Nomogram for Prediction of fatal outcome in Patients with Severe COVID-19 Pneumonia: A Multicenter Study

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Research

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Abstract

Background & Aims: To develop an effective model of predicting fatal outcome in the severe coronavirus disease 2019 (COVID-19) patients.

Methods: Between February 20, 2020 and April 4, 2020, consecutive COVID-19 patients from three designated hospitals were enrolled in this study. Independent high-risk factors associated with death were analyzed using Cox proportional hazard model. A prognostic nomogram was constructed to predict the survival of severe COVID-19 patients.

Results: There were 124 severe patients in the training cohort, and there were 71 and 76 severe patients in the two independent validation cohorts, respectively. Multivariate Cox analysis indicated that age ≥ 70 years (HR 1.184, 95% CI 1.061-1.321), Panting (breathing rate ≥ 30/min) (HR 3.300, 95% CI 2.509-6.286), lymphocyte count < 1.0 × 10^9/L (HR 2.283, 95% CI 1.779-3.267), and IL-6 >10pg/mL (HR 3.029, 95% CI 1.567-7.116) were independent high-risk factors associated with fatal outcome. We developed the nomogram for identifying survival of severe COVID-19 patients in the training cohort (AUC 0.900, [95% CI 0.841-0.960], sensitivity 95.5%, specificity 77.5%); in validation cohort 1 (AUC 0.862, [95% CI 0.763-0.961], sensitivity 92.9%, specificity 64.5%); in validation cohort 2 (AUC 0.811, [95% CI 0.698-0.924], sensitivity 77.3%, specificity 73.5%). The calibration curve for probability of death indicated a good consistence between prediction by the nomogram and the actual observation.

Conclusions: This nomogram could help clinicians to identify severe patients who have high risk of death, and to develop more appropriate treatment strategies to reduce the mortality of severe patients.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a newly pneumonia that has spread rapidly throughout the world [1]. Because of rapid transmission spread of COVID-19, the number of new cases and death is increasing. COVID-19 has become a major public health crisis [1].

Previous studies have indicated that in all COVID-19 patients, the incidence of severe cases is about 15% [2, 3]. The mortality rate of severe COVID-19 patients is reported variously from 8–61.5% and significantly increases among the old patients [4–9]. Early medical intervention is very important to reduce the mortality of severe patients. Thus, it is of great significance to screen out severe patients with high risk of death promptly and accurately at the initial admission [10]. However, this is particularly difficult because of limited medical resources and staff and the large number of patients. Therefore, elucidating the independent risk factors and establishing an accurate model for predicting severe COVID-19 patients at high risk of death is necessary. This study aimed to provide a model to help clinicians identify patients with severe COVID-19 at high risk of death, which may be beneficial for decision making of treatment strategies.
Patients And Methods

Study population

Between February 20, 2020 and April 4, 2020, consecutive confirmed COVID-19 patients were assessed to enter into this study from three designated hospitals of COVID-19: the Guanggu Branch of the Women and Children's Hospital of Hubei Province, Tongji TaiKang Hospital and Huoshen Mountain Hospital. The diagnosis of COVID-19 was based on the WHO interim guidance and guidelines for diagnosis and treatment of novel coronavirus pneumonia (5th version) released by National Health Commission of China [11, 12]. The presence of SARS-CoV-2 in respiratory specimens was confirmed by a positive result of real-time reverse transcriptase-polymerase-chain-reaction assay from nasal or pharyngeal swab specimens. Severe COVID-19 group was defined if meeting at least one of the following criteria: (1) Shortness of breath, breathing rate ≥ 30/min, (2) Arterial oxygen saturation (SaO₂, Resting status) ≤ 93%, or (3) the ratio of partial pressure of arterial oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) ≤ 300 mmHg.

During the study period, a total of 2541 patients were enrolled into this study, 271 severe cases were further analyzed. The selection of the study population was shown in Supplemental Figure. 1. The study was approved by the Ethics Committee of all centers. Written informed consent was waived by the Ethics Commission of each hospital for emerging infections.

Data Collection

All patients received chest CT and serological examinations at admission. Laboratory tests included routine blood tests, liver function, renal function, coagulation profile, C-reactive protein(CRP), procalcitonin (PCT), IL-6, and arterial blood gas. The SaO₂ was measured using pulse oxygen saturation in room air at resting status. Comorbidity was defined as having at least one of the followings: hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic lung disease, and malignant tumor for at least 6 months. All data were confirmed independently by at least two researchers.

Statistical analysis

Continuous variables were expressed as mean (SD). Categorical variables were expressed as frequency (percentage). Categorical variables were compared by the χ² test or Fisher’s exact test. Continuous variables were compared by the student’s t test or Mann–Whitney U test. Survival curves were analyzed using the Kaplan-Meier method. Differences between curves were assessed using the log-rank test.

Univariate and multivariate COX proportional regression analysis was used for investigating the independent risk factors of death. The independent risk factors associated with the risk of mortality of patients with severe COVID-19 were used to build the nomogram in the training cohort. The performance and accuracy of the established nomogram was assessed by receiver operating characteristic (ROC)
curve and calibration with 1000 bootstrap samples. The area under ROC (AUC) and optimal cut-off values were determined. Decision curve analysis (DCA) based on the net benefit was depicted by the package of \textit{rmda} in R. The nomogram was validated in the validation cohorts 1 and 2, respectively. The nomogram was constructed and evaluated using the R software version 3.4.1 package with the \textit{rms} and \textit{hmisc}. All statistical analysis was performed using R version 3.4.1, a $p < 0.05$ in two-tailed was the significance threshold.

\section*{Results}

\subsection*{Patient clinical characteristics}

A total of 271 severe COVID-19 patients were enrolled after admission from three designated centers (Supplemental Figure. 1). Basic characteristics of the study cohorts are listed in Table 1. There were no significant differences in gender, comorbidity, lymphocyte count, platelet (PLT), D-dimer, PCT, and IL-6 between training cohort and test cohorts ($p > 0.05$). Additionally, the level of total bilirubin (TB), glutamic-pyruvic transaminase (ALT), glutamic oxaloacetic transaminase (AST), lactic dehydrogenase (LDH), $\gamma$-glutamyl transferase ($\gamma$-GT), and creatinine (Cre) was also similar between the training cohort and test cohorts ($p > 0.05$). The age, proportion of smoke and Panting (breathing rate $\geq$ 30/min), white blood cell (WBC) and neutrophil count, CRP, and SaO$_2$ at admission was significantly different between these three cohorts ($p < 0.05$). By the end of April 4, 2020, 22 severe COVID-19 patients died in the training group, and 22 and 14 patients died in the validation group 1 and validation group 2, respectively.

The baseline characteristics of patients in the training cohort were shown in Table 2. There were no significant differences in TB, ALT, AST, LDH, $\gamma$-GT, Cre, PLT, and the proportion of smoker between survivors and non-survivors ($p > 0.05$). Survivors were significantly younger than the non-survivors in the training cohort ($p < 0.05$), however, the proportion of patients with multiple comorbidity and panting (breathing rate $\geq$ 30/min) was significantly higher in non-survivors ($p < 0.05$). In addition, WBC and neutrophil count, CRP, D-dimer, PCT, and IL-6 was also significantly higher in non-survivors ($p < 0.05$). The lymphocyte count was significantly lower in non-survivors ($p < 0.05$).

\subsection*{Independent High-risk Factors Associated With The Fatal Outcome}

All variables listed in Table 1 were analyzed by univariate and multivariate Cox regression analysis. Multivariate Cox analysis indicated that age $\geq$ 70 years (HR 1.184, 95% CI 1.061–1.321), Panting (breathing rate $\geq$ 30/min) (HR 3.300, 95% CI 2.509–6.286), lymphocyte count $< 1.0 \times 10^9$/L (HR 2.283, 95% CI 1.779–3.267), and IL-6 $> 10$ pg/mL (HR 3.029, 95% CI 1.567–7.116) were independent risk factors associated with fatal outcomes (Table 3).

\subsection*{Survival Analysis in the Patients with High Level of IL-6}
Due to high level of IL-6 correlating with poor outcomes in severe COVID-19 patients, the therapeutic effect of tocilizumab in the patients with high IL-6 was further analyzed. In the training cohort, it was demonstrated that the prognosis of patients receiving tocilizumab was better than the that of patients not receiving tocilizumab, but without significance ($p = 0.105$) (Supplemental Figure. 2A). Similar results were also observed in the validation cohort 1 and validation cohort 2, respectively ($p = 0.133$, $p = 0.210$) (Supplemental Figure. 2B-C).

**Construction And Validation Of The Nomogram**

Four independent risk factors found to be associated with the risk of mortality of patients in the multivariate analyses were incorporated into the nomogram (Figure. 1). The ROC curve was employed to assess the predictive ability of the established nomogram, and the result demonstrated that the AUC was 0.900 (95% CI: 0.841–0.960) in the taring cohort, with a sensitivity of 95.5% and specificity of 77.5% (Figure. 2A). Moreover, the calibration curves for nomogram predicted mortality indicated that a good consistency between observed actual outcomes and predicted ones in the training cohort (Figure. 3A).

In the validation cohort 1, the AUC was 0.862 (95%CI: 0.763–0.961) for patients with a sensitivity of 92.9% and specificity of 64.5% (Figure. 2B). In the validation cohort 2, the AUC was 0.811 (95%CI: 0.698–0.924) for patients with a sensitivity of 77.3% and specificity of 73.5% (Figure. 2C). The calibration curves also showed good agreement between prediction and observation in the risk of mortality in the two validation cohorts (Figure. 3B-C).

**Clinical Application Of The Nomogram**

DCA based on the net benefit and threshold probabilities was performed to assess the clinical applicability of the risk prediction nomogram. The DCA showed that our risk prediction nomogram had a superior net benefit with a wide range of threshold probabilities in the training cohort and validation cohorts (Figure. 4A-C).

**Discussion**

Previous studies have shown that the mortality rate of severe COVID-19 patients was significantly higher than that of mild patients [6, 13]. Therefore, reduction of the mortality of severe patients is the pivotal in the case of the treatment. Our study revealed the clinic characteristics and risk factors for the fatal outcomes in confirmed severe COVID-19 patients based on multicenter cohorts. To our knowledge, this is the first study of developing a nomogram for estimation of risk of death of severe COVID-19 patients.

Multivariate Cox analysis in this study indicated that age, lymphopenia, respiratory rate $\geq 30$/min, and IL-6 was independent high-risk factors associated with poor prognosis. Older age has been proven to be a risk factor of survival in many previous studies [14–17]. The elderly patients with severe COVID-19 were
more likely to develop fatal outcomes because of rapidly progression of the disease, which reminded us of providing early intervention for elderly severe patients. Similarly, lymphopenia was more common in the non-survivors and severe cases according to the previous reports, suggesting dysregulation of immune response in patients with COVID-19 [18–20]. Nevertheless, most of these were only descriptive studies. A study clarified that lower lymphocyte was predictive of COVID-19 progression [21], whereas the impact of lymphocyte on the survival of severe COVID-19 was unclear. This study demonstrated that lymphocyte count < 1.0 × 10^9/L was independently associated with death in the severe cases.

Recent studies have found cytokine storm is an important factor leading to rapid disease progression and poor prognosis [22, 23]. IL-6 is one of the significant cytokines involved in cytokine storm [24, 25]. A previous univariate analysis showed that IL-6 level was associated with worse survival without significance [15]. Our study showed that high level of IL-6 was a predictor of death in severe COVID-19 patients. Additionally, the survival curve showed that the outcome was better in the patients with tocilizumab than that of patients without tocilizumab in the training cohort. Nonetheless, no significant difference was found. The similar results were also found in the validation cohort 1 and validation cohort 2, respectively. The reason for this result may be attributable to the small sample size. The effect of tocilizumab on survival of severe COVID-19 needs further investigations in larger cohorts.

Increasing respiratory rate is an important clinical feature of acute respiratory distress syndrome (ARDS), which is a major cause of death in severe COVID-19 patients [9, 14, 26]. A previous study has shown that respiratory rate ≥ 24/min was a risk factor of death in the univariate analysis [15], whereas no significance was found after the multivariate regression analysis. Our multivariate regression analysis clarified that respiratory rate ≥ 30/min was a predictor of death. For patients with increasing respiratory rates, especially those with respiratory rate ≥ 30/min, it was necessary for physicians to be aware of the potential progression of ARDS.

Many previous studies have shown that comorbidity was significantly associated with high mortality rate and disease progress [21, 27]. Nevertheless, in this study, the significance of comorbidity was only indicated in the univariate analysis, but not in the multivariate regression analysis, which may be ascribed to different patients enrolled in these studies. All the patients included in this study had severe COVID-19, the proportion of comorbidity was approximate 70%, which was significantly higher than those in other studies.

Our study has some limitations. First, this is a retrospective study, there may be potential biases in the selection of patients. Second, the sample of the study was relative small, the results need to be further validated in a larger cohort.

**Conclusion**

This study firstly developed a nomogram for predicting fatal outcomes in the severe COVID-19 patients. The four predictors included in the model are easy to obtain. The prediction risk of the model indicated a
good consistence with the observed one. Hence, this nomogram may be conducive to more effective treatment to reduce the mortality of those severe cases at high risk of death.

**Abbreviations**: COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; WBC, white blood cell; PLT, platelet; CRP, C-reactive protein; PCT: procalcitonin; IL-6, interleukin-6; SaO2, Oxygen saturation; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; γ-GT, γ-glutamyl transpeptidase; Cre, creatinine; HR, hazard ratio; 95% CI, 95% Confidence interval; ARDS, acute respiratory distress syndrome.

**Declarations**

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**Authors’ contributions**

Both Drs. Yun Yang, Xiaofei Zhu, Jian Huang, and Cui Chen designed this study. Drs. Yang Zheng, Wei He, Linghao Zhao, Qian Gao, Xuanxuan Huang, Lijuan Fu, Yu Zhang, and Yanqin Chang collected the data. Drs. Yun Yang and Jian Huang were responsible for the statistical analysis. Dr. Yun Yang wrote the draft. Drs. Xiaofei Zhu, Yanqin Chang, and Huojun Zhang revised this draft. Dr. Zhijie Lu finalized this manuscript. All the authors approved the final version of this manuscript.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of all the study centers. Written informed consent was waived by the Ethics Commission of each hospital for emerging infectious.

**Consent for publication**
No individual participant data is reported that would require consent to publish from the participant (or legal parent or guardian for children).

**Competing interests**

The authors declare that they have no competing interests

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**References**

1. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report-72. Published April 1st, 2020. Accessed April 1, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-covid-19.pdf?sfvrsn=3dd8971b_2.

2. Gong J, Ou J, Qiu X, et al. A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19): A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis 2020.

3. Wei-jie Guan Zheng-yi, Ni Yu. Hu, et al. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv 2020.02.06.20020974.

4. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020.

5. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.

7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.

8. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020.

9. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020.

10. Zhang G, Zhang J, Wang B, et al. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. Respir Res. 2020;21(1):74.
11. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. [Published January 28, 2020]. Accessed January 31, 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

12. National Health Commission (NHC) of the PRC and National Administration of Traditional Chinese Medicine of the PRC. Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management. Peoples Medical Publishing House. 2020.

13. Yang Y, Lu Q, Liu M, et al. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. medRxiv 2020: 2020.02.10.20021675.

14. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.

15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.

16. Team CC-R. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(12):343–6.

17. Li L, Zhang B, He B, et al. Critical patients with coronavirus disease 2019: Risk factors and outcome nomogram. J Infect 2020.

18. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 2020.

19. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020.

20. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020.

21. Ji D, Zhang D, Xu J, et al. Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score. Clin Infect Dis 2020.

22. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020.

23. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.

24. Zhang C, Wu Z, Li JW, et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020:105954.

25. Zhang S, Li L, Shen A, et al. Rational Use of Tocilizumab in the Treatment of Novel Coronavirus Pneumonia. Clin Drug Investig 2020.

26. Yang F, Shi S, Zhu J, et al. Analysis of 92 deceased patients with COVID-19. J Med Virol 2020.

27. Chen R, Liang W, Jiang M, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest 2020.
| Variables                        | Training Cohort (N=124) | Validation Cohort 1 (N=71) | Validation Cohort 2 (N=76) | P  |
|---------------------------------|-------------------------|-----------------------------|-----------------------------|----|
|                                 | N (%)                   | N (%)                       | N (%)                       |    |
| Age                             |                         |                             |                             | 0.001|
| ≥70 years                       | 73 (58.87)              | 25 (35.21)                  | 29 (38.16)                  |    |
| <70 years                       | 51 (41.13)              | 46 (64.79)                  | 47 (61.84)                  |    |
| Gender                          |                         |                             |                             | 0.810|
| Male                            | 69 (55.65)              | 42 (59.15)                  | 41 (53.95)                  |    |
| Comorbidity                     |                         |                             |                             | 0.291|
| Without comorbidity             | 31 (25.00)              | 27 (38.03)                  | 26 (34.21)                  |    |
| With single comorbidity         | 38 (30.65)              | 16 (22.54)                  | 21 (27.63)                  |    |
| With multiple comorbidity       | 55 (44.35)              | 28 (39.43)                  | 29 (38.16)                  |    |
| Smoke                           | 66 (53.23)              | 16 (22.54)                  | 19 (25.00)                  | <0.001|
| Panting (breathing rate ≥30/min)| 56 (45.16)              | 63 (88.73)                  | 67 (88.16)                  | <0.001|
| WBC                             |                         |                             |                             | 0.005|
| >10*10⁹/L                       | 24 (19.35)              | 29 (40.85)                  | 20 (26.32)                  |    |
| ≤10*10⁹/L                       | 100 (80.65)             | 42 (59.15)                  | 56 (73.68)                  |    |
| Lymphocyte                      |                         |                             |                             | 0.352|
| >1.0*10⁹/L                      | 56 (45.16)              | 28 (39.44)                  | 39 (51.32)                  |    |
| ≤1.0*10⁹/L                      | 68 (54.84)              | 43 (60.56)                  | 37 (48.68)                  |    |
| Neutrophil                      |                         |                             |                             | 0.013|
| >6.3*10⁹/L                      | 36 (29.03)              | 35 (49.30)                  | 24 (31.58)                  |    |
| ≤6.3*10⁹/L                      | 88 (70.97)              | 36 (50.70)                  | 52 (68.42)                  |    |
| PLT                             |                         |                             |                             | 0.346|
| ≥100*10⁹/L                      | 114 (91.94)             | 61 (85.92)                  | 70 (92.11)                  |    |
| <100*10⁹/L                      | 10 (8.06)               | 10 (14.08)                  | 6 (7.89)                    |    |
| Parameter    | Significance | >10mg/L | ≤10mg/L | >0.55mg/L | ≤0.55mg/L | >0.05ng/mL | ≤0.05ng/mL | >10pg/mL | ≤10pg/mL | ≥90%     | <90%     | ≥20umol/L | <20umol/L | ≥40U/L | <40U/L | ≥40U/L | <40U/L | ≥245U/L | <245U/L | y-GT     |
|--------------|--------------|---------|---------|-----------|-----------|------------|------------|----------|----------|-----------|----------|-----------|-----------|--------|--------|--------|--------|--------|--------|---------|
| CRP          | 0.026        | 70(56.45)| 36(50.70)| 28(36.84) |           |            |            |          |          |           |          |           |           |        |        |        |        |        |        |         |
| D-dimer      | 0.992        | 81(65.32)| 46(64.79)| 50(65.79) |           |            |            |          |          |           |          |           |           |        |        |        |        |        |        |         |
| PCT          | 0.312        | 87(70.16)| 57(80.28)| 56(73.68) |           |            |            |          |          |           |          |           |           |        |        |        |        |        |        |         |
| IL-6         | 0.298        | 68(54.84)| 47(66.20)| 44(57.89) |           |            |            |          |          |           |          |           |           |        |        |        |        |        |        |         |
| γ-GT         |              | 70(56.45)| 36(50.70)| 28(36.84) |           |            |            |          |          |           |          |           |           |        |        |        |        |        |        |         |
|                      | ≥50U/L | <50U/L | CRP |
|----------------------|--------|--------|-----|
| WBC                  | 64(51.61) | 28(39.44) | 36(47.37) |
| PLT                  | 60(48.39) | 43(60.56) | 40(52.63) |
| CRP                  | 41(33.06) | 29(40.85) | 21(27.63) |
| Death                | 83(66.94) | 42(59.15) | 55(72.37) |
| Death                | 0.303 |        |     |
| Death                | 22(17.74) | 22(30.99) | 14(18.42) |
| Death                | 102(82.26) | 49(69.01) | 62(81.58) |

Abbreviations: WBC, white blood cell; PLT, platelet; CRP, C-reactive protein; PCT: procalcitonin; IL-6, interleukin-6; SaO2, Oxygen saturation; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; γ-GT, γ-glutamyl transpeptadase; Cre, creatinine.
Table 2. Baseline characteristics of patients in the training cohort

| Variables                              | Death (N=22) | Discharge (N=102) | P    |
|----------------------------------------|-------------|------------------|------|
| N (%)                                  | N (%)       |                  |      |
| Age, years (Mean±SD)                   | 81.55±7.31  | 70.39±12.27      | <0.001|
| Gender                                 |             |                  |      |
| Male                                   | 14 (63.64)  | 55 (53.92)       | 0.407 |
| Comorbidity                            |             |                  | 0.005 |
| Without comorbidity                    | 1 (4.55)    | 30 (29.41)       |      |
| With single comorbidity                | 6 (27.27)   | 32 (31.37)       |      |
| With multiple comorbidity              | 15 (68.18)  | 40 (39.22)       |      |
| smoke                                  | 13 (59.09)  | 53 (51.96)       | 0.545 |
| Panting (breathing rate ≥30/min)       | 17 (77.27)  | 39 (38.24)       | 0.001 |
| WBC                                    |             |                  | 0.001 |
| >10*10⁹/L                              | 10 (45.45)  | 14 (13.73)       |      |
| ≤10*10⁹/L                              | 12 (54.55)  | 88 (86.27)       |      |
| Lymphocyte                             |             |                  | <0.001|
| >1.0*10⁹/L                             | 2 (9.09)    | 54 (52.94)       |      |
| ≤1.0*10⁹/L                             | 20 (90.91)  | 48 (47.06)       |      |
| Neutrophil                             |             |                  | 0.001 |
| >6.3*10⁹/L                             | 13 (59.09)  | 23 (22.55)       |      |
| ≤6.3*10⁹/L                             | 9 (40.91)   | 79 (77.45)       |      |
| PLT                                     |             |                  | 0.076 |
| ≥100*10⁹/L                             | 18 (81.82)  | 96 (94.12)       |      |
| Test   | Value Range | Upper Limit | Lower Limit |
|--------|-------------|-------------|-------------|
| <100*10^9/L | 4(18.18) | 6(5.82) | |
| CRP   | 0.008      | 18(81.82)   | 52(50.98)   |
| >10mg/L | 4(18.18) | 50(49.02) | |
| ≤10mg/L | 4(18.18) | 50(49.02) | |
| D-dimer | 0.006     | 20(90.91)   | 61(59.80)   |
| >0.55mg/L | 2(9.09) | 41(40.20) | |
| ≤0.55mg/L | 2(9.09) | 41(40.20) | |
| PCT   | 0.020      | 20(90.91)   | 67(65.68)   |
| >0.05ng/mL | 2(9.09) | 35(34.32) | |
| ≤0.05ng/mL | 2(9.09) | 35(34.32) | |
| IL-6  | <0.001     | 21(95.45)   | 47(46.08)   |
| ≥10pg/mL | 1(4.55) | 55(53.92) | |
| <10pg/mL | 1(4.55) | 55(53.92) | |
| SaO₂  | 0.294      | 13(59.09)   | 72(70.59)   |
| on admission | 9(40.91) | 30(29.41) | |
| ≥90%  | 10(45.45)  | 35(34.31)   | |
| <90%  | 12(54.55)  | 67(65.69)   | |
| TBIL  | 0.326      | 10(45.45)   | 35(34.31)   |
| ≥20umol/L | 12(54.55) | 67(65.69) | |
| <20umol/L | 12(54.55) | 67(65.69) | |
| ALT   | 0.147      | 9(40.91)    | 26(25.49)   |
| ≥40U/L | 13(59.09) | 76(74.51)  | |
| <40U/L | 13(59.09) | 76(74.51)  | |
| AST   | 0.213      | 10(45.45)   | 31(30.39)   |
| ≥40U/L | 10(45.45) | 31(30.39)  | |
| <40U/L | 12(54.55) | 71(69.61)  | |
| LDH   | 0.352      | 14(63.64)   | 75(73.53)   |
| ≥245U/L | 8(36.36) | 27(26.47)  | |
| <245U/L | 8(36.36) | 27(26.47)  | |
| Parameter | Value | P-value |
|-----------|-------|---------|
| γ-GT | 0.441 | |
| ≥ 50U/L | 13(59.09) | 51(50.00) |
| <50U/L | 9(40.91) | 51(50.00) |
| Cre | 0.718 | |
| >80umol/L | 8(36.36) | 33(32.35) |
| ≤80umol/L | 14(63.64) | 69(67.65) |

Abbreviations: WBC, white blood cell; PLT, platelet; CRP, C-reactive protein; PCT: procalcitonin; IL-6, interleukin-6; SaO2, Oxygen saturation; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; γ-GT, γ-glutamyl transpeptadase; Cre, creatinine.
Table 3. Univariate and Multivariate COX Proportional Hazards Regression Analysis of death in the Training Cohort

| Variable                          | Univariate          | Multivariate         |
|----------------------------------|---------------------|----------------------|
|                                  | HR (95% CI)         | P                    | HR (95% CI)         | P        |
| Age(≥ 70 vs <70)                 | 9.245(2.054-11.624) | 0.004                | 1.184(1.061-1.321)  | 0.003    |
| Gender (Male vs Female)          | 1.495(0.677-2.874)  | 0.407                | -                    | -        |
| Comorbidity                      | -                   | -                    | -                    | -        |
| Without comorbidity              | 1                   | 1                    | 1                    | 1        |
| With single comorbidity          | 3.625(0.639-4.503)  | 0.120                | 1.810(0.794-2.585)   | 0.551    |
| With multiple comorbidity        | 2.250(1.407-4.947)  | 0.022                | 1.155(0.831-3.130)   | 0.479    |
| Smoke (Yes vs No)                | 1.309(0.533-3.212)  | 0.556                | -                    | -        |
| Panting (breathing rate ≥30/min) | 5.492(2.876-7.078)  | 0.002                | 3.300(2.509-6.286)   | 0.004    |
| WBC(>10*10^9/L vs ≤10*10^9/L)    | 5.238(1.906-9.397)  | 0.001                | 2.046(0.726-4.503)   | 0.524    |
| Lymphocyte(<1.0*10^9/L vs ≥1.0*10^9/L) | 5.263(2.513-9.615) | 0.002                | 2.283(1.779-3.267)   | 0.011    |
| Neutrophil(>6.3*10^9/L vs ≤6.3*10^9/L) | 4.961(1.884-8.068) | 0.001                | 2.439(0.717-3.768)   | 0.392    |
| PLT(≥100*10^9/L vs <100*10^9/L)  | 3.556(0.911-6.876)  | 0.068                | -                    | -        |
| CRP(>10mg/L vs ≤10mg/L)          | 4.327(1.369-7.677)  | 0.013                | 1.214(0.721-2.211)   | 0.196    |
| D-dimer(>0.55mg/L vs ≤0.55mg/L)  | 6.721(1.490-9.319)  | 0.013                | 1.395(0.668-3.268)   | 0.195    |
| PCT(>0.05ng/mL vs ≤0.05ng/mL)    | 3.224(1.154-6.645)  | 0.032                | 2.255(0.768-4.767)   | 0.118    |
| IL-6(>10pg/mL)                   | 4.547(3.184-       | 0.002                | 3.029(1.567-         | 0.009    |
| vs ≤10pg/mL | 8.659) | 7.116) |
|-------------|--------|--------|
| SaO₂ on admission (≥90% vs <90%) | 1.662(0.739-2.007) | 0.180 | - | - |
| TBIL (≥20umol/L vs <20umol/L) | 1.595(0.627-2.057) | 0.327 | - | - |
| ALT (≥40U/L vs <40U/L) | 2.024(0.775-5.283) | 0.150 | - | - |
| AST (≥40U/L vs <40U/L) | 1.909(0.746-4.883) | 0.177 | - | - |
| LDH (≥245U/L vs <245U/L) | 1.923(0.739-5.007) | 0.180 | - | - |
| γ-GT (≥50U/L vs <50U/L) | 1.444(0.567-3.677) | 0.440 | - | - |
| Cre (>80umol/L vs ≤80umol/L) | 1.195(0.456-3.129) | 0.717 | - | - |

Abbreviations:
- WBC, white blood cell;
- PLT, platelet;
- CRP, C-reactive protein;
- PCT, procalcitonin;
- IL-6, interleukin-6;
- SaO₂, Oxygen saturation;
- TBIL, total bilirubin;
- ALT, alanine aminotransferase;
- AST, aspartate aminotransferase;
- LDH, lactate dehydrogenase;
- γ-GT, γ-glutamyl transpeptidase;
- Cre, creatinine;
- HR, hazard ratio;
- 95% CI, 95% Confidence interval.

Figures
Figure 1

Risk prediction nomogram for patients with COVID-19.

| Points | Age (year) | IL-6 (pg/mL) | Lymphocyte count | Panting (breathing rate) |
|--------|------------|--------------|------------------|-------------------------|
| 0      | <70        | <10          | >1.0*10^9/L      | ≥30/min                 |
| 10     |            |              |                  |                         |
| 20     |            |              |                  |                         |
| 30     |            |              |                  |                         |
| 40     |            |              |                  |                         |
| 50     |            |              |                  |                         |
| 60     |            |              |                  |                         |
| 70     |            |              |                  |                         |
| 80     |            |              |                  |                         |
| 90     |            |              |                  |                         |
| 100    | ≥70        | ≥10          | ≤1.0*10^9/L      | ≥30/min                 |

Total Points and Risk are not shown in the provided image.

Figure 2

The receiver operating characteristic (ROC) curves of the nomogram in the training cohort (A), validation cohort 1 (B) and validation cohort 2 (C).
Figure 3

The calibration curves of the nomogram in the training cohort (A), validation cohort 1 (B) and validation cohort 2 (C).
Figure 4

Decision curve analysis of the nomogram. DCA compares the net benefits of three scenarios in predicting the risk of mortality: a perfect prediction model (grey line), screen none (horizontal solid black line), and screen based on the nomogram (red line). The DCA curves were depicted in the training cohort (A), validation cohort 1 (B) and 2 (C).

Supplementary Files

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• Supplementalmaterial.docx