Prediction of COVID-19-related mortality and 30-day and 60-day survival probabilities using a nomogram

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Table of Contents

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Abstract

Background: Prediction of mortality in patients with coronavirus disease 2019 (COVID-19) is key to improving the clinical outcomes, considering that the COVID-19 pandemic has led to the collapse of healthcare systems in many regions worldwide.

Objective: This study aimed to identify the factors associated with COVID-19 mortality and to develop a nomogram for predicting mortality using clinical parameters and underlying diseases.

Methods: This study was performed in 5,626 patients with confirmed COVID-19 between February 1 and April 30, 2020 in South Korea. A Cox proportional hazards model and logistic regression model were used to construct a nomogram for predicting 30-day and 60-day survival probabilities and overall mortality, respectively in the train set. Calibration and discrimination were performed to validate the nomograms in the test set.

Results: Age ?70 years; male; presence of fever and dyspnea at the time of COVID-19 diagnosis; and diabetes mellitus, cancer, or dementia as underling diseases were significantly related to 30-day and 60-day survival and mortality in COVID-19 patients. The areas under the curve (AUCs) for 30-day and 60-day survival was 0.914 and 0.954, respectively (C-index, 0.906; 95% CI, 0.883-0.929); the AUC for mortality of 0.926. The nomogram showed good calibration for survival probabilities and mortality. The online calculators can be found at https://koreastat.shinyapps.io/RiskofCOVID19/.

Conclusions: The prediction model could accurately predict COVID-19-related mortality; thus, it would be helpful for identifying the risk of mortality and establishing medical policies during the pandemic to improve the clinical outcomes. Clinical Trial: not applicable

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Running title: Prediction of COVID-19-related mortality

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Abstract

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Conclusions: The prediction model could accurately predict COVID-19-related mortality; thus, it would be helpful for identifying the risk of mortality and establishing medical policies during the pandemic to improve the clinical outcomes.

Keywords: COVID-19; mortality; nomogram; underlying diseases.

Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) has spread worldwide, without decreasing trend. While 80% of COVID-19 patients have a mild clinical course [1], an unexpected increase in the number of deaths related to COVID-19 have resulted in an overwhelming medical burden in some areas. The ongoing pandemic has generated serious socioeconomic and healthcare problems due to the high mortality, especially in high-risk groups, and large number of patients in areas with limited medical resources. The overwhelming number of patients with COVID-19 infection combined with high-risk individuals for mortality makes it difficult to control the COVID-19 pandemic Therefore, prediction of individualized risks for COVID-19 mortality is essential for estimating the severity of the clinical course of the disease. This would help in classifying the high-risk groups, which would help improve survival rates related with COVID-19.

COVID-19 mortality varies across countries ranging 1.4%-4.3%, but the number of deaths due to COVID-19 is higher than that due to other respiratory viral infections, such as seasonal influenza [2, 3]. The individualized prediction of COVID-19-related mortality is important for prioritizing patients with a high risk of mortality in terms of the allocation of limited medical resources.

Previous studies on the estimation of severity and mortality of COVID-19 showed diverse results, with the identification of a limited number of predictors, such as age and sex [4-7]. Age and underlying diseases are known factors associated with higher risks of mortality in patients with COVID-19 [2, 4, 5, 8], which is partially related with increased severity and susceptibility to COVID-19 [9]. However, heterogeneity in age and underlying diseases could affect COVID-19-related mortality, and therefore, findings from previous studies were inconclusive [2, 4, 6, 7]. In other studies, laboratory or radiologic findings were included in the factors predicting severity or mortality associated with COVID-19 [10-14]. However, data

on these factors are available for a limited number of COVID-19 patients in clinical settings and it takes time to obtain the results of laboratory and radiological examinations, thereby delaying the prediction of mortality and severity in patients with COVID-19.

In this study, we investigated the baseline characteristics of patients with COVID-19 and developed nomograms for predicting the probabilities of COVID-19-related mortality and 30-day and 60-day survival using data obtained at the time of admission, including individual's underlying diseases.

Methods

Study population

The present study enrolled 5,626 confirmed cases of COVID-19 from the nationwide multicenter study between February 1 and April 30, 2020. During the study period, all confirmed cases of COVID-19 in South Korea were included since all patients were hospitalized regardless of their clinical presentation. Patients were followed-up until the end of their hospital stay. During the hospital stay, all patients were monitored by the Korea Disease Control & Prevention Agency of the National Medical Center; the database of information on patients with COVID-19 could be obtained from this agency. COVID-19 was confirmed via real-time reverse transcription-polymerase chain reaction assays using nasal and pharyngeal swab samples in accordance with the World Health Organization guidelines [15].

Data on baseline characteristics, such as age, sex, date of death, symptoms at the time of admission due to COVID-19, underlying diseases, and clinical severity were obtained retrospectively and anonymously under the leadership of the Central Disease Control Headquarters of South Korea. This study was approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (IRB No: CNUH-2020-303) and the Korea Disease Control and Prevention Agency. The need for informed consent was waived due to the retrospective nature of the study.

Available items

Data on baseline characteristics, such as age, sex, height, and weight were obtained at the time of admission. Data on age were obtained in the form of age groups, using intervals of 10 years, but not individual age. Clinical manifestations at the time of admission included fever, defined, defined as a body temperature of >37.5°C; cough; sputum; sore throat; rhinorrhea;

myalgia; fatigue; dyspnea; headache; altered consciousness; vomiting/nausea; and diarrhea. Underlying diseases included diabetes mellitus (DM), hypertension, heart failure, cardiovascular diseases, asthma, chronic obstructive pulmonary disease (COPD), chronic kidney disease, cancer, chronic liver disease, rheumatoid/autoimmune disease, and dementia. Clinical severity was investigated based on the following parameters: no interference with daily life; interference with daily life but no need for oxygen therapy; use of nasal oxygen prongs; use of oxygen mask; requirement of non-invasive mechanical ventilation; requirement of invasive mechanical ventilation; occurrence of multi-organ failure/extracorporeal membrane oxygenation (ECMO) use; and death.

Definitions

The severity of COVID-19 was classified as mild, moderate, or severe as follows; mild, no interference with daily life or interference with daily life but no need for oxygen therapy during illness; moderate, requirement of oxygen via diverse routes (use of nasal cannula, oxygen mask, or non-invasive ventilator care); and severe, application of invasive ventilator care, multi-organ failure/ECMO use, or death.

Statistical analysis

Chi-square or Fisher's exact tests were performed to test the association between two nominal variables. Continuous variables were compared using the t-test or Welch t-test. The Mantel-Haenszel Chi-square test was used to test the correlation between two ordinal variables or between dichotomous and ordinal variables.

Logistic regression analyses and a Cox proportional hazards models were used to construct a well-calibrated and discriminative nomogram for predicting mortality as well as 30-day and 60-day survival probabilities. To validate the models, the total population was randomized

into the training and test sets at a ratio of 7:3. The balance between the sets was checked using through the chi-square test, and no significant differences were observed in all variables.

To construct the logistic regression model, we obtained crude odds ratios (ORs) via univariate logistic regression analysis of the trained set. We constructed a multivariate logistic model by including variables with *P* values < 0.02 in the univariate analysis and those with the lowest Akaike information criterion using the backward stepwise approach. Finally, we obtained the final prediction model after extracting insignificant variables. The validation of the logistic regression model was confirmed by the calibration curve and area under the curve (AUC) in the test set. The same approach was used for the construction of a Cox proportional hazards model. The validation of the Cox proportional hazards model was confirmed using Harrell's C-index, time dependent AUCs, and calibration curves. The constructed models can be used on the web-based risk calculator (https://koreastat.shinyapps.io/RiskofCOVID19/).

Overall, statistical analyses were performed using the R programming language and environment version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). *P* values < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

The present study included 5,626 confirmed COVID-19 cases. Table 1 describes the baseline characteristics of the study population: 2,319 (41.22%) patients were male; 15.45% patients were older than 70 years, and 33.47% patients had at least one underlying disease. With respect to underlying diseases, the prevalence of hypertension was the highest (21.35%), followed by that of DM (12.28%) and dementia (3.98%). The mortality rate of COVID-19 was 4.27% in this study.

Symptoms at the time of COVID-19 diagnosis

The most common symptom of COVID-19 was cough in all age groups, followed by sputum except in the 0–9 years age group (Supplementary Table 1). Fever and dyspnea were more common in elderly people, especially those older than 70 years.

Severity of COVID-19 according to underlying diseases

The prevalence of severe COVID-19 was the highest in patients with dementia (33.93%), followed by those with heart failure (33.90%) and chronic kidney disease (32.73%) (Supplementary Table 2). Similar to the prevalence of severe COVID-19, COVID-19-related mortality was the highest in patients with dementia (33.48%) (Supplementary Table 3).

Severity of COVID-19 according to age and sex

There was linear correlation between age and COVID-19 severity (Supplementary Table 4). The prevalence of severe COVID-19 was the highest in elderly people, especially those aged over 70 years.

Prevalence of underlying diseases according to age groups

The prevalence of some underlying diseases, such as hypertension, dementia, and cancer, was the highest in individuals older than 70 years (Supplementary Table 5), whereas that of rheumatoid or autoimmune diseases was the highest in patients aged 50-59 years.

Factors associated with COVID-19-related mortality

To identify potential factors that could predict COVID-19-related mortality, univariate and multivariate logistic regression analyses were performed, as indicated in Table 2. The following factors showed significant associations with COVID-19-related mortality: age ≥70 years; male; the presence of fever and dyspnea at the time of diagnosis; and underlying diseases such as DM, cancer, and dementia. The same predictive factors were identified in the final Cox proportional hazard model for 30-day and 60-day survival in patients with COVID-19 (Table 3).

Construction of a nomogram for predicting mortality in patients with COVID-19

To identify high-risk patients, we constructed a predictive nomogram for mortality due to COVID-19 (Figure 1). Points were assigned to patients based on age, sex, presence of specific symptoms including fever and dyspnea at the time of diagnosis of COVID-19, and the presence of specific underlying diseases (DM, cancer, and dementia), with a vertical line to the “Points” scale at the top of the nomogram (Figure 1A). The actual and predicted mortalities due to COVID-19 were similar, and the calibration plot showed a mean absolute error of 0.006 (Figure 1B), suggesting that the model was acceptable. Figure 1C shows that the under the receiver operating curve (ROC) for COVID-19-related mortality was 0.926.

Construction of a nomogram to predict the 30-day and 60-day survival probabilities in

patients with COVID-19

We constructed a predictive nomogram for 30-day and 60-day survival in patients with COVID-19 (Figure 2A), including the same prognostic factors as those used in the model for COVID-19-related mortality. The nomogram demonstrated good accuracy for predicting 30-day and 60-day survival probabilities in patients with COVID-19 with a C-index of 0.906 (95% confidence interval, 0.883-0.929). Calibration curves indicated that there was no apparent shift from the perfect fit, with a good correlation between the predicted and observed values in the study population (Figures 2B and 2C). The AUCs for 30-day and 60-day survival probability in patients with COVID-19 were 0.914 and 0.954, respectively (Figures 2D and 2E).

Discussion

Principal Results

Even after a year of post the emergence of COVID-19, severe cases of COVID-19 have caused socioeconomic and medical problems due to high mortality, especially in the limited medical resources. Therefore, prediction of mortality early in the clinical course is essential in COVID-19 patients to stratify patients requiring intensive monitoring and aggressive therapy, thereby improving clinical outcomes. In the present study, we identified the predictive factors of COVID-19-related mortality using a nomogram that was validated using calibration plots and ROC curves. The prognostic factors included age ≥70 years; male sex; presence of fever and dyspnea at the time of COVID-19 diagnosis; and DM, cancer, and dementia as underlying diseases; these factors can be easily evaluated in the early phase of diagnosis without any additional tests. In addition, we investigated the factors associated with 30-day and 60-day survival in patients with COVID-19; the same prognostic factors were identified. Our findings can help guide policy makers on medical resource allocation in the uncontrolled COVID-19 epidemic era, thereby, improving public health outcomes. Our results would be more useful even in medium- or low- income countries with limited resources for diagnostic purposes.

Comparison with Prior Work

Although various scoring systems can predict COVID-19-related mortality, we used a nomogram with calibration and discrimination for validation in this study, thereby enabling individualized and evidence-based risk estimation. Previous studies have suggested nomograms for predicting the risk of severe COVID-19 and COVID-19-related mortality using diverse laboratory findings, clinical features, and chest computed tomography (CT) findings [10-14, 16, 17]. In the present study, we considered age, sex, body mass index,

symptoms at the time of COVID-19 diagnosis, and underlying diseases for the prediction model as these parameters can be obtained in the early clinical course. This can be very helpful for identifying patients at risk of mortality at the time of COVID-19 diagnosis. In addition, the AUC for the prediction for COVID-19-related mortality in the present study was the highest compared to those in other previous studies, except for one that included chest CT findings as a predictive factor for severe COVID-19 (Supplementary Table 6). Significant laboratory markers, such as C-reactive protein, could be helpful for predicting the clinical course and outcomes of COVID-19 by reflecting the degree of inflammation [14]. However, we did not include laboratory findings or imaging results as a limited number of patients underwent laboratory and imaging examinations in our study. Thus, our prediction model can be easily applied to predict the mortality of COVID-19 even in low- and middle-income countries.

Older age is known as a risk factor of COVID-19-related mortality, although the cut-off differs according to study populations [5, 6, 18-20]. Older age was identified to be a risk factor of a severe clinical course in other infections, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [21, 22]. Similarly, in COVID-19, age was an independent prognostic factor for mortality and 30-day and 60-day survival. The older age can affect the clinical course of COVID-19 and COVID-19-related mortality, possibly through immunosenescence or a high prevalence of multiple underlying diseases.

Studies on the association of underlying disease with the severity and mortality of COVID-19 included various combinations of diseases, and therefore, these studies reported different results [3]. Nevertheless, several underlying diseases, such as cancer, hypertension, and cardiovascular diseases, act as risk factors for severe COVID-19 or COVID-19-related mortality [2, 23]. In COVID-19 patients with cancer, systemic immunosuppression associated

with the cancer itself or anticancer therapy might affect the vulnerability to severe COVID-19 or COVID-19-related mortality, which is consistent with our findings. Diabetes, known to be a hazardous comorbidity in fatal COVID-19 cases, was also associated with COVID-19-related mortality in the present study. Although the reasons underlying this association have not been identified [2], persistent chronic inflammation in diabetes combined with poor control of blood glucose levels during the COVID-19 illness and combined comorbidities of diabetes in itself can affect the prognosis of COVID-19 in patients with diabetes [24]. Some studies showed that patients with dementia, especially those living in care facilities, had an increased risk of COVID-19 and COVID-19-related mortality, consistent with our findings [25]. Living in care facilities favors the rapid spread of COVID-19 due to the increased likelihood of exposure to the virus in a closed environment, and furthermore, patients with dementia tend to have other underlying comorbidities. A meta-analysis of the association of underlying conditions with COVID-19-related mortality showed that previous studies on this topic included a limited number of underlying diseases and had limited sample sizes [2]. In contrast, the present study included diverse underlying disease and used a nationwide registry of COVID-19 patients.

Limitations

There are some limitations to our study. The sample size was considered to be limited because the study population was enrolled in the early period of the pandemic. However, previous studies on the prediction of COVID-19-related mortality/severity included smaller samples than that in our study (Supplementary Table 6) [10-13, 17, 26-28]. Since the appropriate therapeutic strategies had not been established during the early epidemic of COVID-19, the mortality in the present study was less affected by medications, including anti-viral agents, that can affect the clinical course of COVID-19. The present study included

patients from a care hospital where patients with dementia were hospitalized. The prevalence of dementia differs across study populations. One study reported a 7.5% prevalence [3], while some studies did not included dementia as one of the comorbidities of COVID-19 [2]. Since comorbidities are affected by herd infections in specific institutions, consideration of the specific situations on mass infection is needed while interpreting the results of related studies. Although we performed internal validation by classifying the total population into the training and test sets, external validation of the results is needed to confirm our results. Finally, the present study was performed retrospectively, and therefore, validation using a prospective design is required to improve the statistical power of the results.

Conclusion

Age ≥70 years, male sex, the presence of fever and dyspnea at the time of COVID-19 diagnosis, and DM, cancer, and dementia as underlying diseases are associated with an increased risk of COVID-19-related mortality, and these factors can be used for the prediction of 30-day and 60-day survival in COVID-19 patients. The results of the present study would be helpful in establishing therapeutic strategies for improving the clinical outcomes and guiding policy makers with regard to appropriate medical resource allocation.

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Conflict of Interest

All authors report no conflicts of interest relevant to this article.

Abbreviations

AUC: area under the curve
COPD: chronic obstructive pulmonary disease
COVID-19: coronavirus disease 2019
DM: diabetes mellitus
ECMO: extracorporeal membrane oxygenation
MERS: Middle East respiratory syndrome
SARS: severe acute respiratory syndrome

Author contributions

Concept: H.J.M., K.H.K., E.L., H.J.Y.

Designing of the protocol: H.J.M., K.H.K., E.L., H.J.Y.

Literature search: H.J.M., K.H.K., B.R.L., E.K.K., H.J.Y., E.L.

Study selection: H.J.M., K.H.K., B.R.L., E.K.K., H.J.Y., E.L.

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Data management: H.J.M., K.H.K., B.R.L., E.L., H.J.Y.

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Abbreviations

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-42. PMID: 32091533. doi: 10.1001/jama.2020.2648.
2. Javanmardi F, Keshavarzi A, Akbari A, Emami A, Pirbonyeh N. Prevalence of underlying diseases in died cases of COVID-19: A systematic review and meta-analysis. PLoS One. 2020;15(10):e0241265. PMID: 33095835. doi: 10.1371/journal.pone.0241265.
3. Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. Lancet Respir Med. 2020 Dec 17. PMID: 33341155. doi: 10.1016/S2213-2600(20)30527-0.
4. O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature. 2020 Nov 2. PMID: 33137809. doi: 10.1038/s41586-020-2918-0.
5. Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A, Torralbo A, Shallcross L, et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. Lancet. 2020 May 30;395(10238):1715-25. PMID: 32405103. doi: 10.1016/S0140-6736(20)30854-0.
6. Mohamed MO, Gale CP, Kontopantelis E, Doran T, de Belder M, Asaria M, et al. Sex Differences in Mortality Rates and Underlying Conditions for COVID-19 Deaths in England and Wales. Mayo Clin Proc. 2020 Oct;95(10):2110-24. PMID: 33012342. doi: 10.1016/j.mayocp.2020.07.009.
7. Omori R, Matsuyama R, Nakata Y. The age distribution of mortality from novel coronavirus disease (COVID-19) suggests no large difference of susceptibility by age. Sci Rep. 2020 Oct 6;10(1):16642. PMID: 33024235. doi: 10.1038/s41598-020-73777-8.
8. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-81. doi: 10.1001/jama.2020.5394.
9. De Larochelambert Q, Marc A, Antero J, Le Bourg E, Toussaint JF. Covid-19 Mortality: A Matter of Vulnerability Among Nations Facing Limited Margins of Adaptation. Front Public Health. 2020;8:604339. PMID: 33330343. doi: 10.3389/fpubh.2020.604339.
10. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020 May 20;18(1):206. PMID: 32434518. doi: 10.1186/s12967-020-02374-0.
11. Wu G, Yang P, Xie Y, Woodruff HC, Rao X, Guiot J, et al. Development of a clinical decision support system for severity risk prediction and triage of COVID-19 patients at hospital admission: an international multicentre study. Eur Respir J. 2020 Aug;56(2). PMID: 32616597. doi: 10.1183/13993003.01104-2020.
12. Liu YP, Li GM, He J, Liu Y, Li M, Zhang R, et al. Combined use of the neutrophil-to-lymphocyte ratio and CRP to predict 7-day disease severity in 84 hospitalized patients with COVID-19 pneumonia: a retrospective cohort study. Ann Transl Med. 2020 May;8(10):635. PMID: 32566572. doi: 10.21037/atm-20-2372.
13. Yu Y, Wang X, Li M, Gu L, Xie Z, Gu W, et al. Nomogram to identify severe coronavirus disease 2019 (COVID-19) based on initial clinical and CT characteristics: a multi-center study. BMC Med Imaging. 2020 Oct 2;20(1):111. PMID: 33008329. doi: 10.1186/s12880-020-00513-z.
14. Weng Z, Chen Q, Li S, Li H, Zhang Q, Lu S, et al. ANDC: an early warning score to

predict mortality risk for patients with Coronavirus Disease 2019. J Transl Med. 2020 Aug 31;18(1):328. PMID: 32867787. doi: 10.1186/s12967-020-02505-7.
15. Lee SW, Yang JM, Moon SY, Yoo IK, Ha EK, Kim SY, et al. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. Lancet Psychiatry. 2020 Dec;7(12):1025-31. PMID: 32950066. doi: 10.1016/S2215-0366(20)30421-1.
16. Pan D, Cheng D, Cao Y, Hu C, Zou F, Yu W, et al. A Predicting Nomogram for Mortality in Patients With COVID-19. Front Public Health. 2020;8:461. PMID: 32850612. doi: 10.3389/fpubh.2020.00461.
17. Zhou Y, He Y, Yang H, Yu H, Wang T, Chen Z, et al. Development and validation a nomogram for predicting the risk of severe COVID-19: A multi-center study in Sichuan, China. PLoS One. 2020;15(5):e0233328. PMID: 32421703. doi: 10.1371/journal.pone.0233328.
18. Yanez ND, Weiss NS, Romand JA, Treggiari MM. COVID-19 mortality risk for older men and women. BMC Public Health. 2020 Nov 19;20(1):1742. PMID: 33213391. doi: 10.1186/s12889-020-09826-8.
19. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. J Infect Dev Ctries. 2020 Feb 29;14(2):125-8. PMID: 32146445. doi: 10.3855/jidc.12600.
20. Perez-Saez J, Lauer SA, Kaiser L, Regard S, Delaporte E, Guessous I, et al. Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva, Switzerland. Lancet Infect Dis. 2020 Jul 14. PMID: 32679085. doi: 10.1016/S1473-3099(20)30584-3.
21. Chan JC, Tsui EL, Wong VC, Hospital Authority SCG. Prognostication in severe acute respiratory syndrome: a retrospective time-course analysis of 1312 laboratory-confirmed patients in Hong Kong. Respirology. 2007 Jul;12(4):531-42. PMID: 17587420. doi: 10.1111/j.1440-1843.2007.01102.x.
22. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis. 2013 Sep;13(9):752-61. PMID: 23891402. doi: 10.1016/S1473-3099(13)70204-4.
23. Liu C, Li L, Song K, Zhan ZY, Yao Y, Gong H, et al. A nomogram for predicting mortality in patients with COVID-19 and solid tumors: a multicenter retrospective cohort study. J Immunother Cancer. 2020 Sep;8(2). PMID: 32895296. doi: 10.1136/jitc-2020-001314.
24. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010 Sep;47(3):193-9. PMID: 19333547. doi: 10.1007/s00592-009-0109-4.
25. Matias-Guiu JA, Pytel V, Matias-Guiu J. Death Rate Due to COVID-19 in Alzheimer's Disease and Frontotemporal Dementia. J Alzheimers Dis. 2020;78(2):537-41. PMID: 33074240. doi: 10.3233/JAD-200940.
26. Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis. 2020 Jul 28;71(15):833-40. PMID: 32296824. doi: 10.1093/cid/ciaa443.
27. Zeng F, Deng G, Cui Y, Zhang Y, Dai M, Chen L, et al. A predictive model for the severity of COVID-19 in elderly patients. Aging (Albany NY). 2020 Nov 10;12(21):20982-96. PMID: 33170150. doi: 10.18632/aging.103980.
28. Cao G, Li P, Chen Y, Fang K, Chen B, Wang S, et al. A Risk Prediction Model for Evaluating the Disease Progression of COVID-19 Pneumonia. Front Med (Lausanne).

2020;7:556886. PMID: 33251226. doi: 10.3389/fmed.2020.556886.

Table 1. Baseline characteristics of the study population

Variable	n (%)
Age, years	
0–9	66 (1.17%)
10–19	206 (3.66%)
20–29	1,119 (19.89%)
30–39	564 (10.02%)
40–49	742 (13.19%)
50–59	1146 (20.37%)
60–69	914 (16.25%)
≥ 70	869 (15.45%)
Total	5626 (100.00%)
Sex, male	2319 (41.22%)
Body mass index, kg/m^2	n = 4,426
<18.5	260 (5.87%)
18.5–22.9	1,867 (42.18%)
23.0–24.9	1,039 (23.47%)
25.0–29.9	1,052 (23.77%)
≥ 30	208 (4.70%)
Duration between COVID-19 diagnosis and death, days, mean ± SD	15.31 ± 13.34
Symptoms at the time of admission[†]	
Fever, body temperature≥37.5°C	1,305 (23.2%)
Cough	2,341 (41.63%)
Sputum	1,619 (28.79%)
Sore throat	881 (15.66%)
Rhinorrhea	621 (11.04%)
Myalgia	926 (16.46%)
Fatigue	234 (4.16%)
Dyspnea	666 (11.84%)
Headache	967 (17.19%)
Altered consciousness	35 (0.62%)
Vomiting or nausea	244 (4.34%)
Diarrhea	518 (9.21%)
Body temperature at the time of admission, °C	n =5,586
≤ 37	3,461 (61.96%)
37.1–37.5	1,453 (26.01%)
37.6–37.9	390 (6.98%)
≥ 38	282 (5.05%)
Severity	**n = 5,599**
No interference with daily life	4,455 (79.57%)

Interference with daily life but no need for oxygen therapy	330 (5.89%)
Use of a nasal cannula or oxygen mask	512 (9.14%)
Non-invasive ventilator care	33 (0.59%)
Invasive ventilator care	19 (0.34%)
Multi-organ failure/ECMO	11 (0.2%)
Death	239 (4.27%)
Underlying diseases[†]	
None	3,743 (66.53%)
DM	691 (12.28%)
Hypertension	1,201 (21.35%)
Heart failure	59 (1.05%)
Cardiovascular disease	179 (3.18%)
Asthma	128 (2.28%)
COPD	40 (0.71%)
Chronic kidney diseases	55 (0.98%)
Cancer	144 (2.56%)
Chronic liver disease	83 (1.48%)
Rheumatoid/autoimmune diseases	38 (0.68%)
Dementia	224 (3.98%)

COPD, Chronic obstructive pulmonary disease; DM, Diabetes mellitus; ECMO, Extracorporeal membrane oxygenation; SD, Standard deviation.
[†]Multiple responses

Table 2. Odds ratios for factors associated with COVID-19-related mortality

Variables	n = 4,426	Training set (n=3,098)	Test set (n=1,328)	*P* value	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age, years				0.388				
< 70	3,838 (86.71%)	2,677	1,161		1		1	
≥ 70	588 (13.29%)	421	167		39.90 (22.28-71.46)	<0.001	16.56 (8.65-31.74)	<0.001
Sex				0.974				
Female	2,563 (57.91%)	1793	770		1		1	
Male	1,863 (42.09%)	1305	558		1.98 (1.29-3.06)	0.002	2.93 (1.70-5.06)	<0.001
Body mass index, kg/m^2				0.315				
18.5–22.9	1,867 (42.18%)	1,301	566		1			
23.0–24.9	1,039 (23.47%)	714	325		0.88 (0.48-1.61)	0.681		
25.0–29.9	1,052 (23.77%)	739	313		1.23 (0.72-2.12)	0.445		
≥30	208 (4.7%)	158	50		1.00 (0.35-2.86)	0.997		
<18.5	260 (5.87%)	186	74		2.42 (1.20-4.87)	0.014		
Symptoms at the time of COVID-19 diagnosis[†]								
Fever, temperature ≥ 37.5°C	1,047 (23.66%)	744	303	0.411	2.66 (1.73-4.09)	<0.001	2.63 (1.53-4.50)	<0.001
Cough	1,883 (42.54%)	1323	560	0.766	0.99 (0.64-1.53)	0.973		
Sputum	1,280	886	394	0.495	1.55 (1.00-2.40)	0.052		

	(28.92%)							
Sore throat	714 (16.13%)	496	218	0.771	0.25 (0.09-0.68)	0.007		
Rhinorrhea	494 (11.16%)	347	147	0.940	0.18 (0.04-0.74)	0.017		
Myalgia	683 (15.43%)	465	218	0.254	0.34 (0.14-0.84)	0.019		
Fatigue	216 (4.88%)	160	56	0.206	3.10 (1.65-5.82)	<0.001		
Dyspnea	499 (11.27%)	353	146	0.738	9.88 (6.38-15.30)	<0.001	8.47 (4.84-14.81)	<0.001
Headache	704 (15.91%)	492	212	0.981	0.38 (0.17-0.89)	0.025		
Altered consciousness	17 (0.38%)	11	6	0.832	13.41 (3.49-51.43)	<0.001		
Vomiting/nausea	191 (4.32%)	133	58	0.975	1.37 (0.55-3.45)	0.499		
Diarrhea	362 (8.18%)	251	111	0.822	0.69 (0.28-1.71)	0.417		
Underlying diseases[†]								
DM	506 (11.43%)	368	138	0.170	7.32 (4.73-11.32)	<0.001	3.23 (1.88-5.55)	<0.001
Hypertension	864 (19.52%)	615	249	0.420	6.46 (4.17-10.01)	<0.001		
Heart failure	40 (0.90%)	25	15	0.387	9.12 (3.34-24.89)	<0.001		
Cardiovascular disease	134 (3.03%)	92	42	0.804	5.86 (3.06-11.21)	<0.001		
Asthma	100 (2.26%)	66	34	0.440	3.64 (1.53-8.68)	0.003		
COPD	30 (0.68%)	21	9	1.000	8.49 (2.79-25.78)	<0.001		

Chronic kidney disease	44 (0.99%)	28	16	0.447	6.00 (2.04-17.68)	0.001		
Cancer	107 (2.42%)	71	36	0.468	5.49 (2.63-11.44)	<0.001	3.98 (1.45-10.97)	0.007
Chronic liver disease	59 (1.33%)	43	16	0.731	1.70 (0.41-7.16)	0.467		
Rheumatoid/autoimmune diseases	31 (0.70%)	25	6	0.271	1.45 (0.19-10.82)	0.719		
Dementia	121 (2.73%)	93	28	0.116	21.51 (12.88-35.91)	<0.001	8.37 (4.25-16.50)	<0.001

CI, confidence interval; COPD, Chronic obstructive pulmonary disease; DM, Diabetes mellitus; OR, odds ratio.
[†]Multiple responses

Table 3. Hazard ratios for factors associated with COVID-19-related mortality

Variables	HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age, years				
< 70	1		1	
≥ 70	32.15 (18.14-57.01)	<0.001	13.26 (7.11-24.73)	<0.001
Sex				
Female	1		1	
Male	1.61 (1.25-2.08)	<0.001	2.31 (1.46-3.63)	<0.001
Body mass index, kg/m^2				
18.5–22.9	1			
23.0–24.9	0.91 (0.50-1.65)	0.743		
25.0–29.9	1.20 (0.71-2.05)	0.500		
≥30	0.93 (0.33-2.63)	0.900		
<18.5	2.46 (1.24-4.87)	0.009		
Symptoms at the time of COVID-19 diagnosis[†]				
Fever, temperature ≥ 37.5°C	2.02 (1.56-2.63)	<0.001	1.96 (1.27-3.02)	0.002
Cough	0.67 (0.51-0.87)	0.003		
Sputum	1.01 (0.77-1.34)	0.918		
Sore throat	0.31 (0.17-0.53)	<0.001		
Rhinorrhea	0.20 (0.09-0.45)	<0.001		
Myalgia	0.46 (0.29-0.72)	0.001		
Fatigue	1.70 (1.04-2.79)	0.034		
Dyspnea	6.47 (5.02-8.34)	<0.001	4.87 (3.14-7.53)	<0.001
Headache	0.27 (0.15-0.47)	<0.001		
Altered consciousness	22.44 (14.56-34.6)	<0.001		
Vomiting/nausea	1.41 (0.85-2.34)	0.189		
Diarrhea	0.77 (0.47-1.24)	0.275		
Underlying diseases[†]				
DM	4.66 (3.60-6.04)	<0.001	2.00 (1.10-4.69)	0.002
Hypertension	5.33 (4.11-6.92)	<0.001		
Heart failure	8.00 (4.94-12.94)	<0.001		
Cardiovascular disease	3.49 (2.32-5.25)	<0.00		

Asthma	2.33 (1.33-4.09)	1 0.003		
COPD	4.40 (2.17-8.91)	<0.001		
Chronic kidney disease	7.04 (4.22-11.72)	<0.001		
Cancer	3.50 (2.23-5.48)	<0.001	2.27 (1.10-4.69)	0.027
Chronic liver disease	1.92 (0.91-4.08)	0.088		
Rheumatoid/autoimmune disease	1.86 (0.60-5.82)	0.285		
Dementia	11.66 (8.87-15.34)	<0.001	4.45 (2.69-7.36)	<0.001

COPD, Chronic obstructive pulmonary disease; DM, Diabetes mellitus.
[†]Multiple response

Fig. 1. Prediction of mortality in COVID-19 patients. (A) Nomogram for predicting mortality in patients with COVID-19. (B) Calibration plot of the actual and predicted probabilities in the training set. (C) The area under the curve (AUC) of the nomogram was 0.926 (95% CI, 0.8906-0.9616).

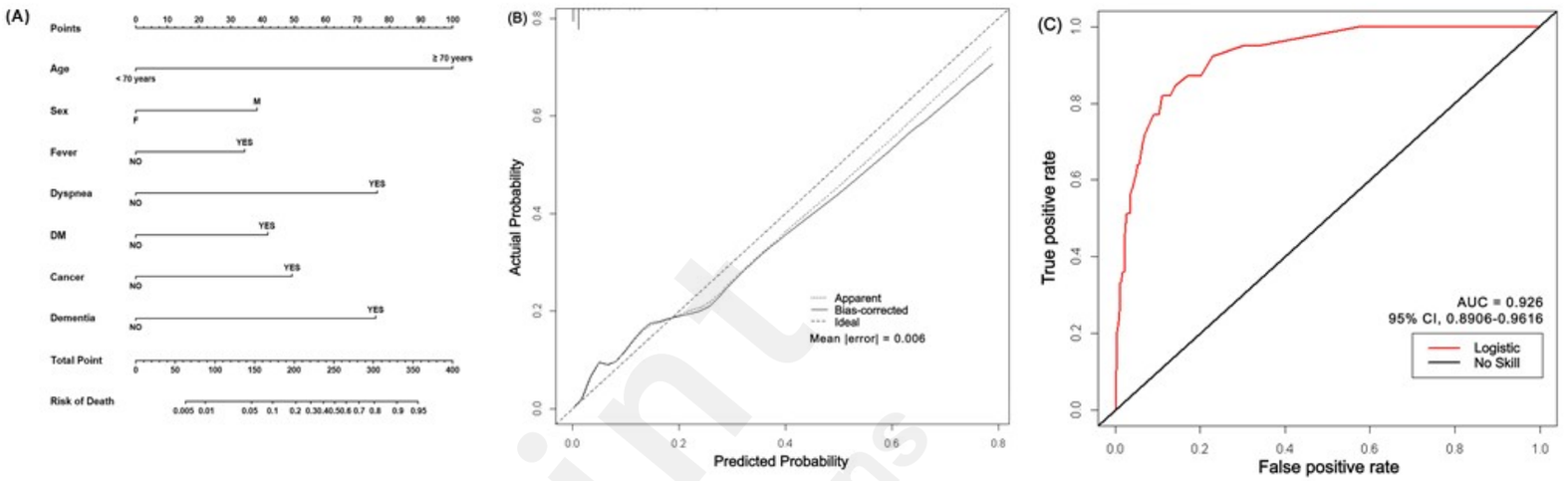
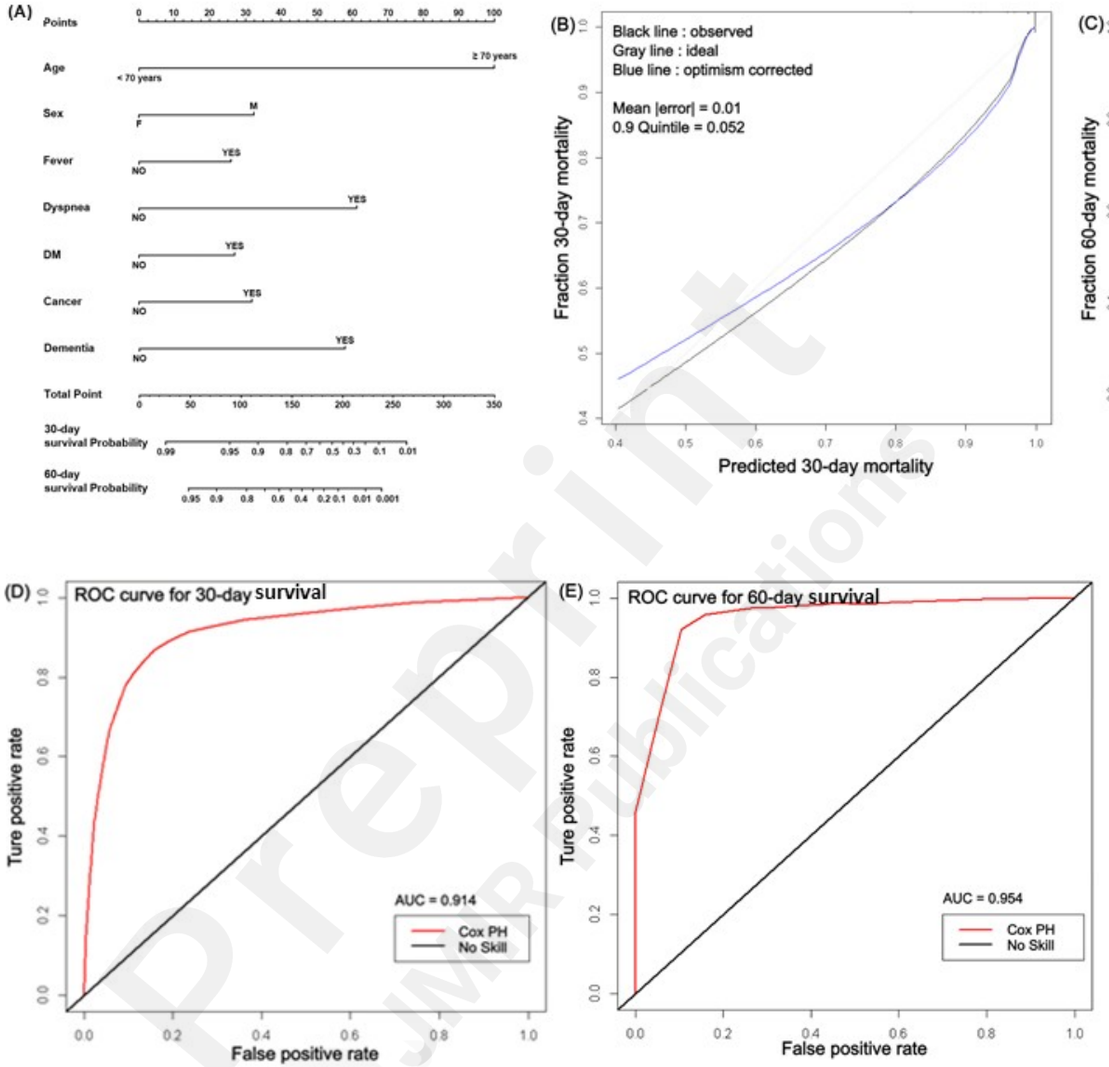


Fig. 2. Prediction of the 30-day and 60-day survival probabilities in COVID-19 patients. (A) and (B) Nomogram predicting the 30-day and 60-day survival probabilities in patients with COVID-19. Calibration plot of the actual and predicted probabilities for 30-day and 60-day survival. (C) survival in patients with COVID-19 in the training set. The area under the curve (AUCs) of the nomogram for predicting 30-day survival (D) and 60-day survival (E) were 0.914 and 0.954, respectively.


(A)
Points
Age
≥ 70 years
< 70 years
Sex
M
F
Fever
Dyspnea
DM
Cancer
Dementia
YES
NO
Total Point
30-day survival Probability
60-day survival Probability
(B)
Black line : observed
Gray line : ideal
Blue line : optimism corrected
Mean |error| = 0.01
0.9 Quintile = 0.052
Fraction 30-day mortality
Predicted 30-day mortality
(C)
Black line : observed
Gray line : ideal
Blue line : optimism corrected
Mean |error| = 0.013
0.9 Quantile = 0.039
Fraction 60-day mortality
Predicted 60-day mortality
(D)
ROC curve for 30-day survival
Ture positive rate
False positive rate
AUC = 0.914
Cox PH
No Skill
(E)
ROC curve for 60-day survival
Ture positive rate
False positive rate
AUC = 0.954
Cox PH
No Skill

Supplementary Files

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