Development a Nomogram to Predict Prognosis in Severe and Critically Ill Patients with COVID-19

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Abstract

Background: The number of deaths caused by COVID-19 are on the rising worldwide. This study focused on severe and critically ill COVID-19, aim to explore independent risk factors associated with disease severity and to build a nomogram to predict patients' prognosis.

Methods: Patients with laboratory-confirmed COVID-19 admitted to the Union Hospital, Tongji Medical College and Hankou Hospital of Wuhan, China, from February 8th to April 6th, 2020. LASSO Regression and Multivariate Analysis were applied to screen independent factors. COX Nomogram was built to predict the 7-day, 14-day and 1-month survival probability.

Results: A total of 115 severe [73 (63.5%)] and critically ill [42 (36.5%)] patients were included in this study, containing 93 (80.9%) survivors and 22 (19.1%) non-survivors. For disease severity, D-dimer [OR 6.33 (95%CI, 1.27-45.57)], eosinophil percentage [OR 8.02 (95%CI, 1.82-45.04)], total bilirubin [OR 12.38 (95%CI, 1.24-223.65)] and lung involvement score [OR 1.22 (95%CI, 1.08-1.40)] were the independent factors associated with critical illness. Troponin [HR 9.02 (95%CI, 3.02, 26.97)] and total bilirubin [HR 3.16 (95%CI, 1.13, 8.85)] were the independent predictors for patients' prognosis. Troponin ≥ 26.2 ng/L and total bilirubin ≥ 20 μ mol/L were associated with poor prognosis. The nomogram based on the independent risk factors had a C-index of 0.92 (95%CI, 0.87, 0.98) for predicting survival probability. The survival nomogram validated in the critically ill patients had a C-index of 0.83 (95%CI: 0.75, 0.94).

Conclusions: In conclusion, in severe and critically ill patients with COVID-19, D-dimer, eosinophil percentage, total bilirubin and lung involvement score were the independent risk factors associated with disease severity. The proposed survival nomogram accurately predicted prognosis. The survival analysis may suggest that early incidence of multiple organ dysfunction may be an important predictor of poor prognosis.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 (1) has spread rapidly throughout the world (2-6) and become a public health emergency of international concern (4-6). Studies on clinical and chest computed tomography (CT) imaging spectrum of COVID-19 is on the rising (7-12). Since severe and critically ill cases might develop adverse clinical outcome, researches focusing on this cohort of patients will be highly conducive to reduce mortality caused by COVID-19.

With the increasing number of confirmed patients and deaths worldwide, it is in urgent need to study the difference between various disease severity and to identify the risk factors associated with the fatal clinical outcome. Till now, there have been some studies compared the clinical, laboratory and CT imaging characteristics between the groups of different severity (1, 3, 13-15). And also, some studies try to predict patients' prognosis (16-18) by the above parameters on admission. However, many of studies only carried out univariate analysis, and its results have limited effectiveness in predicting clinical outcomes (19). Therefore, it is necessary to establish a composite model with higher prediction efficiency based on the independent predictors selected by multivariate analysis. Additionally, severe and critical diseases are the main population leading to death, it is necessary to carry out researches focusing on this cohort. However, studies in this

aspect is still limited. Our current study aimed to build nomograms for severity and prognosis in severe and critically ill patients with COVID-19.

Materials And Methods

Data Sources

For the current retrospective, multi-center study, the medical records of the consecutive patients with laboratory-confirmed COVID-19 were obtained from the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, and Hankou Hospital of Wuhan, China, from February 8th to April 6th, 2020. Laboratory diagnosis were made when a positive result to high-throughput sequencing or real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay for nasal and pharyngeal swab specimens was revealed (3, 20). The hospitals designated by the Chinese government were mainly used for the treatment of severe and critically ill patients with COVID-19 and was managed by the doctors of our hospital who were sent there to provide medical assistance. As ward managers and first-line care physicians, they took charge of data collection and verification, the detailed information was then sent back to the COVID-19 research team consisted of experienced chest radiologists, statisticians and physicians specializing in respiratory diseases of the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China for data analysis. All data were entered into the computer in electronic form and were cross-checked. Any missing or uncertain information were recollected and rechecked by direct contact with the team of the first-line doctors.

Patients with severe and critical illness were included in our study. Patients who died of cerebral hemorrhage and other non-pneumonia causes were excluded. Disease severity and the discharge and release quarantine criteria were determined according to the diagnostic and treatment guideline for SARS-CoV-2 (Trial Version 6) issued by the National Health Commission of the People's Republic of China (14,20). This project was approved by the Ethics Committee and Institutional Review Board of Hankou Hospital (HKYY-2020-028). Written informed consent was waived due to the urgent need of researches on COVID-19. The onset date of the disease was defined as the day when any symptoms was noticed.

Data Collection

The clinical data including epidemiological, demographic, clinical, laboratory, radiological, and treatment were obtained from patients' medical records. The laboratory assessments and CT imaging characteristics on admission were evaluated. CT imaging characteristics were evaluated by two radiologists (ZY and LY) with diagnostic experience of 8 and 25 years and were blinded to patient information, patient order was also disrupted during analysis to control potential bias. Consensus was reached when the radiologists disagreed.

Semi-quantitative scoring methods were applied to quantitatively estimate the GGO percentage indicated the volume percentage of GGO component within the whole lesion (0, no GGO within the lesion; 1, 1%-5% of total lesion volume; 2, 6%-25% of total lesion volume; 3, 26%-49% of total lesion volume; 4, 50%-75% of total lesion volume; 5, 75%-99% of total lesion volume; 6, GGO only), lung involvement score [Each of the 5 lung lobes was scored from 0 to 5: 0, no involvement; 1, <5% involvement; 2, 5%-25% involvement; 3, 26%-49% involvement; 4, 50%-75% involvement; 5, >75% involvement. The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement) (11, 20) , lesion distribution

was classified as subpleural distribution (involving less than one-third of peripheral region of the lung lobe in transverse axial position), or diffuse (continuous involvement without respect to lung segments), random (scattered lesions without distribution predilection for subpleural or diffuse). Imaging features designation: crazy-paving or grid like pattern (GGO with intralobular septal thickening).

Study Outcomes

Clinical, laboratory and CT imaging feature variables of severe and critically ill patients with COVID-19 were grouped according to disease severity (Severe VS Critically ill) and patients' prognosis (Survivors VS Non-survivors). The enrolled patients were monitored up to April 6th, 2020, the final date of follow-up.

The study outcomes included: (1) To investigate the independent risk factors associated with disease severity. (2) To build a survival nomogram for early predicting patients' prognosis.

Statistical Analysis

Continuous variables were described as median (IQR), and were compared using Mann-Whitney-U test. Categorical variables were expressed as frequency rates and percentages [n (%)], and were compared by χ^2 test, or Fisher's exact test when sample size was limited. To explore the risk factors associated with disease severity (Severe VS Critically ill) and patients' clinical outcomes (Recovered VS Died), univariable and multivariable logistic regression models were used. To avoid overfitting, LASSO Regression Model was used for dimension reduction of variables. On this basis, Logistic Regression and Cox Proportional Hazard model were applied to select independent risk factors. Nomogram and calibration were obtained on the basis of these independent risk factors. The prediction efficiency of the survival nomogram was measured by C-statistics. A two-sided $P < 0.05$ was considered as statistically significant. Statistical analyses were performed by using SPSS 22.0 (IBM, USA) and R version 3.6.3.

Results

Demographics and Clinical Characteristics

The study cohort included 115 hospitalized patients with confirmed severe [73 (63.5%)] and critically ill [42 (36.5%)] COVID-19 diseases. The median duration from symptoms onset to hospital admission was 14 (IQR, 10-20) days. The median duration of hospitalization was 21 (IQR, 14-38) days. As given in **Table 1**, for the study population, the median age was 63 years (IQR, 55-70; range 26-97, years), 70 (60.9%) were more than 60 years, and 57 (49.6%) were men. The most common symptoms at illness onset were fever [84 (73%)], dry cough [89 (77.4%)], dyspnea [67 (58.3%)], expectoration [39 (33.9%)] and myalgia/fatigue [32 (27.8%)]. Most patients [68 (59.1%)] had one or more comorbidities, among which hypertension [54 (47%)] and diabetes [29 (25.2%)] were the most common coexisting conditions. Most patients took antibacterial [97 (84.3%)], antiviral [102 (88.7%)] and glucocorticoid therapy [61 (53%)]. 73 (63.5%) patients accepted high flow oxygen inhalation through nasal cannula, noninvasive and invasive mechanical ventilation were performed in 27 (23.5%) and 15 (13%) cases. There were 93 (80.9%) survivors and 22 (19.1%) non-survivors.

Compared with severe patients (given in **Table 1**), the median age of more than 60 years [31 (73.8%) VS 39 (53.4%), $P=0.031$], dry cough [39 (92.9%) VS 50 (68.5%), $P=0.003$] and dyspnea [33 (78.6%) VS 34 (46.6%), $P=0.001$] were more commonly seen in the critically ill patients. The proportion of critically ill patients receiving glucocorticoid therapy [31 (73.8%) VS 30 (41.1%), $P=0.001$] and mechanical ventilation [16 (21.9%) VS 26 (61.9%), $P=0.000$] were higher than that of the severe patients. 22 (52.4%) critically ill patients were died, and 20 (47.6%) were survived. All the severe patients [73 (100%)] were survivors.

Compared with survivors (given in **Table 1**), the median duration from symptoms onset to hospital admission [10 (IQR, 8-14) VS 14 (IQR, 10-23) days, $P=0.015$], the median duration of hospitalization [7 (IQR, 3-15) VS 26 (IQR, 17-44) days, $P=0.000$] and survival time [7 (IQR, 3-15) VS 62 (IQR, 46-62) days, $P=0.000$] were significantly shorter for non-survivors.

Laboratory Parameters on Admission

Compared with severe patients [given in **Table 2** (continuous variables) and **Supplementary Table S1** (categorical variables)], critically ill patients were more prone to express as significantly higher leukocytes, neutrophils, neutrophil percentage, NLR, CRP, procalcitonin, D-dimer, AST, ALT, lactate dehydrogenase, urea, troponin. The critically ill group had a significantly lower lymphocytes, lymphocyte percentage, eosinophils, eosinophil percentage, platelet count and albumin than the severe group.

Compared with survivors [given in **Table 2** (continuous variables) and **Supplementary Table S1** (categorical variables)], non-survivors were more prone to express as significantly higher leukocytes, neutrophils, neutrophil percentage, NLR, CRP, procalcitonin, D-dimer, PT, AST, lactate dehydrogenase, creatine kinase, urea, total bilirubin, troponin, as well as lower lymphocytes, lymphocyte percentage, eosinophils, eosinophil percentage, monocytes, monocyte percentage, platelet count, albumin.

CT Imaging Features on Admission

On admission, chest CT scan was performed to evaluate pulmonary involvement (**Table 3**). Compared with severe patients, the lesions in critically ill patients were more extensive, showing higher incidences of diffuse distribution and higher lung involvement score. Crazy paving was more commonly observed in the lesions of critically ill patients. These findings were similar between the survivors and non-survivors except for crazy paving.

Independent Risk Factors Associated with Disease Severity

Twenty-five variables were included in the LASSO Regression Model, the results showed that, a total of 11 variables with the smallest partial likelihood deviance were included in the Multivariate Logistic Regression Analysis, as given in **Supplementary Figure S1** and **Table 4**. Multivariate Logistic Regression Analysis (**Table 4**) showed that D-dimer, eosinophil percentage, total bilirubin and lung involvement score were the independent risk factors associated with disease severity, with $P < 0.05$. The Odds Ratio (OR) values were 6.33 (95% confidence interval [CI], 1.27-45.57), 8.02 (95%CI, 1.82-45.04), 12.38 (95%CI, 1.24-223.65) and 1.22 (95%CI, 1.08-1.40) respectively. Among them, lung involvement score was treated as a continuous variable, and for each additional point scored, the risk of critically ill illness increased by 1.22 times.

Independent Risk Factors Associated with Patients' Prognosis and A Survival Nomogram Building

Twenty-seven variables were included in the LASSO regression, a total of 8 variables with the smallest partial likelihood deviance were then included in the Cox Proportional Hazard Model, as given in **Figure 1 A-B** and **Table 4**. Cox Proportional Hazard Model (**Table 4**) showed that troponin and total bilirubin were the independent risk factors associated with patient's prognosis. The Hazard Ratio (HR) values were 9.02 (95%CI, 3.02, 26.97), 3.16 (95%CI, 1.13, 8.85) respectively. Patients with troponin ≥ 26.2 ng/L were 9.02 times more likely to die than those with troponin < 26.2 ng/L, and patients with total bilirubin > 20 μ mol/L were 3.16 times more likely to die than those with total bilirubin ≤ 20 μ mol/L.

A nomogram was then built based on troponin and total bilirubin to predict the 7-day, 14-day and 1-month survival probability, as given in **Figure 1 C** and **Table 5**. The nomogram had a C-index of 0.92 (95%CI, 0.87, 0.98) for predicting patient survival probability. The calibration curve (**Figure 1 D**) showed that the predicted rates were consistent with the actual results. Kaplan-Meier survival plots according to troponin and total bilirubin were shown in **Figure 2**.

Validation of the Survival Nomogram in the Critically Ill Population

In the current study, considering that all the dead patients were critically ill patients, we further validated the survival nomogram in the cohort of critically ill patients. The detailed information of basic demographics and clinical characteristics, laboratory parameters and CT imaging features of survivors and non-survivors in the critically ill cohort was given in **Supplementary Table S2, S3, S4**. Troponin and total bilirubin selected by LASSO COX in the total study population were used to build a nomogram (**Figure 3**) for predicting prognosis of critically ill patients. The 7-day, 14-day and 1-month survival probability were given in **Table 5**. The nomogram had a C-index of 0.83 (95%CI: 0.75, 0.94).

Stratified analysis by Gender in the Subgroup of Critically Ill Patients

In order to find out the potential causes of higher female mortality in critically ill patients, this study further performed the subgroup analysis with respect to gender in this cohort, as shown in **Supplementary Table S5**. There was no significant difference between men and women in gender, age and coexisted comorbidities and medication. Only Oxygen support methods were different between female and male patients. The use of mechanical ventilation in female group was significantly higher than that in male group. There was no significant difference in total lung involvement score between the two groups.

Discussion

In the current study, we studied the clinical, laboratory and CT imaging characteristics of severe and critically ill patients with COVID-19. COVID-19 patients were divided into severe and critically ill groups according to the diagnostic and treatment guideline for SARS-CoV-2 (Trial Version 6) issued by the National Health Commission of the People's Republic of China (20). And were divided into survivors and non-survivors according to patients' clinical outcomes.

Firstly, we explored the independent risk factors associated with disease severity (severe VS critically ill). We found that D-dimer [OR 6.33 (95%CI, 1.27-45.57)], eosinophil percentage [OR 8.02 (95%CI, 1.82-45.04)], total bilirubin [OR 12.38 (95%CI, 1.24-223.65)] and lung involvement score [OR 1.22 (95%CI, 1.08-1.40)] were the independent factors associated critical illness. Some reported studies (3, 14, 15, 21) tried to find risk factors associated with disease severity of COVID-19. Feng Y, et al. (14) found that D-dimer, C-reactive protein, aspartate aminotransferase, myohemoglobin and several immune indexes were associated with COVID-19 severity (moderate, severe, and critically ill). Significantly higher levels of D-dimer, C-reactive protein and procalcitonin were associated with severe illness compared to non-severe illness (21). The reported and our findings suggest that COVID-19 may be associated with cellular immune deficiency, coagulation activation and multiorgan dysfunction (7, 15).

Secondly, we tried to find the independent risk factors associated with prognosis and build a nomogram to predict the 7-day, 14-day and 1-month survival probability. We found that troponin [HR 9.02 (95%CI, 3.02, 26.97)] and total bilirubin [HR 3.16 (95%CI, 1.13, 8.85)] were the independent risk factors associated with patient's prognosis. The nomogram had a C-index of 0.92 (95%CI, 0.87, 0.98) for predicting patient survival probability. Our nomogram can be used to predict prognosis of severe and critically ill patients accurately and favourably. In order to explore the independent risk factors for predicting patients' prognosis, we included variables of age, gender, symptom of dyspnea, comorbidity, therapy, laboratory and imaging indicators, and treated age as categorical and continuous variable respectively. We found that only troponin and total bilirubin were the independent predictors of prognosis. This finding may suggest that early incidence of multiple organ dysfunction may be an important predictor of poor prognosis. Our findings are not quite the same with the reported (16-18). In the reported studies, they found that older age (16, 17), symptoms of dyspnea and several comorbidities (17, 18), d-dimer greater than 1 µg/mL (16), low level of lymphocytes (18), increased procalcitonin and aspartate aminotransferase (17) on admission associated with fatal outcome. In our study, the clinical characteristics, blood cell indices and infection indices (such as C-reactive protein and procalcitonin) on admission were not independent risk factors for predicting death. No matter they were treated as continuous or categorical variables, were not included in the final model. The possible reason for this discrepancy may be that the enrolled patients were not the same in our study and in theirs. In their study, they included the mild and/or general type(s), this would result in different independent predictors and the scope of the model application is also not the same.

Additionally, considering that all the dead patients were critically ill patients in our study cohort, we further validated the survival nomogram in the cohort of critically ill patients. Troponin and total bilirubin selected by LASSO COX in the total study population were used to build a nomogram for predicting the 7-day, 14-day and 1-month survival probability of the critically ill patients. The nomogram had a C-index of 0.83 (95%CI: 0.75, 0.94). The relatively limited sample size in the critically ill cohort may affect the robustness of the model.

In our study, considering the higher female mortality occurred in the critically ill patients, we further performed the subgroup analysis with respect to gender in the critically ill cohort and tried to find out the potential causes. We found that there was no significant difference between men and women in gender, age and coexisted comorbidities, medication and lung involvement score on admission. Only Oxygen support methods were different between female and male patients. The use of mechanical ventilation in female group was

significantly higher than that in male group. This may be because the women with critical illness in our study were more seriously ill than men, thus has a higher mortality.

Our study has several limitations. First, the relatively small sample size of the study population may affect the robustness of the model. These results need to be further validated with more patients. Second, our study focused on severe and critically ill patients, the built survival nomogram is only applicable to this cohort of population.

Conclusion

In conclusion, our study focused on the population of severe and critically ill patients with COVID-19 and found that D-dimer, eosinophil percentage, total bilirubin and lung involvement score were the independent risk factors associated with disease severity. The proposed survival nomogram accurately predicted prognosis. The survival analysis suggest that early incidence of multiple organ dysfunction may be an important predictor of poor prognosis. Earlier identification, more intensive surveillance and appropriate treatment intervention is necessary in high-risk patients.

Abbreviations

COVID-19: Coronavirus disease 2019; CT: Computed tomography; RT-PCR: Real-time reverse-transcriptase polymerase-chain-reaction; NLR: Neutrophil-to-Lymphocyte Ratio; CRP: C-Reactive Protein; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; IQR: Interquartile range; Coef: Coefficient; SE: Standard Error; OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; NA: Not applicable.

Declarations

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Author's Contribution

L.Y., Z.Y., W.L. conceptualized the study and conceived the project. Z.Y., W.Z. contributed with study design, sample processing and data analysis. S.X., T.M., H.C., L.Y., Y.Y., C.Z., L.D., L.Y., G.Y. helped with sample processing. L.Y., T.W., K.Y., Y.H., W.L., L.Y., J.K. contributed with the recruitment of the participants and sample collection. Z.Y., L.Y. performed the imaging features analysis. L.Y., T.W., W.L., Y.H. helped with cytometry

analysis and experimental design. L.Y., K.Y., W.L. supervised the work. T.W., Z.Y. wrote the paper with input from all other authors.

Ethics approval and consent to participate

Prior to its start, the study protocol was in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee and Institutional Review Board of Hankou Hospital. The reference number for the study is HKYY-2020-028.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Clinical characteristics of severe and critically ill patients with COVID-19 on admission.

Clinical Characteristics	Total (n=115)	Disease severity		Clinical outcomes			
		Severe (n=73)	Critically ill (n=42)	<i>P</i> value	Survivors (n=93)	Non- survivors (n=22)	<i>P</i> value
Age, Median (IQR), y	63 (55-70)	62 (54-70)	65 (60-70)	0.100 †	62 (55-70)	63 (60-71)	0.307 †
Age, n (%)				0.031 § *			0.08 §
≤60	45 (39.1%)	34 (46.6%)	11 (26.2%)		40 (43%)	5 (22.7%)	
>60	70 (60.9%)	39 (53.4%)	31 (73.8%)		53 (57%)	17 (77.3%)	
Men, n (%)	57 (49.6%)	36 (49.3%)	21 (50%)	0.944 §	50 (53.8%)	7 (31.8%)	0.064 §
Symptoms, n (%)							
Fever	84 (73%)	52 (71.2%)	32 (76.2%)	0.564 §	65 (69.9%)	19 (86.4%)	0.117 §
Dry cough	89 (77.4%)	50 (68.5%)	39 (92.9%)	0.003 § *	70 (75.3%)	19 (86.4%)	0.404 ‡
Dyspnea	67 (58.3%)	34 (46.6%)	33 (78.6%)	0.001 § *	48 (51.6%)	19 (86.4%)	0.003 §
Expectoration	39 (33.9%)	24 (32.9%)	15 (35.7%)	0.757 §	33 (35.5%)	6 (27.3%)	0.464 §
Myalgia/Fatigue	32 (27.8%)	20 (27.4%)	12 (28.6%)	0.892 §	25 (26.9%)	7 (31.8%)	0.642 §
Diarrhea	14 (12.2%)	9 (12.3%)	5 (11.9%)	0.947 §	10 (10.8%)	4 (18.2%)	0.551 ‡
Dizziness/Headache	5 (4.3%)	1 (1.4%)	4 (9.5%)	0.112 ‡	3 (3.2%)	2 (9.1%)	0.528 ‡
Comorbidities, n (%)							
Hypertension	54 (47%)	34 (46.6%)	20 (47.6%)	0.914 §	44 (47.3%)	10 (45.5%)	0.875 §
Diabetes	29 (25.2%)	20 (27.4%)	9 (21.4%)	0.478 §	23 (24.7%)	6 (27.3%)	0.805 §
Chronic respiratory diseases	11 (9.6%)	6 (8.2%)	5 (11.9%)	0.751 ‡	11 (11.8%)	0 (0%)	0.196 ‡
Malignancy	7 (6.1%)	4 (5.5%)	3 (7.1%)	1.000 ‡	4 (4.3%)	3 (13.6%)	0.250 ‡
Chronic kidney disease	5	3	2 (4.8%)	1.000	4 (4.3%)	1 (4.5%)	1.000

	(4.3%)	(4.1%)		‡			‡
Chronic liver disease	5 (4.3%)	1 (1.4%)	4 (9.5%)	0.112 ‡	4 (4.3%)	1 (4.5%)	1.000 ‡
With comorbidities, n (%)	68 (59.1%)	41 (1.3%)	27 (64.3%)	0.394 §			
Treatment, n (%)							
Antiviral	102 (88.7%)	65 (89%)	37 (88.1%)	1.000 ‡	84 (90.3%)	18 (81.8%)	0.448 ‡
Antibacterial	97 (84.3%)	58 (79.5%)	39 (92.9%)	0.057 §	77 (82.8%)	20 (90.9%)	0.538 ‡
Glucocorticoid	61 (53%)	30 (41.1%)	31 (73.8%)	0.001 § *	45 (48.4%)	16 (72.7%)	0.040 §
Immunoabsorption	6 (5.2%)	2 (0.1%)	4 (9.5%)	0.254 ‡	3 (3.2%)	3 (13.6%)	0.149 ‡
Oxygen support, n (%)				0.000 § *			0.054 ‡
High flow nasal cannula	73 (63.5%)	57 (78.1%)	16 (38.1%)		64 (68.8%)	9 (40.9%)	
Noninvasive ventilation	27 (23.5%)	10 (13.7%)	17 (40.5%)		19 (20.4%)	8 (36.4%)	
Invasive mechanical ventilation	15 (13%)	6 (8.2%)	9 (21.4%)		10 (10.8%)	5 (22.7%)	
Clinical outcomes, n (%)				0.000 § *			
Survivors	93 (80.9%)	73 (100%)	20 (47.6%)				
Non-survivors	22 (19.1%)	0 (0%)	22 (52.4%)				
Time from illness onset to hospital admission, Median (IQR), day	14 (10-20)	14 (10-23)	14 (9-18)	0.633 †	14 (10-23)	10 (8-14)	0.015 † *
Hospital stay, Median (IQR), day	21 (14-38)	22 (16-38)	20 (7-40)	0.206 †	26 (17-44)	7 (3-15)	0.000 † *
Survival time, Median (IQR), day	60 (28-62)	62 (45-62)	25 (7-62)	0.000 † *	62 (46-62)	7 (3-15)	0.000 † *

Abbreviations: IQR, interquartile range; NA, not applicable; COVID-19, 2019 novel coronavirus disease. †: Mann-Whitey U test; §: Chi-squared test; ‡: Fisher's Exact Test. *: P≤0.05.

Table 2. Laboratory indices of severe and critically ill patients with COVID-19 on admission.

Laboratory Indices	Normal Range	Disease severity		Clinical outcomes			
		Severe (n=73)	Critically ill (n=42)	<i>P</i> value	Survivors (n=93)	Non-survivors (n=22)	<i>P</i> value
Leukocytes, Median (IQR)	3.5-9.5 g/L	5.3 (4.1-7.4)	10.7 (5.8-12.9)	0.000† *	5.8 (4.4-8.5)	9.7 (6.3-13.0)	0.012† *
Neutrophils, Median (IQR)	1.8-6.3 g/L	3.7 (2.4-5.4)	8.8 (4.6-11.7)	0.000† *	4.1 (2.7-6.5)	8.7 (5.2-12.4)	0.001† *
Neutrophil percentage, Median (IQR)	40-75%	67.4 (57.9-77.6)	88.0 (78.7-91.6)	0.000† *	70.0 (61.4-80.8)	90.4 (84.8-93.5)	0.000† *
Lymphocytes, Median (IQR)	1.1-3.2 g/L	1.2 (0.9-1.5)	0.7 (0.4-0.9)	0.000† *	1.1 (0.8-1.5)	0.5 (0.3-0.7)	0.000† *
Lymphocyte percentage, Median (IQR)	20-50%	21.5 (14.4-30.6)	6.4 (4.8-13.7)	0.000† *	19.2 (12.5-26.8)	5.2 (4.0-8.2)	0.000† *
NLR, Median (IQR)		3.1 (1.9-5.6)	13.8 (5.6-19.6)	0.000† *	3.7 (2.2-6.4)	19.1 (10.6-26.8)	0.000† *
Eosinophils, Median (IQR)	0.02-0.52 g/L	0.1 (0.0-0.1)	0.0 (0.0-0.0)	0.000† *	0.1 (0.0-0.1)	0.0 (0.0-0.0)	0.000† *
Eosinophil percentage, Median (IQR)	0.4-8%	1.1 (0.4-2.4)	0.1 (0.0-0.3)	0.000† *	1.0 (0.3-2.0)	0.1 (0.0-0.3)	0.000† *
Monocytes, Median (IQR)	0.1-0.6 g/L	0.4 (0.3-0.5)	0.3 (0.3-0.4)	0.041† *	0.4 (0.3-0.5)	0.3 (0.1-0.3)	0.001† *
Monocyte percentage, Median (IQR)	3-10%	7.1 (5.6-9.3)	4.4 (2.0-6.3)	0.000§ *	6.9 (5.3-8.8)	3.1 (1.9-4.3)	0.000§ *
CRP, Median (IQR)	0-8 mg/L	12.8 (3.9-31.8)	43.3 (18.5-100.0)	0.000† *	17.6 (4.2-35.3)	81.8 (32.5-117.7)	0.000† *
Procalcitonin, Median (IQR)	<0.05 ng/ml	0.1 (0.0-0.1)	0.2 (0.1-1.1)	0.000† *	0.1 (0.0-0.1)	0.7 (0.1-1.4)	0.000† *
Platelet count, Median (IQR)	125-350 g/L	222.0 (173.5-317.0)	184.5 (106.8-232.8)	0.003† *	220.0 (163.0-310.0)	158.5 (93.0-217.5)	0.000† *
D-dimer, Median (IQR)	0-0.5 ug/ml	0.5 (0.2-1.6)	3.3 (1.0-8.0)	0.000† *	0.7 (0.3-2.2)	2.6 (1.0-8.3)	0.001† *
PT, Median (IQR)	11.0-16.0 s	13.0 (12.1-13.8)	14.0 (12.8-15.0)	0.002† *	13.1 (12.2-14.4)	13.9 (13.1-16.0)	0.015† *

APTT, Median (IQR)	27.0-45.0 s	36.2 (33.0-40.7)	37.4 (34.1-44.7)	0.165 †	36.1 (33.1-41.4)	37.8 (33.6-44.9)	0.219 †
AST, Median (IQR)	8-40 U/L	25.0 (20.0-36.0)	50.5 (26.8-66.0)	0.000 † *	26.0 (20.0-42.0)	54.5 (40.8-75.0)	0.000 † *
ALT, Median (IQR)	5-40 U/L	30.0 (17.0-55.0)	43.5 (25.0-85.0)	0.011 † *	33.0 (18.5-57.0)	39.0 (24.8-85.0)	0.211 †
Albumin, Median (IQR)	33-55 g/L	33.8 (30.7-37.1)	28.1 (24.6-34.6)	0.000 † *	32.7 (28.5-36.5)	26.7 (24.5-34.0)	0.004 † *
Lactate dehydrogenase, Median (IQR)	109-245 U/L	217.0 (173.5-293.5)	438.5 (332.8-630.0)	0.000 † *	239.0 (185.5-339.0)	559.0 (430.8-838.5)	0.000 † *
Alkaline phosphatase, Median (IQR)	40-150 U/L	60.0 (50.0-71.0)	76.0 (55.0-101.5)	0.007 † *	61.0 (50.0-80.5)	78.0 (54.3-108.8)	0.059 †
Creatine kinase, Median (IQR)	24-194 U/L	59.0 (43.5-98.5)	104.5 (56.0-171.5)	0.010 † *	59.0 (42.0-98.5)	141.5 (92.3-268.8)	0.000 † *
Creatinine, Median (IQR)	57-111 µmol/L	67.3 (57.5-84.8)	72.5 (55.8-94.2)	0.523 †	67.8 (57.9-80.0)	89.4 (53.3-115.3)	0.199 †
Urea, Median (IQR)	2.9-8.2 mmol/L	4.8 (3.5-7.0)	8.1 (5.3-12.1)	0.000 † *	5.4 (3.7-7.6)	10.9 (5.9-14.7)	0.000 † *
Total bilirubin, Median (IQR)	3.0-20 µmol/L	9.4 (6.7-12.3)	13.2 (10.2-24.3)	0.000 † *	10.0 (7.1-13.3)	13.5 (8.8-25.2)	0.002 † *
Troponin, Median (IQR)	<26.2 ng/L	6.6 (3.1-15.0)	17.7 (5.8-45.2)	0.000 † *	6.6 (3.1-15.3)	42.0 (19.7-189.5)	0.000 † *

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; CRP, C-Reactive Protein; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase. IQR, interquartile range; COVID-19, 2019 novel coronavirus disease. †: Mann-Whitey U test; §: Chi-squared test; ‡: Fisher's Exact Test. *: P≤0.05.

Table 3. Chest CT imaging characteristics of severe and critically ill patients with COVID-19 on admission.

Imaging Characteristics	Disease severity			Clinical outcomes		
	Severe (n=73)	Critically ill (n=42)	<i>P</i> value	Survivors (n=93)	Non- survivors (n=22)	<i>P</i> value
Distribution, n (%)			0.000 ‡ *			0.005 ‡ *
Subpleural	51 (69.9%)	8 (19%)		54 (58.1%)	5 (22.7%)	
Random	2 (2.7%)	0 (0%)		2 (2.2%)	0 (0%)	
Diffuse	20 (27.4%)	34 (81%)		37 (39.8%)	17 (77.3%)	
Attenuation, n (%)			0.119 §			0.980 §
GGO only	44 (60.3%)	19 (45.2%)		51 (54.8%)	12 (54.5%)	
Mixed GGO and consolidation	29 (39.7%)	23 (54.8%)		42 (45.2%)	10 (45.5%)	
GGO score, Median (IQR)	6 (4-6)	5 (5-6)	0.766 †	6 (5-6)	6 (5-6)	0.495 †
Total lung involvement score, Median (IQR)	6 (4-9)	15 (12-20)	0.000 † *	8 (5-13)	15 (11-20)	0.000 † *
Lung involvement score in each lobe, Median (IQR)						
Right upper lobe	1 (0-2)	2 (2-4)	0.000 † *	1 (1-3)	2 (2-4)	0.008 † *
Right middle lobe	1 (0-1)	2 (1-3)	0.000 † *	1 (0-2)	2 (2-3)	0.000 † *
Right lower lobe	2 (1-3)	4 (3-5)	0.000 † *	2 (1-4)	4 (3-5)	0.000 † *
Left upper lobe	1 (1-2)	2 (1-3)	0.000 † *	1 (1-3)	2 (1-3)	0.053 † *
Left lower lobe	2 (1-3)	5 (3-5)	0.000 † *	2 (1-4)	4 (3-5)	0.002 † *
Reticulation, n (%)	24 (32.9%)	9 (21.4%)	0.191 §	30 (32.3%)	3 (13.6%)	0.082 §
Crazy paving, n (%)	47 (64.4%)	37 (88.1%)	0.006 § *	64 (68.8%)	20 (90.9%)	0.036 §
Pleural effusion, n (%)	12 (16.4%)	10 (23.8%)	0.333 §	18 (19.4%)	4 (18.2%)	1.000 ‡

Abbreviation: GGO, ground-glass opacity; CT, computed tomography; IQR, interquartile range; COVID-19, 2019 novel coronavirus disease. †: Mann-Whitey U test; §: Chi-squared test; ‡: Fisher's Exact Test. *: $P \leq 0.05$.

Table 4. Screening of independent risk factors of disease severity and prognosis.

Variables	LASSO Coef	Logistic Regress Model				
		Coef	SE	Z value	P value	OR [95%CI]
Procalcitonin	0.30	1.70	1.02	1.66	0.10	5.47 (0.87-55.82)
D-dimer	0.41	1.85	0.89	2.08	0.04*	6.33 (1.27-45.57)
Neutrophil percentage	0.29	-0.03	0.97	-0.03	0.98	0.97 (0.14-6.87)
NLR	0.02	0.19	0.13	1.49	0.14	1.21 (0.98, 1.64)
Eosinophil percentage	0.91	2.08	0.80	2.60	0.01*	8.02 (1.82-45.04)
AST	0.27	1.03	0.83	1.25	0.21	2.81 (0.57-15.84)
Alkaline phosphatase	0.11	17.40	1919.82	0.01	0.99	35855732.19 (0, NA)
Total bilirubin	0.78	2.52	1.28	1.96	0.05*	12.38 (1.24, 223.65)
Lactate dehydrogenase	0.22	0.87	0.95	0.92	0.36	2.38 (0.37, 16.70)
Lung involvement score	0.10	0.20	0.06	3.05	0.00*	1.22 (1.08, 1.40)
Leukocytes #, normal (Ref)	-0.17					
≥3.5 g/L		2.15	1.41	1.52	0.13	8.55 (0.55, 162.29)
≥9.5 g/L		1.00	1.01	0.99	0.32	2.73 (0.38, 21.90)
Variables	LASSO Coef	Cox Proportional Hazard Model				
		Coef	SE	Z value	P value	HR [95%CI]
Procalcitonin	0.05	19.30	6530.62	0.00	1.00	2.41 (0.00, Inf)
Troponin	1.50	2.20	0.56	3.94	0.00*	9.02 (3.20, 26.97)
Neutrophil percentage	0.34	1.66	1.10	1.50	0.13	5.24 (0.6, 45.66)
NLR	0.02	0.02	0.01	1.89	0.06	1.02 (1.00-1.04)
Eosinophil percentage	0.20	0.61	0.65	0.94	0.35	1.84 (0.51, 6.63)
AST	0.28	0.28	0.59	0.47	0.64	1.32 (0.42, 4.18)
Total bilirubin	0.38	1.15	0.53	2.19	0.03*	3.16 (1.13, 8.85)
Urea	0.12	0.30	0.52	0.57	0.57	1.35 (0.49, 3.72)

Abbreviations: Coef, Coefficient; SE, Standard Error; OR, Odds Ratio; HR, Hazard Ratio; CI, Confidence Interval. #: The categorical variable of leukocytes was treated as three categories of dummy variables. *: P < 0.05.

Table 5. The 7-day, 14-day and 1-month survival probability predicted by the COX Nomogram in the total population and the critically ill sub-population.

Cohort	Troponin	Total bilirubin	Survival Probability		
			7-day (%)	14-day (%)	1-month (%)
All patients	Normal	Normal	87.758	87.117	92.169
	Increased	Normal	74.677	63.661	50.088
	Normal	Increased	92.066	85.87	76.451
	Increased	Increased	35.656 *	24.526 *	15.093 *
Critically ill patients	Normal	Normal	92.487	90.389	79.612
	Increased	Normal	50.801	33.775	18.019
	Normal	Increased	90.44	81.098	65.035
	Increased	Increased	33.901 *	19.508 *	9.246 *

*: The survival probability of patients with increased troponin and total bilirubin was markedly reduced.

Figures

Figure 1

Independent risk factors associated with prognosis (Survival/Death) of COVID-19 were selected by LASSO regression analyses. (A) LASSO coefficient profiles of the non-zero variables and (B) Mean-Squared Error plot. (C) COX Nomogram predicting 7-day, 14-day and 1-month survival probability of severe and critically ill patients with COVID-19. (D) The calibration curve showed that the predicted rates were consistent with the actual results.

Figure 2

Kaplan-Meier survival plots according to troponin and total bilirubin.

Figure 3

Validation of the survival nomogram in the critically ill population.

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