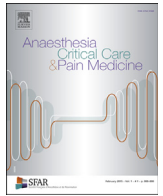**ELSEVIER**

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Short communication

Activation of the renin-angiotensin-aldosterone system is associated with Acute Kidney Injury in COVID-19

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ABSTRACT

The pathophysiology of acute kidney injury (AKI) in COVID-19 patients is still poorly understood. SARS-CoV-2 has been suggested to modulate the renin-angiotensin-aldosterone system (RAAS). In this series of COVID-19 critically ill patients, we report evidence of activation of the RAAS in COVID-19 patients with AKI.

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1. Introduction

About 25–35% of patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonia develop acute kidney injury [1,2], which is associated with higher mortality.

The understanding of the pathophysiological characteristics of AKI in the setting of COVID-19 is limited. A direct renal tropism of the virus, systemic inflammation, and microvascular injury are potential contributors to the renal damaging mechanisms of SARS-CoV-2. The interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system (RAAS) has been intensely discussed, but its role in the pathophysiology of SARS-COV2 associated AKI remains unexplored. Such activation may have important therapeutic implications.

Characterisation and understanding of COVID-19 renal injury would improve the management of patients admitted to the intensive care unit (ICU). Here, we describe the renal response of patients with COVID-19 admitted to an intensive care unit (ICU), with a particular focus on the activation of the renin-angiotensin-aldosterone system.

2. Methods

2.1. Population and Setting

Patients admitted to the ICU of St-Louis Hospital (Paris) between March 22 and April 15, 2020 for acute respiratory distress syndrome (Berlin Definition [3]) with acute kidney injury (AKI, defined according to the Kidney Disease-Improving Global Outcome criteria [4] and using the admission serum creatinine as the baseline) were screened. COVID-19 diagnosis was performed with a positive result of reverse transcription-polymerase chain reaction assay of a nasal swab or bronchoalveolar lavage. COVID-19-associated ARDS management protocol included, lung-protective ventilation, with driving pressure optimisation, prone positioning in severe cases, control of fluid balance, haemodynamic optimisation, early recognition, treatment of ventilator-associated pneumonia (VAP), and daily re-evaluation of sedation. Patients under 18 years, with chronic kidney disease, and those who refused to participate were not included, whereas those who

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Table 1
Characteristics of patients.

Characteristics	All patients ($n=51$)	AKI ($n=26$)	No AKI ($n=25$)	P
Age (y)	63 [57–69]	62 [55–71]	62 [60–68]	1.000
Sex male, n (%)	39 (76.5)	22 (84.6)	16 (66.7)	0.249
Weight (kg)	85 [77–95]	85 [74–95]	84 [80–93]	0.787
Size (cm)	175 [166–180]	176 [168–179]	173 [165–180]	0.696
BMI (kg/m^2)	28 [26–30]	28 [25–32]	27 [26–30]	0.944
Severity of illness				
SAPS II	37 [28–45]	37 [30–53]	34 [26–41]	0.182
SOFA	5 [4–7]	5 [4–7]	5 [3–7]	0.400
Mechanical ventilation in the first 24 h, n (%)	45 (88)	26 (100)	19 (76)	0.026
Use of norepinephrine 48 h, n (%)	39 (77)	23 (89)	16 (64)	0.084
Prone positioning, n (%)	41 (82)	23 (88)	18 (72)	0.141
Admission PaO$_2$/FiO$_2$	126 [81–178]	117 [80–162]	139 [83–198]	0.506
Worst PaO$_2$/FiO$_2$	80 [70–112]	73 [69–86]	91 [77–132]	0.057
Worst driving pressure (cmH$_2$O)	14 [12–16]	16 [12–22]	13 [12–14]	0.293
Worst compliance (mL/cmH$_2$O)	30 [25–40]	28 [22–34]	37 [26–40]	0.274
Comorbidities				
Hypertension, n (%)	31 (62)	14 (54)	17 (68)	0.345
Heart failure, n (%)	3 (6)	2 (8)	1 (4)	1.000
ARB/ACEI, n (%)	17 (33)	8 (31)	9 (36)	0.921
Coronary disease, n (%)	5 (10)	2 (8)	3 (12)	0.925
Diabetes mellitus, n (%)	20 (40)	11 (42)	9 (39)	1.000
Stroke, n (%)	1 (2)	0 (0.0)	1 (4.0)	0.984
Tobacco use, n (%)	6 (12)	4 (15)	2 (8)	0.741
COPD, n (%)	6 (12)	3 (12)	3 (12)	1.000
Cancer, n (%)	4 (8)	4 (15)	0 (0.0)	0.138
Biological admission characteristics				
pH arterial	7.40 [7.34–7.47]	7.35 [7.28–7.42]	7.46 [7.40–7.50]	0.001
PaCO$_2$ (mmHg)	42 [35–43]	42 [41–53]	39 [35–42]	0.069
Bicarbonates (mmol/L)	26 [23–28]	20 [17–22]	21 [20–23]	0.151
Lactate arterial (mmol/L)	1.1 [0.8–1.4]	1.1 [1.0–1.4]	1.1 [0.8–1.5]	0.424
Sodium (mmol/L)	138 [135–139]	136 [131–140]	138 [137–139]	0.188
Potassium (mmol/L)	4.1 [3.6–4.3]	4.1 [3.9–4.2]	4.0 [3.4–4.3]	0.529
Creatininaemia (µmol/L)	74 [62–94]	90 [72–111]	66 [56–79]	0.005
Urea (mmol/L)	5.8 [3.9–8.2]	7.0 [5.4–10.6]	4.8 [3.8–6.0]	0.037
Albumin (g/L)	32 [29–34]	30 [29–35]	32 [30–33]	0.587
Renin plasmatic concentration (pg/mL)	22.3 [8.1–48.3]	37.5 [16.2–130.4]	14.3 [5.5–29.6]	0.012
Aldosterone plasmatic concentration (pmol/L)	234 [123–483.5]	387 [211.5–1312.5]	153 [112.8–287.5]	0.011
Proteinuria (g/L)	1.0 [0.5–1.9]	1.3 [0.8–1.9]	0.7 [0.3–1.7]	0.248
Urine proteinuria/creatinine (g/mmol)	0.07 [0.05–0.12]	0.14 [0.06–0.23]	0.06 [0.03–0.09]	0.049
D-dimers (ng/mL)	2375 [1475–7870]	2220 [1520–3110]	2870 [1400–13010]	0.256
Lactate deshydrogenase (UI/L)	776 [682–993]	747 [658–1018]	776 [709–931]	0.741

AKI: acute kidney injury; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker, ARDS: acute respiratory distress syndrome; BMI:body mass index, COPD: chronic obstructive pulmonary disease; RRT: renal replacement therapy; SAPS II: simplified acute physiology score II; SOFA: simplified organ failure assessment.

died within 72 hours of admission were excluded. All patients or their surrogate had information about the data collection and could refuse to participate (Ethical Committee of SFAR, IRB 00010254–2019–203).

2.2. Measurements

As usually performed in our unit, plasma and urine chemistry and 24 hours proteinuria were collected every morning at 6 a.m. Plasma renin and aldosterone levels were measured by chemiluminescence immunoassay (CLIA) at ICU admission.

2.3. Statistical Analysis

Descriptive statistics were used to summarise clinical data. Results are reported as medians and interquartile ranges (IQR). Categorical variables are reported as counts and percentages. To compare the two groups, Wilcoxon signed-rank test or Wilcoxon rank-sum test were used as appropriate. One-way ANOVA or Kruskal-Wallis test were performed for comparison over time as appropriate.

3. Results

3.1. Demographic and clinical characteristics

Fifty-one patients with laboratory-confirmed COVID-19 were included. Demographic, clinical characteristics, comorbidities, and urinary profile are summarised in Table 1.

3.2. Acute Kidney injury

Twenty-six (51%) patients developed AKI, and most (80%) were severe AKI (stage 2 or 3, supplement), in a median of 4 [5–7] days after admission. Among them, 10 (39%) patients required renal replacement therapy (RRT). The main indications were the need to control fluid balance in patients with anuria (50% of patients), hyperkalaemia in 3 patients (30%), and metabolic acidosis in 2 patients (20%). Seventy percent were treated with continuous RRT and 30% with intermittent RRT. On admission, patients with AKI had higher serum creatinine, but most other biomarkers, including proteinuria, D-dimers, and lactate deshydrogenase, were not significantly different from the non-AKI group. There was no
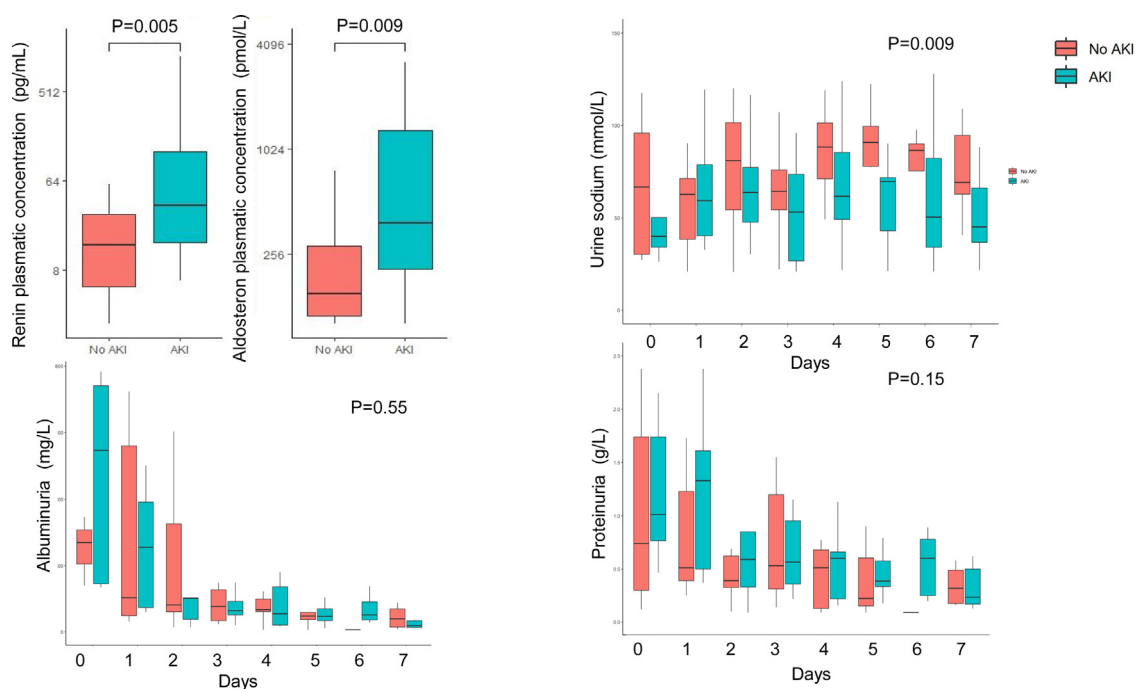
Fig. 1. Renin and aldosterone concentration at admission and albuminuria, proteinuria and urine sodium concentration from admission to day 7 in patients with no acute kidney injury (AKI) and patients with AKI.

difference between patients with and without AKI in terms of comorbidities or chronic treatment with Angiotensin-converting Enzyme inhibitors (ACEi) or Angiotensin-receptors blockers (ARBs) (Table 1). Three (5%) of non-AKI vs. 11 (55%) of AKI patients died. Among survivors, 7% of patients remain on RRT. Creatinine clearance is 95 [51–115] ml.min.1.73m^2 and proteinuria 0.37 [0.23–0.54] g/L among non-dialysed survivors.

3.3. Renin-angiotensin-aldosterone system (RAAS)

Patients with AKI had higher renin and aldosterone levels at admission (Fig. 1), respectively 37.5 [16.2–130.4] vs. 14.3 [5.5–29.6], P = 0.005 and 387 [211.5-1312.5] vs.153 [112.8–287.5], P = 0.009 compared to patients with no AKI.

In line with the activation of the RAAS, patients with AKI showed lower urine Na$^+$ concentration during follow-up. Total proteinuria was not different between AKI and non-AKI patients. The patients with AKI had higher albuminuria (644 vs. 308 mg/L) at admission and during the following seven days (Fig. 1).

4. Discussion

In 51 patients with COVID-19 ARDS, half of the patients showed AKI and all proteinuria. Patients with AKI showed direct (increased plasma renin and aldosterone concentration) and indirect (low urine sodium concentration) markers of activation of the RAAS [5].

The interaction between SARS-CoV-2 and the RAAS has long been debated. Binding of the virus to the ACE2 receptor is believed to increase the availability of angiotensin II to bind to the angiotensin II type 1 receptor. Activation of the RAAS is associated with kidney damage through the activation of inflammation and fibrosis [6]. The RAAS is also a key player in the development of remote cardiovascular injury after AKI [7].

This study has a few limitations. First, the sample size is relatively small. However, we had enough power to detect significant differences between AKI and no AKI patients regarding

the RAAS activation. Then, angiotensin II was not measured directly. Finally, no renal tissue histology was performed.

To conclude, biological features compatible with an activation of the renin-angiotensin-aldosterone system were observed in COVID-19 patients with AKI [8]. Our findings call for a more extensive study exploring the role of the RAAS among COVID-19-associated AKI and for a trial investigating the impact of inhibitors of the RAAS on outcomes.

Disclosure of interest

The authors declare that they have no competing interest.

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