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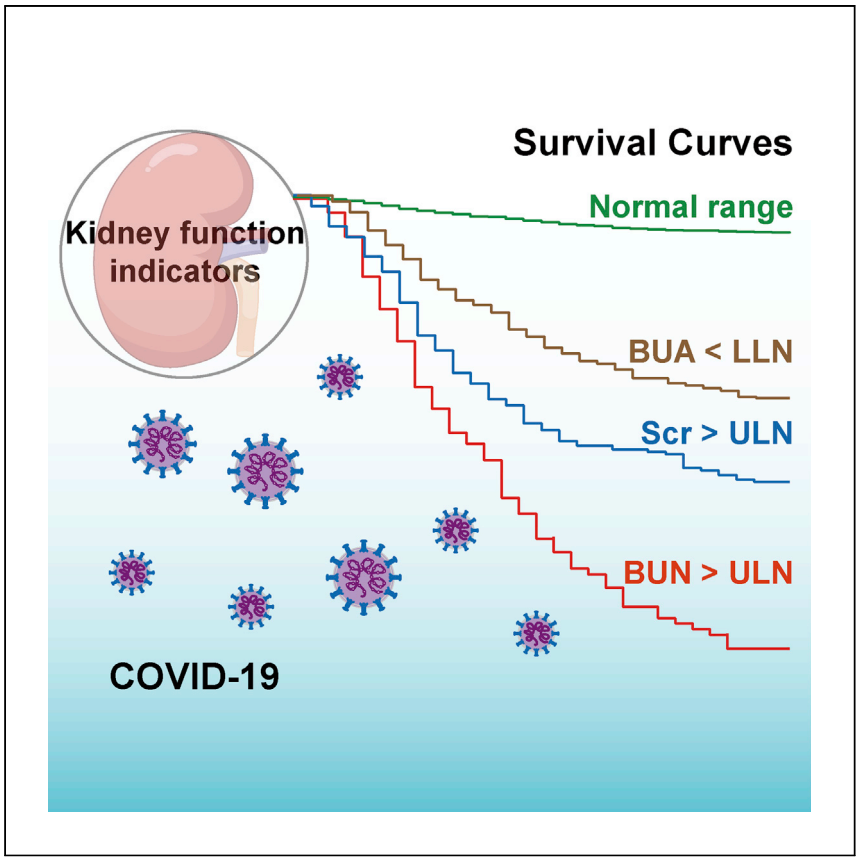
Kidney Function Indicators Predict Adverse Outcomes of COVID-19



Liu et al. show that among 12,413 cases of COVID-19, an elevation in baseline BUN and Scr levels and a decrease in baseline BUA level were associated with adverse outcomes in patients. These findings may assist in the risk stratification and triage of COVID-19 patients according to kidney function indicators.

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HIGHLIGHTS

A cohort of 12,413 COVID-19 patients was retrospectively investigated

Elevated baseline levels of BUN and Scr correlated with high risk of COVID-19 mortality

Decreased BUA level on admission was associated with high risk of COVID-19 mortality

Translation to Patients

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Clinical and Translational Article

Kidney Function Indicators Predict Adverse Outcomes of COVID-19

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SUMMARY

Background: The coronavirus disease 2019 (COVID-19) is a recently emerged respiratory infectious disease with kidney injury as a part of the clinical complications. However, the dynamic change of kidney function and its association with COVID-19 prognosis are largely unknown.

Methods: In this multicenter retrospective cohort study, we analyzed clinical characteristics, medical history, laboratory tests, and treatment data of 12,413 COVID-19 patients. The patient cohort was stratified according to the severity of the outcome into three groups: non-severe, severe, and death.

Findings: The prevalence of elevated blood urea nitrogen (BUN), elevated serum creatinine (Scr), and decreased blood uric acid (BUA) at admission was 6.29%, 5.22%, and 11.66%, respectively. The trajectories showed the elevation in BUN and Scr levels, as well as a reduction in BUA level for 28 days after admission in death cases. Increased all-cause mortality risk was associated with elevated baseline levels of BUN and Scr and decreased levels of BUA.

Conclusions: The dynamic changes of the three kidney function markers were associated with different severity and poor prognosis of COVID-19 patients. BUN showed a close association with and high potential for predicting adverse outcomes in COVID-19 patients for severity stratification and triage.

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Context and Significance

Kidney injury is a common complication of coronavirus disease 2019 (COVID-19); however, the dynamic changes in kidney injury markers and their associations with COVID-19 prognosis remain largely uncertain. Here, using a multicenter retrospective cohort of 12,413 patients with COVID-19 from 17 hospitals in Hubei Province, China, Liu et al. reveal that elevated baseline levels of blood urea nitrogen (BUN) and serum creatinine (Scr), as well as a decreased baseline level of blood uric acid (BUA), are correlated with adverse outcomes of COVID-19. These results confer clinical evidence that kidney function markers may be simple tools for predicting adverse outcomes in COVID-19 patients for severity stratification.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a recently emerged disease with unprecedented scale and high infectivity.[1–3] There is accumulating evidence indicating that the respiratory system is not the only organ damaged by the virus. Kidney impairment has been reported to be a frequent complication resulting from this infection, especially among patients with severe symptoms.[4,5] The latest data show that acute kidney injury (AKI) occurred in ~37% of COVID-19 patients in New York[6] and a history of kidney diseases and AKI during hospitalization were linked to an increased risk of

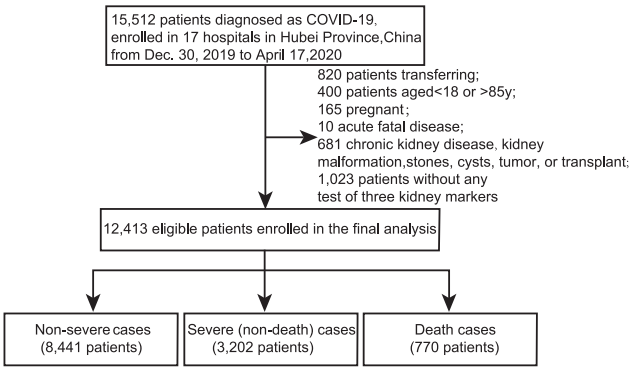

Figure 1. Flowchart of Patient Selection

mortality.[7] However, the dynamic changes in kidney function after severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection and its predictive value for poor prognosis of COVID-19 have not yet been reported. To answer these fundamental questions, we conducted a large-scale analysis based on 12,413 COVID-19 cases from multiple centers in Hubei Province, China. We demonstrated the dynamic trajectories of kidney injury indicators in patients stratified based on disease severity and outcome, and uncovered that these kidney injury indicators, in particular blood urea nitrogen (BUN), were significantly associated with and had significant predictive properties for poor outcomes of COVID-19.

RESULTS

Baseline Characteristics of the Study Cohort

We enrolled a total of 15,512 patients with COVID-19, of whom 12,413 (80.02%) met the eligibility criteria (Figure 1), including 8,441 non-severe cases, 3,202 severe (non-death) cases, and 770 deaths (Figure 1). The clinical and biochemical characteristics and preexisting complications of the study cohort at baseline, as well as treatment information during hospitalization, are described in Table 1. The median age of the entire study cohort was 58 years (interquartile range, 46–67 years), and 48.22% were male. The median duration from the first symptom to hospitalization was 11 days for all of the patients. At admission, 764 (6.29%) had an elevated level of BUN, 633 (5.22%) patients had an elevated level of serum creatinine (Scr), and 1,422 (11.66%) had a decreased level of blood uric acid (BUA). Coexisting chronic diseases, including diabetes, hypertension, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, and chronic liver disease had higher frequencies in the death group than in other groups. Of note, compared to the other groups, the patients from the death group had higher proportions of elevated BUN (37.86%), elevated Scr (18.64%), and decreased BUA (25.49%). During hospitalization, the highest incidence of AKI was observed in the patients who died of COVID-19 (death group: 29.22%, severe group: 1.59%, non-severe group: 0.49%). A total of 62 patients and 81 patients received renal replacement therapy (RRT) and continuous renal replacement therapy (CRRT), respectively. The patients in the death group had a significantly higher ratio to receive RRT and CRRT relative to other groups. There were still 73 patients who met indications but did not receive RRT or CRRT (death group: 9.09%, severe group: 0.03%, non-severe group: 0.02%).

The Longitudinal Trajectories of Three Kidney Function Indicators within 28 Days after Admission

As depicted in Figure 2, locally weighted scatterplot smoothing (Loess) was used to determine the distribution and trajectory of the three renal parameters in the

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Table 1. Baseline Characteristics of Study Patients

Parameters	All (N = 12,413)	Non-severe (n = 8,441)	Severe (n = 3,202)	Death (n = 770)	p[a]
Age, y, median (IQR)	58 (46–67)	57 (44–66)	60 (48–68)	68 (62–76)	<0.001
Male gender, n (%)	5,986 (48.22)	3,901 (46.21)	1,581 (49.38)	504 (65.45)	<0.001
Heart rate, median (IQR)	84 (78–96)	82 (77–91)	100 (80–109)	88 (78–101)	<0.001
Respiratory rate, median (IQR)	20 (19–21)	20 (19–20)	20 (20–22)	21 (20–25)	<0.001
Days from symptom onset to hospitalization, median (IQR)	11 (7–20)	12 (7–21)	11 (7–18)	10 (6–14)	<0.001
Symptoms and status upon admission, n (%)					
Fever	9,192 (74.05)	6,015 (71.26)	2,559 (79.92)	618 (80.26)	<0.001
Cough	7,846 (63.21)	5,149 (61.00)	2,198 (68.64)	499 (64.81)	<0.001
Fatigue	3,852 (31.03)	2,577 (30.53)	999 (31.20)	276 (35.84)	0.009
Dyspnea	2,523 (20.33)	1,347 (15.96)	862 (26.92)	314 (40.78)	<0.001
Smoking status	2,985 (24.05)	2,274 (26.94)	596 (18.61)	115 (14.94)	<0.001
Coexisting chronic diseases, n (%)					
Diabetes	1,952 (15.73)	1,163 (13.78)	593 (18.52)	196 (25.45)	<0.001
Hypertension	4,053 (32.65)	2,511 (29.75)	1,162 (36.29)	380 (49.35)	<0.001
Coronary heart disease	1,030 (8.30)	603 (7.14)	279 (8.71)	148 (19.22)	<0.001
COPD	132 (1.06)	71 (0.84)	38 (1.19)	23 (2.99)	<0.001
Cerebrovascular disease	332 (2.67)	193 (2.29)	94 (2.94)	45 (5.84)	<0.001
Chronic liver disease	253 (2.04)	145 (1.72)	83 (2.59)	25 (3.25)	<0.001
Lab tests on admission					
BUN increase, n (%)	764 (6.29)	292 (3.56)	185 (5.83)	287 (37.86)	<0.001
Scr increase, n (%)	633 (5.22)	288 (3.50)	205 (6.50)	140 (18.64)	<0.001
BUA decrease, n (%)	1,422 (11.66)	731 (8.86)	497 (15.65)	194 (25.49)	<0.001
Leukocyte count, median (IQR)	5.53 (4.32–7.09)	5.38 (4.27–6.74)	5.64 (4.33–7.48)	8.19 (5.53–11.72)	<0.001
Neutrophil count, median (IQR)	3.47 (2.51–4.93)	3.26 (2.42–4.45)	3.76 (2.64–5.54)	7.16 (4.43–10.46)	<0.001
Lymphocyte count, median (IQR)	1.25 (0.86–1.70)	1.37 (0.98–1.80)	1.07 (0.73–1.52)	0.61 (0.42–0.88)	<0.001
Complications, n (%)					
Acute kidney injury	317 (2.55)	41 (0.49)	51 (1.59)	225 (29.22)	<0.001
ARDS	1,963 (15.81)	586 (6.94)	678 (21.17)	699 (90.78)	<0.001
Septic shock	366 (2.95)	45 (0.53)	70 (2.19)	251 (32.6)	<0.001
DIC	107 (0.86)	10 (0.12)	19 (0.59)	78 (10.13)	<0.001
Intervention, n (%)					
Systemic corticosteroids	2,116 (17.05)	904 (10.71)	914 (28.54)	298 (38.7)	<0.001
Oxygen therapy	9,701 (78.15)	5,894 (69.83)	3,075 (96.03)	732 (95.06)	<0.001
Invasive ventilation	443 (3.57)	53 (0.63)	87 (2.72)	303 (39.35)	<0.001
Noninvasive ventilation	1,169 (9.42)	328 (3.89)	363 (11.34)	478 (62.08)	<0.001
RRT	62 (0.50)	11 (0.13)	8 (0.25)	43 (5.58)	<0.001
CRRT	81 (0.65)	9 (0.11)	19 (0.59)	53 (6.88)	<0.001
No. of patients with indications but did not receive RRT and CRRT	73 (0.59)	2 (0.02)	1 (0.03)	70 (9.09)	<0.001
ECMO	45 (0.36)	9 (0.11)	17 (0.53)	19 (2.47)	<0.001

ARDS, acute respiratory distress syndrome; BUA, blood uric acid; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; RRT, renal replacement therapy; Scr, serum creatinine.

[a]The p values were calculated by the Mann-Whitney *U* test for non-normally distributed continuous variable and Fisher's exact test or χ^2 test for categorical variables.

three different severity groups. At admission, the baseline levels of kidney markers in non-survivors were the highest among all of the patients. Within 28 days after admission, there was a modest fluctuation of the three renal indicators over time in the non-severe-case and severe-case groups. In sharp contrast, however, the temporal specific pattern of the kidney parameters in the death group was markedly different. The plot linear fitting curve revealed a marked elevation in BUN and Scr levels, while a sustained downtrend followed by a plateau of BUA level was observed. A subgroup analysis demonstrated that males and females had comparable temporal dependent profiles; however, the trends in the males were more significant than those in the females (Figure S1). The dynamic trends suggested a potential association between levels of kidney function markers and the mortality of patients with COVID-19.

Association between Baseline Levels of Three Kidney Function Indicators and Poor Outcomes

Mixed-effects Cox regression analyses (Table 2) and Kaplan-Meier survival curves (Figure 3) were used to demonstrate the associations of BUN, Scr, and BUA with the mortality risk within the study cohort. Increased all-cause mortality risk was found to be associated with elevated levels of BUN (adjusted hazard ratio [aHR]: 6.27, 95% confidence interval [CI]: 5.29–7.42) and Scr (aHR: 2.65, 95% CI: 2.17–3.23) or decreased levels of BUA (aHR: 2.10, 95% CI: 1.75–2.51) at admission, by applying a mixed-effects Cox model treating hospital site as a random effect and adjusting for age, gender, and comorbidities. Among the three biomarkers, an elevated baseline BUN was associated with the highest risk of mortality. Figure 3 shows that patients with elevated baseline BUN, elevated baseline Scr, or decreased BUA had a markedly lower survival rate than those with normal levels of the three kidney function indicators.

We further analyzed the associations between baseline levels of BUN, Scr, and BUA and secondary outcomes in COVID-19 patients. Mixed-effects Cox models demonstrated that the increased BUN and Scr levels, as well as the decreased BUA level at admission were also significantly associated with poor secondary outcomes in patients with COVID-19 (Table 3). Again, among the three markers, an elevated baseline BUN was associated with the highest risk of poor prognosis.

Associations between Clinical Characteristics and Laboratory Indexes with Baseline Levels of Kidney Function Indicators

Logistic regression analyses were used to investigate the effects of baseline characteristics and laboratory indexes on the baseline levels of kidney function indicators in the study cohort (Table 4). The results showed that male gender, age, neutrophil count increase, lymphocyte count decrease, oxyhemoglobin saturation (SpO_2) < 95, and diabetes were positively correlated with elevated BUN, elevated Scr, and decreased BUA. Among them, neutrophil count increase and lymphocyte count decrease were the most significant factors, indicating the potential association of inflammation with kidney markers after SARS-CoV-2 infection.

DISCUSSION

To our knowledge, this is one of the largest cohorts to verify the relation between kidney function indicators and adverse outcomes in COVID-19 patients. From 12,413 cases, we found a remarkable increase in BUN and Scr and a reduction of BUA in the patients who died during hospitalization, but only modest fluctuation within normal ranges of the three kidney markers in the survivors with COVID-19. Furthermore, elevated baseline levels of BUN and Scr, as well as decreased baseline BUA, were associated with increased risks of adverse outcomes. This is the first

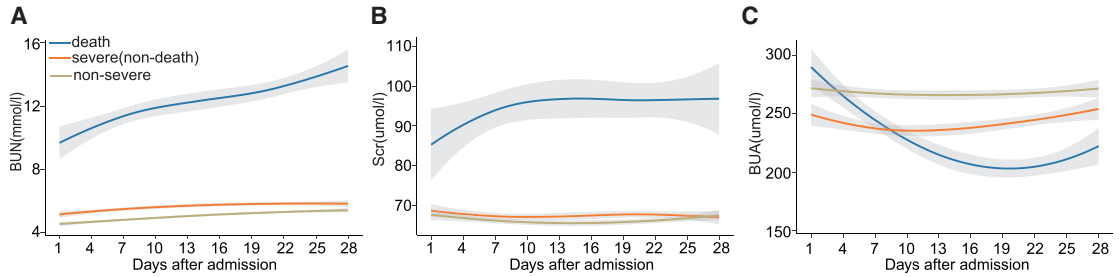

Figure 2. Loess Curves for Kidney Function Indicator Trajectories in COVID-19 Patients

Loess curves of mean BUN, Scr, and BUA by severity of the disease within 28 days after admission.

(A) BUN levels, (B) Scr levels, and (C) BUA levels. Yellow indicates non-severe cases, orange indicates severe (non-death) cases, and blue indicates death cases. The shaded regions represent 95% confidence intervals.

report demonstrating that BUA is dramatically lower in COVID-19 patients with more severe symptoms and is significantly associated with a higher risk of COVID-19 death. Among the three indicators, an elevated baseline BUN was most significantly associated with the highest risk of adverse outcomes. These findings suggest that three kidney function indicators could reliably predict the risk of COVID-19 patients, among which BUN was the indicator with the most impact.

Our study illustrated the important role of kidney markers on admission in predicting the adverse outcomes of hospitalized patients with COVID-19. The results suggest that patients with elevated BUN and Scr or decreased BUA on admission should be monitored more carefully for early intervention, which may improve the survival rate of patients with COVID-19. These results are further corroborated by a study by Cheng et al.,[7] which also reported that elevated BUN and elevated Scr increased the mortality risk in COVID-19 patients, based on a relatively small cohort of 701 cases. In addition, our findings linked a decrease in BUA with higher all-cause mortality, which is consistent with an observational study on SARS patients.[8]

Our results indicate that patients with an elevated baseline of BUN level are at a higher risk of all-cause death and poor outcomes than those with a normal range of BUN level. Thus, it is critically important that the BUN levels should be closely monitored. When the medical resources are limited, the BUN level on admission can provide a simple tool for early risk stratification among COVID-19 patients and guide physicians to reserve more medical resources to patients at higher risk to reduce the death rate. While an optimized management strategy is not the focus of this study, aggressive treatment with proper medication to reduce BUN level and related organ injury may contribute to mitigating the death risk and adverse outcome for COVID-19. However, due to the inherent limitations of a retrospective study, the present study cannot directly address whether increased BUN is a causal factor of poor prognosis and whether reducing BUN would benefit COVID-19 patients. These questions need to be addressed in future prospective studies and clinical trials.

The mechanism involved in the increase in BUN level after SARS-CoV-2 infection has not been fully elucidated. Given that angiotensin-converting enzyme 2 (ACE2) is the primary cellular receptor of SARS-CoV-2 and highly expressed in renal epithelial cells, it is possible that the viral infection may directly lead to an interaction of SARS-CoV-2 with its receptor in the kidney to reduce ACE2 expression, resulting in abnormal activation of the renin-angiotensin-aldosterone system

Table 2. Associations between Baseline Levels of Kidney Function Indicators with Mortality under the Mixed-Effects Cox Model

Variables	Crude			Adjusted[a]		
	HR	95% CI	p[b]	HR	95% CI	p[b]
BUN						
Normal	ref					
Elevated	11.07	(9.49–12.91)	<0.001	6.27	(5.29–7.42)	<0.001
Scr						
Normal	ref					
Elevated	4.72	(3.90–5.72)	<0.001	2.65	(2.17–3.23)	<0.001
BUA						
Normal	ref					
Decreased	2.92	(2.45–3.48)	<0.001	2.10	(1.75–2.51)	<0.001

BUA, blood uric acid; BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio; Scr, serum creatinine. "Normal" indicates within the reference range; "elevated" indicates above the upper limit of normal; "decreased" indicates below the lower limit of normal.

[a]In the mixed-effects Cox model, adjusted variables included age, gender, and comorbidities (hypertension, coronary heart disease, diabetes), and hospital site was treated as a random effect.

[b]The p values were calculated based on the mixed-effects Cox model.

(RAAS).[9,10] The activated RAAS can significantly increase the absorption of water by kidney tubules while enhancing the resorption of urea, leading to elevated BUN levels.[11] The elevation in BUN level is not only a kidney dysfunction indicator but it can also reflect inflammatory status, catabolism, nitrogen equilibrium, and renal hypoperfusion from hypovolemia, sepsis, or reduced cardiac output, many of which have been reported to be closely associated with the adverse outcomes in COVID-19 patients.[11–18] The coagulation status may progress and exacerbate along with the systematic inflammatory response and multiple organ injury. This is perhaps the reason why we observed a strong correlation between abnormal BUN with a broad spectrum of symptoms during pneumonia progression and why the high BUN level showed a more significant association with adverse outcomes than Scr, because the latter mainly represents a status of kidney injury and metabolic disturbance.[19] Finally, the elevated BUN level may also be caused by cortisone therapy or an abnormal catabolic state. Nevertheless, findings from this retrospective study cannot provide a direct causal effect of BUN increase on all-cause mortality of COVID-19. Thus, the predictive value of BUN on the prognosis of COVID-19 still needs to be validated further by prospective studies and clinical trials, and more basic research is required to elucidate the underlying mechanisms.

In the present study, the level of BUA was much lower in the severe group than the non-severe group and was associated with increased risks of adverse outcomes in COVID-19 patients. Because uric acid is mainly dissolved in the blood, filtered through the kidneys, and expelled in the urine, it was commonly recognized as a kidney function marker.[20] Under normal conditions, the reabsorption and excretion by kidney tubules of BUA are maintained in a balanced state. In the setting of SARS, decreased levels of BUA may as a result of defective tubular handling of uric acid and may be associated with cytokine storm.[8] Because the dysfunction of kidney tubules was also observed after SARS-COV-2 infection,[21] the lower uric acid level may be correlated with cytokine storm in the setting of COVID-19. Also, the decreased uric acid level may be a marker of kidney involvement severity (e.g., proximal tubular damage) in patients infected with SARS-COV-2. Except for kidney dysfunction, the reduced BUA may be related to the increase in decomposition by the intestinal tract, but the mechanism is unclear. It has been reported that the gut

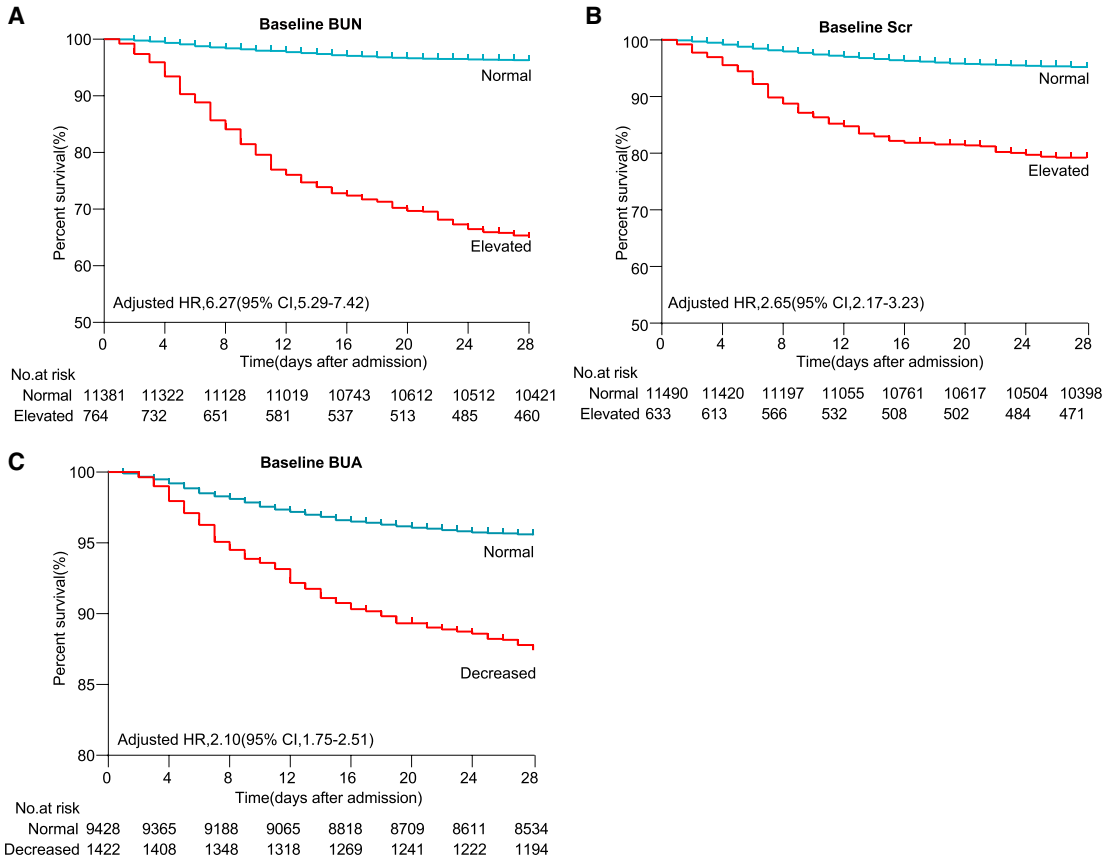

Figure 3. Kaplan-Meier Curves for Survival Probability of COVID-19 Patients with Different Baseline Levels of Kidney Function Indicators
The follow-up duration was 28 days. The blips indicate censoring. For Figure 3 A-C, P<0.001.

microbiome was disturbed in patients with COVID-19,[22,23] which may lead to reduced uric acid in those patients.[24–26] Thus, decreased BUA levels during SARS-CoV-2 infection may be due to an abnormal increase in BUA excretion by abnormal renal handling from inflammatory injury or hypoxemia, or an intensive uricolysis caused by enteric dysbacteriosis. However, these postulated mechanisms will still need to be investigated further.

Remarkably, not only can the baseline renal parameters predict adverse outcomes of COVID-19 but the dynamic changes of these renal parameters may also serve as warning signs for mortality in COVID-19 patients. In our study, we found that the dynamic changes in these kidney function indicators were associated with different severities and outcomes of COVID-19. Importantly, the sharp differences in the dynamic changes in the three markers for kidney function in non-survivors versus the relatively stable patterns observed in the survivors implied a significant association between the aggravation of kidney injury and the deterioration of the disease and death in the pathogenesis of COVID-19. Similar results were observed in male and female subgroups, with more significant trends in males than in females. It is known that estrogen affects ACE2 expression in the kidney, which could be one of the reasons for gender-related differences in the dynamic patterns of kidney parameters during hospitalization observed in our study.[27–29]

Limitations of Study

Several limitations of this study should be noted in interpreting the results. First, it was a retrospective study on a limited number of available kidney markers, and

Table 3. Associations between Baseline Levels of Kidney Function Indicators with Secondary Outcomes under the Mixed-Effects Cox Model

	Elevated BUN		Elevated Scr		Decreased BUA	
Secondary outcomes	HR (95% CI)[a]	p[b]	HR (95% CI)[a]	p[b]	HR (95% CI)[a]	p[b]
Septic shock	4.80 (3.74–6.17)	<0.001	2.26 (1.66–3.08)	<0.001	2.31 (1.79–2.98)	<0.001
DIC	4.49 (2.91–6.94)	<0.001	2.11 (1.24–3.57)	0.006	2.10 (1.31–3.36)	0.002
ARDS	3.11 (2.76–3.51)	<0.001	1.67 (1.45–1.94)	<0.001	2.17 (1.95–2.43)	<0.001

ARDS, acute respiratory distress syndrome; BUA, blood uric acid; BUN, blood urea nitrogen; CI, confidence interval; DIC, disseminated intravascular coagulation; HR, hazard ratio; Scr, serum creatinine. "Elevated" indicates above the upper limit of normal; "decreased" indicates below the lower limit of normal.

[a]In the mixed-effects Cox model, adjusted variables included age, gender, and comorbidities (hypertension, coronary heart disease, diabetes), and hospital site was treated as a random effect.

[b]The p values were calculated based on the mixed-effects Cox model.

other biomarkers of kidney function, such as urine protein level and hematuria, were not investigated due to data availability. Second, smoking status and the medical history of chronic kidney diseases may not be collected sufficiently, especially from severely ill patients under urgent circumstances of COVID-19 surge. Third, we cannot determine the causal relationships between kidney function indicators and the severity as well as the mortality of COVID-19. Fourth, due to limited medical resources, an increase in Scr within 48 h was the only criterion for the diagnosis of AKI; thus, this may have resulted in an underdiagnosis of AKI in our population. A combination with a 7-day Scr and urine output criterion may increase the accuracy of AKI diagnosis. We noticed there were geographical differences in the incidence of AKI in patients with COVID-19. For instance, the AKI incidence in the United States was reported to be ~37%,[6] which is much higher than the 2.55% in our study and the 0.5% in another multicenter study in China.[30] This discrepancy may be related to the difference in the occurrence of comorbidities, the severity of symptoms, and the exclusion of patients with chronic kidney diseases in our study. Therefore, the conclusions in this study require validation by prospective studies and randomized controlled trials (RCTs) in cohorts from extensive geographical regions. Fifth, the levels of kidney function indicators may be influenced by other factors. For example, the increased BUN may also be due to cortisone therapy or catabolic state, while the Scr level may be influenced by persistent muscle wasting in critically ill patients. Sixth, in our study cohort, the relatively small number and percentage of patients who received RRT may be related to the shortage of medical resources during the COVID-19 pandemic and the varied criteria of RRT initiation in different hospitals. Not all patients with indications of RRT received that therapy during hospitalization, which may induce potential confounders into the conclusion.

Conclusions

The dynamic changes in three markers of kidney function, elevated BUN, elevated Scr, and decreased BUA, were associated with different severity and mortality of patients with COVID-19. Among the three markers, an elevated baseline BUN was associated with the highest risk of adverse outcomes. The BUN level at admission may represent a sensitive factor for predicting death and adverse outcomes in COVID-19 patients and can be valuable for patient stratification and triage.

Table 4. Associations between Clinical Characteristics and Laboratory Indexes at Admission with Baseline Levels of Kidney Function Indicators

	Elevated BUN		Elevated Scr		Decreased BUA	
Parameters	OR (95% CI)	p[a]	OR (95% CI)	p[a]	OR (95% CI)	p[a]
Male sex	2.25 (1.89–2.67)	<0.001	1.68 (1.41–1.99)	<0.001	1.73 (1.53–1.95)	<0.001
Age	1.05 (1.04–1.06)	<0.001	1.03 (1.03–1.04)	<0.001	1.02 (1.01–1.02)	<0.001
Neutrophil count increase	4.01 (3.38–4.75)	<0.001	1.87 (1.53–2.28)	<0.001	1.74 (1.51–2.01)	<0.001
Lymphocyte count decrease	2.16 (1.81–2.59)	<0.001	1.27 (1.06–1.51)	0.010	3.24 (2.85–3.68)	<0.001
ALT increase	1.26 (1.05–1.51)	0.011	1.14 (0.94–1.38)	0.196	1.41 (1.24–1.60)	<0.001
SpO2 < 95	1.39 (1.12–1.71)	0.003	1.34 (1.06–1.70)	0.015	1.36 (1.18–1.57)	<0.001
Hypertension	1.35 (1.14–1.59)	0.001	1.88 (1.57–2.25)	<0.001	0.58 (0.50–0.66)	<0.001
Diabetes	1.46 (1.22–1.76)	<0.001	1.32 (1.09–1.61)	0.004	1.44 (1.24–1.67)	<0.001
Coronary heart disease	1.14 (0.91–1.43)	0.248	1.14 (0.90–1.44)	0.284	0.76 (0.62–0.95)	0.014

ALT, alanine aminotransferase; BUA, blood uric acid; BUN, blood urea nitrogen; CI, confidence interval; OR, odds ratio; Scr, serum creatinine; SpO2, oxyhemoglobin saturation.
[a]The p values were calculated based on the logistic model.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.medj.2020.09.001.

AUTHOR CONTRIBUTIONS

Y.-M.L., J.X., M.-M.C., and Xiao Zhang designed the study, collected and analyzed the data, and wrote the manuscript. X.C., H.L., F.Z., J.-J.Q., and F.L. collected the data and performed the statistical analysis. Z.C., J.C., and X.-J.Z. wrote the manuscript and provided valuable suggestions for study. L.L., C.Y., W.M., G.C., H.L., X.X., D.W., X.L., J.Y., X.H., B.-H.Z., and Y.Y. collected and reviewed the clinical, laboratory, and radiological data. Y.W., Xin Zhang, Z.-G.S., and H.L. contributed equally, designed the project, edited the manuscript, and supervised the study. All of the authors approved the final version of the article.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

RESOURCE	SOURCE	IDENTIFIER
Software and Algorithms		
R-3.6.3	R Foundation for Statistical Computing	https://www.r-project.org/
SPSS statistics 23.0	IBM Corporation	http://www.spss.com.hk/software/statistics/
Adobe illustrator CC 2019	Adobe company	https://www.adobe.com/cn
Coxme-2.2.16	Therneau et al.	https://cran.r-project.org/web/packages/coxme/index.html
Tableone-0.11.1	Kazuki Yoshida	https://github.com/kaz-yos/tableone
Survival-3.1-12	Terry M Therneau et al.	https://cran.r-project.org/web/packages/survival/index.html
Ggplot-3.3.2	Hadley Wickham et. al.	https://cran.r-project.org/web/packages/ggplot2/index.html

RESOURCE AVAILABILITY

Lead Contact

Further information and requests for resources and reagents should be directed to the Lead Contact, Hongliang Li (lihl@whu.edu.cn).

Materials Availability

The study did not generate any new reagents or materials.

Data and Code Availability

Data and codes involved in this research are available from the corresponding author upon reasonable request. The research team will provide an email address for communication once the information sharing are approved. The proposal should include detailed aims, statistical plan, and other information/materials to guarantee the rationality of requirement and the security of the data. The related patient data will be shared after review and approval of the submitted proposal and any related requested materials. Of note, data with patient names, national identification number, and other identifiers cannot be shared.

METHOD DETAILS

Study Design and Participants

This was a multicenter retrospective longitudinal cohort study, including 15,512 adults with confirmed COVID-19 who were diagnosed from December 30, 2019, to April 17, 2020, and admitted to 17 participating COVID-19 designated hospitals in Hubei province. The study procedures were approved by the institution ethic committee of Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University, and were accepted or approved by each local collaborating hospitals. This retrospective study just extracted and analyzed existing data without change of individuals' intervention or welfare, and patient informed consent was thus waived by each ethics committee. The main inclusion and exclusion criteria for the present study were depicted in Figure 1. 820 cases transferred to other hospitals, 4040 patients aged > 85 or < 18 years, 165 cases with pregnancy, 10 cases with the acute fatal disease, 681 cases with a medical history of kidney diseases (599 with chronic kidney diseases of unknown causes, 16 with chronic glomerulonephritis, 3 with chronic pyelonephritis, 5 with diabetic nephropathy, 1 with hypertensive nephropathy, 4 with nephrotic syndrome, and 53 with kidney stones or cysts that

might affect kidney function, kidney malformation, tumor, or transplant), and 1,023 patients without any test of three kidney markers during 28-day hospitalization were excluded. Patients with kidney stones or cysts but without renal dysfunction were not excluded. At last, 12,413 cases met the eligibility criteria and were enrolled in further analysis.

Data Collection and Definition

We extracted clinical characteristics from each patient's clinical electronic medical records, nursing records, laboratory findings, and radiological examinations. A trained team of experienced physicians reviewed the data. The diagnosis and severity of COVID-19 were determined based on the guidelines for diagnosis and treatment of COVID-19 (trial fifth edition) published by the Chinese National Health Commission.[31] The cases were stratified into non-severe, severe (non-death) and death groups. In details, patients with severe disease were defined as with fever or suspected respiratory infection, plus clinical manifestations as either: (1) respiratory rate > 30 breaths/min, or severe respiratory distress, or (2) SpO2 $\leq$ 93%, or (3) PaO2/FiO2 $\leq$ 300 mmHg on room air. Patients diagnosed as COVID-19 but without above mentioned symptoms were classified into the "non-severe" group. AKI was defined by an increase in serum creatinine by 26.5 mmol/l within 48 hours according to the 2012 Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group.[32] The urine output was not applied for defining AKI. The initiation of RRT and CRRT was defined as KDIGO AKI stage 2 that was defined by a 2-fold increase in serum creatinine compared with baseline.[33,34] Disseminated intravascular coagulation (DIC) was defined according to the criteria defined by the International Society on Thrombosis and Hemostasis (ISTH).[35] Acute respiratory distress syndrome (ARDS) and septic shock were defined according to the World Health Organization (WHO) interim guideline.[36] The increase of BUN, creatinine and uric acid was defined as their level higher than their upper limit of normal (ULN), while the decrease of those markers means lower than their lower limit of normal (LLN). The ULN and LLN of BUN, Scr, and BUA were provided in Table S1. The primary endpoint was defined as 28-day all-cause death of COVID-19, and the secondary endpoints included the occurrence of DIC, septic shock, and ARDS.

QUANTIFICATION AND STATISTICAL ANALYSIS

Categorical variables were presented as absolute numbers (percentages). Continuous variables were described as median (interquartile range, IQR). Analysis of Variance for comparison of means or Kruskal-Wallis test for comparison of medians was used for continuous variables and Fisher's exact test for categorical variables. Dynamic trajectories of renal parameters were established using Loess. The proportional hazard assumptions were verified by correlation testing based on the Schoenfeld residuals. Mixed-effect Cox regression models were used to investigate the relationship between renal index levels and death among COVID-19 patients. Age, gender, coexisting chronic diseases (hypertension, coronary heart disease, and diabetes) were adjusted, and hospital site was treated as a random effect in this model. Logistic regression was conducted to assess the effect of clinical characteristics and laboratory indexes on the level of renal indicators. A two-sided P value of less than 0.05 was used as the threshold of statistical significance. All analyses were conducted using SPSS version 23.0 (IBM, Armonk, NY, USA) or R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).