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Research Article

Renal Morphofunctional Findings in Convalescents of COVID-19

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Abstract

Back ground: We aimed to represent the effects of SARS Co V -2 on kidney functioning during the COVID-19 pandemic in patients of varied baseline GFR values staged into renal categories of one to five.

Methods: We conducted a single-center, retrospective study using data of patients hospitalized for COVID-19 with acute kidney injuries. Demographic characteristics, clinical findings, laboratory parameters [glomerular filtration rate (GFR), Creatinine, Blood urea nitrogen (BUN)] of pre covid, during covid, post-COVID infection, were reviewed. Predicted changes in the GFR were analyzed. The study's primary outcome was a predicted decline in GFR observed during the covid infection period compared to pre covid. The secondary outcome was predicted improvement in GFR after resolution of infection or covid -19 tested negative.

Results: The study included one hundred patients (mean age: 57.35+/- 17.5 years). The odds ratio of multivariate logistic regression analysis shows the association of kidney functioning during the pre-covid period with an odds ratio of 1.699 (95% CI- 1.299 to 2.551), during COVID with an odds ratio of 0.5404 (95% CI- 0.3620 to 0.7025), and post-covid with an odds ratio of 0.98 (CI- 0.9646 to 1.000). A decrease in GFR from Pre-COVID to during-COVID was observed with the estimated odds ratio of 1.001 (CI-0.9999 to 1.002, z- value 1.795, p-value-< 0.001). The positive and negative predictive powers were 92.86% and 96.67%, respectively. An association of an improvement in GFR was observed during the post-covid infection period with an odds ratio of 0.999 (CI-0.99-1.002, p-value-0.79). Indeed, the average decrease in GFR was prominent in second renal category patients, and the white race showed a 75% mortality rate, 14% in African Americans, and 11% in other races.

Conclusion: COVID-19 can cause acute ischemic kidney injury. Patients with CKD stage 3A are most affected. Patients who had longer lengths of stay in the hospital had greater severity of acute kidney injury. We found a higher mortality ratio in patients assigned to renal categories 2 and 3.

ABBREVIATIONS

COVID-19: Coronavirus Disease 2019; SARS-Cov-2: Acute Respiratory Syndrome Coronavirus-2; ACE2: Angiotensin Converting Enzyme 2; TMPRSS2: Transmembrane Serine Protease; GFR: Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; Fena: Fractional Excretion of Sodium; FEK: Fractional Excretion of Potassium; FEAU: Fractional Excretion of Uric Acid; PEF: Fractional Excretion of Phosphate; ACR: Albumin/Creatinine Ratio; PCR: Protein/Creatinine Ratio; ACE: Angiotensin Converting Enzyme; CKD: Chronic Kidney Disease

Dedicatory: To professors Reynaldo Mañalich Comas and Charles Magrans Buch, initiators of Nephrology in Cuba, who died from COVID-19

INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus (Severe acute respiratory syndrome coronavirus-2) has caused a significant impact on health systems and economies around the world [1]. SARS-CoV-2 is an RNA virus that belongs to the beta coronavirus genus, whose functional receptor in humans is angiotensin-converting enzyme 2 (ACE2) [2,3]. SARS-CoV-2, like other coronaviruses, also requires a transmembrane serine protease (TMPRSS2) for entry into the cell [2]. Another potential route of entry for the virus, demonstrated in vitro, is the CD147 cell receptor [4].

In the kidney, both ACE2 and TMPRSS2 are located in the proximal tubule and collecting ducts, and to a lesser extent in podocytes and mesangial cells [2]. CD147 is also widely

expressed in proximal tubules [4]. These characteristics make the kidney an ideal target for direct viral infection. However, other elements may cause or contribute to kidney damage, such as hemodynamic factors, rhabdomyolysis, cytokines release, coagulatory disorders, systemic sepsis, hypoxia, and drug toxicity [5,6].

In the clinical order, kidney damage during COVID-19 is characterized by elevated creatinine levels, variable degrees of hematuria, proteinuria, and disturbances in tubular function, which are distinguished by the appearance of urinary losses of neutral amino acids, low molecular weight proteinuria, hypophosphatemia, and hypouricemia [7,8]. Hypouricemia due to hyperuricosuria seems to be related to the severity of the disease and its progression [8]. However, the progress of these damage markers in convalescent COVID-19 is unknown, so this research is carried out to identify the presence of morphological (ultrasound), urinary and tubular function markers of kidney damage in convalescent COVID-19 and its possible relationship with the clinical condition of patients during infection.

MATERIALS AND METHODS

A prospective cohort descriptive observational exploratory study was carried out in 92 convalescent adults of COVID-19, diagnosed by a real-time polymerase chain reaction in the nasopharyngeal swab, admitted to the Hospital "Dr. Salvador Allende," in Havana, Cuba, between March 13-June 20, 2020.

The data used in the study were collected from a structured interview (general characteristics and clinical elements of interest), the physical examination, the report of ultrasound study, and the report of laboratory tests.

The variables used were: age, sex, skin color, clinical condition during admission (asymptomatic, mild symptomatic, severe [admitted to intensive care unit], critical [with mechanical ventilation]), weight, height, toxic habits (smoking, alcoholism), comorbidities, medications, oxygen saturation, kidney's ultrasound findings; in the direct urine examination, the variables used were: hematuria, leukocyturia, bacteriuria, casts, crystalluria, glucosuria, and dibasic aminoaciduria; while in the biochemical measurements the variables were: plasma and urinary concentrations of sodium, potassium, phosphorus, uric acid, and creatinine, in addition to plasma bicarbonate and urinary pH.

After signing their informed consent, the patients attended the Institute of Nephrology "Dr. Abelardo Buch López," in Havana, Cuba, on two occasions, six months and a year after the diagnosis. On their visits, patients were fasting and subjected to a medical interview to obtain the data to complete the form designed for the research purpose. Patients also had a physical assessment conducted (including weight and height measurement), and a measure of oxygen saturation was taken at rest. In addition, a 10 ml venous blood sample and a urine sample were taken, and a renal ultrasound was performed (the latter only at six months).

Oxygen saturation was measured with an Oxy 9800 pulse oximeter from Combiomed. Renal ultrasound was performed on a Philips machine, Affiniti 70G model with color-Doppler effect. The urine was examined for red blood cells, leukocytes, bacteria, and glucose with Roche Combur10 Test® M dipstick; a microscopic study was done if cells or bacteria were found. Electrolytic measurements were made on a Radiometer ABL 800 Flex gas analyzer. Biochemical measurements in urine and blood were performed in a Spinreact spectrophotometric autoanalyzer, model 200E. Urinary pH was measured with a Crison GLP 21+ equipment.

The body mass index was calculated, and the patients were divided into the following categories: <18.5 kg/m2 (malnourished), 18.5-24.9 (normal weight), 25-29.9 (overweight), and ≥30 (obese) [9]. The Glomerular Filtration Rate (GFR) (estimated by the CKD-EPI equation from serum creatinine), the fractional excretion of sodium (FENa), potassium (FEK), uric acid (FEUA), and phosphate (FEP) were also calculated. In addition to albumin/creatinine ratio (ACR) and protein/creatinine ratio (PCR) [10,11].

The following values were considered normal: resting oxygen saturation greater than 95%, serum sodium concentrations between 135 and 145 mEq/l, potassium between 3.5 and 5.5 mEq/l, phosphorus from 2.5 to 4.5 mg/dl (0.8 to 1.45 mmol/l), bicarbonate from 22 to 28 mEq/l, uric acid in men from 2.5 to 7 mg/dl (148.71-416.4 μmol/l) and in women from 2.5 to 6 mg/dl (148.71-356.9 μmol/l), and creatinine levels below 1.18 mg/dl (104.3 μmol/l). Increased FENa was considered if greater than 2%, increased FEK, if greater than 17%, increased FEUA if greater than 10% with plasma uric acid concentrations lower than 2.5 mg/dl (148.71 μmol/l) (hypouricemia) or greater than 15% in subjects without hypouricemia, increased FEP, if greater than 20%, ACR increased if equal or greater than to 30 mg/g and PCR increased if equal or greater than 0.2 g/g.

Ethical considerations

The study was approved by the Research Ethics Committee of the Institute of Nephrology "Dr. Abelardo Buch López." The research was designed and developed following the principles of the Declaration of Helsinki. All participants gave their written informed consent to take part in the study. In addition, patients with any abnormality were guaranteed adequate clinical follow-up. It was agreed not to release the information individually but as part of the work.

Statistics

The data were processed with the SPSS statistical software version 22.0. Frequency distribution analysis was performed. Summary measures were calculated for qualitative variables such as proportion and percentage and measures of central tendency and dispersion for quantitative variables such as the mean and standard deviation. To assess the association between the clinical condition of the patients and the presence of urinary disorders and tubular function tests, association analyzes were performed using contingency tables and the Chi-square test of independence. A significance level $\alpha = 0.05$ was set for this hypothesis test.

RESULTS

The study's first phase (six months after infection) included 92 patients, and the second phase (one year after infection)

included 85 patients. The difference was two patients who did not participate in the second phase and five who had difficulties collecting urine samples.

When analyzing the characteristics of the patients (Table 1), it stands out slightly higher participation of females and the predominance of subjects between 40 and 59 years of age, who constituted little more than 60% of the cases. Individuals with black and mestizo skin color were over 50% of the patients (51.1% in the first phase and 51.8% in the second). Nearly half of the subjects were asymptomatic during the infection (46.7% in the first phase and 49.4% in the second), while under 20% were severe or critical. Four required mechanical ventilation, one of them non-invasively (without orotracheal intubation).

No patient had a GFR lower than 45 ml/min/1.73 m^2BS, which means all the patients had a normal renal function or were in stages 1-3a of Chronic Kidney Disease (CKD). It stands out a lower frequency of stage 2 patients in the second phase with an increase in subjects without CKD and patients in stages 1 and 3a. Overweight and obese individuals constituted 63% and 60% of the first and second phases, respectively.

Smoking was present in just under 30% of the patients in both phases, and five subjects were alcoholics. The most common comorbidities reported were hypertension (first phase-48.9%, second phase-50.6%), and diabetes mellitus (first phase-16.3%, second phase-15.3%). Two patients (participants in both phases) had a diagnosis of CKD (stage 2), and another two were infected with HIV. The most commonly used medications regularly were diuretics and angiotensin-converting enzyme inhibitors. Hydrochlorothiazide (17 patients), and Enalapril (16 patients), were the most widely used individual drugs.

All patients examined had normal levels of oxygen saturation at rest. The most common findings in renal ultrasound (Table 2), were: cysts and microcysts (9.8% of kidneys and 7.6% of patients), nephrolithiasis (9.8% of kidneys and 6.5% of patients), the irregular surface (8.7% of kidneys and 6.5% of patients) and the double excretory system (7.6% of kidneys and 5.4% of

Table 1: Characteristics of patients.

Variable	Categories	Six months (n=92)		One year (n=85)	
		№	%	№	%
Sex	Male	42	45.7	36	42,4
	Female	50	54.3	49	57,6
Age (years)	20-39	19	20.7	18	21,2
	40-59	56	60.9	52	61,2
	60-79	14	15.2	12	14,1
	80-89	3	3.3	3	3,5
Skin color	White	45	48.9	41	48,2
	Black	27	29.3	25	29,4
	Mestizo	20	21.7	19	22,4
Clinical condition during admission	Asymptomatic	43	46,7	42	49,4
	Mild symptomatic	31	33,7	28	32,9
	Serious/Critical	18	19,6	15	17,6
Glomerular filtration rate (ml/min/1.73m^2BS)	≥ 90	66	71,7	69	81,2
	60-89.9	24	26,1	12	14,1
	45-59.9	2	2,2	4	4,7
Body mass index (Kg/m^2)	<18.5	2	2,2	2	2,4
	18.5-24.9	32	34,8	32	37,6
	25-29.9	27	29,3	25	29,4
	≥30	31	33,7	26	30,6
Toxic habits	Smoking	27	29.3	25	29.4
	Alcoholism	5	5.5	5	5.9
Comorbidities	Hypertension	45	48.9	43	50.6
	Diabetes mellitus type 2	15	16.3	13	15.3
	Cardiovascular disease	8	8.7	8	9.4
	Cerebrovascular disease	2	2.1	2	2.4
Medications commonly used	Diuretics	24	26.1	23	27.1
	ACE inhibitors	20	21.7	19	22.4
	Calcium-channel blockers	8	8.7	6	7.1
	Beta-blockers	4	4.3	4	4.7
	Oral hypoglycemic medications	8	8.7	8	9.4
	Insulin	3	3.3	3	3.5
	Aspirin	5	5.4	5	5.9
	Others	11	12.0	9	10.6

ACE- Angiotensin-converting enzyme

Table 2: Ultrasound findings of kidneys six months after COVID-19.

Finding	Right kidney (n=92)		Left kidney (n=92)	
	№	%	№	%
Cysts and microcysts	5	5,4	4	4,3
Lithiasis and microlithiasis	6	6,5	3	3,3
Irregular surface	4	4,3	4	4,3
Double excretory system	4	4,3	3	3,3
Increased echogenicity of the parenchyma	2	2,2	1	1,1
Renal ptosis	2	2,2	1	1,1
Parenchymal calcification	1	1,1	1	1,1
Nephrectomy (absence of kidney shadow)	1	1,1	1	1,1
Fetal lobulations	1	1,1	1	1,1
Kidney malrotation	0	0	2	2,2
Caliectasia/mild hydronephrosis	0	0	1	1,1

patients). Renal perfusion was preserved in all cases, and no thrombi were evident in the renal vessels.

The urine study (Table 3), revealed the presence of microscopic hematuria in 12% of patients studied in the first phase and 17.6% of those in the second. Leukocyturia and bacteriuria were identified in less than 5% of the samples examined. In the microscopic study of the urine, it was found that 2.2% of hematuria identified in the first phase was dysmorphic, while it was 3.5% of the second phase. In addition, casts (hyaline) and crystals (calcium oxalate) were found in two cases. There was insufficient evidence to suggest a relationship between the presence of urinary sediment alterations and the clinical condition of the subjects during admission due to the infection (p> 0.05).

The mean plasma concentrations of sodium, potassium, phosphorus, bicarbonate, and uric acid (Table 4) in both phases were within the limits of normality. However, the means of sodium concentrations in the upper limit of normality were remarkable in both phases (144.5 mEq/L and 145.0 mEq/L, respectively). No patient had a plasma sodium concentration greater than 150 mEq/L or uric acid less than 2.5 mg/dl (148.71 µmol/l) (hypouricemia). Mean plasma creatinine was 1.03 mg/dl (91 µmol/l) at six months and 0.99 mg/dl (87.5 µmol/l) at one year, below the upper limit of normality.

The urinary concentrations (Table 4), of the different analytes correspond with the plasma concentrations (they do not have exact normality values). The average urinary pH, expression of the concentration of free hydrogen ions, of 5.75 and 5.79, in the first and second phases, respectively, was expected for subjects with a typical western diet.

Fractional excretions of solutes, expression of tubular function, (Table 5), were increased in less than 5% of patients in both phases; FENa was the highest in both phases and corresponded to patients receiving diuretics. The case with increased FEK was also using diuretics. Of those patients with increased FEAU, one used aspirin (in low doses), another was diabetic, and the other was HIV positive. Increased FEP occurred in the same three patients in both phases; one of them had diabetes, and the three had a history of alcoholism. There was insufficient evidence to suggest a relationship between the increased fractional excretions of solutes and the clinical condition of subjects during admission due to the infection (p> 0.05). No patient had normoglycemic glycosuria, and the same patient had a positive Brand's test (expression of dibasic aminoaciduria) in both phases.

The ACR was increased in 12.0% of patients in the first phase and 15.3% of those in the second (Table 5), while the increased PCR decreased from 16.3% in the first phase to 8.2% in the second. The persistence of increased PCR in the second phase was related to the clinical condition of subjects during admission

Table 3: Characteristics of urinary sediment.

Finding	Six months (n=92)		One year (n=85)	
	№	%	№	%
Hematuria (dysmorphic)	11 (2)	12 (2.2)	15 (3)	17.6 (3.5)
Leukocyturia	4	4.3	4	4.7
Bacteriuria	2	2.2	3	3.5
Casts *	1	7.7	0	0
Crystalluria *	1	7.7	2	13.3

*- Since the microscopic urine examination was only performed in those patients with positive findings in the dipstick examination (hematuria, leukocyturia, or bacteriuria), the percentages were calculated to the total of patients with microscopic study, 13 at six months and 15 at year.

Table 4: Serum and urinary concentrations.

Fluid	Analyte	Six months (n=92)		One year (n=85)	
		Mean	S.D	Mean	S.D
Blood (serum)	Sodium (mEq/l)	144,50	2,05	145,00	3,38
	Potassium (mEq/l)	4,52	0,48	4,52	0,61
	Phosphorus (mg/dl)	3,59	0,52	3,77	0,50
	Uric Acid (mg/dl)	5,50	1,70	5,55	1,93
	Creatinine (mg/dl)	1.03	0.18	0.99	0.20
	Bicarbonate (mEq/l)	24.20	2.01	24.11	2.36
Urine	Sodium (mEq/l)	134,30	37,24	148,83	17,77
	Potassium (mEq/l)	14,46	7,54	13,97	6,88
	Phosphorus (mg/dl)	40,80	28,28	45,99	32,15
	Uric Acid (mg/dl)	46,01	24,01	42,93	25,71
	Creatinine (mg/dl)	119.91	64.78	114.23	64.42
	Morning pH	5.75	0.61	5.79	0.65

S.D.-Standard deviation

Table 5: Tubular function disturbances.

Disorder	Six months (n=92)		One year (n=85)	
	№	%	№	%
FENa increased	4	4,3	4	4,7
FEK increased	0	0	1	1.2
FEUA increased	2	2,2	3	3.6
FEP Increased	3	3,3	3	3.5
Dibasic aminoaciduria	1	1,1	1	1,2
Normoglycemic glycosuria	0	0	0	0
ACR increased	11	12,0	13	15,3
PCR Increased	15	16,3	7	8,2
Normal ACR and increased PCR	7	7.6	1	1.2

for the acute infection (p-0.01). In other words, the increased PCR persisted longer as the patients presented worse clinical conditions. The evaluation of patients with normal ACR and increased PCR shows a notable decrease from 7.6% in the first phase to 1.2% in the second (it should be clarified that no patient with increased PCR in the first phase stopped participating in the second).

DISCUSSION

This research is one of the firsts to study kidney damage markers in convalescent COVID-19 patients. This makes it difficult to compare its results because, unlike the considerable accumulation of information from studies conducted during the infection, the data in convalescents are scarce [12].

The greater participation of women could be due to local causes since, at that time of the Cuban epidemic, men constituted 50.2% of patients [13]. The highest number of cases among subjects between 40 and 59 years of age corresponds to the characteristics of the epidemic in Cuba and coinciding with the highest number of adult subjects in the country as a result of the demographic explosion of the 1960s. [13,14]. It is noteworthy that more than half of the patients have black and mestizo skin color when the population with white skin color constitutes more than 65% of the Cuban population. However, variations by territories could explain this difference [15].

The high frequency of asymptomatic patients seems to be related to the medical action protocol enforced at that time, where all cases were admitted. Additionally, the original Wuhan strain of SARS-CoV-2 and its variant D614G were prevailing in the country at the beginning of the epidemic, and they caused many asymptomatic infections [13,16,17].

The percentage of the population with overweight and obesity exceeds the figures identified in the adult population in the Third National Survey of Risk Factors, which was 43.8% [18]. On the other hand, the frequency of smoking is somewhat higher than that found in the adult Cuban population, which is 23.7%, as well as the frequency of alcoholism, since, in the aforementioned survey of risk factors, 5.1% of the population is identified as "harmful drinkers" [18,19].

The drugs most used in this population agree with those most used in pharmacoepidemiological studies carried out in the country [20]. The most common comorbidities also correspond to national reports [21].

The modification experienced in the GFR between the two phases of the study with a decrease in stage 2 cases is noteworthy. This could be because a part of the patients experienced recovery of renal function after the infectious noxa, while in another group, CKD progressed, but this is no more than a speculative hypothesis that must be confirmed and studied in research designed for this purpose since in the study in convalescent patients by Huang et al. the trend was towards CKD progression [12].The frequency of the most common renal ultrasound findings, such as lithiasis and cysts, correspond to those identified in the general population [22,23]. Likewise, the size of the viscera matched that expected in this population [24]. Thus, no characteristic findings were identified in these patients, as in a previous study in convalescents of COVID-19 [12]. However, in patients with COVID-19, particular results have been identified about specific diagnoses, thus increasing echogenicity of the parenchyma and decreased perfusion have been documented in a patient with a collapsing glomerulopathy related to COVID-19 [25].

The identified frequency of hematuria is striking. The high frequency of hematuria during infection is well known, although with notable variations between different studies [6,26]. However, there are no previous reports regarding the frequency of hematuria in convalescent from COVID-19, so it is impossible to make comparisons. However, it should be borne in mind that in this study, the dipstick was used for the diagnosis of hematuria and its sensitivity exceeds that of microscopic examination, and the frequency of dysmorphic hematuria was low [27]. In addition, studies in the general adult population, both in Cuba and in other countries, have found a frequency of isolated hematuria greater than 10% [28,29]. Consequently, this finding should be corroborated in further investigations, but it could constitute a marker of latent kidney damage post-COVID-19.

The frequency of the rest of the urinary sediment alterations was shallow and could be caused by causes other than COVID-19.

In this study, no patients with hypouricemia or hypophosphatemia were found, unlike the study by Werion et al., developed in patients admitted due to COVID-19 in Belgium, who found a frequency of hypouricemia of 47% and hypophosphatemia of 56% [8]. Although the creatinine figures were normal, for their adequate interpretation, it is necessary to evaluate the estimated GFR, which, as mentioned before, did show the presence of deterioration of renal function in a group of patients [10].

Before analyzing the fractional excretions used in the tubular functional evaluation, it should be clarified that these are modified in the event of significant renal dysfunction since the filtered load of the different solutes must be eliminated by a smaller number of functional units (nephrons), and this is achieved with a decrease in the tubular reabsorption of solutes. Still, we do not consider that it is particularly important in this cohort of patients with relatively preserved renal function [30].

The cases with increased FENa and FEK coincided with patients using diuretics, which must have resulted in increased urinary sodium and potassium losses, although previously identified tubular disorders during COVID-19 are limited to the proximal tubule, and in potassium management, the distal nephron plays a critical role [8,11].

Increased FEUA in patients without kidney damage has been associated with the use of uricosuric drugs such as aspirin, probenecid, sulfaprim, and losartan, among others, and is frequently found in diabetic and HIV patients [31]. In this cohort, all patients with increased FEUA had some predisposing condition to its appearance. Even though uricosuria due to aspirin usually appears with high doses, it was not the case in the patient studied [32]. However, the disorder was mild because, as previously mentioned, hypouricemia did not appear. The increase in FEUA in infected patients may be because it has been found in experimental models that viral infection can cause a downregulation of specific tubular transporters, such as URAT1 (transporter of urates) [33].

Increased FEP, which was not a frequent finding in this cohort and was not accompanied by hypophosphatemia, appears in patients without systemic diseases or hormonal disturbances or of substances that influence phosphorus metabolism (vitamin D, parathyroid hormone, FGF-23), with glucosuria, with the use of carbonic anhydrase inhibitors, with metolazone (a thiazide diuretic with a certain inhibitory effect on carbonic anhydrase) and in subjects with volume expansion [34]. In the study of patients with increased FEP, only one patient had diabetes and did not have glycosuria at the time of the survey. Still, remarkably all three patients had a history of alcoholism, which is a cause of urinary phosphate losses [34,35].

The patient with a positive Brand test for cystine in both phases of the study (with microlithiasis by ultrasound) could correspond to a carrier of the cystinuria gene (SLC3A1 or SLC7A9), who may present mild cystinuria without severe clinical manifestations of the disease [36]. About COVID-19, it has been documented that ACE2, in addition to its role in the renin-angiotensin system, facilitates the passage of B^0AT1 (sodium-dependent neutral amino acids transporter) to the apical membrane, so that the aminoaciduria identified in patients with SARS-CoV-2 infection, that is basically of neutral amino acids, could be a consequence of the binding of SARS-CoV-2 to its functional receptor (ACE2), which partially prevents its function in the passage of B^0AT1 to the luminal membrane [3,33,37].

The identified proteinuria pattern with sustained albuminuria and decreased urinary losses of proteins other than albumin, both in patients with and without albuminuria, is very interesting. It should be borne in mind that considering proteins other than albumin in the urine (once proteinuria due to overflow has been ruled out) as low molecular weight proteins (tubular reabsorption proteins), is an inaccurate generalization, but it is of clinical utility when direct measurement of low molecular weight proteins is not available [11,38,39].

The origin of low molecular weight proteinuria as part of proximal tubular dysfunction in infected patients appears to result from decreased megalin expression [8]. This multiligand receptor is critical for reabsorption [11,39]. Remarkably, the expression of megalin is preserved in patients with acute tubular damage due to sepsis, aminoglycosides, or hepatorenal syndrome [40]; so the causal noxa seems to determine the changes in the expression of megalin and, we could hypothesize its gradual recovery based on the magnitude of the tubular damage in direct relation to the severity of the patient during the infection, but this should be studied in depth.

All findings described suggest that in COVID-19 convalescents, the proximal tubular damage, identified in previous studies during infection, with the development of incomplete renal Fanconi syndrome (hyperuricosuria, hyperphosphaturia, aminoaciduria, and low molecular weight proteinuria) is recovered. Tubular proteinuria is the element that takes the longest time to disappear, in direct relation to the clinical condition of patients during infection. However, albuminuria and hematuria as expressions of glomerular damage persist.

Nevertheless, since this cohort of patients was not studied before or during their admission due to the infection, it cannot be asserted that they developed these markers of damage during the infection, especially if it is taken into account that almost half of the patients were asymptomatic during infection and a direct relationship has been found between the appearance of damage markers and the severity of the patients [6,8].

This study has the strength of having used the same protocol in the renal functional evaluation of COVID-19 convalescents in the medium and long term, as has not been done previously. Conversely, this research has some limitations, such as the lack of clinical and laboratory information during admission for COVID-19, and the fact that low molecular weight proteins, specific aminoacids, and B_2-microglobulin in urine were not measured.

CONCLUSION

In this cohort of Cuban adult convalescents from COVID-19 with a predominance of asymptomatic or mild symptomatic patients during infection, no characteristic ultrasound findings are identified. Hematuria is found with considerable frequency. There is no evidence of disturbances in the renal management of electrolytic or non-electrolytic solutes, except for increased protein losses. The losses of proteins other than albumin are related to the clinical condition of patients during infection.

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CONFLICT OF INTEREST

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