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Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China

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Title Page

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Abbreviation List

ACE: angiotensin-converting enzyme

ACEI: angiotensin-converting enzyme inhibitor

ALT: alanine aminotransferase

ARB: angiotensin II receptor blocker

AST: aspartate aminotransferase

CFR: case fatality rate

CHD: coronary heart disease

CK: creatine kinase

COPD: chronic obstructive pulmonary disease

COVID-19: coronavirus disease 2019

Cr: creatinine

CRP: C-reactive protein

CRRT: continuous renal replacement therapy

CVD: cerebrovascular disease

ECMO: extracorporeal membrane oxygenation

IMV: invasive mechanical ventilation

LDH: lactate dehydrogenase

NIV: non-invasive ventilation

PCT: procalcitonin

RAS: renin-angiotensin system

TBIL: total bilirubin

Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China

BACKGROUND:

The novel coronavirus disease 2019 (COVID-19) has become a global health emergency. Cumulative number of new confirmed case and death are still increasing out of China. However, the independent predicted factors associated with the fatal outcome remain uncertain.

METHODS:

A retrospective cohort of 1590 hospitalized subjects with COVID-19 throughout China was established. The prognostic effects of variables, including clinical features and laboratory findings, were analyzed using Kapla-Meier method and Cox proportional hazard model. A prognostic nomogram was formulated to predict the survival of patient with COVID-19.

RESULTS:

In this nationwide cohort, non-survivors showed higher incidence of elderly people, subjects with co-existing chronic illness, dyspnea and laboratory abnormalities on admission, compared with survivors. Multivariate Cox regression analysis showed that age≥75 (HR: 7.86, 95% CI: 2.44-25.35), age between 65-74 years (HR:3.43, 95%CI: 1.24-9.5), coronary heart disease (HR:4.28, 95%CI:1.14-16.13), cerebrovascular disease(HR:3.1, 95%CI:1.07-8.94), dyspnea (HR: 3.96, 95%CI:1.42-11), procalcitonin>0.5ng/ml(HR:8.72, 95%CI:3.42-22.28), aspartate aminotransferase>40U/liter (HR: 2.2, 95% CI: 1.1- 6.73) were independent risk factors associated with fatal outcome. A nomogram was established based on the results of multivariate analysis. The internal bootstrap resampling approach suggested the nomogram has sufficient discriminatory power with the C-index of 0.91 (95%CI 0.85-0.97). The calibration plots also demonstrated good consistence between the prediction and the observation.

CONCLUSIONS:

The proposed nomogram accurately predict clinical outcomes of patients with COVID-19 based on individual characteristics. Earlier identification, more intensive surveillance and appropriate therapy should be considered in patients with high risk.

KEY WORDS: COVID-19; fatal outcome; risk factors; nomogram

Introduction

Since December 2019, China has been experiencing an outbreak of a novel coronavirus disease 2019 (COVID-19). Up to date, it has become the newest global health threats and over 800 thousands people have been infected. The European and the Unite State of America have become the epicenters of the COVID-19 which has a total of 464212 and 163199 confirmed cases by April 1st, respectively.[1] Since severe cases might develop adverse outcome, the numbers of the death are persistently increasing outside of China. The case fatal ratio (CFR) in Italy was up to 11.7%. [1]

As the pandemic evolves, it is urgent to identify the risk factors associated with the fatal outcome. Earlier intensive surveillance or treatment then could be performed to saves lives. Previous reports had descried the clinical characters of the patients with COVID-19. The difference between the mild and severe subjects were compared. [2-4] Nonetheless, previous studies have limitations including the relatively small sample sizes, single center observations and using the univariate analysis along. The independent predicted factors of fatal outcome remain uncertain. What more, it has been suggested that the use of a single risk factor could hardly estimate the comprehensive clinical outcome of individual patients.[5] Therefore, based on a national cohort, our study attempts to investigate the potential risk factors associated with fatality through multivariate Cox regression analysis and nomogram model .

Materials and Methods

Study Subjects

Led by the national health commission of the People's Republic of China, a retrospective cohort to study the COVID-19 admitted cases from 575 hospitals throughout China was established[6]. The diagnosis of COVID-19 was made based on the World Health Organization interim guidance[7]. It was confirmed by a positive result of real-time reverse transcriptase-polymerase-chain-reaction assay or high throughput sequencing findings from nasal or pharyngeal swab specimens. By the cut-off time of January 31st 2020, a total of 2007 cases diagnosed with laboratory-confirmed COVID-19 were collected, and 417 cases were excluded due to

incomplete medical record. The study was approved by the ethics commission of the First Affiliated Hospital of Guangzhou Medical University (IRB:202051). Due to the urgent need to collect data on this emerging infectious disease, the requirement for written informed consent was waived.

Design and Data extraction

After careful medical chart review, the clinical data (including epidemiological history, demographic data, clinical symptoms and signs, comorbidities, Radiologic assessments, laboratory findings upon admission, treatments, clinical outcome) were extracted from electronic medical records. Laboratory assessments consisted of complete blood count, blood chemistry, coagulation test, liver and renal function, electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase and creatine kinase, etc.. All medical records were copied and sent to the data processing center in Guangzhou, under the coordination of the National Health Commission. A team of experienced respiratory clinicians reviewed and abstracted the data. Data were entered into a computerized database and cross-checked. If the core data were missing, requests of clarification were immediately sent to the coordinators who subsequently contacted. The primary endpoint of outcome is death. Independent predicted factors associated with the fatal outcome would be investigated.

Statistical Analysis

Continuous variables were described using mean(standard deviation, SD) or median(interquartile range, IQR). Categorical variables were described as number (percentage). Statistical comparisons between continuous variables were performed with independent t-test. for normally distributed data, otherwise, the Mann-Whitney test was performed. Chi-square test and Fisher’s exact test were applied to categorical variables as appropriate. Survival curves were ploted using the Kaplan-Meier method and compared using the log-rank test.

Cox regression analysis was used for univariate and multivariate analyses.To estimate risk factors associated with fatal outcome, variables including baseline characteristics,

laboratory findings were analyzed by univariate Cox regression analyses. A final model selection was performed via a backward stepdown selection process with the Akaike information criterion. A nomogram was builted based on the results of multivariate analysis and through the rms package in R version 3.3.1 (http://www.r-project.org/). The maximum score of each variable was set as 100. The performance of the nomogram was measured based on the Harrel concordance index (C-index). The nomogram was also evaluated by comparing between nomogram-predicted and observed Kaplan–Meier estimates of survival probability. Bootstraps of 1000 resamples were set, and calibration curves were calculated by the regression analysis. All statistical analysis was performed using R version3.3.1. *P*-value <0.05 was considered statistically significant.

Results:

Of the 1590 cases included in this cohort, 50 cases were reported death by Jan 31st. The median age of fatal cease was 69 years (range: 51-86 years). Thirty of them were male. The median duration from initial treatment to death was 11(IQR:7-16.5) days. Thirty-five (70%) cases reported 1 or more co-existing illness : twenty-eight (56.0%) with hypertension, thirteen(26.0%) with diabetes, eight(16.0%) with coronary heart disease(CHD), six(12.0%) with cerebrovascular disease(CVD), six (12.0%) with chronic obstructive pulmonary disease (COPD), five (10.0%) with renal disease(Fig 1A). The most common symptoms since the diseases onset were fever (87.5%), cough (77.1%) and dyspnea (74.0%). The incidence of dyspnea in fatal cases was higher than that in non-fatal cases(19.1%) (*P*<0.001). Other symptoms included fatigue, headache, Myalgia, nausea or vomiting, diarrhea and chill (Appendix Table E1).

On admission, abnormalities of laboratory findings were found in the fatal cases: lymphopenia (97.6%); elevated levels of C-reactive protein (CRP) (100%), lactose dehydrogenase (LDH) (91.4%) , D-dimer (87.2%), aspartate aminotransferase (AST) (68.6%), alanine aminotransferase (ALT) (54.3%), leucocyte (42.5%), procalcitonin (PCT) (41.2%), total bilirubin (TBIL) (39.0%). Compared with non-fatal cases, more prominent laboratory abnormalities and abnormal chest X-ray were observed in fatal

cases (i.e. leukopenia, lymphopenia, elevated CRP, PCT, LDH, AST, ALT, TBIL, CK, Cr, D-dimer level) by univariate analysis (Appendix Table E1).

All fatal patients had received antibiotics therapy. Anti-fungal therapy was given to 22% of them. 36.1% of patients received oseltamivir and 56.3% of them received systemic glucocorticoid. non-invasive ventilation (NIV) and invasive mechanical ventilation(IMV) were performed in 68.8% and 62.5% of cases, respectively. The median age of fatal cases who received NIV and IMV were 69 years (range: 53-84 years), 66 years (range: 51-82 years), respectively. 10.8% of cases were given ECMO, 21.1% with CRRT therapy. Acute respiratory distress syndrome, secondary infection, septic shock were the common reported complications (Figure 1B&C). Figure E1 in appendix showed a progression of a 63-year-old patient with a fatal outcome.

The multivariate Cox regression model finally demonstrated some independent predicted factors for the fatal outcome. Age≥75 (HR: 7.86, 95% CI: 2.44-25.35), age between 65-74 years (HR:3.43, 95%CI: 1.24- 9.5), CHD (HR:4.28, 95%CI:1.14-16.13), CVD (HR:3.1, 95%CI:1.07-8.94), dyspnea(HR: 3.96, 95%CI:1.42-11), PCT>0.5ng/ml(HR:8.72, 95%CI:3.42-22.28), AST>40U/liter (HR: 2.2, 95% CI: 1.1- 6.73) were independent risk factors associate with fatal outcomes(Figure 2). Kaplan-Meier survival plots for these prognostic factors are shown in Figure 3.

The nomogram was constructed based on the final multi-variate model. To calculate 14 days, 21 days and 28 days overall survival probability, we first identify each factor based on the points scale at the top of the nomogram and then sum the points of each factor. Finally, the 14 days, 21 days and 28 days overall survival probability was obtained based on the bottom point scale of the nomogram (Figure 4). The calibration plots on bootstrap resampling validation are illustrated in Figure 5. The C-index for prediction of overall survival was 0.91 (95%CI 0.85-0.97), demonstrating that the nomogram is consistent with the actual observation for patients with COVID-19.

Discussion:

Out study unraveled the clinic features and risk factors for the fatal outcome in subjects with laboratory confirmed COVID-19 based on a national cohort. By January 31st 2020, the National Health Commission had issued 11,791 patients with laboratory-confirmed COVID-19 in China. Our cohort represent 13.5% of infected patients and is able to provide a more panoramic picture regarding on the fatal cases with COVID-19.

In our study, some independent risk factors for the fatal outcome were found using a multivariate Cox regression analysis. Further, our study firstly developed a nomogram model to accurately predict clinical outcomes of patients with COVID-19 based on individual characteristics risk factors. The prognostic nomogram performed well in predicting survival, supported by the C-index (0.91, 95%CI 0.85-0.97) and the calibration curve, which is helpful for further understanding and improve clinical strategies against the disease.

In our cohort, an overall confirmed case fatality ratio is 3.14%, which resemble that in WHO report in March 8 (3.39%).[1] This is lower than the earlier reports from single site in Wuhan. [3,8] It might due to difficulty of insufficient laboratory diagnosis ability and admission of infected patients with mild symptom at early stage of disease outbreak. Though the CFR is obviously lower than SARS(10%)[9] and Middle Eastern respiratory syndrome MERS(36%),[10] the transmissibility of COVID seem to be much higher. Recent study has found the 2019-nCoV (SARS-CoV-2) spike (S) is approximately 10- to 20-fold higher affinity than SARS-CoV binding to functional host-cell receptor- angiotensin-converting enzyme 2(ACE2), which may be a potential mechanism for the large number of infected population around world. [11]

Consistent with previous reports[12,13], our study indicated that SARS-CoV-2 is susceptible to all aged groups. However, the elderly patients are more severe and generally have a higher probability of the fatal outcome. Previous report indicated

elderly people were more common in critical ill cases with COVID-19.[2-4] Our study demonstrated that advanced age is the most strong risk factor for the fatal outcome. Our study showed that risk of death was increased 7.86-fold in patients older than 75 years and 3.43-fold in patients of age between 65 to 75, compared with patients younger than 65 years old. In the nomogram model, age was the most important predictor for the fatal outcome. Base the report from China CDC including 44672 confirmed cases(updated through February 11), Case-fatality rate reach 14.8% in patients aged≥80 years (208 of 1408), 8.0% in patients aged 70-79 years (312 of 3918)[12]. More intensive surveillance is needed in elderly patients. Earlier reports showed that male seems more common in infected patients, which may be due to a higher probability of occupational exposure.[3,8] However, the subsequent reports showed equivalence of gender in infected cases.[14] Our study indicates that gender is not the core factor accounting for death based on the multivariate Cox regression analysis.

Non-survivors present higher proportion of various co-existing chronic illness in univariate analysis. Previous studies reported similar findings.[2,4,15] CHD and CVD are confirmed to be independent risk factors for death through the multivariate Cox regression analysis and enter the nomogram model. As the functional receptor of SARS-CoV-2, ACE2 is mainly expressed not only in lung alveolar type II (AT2) epithelial cells but also in blood vessels.[16,17]ACE2 also serves as a negative regulatory factor for the renin-angiotensin system (RAS) via ACE2/Ang 1-7 axis.[18] Exhaustion of ACE2 could activate RAS and enhance susceptibility to heart failure or pulmonary edema.[19] SARS-CoV-2 may act similarly as SARS-CoV and result in an over activation of RAS in patients with pre-existing chronic cardiovascular diseases, which lead to a poor outcome of fatality.[20] Though hypertension is common in non-survivors, whether taking RAS inhibitors (ACEI or ARB) in patients with hypertension would be a protector or not need further investigation.

Dyspnea was found in 74% of fatal cases at disease onset and it was proved to be an independent risk factor for developing death. With the progress of disease in some

cases , hypoxemia would get worse and acute respiratory distress syndrome(ARDS) may develop. It is needed to identify these patients with hypoxemia and provide appropriate intervention. ARDS, is the most common complication associated with death , following by secondary infection and septic shock. A pathological evidence of ARDS in case with COVID-19 showed obvious desquamation of pneumocytes, hyaline membrane formation and pulmonary edema,[21] which is similar to those seen in SARS and MERS coronavirus infection. In our cohort, NIV(noninvasive ventilation) and IMV were performed in 68.8% and 62.5% of fatal cases, respectively. 11% of cases were given ECMO. There is still controversy the usage of the high flow nasal cannula(HFNC) or NIV in patients with ARDS. However, two recent study indicated that early application of HFNC or HFNC with prone positioning could be considered as first-line therapy in acute respiratory failure, and may help avoid intubation in patients with ARDS.[22,23]

A series of laboratory abnormalities on admission were more common in fatal cases, compared with the survivors. Some independent laboratory predictors of the fatal outcome were found via multivariate Cox regression analysis. Procalcitonin (PCT) is a calcitonin pro-peptide synthesized by C cells of the thyroid gland and released from leukocytes, which is significantly increased in bacterial infections and the SEPSIS. It has been proved a high specificity for bacterial infection and an good correlation with severity of illness.[24] Procalcitonin (PCT)-guided antibiotic stewardship (ABS) has been shown to reduce antibiotics, with lower side-effects and an improvement in clinical outcomes.[25] In the nomogram model of our study , an elevated level of PCT (>0.5ng/ml) was a strong reliable predictor for case fatality. The results indicated that secondary bacterial infections on the earlier stage may play an important role in progressive of the disease .

Elevated AST (>40U/liter) was also associated with a greater risk for death in the nomogram model. Increased creatinine (≥133 μmol/liter) and total bilirubin(>17.1 μmol/liter) might associated with the death outcome. Since ACE2 is widely expressed in multiple organs besides lung , it is possible that SARS-CoV-2 could invade the

local tissues and lead to a direct damage and indirect damage. The following activation of immune response and cytokines storm will also play an important role in the organ dysfunction. Over activation of peripheral T cells, present as increase of CC4+CCR6+Th17 and high cytotoxicity of CD8 T cells，may contribute to the immune injury in severe case with COVID-19.[21] What's more, the usage of the nonsteroidal anti-inflammatory drugs, antivirus, antibiotics, and traditional Chinese medicine which might associated with liver and renal injury. These findings call for multidisciplinary cooperation and monitoring of the organ dysfunction.

There are some limitations of this study. First, in some cases, there were incomplete documentation of the history, symptoms or laboratory findings in the electronic database, even after trying effort to feedback and recollect. Some diagnosis of co-existing illness were from patients' self-reports at admission, which might lead to the recalling bias. Although the cohort had a broad coverage of all patients and regions, the non-responsive bias cannot be fully excluded. Second, as a retrospective and observational study, we currently could not set up a validation cohort to assess the predictive accuracy due to the urgent timeline under this special situation. However, we use the bootstrap resampling cohort and show that the C-index is ideal, suggesting the nomogram is a good model for predicting outcomes. Likewise, the calibration curves for survival probability also demonstrated a good consistence between the prediction and the observation.

Collectively, our study provided the evidence that advanced age, dyspnea, coronary heart disease, cerebrovascular disease, elevated PCT and AST are independent risk factors associated with fatal outcome. The nomogram proposed in our study objectively predicted the prognosis of patients with COVID-19. Earlier identification, more intensive surveillance and appropriate therapy should be considered in these patients with high risk.

Author's contributions: N.S.Z and S.Y.L had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. R.C.C, W.H.L, M.J, W.J.G, C.Z, N.S.Z and S.Y.L participated in study conception. Z.Y.N, Y.H, L.L, H.S, H.L.L, Y.X.P, L.W, Y.L, Y.H.H, P.P, J.M.W, J.Y.L, Z.C, G.L, Z.J.Z, S.Q.Q, J.L, C.J.Y, S.Y.Z, X.Q.L, L.L.C, F.Y, J.P.Z, N.F.Z, Y.M.L, J.X.H recruited patients. R.C.C, W.H.L, M.J, W.J.G, C.Z, T.W, C.L.T, L.S, J.X.L performed data analysis. R.C.C, W.H.L, W.J.G, M.J, C.Z, S.Y.L, N.S.Z drafted and revised the paper. All authors approved the final draft of the manuscript for publication.

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Figure Legend

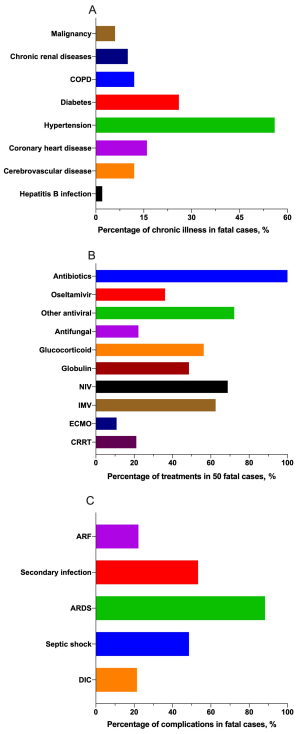
Fig 1. Clinical characteristics of 50 fatal cases with COVID-19. (A) The percentages of coexisting chronic illness in fatal cases. (B) The treatments in fatal cases. (C) The percentages of complications in fatal cases. Abbreviations: COPD: chronic obstructive pulmonary disease, NIV: noninvasive ventilation, IMV: invasive mechanical ventilation, ECMO: extracorporeal membrane oxygenation, CRRT: continuous renal replacement therapy.

Fig 2. Risk factor of the fatal outcome in the Multivariate Cox proportional hazards regression model. Shown in the figure are the hazards ratio (HR) and the 95% confidence interval (95%CI) associated with the endpoint. Abbreviations: CHD: coronary heart disease, CVD: cerebrovascular disease, PCT: Procalcitonin, AST: Aspartate aminotransferase, TBIL: Total bilirubin, Cr: Creatinine

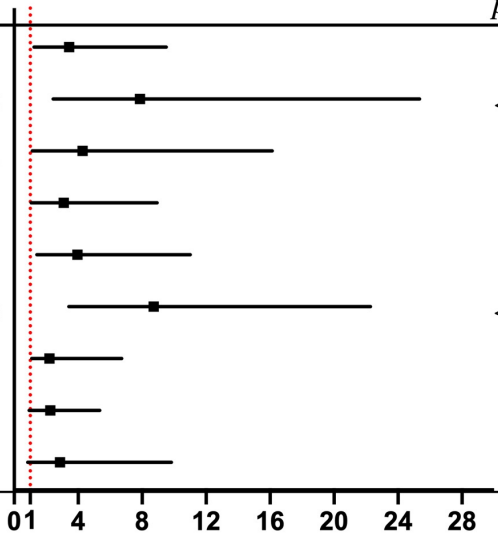
Fig 3. Kaplan-Meier survival plots for different prognostic factors. Shown in the figure are the Kaplan-Meier survival plots according to (A) Age, (B) CHD, (C) CVD, (D) Dyspnea, (E) PCT, (F) AST. Abbreviations: CHD: coronary heart disease, CVD: cerebrovascular disease, PCT: Procalcitonin, AST: Aspartate aminotransferase.

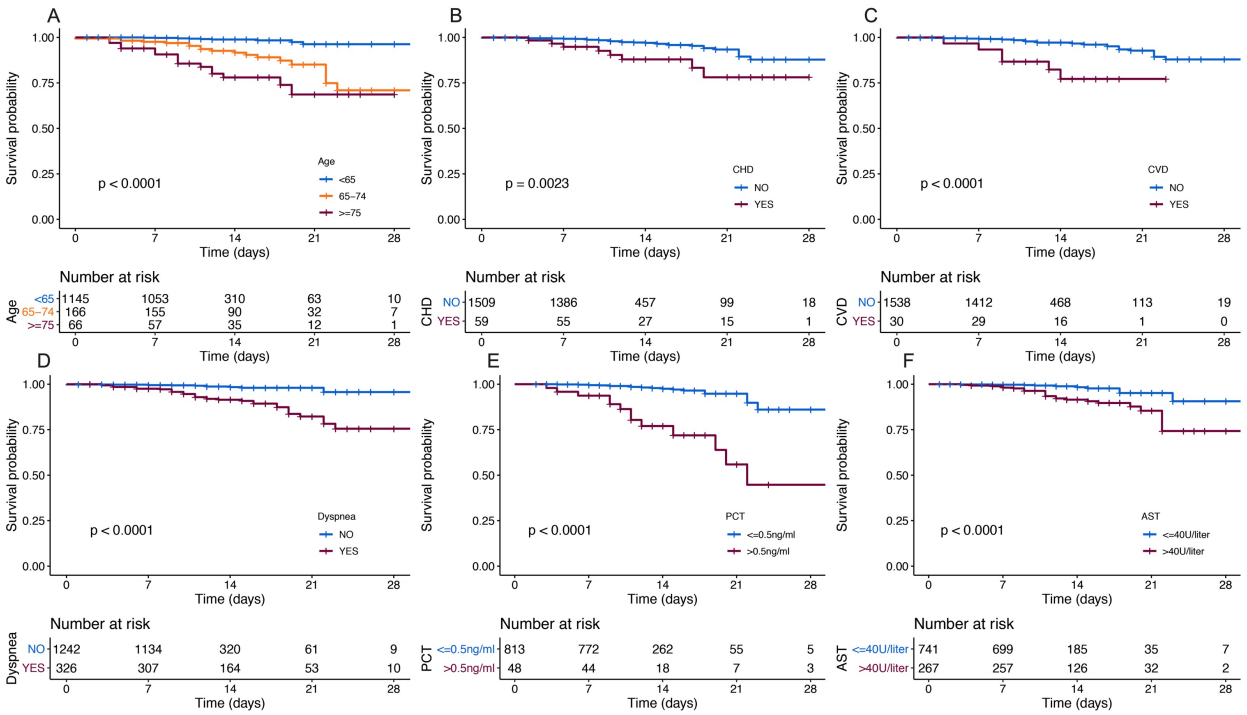
Fig 4. Prognostic nomogram for predicting overall survival probability of patients with COVID-19. Prognostic patient's value is located on each variable axis, and a line is drawn upward to determine the number of point nomogram for predicting overall survival probability of patients with COVID-2019. (To use the nomogram, an individual ts received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the likelihood of 14-day, 21-day, 28-day survival). Abbreviations: CHD: coronary heart disease, CVD: cerebrovascular disease, PCT: Procalcitonin, AST: Aspartate aminotransferase.

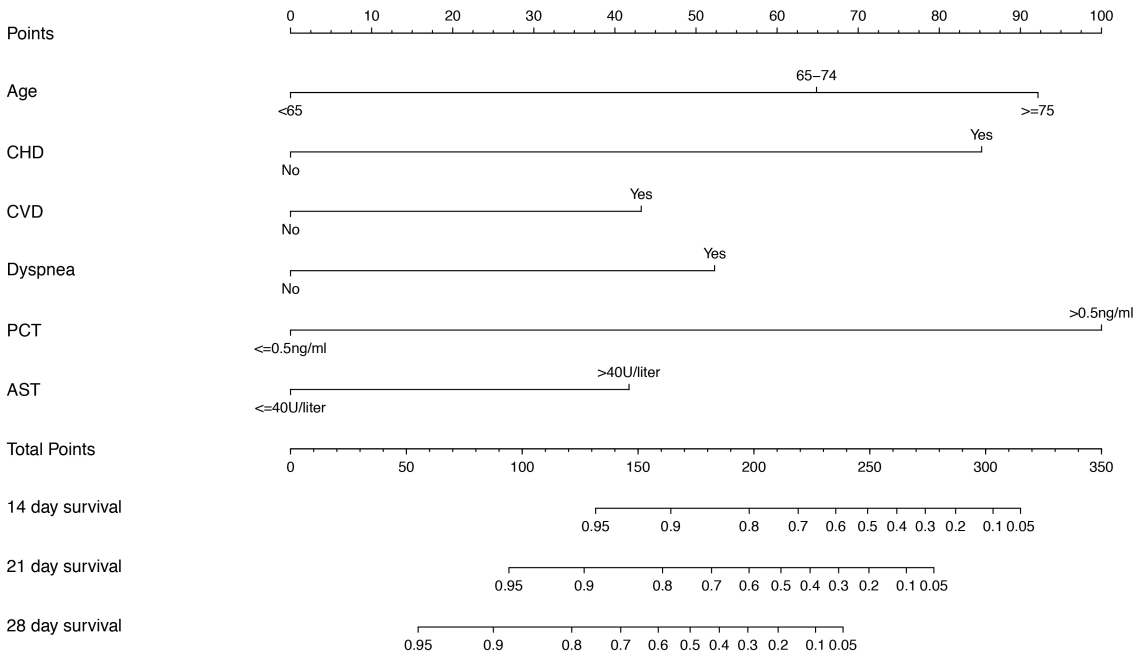
Fig 5. Calibration curves of the nomogram predicting overall survival in patients with COVID-19. Calibration curves of the nomogram predict (A)14-day, (B) 21-day and (C) 28-day overall survival in COVID-19 patients. Nomogram-predicted probability of overall survival is plotted on the x-axis; actual overall survival is plotted on the y-axis.



Variables	Level	HR	95%CI	*p* value
Age	65-74 vs <65	3.43	1.24-9.5	0.018
Age	≥75 vs <65	7.86	2.44-25.35	<0.001
CHD	Yes vs No	4.28	1.14-16.13	0.032
CVD	Yes vs No	3.1	1.07-8.94	0.037
Dyspnea	Yes vs No	3.96	1.42-11	0.008
PCT	>0.5 vs ≤0.5	8.72	3.42-22.28	<0.001
AST	>40 vs ≤40	2.2	1.1-6.73	0.03
TBIL	≥17.1 vs <17.1	2.25	0.94-5.35	0.068
Cr	≥133 vs <133	2.87	0.84-9.83	0.093






Points
0 10 20 30 40 50 60 70 80 90 100
Age
65–74
<65
>=75
CHD
Yes
No
CVD
Yes
No
Dyspnea
Yes
No
PCT
>0.5ng/ml
<=0.5ng/ml
AST
>40U/liter
<=40U/liter
Total Points
0 50 100 150 200 250 300 350
14 day survival
0.95 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05
21 day survival
0.95 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05
28 day survival
0.95 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05