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Subclinical Acute Kidney Injury in COVID-19 Patients: A Retrospective Cohort Study

Dan-Qin Sun[a] Ting-Yao Wang[b] Kenneth I. Zheng[c] Giovanni Targher[d]
Christopher D. Byrne[e] Yong-Ping Chen[c, f, g] Ming-Hua Zheng[c, f, g]

[a]Department of Nephrology, The Affiliated Wuxi No. 2 People's Hospital of Nanjing Medical University, Wuxi, China; [b]Department of Nephrology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [c]NAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [d]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [e]Southampton National Institute for Health Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Southampton, UK; [f]Institute of Hepatology, Wenzhou Medical University, Wenzhou, China; [g]Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China

Dear Editor,

We read with great interest the recent article "COVID-19 Infection in a Patient with End-Stage Kidney Disease" by Fu et al. [1]. Previous studies have reported that ~10% of infected patients may develop acute kidney injury (AKI), which is a strong prognostic factor increasing risk of death [2–4]. We agree with the authors that SARS-CoV2 affects the kidney function and special care of renal function should be taken into account in COVID-19 patients. However, the current definition of AKI does not provide a measurement of loss of kidney function because serum creatinine level is not a sensitive marker of early tubular injury (elevation of serum creatinine requires damage/dysfunction of >50% of the nephron mass), whereas biomarkers of tubular injury provide information on early kidney injury and response to noxious stimuli [5].

All COVID-19 infection patients without a prior history of chronic kidney disease included in our study (n = 32) were consecutively admitted to our hospital in February, who were confirmed, classified as 3 subtypes (common, severe, and critical), and discharged from our hospital based on the guidelines for the diagnosis and treatment of novel coronavirus disease (version 6) [6].

Most of these patients had mean levels of estimated glomerular filtration rate (eGFR) within the normal range, whereas 31.3% (n = 10) had proteinuria, 9.4% (n = 3) had macroalbuminuria, and 12.5% (n = 4) had microalbuminuria (Table 1). The proportion of patients with increased urinary levels of β2-microglobulin (β2MG), α1-microglobulin (α1MG), retinol binding protein (RBP), and *N*-acetyl-β-d-glucosaminidase (NAG) levels were 20, 20, 10, and 10%, respectively. On the first day of hospital admission, there were no significant differences in mean levels of serum creatinine, blood

Dan-Qin Sun and Ting-Yao Wang are co-first authors.

karger@karger.com
www.karger.com/nef

Dr. Ming-Hua Zheng
NAFLD Research Center, Department of Hepatology
The First Affiliated Hospital of Wenzhou Medical University
No. 2 Fuxue Lane, Wenzhou 325000 (China)
zhengmh@wmu.edu.cn

Karger

Table 1. Baseline characteristics of patients with COVID-19 infection

	All patients	Disease subtypes			
	n = 32	common subtype (*n* = 5)	severe subtype (*n* = 18)	critical subtype (*n* = 9)	*p* value
Demographic parameters					
Age	61 (54–73)	61 (55–73)	64 (55–72)	55 (53–81)	0.957
Male sex, *n* (%)	20 (62.5)	3 (60)	10 (55.6)	7 (77.8)	0.608
Clinical parameters					
Fever, *n* (%)	17 (53.1)	1 (20)	12 (66.7)	4 (44.4)	0.159
Heart rate, beats per minute	82 (76–94)	82 (72–87)	85 (76–96)	79 (68–94)	0.692
Respiratory rate, breaths per minute	20 (20–22)	20 (18–20)	20 (20–23)	21 (19–33)	0.155
Systolic blood pressure, mm Hg	136 (124–144)	138 (132–157)	129.5 (119–144)	139 (130–167)	0.102
Diastolic blood pressure, mm Hg	79 (72–82)	82 (75–88)	75 (68–82)	82 (74–87)	0.091
Hypertension, *n* (%)	10 (31.3)	2 (40)	5 (27.8)	3 (33.3)	0.879
Diabetes, *n* (%)	5 (15.6)	1 (20)	3 (16.7)	1 (11.1)	1,000
CRRT, *n* (%)	1 (3.1)	0	0	1 (11.1)	0.438
Invasive ventilation, *n* (%)	9 (28.1)	0	1 (5.6)	8 (88.9)[b, c]	<0.001
ECMO, *n* (%)	4 (12.5)	0	0	4 (44.4)[c]	0.006
Length of hospital stay, days	23 (17–27)	14 (11–15)	22 (18–26)[a]	27 (24–35)[b, c]	<0.001
Laboratory parameters					
Leukocyte count, $\times 10^9$/L	7.7 (5.7–11.8)	5.9 (5.5–12.7)	7.2 (5.2–11.4)	8.2 (7.5–12.1)	0.466
Lymphocyte count, $\times 10^9$/L	0.8±0.4	0.9±0.4	0.9±0.3	0.6±0.4	0.183
Hemoglobin, g/L	124.6±17.4	117.4±16.9	123.9±16.2	130±20.2	0.431
Platelet count, $\times 10^9$/L	229.4±100.3	353.0±109.7	226.8±80.1[a]	166.1±72.7[b]	0.002
C-reactive protein ≥10 mg/L, *n* (%)	29 (90.6)	4 (80)	16 (88.9)	9 (100)	0.395
Alanine aminotransferase, U/L	24 (20–42)	39 (20–85)	23.5 (19–27)	42 (22–102)	0.197
Aspartate aminotransferase, U/L	31 (25–61)	28 (21–48)	30 (25–35)	57 (39–96)[c]	0.008
Lactose dehydrogenase, U/L	401±151	257±77	365±103	553±145[b, c]	<0.001
Creatinine kinase, U/L	70 (56–207)	64 (41–75)	64 (54–172)	164 (72–361)	0.037
Serum albumin, g/L	31.6 (29–35)	32.7 (29–37)	31.6 (29–35)	30.5 (29–33)	0.618
Blood urea nitrogen, mg/dL	15.6±6.7	17.6±5.7	14.3±7.9	17.1±3.8	0.475
Serum creatinine, mg/dL	0.7±0.1	0.8±0.1	0.7±0.2	0.8±0.1	0.566
eGFR, mL/min/1.73 m^2	100.7±20.3	99.8±18.3	103.1±21.7	96.4±20.0	0.731
Urinary β2MG ≥0.195 μg/mL, *n* (%)	20 (62.5)	2 (40)	11 (61.1)	7 (77.8)	0.417
Urinary α1MG ≥12 mg/L, *n* (%)	20 (62.5)	1 (20)	12 (66.7)	7 (77.8)	0.086
Urinary RBP ≥0.7 μg/mL, *n* (%)	10 (31.3)	0	4 (22.2)	6 (66.7)	0.019
Urinary NAG ≥14.6 U/L, *n* (%)	10 (31.3)	1 (20)	4 (22.2)	5 (55.6)	0.191
Urinary β2MG-creatinine ratio, mg/g	0.4 (0.1–2.1)	0.2 (0.1–0.5)	0.2 (0.1–1.0)	4.8 (0.4–150)[c]	0.024
Urinary α1MG-creatinine ratio, mg/g	16.3 (8.1–37.6)	7.8 (3.7–15.9)	14.2 (7.5–28.8)	222 (26.6–593)[b, c]	0.001
Urinary RBP-creatinine ratio, mg/g	0.4 (0.2–4.7)	0.1 (0.1–0.3)	0.3 (0.2–0.6)	24.3 (0.5–166)[b, c]	0.001
Urinary NAG-creatinine ratio, mg/g	8.1 (4.6–17.0)	6.6 (4.5–8.4)	7.5 (4.6–13.8)	68.1 (6.1–172)[c]	0.049
Urinary ACR category, *n* (%)					0.002
ACR ≥30 mg/g	7 (21.9)	0	1 (5.6)	6 (66.7)	
ACR <30 mg/g	25 (78.1)	5 (100)	17 (94.4)	3 (33.3)	
Proteinuria, *n* (%)					0.019
Negative	22 (68.8)	5 (100)	14 (77.8)	3 (33.3)	
Positive	10 (31.2)	0	4 (22.2)	6 (66.7)	
Clinical outcome					
Remained in hospital, *n* (%)	12 (37.5)	0	6 (33.3)	6 (66.7)	0.036
Discharged, *n* (%)	20 (62.5)	5 (100)	12 (66.7)	3 (33.3)	

Data are expressed as numbers (percentages) for categorical variables, means±SD for normally distributed continuous variables, and medians (interquartile ranges) for skewed distributed continuous variables. Differences between the groups were tested either by one-way ANOVA analysis (Bonferroni correction for comparisons) and the Kruskal-Wallis test (for continuous variables) or by the χ^2 test and Fisher's exact test (for categorical variables). ACR, albumin to creatinine ratio; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; ECMO, extracorporeal membrane oxygenation; RBP, retinol binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; β2MG, β2-microglobulin; α1MG, α1-microglobulin. [a] $p < 0.05$ between common and severe subtype. [b] $p < 0.05$ between common and critical subtype. [c] $p < 0.05$ between severe and critical subtype.

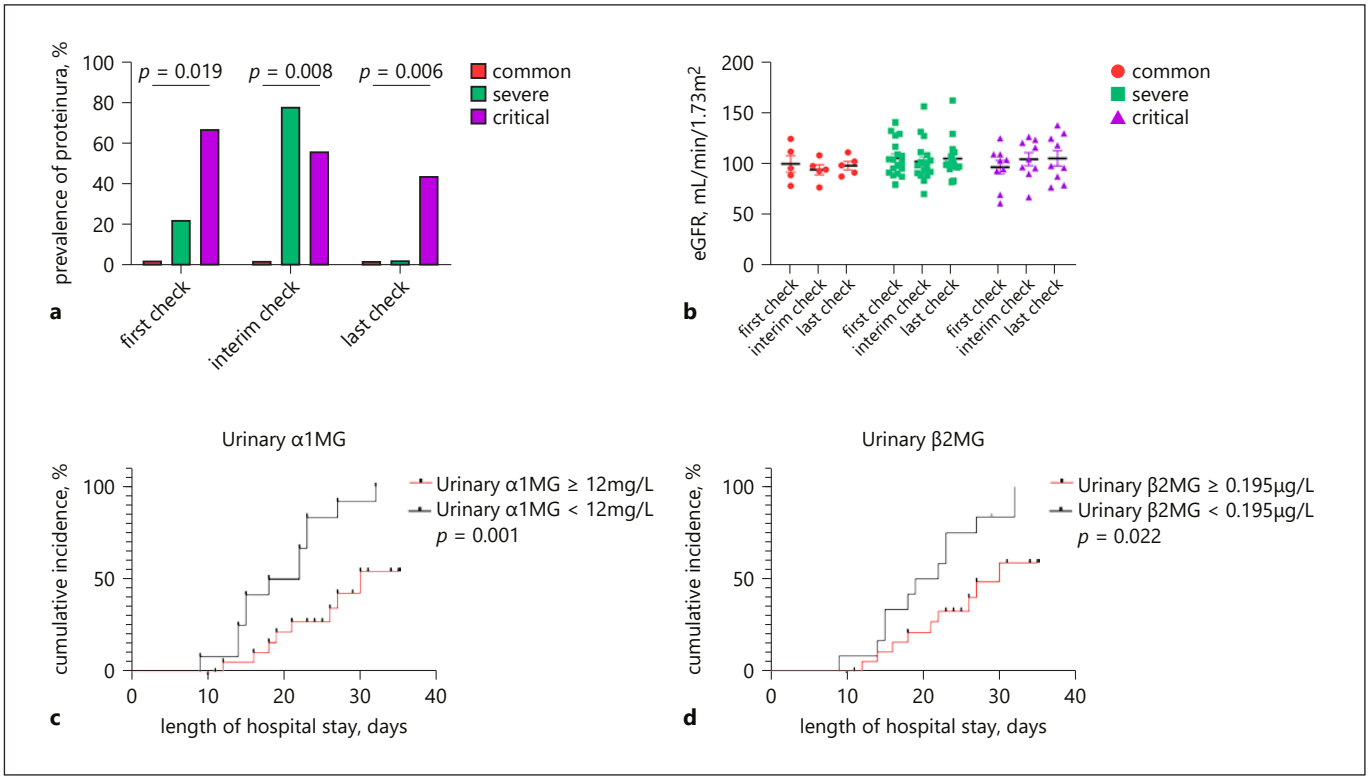

Fig. 1. The proportion of proteinuria (**a**) and the mean levels of eGFR (**b**) across different disease subtypes of COVID-19 patients during the hospital stay; Kaplan-Meier curves for cumulative hospital discharge rates of COVID-19 patients stratified by urinary levels of kidney injury biomarkers (urinary α1MG (**c**); urinary β2MG (**d**)). eGFR, estimated glomerular filtration rate; α1MG, α1-microglobulin; β2MG, β2-microglobulin.

urea nitrogen, and eGFR among the common, severe, and critical subtypes. However, the proportion of albuminuria as well as the levels of urinary β2MG-creatinine ratio, α1MG-creatinine ratio, RBP-creatinine ratio, and NAG-creatinine ratio significantly increased according to the severity of disease. During the hospital stay, the proportion of proteinuria (dipstick >1+) in critically ill COVID-19 patients was significantly higher than that observed in common COVID-19 patients on the first check and gradually improved during the patients' hospital admission (Fig. 1). No significant differences were observed in the mean levels of eGFR both on the first day of admission and during the hospital stay amongst the 3 patient subtypes. Furthermore, Kaplan-Meier survival curves showed that patients with elevated urinary β2MG and α1MG levels had significantly lower rates of hospital discharge compared to those with normal urinary β2MG and α1MG levels.

In conclusion, we suggest that COVID-19 infection may induce early development of abnormal albuminuria and impair kidney tubular function. Because SARS-CoV-2 has been isolated from urinary samples of an infected patient and the receptor of this virus is the angiotensin converting enzyme II which is expressed on podocytes and proximal straight tubule cells [4, 7]. Notably, podocytes and proximal straight tubule cells are particularly vulnerable to viral attacks, and our findings suggested that the excretion of these urinary biomarkers may be related to the severity of the infection. Therefore, more careful medical surveillance of urinary biomarkers of early AKI is required in COVID-19-infected patients because early detection and treatment can slow or prevent progression of kidney disease.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dan-Qin Sun and Ming-Hua Zheng conceived and designed the study; Ting-Yao Wang and Yong-Ping Chen collected the data; Dan-Qin Sun and Ting-Yao Wang analyzed and interpreted the data; Dan-Qin Sun and Kenneth I. Zheng drafted the manuscript; Giovanni Targher and Christopher D. Byrne reviewed and edited the manuscript. All authors contributed to the manuscript for important intellectual content and approved the submission.

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