Prognostic Value of Serum Creatinine in Severe Covid-19 Patients in Wuhan, China: A Retrospective Cohort Study

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Research

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Abstract

Objectives: Although the respiratory and immune systems are the major targets of SARS-CoV-2, increasing evidence revealed that kidney injury was not rare in coronavirus disease 2019 (COVID-19). However, the incidences of kidney abnormalities were significantly different, from 0.5 to 75.4% in several reports. The association of kidney injury with prognosis remain controversial.

Methods: In this retrospective single center cohort study, laboratory confirmedCOVID-19inpatients with severe type were enrolled. Demographic, clinicaland laboratory data were collected. Association ofserum creatinine (SCr)with 28-days mortality in severe COVID-19 patients was analyzed.

Results:18.79% (48/304) patients died during the first 28-days of hospitalization.Non-survivors had a significantly higher SCr levels than survivors (109.27μmol/L vs. 69.99μmol/L, P <0.001). The 28-days mortality in high SCr group (>76μmol/L) was significantly higher than that in low SCr group (31.7% vs. 7.5%, P <0.001). Multivariate logistic regression revealed that the independent risk factors of 28-days outcome included age(OR: 2.95, 95%CI: 1.08-8.05), WBC (OR: 6.09, 95%CI: 2.27-6.39), lymphopenia (OR: 3.49, 95%CI: 1.55-7.92), IL-6 (OR: 4.44, 95%CI: 1.64-11.99) and SCr (OR: 2.69, 95%CI: 1.18-6.11). Kaplan-Meier analysis demonstrated the survival disadvantage in patients with high SCr levels (>76μmol/L). ROC curve showed the SCr cut-off value for predicting 28-days death was 77.5 μmol/L, with the sensitivity of 68.8% and speciality of 74.1%.

Conclusion: SCr was associated with poor prognosis and might be an independent risk factor for in-hospital death. The cut-off value of SCr for prognosis prediction was 77.5 μmol/L, with the sensitivity of 68.8% and speciality of 74.1%.

Background

Coronavirus disease 2019 (COVID-19) has resulted in considerable morbidity and mortality worldwide since December 2019. Recent reports showed the mortality of COVID-19 patients with severe form or critical illness as high as 28.3% [1]. Although the respiratory and immune systems are the major targets of COVID-19, increasing evidence revealed that SARS-CoV-2 infection could also be found out of lung, such as digestive system, cardiovascular system and coagulant system [1]. Disorder of coagulation and injury of cardiovascular system have been proved associated with in-hospital mortality in COVID-19 patients [1–2].

The incidences of kidney injury in COVID-19 of different regions showed large difference. Some studies revealed acute kidney injury (AKI) occurred in 0.5-7% of cases and in 2.9–23% of ICU patients [2–5]. A recent report indicated 75.4% patients had abnormal urine dipstick tests or AKI [6]. However, other report demonstrated that COVID-19 did not result in AKI [7].

Although many patients showed mild increase of blood urea nitrogen, creatinine and emerging of proteinuria, most of them did not meet the diagnostic criteria of AKI. Transit blood urea nitrogen elevation

or proteinuria might be due to many kind of factors, such as infection, inflammation, hypoxaemia, shock or drugs. Whether the AKI of COVID-19 is caused by a coronavirus-induced cytopathic effect or cytokine storm-induced systemic inflammatory response remains unclear.

The purpose of this study was to explore the potential association of kidney function with prognosis of severe COVID-19 patients, which would be benefit for early identification of patients at risk of deterioration.

Methods

Subjects

In this retrospective cohort study, 304 adult inpatients (≥ 18 years old) with severe COVID-19 admitted to Wuhan Tongji Hospital were enrolled from February 09 to March 09, 2020. Diagnosis and disease severity of all COVID-19 patients were determined according to World Health Organization interim guidance and the Chinese management guideline for COVID-19 (version 7.0). This study was approved by the institutional review boards at Wuhan Tongji Hospital and The First Affiliated Hospital of Soochow University. Written informed consent was exempted as COVID-19 is an emerging infectious disease.

Severe form COVID-19 patients should meet any one of the following: 1. Shortness of breath, respiratory rate ≥ 30 breaths/minute; 2. SaO_2 or SPO_2 ≤ 93% on room air; 3. PaO_2/FiO_2 ≤ 300 mmHg. The clinical classification of severe form were determined by two trained physicians via analyzing the data of all available electronic medical records and patient care resources. Patients with a history of chronic kidney disease were excluded.

Data Collection

Baseline demographic data and clinical features (age, gender, comorbidities, laboratory findings, severity of illness scores, treatments, complications and outcomes) were recorded. Patients were followed-up from admission to 28 days in hospital, hospital discharge, or death, whichever came first. The criteria for discharge were defined as all the following: absence of fever for at least 3 days; substantial improvement in both lungs in chest CT; clinical remission of respiratory symptoms; and two throat-swab samples with SARS-CoV-2 RNA negative obtained at least 24 hours apart.

Statistical analysis

Continuous data with normal distribution were presented as mean ± standard deviation. If continuous data showed a skewed distribution, they were presented as median [interquartile range (IQR)]. Frequency data were expressed as proportions. Comparisons of continuous variables were made with Student's t test or the Mann-Whitney U test when appropriate, while differences in categorical variables were assessed using the x^2 test or Fisher's exact test, as appropriate. Survival curves were plotted using the

Kaplan-Meier method using the log-rank test. Multivariate logistic regression models were used to determine the independent risk factors for 28-days mortality after hospitalization. Data were analyzed using SPSS 25.0. A two-tailed *P* value < 0.05 was considered statistically significant.

Results

The baseline characteristics

A total of 304 adult inpatients were included. The median age was 63 years old (IQR: 52.0, 71.0), 49.67% (151/304) were male, and 18.79% (48/304) died during the first 28 days of hospitalization. The most common symptoms were fever (81.9%) and cough (78.0%). The most popular comorbidities was hypertension (36.5%).

Survivors were younger (60ys vs. 71ys, $P < 0.001$), have a higher levels of lymphocyte count (1.3 [IQR: 0.9,1.7] × 10^9 /L *vs.* 0.6 [IQR: 0.4, 0.9] × 10^9 /L, $P < 0.001$) and platelet count (232.0 [175.0, 315.0] × 10^9 /L *vs.* 150.5 [96.5, 231.3] × 10^9 /L, $P < 0.001$), a lower levels of WBC count (5.6 [IQR: 4.6,7.4] × 10^9 /L *vs.* 8.4 [IQR: 6.0, 12.9] × 10^9 /L, $P < 0.001$), hs-CRP (6.3 [IQR: 1.4, 37.2] mg/L *vs.* 93.0 [IQR: 63.7, 140.8] mg/L, $P < 0.001$), IL-6 (3.9 [IQR: 1.8, 10.7] pg/mL *vs.* 47.8 [IQR: 16.9, 159.2] pg/mL, $P < 0.001$) and AST (25.0 [IQR: 18.0, 35.0] U/L *vs.* 44.5 [IQR: 25.0, 62.8] U/L, $P < 0.001$) than that in non-survivors. Non-survivors had a significantly higher SCr levels than survivors (93.5 [IQR: 73.0, 120.5] μmol/L *vs.* 66.0 [IQR: 56.0, 78.0] μmol/L, $P < 0.001$). Non-survivors received higher ratio of CRRT (29.2% *vs.* 3.9%, $P < 0.001$) and IMV (85.4% vs. 7.0%, P < 0.001) treatment.

Clinical features of patients with or without high SCr levels

Patients with high SCr level (> 76 μmol/L) have a higher levels of WBC count (6.7 [IQR: 5.1, 9.0] × 10^9 /L *vs.* 5.5 [IQR: 4.4, 7.2] × 10^9 /L, $P < 0.001$), hs-CRP (46.4 [IQR: 7.0, 104.0] mg/L *vs.* 4.8 [IQR: 1.2, 36.3] mg/L, $P < 0.001$) and IL-6 (11.8 [IQR: 3.0, 45.8]pg/mL *vs.* 3.8 [IQR: 1.9, 10.0]pg/mL, $P = 0.047$), a lower levels of lymphocyte count (0.9 [IQR: 0.6, 1.4] × 10^9 /L *vs.* 1.3[IQR: 0.9, 1.7] × 10^9 /L, $P < 0.001$) and platelet count (188.0 [IQR: 133.0, 251.8] × 10^9 /L *vs.* 245.0 [IQR: 187.0, 317.0] × 10^9 /L, $P < 0.001$) as compared with patients with low SCr levels. Patients in high SCr group received a higher ratio of CRRT (15.4% vs. 4.0%, P < 0.001) and IMV (32.7% vs. 12.5%, P < 0.001) treatment.

Scr Associated With Prognosis In Severe Covid-19 Patients

As shown in Table 2, the 28-days mortality in high SCr group was significantly higher than that in low SCr group (31.7% vs. 7.5%, P < 0.001). Multivariate logistic regression analysis (Table 3) revealed that the independent risk factors of 28-days outcome included age > 60ys (OR: 2.95, 95%CI: 1.08–8.05), WBC count > 10 × 10^9 /L (OR: 6.09, 95%CI: 2.27–6.39), lymphocyte count < 0.8 × 10^9 /L (OR: 3.49, 95%CI: 1.55–7.92), IL-6 > 7 pg/mL (OR: 4.44, 95%CI: 1.64–11.99) and SCr > 76 μmol/L (OR: 2.69, 95%CI: 1.18–6.11).

Table 1
Baseline characteristics of 304 severe COVID-19 patients with different eGFR levels.

Characteristics	Total (n = 304)	Survivor (n = 256)	Non-survivor (n = 48)	P value
Age, y	63 (52.0, 71.0)	60 (49.8, 69.0)	71(65.0, 79.3)	< 0.001
Male sex	151(49.7%)	120(46.9%)	31(64.6%)	0.024
Symptoms				
Fever	249(81.9%)	207(80.9%)	42(87.5%)	0.27
Cough	237(78.0%)	201(78.5%)	36(75.0%)	0.59
Dyspnea	128(42.1%)	101(39.4%)	27(56.3%)	0.031
Comorbidity				
Hypertension	111(36.5%)	90(35.2%)	21(43.8%)	0.26
Diabetes	44(14.5%)	35(13.7%)	9(18.8%)	0.36
Cardiac disease [a]	34(11.1%)	22(8.6%)	12(25.0%)	< 0.001
Chronic lung disease	18(5.9%)	14(5.5%)	4(8.3%)	0.44
Chronic kidney disease	3(1.0%)	3(1.2%)	0	0.45
Laboratory finding				
WBC count, $\times 10^9$ /L	5.9 (4.6, 7.8)	5.6(4.6 ,7.4)	8.4(6.0, 12.9)	< 0.001
Lymphocyte count, $\times 10^9$ /L	1.1 (0.8 ,1.6)	1.3(0.9 ,1.7)	0.6(0.4, 0.9)	< 0.001
Platelet count, $\times 10^9$ /L	223.0 (163.5, 297.5)	232.0(175.0, 315.0)	150.5(96.5, 231.3)	< 0.001
Creatinine level, μmol/L	69.0 (57.0, 83.5)	66.0(56.0, 78.0)	93.5(73.0, 120.5)	< 0.001
hs-CRP, mg/L	10.6 (1.7, 65.0)	6.3(1.4, 37.2)	93.0(63.7, 140.8)	< 0.001

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

[a] Includes congestive heart disease and coronary atherosclerotic heart disease.

Abbreviations: WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: nonivasive positive pressure ventilation.

Characteristics	Total (n = 304)	Survivor (n = 256)	Non-survivor (n = 48)	P value
IL-6, pg/mL	5.1 (1.9, 20.6)	3.9(1.8, 10.7)	47.8(16.9, 159.2)	< 0.001
AST, U/L	26.0 (19.0, 38.5)	25.0(18.0, 35.0)	44.5(25.0, 62.8)	0.0012
Complication				
Shock	48(15.8%)	16(6.3%)	32(66.7%)	< 0.001
ECMO	3(1.0%)	3(1.2%)	0	0.45
CRRT	24(7.9%)	10(3.9%)	14(29.2%)	< 0.001
IMV	59(19.4%)	18(7.0%)	41(85.4%)	< 0.001
Outcome				
Hospital length of stay, d	22(13, 30)	24(15, 32.5)	13(9.5, 19.5)	< 0.001
28-days death	48(15.8%)	0	48	

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

[a] Includes congestive heart disease and coronary atherosclerotic heart disease.

Abbreviations: WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: nonivasive positive pressure ventilation.

Table 2
Baseline characteristics of 304 severe COVID-19 patients with different eGFR levels.

Characteristics	Cr > 76 (n = 104)	Cr ≤ 76 (n = 200)	P value
Age, y	67.5(56, 79)	60(50, 68.5)	< 0.001
Male sex	68(65.4%)	83(4.5%)	< 0.001
Symptoms			0.38
Fever	88(84.6%)	161(80.5%)	
Cough	81(77.9%)	156(78.0%)	0.98
Dyspnea	43(41.3%)	85(42.5%)	0.85
Comorbidity			0.21
Hypertension	43(41.3%)	68(34.0%)	
Diabetes	19(18.3%)	25(12.5%)	0.17
Cardiac disease [a]	16(15.4%)	18(9.0%)	0.094
Chronic lung disease	10(9.6%)	8(4.0%)	0.049
Chronic kidney disease	2(1.9%)	1(0.5%)	0.23
Laboratory finding			
WBC count, $\times 10^9$ /L	6.7(5.1, 9.0)	5.5(4.4, 7.2)	< 0.001
Lymphocyte count, $\times 10^9$ /L	0.9(0.6, 1.4)	1.3(0.9, 1.7)	< 0.001
Platelet count, $\times 10^9$ /L	188.0(133.0, 251.8)	245.0(187.0, 317.0)	< 0.01
Creatinine level, μmol/L	95.0(83.0, 114.0)	60.0(54.0, 69.0)	< 0.001
hs-CRP, mg/L	46.4(7.0, 104.0)	4.8(1.2, 36.3)	< 0.001
IL-6, pg/mL	11.8(3.0, 45.8)	3.8(1.9, 10.0)	0.047
AST, U/L	32.0(23.0, 46.8)	24.0(18.0, 34.5)	0.065
Complication			

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

[a] Includes congestive heart disease and coronary atherosclerotic heart disease.

Abbreviations: WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: nonivasive positive pressure ventilation.

Characteristics	Cr > 76 (n = 104)	Cr ≤ 76 (n = 200)	P value
Shock	29(27.9%)	19(9.5%)	< 0.001
ECMO	3(2.9%)	0	0.016
CRRT	16(15.4%)	8(4.0%)	< 0.001
IMV	34(32.7%)	25(12.5%)	< 0.001
Outcome			
Hospital length of stay, d	22(12, 32)	22(13.5, 28)	
28-days death	33(31.7%)	15(7.5%)	< 0.001
Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).			
[a] Includes congestive heart disease and coronary atherosclerotic heart disease.			
Abbreviations: WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: nonivasive positive pressure ventilation.			

Table 3
Multivariate logistic regression analysis of risk factors for 28-days mortality in severe COVID-19 patients.

Variables	Multivariate	
	OR (95% CI)	P
Age > 60ys	2.95 (1.08–8.05)	0.035
WBC > 10×10^9 /L	6.09 (2.27–16.39)	< 0.001
Lymphocyte count < 0.8×10^9 /L	3.49 (1.55–7.92)	0.003
IL-6 > 7 pg/mL	4.44 (1.64–11.99)	0.003
Cr > 76 μmol/L	2.69 (1.18–6.11)	0.018

Kaplan-Meier analysis (Fig. 1A) indicated that patients with high SCr levels (SCr > 76 μmol/L) had a significant survival disadvantage (Fig. 1, log-rank P < 0.01)as compared to patients with low SCr levels (SCr ≤ 76 μmol/L). The ROC curve (Fig. 1B) showed that the area under curve (AUC) was 0.753. The cut-off value of SCr for prognosis prediction was 77.5 μmol/L, with the sensitivity of 68.8% and speciality of 74.1%.

Discussion

This retrospective report identified the serum creatitine independently associated with poor prognosis in severe COVID-19 patients, and the cut-off value for predicting the 28-days mortality was 77.5 μmol/L, with the sensitivity of 68.8% and speciality of 74.1%. This cut-off value is significantly lower than normal range, which suggesting that potential kidney injury on admission represented a higher risk of deterioration. Early detection and treatment of renal abnormalities might benefit to improve the vital prognosis of severe COVID-19.

Epidemiological data indicate that at least 20% of COVID-19 patients have severe disease. Although the respiratory and immune systems are the major targets of COVID-19, kidney injury is a major complication. It is reported showed that 6.7% of patients with SARS developed acute kidney injury (AKI) [8]. However, the incidences of kidney injury were significantly different, from 0.5 to 75.4% in several reports [2–5]. This might be due to the different methods of kidney injury evaluation and definition. About 68.5% patients experienced remission of proteinuria, 45.7% experienced complete recovery of kidney function [6]. Although renal abnormalities occurred in the majority of patients with COVID-19, it is controversial how to evaluated AKI precisely in COVID-19. Classical assessment of AKI is still based on SCr and urine output, but they represent only indicators of established kidney damage. Update, it remain difficult to determined a perfect bio-marker for AKI. In this study, we used SCr as a substituted method for kidney function evaluation. The incidence of elevated serum creatitine was 24.7% (75/304), which was significantly higher than previous report (14.1%) [5]. It might due to the different proportion of enrolled subjects.

Previous studies have focused on the clinical features and risk factors for death. Although AKI was popular in non-survivors in many previous reports, the affect of kidney injury on COVID-19 prognosis remain controversial. Some reports indicated that kidney disease or AKI associated mortality in COVID-19 patients [5–6]. But a recent study revealed that COVID-19 did not result in acute kidney injury (AKI) [8]. In previous study of patients with H1N1 virus infection, only those cases in the AKI III category were independently associated with mortality[9]. Most recent reports in COVID-19 evaluated kidney impairment using AKI or elevated SCr [5–6, 10]. However, the cut-off value of SCr for prognosis prediction in our study is 77.5 μmol/L, which is significantly lower than normal range. Furthermore, the hazard ratios of elevated baseline SCr in OVID-19 patients mortality was obviously lower than hematuria (2.04 vs. 8.89) or proteinuria (2.04 vs. 6.80) [5]. In our study, the OR for a nornal SCr level (> 76 μmol/L) was 2.69 (95%CI: 1.18–6.11), which was higher than previous report. It might be due to two reasons. Firstly, the proportion of enrolled subjects was different. Our study mainly enrolled severe or critical COVID-19 patients, but previous report enrolled 57.3% mild or moderate patients [5]. Secondly, we excluded patients with chronic kidney diseases. Lastly, elevated SCr might be not a sensitive bio-marker for kidney impairment evaluation in early stage. SCr is a delayed renal functional marker when it is generally increased after sever kidney damage. A recent study demonstrated that among patients with baseline SCr ≥ 0.7 mg/dl (61.9 μmol/l) those who experienced a 0.3 mg/dl increase in SCr within 48 h had clinically meaningful differences in outcomes (including length of hospital stay and mortality) when comparing with those who experienced a 50% increase in SCr from baseline within 7 days. These findings suggest that the KDIGO AKI definition should be revised because the staging may equate states that are not the same. In

addition, the AKI definition should also potentially incorporate aetiology, pathophysiology and novel biomarkers [11].

The etiology of kidney disease involvement in patients with COVID-19 is likely to be multifactorial. The direct cytopathic effects of SARS-CoV-2 on kidney tissue might be the most important reason.The receptor of SARS-CoV-2, ACE2 was found to be upregulated in patients with COVID-19, and immunostaining with SARS-CoV nucleoprotein antibody was positive in tubules [12–13]. Electron microscopic examination showed clusters of coronavirus particles with distinctive spikes in the tubular epithelium and podocytes. In addition, kidney injury may be ascribed to several causes including an inflammatory/immune reaction characterized by an enhanced release of circulating mediators able to interact and damage kidney-resident cells [8, 14]. This study showed that patients with higher SCr levels (> 76 μmol/L) had lower lymphocyte counts, higher levels of IL-6, and higher hs-CRP which indicated that they were in the state of immune system dysregulation and cytokine storm. Cytokine storm associated with COVID-19 may be another important mechanism of kidney injury in these patients and it is clear that all of these mechanisms require further exploration.

Some limitations existed in this study. Firstly, it is a single-center retrospective study, which only represented a part of severe COVID-19 patients in Wuhan, China. It could not be extrapolated completely to patients with non-severe COVID-19 or patients outside of Wuhan, China, as the diversity of epidemiological feature in different areas. Secondly, the impact of potential therapies, including immunosuppressive medications, antiretrovirals, and immunologic antibody therapy, could not be assessed as these were not uniformly implemented and often unavailable.

Conclusion

In conclusion, SCr was independently associated with short-term prognosis in severe COVID-19 patients (OR: 2.69, 95%CI: 1.18–6.11). The SCr cut-off value for predicting the 28-days mortality was 77.5 μmol/L, with the sensitivity of 68.8% and speciality of 74.1%. Surveillance for SCr may help to identify patients at high risk of death, for which early intervention may be an important prevention strategy.

Abbreviations

COVID-19
coronavirus disease 2019; SCr:serum creatinine; ROC:receiver operating characteristic curve; AKI:acute kidney injury; IQR:interquartile range; WBC:white blood cell; hs-CRP:high-sensitive C-reactive protein; IL-6:interleukin-6; IMV:invasive mechanical ventilation; NIPPV:nonivasive positive pressure ventilation.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review boards at Wuhan Tongji Hospital and The First Affiliated Hospital of Soochow University. Written informed consent was exempted as COVID-19 is an emerging infectious disease.

Consent for publication

Not applicable.

Availability of data and material

All data will be shared after request to corresponding authors.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Zeng DX and Jiang JH conceptualized the research aims, design the study, and takeresponsibility for the integrity of the data. Zhang WY and Xu DYcollected the data, performed the statistical analysis, wrote the first draft of the paper. Wang CG, Liu YY and Huang JA performed the statistical analysis.

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Figures

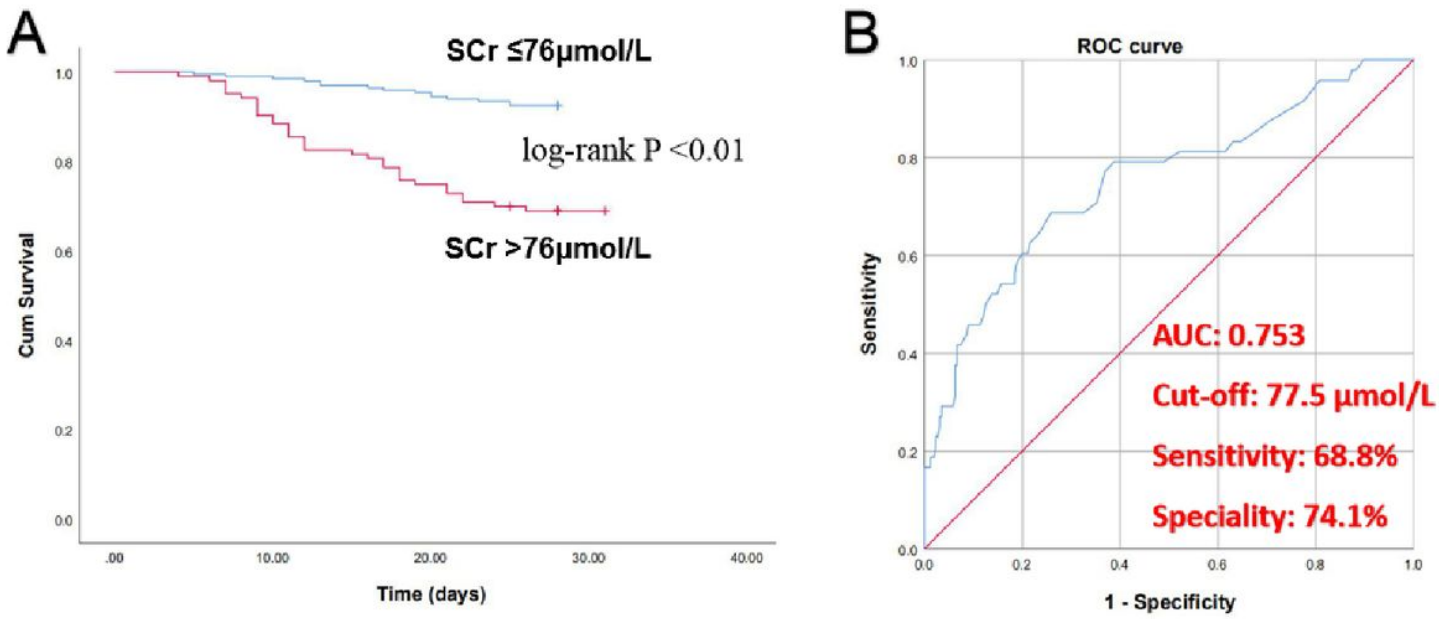

Figure 1

Association of SCr with prognosis in severe COVID-19 patients. A: Kaplan-Meier analysis of the 28-days mortality among COVID-19patients with different serum creatitine levels. B: The ROC curve of serum creatitine for predicting prognosis of severe COVID-19 patients.