Prognostic Model for Mortality of Hospitalized Patients with COVID-19 Pneumonia in Wuhan, China: A Multi-center retrospective cohort study

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Keywords: COVID-19, Infection, Mortality, Overall Survival, Prognosis, Coronavirus, SARS-CoV-2

Posted Date: May 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-28186/v1

Version of Record: A version of this preprint was published on December 31st, 2020. See the published version at https://doi.org/10.1038%2Fs41598-020-78870-6.

Abstract

Background: Novel coronavirus (COVID-19) infection is a global public health issue and has now affected more than 70 countries worldwide. Severe adult respiratory syndrome-CoV-2 (SARS-CoV-2) pneumonia is associated with high risk of mortality. However, prognostic factors assessing poor clinical outcomes of individual patients with SARS-CoV-2 pneumonia remain unclear.

Methods: We conducted a retrospective, multicenter study of patients with SARS-CoV-2 who were admitted to four hospitals in Wuhan, China from December 2019 to February 2020. Mortality at the of end of follow up period was the primary outcome. Prognostic factors for mortality were also assessed and a prognostic model was developed, calibrated and validated.

Results: The study included 492 patients with SARS-CoV-2, which were divided into three cohorts, the training cohort (n=237), the validation cohort 1 (n=120), and the validation cohort 2 (n=135). Multivariate analysis showed that five clinical parameters were predictive of mortality at the end of follow up period, including age, odds ratio (OR), 1.1 / years increase (p<0.001); neutrophil-to-lymphocyte ratio OR, 1.14 (p<0.001), body temperature on admission OR, 1.53 / °C increase (p=0.005), increase of aspartate transaminase OR, 2.47 (p=0.019), and decrease of total protein OR, 1.69 (p=0.018).

Furthermore, the prognostic model drawn from the training cohort was validated with the validation cohort 1 and 2 with comparable area under curve (AUC) at 0.912, 0.928, and 0.883, respectively. While individual survival probabilities were assessed, the model yielded a Harrell's C index of 0.758 for the training cohort, 0.762 for the validation cohort 1, and 0.711 for the validation cohort 2, which were comparable among each other.

Conclusions: A validated prognostic model was developed to assist in determining the clinical prognosis for SARS- CoV-2 pneumonia. Using this established model, individual patients categorized in the high risk group were associated with an increased risk of mortality, whereas patients predicted in the low risk group had a high probability of survival.

Introduction

Novel coronavirus (COVID-19) infection is a global public health issue and has now affected more than 70 countries worldwide1. Severe adult respiratory syndrome-CoV-2 (SARS-CoV-2) pneumonia is associated with high risk of mortality. However, prognostic factors that assess poor clinical outcomes of individual patients with SARS-CoV-2 pneumonia remains unclear.

Current studies showed that patients with SARS-CoV-2 pneumonia exhibit a wide range of symptoms such as fever, cough, myalgia, fatigue, or others2 3 4 5. Many patients experience a mild disease course, although approximate 15-25% develop more severe disease symptoms. Progression may result in acute respiratory distress syndrome (ARDS), multiple organ failure, and death6. Therefore, it is of ultimate

importance to identify the high-risk group of patients in order to implement a prompt medical intervention to improve their clinical outcomes.

The aim of this study was to establish and validate a prognostic model to predict the risk of mortality and survival time for individual patients with SARS-CoV-2 pneumonia in order to assist in early identification of patients at a high risk of having poor clinical outcomes. This model can not only enable a clinical patient stratification, but also facilitate clinicians to promptly managing this pandemic condition.

Methods

Study design and participants

This retrospective,multi-center cohort study involved adults patients who were diagnosed with COVID- 19 pneumonia in four major government designated hospitals in Wuhan: Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology (TJH), Renmin Hospital of Wuhan University (RHWU), Wuhan Pulmonary Hospital (WPH), and Wuhan No.1 Hospital of Tongji Medical College of Huazhong University of Science and Technology (WNH) (Supplement Figure 1).

They were followed up until the 8th March, 2020. It included three cohorts, the training cohort used for establishment of a prognostic model, and 2 validation cohorts used for external validation and assessment of robustness of the models. The training cohort was from data collected from TJH between Jan 21th and Feb 16th, 2020. The validation 1 cohort consisted of patients from RHW and WNH admitted between Jan 23rd and Feb 16th, 2020. The validation 2 cohort included patients from WPH admitted between Jan 10th and Feb 27th, 2020. The primary outcomes was mortality at the end of the study period. The included study participants had to meet one of the following diagnostic criteria for COVID-19 pneumonia in addition to availability of data on clinical outcomes 1) confirmed diagnosis of SARS-CoV-2 pneumonia using RT-PCR in these sites, 2) Computerised tomography (CT) evidence of viral pneumonia, defined as COVID-19. The exclusion criteria included 1) deceased within the 24 hours after hospital admission with no related health records, 2) no data on clinical outcomes available,

3) suspected cases without positive result for F137nCoV test, and 4) refusal to participate in this study. Following informed consent, the following data were collected on admission:age, sex, symptoms from onset to hospital admission (fever, cough, dyspnea, myalgia, rhinorrhea, arthralgia, chest pain, headache, and vomiting), comobidities (cardiovascular disease, chronic pulmonary disease, cerebrovascular disease and chronic neurological disorders, diabetes, malignancy, and smoking), vital signs (heart rate, respiratory rate, and blood pressure), laboratory values on admission (serum hemoglobin concentration, lymphocyte counts, platelet counts, diverse protein markers), treatment regime used for COVID-19 pneumonia (antiviral agents, antibacterial agents, corticosteroids, and interferon therapy), date of symptom onset, admission, virus testing, CT-scan, as well as condition improvement and living status.

Treatment Protocol and Criteria for Discharged from Hospitals for SARS-CoV-2 Pneumonia

The treatment strategy for patients with COVID-19 pneumonia was based on the guidelines of world health organization (WHO)7, which included symptoms relief, treatment of underlying diseases, prevention of superimposed bacterial infections, active prevention of complications such as sepsis and ARDS and support organ vital function in the timely fashion. Oxygen supplementation was provided in patients with desaturation in the means of high flow oxygen via nasal prong, non-invasive and invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) if required.

The discharge criteria for patients with SARS-CoV-2 pneumonia included following: 1) haemodynamically stable and been afebrile for > 3 days, 2) radiological evidence of significant resolution of pneumonia on CT-scan, 3) double negative results for the F137nCoV test with at least 1 day interval, and 4) no concurrent acute medical issues transfer to another medical facility.

Statistical Considerations

The time interval for survival was calculated from the date of hospital admission until death due to SARS-CoV-2 pneumonia or the date of the last follow-up. Death due to SARS-CoV-2 pneumonia was considered as an event. Continuous variables were reported as means with standard deviations (SD) for normally distributed variables and as medians and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables were reported as proportion.

According to the transparent reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines8, we developed a model using the training and validation cohorts. During the model development, all patients' demographic characteristics, clinical information, vital signs and laboratory values were analyzed for a possible association between the vital status (death versus live) and survival time using the least absolute shrinkage and selection operator (LASSO) for multivariable selection9. An iterative process combining forward and backward selection was applied to remove non- significant covariates. During each step of the iteration, the Akaike information criterion (AIC) was used to evaluate model fit10. The final model was then established with a minimum value of AIC. The AUC value was used to evaluate the accuracy of the prediction for the vital status. Model calibration was performed to ensure the robustness. The Cox proportional hazards regression analysis was used to evaluate the assessment of the prognostic model for individual survival times. Proportional hazards assumption for the Cox proportional hazards regression model was assessed by using the Schoenfeld residuals test.

In order to validate the prognostic model, two independent validation cohorts with the same discrimination method and survival function were used. The 95% confidence intervals (CIs) were estimated via 5,000 bootstraps replicates. All statistical analyses were performed using R software version 3.6 and SAS software version 9.4. A $p<0.05$ was considered as statistically significant.

Role of Funding

The funders were not involved in any activities of this study, aside from providing financing.

Results

Demographic and Clinical Features in Training and Validation Cohorts

Overall 492 patients were recruited in this study. The demographic characteristics and clinical features of patients from the training cohort (n=237; TJH), validation cohort 1 (n=120; RHWU+WNH), and validation cohort 2 (n=135; WPH) cohorts were listed in the Table 1. The mortality rates in the three cohorts were 44.3%, 25.8% and 33.3% for the training cohort, validation cohort 1 and validation cohort 2, respectively. A total of 105 events occurred in the training cohort, 31 in the validation cohort 1, and 45 in the validation cohort 2. The median survival time were comparable among these three cohorts (15.0 days for the training cohort, 17.0 days for the validation cohort 1 and 14.0 days for the validation cohort 2. The patients in the training cohort with median age of 62 (IQR 50 - 70) was older than the validation cohort 1 (median age 46, IQR 37 - 66), but similar to the validation cohort 2 (median age 63, IQR 52 - 70.5). There was no significant difference in sex distribution among the three cohors. Most of patients were non-smokers (92% [training], 97.5% [validation 1], and 83% [validation 2]). The number of patients associated with comorbidities varied somewhat between three cohorts (52.7% [training] vs. 37.5% [validation 1] vs. 73.3% [validation 2]; Table 1). The number of severe cases requiring intensive care unit (ICU) admission varied among the three cohorts (8.9% [training], 1.7% [validation 1], and 20% [validation 2]). Lymphopenia occurred in the majority of patients in three cohorts (69.2% [training], 60.8% [validation 1], and 75.6% [validation 2], Table 1). Leucocytosis was observed 24.5% in the training cohort, 21.7% in the validation cohort 1, and 20.7% in the validation cohort 2.

Neutrophilia was observed in 34.6% in the training cohort, 3.1% in the validation cohort 1, and 31.1% in the validation cohort 2.

The median time of symptom onset to hospital admission was longer in the training cohort (median 10.0 days, IQR 7 - 14 days), than the validation cohort 1 (median 7.0 days, IQR 4 – 10 days), but the same as the validation cohort 2 (median 10.0 days, IQR 7 - 13 days) with fever as the most common symptom on admission. The duration of hospitalization and treatment were 15.0 days (IQR 7 – 24 days) for the training cohort, 17.0 days (IQR 11.8 - 25.0 days) for the validation cohort 1, and 14.0 days (IQR 10.0 - 19.0 days) for the validation cohort 2. The majority of patients treated with antibiotics (86.5%, 92.5, and 85.9% for the trainig cohort, validation cohort 1 and validation cohort 2, respectively and antivirals (lopinavir/ritonavir) (99.6%, 95.8% and 97.0% for the training cohort, validation cohort 1 and validation cohort 2, respectively).

Potential Risk Factors Associated with Vital Status for COVID-19

In an univariate analysis, advanced age, increased body temperature, and presence of underlying diseases were associated with higher mortality rate in patients with high COVID-19 infection (Table 2). Tachypnoea and hypertension, as well as treatment with antibiotics, corticosteroids or intravenous immunoglobulin were also associated with increased mortality (Table 2). Several laboratory parameters including serum bilirubin, urea, D-dimer, potassium level, prothrombin time (s), lactate dehydrogenase,

aspartate transaminase (AST), and urea were also found to be associated with death. In addition, patients with lymphopenia, leucocytosis, or neutrophilia also had an increased risk of death (Table 2).

Of note, the ratio of neutrophils and lymphocytes, lymphocyte ratio, and neutrophile ratio were also significant risk factors for mortality.

Construction of a Prognostic Model for Vital Status and Survival in SARS-CoV-2

For the training cohort, a multivariate analysis was performed to analyze the association between vital status, survival time, and all the covariates listed in Table 1. Statistically significant predictors for vital status and survival time in a multivariable analysis were age (adjusted odds ratio (AOR): 1.1/years increase [95% CI 1.06 - 1.13]; Wald's p<0.001), neutrophil-to-lymphocyte ratio (AOR: 1.14 [95% CI 1.08 - 1.2]; p<0.001), body temperature at admission (AOR: 1.53 / °C increase [95% CI 1.0 - 5.26]; p=0.005), aspartate transaminase (AST) (AOR: 2.47 [95% CI 1.16 - 5.26] for increase vs. normal; p=0.019), and total protein (AOR: 1.69 [95% CI 0.78 - 3.64] for decrease vs. normal ; p=0.018; Table 2). Based on the weights (coefficients) of these five significant covariates (Table 2), a model prognostic model was constructed and applied to predict the vital status of the training cohort. The results of this analysis yielded an AUC of 0.912 (95% CI 0.878 - 0.947; Fig. 1A). This indicated that the prognostic model was able to effectively dichotomize patients with SARS-CoV-2 pneumonia who subsequently discharged and those who later died. In the prediction of overall survival, the model reached a Harrell's c-index of 0.758 (95% CI 0.723 - 0.793; Fig. 1C). The model was able to define a high-risk subgroup with a significantly increased likelihood of death due to SARS-CoV-2 pneumonia (hazard ratio [HR]: 24.22 [95% CI 10.57 - 55.5]) versus a low-risk subgroup. The predicted survival probabilities were compared with observed survival probabilities on the 7th, 14th, 21th, and 28th day after admission (Fig. 1B). The nomogram was constructed to assess impact of these factors (Supplement Figure 2). The predicted 30-days survival rates of the high- and low-risk subgroups in the training cohort were visualized in Fig. 1C (=>799 and <799). Here, 799 represented the cutoff in the model based on the average of minimum calculated scores among deceased patients.

Validation of the Model for Vital Status and Survival

In order to validate the prognostic value of the established prognostic model for SARS-CoV-2 pneumonia, external validation using 2 cohorts to test the predictive model was performed. The model reached an AUC of 0.928 [95% CI 0.884 - 0.971; validation cohort 1] and 0.883 [95% CI 0.815 - 0.952; validation cohort 2] to predict the vital status (Fig. 1A). For the prediction of survival of both validation cohorts, the model yielded C indices of 0.762 [95% CI 0.723 - 0.801; validation cohort 1] and 0.711 [95% CI 0.672 - 0.75; validation cohort 2] (Figure 2). By applying the same cutoff of model score, high-risk subgroups with lower survival rate were defined to clearly differentiated between the low-risk subgroups in both validation cohorts (HR: 11.53 [95% CI 4.01 - 33.15 for the validation cohort 1 and HR: 9.3 [95% CI 3.32 - 26.03] for the validation cohort 2) (Figure 2). Of note, the predicted 30-day survival rates in high- and low-risk subgroups in both validation cohorts were similar to the observed survival rates in the training cohort (Fig. 2), thereby confirming the strength of the model for the prognosis for SARS-CoV-2 pneumonia.

For the investigation of age-related impact on the prognostic model, these two validation cohorts were merged and then divided into three groups by age to form three subgroups: <50 year (cohort_5), 50~70 year (cohort_6), and >70 year (cohort_7), respectively. For the prediction of the vital status, the model yielded an AUC of 0.911 [95% CI 0.853 - 0.97; cohort_5], 0.809 [95% CI 0.713 - 0.904; cohort_6], and 0.825 [95% CI 0.719 - 0.931; cohort_7; Fig. 1A]. For the survival prediction, the model yielded C indices of 0.572 [95% CI 0.533 - 0.611; cohort_5], 0.721 [95% CI 0.682 - 0.76; cohort_6], and 0.706 [95% CI 0.667 - 0.745; cohort_7; Table 3]. Finally, to aid in the current clinical management of SARS- CoV-2, a web-based application (http://138.245.80.137:8013/SIMTaskMaster/COVID_Tool) was developed to enable broad testing and utilization of the developed prognostic model (Supplement Figure 3).

Discussion

In this retrospective multicenter study of 492 hospitalised patients with SARS-CoV-2 pneumonia, we found that advanced age, high body temperature, low neutrophil to lymphocyte ratio, elevated AST as well as decrease of total protein was associated with increased risk of mortality. The prognostic model established based on the above five clinical parameters was robust validated using two validation cohorts. The aim of model application was the early identification of individual patients for the prioritizing of initialization of treatment strategies.

The current literature demonstrates that the mortality rate of SARS-CoV-2 pneumonia is estimated to be about 4%, which is lower than that (10%) of SARS in 200311 12 and that (34%) of MERS in 2012-201313. However, deaths caused by SARS-CoV-2 in the past two months alone have already exceeded the combined numbers of deaths by SARS and MERS14. The SARS-CoV-2 is highly contagious, resulting in the changes from epidemic to pandemic disease by WHO lately. The rapid transmission of the disease has a great impact on public health globally. To avoid the disruption of public health systems and further economic burden, strategies that can control and overcome this pandemic outbreak should be explored.

A number of studies have reported various potential risk factors associated with mortality in the setting of SARS-CoV-2 pneumonia (reference). For instance, Chen et alfound that age, obesity, and comorbidity were three identifiable risk factors for mortality5. Huang et al showed that patients with SARS-CoV-2 pneumonia exhibited higher concentrations of cytokines including IL1B, IFNγ, GCSF, IP10, MCP1, MIP1A, and TNFα, suggesting that a cytokine storm could be associated with disease severity and mortality4. Furthermore, Wang and his colleagues identified that neutrophilia, lymphopenia, elevated D-dimer level, and elevated creatinine level were observed in deceased patients,

implying that cellular immune deficiency and coagulation activation could be potentially associated with disease severity15. Our results were consistent with the above findings. In particular, an association of a reduction in neutrophil to lymphocytes ratio and mortality observed in our study indicated that immune cells, representing functional status of immunity, indeed play an important role in progression of SARS-CoV-2 pneumonia.

Aspartate transaminase (AST) is an important clinical marker to assist in early diagnosis of diseases and help to assess the prognostic value in solid tumor16 17. Further, AST functions as an important metabolic enzyme involving in diverse metabolic pathways including purine metabolism18, steroid biosynthesis19, and different amino-acid synthesis and metabolism such as arginine20, phenylalanine21, tyrosine22, and others23. Elevated serum AST levels may be an indicator of metabolic dysfunction.

Furthermore, hypoalbuminaemia is usually related to malnutrition. Recent studies demonstrated that an increase of glucose or diminished availability of metabolic nutrients let directly to changes of immune responses24 25 26, suggesting that elevated AST level and decrease of total protein could be related to reduced immunity. In addition, an increase in body temperature is also related to an immune response. In sum, the five clinical parameters in this model are to some degrees related to the strength of immunity.

Our study has several strengths. To our knowledge, this is the first study assessing prognostic factors for mortality of individual patients with SARS-CoV-2 pneumonia. Our model consisted of five commonly used clinical parameters, which were easily applicable in the clinical setting. The study recruited large number of patients and the model was validated using two external cohorts in order to test its robustness. This established model can not only assist clinicians in stratification of high risk patients, but also and early identify sick patients requiring prompt initialization of treatment strategies.

Our multi-center study presents a prognostic model for the SARS-CoV-2 pneumonia based on the optimal selection of conventional clinical measurements (age and body temperature by admission) and laboratory values from peripheral blood (neutrophil-to-lymphocyte, AST, and total protein). These five clinical data points and laboratory values are part of routine tests performed on hospital admission. At this time clinical stratification is not confounded by any treatment since this has not yet been initiated. In this manner, the limited medical resources available in each hospital setting can be optimally utilized, and clinical care can be prioritized to manage local occurrences. Although several studies recently analyzed clinical relevant risk factors associated with SARS-CoV-2 pneumonia, these studies only explained the potential risk factors. No final applicable model for the purpose of prognosis was constructed27 28 29. In comparison with them, our study recruited the largest cohorts and demonstrated superior prediction performance not only for two independent validation cohorts, but also for age- specific cohorts. The high AUC and C-indices of the prediction of the vital status and survival in age- related cohorts with age of 50~70 and >70 indicated the suitability of the prognostic model for elder patients. The high AUC and low C-index for the cohort with age<50 may be due to the low mortality of this cohort.

The major limitation of this study is that the model was developed and validated purely based on Chinese population. Therefore, its application to the regions outside of China needs to be further determined. We speculate that the model could still reach a high prediction rate, however, the cutoff of optimal model score of 799 might need to be adjusted correspondingly to cover a broader spectrum of disease trajectories. In addition, due to the nature of an observational study, potential confounders may exist

which can have impacts on the results. Therefore, further prospective international multicenter studies are needed to test the robustness of this model.

Conclusion

In this retrospective multi-center cohort study, the prognostic model was developed and validated to predict the vital status and survival time of individual patients suffering from SARS-CoV-2 pneumonia. We identified that age, neutrophil-to-lymphocyte ratio, body temperature at admission, deranged liver functions as well as decrease of total protein were predictors for mortality. This enables a broad application for clinical stratification to efficiently prioritize medical resources in the treatment and clinical management of SARS-CoV-2 pneumonia. The model application may also assist in treatment recommendations to save more lives in a high-risk group of patients while avoiding overtreatment in those at lower risk.

Declarations

Funding

The study was funded by Public Health and Family Planning Research Project of Hubei Province (NO.WJ2019M128), Natural Science Foundation of Hubei Province (NO.2019CFB449) and General program of National Natural Science Foundation of China (NO. 81372664).

Ethics, Consent and Permission

This study followed the institutional guidelines and was approved by the institutional ethics board of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology (No.

IRBID:TJ-C 20200107).

Consent to Publish

Consents were obtained from participants for the participation and purpose of publication. All written informed consent for the deceased patients from their next to kin were obtained for the participation and the purpose of publication.

Funding

The Public Health and Family Planning Research Project of Hubei Province (NO.WJ2019M128), Natural Science Foundation of Hubei Province (NO.2019CFB449) and General program of National Natural Science Foundation of China (NO. 81372664).

Author Contribution

Q.M., AYW, J.I.L and JWZ.: contributed to data collection and drafting the manuscript; K.H. and M.L.: contributed to statistical analysis; L.W., H.C., Y.Y., and F.W. : contributed to data collection; J.L., Y.L., and S.D. : contributed to data preparation and analysis; G.H., X.Y. : contributed to conceptualization.

Conflict of Interest

All authors declare that there is no conflict of interest to report. All authors completed the unified competing interest form; no support from any organization for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author.

Acknowledgment

We thank all patients and their families involved in this study.

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Tables

Table 1. Clinical characteristics, treatments and laboratory findings of the Training (TJH), Validation 1 (RHWU+WNH), and Validation 2 (WPH) cohorts

Characteristics	Overall	Training Cohort (TJH)	Validation 1 (RHWU+WNH)	Validation 2 (WPH)
Number of patients	492	237	120	135
Median age, years	61.0 (45.0-70.0)	62 (50.0-70.0)	46.0 (37.0-66.0)	63.0 (52.0-70.5)
Survival outcome	…	…	…	…
Cured	311 (63.2)	132 (55.7)	89 (74.2)	90 (66.7)
Deceased	181 (36.8)	105 (44.3)	31 (25.8)	45 (33.3)
Sex	…	…	…	…
Male	221 (44.9)	100 (42.2)	52 (43.3)	69 (51.1)
Female	271 (55.1)	137 (57.8)	68 (56.7)	66 (48.9)
ICU care	…	…	…	…
Yes	50 (10.2)	21 (8.9)	2 (1.7)	27 (20.0)
No	442 (89.8)	216 (91.1)	118 (98.3)	108 (80.0)
Smoking	…	…	…	…
Yes	45 (9.1)	19 (8.0)	3 (2.5)	23 (17.0)
No	447 (90.9)	218 (92.0)	117 (97.5)	112 (83.0)
Comorbidities	269 (54.7)	125 (52.7)	45 (37.5)	99 (73.3)
Hypertension	161 (32.7)	83 (35.1)	27 (22.5)	51 (37.8)
Diabetics	74 (15.0)	38 (16.0)	11 (9.2)	25 (18.5)
CVDs	42 (8.5)	25 (10.5)	5 (4.2)	12 (8.9)
Carcinoma	18 (3.7)	7 (3.0)	3 (2.5)	8 (6.3)
Initial common symptome	…	…	…	…
Fever	329 (66.9)	174 (73.4)	73 (60.8)	82 (60.7)
Cough	270 (54.9)	136 (57.4)	62 (51.7)	71 (53.3)
Myalgia or Fatigue	185 (37.6)	93 (39.2)	35 (29.2)	57 (42.2)
Dyspneu	137 (28.3)	76 (32.1)	26 (21.7)	37 (27.4)
Admission body temperature, °C	36.0 (36.5-37.5)	36.9 (36.5-37.8)	36.8 (36.5-37.4)	36.6 (36.4-36.9)

Symptom onset to admission, days	9.0 (6.0-12.0)	10 (7.0-14.0)	7.0 (4.0-10.0)	10.0 (7.0-13.0)
Hospitalization, days	15.0 (9.8-23.0)	15 (7.0-24.0)	17.0 (11.8-25.0)	14.0 (10.0-19.0)
Systolic pressure, mm Hg (113.0-135.0)	126.0 (116.0-140.0)	130 (119.0-143.0)	124.5 (117.0-136.0)	125.0
Respiratory rate, breaths per min	20.0 (20.0-24.0)	20 (20.0-24.0)	20.0 (19.8-22.0)	21.0 (20.0-25.0)
Pulse rate, beats per min	89.0 (80.0-101.0)	89 (78.0-103.0)	90.0 (78.8-100.0)	87.0 (80.0-98.0)
Treatments				
Therapy	…	…	…	…
Antibiotics	432 (87.8)	205 (86.5)	111 (92.5)	116 (85.9)
Antiviral treatment	481 (97.8)	235 (99.6)	115 (95.8)	131 (97.0)
Corticosteroids	338 (68.7)	150 (63.3)	82 (68.3)	106 (78.5)
Interferon treatment	238 (48.4)	89 (37.6)	27 (22.5)	122 (90.4)
Immunoglobin	179 (36.4)	78 (32.9)	27 (22.5)	74 (54.8)
Oxygen therapy	376 (76.4)	200 (84.4)	90 (75.0)	86 (63.7)
Nasal catheter inhalation	390 (79.3)	204 (86.1)	92 (76.7)	94 (69.6)
NIMV	141 (28.7)	95 (40.1)	28 (23.3)	18 (13.3)
IMV	58 (11.8)	27 (11.4)	9 (7.5)	22 (16.3)
ECMO	10 (2.0)	1 (0.4)	1 (0.8)	8 (5.9)
Laboratory findings				
WBC count, $\times 10^9$/L	…	…	…	…
Decrease	69 (14.0)	28 (11.8)	20 (16.7)	21 (15.6)
Normal range	311 (63.2)	151 (63.7)	71 (59.2)	86 (63.7)
Increase	112 (22.8)	58 (24.5)	26 (21.7)	28 (20.7)
Neutrophil count, $\times 10^9$/L	…	…	…	…
Decrease	51 (10.4)	16 (6.8)	23 (19.2)	12 (8.9)
Normal range	280 (56.9)	139 (58.6)	60 (50.0)	81 (60.0)

Increase	161 (32.7)	82 (34.6)	3.7	(3.1)	42	(31.1)
Lymphocyte count, $\times 10^9$/L	…	…		…		…
Decrease	339 (68.9)	164 (69.2)	73	(60.8)	102	(75.6)
Normal range	153 (31.1)	73 (30.8)	47	(39.2)	33	(24.4)
PLT count, $\times 10^9$/L	…	…		…		…
Decrease	80 (19.0)	47 (19.8)	13	(10.8)	20	(14.8)
Normal range	320 (76.0)	178 (75.1)	31	(25.8)	111	(82.2)
Increase	21 (5.0)	12 (5.1)	5	(4.2)	4	(3.0)
APTT, s	…	…		…		…
Decrease	58 (11.8)	13 (5.5)	34	(28.3)	11	(8.1)
Normal range	345 (70.1)	161 (67.9)	77	(64.2)	107	(79.3)
Increase	89 (18.1)	63 (26.6)	9	(7.5)	17	(12.6)
PT, s	…	…		…		…
Normal range	360 (151.3)	150 (168.5)	109	(403.7)	101	(82.8)
Increase	132 (55.5)	87 (97.8)	11	(40.7)	34	(27.9)
D-D dimer, μg/mL FEU	…	…		…		…
Normal range	206 (86.6)	63 (70.8)	72	(266.7)	71	(58.2)
Increase	286 (120.2)	174 (195.5)	48	(177.8)	64	(52.5)
ALT, U/L	…	…		…		…
Normal range	365 (74.2)	173 (73.0)	95	(79.2)	97	(71.9)
Increase	127 (25.8)	64 (27.0)	25	(20.8)	38	(28.1)
AST, U/L	…	…		…		…
Normal range	311 (63.2)	140 (59.1)	87	(72.5)	84	(62.2)
Increase	181 (36.8)	97 (40.9)	33	(27.5)	51	(37.8)
LDH, U/L	…	…		…		…
Normal range	128 (26.0)	47 (19.8)	57	(47.5)	24	(17.8)
Increase	364 (74.0)	190 (80.2)	63	(52.5)	111	(82.2)
ALP, U/L	…	…		…		…

Decrease	27/421 (6.4)	5 (2.1)	2/49	(4.1)	20	(14.8)
normal range	351/421 (83.4)	208 (87.8)	39/49	(79.6)	104	(77.0)
Increase	43/421 (10.2)	24 (10.1)	8/49	(16.3)	11	(8.1)
y-GT, U/L	…	…		…		…
Decrease	2/421 (0.5)	1 (0.4)	0		1	(0.7)
normal range	324/421 (77.0)	182 (76.8)	39/49	(79.6)	103	(76.3)
Increase	95/421 (22.6)	54 (22.8)	10/49	(20.4)	31	(23.0)
Urea, mmol/L	…	…		…		…
Decrease	33/421 (7.8)	20 (8.4)	3/49	(6.1)	10	(7.4)
normal range	294/421 (69.8)	166 (70.0)	23/49	(46.9)	105	(77.8)
Increase	94/421 (22.3)	51 (21.5)	23/49	(46.9)	20	(14.8)
Albumin, g/L	…	…		…		…
Decrease	229 (46.5)	139 (58.6)	38	(31.7)	52	(38.5)
Normal range	263 (53.5)	98 (41.4)	82	(68.3)	83	(61.5)
Total cholesterol, mmol/L	…	…		…		…
normal range	247/266 (92.9)	210/222 (94.6)	6/7	(85.7)	31/37	(83.8)
Increase	19/266 (7.1)	12/222 (5.4)	1/7	(14.3)	6/37	(16.2)
Total bilirubin, μmol/L	…	…		…		…
normal range	454 (92.3)	219 (92.4)	114	(95.0)	121	(89.6)
Increase	38 (7.7)	18 (7.6)	6	(5.0)	14	(10.4)
hs-CRP, mg/L	…	…		…		…
Normal range	114 (23.2)	54 (22.8)	43	(35.8)	17	(12.6)
Increase	378 (76.8)	183 (77.2)	77	(64.2)	118	(87.4)

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. ICU = Intensive care unit; (N)IMV = (Non-) Invasive mechanical ventilation; ECMO = Extracorporeal membrane oxygenation; WBC = White blood cell; PLT = Blood platelet; APTT = Activated partial thromboplastin time; PT = Prothrombin time; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; LDH = Lactate dehydrogenase; ALP = Alkaline phosphatase; y-GT = gamma-Glutamyl transpeptidase; hs-CRP = high-sensitivity C-reactive protein.

Table 2. Risk factors associated with mortality of COVID-19

Univariate analysis	AOR (95%CI)	Wald's *P*-value
Demographic and clinical characteristics		
Median age, years *	1.10 (1.07 - 1.14)	<.001
Comorbidity: 1 *vs.* 0	2.94 (1.68 - 5.14)	<.001
No. of comorbidities *	1.72 (1.31 - 2.26)	<.001
Hypertension: 1 *vs.* 0	2.87 (1.62 - 5.10)	<.001
Diabetics: 1 *vs.* 0	2.23 (1.04 - 4.79)	0.039
Admission body temperature, °C *	1.32 (0.99 - 1.77)	0.030
Systolic pressure, mmHg *	1.03 (1.01 - 1.04)	<.001
Respiratory rate, breaths per min *	1.17 (1.10 - 1.25)	<.001
Pulse rate, beats per min *	1.04 (1.02 - 1.06)	<.001
Treatments		
Antibiotics: 1 *vs.* 0	7.80 (2.28 - 26.65)	0.001
Corticosteroids ≥ 60 mg/day: 1 *vs.* 0	7.45 (3.63 - 15.31)	<.001
Interferon treatment: 1 *vs.* 0	0.40 (0.22 - 0.71)	0.002
Immunoglobulin: 1 *vs.* 0	2.82 (1.56 - 5.10)	<.001
Nasal catheter inhalation: 1 *vs.* 0	3.97 (1.72 - 9.17)	0.001
Noninvasive mechanical ventilation (NIMV): 1 *vs.*0	370.36 (105.14 - 1304.61)	<.001
Immune components		
White blood cell (WBC) count, ×109/L *	1.38 (1.24 - 1.53)	<.001
Neutrophil count, ×109/L *	1.45 (1.29 - 1.63)	<.001
Lymphocyte count, ×109/L *	0.07 (0.03 - 0.16)	<.001
Neutrophil ratio *	1.39 (1.25 - 1.46)	<.001
Lymphocyte ratio *	0.18 (0.06 - 0.25)	<.001
Neutrophil / Lymphocyte ratio *	1.19 (1.13 - 1.26)	<.001
Other laboratory findings		
Aspartate aminotransferase (AST), U/L *	1.05 (1.03 - 1.07)	<.001
Alkaline phosphatase (ALP), U/L *	1.02 (1.01 - 1.03)	<.001

Lactate dehydrogenase (LDH), U/L *	1.02 (1.01 - 1.02)	<.001
gamma-Glutamyl transpeptidase (γ-GT), U/L *	1.0081 (1.0014 - 1.0148)	0.017
Total bilirubin, μmol/L *	1.11 (1.06 - 1.17)	<.001
Albumin, g/L *	0.75 (0.69 - 0.81)	<.001
Urea, mmol/L *	1.53 (1.33 - 1.77)	<.001
Uric acid, μmol/L *	1.0032 (1.0008 - 1.0055)	0.007
K+, mmol/L*	2.50 (1.53 - 4.08)	<.001
Ca**2+**, mmol/L*	0.26 (0.12 - 0.51)	<.001
high-sensitivity C-reactive protein (hs-CRP), mg/L*	1.02 (1.02 - 1.03)	<.001
Erythrocyte sedimentation rate (ESR), mm/hr *	1.03 (1.02 - 1.04)	<.001
Blood platelet (PLT) count, ×109/L *	0.9907 (0.9865 - 0.9950)	<.001
Prothrombin time (PT), s *	2.15 (1.67 - 2.78)	<.001
Activated partial thromboplastin time (APTT), s *	1.09 (1.03 - 1.14)	0.001
D-D dimer, μg/mL FEU *	1.33 (1.17 - 1.51)	<.001
Multivariate analysis		
Number of events / patients (%) Age, years *	105 / 237 (44.3%)	…
	1.10 (1.06 - 1.13)	< .001
Neutrophil / Lymphocyte ratio *	1.14 (1.08 - 1.20)	< .001
Admission body temperature, °C *	1.53 (1.00 - 2.35)	0.005
AST: 1 (increase) vs. 0 (reference)	2.47 (1.16 - 5.26)	0.019
Total protein: 1 (decrease) vs. 0 (reference)	1.69 (0.78 - 3.64)	0.018

Table 3. Vital status and overall survival prediction in age-specific cohorts

Covariate	Coefficient	Score
Age, years *	0.17	2 × Age (years)
Neutrophil / Lymphocyte ratio *	0.45	4 × Ratio
Admission body temperature, °C *	1.73	17 × Temperature (°C)
Aspartate transaminase (AST)	2.62	26 × (0/1; 0: reference, 1: increase)
Total Protein	2.71	30 × (0/1; 0: reference, 1: decrease)
Total computed score and risk stratification		
Low risk		:: 799
High risk		> 799

Cohort	Age (IQR)	No.	Mortality	AUC (95%CI)	C-index	*P*-value	PM score
Cohort 5	39.0 (35.0 - 45.0)	97	4.1%	0.91 (0.85 - 0.97)	0.572	0.050	785 (756 - 818)
Cohort 6	63.5 (57.8 - 66.0)	100	33.0%	0.81 (0.71 - 0.90)	0.721	<.001	809 (777 - 841)
Cohort 7	77.5 (72.0 - 82.0)	58	67.2%	0.83 (0.72 - 0.93)	0.706	<.001	856 (824 - 879)

* = Continous variable; No. = Number of patients; AUC = Area under the curve; CI = Confidence interval; PM = Prognostic model.

Figures

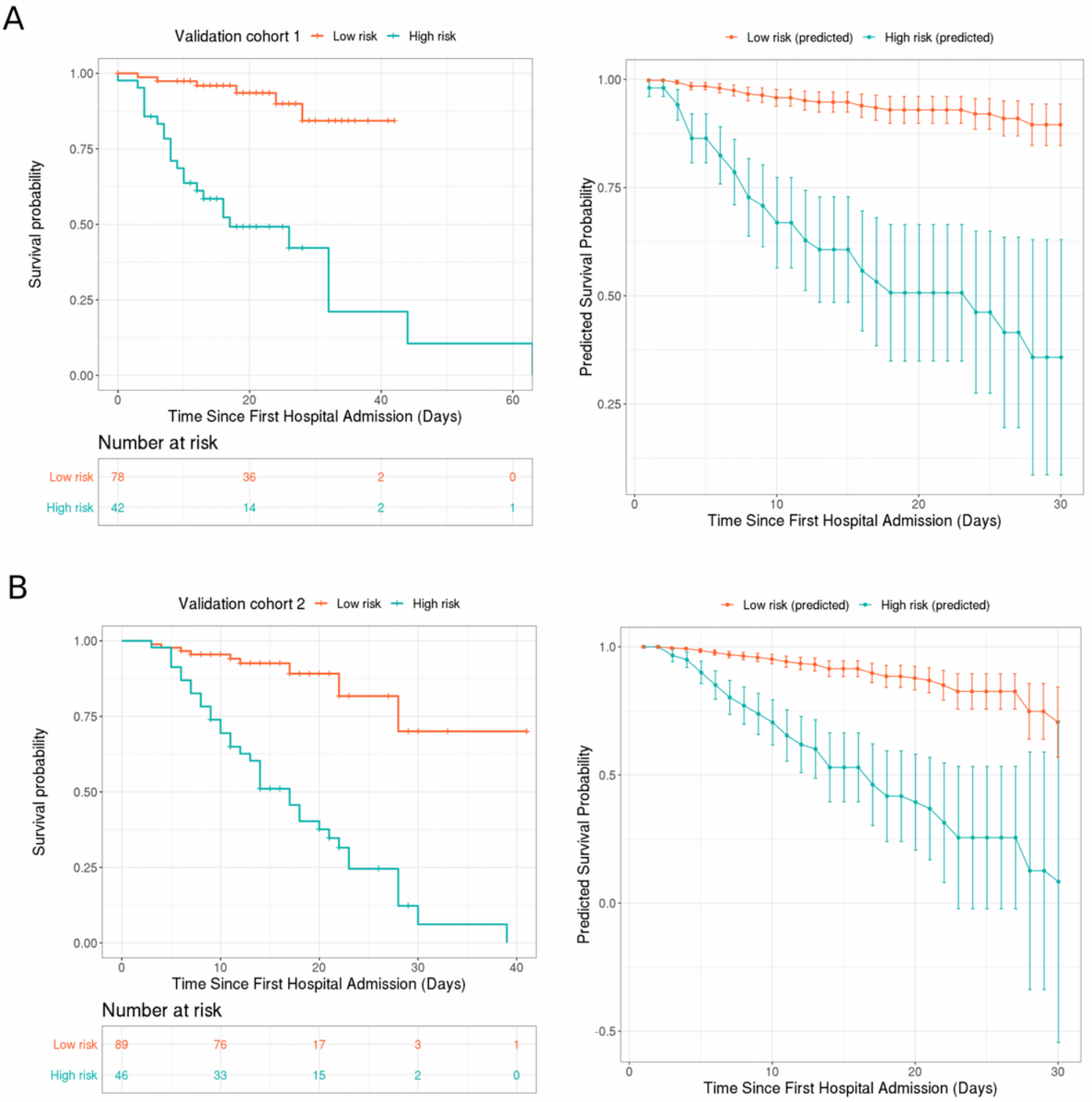

Figure 1

A. AUC (area under curve) of the ROC (receiver operating characteristic) analysis for the training cohort and two validation cohorts (left), and for the age-specific three cohorts (<50 year, 50~70 year, and >70 year, right). B. Calibration plot showed the comparison between predicted and observed survival rates of patients in training cohort on 7th, 14th, 21th, and 28th after hospital admission. C. Clinical stratification and prediction of survival rate on the basis of the developed prognostic model. Survival in the low and high risk subgroups in training cohort (TJH) were stratificated by the a cutoff of <=799 and >799,

respectively (left), predicted survival rates in the this cohort (right). Smooth lines represent mean predicted survival probabilities for each risk group; dots symbolize corresponding predicted rates with 95% CI (vertical lines).

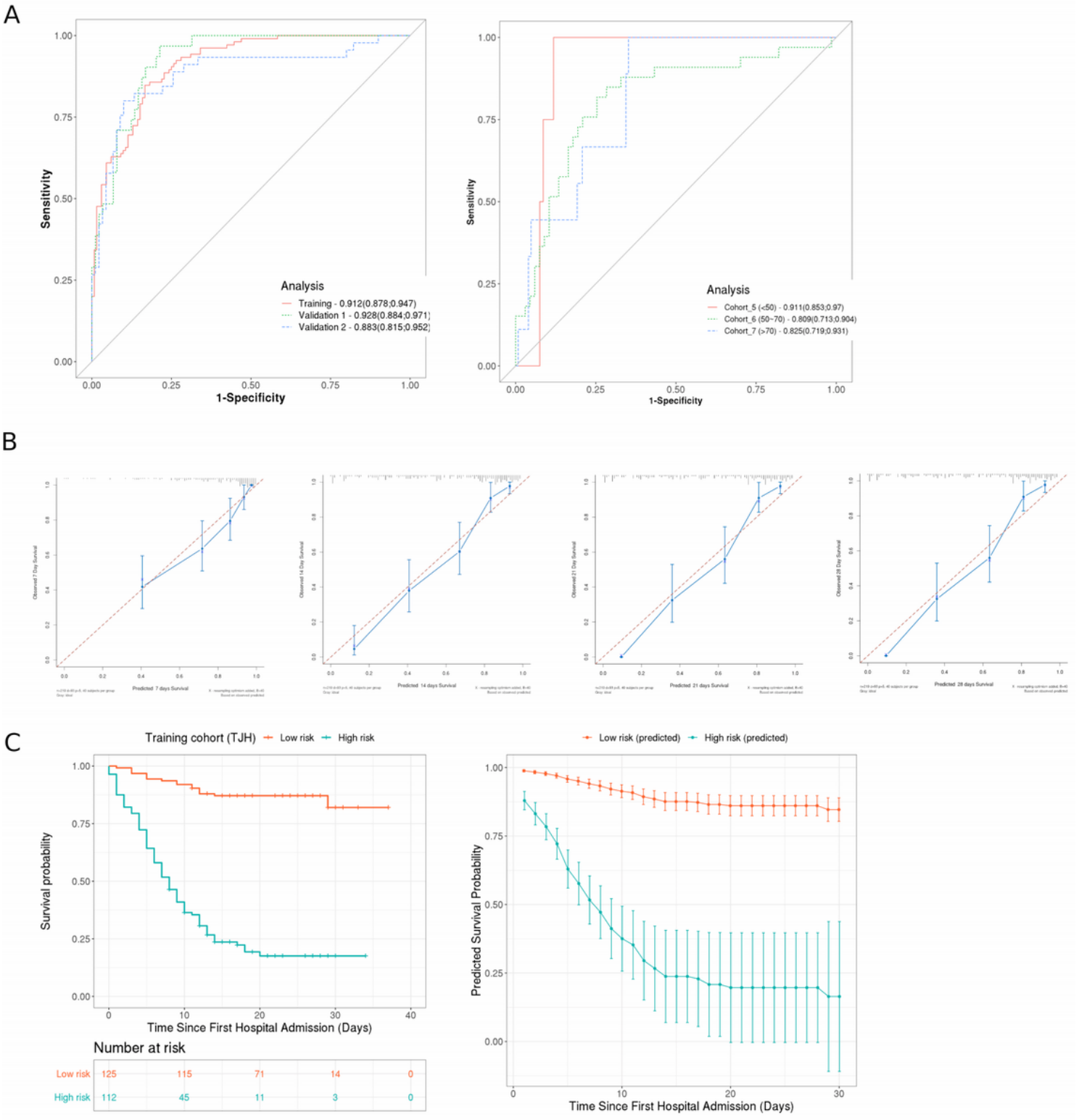

Figure 2

Prognostic model achieves clinical stratification and predicts overall survival (OS) in two validation cohorts. A. Survival probabilities in the low- and high-risk subgroups defined by the consistent cutoff of

799 in the validation cohort 1 (RHWU+WNH) (left), correspondingly predicted survival probabilities in this cohort (right). B. Survival probabilities in the low- and high-risk subgroups defined by the same cutoff in the validation cohort 2 (WPH) (left), correspondingly predicted survival probability in this cohort (right).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- test5.csv
- Supplementalfigures.pdf