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Clinical characteristics of acute kidney injury in the first 13 critically ill patients infected with SARS-CoV-2 (COVID-19) at a Peruvian hospital; a preliminary report

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ABSTRACT

Introduction: The high transmissibility and lethality of the novel coronavirus SARS-CoV-2 (COVID-19) have been catastrophic. Acute kidney injury (AKI) is one of the frequent complications in patients with respiratory insufficiency caused by the virus. The pathogenic mechanism is based on the binding of its S-proteins to the angiotensin-converting enzyme (ACE) receptors, which will trigger a cellular damage. A podocyte and tubular compromise are found in the kidneys which can lead to tubular necrosis and the consequent AKI.

Objectives: The objective of this report is to identify the main risk factor to develop AKI in patients infected with SARS-CoV-2 with critical acute respiratory distress.

Patients and Methods: We performed this report study, collecting data from 48 ICU patients. Data from 13 of them who developed AKI and needed renal replacement therapy (RRT) were analyzed. Clinical characteristics and laboratory findings were reported using STATA 10.0.

Results: AKI was present in 27.08% of patients, mostly male (92.3%) with a mean age of 63.8 years old. Hypertension, diabetes and obesity were the main comorbidities in those patients. Additionally, the meantime between admission and AKI diagnosis was 2.69 days. All patients showed fibrinogen, D-dimer, ALT and values above normal range. Mortality was seen in 61.5% of patients.

Conclusion: This report tries to show AKI as an important clinical manifestation in critically ill patients infected with SARS-CoV-2, with high mortality. Further studies are needed to demonstrate if there are independent risk factors.

Brief Communication

Implication for health policy/practice/research/medical education:

This report will improve the knowledge about the main risk factors for developing acute kidney injury in patients infected with SARS-CoV-2 who underwent renal replacement therapy during hospitalization.

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Introduction

The virus is a single-stranded RNA, it is assigned to the genus *Betacoronavirus* of the *Coronaviridae* family (1). In February of this year, the International Committee on Taxonomy of Viruses classified the virus as 'Severe Acute Respiratory Syndrome Coronavirus 2' (SARS-CoV-2) (2), and the WHO named the epidemic disease caused by SARS-CoV-2 as 'coronavirus disease 2019' (COVID-19) (3).

The clinical picture can be varied, sometimes mild

symptoms such as fever and dry cough, but also severe respiratory distress and multiorgan failure may supervene. The pulmonary compromise is characterized by an alveolar fibro-myxoid exudate with pulmonary edema and the formation of hyaline membranes. SARS-CoV-2 affects cells by binding its spike S-proteins to the angiotensin-converting enzyme 2 (ACE2), where they are activated and cleaved by a group of transmembrane protease serine 2 (TMPRSS2), allowing the virus to carry out the fusion of membranes (4). The TMPRSS2 is essential for the

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entry of the virus and its damage to the host cells. It has been shown that, co-location for genes corresponding to ACE and TMPRSS2 in existed in podocytes and proximal tubular cells, while are expressed in much larger quantities among people from western countries than Asians (5). One of the main complications of COVID-19 is acute kidney injury (AKI), which is present, according to different sources, in 0.5%-7.3% of the patients(6). The classical definition of AKI is the sudden loss of renal function, characterized by an increment of serum creatinine (sCr), or a decrease in urine output. According to the KDIGO classification (Kidney Disease Improving Global Outcomes) the AKI diagnosis is a rise in sCr of 50% or higher from the baseline, or 0.3 mg/dL over its base value (7).

The post-mortem study of 26 patients diagnosed with COVID-19 revealed injury in the proximal tubule with brush border loss, vacuolar degeneration and even tubular necrosis. The electron microscopy showed clusters of SARS-CoV-2 particles with distinctive spikes, while immunofluorescence showed antibodies against SARS-CoV-2 in tubules (8).

The virus transmissibility is important, as it has become a worldwide pandemic. At the date of the elaboration of this report, 10:00 CEST – May 16, 2020; SARS-CoV-2 is responsible for more than 2583256 infected cases worldwide, with a number of deaths totaling 311 400, and a fatality rate of 6%-10%(9).

Accordingly, at the date of the elaboration of this article's final draft, 88 541 infected patients have been reported in Peru, of which 840 are in the ICU under mechanical ventilation and 2523 in casualties, with a fatality rate of 2.85% (10).

Objectives

The objective of this study was to report the main clinical characteristic of the first critically ill patients infected with SARS-CoV-2 who developed AKI.

Patients and Methods

Study design

A longitudinal retrospective study was done, consecutively collecting data from patients who were admitted to the hospital Nacional Edgardo Rebagliati Martins (HNERM) emergency room with a diagnosis of confirmed SARS-CoV-2 infection; from March 16 to April 16, 2020. The study included patients 18 years, old or older with or without comorbidities who developed AKI according to the KDIGO definition described before, with a positive molecular test (reverse transcription polymerase chain reaction, RT-PCR) for SARS-CoV-2. Furthermore, the study excluded patients with chronic kidney disease (CKD) in renal replacement therapy (RRT). A total of 13

patients were found to comply with the inclusion criteria.

The authors obtained the clinical, epidemiological, demographic, and laboratory characteristics from the electronic registry of clinical histories through a data collection sheet.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Edgardo Rebagliati Martins National Hospital approved this study (CARTA 195-GRAR-HNERM-ESSALUD). Patients were signed the consent form automatically at the time hospital admission.

Data analysis

The data process was done through a database created using Excel 2016. STATA 10.0 was used to process quantitative variables to obtain means, medians, minimums and maximums. To analyze qualitative variables, frequency tables were obtained. The main objective of this investigation was to describe the characteristics of the patients with COVID-19 disease who developed AKI and needed RRT at the hospital Nacional Edgardo Rebagliati Martins.

Results

Clinical and epidemiological characteristics

On March and April of 2020, 48 patients with acute pulmonary COVID-19 insufficiency were hospitalized in the ICU of the HNERM, receiving mechanical ventilation. The study included 13 of these patients who also received RRT due to AKI, making up 27.08% of the aforementioned total. The mean age was 63.8 years [range; 51-78 years] (Table 1), from which 92.3% were male. Moreover, in more than half of them (53.8%), we identified one or more comorbidities, being hypertension the most common with 23.08% (3 out of 13), followed by diabetes and obesity, both with 15.3% (2 out of 13), and CKD evidenced only in 7.6% (1 out of 13). Furthermore, we found other comorbidities, such as asthma, diabetic ketoacidosis, malignancy, renal lithiasis and hypothyroidism, with 7.6% (1 out of 13) prevalence.

The most common symptoms at the beginning of the disease were dry cough in 92.3% patients, fever in 69.2%, and dyspnea in 53.8%. Less common symptoms, which were found in less than half of the patients were odynophagia and diarrhea, both in 23.08% of patients, followed by headache, rhinorrhea and myalgia with 15.3%, 15.3% and 7.6% respectively.

The median of the time since the onset of symptoms and the admission into the hospital was 8.4 [1-18] days. All of them were transferred to the ICU, in need of mechanical ventilation, while 76.9% were given inotropic drugs. The

Table 1. Baseline clinical characteristics of patients infected with COVID-19

	Patients (n=13)	
	N	%
Age *	63.8 (51–78)	100
Gender		
Male	12	92.31
Female	1	7.69
Comorbidities		
Diabetes	2	15.38
Hypertension	3	23.08
CKD	1	7.69
Obesity	2	15.38
Malignancy	1	7.69
Coronary Disease	1	7.69
Others (Asthma, BHP, renal lithiasis, hypothyroidism)	3	23.07
Signs and symptoms		
SO ₂ (%) *	86.9 (75 – 97)	
Respiratory rate, median (min–max)*	25.8 (18 – 31)	
Heart rate; median (min–max) *	98.8 (78 – 147)	
Dry cough	12	92.31
Fever	9	69.23
Dyspnea	7	53.85
Myalgias or fatigue	1	7.69
Rhinorrhea	2	15.38
Odynophagia	3	23.08
Diarrhea	3	23.08
Days since onset to hospital admission*	8.4 (1–18)	
Days to ICU*	1.5 (1–3)	
Days to need inotropic drugs *	3 (1–6)	
Days since admission to develop AKI*	2.69 (1–5)	
Days since admission to start RRT*	6.5 (4–12)	
Days since admission to death **	12.62 (6–26)	
Number of deaths	8	61.54

median of time since the onset of the disease until the use of invasive mechanical ventilation and use of inotropic drugs was 1.3 [0-3] days and 2.3 [0-6] days respectively. The vital signs at the time of admission were, on average; the heart rate was 98.8 bpm [78-147]; the breath rate was 18.2 rpm [18-31] and the oxygen saturation at FiO₂ 21% was 86.9% [75-97]. Table 1 shows baseline clinical characteristics of patients infected with COVID-19.

Laboratory findings

The main laboratory markers were evaluated both at admission and at the time of AKI diagnosis. The mean

basal leukocyte count was of 13 260 cel/μL [5 900-21 700] and the lymphocyte count was of 363 cel/μL [310-1210], although lymphopenia remained in the totality of the patients at the time of AKI diagnosis (672 cel/μL [190-1190]). Mean hemoglobin at admission was of 12.1 mg/dL [11.38-15.5]. C-reactive protein (CRP) levels were high, both at admission with a mean value of 27.2 mg/dL [13.4-46], and at the time of the AKI diagnosis; 30.3 mg/dL [21-39.5] (Table 2).

The hepatic function tests were abnormal in some of the patients both at admission and at the time of AKI diagnosis, showing no significant differences with a level of ALT averaging 62.5 U/L [18-323] and albumin concentration of 3.1 g/dL [2.3-4.3]. Fibrinogen, serum lactate dehydrogenase and D-dimer levels at admission were of 873 mg/dL [298-1293], 5189 U/L [144-758], and 5.7 U/L [0.34-16.8] respectively; these values did not present significant variations in the AKI patients except for the D-dimer levels, which increased to 9.7 U/L [0.9-34.6].

In regard to renal function, during admission the patients presented values of sCr averaging 1.01 mg/dL [0.69-1.68] and urea of 48.8 mg/dL [14.7-86]; showing no alteration or abnormality in renal function at admission, with the maximum sCr value being 1.68 mg/dL in a patient with CKD antecedents. During hospitalization, all of the patients studied complied with the diagnosis criteria for AKI, following KDIGO guidelines; the sCr mean peak at the moment of diagnosis was of 3.07 mg/dL [1.4-5.8], and the urea mean peak was of 108 mg/dL [24-232], the meantime between admission and AKI diagnosis was 2.69 days [1-5 days].

Furthermore, all patients eventually required RRT, which in the case of our hospital was intermittent hemodialysis; with a meantime between admission and the beginning of hemodialysis of 6 days [3-12 days].

Other observed clinical parameters to measure renal compromise were proteinuria and hematuria for 87.5% of the patients (Table 2), taking into account the fact that these specific tests were only taken in 8 patients.

All patients received hydroxychloroquine, azithromycin and low-molecular weight heparin, and a total of 6 patients received treatment with methylprednisolone in different doses.

In-hospital death occurred in 61.5% (8 out of 13) of the patients. The time median between admission and death was 12 days [6-26].

Discussion

The first cases of COVID-19 in Peru were sent to the HNERM in Lima. In March 2020, the first cases of atypical pneumonia requiring mechanical ventilation with a positive test for coronavirus (RT-PCR) were registered.

Table 2. Laboratory data of patients infected with SARS-COV-2 on admission to hospital

	Patients (n=13)			
	Admission		AKI	
	Median	Range	Median	Range
White blood cell count, $\times 10^9/L$	13.26	5.9–21.7	14.54	5.29–23.8
Lymphocytes, $\times 10^9/L$	683	310–1210	672	190–1190
Creatinine, mg/dL	1.01	0.69–1.68	3.07	1.43–5.87
Urea, mg/dL	48.82	14.7–86	108.41	24–232
CRP, mg/dL	27.27	13.43–46	30.30	21–39.5
D-dimer, mg/L	5.78	0.34–16.88	9.07	0.98–34.6
LDH, U/L	518.91	144–758	531.91	144–758
ALT, U/L	92.5	18–323	103	18–323
Fibrinogen, mg/dL	873.81	298–1293	820.08	298–1293
Hemoglobin, g/dL	12.12	11.38–15.5	11.62	8.3–14.8
Albumin, g/dL	3.12	2.36–4.3	2.97	2.59–3.7
Blood gas analysis				
pH	7.31	7.1–7.45	7.16	6.94–7.46
pCO ₂ , mm Hg	40.23	20–70	66.09	30.4–102
pO ₂ , mm Hg	74.95	41.4–128	82.09	47.3–134
Bicarbonate, mmol/L	22.17	19–28	22.08	16–27.7
Lactate, mmol/L	1.81	0.6–4.5	1.35	0.6–2.4
Urinalysis				
	Number	%		
Leukocytes *	5	38.46		
Hematuria *	7	53.85		
Proteinuria *	7	53.85		

To the date of this study, 48 patients are registered in the ICU, of which 13 presented AKI of rapid evolution, without signs of hypovolemia, even with a positive fluid balance in 6 of them, ruling out pre-renal causes, and the rise of creatinine started before the need of inotropic drugs or nephrotoxic antibiotics, all of which required intermittent RRT.

In critical patients hospitalized because of sepsis of bacterial pneumonia, the incidence of AKI can be as high as 30%–60%, which implies a high death rate, although since convective therapies such were implemented, mortality has been in decline. The number of critically diseased patients who required RRT was 13% (11).

Patients with pneumonia due to COVID-19 who require hospitalization in the ICU because of critical condition is of 7.3%, of which 61.5% die before 28 days, in a meantime of 7 days (12).

Acute renal failure is one of the complications that can present in patients infected with SARS-CoV-2, especially in critical patients. The incidence of AKI in some studies varies from 0.5 - 7.3%; however, in ICU patients it can reach 23% (13-15). In this investigation, 27% of patients

diagnosed with COVID-19 who were critically sick in the ICU which developed AKI.

The initial data from Wuhan reports shows that proteinuria and hematuria were present only in 43.9% and 26.7% respectively. AKI prevalence was 5.1%, moreover, elevated basal sCr (HR: 2.10, IC 95%: 1.36-3.26), elevated basal BUN (3.97, 2.57-6.14), AKI 1 (1.80, 0.76-4.76), AKI 2 (3.51, 1.49-8.26), AKI 3 (4.38, 2.31-8.31), proteinuria 1+ (1.90, 0.81-4.00), 2+ and 3+ (4.84, 2.00-11.7); hematuria 1+ (2.99, 1.39-6.42), 2+ and 3+ (5.56, 2.58-12.01), were the independent risk factors for in-hospital mortality (16).

While this study shows that most of our patients (87.5%) showed renal damage according to the markers such as proteinuria and hematuria. Although biomarkers such as albuminuria/creatinuria ratio, or TIMP/IGFBP7 index are more specific in AKI (17), we could only use only proteinuria and hematuria because of lack of these biomarkers.

Though our patients were admitted with a mean basal sCr of 1.01 mg/dL, AKI rapidly developed in a period of time averaging 6 days between admission and the start

of hemodialysis; hence it was necessary to observe the pertinence of any independent risk factor to the damage severity.

In recent studies and meta-analysis, serum albumin has been determined as an independent risk factor (OR: 0.46). Serum albumin acts not only as a parameter to evaluate the development of AKI but also to be able to predict mortality (18-21). Since our investigation only covers the first 13 cases, which is insufficient to establish serum albumin as a risk factors, however 100% of our patients had serum albumin levels below normal, averaging 3.1 mg/dL. Similarly, transaminases were elevated in all patients, being ALT the most prevalent with 92 [18-323] at the time of admission and 103 [18-323] at the time of AKI diagnosis, which would correlate with the multi-organ damage in critical patients, such as reported by Li et al (22), where transaminase values are shown to be elevated in patients with SARS-CoV-2 infection, despite there is no significant difference between those with a severe case and those with a critical one ($P=0.065$).

Fibrinogen, D-dimer, and reactive CRP levels were elevated in all patients since admission, but this elevation progressed alongside the AKI, until the beginning of RRT, reaching levels above normal values. In the study by Li et al, fibrinogen degradation products and D-dimer levels were shown to be elevated above normal values, especially in those who were critical (0.003 and <0.001 respectively). These results could be related to the high risk of thrombosis, mainly in lungs (16.7%) with a significant difference with those who were not infected with SARS-CoV-2 ($P=0.008$); and extracorporeal circuit thrombosis in 96.6% of the AKI patients treated with continuous RRT. Likewise, more than 95% presented elevated D-dimer and fibrinogen levels (23). However, larger studies are required to determine its role as an independent risk factor of AKI development.

Regarding lymphopenia, the study by Li et al (22) showed a below normal value in patients with COVID-19, but a more significant decrease was shown in critical patients, in comparison to those with a severe condition ($P<0.001$). In this study, lymphopenia is shown to be severe at the time of AKI diagnosis.

Other independent risk factors for in-hospital death on patients who developed AKI and eventually required dialysis therapy were mean arterial pressure, serum lactate levels, and serum potassium(24). Unlike our investigation, the serum lactate levels were normal in all our patients since the beginning, despite the severe desaturation in all of them, and the use of inotropic drugs in most.

Conclusion

AKI has a considerable incidence in critically ill patients infected with COVID-19 and has a high mortality

rate. Although the risk factors for critical patients with different infections to develop AKI are well-defined, for COVID-19 patients, there are different pathogenic mechanisms that could produce renal damage particularly associated with SARS-CoV-2, such as the cytokine storm, the organ failure, and the prothrombotic effects that deserve to be studied to determine their potential risk factor of developing AKI and related mortality.

Limitations of the study

The fast evolution to multi-organ failure of critically ill patients, the increasing mortality rate, and the lack of logistic resources at our hospital.

The electronic record of clinical report is still in implementation, that is why we have not full access to all data.

The hospital does not have still with better renal biomarkers to make a better analysis.

Authors' contribution

IRBF, RPVV, HJER, SFAR were the principal investigators of the study. IRBF and RPVV were included in preparing the concept and design. HJER and SFAR revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

All authors declare there is no conflict of interest with any person or institution.

Ethical considerations

Ethical issues (including plagiarism, data accuracy, duplicate publication) have been ultimately obeyed by the authors.

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