 (13.8 %)	38 (16.0 %)	0.540
Creatinine> 84 (F) and > 104 (M) μmol/L	69 (11.0 %)	38 (9.7 %)	31 (13.0 %)	0.257
Lactose dehydrogenase> 225 U/L	402 (64.9 %)	251 (65.4 %)	151 (64.3 %)	0.768
C□reactive protein> 10 mg/L	352 (56.5 %)	217 (55.8 %)	135 (57.7 %)	0.185
N-terminal pro-B-type natriuretic peptide (median (IQR)), pg/mL	132 (46, 458)	122(43, 410)	138 (54, 552)	0.184

Procalcitonin> 0.05 ng/mL	169 (34.1 %)	95 (31.2 %)	74 (38.5 %)	0.247
Interleukin 6 ≥ 7 pg/mL	251 (54.6 %)	151 (53.7 %)	100 (55.9 %)	0.725
Treatment and outcome				
Oxygen inhalation	401 (65.1 %)	253 (66.1 %)	148 (63.5 %)	0.460
Ventilation	22 (3.6 %)	11 (2.9 %)	11 (4.7 %)	0.658
Antibacterial therapy	396 (63.1 %)	253 (64.9 %)	143 (60.1 %)	0.262
Antivirus therapy	441 (70.2 %)	288 (73.8 %)	153 (64.3 %)	0.014
Glucocorticoids	170 (27.1 %)	110 (28.2 %)	60 (25.2 %)	0.467
Intravenous immunoglobulin therapy	148 (23.6 %)	91 (23.3 %)	57 (23.9 %)	0.937
Hospital stay (median (IQR)), days	19 (12, 27)	19 (11, 27)	19 (12, 27)	0.589
Outcome				0.239
Discharged	507 (80.7 %)	321 (82.3 %)	186 (78.2 %)	
Died	121 (19.3 %)	69 (17.7 %)	52 (21.8 %)	

a. Interquartile range
b. Any type of cancer
c. Chronic Obstructive Pulmonary Disease
d. Comparison of the training and validation group

Table 2 Multivariate cox analysis of potential prognostic factors identified by LASSO regression in the training cohort.

Factors	Coefficients	HR [c] [95% CI [d]]	p value
Age			
Age < 60		Reference	
Age≥60	0.393	1.481 [0.739, 2.969]	0.268
Hypertension			
No		Reference	
Yes	0.619	1.857 [1.034, 3.337]	0.038
Cancer			
No		Reference	
Yes	0.921	2.512 [0.525, 12.025]	0.248
Coronary Heart Disease			
No		Reference	
Yes	0.694	2.002 [0.876, 4.575]	0.100
NLR [a]			
< 2.9		Reference	
3 ~ 5.9	2.439	11.470 [1.461, 90.069]	0.020
6 ~ 9.9	3.192	24.343 [2.888, 205.209]	0.003
> 10	3.603	36.722 [4.795, 281.216]	0.001
NT-proBNP[b],pg/mL			
< 200		Reference	
200 ~ 400	1.327	3.771 [1.365, 10.420]	0.010
401 ~ 800	1.478	4.387 [1.672, 11.512]	0.003
801 ~ 1600	1.901	6.690 [2.703, 16.557]	< 0.001
1601 ~ 2000	1.418	4.130 [1.346, 12.673]	0.013
> 2000	1.987	7.290 [2.656, 20.012]	< 0.001
Albumin			
≥ 35g/L		Reference	
< 35g/L	0.197	1.217 [0.548, 2.702]	0.629
C□reactive protein			
≤ 10 mg/L		Reference	
>10 mg/L	-0.012	0.987 [0.102, 9.549]	0.991
Creatinine			
≤ 104 g/L		Reference	
> 104 g/L	0.645	1.907 [0.950, 3.825]	0.069

a, neutrophil-to-lymphocyte ratio;

b, N terminal pro B type natriuretic peptide

c, hazard ratio;

d, confidence interval

Table 3 Coefficients, hazard ratio and 95% confidence interval of the three predictors in the final model.

	Coefficients	HR (95% CI)	p-value
Hypertension			
No	Reference		
Yes	0.742	2.100 (1.290, 3.419)	0.003
NLR			
< 2.9	Reference		
3 ~ 5.9	2.372	10.722 (1.377, 83.490)	0.023
6 ~ 9.9	2.912	18.386 (2.240, 150.928)	0.007
> 10	3.729	41.622 (5.472, 316.624)	<0.001
NT-proBNP, pg/mL			
< 200	Reference		
200 ~ 400	1.282	3.605 (1.365, 9.522)	0.01
401 ~ 800	1.526	4.601 (1.796, 11.785)	0.001
801 ~ 1600	2.018	7.524 (3.105, 18.231)	<0.001
1601 ~ 2000	1.969	7.164 (2.523, 20.343)	<0.001
> 2000	2.586	13.276 (5.283, 33.359)	<0.001

Table 4 C-index and AUC of 7-day and 14- day overall survival in each of the PLR, NLR, NT-proBNP, PLR+NLR and gender+ NLR+ NT-proBNP models.

models	**Training cohort**			**Validation cohort**		
	c-index	AUC		c-index	AUC	
		14- day	21- day		14- day	21- day
PLR	0.667	0.674	0.702	0.649	0.625	0.658
NT-proBNP	0.84	0.855	0.858	0.811	0.877	0.803
NLR	0.845	0.879	0.889	0.815	0.849	0.819
Hypertension +NLR + NT- proBNP	0.901	0.922	0.919	0.892	0.922	0.881

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NT- proBNP, N terminal pro B type natriuretic peptide

Figure 1

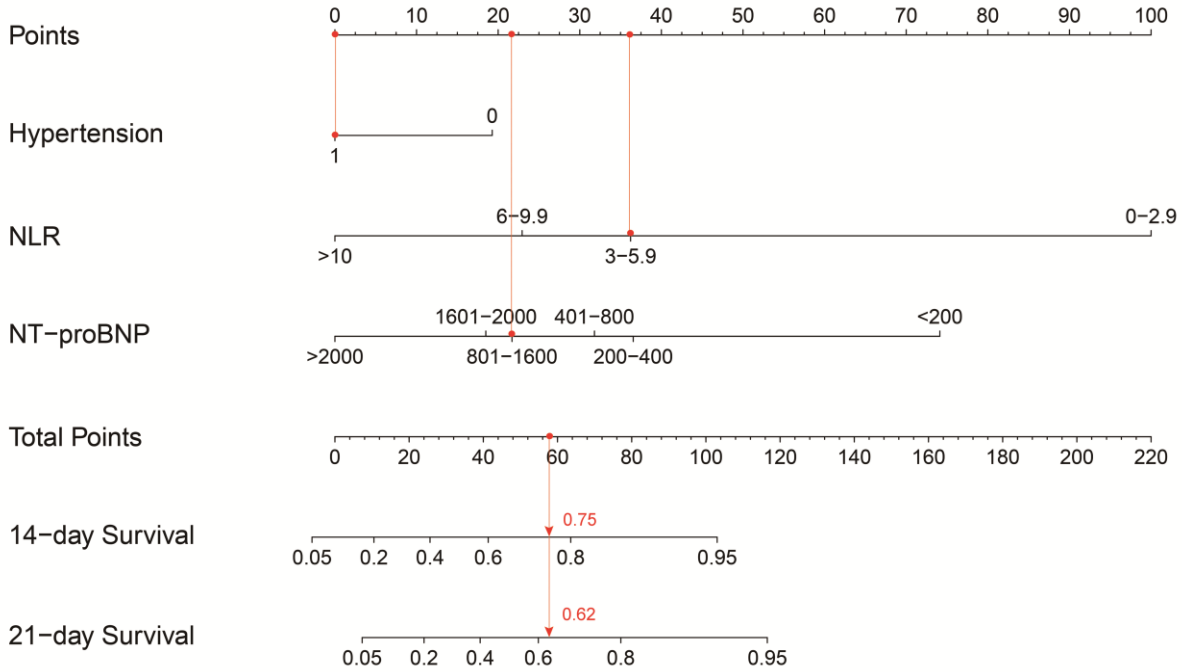

Figure 2

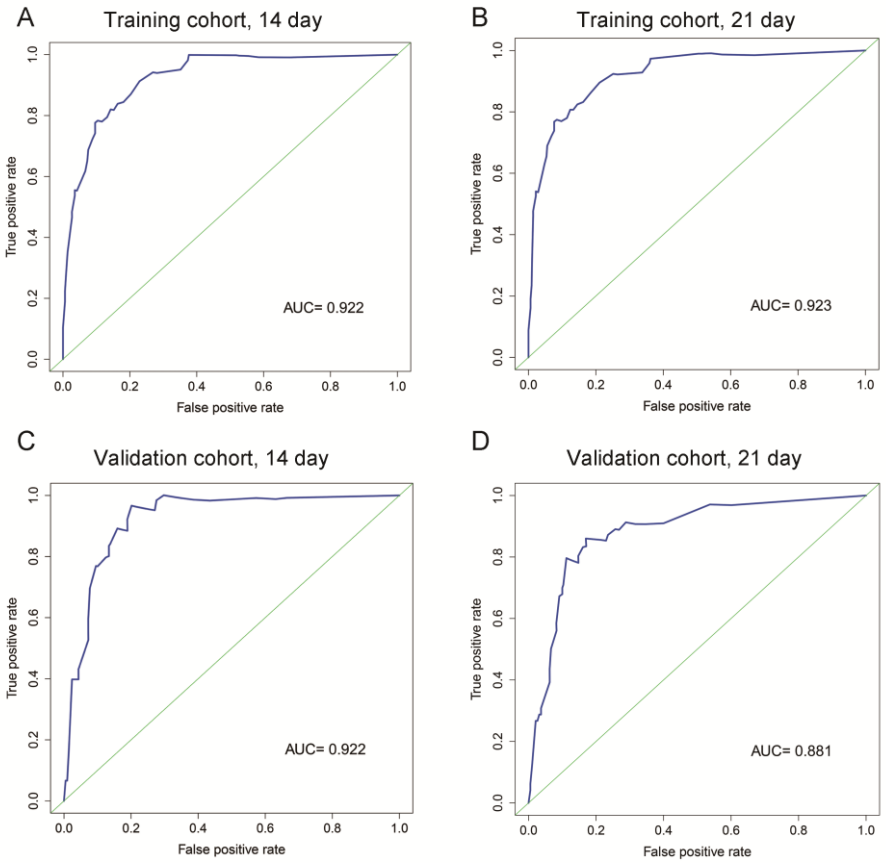

Figure 3