Original Article
Renal injury in hypertensive patients plays a role in promoting the worsening condition after they are infected with SARS-CoV-2

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Abstract: Objective: To explore potential mechanism about the experience that hypertension is associated with poor outcome in patients with coronavirus disease 2019 (COVID-19). Methods: In this retrospective study, 134 hypertensive patients diagnosed with COVID-19 were included from February 1, 2020 to March 15, 2020. We assessed the associations between renal injury on admission and risks of acute kidney injury (AKI) and in-hospital mortality and analyzed the dynamic changes of serum creatinine and blood urea nitrogen (BUN). Result: Among the 134 COVID-19 patients, 95 (70.9%) were discharged and survived, and 39 (29.1%) died. On admission, BUN and serum creatinine were elevated in 24 (17.9%) and 39 (29.1%) patients, respectively. Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 was reported in 18 (13.4%) patients. Multiple regression analysis showed that elevated baseline BUN and eGFR less than 60 ml/min/1.73 m^2 on admission were independent risk factors for both AKI and in-hospital death in COVID-19 patients with hypertension. Level of serum creatinine or BUN increased faster in patients with elevated baseline serum creatinine or BUN respectively than those with normal levels. Conclusion: Renal injury of hypertensive patients can result in poor outcomes including AKI and death after they are infected with SARS-CoV-2, and clinicians should be vigilant for these patients with abnormal renal function at admission.

Keywords: COVID-19, hypertension, renal injury, serum creatinine, blood urea nitrogen

Introduction

Several cases of acute respiratory disease with unknown etiology had been reported in Wuhan, China since December 2019 [1]. Then severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the virus causing the disease named coronavirus disease 2019 (COVID-19) [2]. The disease rapidly spread across the world and became a pandemic. Symptoms of most COVID-19 patients are mild, but a few patients may develop severe pneumonia and progress to fatal complications, including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and death [3]. Although there has been already a lot of research suggesting that specific comorbidities are associated with worse outcomes or increased mortality in patients with COVID-19, and hypertension is the most common one in these

comorbidities [4-8]. Specific mechanism by which hypertension affects COVID-19 patients is not yet clear. Previous study mentioned that end-organ damage in hypertensive patients was an explanation for why hypertension would be a risk factor [6]. We hypothesize that renal injury in hypertensive patients plays a role in promoting the worsening condition after they are infected with SARS-CoV-2. The aim of this present study is to evaluate the rationality of the hypothesis using a single-center data during the pandemic.

Materials and methods

Study design and participants

In this retrospective study, 134 consecutive patients diagnosed with COVID-19 were included from February 1, 2020 to March 15, 2020 in

Table 1. The upper limits of normal serum creatinine and blood urea nitrogen

	Age	Male	Female
Serum creatinine (μmol/L)		104	84
BUN (mmol/l)	< 60, years	8.0	7.5
	60-80, years	9.5	8.8
	> 80, years	8.3	8.3

Bun: blood urea nitrogen.

Sino-French New City Branch of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The hospital was designated as one of the medical centers for treatment of the patients with COVID-19 who were in a worse condition in clinic. Diagnostic criteria for COVID-19 were based on positive results of sequencing or real-time reverse transcription polymerase chain reaction (real-time RT-PCR) assay of nasal or pharyngeal swab specimens. Hypertension with or without chronical renal insufficiency was inclusion criteria, and any comorbidity other than hypertension or renal disease caused by hypertension was exclusion criteria. Patients with a history of maintenance dialysis or renal transplantation or AKI were also excluded from the study. All procedures performed involving human participants were approved by the Medical Ethics Committee of Tongji Hospital and in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data collection and definition

Two independent researchers collected data from patients' electronic medical records, including demographic characteristics, clinical symptoms, chest computed tomography (CT) findings, laboratory data, treatment, complications and outcomes. Laboratory data consisted of blood routine, coagulation function and blood biochemistry, and we discarded some parameters with more than 20% missing values.

The thresholds of the laboratory parameters were offered by our laboratory. The upper limits of normal serum creatinine and blood urea nitrogen (BUN) were shown in **Table 1**. We defined baseline serum creatinine or BUN as value of serum creatinine or BUN on admission. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition

[9]. Acute kidney injury (AKI) was identified according to the Kidney Disease: Improving Global Outcomes definition [10]. Septic shock was defined according to the surviving sepsis guideline [11].

Statistical analysis

Categorical variables were summarized as frequencies and percentages, and continuous variables were described using mean ± SD or median (IQR: interquartile range). We assessed differences between survivors and non-survivors using two sample t test or Mann-Whitney U test depending on normal or nonnormal distribution for continuous variables, and chi square (χ^2) or Fisher's exact tests were used for categorical variables as appropriate. Survival curve was plotted using the Kaplan-Meier method and examined using the log-rank test. Multivariate logistic regression analysis was performed to evaluate the association between baseline renal function parameters and risk of AKI with adjustment of age, sex, antiviral treatment, and antibacterial treatment. Based on previous research [12, 13], the association between baseline renal function parameters and in-hospital mortality risk was estimated by Cox proportional hazards regression models in terms of the following confounders: age, sex, lymphocyte count, and platelet count. We used generalized linear mixed model for comparing the repeated measures. All statistical analyses were performed using R software (version 3.6.1; R Foundation, Vienna, Austria). A two-sided significance level of $P = 0.05$ was used to evaluate statistical significance.

Results

Clinical characteristics

Among the 134 COVID-19 patients, 95 (70.9%) were discharged and survived, and 39 (29.1%) died. The baseline characteristics, imaging findings, complications and treatment of the study population are summarized in **Table 2**. The mean age was 65.6±10.0 years, and 64 (47.8%) patients were male. The mean duration from onset of symptoms to admission was 11.7±6.0 days. In terms of medical treatment of hypertension, the most common medication among these patients was calcium channel antagonist (45.5%), followed by angioten-

Table 2. The baseline characteristics, imaging findings, complications, and treatment of the 134 patients stratified by survivors and non-survivors

	All patients n = 134	Survivors n = 95	Non-survivors n = 39	P value
Age, years	65.6±10.0	64.2±10.2	69.1±8.6	0.010
Sex (Male)	64 (47.8%)	42 (44.2%)	22 (56.4%)	0.199
Duration from onset of symptoms to admission, days	11.7±6.0	11.1±6.0	13.2±7.8	0.101
History of medications				
CCB	61 (45.5%)	39 (41.1%)	22 (56.4%)	0.105
ACEI/ARB	37 (27.6%)	27 (28.4%)	10 (25.6%)	0.744
Beta blocker	30 (22.4%)	19 (20.0%)	11 (28.2%)	0.301
Diuretic	21 (15.7%)	13 (13.7%)	8 (20.5%)	0.323
Symptoms				
Fever	99 (73.9%)	67 (70.5%)	32 (82.1%)	0.168
Fatigue	37 (27.6%)	22 (23.2%)	15 (38.5%)	0.072
Cough	70 (52.2%)	47 (49.5%)	23 (59.0%)	0.317
Dyspnea	45 (33.6%)	26 (27.4%)	19 (48.7%)	0.017
Chest pain	17 (12.7%)	9 (9.5%)	8 (20.5%)	0.093
Headache	20 (14.9%)	18 (18.9%)	2 (5.1%)	0.041
Muscle ache	31 (23.1%)	19 (20.0%)	12 (30.8%)	0.179
Nausea or vomiting	9 (6.7%)	6 (6.3%)	3 (7.7%)	0.719
Chest CT images				
Bilateral pneumonia	116 (86.6%)	83 (87.4%)	33 (84.6%)	0.699
Unilateral pneumonia	17 (12.7%)	11 (11.6%)	6 (15.4%)	
Normal	1 (0.7%)	1 (1.1%)	0 (0%)	
Complications				
ARDS	39 (29.1%)	12 (12.6%)	27 (69.2%)	< 0.001
Acute kidney injury	17 (12.7%)	3 (3.2%)	14 (35.9%)	< 0.001
Septic shock	22 (16.4%)	11 (11.6%)	11 (28.2%)	0.018
Treatment				
Antiviral agents	118 (88.1%)	86 (90.5%)	32 (82.1%)	0.239
Antibacterial agents	94 (70.1%)	60 (63.2%)	34 (87.2%)	0.006
Glucocorticoids	62 (46.3%)	33 (34.7%)	29 (74.4%)	< 0.001
Immunoglobulin	30 (22.4%)	17 (17.9%)	13 (33.3%)	0.051
CRRT	19 (14.2%)	8 (8.4%)	11 (28.2%)	0.003
Mechanical ventilation	35 (26.1%)	5 (5.3%)	30 (76.9%)	< 0.001

Data are mean ± SD or n (%). CCB: calcium channel; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ARDS: acute respiratory distress syndrome; CRRT, continuous renal replacement therapy.

sin-converting enzyme inhibitor or angiotensin receptor blocker (27.6%), beta blocker (22.4%), and diuretic (15.7%), and there was no statistically significant difference between survivors and non-survivors. The commonly experienced symptoms were fever (73.9%) and cough (52.2%). Of the 134 patients with chest CT scan on admission, the majority (86.6%) showed bilateral pneumonia. During hospitalization, the incidence was 29.1%, 12.7% and 16.4% in complications of ARDS, AKI, and sep-

tic shock, respectively. Compared with survivors, non-survivors were more likely to develop these three complications. During hospitalization, 118 (88.1%) received antiviral agents and 94 (70.1%) received antibacterial agents. There were 62 (46.3%) patients with treatment of glucocorticoids, and 30 (22.4%) patients with immunoglobulin. Mechanical ventilation was applied in 35 (26.1%) patients while continuous renal replacement therapy (CRRT) was applied in 19 (14.2%) patients.

Table 3. Laboratory results of the patients on admission

	All patients n = 134	Survivors n = 95	Non-Survivors n = 39	P value
Leukocytes (×10^9/L; NR 3.5-9.5)	5.5 (4.4-9.3)	5.0 (4.0-6.6)	10.8 (7.1-14.1)	< 0.001
Increased	32 (23.9%)	10 (10.5%)	22 (56.4%)	< 0.001
Lymphocytes (×10^9/L; NR 1.1-3.2)	3.8 (2.8-7.9)	3.2 (2.7-4.6)	9.4 (6.2-13.0)	< 0.001
Decreased	77 (57.5%)	41 (43.2%)	36 (92.3%)	< 0.001
Neutrophils (×10^9/L; NR 1.8-6.3)	0.9 (0.6-1.4)	1.2 (0.8-1.5)	0.6 (0.4-0.8)	< 0.001
Increased	46 (34.3%)	17 (17.9%)	29 (74.4%)	< 0.001
Platelets (×10^9/L; NR 125-350)	127 (118-144)	126 (118-143)	133 (119-150)	0.263
Decreased	23 (17.2%)	14 (14.7%)	9 (23.1%)	0.245
Hemoglobin (g/L; NR 130-175)	195 (144-247)	197 (154-260)	182 (130-231)	0.301
Decreased	71 (53.0%)	55 (57.9%)	16 (41.0%)	0.076
PT (s; NR 10.5-13.5, data available for 126 patients)	14.3 (13.5-15.0)	14.2 (13.4-14.8)	14.9 (14.5-16.3)	< 0.001
APTT (s; NR 21.0-37.0, data available for 108 patients)	40.4 (36.4-44.8)	40.3 (36.1-45.5)	40.2 (36.1-45.5)	0.972
D-dimer (µg/L; NR 0.0-1.5, data available for 125 patients)	4.6 (1.5-21.0)	1.2 (0.5-3.1)	0.6 (0.3-1.6)	< 0.001
Albumin (g/L; NR 35.0-52.0)	35.1 (31.5-37.8)	36.2 (34.0-39.0)	30.9 (27.9-34.3)	< 0.001
Decreased	66 (49.3%)	34 (35.8%)	32 (82.1%)	< 0.001
Alanine aminotransferase (U/L; NR 0.0-41.0)	25.5 (16.0-37.0)	23.0 (15.0-35.0)	30.0 (23.0-51.0)	0.001
Increased	24 (17.9%)	10 (10.5%)	14 (35.9%)	0.001
Aspartate aminotransferase (U/L; NR 0.0-40.0)	29.0 (20.0-48.5)	26.0 (19.0-33.5)	45.0 (30.5-62.0)	< 0.001
Increased	42 (31.3%)	19 (20.0%)	23 (59.0%)	< 0.001
TB (µmol/L; NR 0.0-26.0)	9.45 (7.68-13.7)	8.70 (7.20-11.4)	13.5 (9.55-17.4)	< 0.001
Increased	10 (7.5%)	3 (3.2%)	7 (17.9%)	0.007
BUN (mmol/L)	5.20 (3.80-7.68)	4.40 (3.75-5.60)	8.30 (5.70-15.2)	< 0.001
Increased	24 (17.9%)	7 (7.4%)	17 (43.6%)	< 0.001
Serum creatinine (µmol/L)	78.5 (61.5-95.0)	76.0 (56.0-93.0)	89.0 (68.0-113)	0.013
Increased	39 (29.1%)	25 (26.3%)	14 (35.9%)	0.267
eGFR (ml/min/1.73 m^2)	89.6 (77.0-95.4)	91.9 (86.6-97.0)	72.0 (48.0-87.0)	< 0.001
< 60	18 (13.4%)	4 (4.2%)	14 (35.9%)	< 0.001

Data are n (%) and median (IQR). NR: normal range; IQR: interquartile range; PT: prothrombin time; APTT: activated partial thromboplastin time; TB: total bilirubin; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate.

Laboratory data on admission

Laboratory findings of the 134 patients on admission are summarized in **Table 3**. There were numerous differences in laboratory findings between survivors and non-survivors, including leucocytes, lymphocytes, neutrophils, coagulation biomarkers and blood biochemistry parameters. On admission, BUN and serum creatinine were elevated in 24 (17.9%) and 39 (29.1%) patients, respectively. Estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 was reported in 18 (13.4%) patients. Compared to survivors, non-survivors were more likely to have elevated baseline BUN (7.4% *vs* 43.6%, *P* < 0.001) and eGFR less than 60 ml/min/1.73 m^2 on admission (4.2% *vs* 35.9%, *P* < 0.001), while there was no statistical difference between the survivors and non-

survivors in patients with an elevated baseline serum creatinine.

Risk of AKI and in-hospital survival analysis

Univariate and multivariate logistic regression analysis showed eGFR less than 60 ml/min/1.73 m^2 on admission, and elevated baseline serum creatinine and BUN were identified as independent predictors of AKI (**Table 3**). Kaplan-Meier survival curve suggested that elevated baseline BUN and eGFR less than 60 ml/min/1.73 m^2 on admission were risk factors for in-hospital mortality (**Figure 1B** and **1C**). However, elevated baseline serum creatinine was not associated with in-hospital mortality (*P* = 0.17, **Figure 1A**). Meantime, Cox proportional hazards model indicated that elevated baseline BUN was an independent risk factor
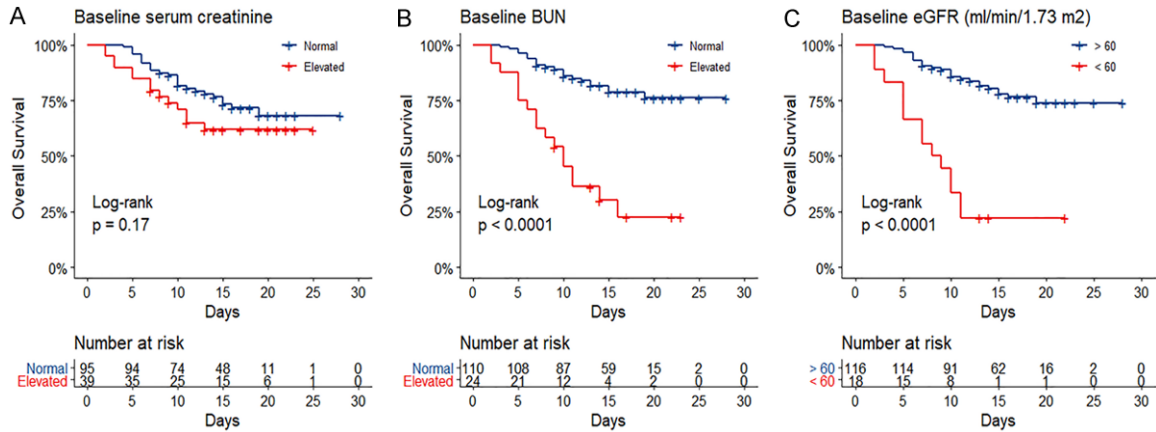
Figure 1. Kaplan-Meier survival curves for in-hospital death of the study population subgrouped by biochemical parameters of renal function. (A) baseline serum creatinine (B) baseline blood urea nitrogen (BUN) (C) estimated glomerular filtration rate (eGFR).

Table 4. Univariate and multivariate regression analysis for evaluating the risk of AKI and in-hospital mortality

	AKI		In-hospital death	
	OR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Elevated baseline serum creatinine				
Crude	8.00 (2.59-24.73)	< 0.001	1.57 (0.82-3.02)	0.178
Adjusted	5.38 (1.60-18.11)	0.007	1.40 (0.71-2.76)	0.325
Elevated baseline BUN				
Crude	21.00 (6.31-69.87)	< 0.001	5.34 (2.82-10.13)	< 0.001
Adjusted	12.48 (3.31-47.04)	< 0.001	3.15 (1.61-6.19)	0.001
eGFR less than 60 ml/min/1.73 m^2 on admission				
Crude	28.81 (8.22-100.98)	< 0.001	6.43 (3.28-12.60)	< 0.001
Adjusted	16.61 (4.17-66.16)	< 0.001	4.46 (2.19-9.08)	< 0.001

BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate.

for in-hospital mortality (*P* = 0.001, **Table 4**) as well as eGFR less than 60 ml/min/1.73 m^2 on admission (*P* < 0.001), while elevated baseline serum creatinine was not independently associated with in-hospital mortality (*P* = 0.325, **Table 4**).

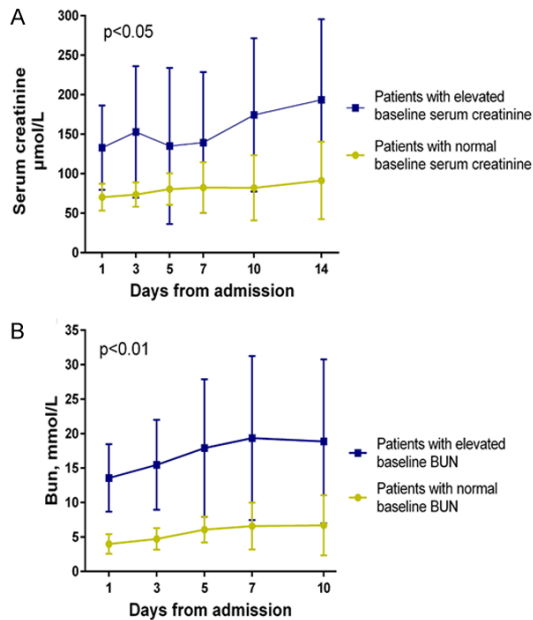*Dynamic change of serum creatinine and BUN*

Dynamic profile of serum creatinine was tracked on day 1, day 3, day 5, day 7, day 10 and day 14 after admission in 82 patients (25 patients with elevated baseline serum creatinine and 57 patients with normal baseline serum creatinine), and it showed that the level of serum creatinine increased faster in patients with elevated baseline serum creatinine (*P* < 0.05, **Figure 2A**). Likewise, dynamic change of BUN was tracked on day 1, day 3, day 5, day 7

and day 10 after admission in 43 patients (12 patients with elevated baseline BUN and 31 patients with normal baseline BUN), and it showed that the level of BUN increased faster in patients with elevated baseline BUN (*P* < 0.01, **Figure 2B**). Moreover, the level of serum creatinine in patients with normal baseline serum creatinine increased slowly and maintained at the normal range during observation period. The same result was observed in the dynamic change of BUN in patients with normal baseline BUN.

Discussion

When the epidemic of SARS-CoV-2 is still raging, its veil is lifted gradually. Research is continually pointing that as the most common comorbidity in patients with COVID-19, hyper-

Figure 2. Dynamic changes of serum creatinine and blood urea nitrogen (BUN). (A) subgrouped by patients with elevated or normal baseline serum creatinine (B) subgrouped by patients with elevated or normal baseline BUN.

tension is associated with disease progression and bad outcomes including death [4-8, 14, 15]. However, inherent connection between hypertension and the poor prognosis in COVID-19 patients is unclear, which is thought to be related to older age and pathological process of hypertension [6]. On the other hand, hypertension is one of the main reasons for renal injury and the most common comorbidity in patients with chronical kidney disease (CKD), which forms a vicious cycle during disease development [16, 17]. Meantime, kidney disease has been reported to add the risk of in-hospital mortality in patients with COVID-19 [18-20]. Therefore, we put forward our hypothesis that as a kind of end-organ damage in hypertensive patients, renal injury can result in poor outcomes in patients with COVID-19 and hypertension.

Our approach to test this hypothesis is of two features. First, several comorbidities, including cardiovascular disease, cerebrovascular disease diabetes, cancer, and chronic obstructive pulmonary disease, were reported to be not only risk factors of major complications in patients with COVID-19, but some of them were also associated with increasing incidence and prevalence of kidney disease [21-25]. There-

fore, we excluded patients with these comorbidities and other similar diseases when designing the study to avoid the potential confounding effects. Second, just like hypertension, the comorbidity of CKD was reported many times to be associated with poor prognosis [18, 20, 25]. However, according to the guidelines, the diagnosis of CKD was a dynamic process (at least for 3 months of kidney damage or eGFR < 60 ml/min/1.73 m^2) [26]. Besides, in the early stages of CKD, patients might be asymptomatic without awareness of medical assessment. Thus, it was difficult to label the COVID-19 patients with renal functional impairment on admission with CKD or without CKD, except for those with a clear history of CKD. This viewpoint was also an alternative for the research from Guo et al that the proportion of CKD in COVID-19 patients was quite different in different countries [27]. In our study, we used the biochemical parameters of renal function on admission instead of CKD to evaluate the association between kidney disease and in-hospital mortality.

Our results indicated that elevated baseline BUN and eGFR less than 60 ml/min/1.73 m^2 on admission were independent risk factors for in-hospital death in COVID-19 patients with hypertension. While elevated baseline serum creatinine was not associated with the in-hospital mortality, which was different from the previous study [18]. Possible explanations besides study design and sample size was that the three parameters of eGFR less than 60 ml/min/1.73 m^2, elevated baseline serum creatinine and BUN were of different characteristics in regard to evaluation of kidney damage. Serum creatinine was more sensitive with a wider range of abnormal value and the elevated level of serum creatinine did not necessarily reach the threshold for renal injury to add the risk of in-hospital mortality, which was why we included the factor of eGFR less than 60 ml/min/1.73 m^2 that was defined as reduced renal function in a cross-sectional survey of prevalence of chronic kidney disease in China [28].

Previous study reported that compared with survivors, levels of serum creatinine and BUN increased significantly in non-survivors during hospitalization [29]. Back to the hypothesis, our results indicated that in patients with elevated baseline serum creatinine or BUN, the renal function deteriorated under attack of

SARS-CoV-2 on the kidney [30], while the renal function showed little fluctuation in patients with normal baseline serum creatinine or BUN. Finally, the deteriorating renal function would be closely linked to AKI or death [31-33].

The study has some limitations. First, because most patients did not come to the hospital as soon as they were infected with SARS-CoV-2, we could not eliminate interference from the latency stage and the period from symptoms to admission. Second, our center is primarily oriented toward the patients in a worse condition and the in-hospital mortality is higher, which could not represent the normal population. Last, the sample size is small, which leads to lower statistical efficiency.

In conclusion, using the blood biochemical renal parameters on admission, we simulated two stages of hypertension that isolated hypertension and hypertension with renal injury. After they are infected with SARS-CoV-2, the hypertensive patients with renal injury are more likely to progress to AKI and death. Clinicians should be vigilant for the COVID-19 patients with hypertension who show elevated baseline BUN and eGFR less than 60 ml/min/1.73 m^2 on admission.

Disclosure of conflict of interest

None.

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