

# The Prognostic Value of the SOFA Score in Patients with COVID-19: A Retrospective, Observational Study

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## Research

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## Abstract

**Background:** Patients with Coronavirus disease 2019 (COVID-19) have a high mortality rate, and thus, it is particularly important to predict the severity and prognosis of COVID-19. The Sequential Organ Failure Assessment (SOFA) score has been used to predict the clinical outcomes of patients with multiple organ failure requiring intensive care. Therefore, we retrospectively analyzed the clinical characteristics, risk factors, and relationship between the SOFA score and the prognosis of COVID-19 patients.

**Methods:** Clinical variables were compared between patients with mild and severe COVID-19. Univariate and multivariate logistic regression analyses were performed to identify the risk factors for severe COVID-19. The Cox proportional hazards model was used to analyze risk factors for hospital-related death. Survival analysis was performed by the Kaplan-Meier method, and survival differences were assessed by the log-rank test. Receiver operating characteristic (ROC) curves of the SOFA score in different situations were drawn, and the area under the ROC curve was calculated.

**Results:** The median SOFA score of all patients was 2 (IQR, 1-3). Patients with severe COVID-19 exhibited a significantly higher SOFA score than patients with mild COVID-19 [3 (IQR, 2-4) vs 1 (IQR, 0-1);  $P<0.001$ ]. The SOFA score increased the risk of severe COVID-19, with an odds ratio of 5.851 (95% CI: 3.044-11.245;  $P<0.001$ ). The area under the ROC curve (AUC) was used to evaluate the diagnostic accuracy of the SOFA score in predicting severe COVID-19 [cutoff value = 2; AUC = 0.908 (95% CI: 0.857-0.960); sensitivity: 85.20%; specificity: 80.40%] and the risk of death in COVID-19 patients [cutoff value = 5; AUC = 0.995 (95% CI: 0.985-1.000); sensitivity: 100.00%; specificity: 95.40%]. Regarding the 60-day mortality rates of patients in the two groups classified by the optimal cutoff value of the SOFA score (5), patients in the high SOFA score group (SOFA score  $\geq 5$ ) had a significantly greater risk of death than those in the low SOFA score group (SOFA score <5).

**Conclusion:** The SOFA score could be used to evaluate the severity and 60-day mortality of COVID-19. The SOFA score may be an independent risk factor for in-hospital death.

## Introduction

In late December 2019, the World Health Organization (WHO) China National Representative Office was informed that a series of unexplained cases of pneumonia had been found in Wuhan. Gene sequencing analysis showed that it was a novel coronavirus, and it was later classified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. The novel coronavirus disease 2019 was caused by SARS-CoV-2, which was termed COVID-19 on February 11<sup>[2]</sup>. SARS-CoV-2 can simultaneously infect ciliated cells and secretory cells of human respiratory epithelium. Therefore, compared with common coronaviruses, it is more infectious and pathogenic [3]. As of August 14, 2020 (03:37 pm CEST), the WHO website reported that there were 89,625 confirmed cases in China, of which 4,707 patients died. The number of confirmed infections worldwide reached 20,730,456, including 751,154 deaths and 216 countries or regions infected [2]. In fact, the number of deaths caused by COVID-19 epidemic may be greater than officially reported [4].

The world is currently in the midst of a COVID-19 pandemic. Patients with COVID-19 may be clinically asymptomatic, but severe patients may have poor clinical prognosis and may experience acute respiratory distress syndrome (ARDS), organ dysfunction, shock, acute kidney injury and acute heart injury or even death [5]. Patients with severe illness, within 1 week of onset may develop hypoxemia and dyspnea and then rapidly progress to ARDS or end-stage organ failure [6]. In the early series of cases in Wuhan, China, 26% of patients were admitted to the intensive care unit (ICU), with a mortality rate of 4.3% [7]. Therefore, reliable prognostic indicators are greatly needed because they can provide an accurate evaluation of the disease and aid in the selection of more effective treatment strategies. However, effective and simple methods to evaluate the severity and prognosis of COVID-19 patients are still challenges for clinicians. The Sequential Organ Failure Assessment (SOFA) score is one of the scoring systems used to evaluate organ failure and can predict the severity and outcome of the disease [8, 9]. The SOFA scoring system was launched in 1996, and its performance is based on the evaluation of the following six major organ functions: circulation, respiration, liver, renal function, central nervous system and coagulation function. The score of each organ is between 0 and 4. It is an easy-to-use tool for systematically and continuously evaluating organ functions during hospitalization [10]. At present, there are no systematic studies to show whether the SOFA score can correctly evaluate the prognosis and severity of COVID-19. Therefore, a retrospective study was conducted to evaluate the accuracy of the SOFA score in predicting the severity and prognosis of COVID-19.

## Methods

### Study Population

This is a retrospective observational study involving 117 hospitalized patients with COVID-19, all of whom were from Jingzhou Central Hospital between January 16, 2020 and March 23, 2020. The study was approved by the Institutional Ethics Committee of Jingzhou Central Hospital, and the requirement for informed consent from the study participants was waived. All adult patients diagnosed with the coronavirus disease 2019 according to the WHO interim guidelines [11] were screened for multidisciplinary diagnosis and treatment by infectious disease, respiratory and intensive care physicians. Patients who were discharged or died from January 16, 2019 (when the first patient was admitted to the hospital), to March 23, 2020, were included in the study. Clinical outcomes (such as death) were recorded from March 23, 2020, to the last date of follow-up.

### Data collection

Trained physicians collected patient epidemiological, demographic, and clinical and laboratory data through the electronic medical record system. All patients were followed up until May 10, 2020. The SOFA score was evaluated when the patient had the worst physiological data after admission. The patients were classified into two groups: mild (including mild and common) group and severe (including severe and critical) group. The mild group exhibited mild clinical symptoms, no imaging manifestations of

pneumonia. The common group had fever and respiratory symptoms, and imaging showed pneumonia. Patients in the severe group had dyspnea, with RR  $\geq$  30 beats/min at rest, average oxygen saturation  $\leq$  93%, and arterial partial pressure of oxygen (PaO<sub>2</sub>)/oxygen concentration (FiO<sub>2</sub>)  $\leq$  300 mmHg. Patients in the critical group had the occurrence of shock, respiratory failure requiring mechanical ventilation, and multiple organ failure requiring ICU monitoring and treatment [12].

## Procedures

Before admission, the nasopharyngeal swabs of all patients were routinely collected for SARS-CoV-2 real-time PCR detection, and patients with positive findings were admitted to the hospital. After admission, laboratory testing and imaging examination (CT scan) were routinely performed in all patients. Routine examinations included liver and renal function, electrolytes, procalcitonin (PCT), myocardial zymogram, interleukin-6 (IL-6), complete blood count, blood gas analysis, high sensitivity C-reactive protein (hs-CRP), etc. Patients reached the discharge criteria when they had a normal body temperature for  $\geq$  3 days, their respiratory symptoms were relieved, the lung CT manifestations significantly improved, and they had two consecutive nasopharyngeal swabs with negative results from nucleic acid tests (the sampling time was at least 24 hours apart).

## Statistical analysis

Continuous variables with a normal distribution and nonnormal distribution are summarized as the mean  $\pm$  standard deviation (SD) and the median (interquartile range, IQR), respectively. Categorical variables are expressed as frequencies or percentages. Differences between severe and mild cases were analyzed using the  $\chi^2$  test, Mann-Whitney U test or Fisher exact test, where appropriate. Univariate and multivariate logistic regression models were used to identify the risk factors associated with the severity of COVID-19. All clinically important covariates and those with a significant correlation in the univariate analyses ( $P < 0.15$ ) were included in the multivariate analysis. Survival curves were drawn and the differences in survival were assessed by using the Kaplan-Meier method and log rank test. The cutoff value of the SOFA score was determined by receiver operating characteristic (ROC) curve analysis. Based on the cutoff value of the SOFA score, the patients were classified into 2 groups. The hazard ratios (HRs) with 95% confidence intervals for the risk factors for death were determined using Cox proportional hazards regression models. The Cox proportional hazards model was used to analyze the potential risk factors associated with the SOFA score for in-hospital death. All statistical analyses were carried out with SPSS (IBM, version 25.0). Graphs were plotted using the GraphPad Prism 8.0 (San Diego, CA, USA). A  $P$  value of  $< 0.05$  was considered statistically significant, and all tests were two-tailed.

## Results

### Demographic, baseline and clinical characteristics of patients with COVID-19

We analyzed 117 confirmed COVID-19 patients, including 60 males, accounting for 51.3%. More than half (61) of the patients were identified as critical patients, and 9 of them died. The majority of severe patients were men, accounting for 55.7%. The median age of the patients was 50.00 years (IQR, 35.50–62.00 years), ranging from 18 to 83 years. The median age of seriously ill patients was significantly higher than that of mild patients [56.00 (IQR, 45.00–68.00) vs 38.00 (IQR, 31.00-54.50)]. Sixty-three patients had complications, and hypertension (27.4%) was the most common complication, followed by diabetes (8.5%), stroke (4.3%), coronary heart disease (3.4%), chronic liver disease (CLD1) (3.4%) and so on. The proportion of hypertension in severe patients was higher than that in mild patients (42.6% vs 10.7%,  $P < 0.001$ ). It is observed that on admission, fever (82.9%) and dry cough (70.1%) were the most common symptoms, followed by dyspnea (39.3%), fatigue (29.1%), and sore throat (9.4%). The median time from onset to admission of all patients was 5 days (IQR, 3–7 days), no difference found between the mild and severe group (Table 1). The median SOFA score of the patients was 2 (IQR, 1–3), the minimum SOFA score was 0, and the maximum SOFA score was 16. The distribution of SOFA scores is shown in Fig. 1A. The median SOFA score of severe patients was higher than that of mild patients [3 (IQR, 2–4) vs 1 (IQR, 0–1);  $P < 0.001$ ].

**Table 1**  
**Demographics and baseline characteristics of patients with COVID-19**

<b>Demographics and clinical characteristics</b>	<b>All patients(n = 117)</b>	<b>Mild(n = 56)</b>	<b>Severe(n = 61)</b>	<b>P value</b>
Age, years	50.00(35.50–62.00)	38(31.00–54.50)	56.00(45.00–68.00)	0.000
Sex				0.302
Male	60, 51.3%	26, 46.4%	34, 55.7%	
Female	57, 48.7%	30, 53.6%	27, 44.3%	
<b>Comorbidity</b>				
Hypertension	32, 27.4%	6, 10.7%	26, 42.6%	0.000
Diabetes	10, 8.5%	2, 3.6%	8, 13.1%	0.058
Coronary heart disease	4, 3.4%	1, 1.8%	3, 4.9%	0.352
Stroke	5, 4.3%	2, 3.6%	3, 4.9%	0.655
Carcinoma	3, 2.6%	0	3, 4.9%	0.093
Chronic liver disease	4, 3.4%	3, 5.4%	1, 1.6%	0.269
Chronic kidney disease	1, 0.9%	0	1, 1.6%	0.336
Chronic lung disease	2, 1.7%	0	2, 3.2%	0.172
Other	2, 1.7%	0	2, 3.2%	0.172
<b>Signs and symptoms</b>				
Fever	97, 82.9%	48, 85.7%	49, 80.3%	0.919
Cough	82, 70.1%	35, 62.5%	47, 77.0%	0.185
Dyspnea	46, 39.3%	8, 14.3%	38, 62.3%	0.000
Diarrhea	5, 4.3%	3, 5.4%	2, 3.3%	0.655
Fatigue	34, 29.1%	18, 32.1%	16, 26.2%	0.732
Sore throat	11, 9.4%	7, 12.5%	4, 6.6%	0.366
Myalgia	5, 4.3%	3, 5.4%	2, 3.3%	0.655
Sputum production	6, 5.1%	2, 3.6%	4, 6.6%	0.414

Abbreviations: COVID-19, Coronavirus disease 2019; SOFA score, Sequential Organ Failure Assessment score; SPO<sub>2</sub>, oxygen saturation; Values are medians (interquartile ranges) or number (percentages), where N is the total number of patients with available data. P values comparing severe and mild patients are from  $\chi^2$ , Fisher's exact test, or Mann-Whitney U test.  $P < 0.05$  are considered statistically significant.

Demographics and clinical characteristics	All patients(n = 117)	Mild(n = 56)	Severe(n = 61)	P value
Highest temperature (°C)	38.40(37.75–38.80)	38.25(37.70–38.70)	38.50(37.80–39.00)	0.058
SOFA score	2(1–3)	1(0–1)	3(2–4)	0.000
Lowest SPO2(%)	94(90–95)	95(94–95)	90(86–92)	0.000
Days from symptoms to hospital admission	5(3–7)	4(3–7)	5(3–7)	0.867

Abbreviations: COVID-19, Coronavirus disease 2019; SOFA score, Sequential Organ Failure Assessment score; SPO2, oxygen saturation; Values are medians (interquartile ranges) or number (percentages), where N is the total number of patients with available data. P values comparing severe and mild patients are from  $\chi^2$ , Fisher's exact test, or Mann-Whitney U test.  $P < 0.05$  are considered statistically significant.

## Laboratory characteristics of the study population

Table 2 summarizes the laboratory test results of the patients after admission. The median lymphocyte count (LYM) of the patients was  $0.860 \times 10^9/\text{ml}$ . The LYM in severe patients was lower than that in mild patients [0.640 (IQR, 0.420–0.965) vs 1.035 (IQR, 0.690–1.360);  $P < 0.001$ ]. The hs-CRP, white blood cell (WBC), neutrophil (NE), and gamma-glutamyl transpeptidase ( $\gamma$ -GGT) levels in severe patients were higher than those in mild patients [16.830 (IQR, 4.730–43.665) vs 4.815 (IQR, 0.870–16.967); 9.990 (IQR, 6.525–12.940) vs 6.185 (IQR, 4.400–9.175); 8.320 (IQR, 4.925–11.900) vs 4.495 (IQR, 2.872–7.247); 65.200 (IQR, 38.650–132.200) vs 40.700 (IQR, 17.025–65.475); all  $P < 0.001$ ]. In addition, the PCT, direct bilirubin (DBIL), alanine aminotransferase (ALP), cystatin C, and creatine kinase muscle-brain isoform (CK-MB) levels of severe patients were higher than those of mild patients[0.080 (IQR, 0.050–0.165) vs 0.040 (IQR, 0.030–0.060); 4.300 (IQR, 2.800–7.150) vs 3.200 (IQR, 2.325–4.400); 59.200 (IQR, 44.350–79.750) vs 53.750 (IQR, 42.275–63.300); 0.960 (IQR, 0.820–1.110) vs 0.820 (IQR, 0.712–0.947); 16.900 (IQR, 12.900–23.300) vs 13.500 (IQR, 9.750–16.312); all  $P < 0.05$ ], but the levels of severe patients were all within the normal range.

Table 2  
Laboratory findings of patients with COVID-19

Laboratory findings	Normal Range	All patients(n = 117)	Mild(n = 56)	Severe(n = 61)	P value
Procalcitonin, ng/mL	0-0.5	0.060(0.0350–0.110)	0.040(0.030–0.060)	0.080(0.050–0.165)	0.000
IL-6, pg/L	0-7	27.489(8.685–27.489)	27.489(7.247–27.489)	22.700(8.685–34.290)	0.224
White blood cells, $\times 10^9/\text{ml}$	3.5–9.5	7.300(5.025–11.270)	6.185(4.400–9.175)	9.990(6.525–12.940)	0.000
Neutrophils, $\times 10^9/\text{ml}$	1.8–6.3	6.190(3.460–9.910)	4.495(2.872–7.247)	8.320(4.925–11.900)	0.000
Lymphocytes, $\times 10^9/\text{ml}$	1.1–3.2	0.860(0.560–1.215)	1.035(0.690–1.360)	0.640(0.420–0.965)	0.000
Monocytes, $\times 10^9/\text{ml}$	0.1–0.6	0.400(0.300–0.530)	0.400(0.292–0.497)	0.380(0.305–0.535)	0.733
Eosinophil, $\times 10^9/\text{mL}$	0.02–0.52	0.000(0.000–0.055)	0.005(0.000–0.067)	0.000(0.000–0.045)	0.233
Basophil, $\times 10^9/\text{mL}$	0-0.06	0.010(0.010–0.030)	0.010(0.010–0.020)	0.020(0.010–0.035)	0.114
Red blood cell, $\times 10^{12}/\text{mL}$	3.8–5.1	4.214 ± 0.623	4.339 ± 0.530	4.099 ± 0.683	0.035
Hemoglobin, g/L	115–150	134.000(118.500–145.000)	134.000(121.000–146.750)	133.000(116.000–141.500)	0.125
Platelets, $\times 10^9/\text{ml}$	125–350	198.000(157.500–259.000)	194.500(156.000–231.500)	217.000(159.000–279.000)	0.200
hs-CRP, mg/L	0-10	8.760(2.560–25.410)	4.815(0.870–16.967)	16.830(4.730–43.665)	0.000
Total bilirubin, umol/L	< 21	11.400(9.100–16.200)	11.000(8.650–13.925)	13.000(9.300–18.150)	0.053
Direct bilirubin, umol/L	< 7.5	3.700(2.500–5.800)	3.200(2.325–4.400)	4.300(2.800–7.150)	0.009
Indirect bilirubin, umol/L	< 18.9	7.800(6.250–10.600)	7.700(6.000–9.875)	8.200(6.500–11.250)	0.180

Abbreviations: COVID-19, Coronavirus disease 2019; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; CK, creatine kinase; CK-MB, creatine kinase muscle-brain isoform; cTnI, cardiac troponin I; Data are mean ± SD, or median (IQR). P values comparing severe and mild patients are from Fisher's exact test or Mann-Whitney U test. P<0.05 are considered statistically significant.

Laboratory findings	Normal Range	All patients(n = 117)	Mild(n = 56)	Severe(n = 61)	P value
Alanine aminotransferase, U/L	7–40	63.400(28.700–117.450)	55.600(22.050–104.475)	68.500(33.700–127.500)	0.167
Aspartate aminotransferase, U/L	13–35	33.200(21.050–47.650)	28.200(19.075–43.400)	36.700(22.250–51.000)	0.114
Alkaline phosphatase, U/L	40–150	54.800(42.900–71.300)	53.750(42.275–63.300)	59.200(44.350–79.750)	0.041
Gamma-glutamyl transpeptidase, U/L	7–45	54.600(28.500–87.400)	40.700(17.025–65.475)	65.200(38.650–132.200)	0.000
Urea nitrogen, mmol/L	2.6–7.5	5.140(4.130–6.515)	4.620(3.790–5.520)	5.540(4.645–7.665)	0.000
Creatinine, umol/L	41–73	60.800(49.050–67.700)	61.250(49.250–68.175)	60.600(48.200–66.900)	0.631
Uric acid, umol/L	142–339	238.740 ± 92.149	264.960 ± 81.093	214.660 ± 95.694	0.003
Cystatin C, mg/L	0.54–1.15	0.870(0.750–1.030)	0.820(0.712–0.947)	0.960(0.820–1.110)	0.000
Glomerular filtration rate, ml/min/	>90	130.500(107.350–153.050)	129.250(114.125–148.875)	132.000(103.000–161.450)	0.849
Potassium, mmol/L	3.5–5.3	4.340 ± 0.600	4.431 ± 0.575	4.257 ± 0.615	0.119
Sodium, mmol/L	137.0–147.0	140.182 ± 3.315	141.094 ± 2.592	139.344 ± 3.368	0.002
Chlorine, mmol/L	99.0–110.0	103.800(101.100–105.400)	104.350(102.425–105.775)	102.200(100.600–104.800)	0.006
Calcium, mmol/L	2.11–2.52	2.000(1.900–2.155)	2.025(1.940–2.187)	1.980(1.850–2.145)	0.122
Magnesium, mmol/L	0.70–1.15	0.986 ± 0.093	0.988 ± 0.093	0.984 ± 0.093	0.857
Phosphorus, mmol/L	0.85–1.51	1.107 ± 0.247	1.183 ± 0.185	1.036 ± 0.277	0.001

Abbreviations: COVID-19, Coronavirus disease 2019; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; CK, creatine kinase; CK-MB, creatine kinase muscle-brain isoform; cTnI, cardiac troponin I; Data are mean ± SD, or median (IQR). P values comparing severe and mild patients are from Fisher's exact test or Mann-Whitney U test. P<0.05 are considered statistically significant.

Laboratory findings	Normal Range	All patients(n = 117)	Mild(n = 56)	Severe(n = 61)	P value
CK, U/L	< 167	73.800(48.500-109.925)	74.600(45.175-105.331)	72.900(49.400-124.000)	0.561
CK-MB, U/L	< 24	14.400(10.500-18.775)	13.500(9.750-16.312)	16.900(12.900-23.300)	0.001
cTnI, ug/L	< 0.04	0.010(0.010-0.040)	0.010(0.010-0.035)	0.010(0.010-0.042)	0.579
Myoglobin, ug/L	1.5–70.0	31.000(18.900-54.750)	27.250(17.475-42.600)	33.650(24.300-55.500)	0.069

Abbreviations: COVID-19, Coronavirus disease 2019; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; CK, creatine kinase; CK-MB, creatine kinase muscle-brain isoform; cTnI, cardiac troponin I; Data are mean  $\pm$  SD, or median (IQR). P values comparing severe and mild patients are from Fisher's exact test or Mann-Whitney U test.  $P < 0.05$  are considered statistically significant.

## Analysis of risk factors for severe COVID-19

To determine the risk factors for the bad prognosis of patients with severe disease, we compared the clinical and laboratory characteristics of mild and severe patients. Univariate logistic regression analysis showed that age, hypertension, SOFA score, and the levels of IL-6, WBC, NE, LYM, red blood cell (RBC), hs-CRP, DBIL, ALP, GGT, urea nitrogen, uric acid, cystatin C, sodium (Na), chlorine (Cl), phosphorus (P) and CK-MB were related to the aggravation of the patient's condition. Multivariable logistic regression analysis showed that SOFA score, advanced age, and hypertension were independently associated with the risk of severe COVID-19. In addition, the levels of WBC, NE, LYM, ALP, P, urea nitrogen, cystatin C and CK-MB were also related with severe COVID-19. Univariate analysis showed that SOFA score was a risk factor for patients with severe COVID-19, with an odds ratio of 5.328 (95% CI: 2.932–9.681;  $P < 0.001$ ). Multivariate analysis also revealed that SOFA score was a risk factor for patients with severe COVID-19 (OR = 5.851; 95% CI: 3.044–11.245;  $P < 0.001$ ) (Table 3).

Table 3  
Risk factors associated with severe COVID-19 patients

Risk factors	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Age, years	1.064(1.034–1.094)	0.000	1.069(1.036–1.103)	0.000
Hypertension	6.190(2.307–16.614)	0.000	7.310(1.705–31.350)	0.007
Diabetes	4.075(0.827–20.088)	0.084		
SOFA score	5.328(2.932–9.681)	0.000	5.851(3.044–11.245)	0.000
IL-6	1.021(1.002–1.041)	0.029		
White blood cells	1.196(1.078–1.327)	0.001	1.195(1.060–1.346)	0.004
Neutrophils	1.232(1.107–1.371)	0.000	1.210(1.084–1.351)	0.001
Lymphocytes	0.222(0.094–0.526)	0.001	0.280(0.107–0.730)	0.009
Red blood cell	0.520(0.278–0.973)	0.041		
hs-CRP	1.026(1.008–1.045)	0.006		
Direct bilirubin	1.207(1.016–1.434)	0.032		
Alkaline phosphatase	1.020(1.002–1.039)	0.032	1.032(1.007–1.057)	0.013
Gamma-glutamyl transpeptidase	1.006(1.001–1.012)	0.027		
Urea nitrogen	1.484(1.173–1.876)	0.001	1.480(1.154–1.898)	0.002
Uric acid	0.993(0.989–0.998)	0.005		
Cystatin C	33.239(4.316–255.970)	0.001	30.893(2.988–319.403)	0.004
Sodium	0.819(0.715–0.937)	0.004		
Chlorine	0.844(0.743–0.960)	0.010		
Phosphorus	0.068(0.012–0.380)	0.002	0.055(0.007–0.462)	0.008
CK-MB	1.092(1.027–1.161)	0.005	1.086(1.017–1.161)	0.030
Procalcitonin	5.689(0.710–45.575)	0.102		
Hemoglobin	0.980(0.960–1.000)	0.056		
Platelets	1.004(0.999–1.009)	0.096		

Abbreviations: COVID-19, Coronavirus disease 2019; SOFA score, Sequential Organ Failure Assessment score; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; CK-MB, creatine kinase muscle-brain isoform; OR, odds ratio; CI, confidence interval.

Risk factors	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Total bilirubin	1.057(0.995–1.123)	0.072		
Indirect bilirubin	1.068(0.981–1.163)	0.128		
Potassium	0.608(0.325–1.139)	0.120		
Calcium	0.220(0.032–1.485)	0.120		
Myoglobin	1.004(0.999–1.009)	0.112		

Abbreviations: COVID-19, Coronavirus disease 2019; SOFA score, Sequential Organ Failure Assessment score; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; CK-MB, creatine kinase muscle-brain isoform; OR, odds ratio; CI, confidence interval.

## ROC curves and cumulative survival curves for predicting the severity and prognosis of COVID-19

ROC curves were constructed to evaluate the predictive value of the SOFA score for the severity and prognosis of COVID-19 (Fig. 1B and Fig. 1C). The area under the receiver operating characteristic curve (AUC) was used to evaluate the diagnostic accuracy of the SOFA score for predicting severe COVID-19 [cutoff value = 2; AUC = 0.908 (95% CI: 0.857–0.960); sensitivity: 85.20%; specificity: 80.40%] and the risk of death in COVID-19 patients [cutoff value = 5; AUC = 0.995 (95% CI: 0.985–1.000); sensitivity: 100.00%; specificity: 95.40%]. Kaplan-Meier curve analysis and the log-rank test were performed to assess the cumulative survival rates and compare the 60-day survival curves between the high SOFA score group (SOFA score  $\geq$  5) and the low SOFA score group (SOFA score < 5). Patients in the high SOFA score group had a significantly higher risk of death than those in the low SOFA score group (*log-rank*,  $P < 0.001$ ) (Fig. 1D).

## Results of Cox proportional hazards regression analysis

Cox proportional hazards regression analysis was used to assess the potential association between the SOFA score and hospital death. The univariate analysis indicated that the SOFA score was associated with a higher risk of hospital death (HR = 1.279, 95% CI: 1.123–1.456,  $P < 0.001$ ). In addition, patient age, lowest SPO<sub>2</sub>, hypertension, CLD1, chronic lung disease (CLD2), chronic kidney disease (CKD), and the levels of RBC, hemoglobin (Hb), hs-CRP, total bilirubin (TBIL), DBIL, aspartate aminotransferase (AST), ALP, urea nitrogen, creatinine, cystatin C, cardiac troponin I (cTnI) and myoglobin were associated with the risk of death in the hospital (Table 4). Multivariate Cox proportional hazards regression analysis was used to evaluate the independent prognostic effect of the SOFA score. After adjusting for CLD2, CKD, and CLD1 (model 1), the HR of the SOFA score for predicting hospital deaths was 1.405 (95% CI: 1.132–1.744,  $P = 0.002$ ). After adjusting for age, CLD1, and CLD2 (model 2), the HR was 1.336 (95% CI: 1.069–1.670,  $P = 0.011$ ). After adjusting for hypertension, CLD2, and CKD (model 3), the HR was 1.292 (95% CI: 1.090–1.532,  $P = 0.003$ ). After adjusting for cystatin C (model 4), the HR was 1.276 (95% CI: 1.083–1.504,  $P = 0.004$ ).

*0.004*). After adjusting for LYM, hs-CRP, creatine kinase (CK), and CK-MB (model 5), the HR was 1.341 (95% CI: 1.045–1.721, *P* = *0.021*). After adjusting for CK-MB (model 6), the HR was 1.270 (95% CI: 1.096–1.472, *P* = *0.001*). After adjusting for Na (model 7), the HR was 1.320 (95% CI: 1.127–1.546, *P* = *0.001*). In this process, age, CLD1, CKD, CLD2, cystatin C, hs-CRP, CK and CK-MB also showed significance for independently predicting hospital death, while Na showed a protective effect (*Table 5*). Forest plots depicting the results of the multivariate analysis of each SOFA score model assessed by the Cox proportional hazards regression model are shown in Fig. 2.

Table 4

Results of univariate Cox proportional-hazards regression analyzing the effect of variables on in hospital death

Risk factors	HR (95%CI)	p value
Age	1.101 $\square$ 1.026-1.181 $\square$	0.007
SOFA score	1.279 $\square$ 1.123-1.456 $\square$	0.000
Lowest SPO2	0.910 $\square$ 0.872-0.950 $\square$	0.000
Hypertension	6.083 $\square$ 1.173-31.540 $\square$	0.032
Chronic lung disease	13.079 $\square$ 1.450-117.959 $\square$	0.022
Chronic kidney disease	24.937 $\square$ 2.768-224.666 $\square$	0.004
Chronic liver disease	12.467 $\square$ 1.270-122.355 $\square$	0.030
Red blood cell	0.141 $\square$ 0.045-0.441 $\square$	0.001
Hemoglobin	0.942 $\square$ 0.909-0.976 $\square$	0.001
hs-CRP	1.020 $\square$ 1.004-1.037 $\square$	0.015
Total bilirubin	1.022 $\square$ 1.004-1.041 $\square$	0.019
Direct bilirubin	1.034 $\square$ 1.008-1.062 $\square$	0.010
Aspartate aminotransferase	1.006 $\square$ 1.002-1.011 $\square$	0.005
Alkaline phosphatase	1.007 $\square$ 1.002-1.011 $\square$	0.002
Urea nitrogen	1.318 $\square$ 1.172-1.483 $\square$	0.000
Creatinine	1.006 $\square$ 1.003-1.009 $\square$	0.000
Cystatin C	2.400 $\square$ 1.618-3.558 $\square$	0.000
Sodium	0.779 $\square$ 0.626-0.969 $\square$	0.025
CK	1.007 $\square$ 1.003-1.011 $\square$	0.000
CK-MB	1.040 $\square$ 1.017-1.064 $\square$	0.001
cTnI	1.072 $\square$ 1.022-1.125 $\square$	0.004
Myoglobin	1.007 $\square$ 1.004-1.010 $\square$	0.000
Highest temperature	0.449 $\square$ 0.194-1.041 $\square$	0.062
Fever	0.212 $\square$ 0.043-1.051 $\square$	0.058
Dyspnea	6.088 $\square$ 0.692-53.598 $\square$	0.104
Lymphocytes	0.128 $\square$ 0.009-1.904 $\square$	0.136

Eosinophil	55.502±0.613-5029.250±	0.081
Platelets	0.990±0.978-1.002±	0.103
Indirect bilirubin	1.060±0.997-1.127±	0.064

Abbreviations: SOFA score, Sequential Organ Failure Assessment score; SPO<sub>2</sub>, oxygen saturation; hs-CRP, high-sensitivity C-reactive protein; CK, creatine kinase; CK-MB, creatine kinase muscle-brain isoform; cTnI, cardiac troponin I; HR, hazard ratio; CI, confidence interval.

Table 5

Results of multivariate Cox proportional-hazards regression analyzing the effect of variables on in hospital death

Risk factors	HR (95%CI)	<i>p</i> value
Not Adjusted SOFA score	1.279(1.123-1.456)	0.000
Mode 1		
SOFA score	1.405(1.132-1.744)	0.002
Chronic lung disease	93.516(4.063-2152.432)	0.005
Chronic kidney disease	10.216(0.957-109.050)	0.054
Chronic liver disease	69.136(3.226-1481.626)	0.007
Mode 2		
SOFA score	1.336(1.069-1.670)	0.011
Age	1.152(1.018-1.302)	0.024
Chronic lung disease	43.406(1.869-1008.004)	0.019
Chronic liver disease	1515.310(10.430-220156.492)	0.004
Mode 3		
SOFA score	1.292(1.090-1.532)	0.003
Hypertension	5.995(0.655-54.887)	0.113
Chronic lung disease	16.956(1.197-240.105)	0.036
Chronic kidney disease	21.147(1.224-365.495)	0.036
Mode 4		
SOFA score	1.276(1.083-1.504)	0.004
Cystatin C	1.913(1.304-2.806)	0.001
Mode 5		
SOFA score	1.341(1.045-1.721)	0.021
Lymphocytes	22.140(0.756-647.954)	0.072
hs-CRP	1.035(1.001-1.071)	0.043
CK	1.007(1.002-1.012)	0.009
CK-MB	1.055(1.006-1.107)	0.027
Mode 6		

SOFA score	1.270±1.096-1.472±	0.001
CK-MB	1.034±1.007-1.061±	0.014
Mode 7		
SOFA score	1.320±1.127-1.546±	0.001
Sodium	0.775±0.623-0.964±	0.022

Abbreviations: SOFA score, Sequential Organ Failure Assessment score; hs-CRP, high-sensitivity C-reactive protein; CK, creatine kinase; CK-MB, creatine kinase muscle-brain isoform; HR, hazard ratio; CI, confidence interval.

## Discussion

Severe COVID-19 can easily cause ARDS, multiple organ dysfunction, acute heart injury, acute kidney injury and even death [5]. Identifying the death risk associated with critically ill patients early and giving these patients priority treatment in a timely manner are particularly important in global health emergencies. Studies have shown that a total of 60 predictors can assess the severity of COVID-19, of which 7 factors are considered to be highly correlated and consistent, including SOFA score, age, D-dimer, hs-CRP, body temperature, albumin and diabetes [13]. The results of this study revealed that SOFA score, age, CKD, CLD1, CLD2, cystatin C, hs-CRP, CK, CK-MB and other factors were independent risk factors for in-hospital death, which was similar to the results of the above study.

Zhou et al. showed that older age, higher D-dimer levels and higher SOFA scores in COVID-19 patients at admission were associated with high in-hospital mortality. In addition, increased levels of cTnI, lactate dehydrogenase and lymphocytopenia were more common in patients with severe COVID-19 [14]. Also, studies have shown that SARS-CoV-2 can participate in and induce the activation of complement and coagulation system, which is related to the severity of COVID-19 patients [15]. Myocardial injury was another an independent risk factor for deterioration and death in patients with COVID-19. The risk of death of hospitalized patients with myocardial injury was 6.6–26.9 times higher than that of patients without myocardial injury [16].

In this study, the median age of seriously ill patients was 56.00 years, which was significantly higher than that of mild patients (38 years). Hypertension was the most common complication of COVID-19, especially in severe patients. A review of the literature showed that COVID-19 patients with hypertension, especially elderly patients, had a 2.5-fold increased risk of serious or even fatal events [17]. Another large cohort study showed that in addition to some factors, such as advanced age, male, asthma, diabetes, increased the risk of death in COVID-19 patients, poverty and ethnicity (Blacks and South Asians) were also associated with death of COVID-19 patients [18].

At present, published studies have not systematically evaluated the accuracy of the SOFA score in the diagnosis of COVID-19 severity and its predictive value. The SOFA score was originally used to assess the severity of organ dysfunction in patients with severe sepsis and has been validated in ICU patients in

multiple regions [19]. As critically ill patients usually have multiple organ dysfunction, the SOFA score has been widely used to predict the clinical outcomes of critically ill patients, such as predicting mortality in patients with chronic liver failure and hematological malignancies [20, 21]. Gupta et al. summarized the clinical characteristics of SARS-CoV-2 infection, which could not only cause severe lung injury, but also damaged the heart, liver, kidney, nervous system, endocrine system, blood system and skin, resulting in arrhythmia, acute coronary syndrome, thrombosis, gastrointestinal symptoms, hyperglycemia and skin rash [22]. Thus, the SOFA score can comprehensively assess multiple organ dysfunction caused by SARS-CoV-2.

In our study, the SOFA score was also recognized as a valuable prognostic tool for the outcome of patients with COVID-19. Univariate regression analysis showed that the increase in SOFA score and IL-6 and the decrease in lymphocyte count were related to the aggravation of the patient's condition. Multivariable regression analysis demonstrated that SOFA score, advanced age, and hypertension were independently associated with the risk of severe COVID-19. At present, it is believed that COVID-19 leads to organ failure, which is mainly related to cytokine storm and immunosuppression; the clinical manifestations are persistent fever, hemocytopenia and organ involvement [23]. The laboratory results were characterized by increased levels of inflammatory factors such as granulocyte colony-stimulating factor (G-CSF), interleukin-2 (IL-2), IL-6, interleukin-7 (IL-7), interferon- $\gamma$ -inducible protein-10 (IP-10), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), macrophage inflammatory protein-1  $\alpha$  (MIP-1  $\alpha$ ) and monocyte chemoattractant protein 1 (MCP-1) [24, 25]. The analysis of the immune system of patients with severe COVID-19 showed that the number of innate immune cells increased, while T cells decreased. In COVID-19 patients, the early increase of cytokines was positively correlated with poor prognosis [26]. This may well explain why only dexamethasone has been found to reduce mortality in many clinical trials for COIVD-19 [27]. Therefore, the SOFA score can reflect not only multiple organ failure but also the degree of inflammation and can accurately predict the severity of the patient's disease.

Sepsis is a life-threatening organ dysfunction, caused by dysregulated host response to infection. Rapid change in SOFA score  $\geq 2$  points after infection is regarded as the clinical criterion of sepsis-associated organ dysfunction. The SOFA score  $\geq 2$  reflects approximately 10% of the overall risk of death of suspected infected patients in general hospitals, and even patients with moderate organ dysfunction may further deteriorate. Therefore, it emphasizes the seriousness of this situation and reminds clinicians to intervene in a timely and appropriate manner [28]. In this study, the area under the ROC curve (AUC) of the SOFA score was 0.908 (95% CI: 0.857–0.960) with a diagnostic cut-off value of 2 and a sensitivity and specificity of 85.20% and 80.40%, respectively. This result suggests that a SOFA score  $\geq 2$  can predict the severity of COVID-19 patients. Another study also showed that among 184,875 patients admitted to the ICU, an increase of 2 or more in the SOFA score had greater prognostic accuracy for in-hospital mortality than quick SOFA (qSOFA) score or the systemic inflammatory response syndrome standard [29]. When the cut-off value of the optimal SOFA score is 5 (AUC: 0.995, 95% CI: 0.985-1.000, sensitivity: 100.00%, specificity: 95.40%), the risk of mortality in patients with COVID-19 can be predicted. Regarding the 60-day mortality rate of patients in the high and low SOFA score groups, patients in the high SOFA score group

(SOFA score  $\geq 5$ ) had a significantly higher risk of death than those in the low SOFA score group (SOFA score  $< 5$ ). Wang et al. used the SOFA score to assess the predictive value of early sepsis and 30-day mortality after liver transplantation, indicating that the survival rate of patients with SOFA score  $> 5$  within 1–7 days after liver transplantation was significantly lower than that of patients with SOFA score  $\leq 5$  [30]. Therefore, SOFA score  $\geq 5$  can be used as a good predictor of hospital mortality in COVID-19 patients. In addition, univariate and multivariate Cox proportional hazards regression analyses demonstrated that there was a high correlation between the SOFA score and hospital mortality, and the SOFA score was a risk factor for death in COVID-19 patients. These results provide strong evidence for priority in treatment and early special care for patients.

## Limitations

Nevertheless, some limitations should be considered when interpreting the results of this study. First, this is a single center retrospective study involving a relatively small number of patients. Second, our study was limited by its retroactive design, which resulted in some data unavailable in the electronic medical records. In some cases, if the patient's condition was stable during hospitalization without dyspnea and hypoxia, blood gas analysis was not performed, so the SOFA score could not be calculated accurately and had to be estimated by the EM algorithm. However, in our study, the data loss rate of this variable was less than 25%. Finally, the retrospective nature of our study may lead to selection bias, and the findings need to be verified and refined by future prospective studies.

## Conclusions

The world is currently in the midst of a pandemic of COVID-19. The impact of the COVID-19 epidemic on human health, modern society and global economy is self-evident. At present, there is no specific drug for anti-viral treatment of COVID-19. Clinically, respiratory support and symptomatic treatment are mainly used in patients with COVID-19, while the related prophylactic vaccine is still in clinical trial. Given this background, a simple and practical tool for predicting the prognosis of patients with COVID-19 is particularly important. It will help hospitals improve their priority setting, and, based on this, special care will be provided for critically ill patients to reduce economic burden to patients and society. In conclusion, the SOFA score may be an independent risk factor for hospital death and can be well used to assess the severity and prognosis of COVID-19.

## Abbreviations

COVID-19: Coronavirus disease 2019; SOFA: Sequential Organ Failure Assessment; ROC: Receiver operating characteristic; AUC: area under the ROC curve; WHO: World Health Organization; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; FiO<sub>2</sub>: oxygen (PaO<sub>2</sub>)/oxygen concentration; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; SD: standard deviation; IQR: interquartile range; HRs: hazard ratios; HR: hazard ratio; qSOFA: quick SOFA; G-CSF: granulocyte colony-stimulating factor; IL-2: interleukin-2; IL-6: interleukin-6; IL-7: interleukin-7; IP-10: interferon- $\gamma$ -inducible protein-10; TNF-

a: tumor necrosis factor  $\alpha$ ; MIP-1  $\alpha$ : macrophage inflammatory protein-1  $\alpha$ ; MCP-1: monocyte chemoattractant protein 1; SpO<sub>2</sub>: oxygen saturation; hs-CRP: high-sensitivity C-reactive protein; CK: creatine kinase; CK-MB: creatine kinase muscle-brain isoform; cTnI: cardiac troponin I; OR: odds ratio; CI: confidence interval; CLD1: Chronic liver disease; CLD2: Chronic lung disease; CKD: Chronic kidney disease; HP: Hypertension; LYM: Lymphocytes; Hb: hemoglobin; WBC: white blood cell; NE: neutrophil;  $\gamma$ -GGT: gamma-glutamyl transpeptidase; DBIL: direct bilirubin; ALP: alanine aminotransferase; PCT: procalcitonin; RBC: red blood cell; Na: sodium; Cl: chlorine; P: phosphorus

## Declarations

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### Authors' contribution

Zheng Yang, Qinming Hu and Yi Sun conceived the study idea, and performed interpretation, manuscript writing and final approval. Fei Huang, and Shouxin Xiong performed data analysis and collection. All authors reviewed and approved the final version of the manuscript.

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### Availability of supporting data

Due to the finalization of the clinical study report, the data analyzed during the current study are not publicly available, but can be obtained from the correspondent author under reasonable request.

### Ethics approval and consent to participate

The study was reviewed and approved for publication by the Institutional Review Board of Jinghzou Central Hospital, and the requirement for informed consent from the study participants was waived.

### Consent for publication

Not applicable

### Competing interests

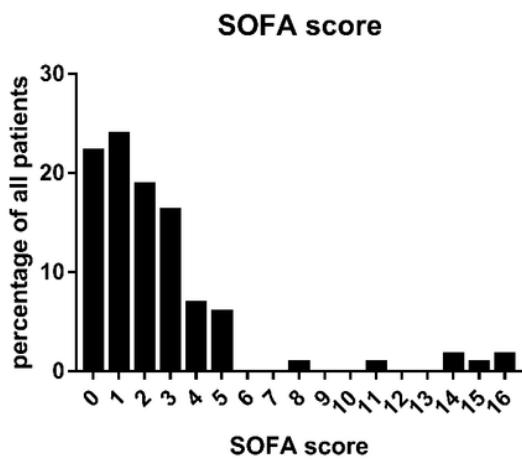
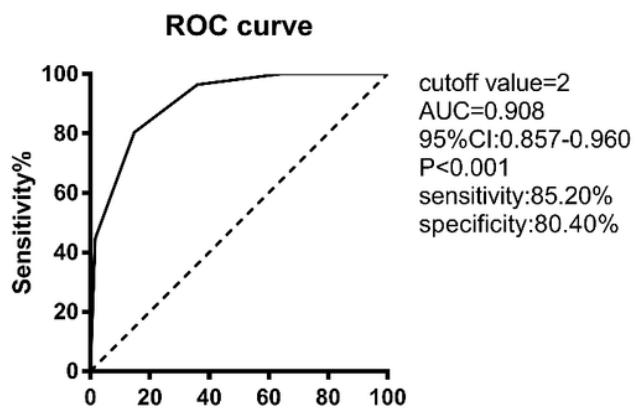
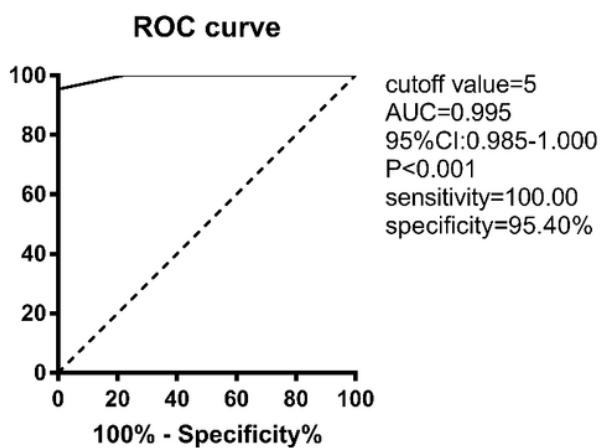
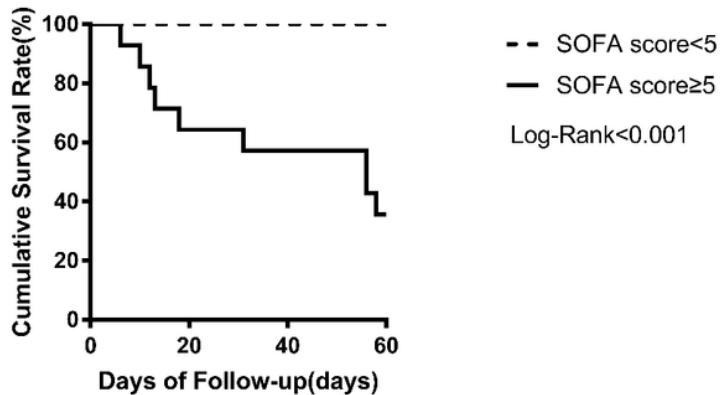
The authors declare that there is no conflict of interest.

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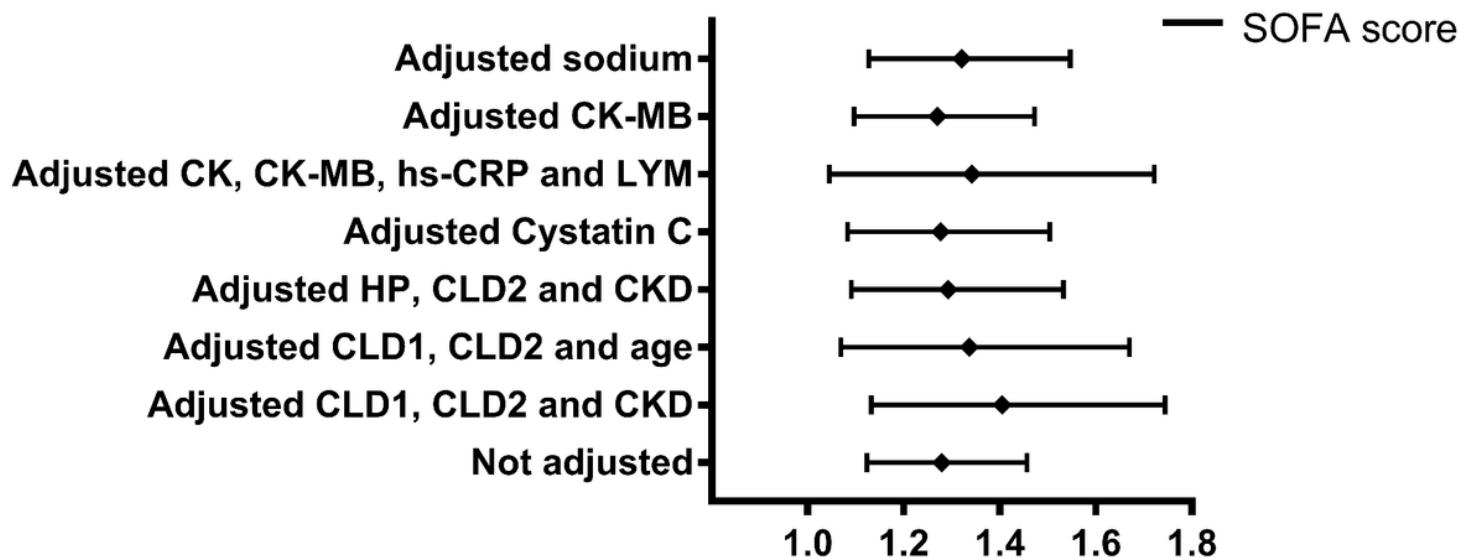
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## Figures

**A****B****C****D****Figure 1**

A. Distribution of SOFA scores in patients with COVID-19 B. ROC curves for patients with SOFA score =2 in predicting the severity of COVID-19 C. ROC curves for patients with SOFA score =5 in predicting the death in the hospital D. Kaplan-Meier survival curves for patients with COVID-19 in the SOFA score  $\geq 5$  group and in the SOFA score <5 group



**Figure 2**

Forest plots demonstrating the association of SOFA score with the death of COVID-19 patients in the hospital. Abbreviations: SOFA score, Sequential Organ Failure Assessment score; COVID-19, Coronavirus disease 2019; CLD1, Chronic liver disease; CLD2, Chronic lung disease; CKD, Chronic kidney disease; HP, Hypertension; CK, creatine kinase; CK-MB, creatine kinase muscle-brain isoform; hs-CRP, high-sensitivity C-reactive protein; LYM, Lymphocytes.