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Characteristics of patients with kidney injury associated with COVID-19

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ABSTRACT

To explore the characteristics of COVID-19 infection related kidney injury, we retrospectively collected cases of COVID-19 patients with definite clinical outcomes (discharge or death) and relevant laboratory results from Jan 3 to Mar 30, 2020 in Tongji hospital, Wuhan, China. 1509 patients were included, 1393 cases with normal baseline serum creatinine, and 116 cases with elevated baseline serum creatinine (EBSC). On admission, the prevalence of elevated serum creatinine, elevated blood urea nitrogen (BUN) and estimated glomerular filtration (eGFR) under 60 ml/min/1.73 m^2 were 7.7%, 6.6% and 7.2%, respectively. The incidence of in-hospital death in the patients with EBSC was 7.8%, which was significantly higher than those with normal serum creatinine (1.2%). Inflammatory, immunological, and organ damage indices were relatively higher in the EBSC group, in which lymphocytes, albumin, and hemoglobin were significantly lower. Kaplan-Meier analysis revealed age above 65 years, males, comorbidities (especially for cardiovascular disease and tumor patients), lymphocyte count $< 1.5 \times 10^9$/L, leukocyte count $> 10 \times 10^9$/L, EBSC, eGFR < 60 ml/min/1.73 m^2 were associated with in-hospital death. Multivariate Cox proportional hazard regression confirmed that EBSC (HR: 2.643, 95% CI: 1.111–6.285, $P = 0.028$), eGFR < 60 ml/min/1.73 m^2 (HR: 3.889, 95% CI: 1.634–9.257, $P = 0.002$), were independent risk factors after adjusting for age, sex, any comorbidity, leukocyte and lymphocyte count. Therefore, the prevalence of kidney injury in patients with COVID-19 was high and associated with in-hospital mortality. Early detection and effective intervention of kidney injury may reduce COVID-19 deaths.

1. Introduction

SARS-CoV-2 pandemic has caused millions of infections since its outbreak in Wuhan. COVID-19, with acute respiratory disease as the main manifestation, can affect multiple organs such as kidneys, cardiovascular systems, digestive system, and nerves at the same time [1–5]. The disease is highly contagious, with diverse clinical manifestations, renal dysfunction as one of them [6]. However, there are still many deficiencies in the attention of kidney injury.

The kidney is one of the main targets of SARS-CoV-2 infection. Cytokine storm, inflammatory cell infiltration and direct virus attack can all cause kidney damage [6]. In a study of 99 COVID-19 patients, 7 patients (7.1%) had kidney injury of varying degrees, accompanied by serum creatinine and/or blood urea nitrogen (BUN) elevation [4]. In another report, acute kidney injury (AKI) occurred in 5 of 138 patients (3.7%) and 2 received renal replacement therapy [7]. Guan et al. [5] recently reported 1 099 COVID-19 patients, the incidence of AKI was 0.5%, and 5 out of 173 severely ill patients developed AKI (2.9%). Cheng et al. [8] data from 710 COVID-19 hospitalized patients in a single center showed that 44% of patients had proteinuria and hematuria at admission, 14.1% had elevated serum creatinine, and the incidence of AKI was 3.2%. Elevated serum creatinine or urea nitrogen, acute kidney injury, proteinuria, and hematuria are all independent risk factors for death in hospitalized patients [8–10]. Early continuous renal replacement

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; eGFR, estimated glomerular fifiltration rate; BUN, blood urea nitrogen; CHD, cardioheart disease; COPD, chronic obstructive pulmonary disease; T cell, T lymphocyte; B cell, B lymphocyte; Th cell, helper T lymphocyte; Ts cell, suppressor T lymphocyte; NK cell, nature killer cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; C3, complement component 3; C4, complement component 4; IgM, immunoglobulin M; IgG, immunoglobulin G; TNF-α, tumor necrosis factor α; CK-MB, Creatine Kinase Isoenzyme-MB; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro brain natriuretic peptide; HRs, hazard ratios; 95%CI, 95% confidence interval; IL6, interleukin 6; IL-2R, interleukin 2 receptor; PT, prothrombin time; ALT, alanine aminotransferase; Alb, albumin; PLT, platelets; Hb, hemoglobin.

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therapy (CRRT) may improve the prognosis of critically ill patients [11–13]. The results of the previous studies differ significantly, possibly due to a limited sample size and selective bias.

The identification of prognostic factors of COVID-19 patients is the key to improve the prognosis. In this study, 1509 patients in Tongji hospital were analyzed in detail to characterize COVID-19 associated renal injury.

2. Patients and methods

2.1. Study design and participants

In this single center, retrospective case-control study, we included 1509 COVID-19 inpatients transferred or admitted to Wuhan Tongji Hospital (the specific and largest hospital for the treatment of severe patients with COVID-19 in Wuhan designated by the government) from Jan 3 to Mar 30, 2020 with definite clinical outcomes (discharge or death) and relevant laboratory results. Exclusion criteria: 1). Novel Coronavirus specific antibodies IgM and IgG are all less than 10 AU/ml, and multiple nucleic acid tests in this hospital and other hospitals are negative; 2). Patients was under 14 years old. 3). Patients with a history of maintenance dialysis, chronic kidney disease, or renal transplantation were excluded based on medical history data. 4). Patients with a tendency to shock or whose systolic blood pressure is lower than 90 mmHg. All patients who were enrolled in this study were diagnosed COVID-19 according to the "Novel Coronavirus Infected Pneumonia Diagnosis and Treatment Program (Trial Seventh Edition)" issued by the National Health Commission [13].

The 1509 patients were divided into normal baseline serum creatinine group and EBSC group. The upper limits of normal serum creatinine in men and women were 104 mmol/L and 84 mmol/L, respectively. The upper limits of normal BUN in men with age <60, 60–80, >80 years were 8.0, 9.5, and 8.3 mmol/L, respectively. The upper limits of normal BUN in women with age <60, 60–80, >80 years were 7.5, 8.8, and 8.3 mmol/L, respectively. Estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14].

2.2. Data collection

Data entry and management are the responsibility of a trained team of physicians and postgraduate students. Information collection was accomplished through our hospital's electronic medical record system. The demographic characteristics, clinical symptoms and laboratory data were obtained with standardised forms for all subjects involved. Laboratory data consisted of blood routine, blood biochemistry, cytokines, hemostasis parameters, heart function, complement, antibodies and organ damage indices, etc.

2.3. Statistical analysis

Categorical variables were summarized as percentages, and continuous variables were expressed as the mean ± SD or median with interquartile range. Differences in continuous variables were analyzed using t tests when normalized distributed. Categorical variables were compared using the Chi-squared test. The Fisher exact test was used when the data were limited. Kaplan-Meier analysis and Cox proportional hazards model were used to assess the prognostic factors related to survival. SPSS (version 23.0, IBM Corp) was used for all analyses of data. A 2-sided α of less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of COVID-19 patients

2,977 patients admitted into Tongji hospital (Wuhan China) were screened according to study protocol, from Jan 3 to Mar 30, 2020. Excluding hospitalized patients, we pooled 1623 patients, and 1509 eligible patients were included in this study. 114 patients were excluded, including 23 children under the age of 14; There were 7 patients with chronic renal failure and 12 patients with a tendency to shock or whose systolic blood pressure is lower than 90 mmHg. Novel Coronavirus specific antibodies IgM and IgG of 72 patients were all less than 10 AU/mL, and a number of nucleic acid tests in this hospital and other hospitals were negative (Fig. 1).

Among the 1509 included patients for the final analysis, 116 cases had elevated serum creatinine levels, and 1393 cases with normal baseline serum creatinine. Compared with normal serum creatinine group, EBSC group were significantly older, longer time of hospitalization but shorter time from onset to hospital admission ($P < 0.001$). The types of comorbidities and initial symptoms were similar in both groups, but the EBSC group had more comorbidities and more obvious clinical symptoms ($P < 0.001$). This may also explain why the EBSC group had a shorter time from onset to hospital admission and a longer hospital stay. In-hospital death occurred in 1.7% of patients. The incidence of in-hospital death in the patients with EBSC was 7.8%, which was significantly higher than in those with normal baseline serum creatinine (7.8% vs 1.2%, $P < 0.001$). (Table 1).

3.2. Laboratory findings of COVID-19 patients

On admission, serum creatinine and BUN were elevated in 7.7% and 6.6% of the patients, respectively. eGFR < 60 ml/min/1.73 m^2 was reported in 7.2% of patients. Inflammatory cytokines (IL6, IL2, TNF-a) and infection-related biomarkers (C-reactive protein, Erythrocyte sedimentation rate, Ferritin, Procalcitonin) were much higher in the EBSC group ($P < 0.05$). Complement 4, D-dimer and organ damage biomarkers (aspartate aminotransferase, CK-MB) were significantly higher in EBSC group ($P < 0.05$). (Table 2).

3.3. Association of clinical parameters with in-hospital death

Kaplan-Meier analysis revealed age above 65 years, male sex, comorbidities (especially for cardiovascular disease and tumor patients), lymphocyte count $< 1.5 \times 10^9$/L, leukocyte count $> 10 \times 10^9$/L, EBSC, eGFR < 60 ml/min/1.73 m^2 were associated with in-hospital death (Table3, Fig. 2). Multivariate Cox proportional hazard regression confirmed that EBSC (HR: 2.643, 95% CI: 1.111–6.285, $P = 0.028$), eGFR < 60 ml/min/1.73 m^2 (HR: 3.889, 95% CI: 1.634–9.257, $P = 0.002$), were independent risk factors after adjustment for age, sex, any comorbidity, leukocyte and lymphocyte count (Table 4).

3.4. Correlation analysis between kidney disease indicators, blood cell counts, organ damage indices and inflammatory factors

Correlation analysis between kidney disease indicators (creatinine, eGFR, BUN), blood cell counts (lymphocytes, neutrophils, platelets, hemoglobin), organ damage indices (PT, D-dimer, CK-MB, ALT, AST, Albumin) and inflammatory factors (IL-2R, IL6, TNF-α, C3, C4 and CRP) were evaluated by the Pearson test (Table 5). IL6, IL-2R and TNF-α were positively correlated with creatinine ($r = 0.184$, $P < 0.01$; $r = 0.361$, $P < 0.01$; $r = 0.374$, $P < 0.01$), but negatively with eGFR ($r = -0.209$, $P < 0.01$; $r = -0.372$, $P < 0.01$; $r = -0.343$, $P < 0.01$). Meanwhile, lymphocytes, hemoglobin, platelets and albumin were negatively related to creatinine. Positive associations exsited between eGFR and lymphocytes ($r = 0.290$, $P < 0.01$), hemoglobin($r = 0.188$, $P < 0.01$). Last but not least, the time from onset to hospital admission was negatively correlated with eGFR ($r = -0.195$, $P < 0.01$). From the above correlation, it may be related to kidney metabolic disorders and substantial damage to the kidney.

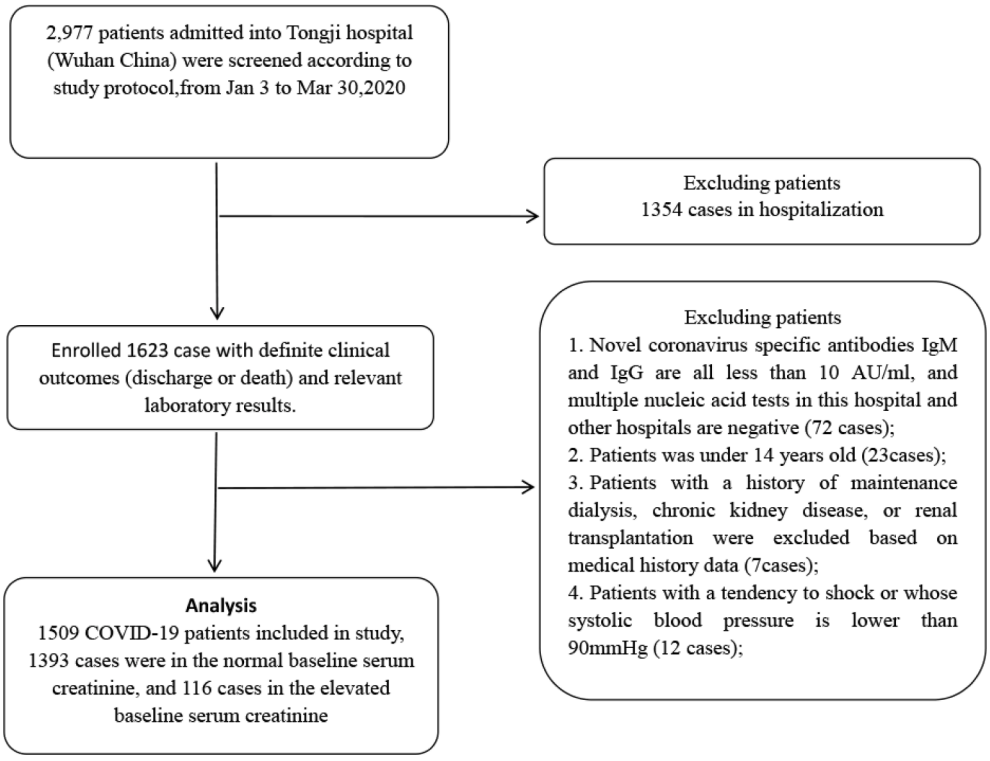

Fig. 1. Study flow diagram.

Table 1
Demographic and clinical findings of COVID-19 patients included in the study.

Indicators	Total (N = 1509)	Normal baseline serum creatinine (N = 1393)	Elevated baseline serum creatinine (N = 116)	P value
Characteristics				
Age, years	60(50–68)	59(49–67)	70(62–79)	<0.001
Sex				0.010
Male	699(46.3%)	632(45.4%)	67(57.8%)	
Female	810(53.7%)	761(54.6%)	49(42.2%)	
Hospital stay, days	24.0 (11.0–34.0)	23.0 (10.0–34.0)	30.5 (22.0–39.0)	<0.001
Days from illness onset to admission, days	17.2 (10.5–32.6)	17.7 (10.7–32.9)	11.8(7.8–22.7)	<0.001
In-hospital death	26(1.7%)	17(1.2%)	9(7.8%)	<0.001
Comorbidities				
Comorbidities				<0.001
Yes	773(51.2%)	685(49.2%)	88(75.9%)	
No	736(48.8%)	708(50.8%)	28(24.1%)	
Hypertension	447(29.6%)	383(27.5%)	64(55.2%)	<0.001
Diabetes	198(13.1%)	174(12.5%)	24(20.7%)	0.012
CHD	139(9.2%)	114(8.2%)	25(21.6%)	<0.001
COPD	9(0.6%)	7(0.5%)	2(1.7%)	0.310
Malignancy	35(2.3%)	28(2.0%)	7(6.0%)	0.006
Surgery	259(17.2%)	233(16.7%)	26(22.4%)	0.119
Allergy	121(8.0%)	116(8.3%)	5(4.3%)	0.126
Initial symptoms				
Fever	1028 (68.1%)	951(68.3%)	77(66.4%)	0.675
Cough	812(53.8%)	741(53.2%)	71(61.2%)	0.096
Dyspnea	612(40.6%)	551(39.6%)	61(52.6%)	0.006
Fatigue	215(14.2%)	187(13.4%)	28(24.1%)	0.002
Diarrhoea	182(12.1%)	160(11.5%)	22(19.0%)	0.017
Others	109(7.2%)	101(7.3%)	8(6.9%)	0.887

Abbreviation: CHD, Cardioheart disease; COPD, Chronic obstructive pulmonary disease; Continuous variables were described as median (Interquartile range).

4. Discussion

Since the outbreak of COVID-19, kidney injury has begun to attract scholars' attention. Researchers found that angiotensin converting enzyme 2 (ACE2) is one of the main cell surface receptors of viral spike protein, and the organs affected by SARS-CoV-2 are related to the organ distribution of ACE2 [15,16]. RNA for ACE2, transmembrane serine protease 2 (TMPRSS2), and cathepsin L (CTSL) — RNA of genes that are considered to facilitate SARSCoV-2 infection — is enriched in multiple kidney-cell types from fetal development through adulthood, and SARS-CoV-2 can be detected in multiple organs, including the lungs, pharynx, heart, liver, brain, and kidneys [6]. Recent human tissue RNA-sequencing data demonstrated that ACE2 expression in urinary organs (kidney) was nearly 100-fold higher than in respiratory organs (lung) [17]. Kidney pathology revealed focal necrosis and inflammatory infiltrates dominated by monocytes and lymphocytes. In addition, immunohistochemistry showed that the virus nucleocapsid protein antigen was enriched in the renal tubules, which was confirmed by severe renal tubular necrosis [18]. The pathological changes of the kidney are mainly due to local SARS-CoV-2 replication or indirectly by pro-inflammatory cytokine response [19]. These suggest that the kidney is one important target organ for SARS-CoV-2 invasion, not just a secondary lesion.

Compared with the normal baseline serum creatinine group, the inflammatory factors, immunology, and organ tissue damage indicators were significantly increased in the EBSC group, while lymphocytes, albumin, and hemoglobin were significantly reduced. It suggests that the possible mechanism is that the kidney system damage of COVID-19 patients may be caused by inflammatory response disorders, which may include excessive activation of immune cells [20]. The decrease of lymphocyte in patients may be caused by a large number of chemotactic chemotaxis to the lungs, kidneys and other target organs after the activation of inflammatory cells, releasing inflammatory factors, thus recruiting more inflammatory cells and causing a vicious cycle. This process also produces a large number of oxygen free radicals, which jointly cause tissue and organ damage [20,21].

Table 2
Laboratory findings of COVID-19 patients.

Indicators	Total (*N* = 1509)	Normal baseline serum creatinine (*N* = 1393)	Elevated baseline serum creatinine (*N* = 116)	*P* value
Blood cell counts				
Leucocytes, × 10^9 per L	5.8(4.7–7.4)	5.8(4.7–7.3)	6.6(5.0–8.4)	0.001
Neutrophils, × 10^9 per L	3.7(2.7–5.1)	3.6(2.7–4.9)	5.1(3.4–7.0)	<0.001
Lymphocytes, × 10^9 per L	1.3(0.9–1.8)	1.4(1.0–1.8)	1.0(0.6–1.4)	<0.001
Monocytes, × 10^9 per L	0.5(0.4–0.6)	0.5(0.4–0.6)	0.5(0.4–0.7)	0.197
T cells (CD3 + CD19-), /μl	1071.0(797.0–1409.0)	1072.0(797.0–1409.0)	1059.0(795.5–1464.5)	0.799
B cells (CD3-CD19 +), /μl	79.7(47.2–116.1)	79.0(46.2–113.6)	85.2(58.6–139.2)	0.217
Th cells (CD3 + CD4 +), /μl	650.0(477.0–859.0)	650.0(476.0–857.0)	649.0(486.8–900.0)	0.786
Ts cells (CD3 + CD8 +), /μl	351.0(245.0–478.0)	352.0(245.0–480.0)	349.5(260.5–475.8)	0.896
NK cells (CD3-/CD16 + CD56 +), /μl	193.0(122.0–292.0)	191.0(123.0–293.0)	218.0(120.3–281.8)	0.661
T cells + B cells + NK cells, /μl	1490.0 (1157.0–1928.0)	1496.0(1154.5–1924.0)	1480.5(1167.8–2016.0)	0.751
Hemoglobin, g per L	128.0(118.0–139.0)	128.0(118.0–139.0)	125.0(108.3–137.8)	0.010
Inflammatory and immunological factors				
Interleukin 2 receptor, U/mL	436.5(285.0–697.8)	412.0(279.0–651.0)	848.0(576.0–1251.0)	<0.001
Interleukin 6, pg/mL	5.3(2.7–17.2)	4.9(2.6–14.3)	15.7(5.4–44.1)	0.002
Interleukin 8, pg/mL	11.4(7.9–19.4)	11.1(7.7–18.8)	13.8(9.4–27.4)	0.854
Interleukin 10, pg/mL	7.8(6.1–11.0)	7.6(6.0–10.6)	8.8(6.1–15.2)	0.643
TNF-α, pg/mL	8.1(6.4–10.4)	7.9(6.3–9.9)	12.0(9.4–17.6)	<0.001
CRP, mg/L	5.3(1.2–40.5)	4.4(1.1–34.0)	10.3(7.2–47.4)	<0.001
ESR, mm/hour	26.0(11.0–56.0)	25.0(11.0–54.0)	45.0(24.0–80.0)	<0.001
Ferritin, ng/ml	441.5(235.1–800.4)	432.3(222.9–761.9)	680.4(381.8–1691.9)	0.003
C3, g/L	0.9(0.8–1.0)	0.9(0.8–1.0)	0.9(0.8–1.0)	0.819
C4, g/L	0.2(0.2–0.3)	0.2(0.2–0.3)	0.3(0.2–0.3)	0.006
IgM, AU/ml	40.2(13.8–101.5)	40.2(13.8–101.2)	40.1(13.1–52.0)	0.333
IgG, AU/ml	178.3(134.5–219.4)	178.2(134.7–219.0)	180.1(123.7–228.3)	0.245
Coagulation function				
Prothrombin time, second	13.6(13.1–14.2)	13.6(13.1–14.1)	14.0(13.2–14.8)	0.014
D-dimer, μg/mL	0.6(0.3–1.4)	0.5(0.3–1.3)	1.3(0.6–2.9)	<0.001
Platelets, × 10^9 per L	225.5(177.0–285.0)	228.5(179.0–285.0)	195.0(150.5–263.3)	0.008
Organ damage indices				
Alanine aminotransferase, U/L	23.0(14.8–39.0)	23.0(14.0–39.0)	23.5(15.0–41.5)	0.792
Aspartate aminotransferase, U/L	24.0(18.0–34.0)	23.0(18.0–33.0)	28.0(20.0–47.5)	0.027
Albumin, g/L	38.2(33.3–41.8)	38.5(33.7–42.1)	33.9(30.6–38.4)	<0.001
Total bilirubin, μmol/L	9.0(6.6–12.3)	8.8(6.6–12.1)	9.8(6.2–14.5)	0.131
Lactate dehydrogenase, U/L	228.0(184.0–304.0)	224.0(181.5–299.0)	298.0(228.0–389.5)	<0.001
CK-MB	0.6(0.4–1.1)	0.6(0.4–1.0)	1.2(0.8–2.1)	<0.001
hs-cTnI, pg/mL	5.5(3.1–10.8)	5.0(3.0–9.2)	12.6(5.4–28.6)	0.341
NT-proBNP, pg/mL	82.0(33.0–242.0)	74.0(30.0–199.0)	358.0(109.0–895.5)	0.013
Blood urea nitrogen, mmol/L	4.5(3.5–5.6)	4.4(3.5–5.4)	7.9(5.9–11.4)	<0.001
Creatinine, μmol/L	67.0(56.0–81.0)	66.0(56.0–77.0)	114.0(105.3–130.0)	<0.001
eGFR, ml/min per 1.73 m^2	95.4(81.4–106.8)	97.0(86.1–108.2)	51.1(41.7–58.7)	<0.001
Procalcitonin, ng/mL	0.1(0–0.1)	0.1(0–0.1)	0.1(0–0.1)	<0.001

Abbreviation: T cell, T lymphocyte; B cell, B lymphocyte; Th cell, helper T lymphocyte; Ts cell, suppressor T lymphocyte; NK cell, nature killer cell; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; C3, complement component 3; C4, complement component 4; IgM, Immunoglobulin M; IgG, Immunoglobulin G; TNF-α, Tumor necrosis factor α; CK-MB, Creatine Kinase Isoenzyme-MB; hs-cTnI, High-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro brain natriuretic peptide. Continuous variables were described as median (Interquartile range).

Previous study showed that higher D-dimer and prolonged PT always existed in more severe COVID-19 patients [22,23]. In our study, we also found that D-dimer and PT were higher in the EBSC group as compared to the normal baseline serum creatinine group. Increased D-dimer, prolonged PT, and thrombocytopenia were recently reported to be associated with 28-day mortality in patients with severe COVID-19 infection [24], and the combination of these could be explained by the coagulation system activation and always indicated the possibility of disseminated intravascular coagulation (DIC) [25]. Viral infections can lead to inflammatory response and imbalance between procoagulant and anticoagulant homeostasis [26]. The inflammatory response elicits vascular endothelial dysfunction, disrupts the balance between the coagulation and fibrinolytic systems, and as a result leads to DIC and microcirculation disorder and finally multiple organ dysfunction syndrome (MODS) [27,28].

Survival analysis found that the incidence of in-hospital death in the patients with EBSC was 7.8%, which was significantly higher than in those with normal baseline serum creatinine (1.2%). The shorter time from onset to admission and longer hospital stay indicates rapid progress in EBSC group. Altered kidney function should be given particular attention in clinical practice. Early detection and treatment of renal abnormalities, including adequate hemodynamic support and avoidance of nephrotoxic drugs, may help to improve the prognosis of COVID-19 [13]. There are also many studies confirming that continuous renal replacement therapy can alleviate the condition and improve survival [11,12]. Earlier admission to hospital and active medical intervention might help to prevent disease deterioration.

Older age, males, comorbidities, lymphopenia, leukocytosis, elevated creatinine or eGFR were associated with in-hospital death. Elderly patients are more prone to multi-system organ dysfunction (including acute kidney injury) [29]. Males are more susceptible to SARS-CoV-2 infections based on different innate immunity, steroid hormones, and factors related to sex chromosomes [30]. In addition, estradiol can down-regulate the outbreak of pro-inflammatory cytokines, and reduce further organ damage [31]. Moreover, females may benefit from the effect of estrogen on immune system [32]. In COVID-19 patients with a history of CVD, acute myocardial injury is also the most common complication and prognostic indicator of death [7,33]. Similarly, cardiovascular disease is a risk factor for death in this study. We ruled out the interference of basic diseases on kidney injury.

Table 3
Univariate Cox regression analysis of association between kidney disease and in-hospital death in patients with coronavirus disease 2019.

Variables	Hazard ratios	95% Confifidence interval	P value
Age > 65 years	2.920	1.290–6.610	0.01
Sex, male	4.129	1.692–10.519	0.002
Any comorbidity	3.536	1.332–9.392	0.011
CHD	4.473	1.786–11.203	0.001
Malignancy	5.733	1.713–19.188	0.005
Leukocyte count > 10 × 10^9/l	6.283	2.756–14.323	<0.001
Lymphocyte count < 1.5 × 10^9/l	3.464	1.193–10.055	0.022
Elevated baseline serum creatinine	5.969	2.653–13.429	<0.001
eGFR, < 60 ml/min per 1.73 m^2	7.717	3.490–17.064	<0.001
IL-6, per 1 pg/mL increased	1.006	1.004–1.007	<0.001
PLT, per 1 × 10^9 increased	0.992	0.986–0.997	0.002
Lymphocyte, per 1 × 10^9 increased	0.156	0.063–0.383	<0.001
TNF-α, per 1 pg/mL increased	1.093	1.045–1.143	<0.001
IL-2R, per 1 U/mL increased	1.002	1.001–1.002	<0.001
Albumin, per 1 g/L increased	0.864	0.806–0.927	<0.001

Abbreviation: CHD, Cardioheart disease; eGFR, Estimated glomerular fifiltration rate; IL-6, Interleukin 6; PLT, Platelets; TNF-α, Tumor necrosis factor α; IL-2R, Interleukin 2 receptor.

Reviewing the previous published literature on COVID-19, patients with COVID-19 presented varying degrees of renal injury, with incidence varies from 0.5 to 22.6% [4,5,7,8,34–36]. The incidence of acute kidney injury was lower among mild COVID-19 cases, while that of severe or critical cases was increased. Chronic kidney disease, COVID-19 clinical classification, eGFR < 60 ml/min/1.73 m^2, CRP, ventilation support, procalcitonin more than 0.1 ng/mL, elevated serum creatinine, proteinuria and hematuria are all associated with renal injury. COVID-19-related death was associated with males, greater age, comorbidities, kidney injury and so on [8,19,23,34–36]. Compared with people of white ethnicity, Black and South Asian people were at higher risk, even after adjustment for other factors [37]. Patients with COVID-19

Table 4
Multivariate COX regression analysis for mortality.

Factors	β	S$\bar{x}$	*P* Value	HRs for Mortality (95% CI)
Elevated baseline serum creatinine	0.972	0.442	0.028	2.643 (1.111–6.285)
eGFR < 60 ml/min per 1.73 m^2	1.358	0.442	0.002	3.889 (1.634–9.257)

Hazard ratios (HRs) of each variable were obtained using separate proportional hazard Cox models after adjustment for age, sex, any comorbidity, leukocyte and lymphocyte count. Comorbidities include hypertension, diabetes, CHD and malignancy. 95% CI, 95% confifidence interval; eGFR, estimated glomerular fifiltration rate.

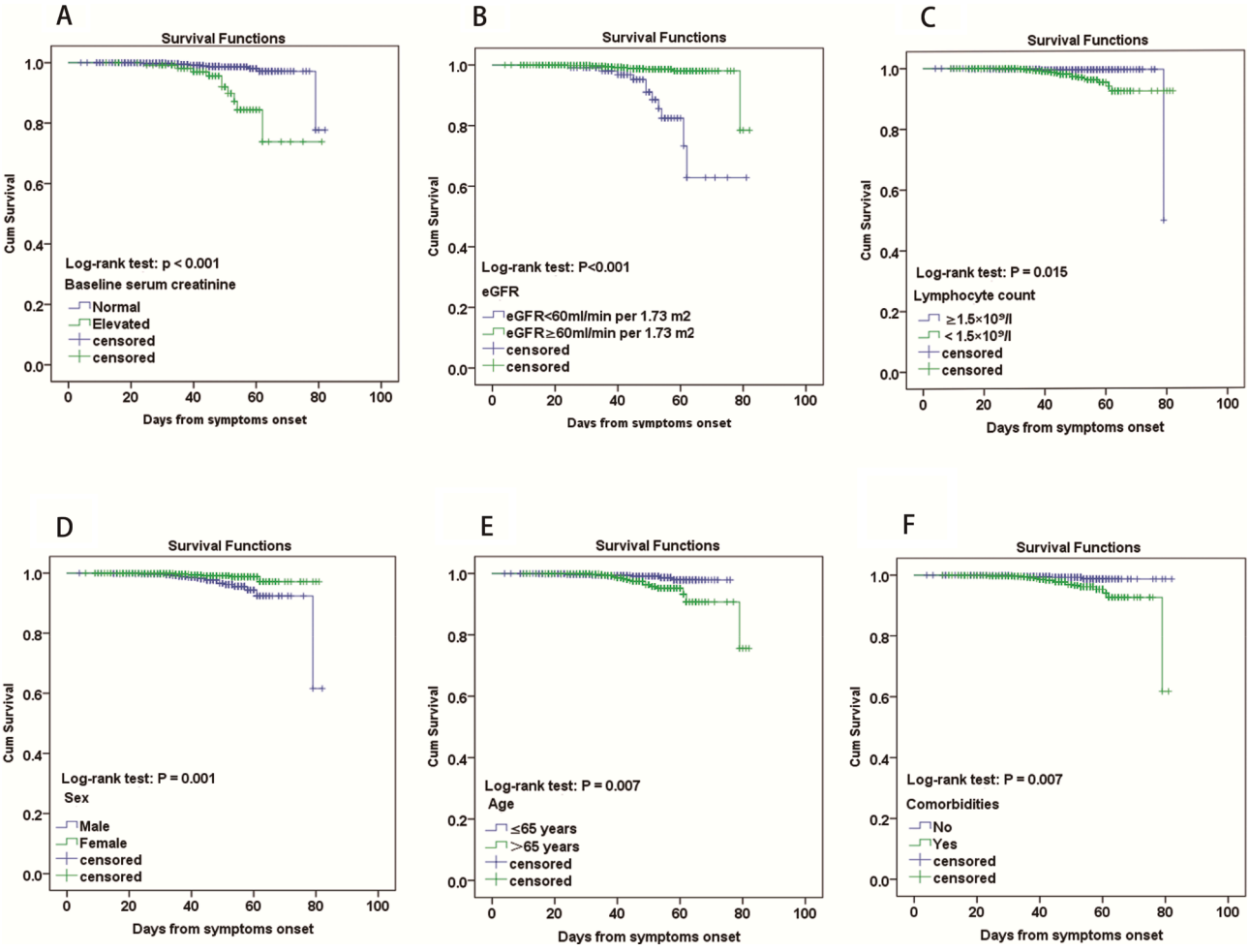

Fig. 2. Kaplan-Meier estimates on survival by A: Baseline serum creatinine; B: eGFR (estimated glomerular fifiltration rate); C: Lymphocyte count; D: Sex; E:Age; F: comorbidity.

Table 5
Correlation analysis was evaluated between kidney disease indicators, blood cell counts, organ damage indices and inflammatory factors.

	Inflammatory factors				Organ damage indices					Blood cell counts				
Indicators	IL-6	IL-2R	TNF-α	CRP	PT	D-dimer	CK-MB	ALT	AST	Alb	PLT	Hb	Lymphocytes	Neutrophils	Days from illness onset to admission
Creatinine	0.184**	0.361**	0.374**	0.021	0.026	0.009	0.014	0.029	0.066*	−0.129**	−0.095**	−0.044	−0.150**	0.160**	0.084**
eGFR	−0.209**	−0.372**	−0.343**	0.056*	0.018	0.009	0.026	0.071**	0.055*	0.309**	0.070**	0.188**	0.290**	−0.174**	−0.195**
BUN	0.018	0.011	0.014	0.074**	0.052	0.084**	0.163**	0.018	0.011	−0.034	−0.013	0.037	−0.022	0.011	−0.003
IL-6	–	0.364**	0.284**	−0.010	0.017	−0.023	−0.010	0.063*	0.149**	−0.216**	−0.098**	−0.039	−0.144**	0.195**	−0.160**
C3	0.012	0.078	0.057	0.002	−0.214**	0.031	−0.074	−0.004	−0.017	0.047	−0.015	0.163**	0.034	−0.062	−0.040
C4	0.106	0.058	−0.031	0.144**	−0.052	0.005	0.061	0.007	0.007	0.009	−0.057	0.139**	0.017	−0.029	−0.053

Data expressed as correlation coefficient. * $P < 0.05$; ** $P < 0.01$.
Abbreviation: IL6, Interleukin 6; IL-2R,Interleukin 2 receptor; TNF-α, Tumor necrosis factor α; CRP, C-reactive protein; PT, Prothrombin time; CK-MB, Creatine Kinase Isoenzyme-MB; ALT, Alanine aminotransferase; AST, Alanine aminotransferase; Alb, Albumin; PLT, Platelets; Hb, Hemoglobin; BUN, Blood urea nitrogen; eGFR, Estimated glomerular fiiltration rate; C3, complement component 3; C4, complement component 4.

presented varying degrees of kidney-related death, with incidence varies from 0.4% to 63% [1,8,23,34,35,37], which may be related to limited sample size, selection bias and medical condition. The conclusions drawn in this study were consistent with relevant literature.

The last but not least, the kidney is an important target for virus attack, and it is itself a "silent organ". Even after injury, the patient has no subjective discomfort. Thus, it is also possible that asymptomatic infected persons do not exhibit respiratory symptoms, but there is kidney damage, which could potentially be missed in a small percentage of the population. Our recommendation: Urine should be used as one of the screening specimens in asymptomatic infected persons, especially close contacts with negative throat swab and suspected infected persons, to determine whether there are significant changes in progressive proteinuria, hematuria and renal function. This is of great significance for epidemic screening, epidemic prevention, patient condition judgment and prognosis evaluation.

There were several limitations in this study. First, this was a retrospective, single center study of patients admitted to Tongji Hospital. The results should be validated in multicenter prospective study with larger samples. Second, selection bias may exist. Third, due to the lack of urine sediment test and multiple creatinine value tests, it is impossible to estimate the proportion of acute kidney injury and the impact of urine test data on survival.

5. Conclusions

The prevalence of kidney injury in patients with COVID-19 hospitalized in Tongji hospital, Wuhan, China, was high and associated with in-hospital mortality. Early detection and effective intervention of kidney injury may help to reduce deaths of COVID-19 patients.

CRediT authorship contribution statement

Chunjin Ke: Software, Writing - original draft, Writing - review & editing. **Jun Xiao:** Supervision, Writing - review & editing. **Zhihua Wang:** Data curation, Formal analysis. **Chong Yu:** Data curation, Supervision. **Chunguang Yang:** Funding acquisition, Writing - review & editing. **Zhiquan Hu:** Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Lifespan institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2021.107794.

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