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Investigation of renal function in patients with long COVID in the Amazon region: a cross-sectional study

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Abstract

Background COVID-19 became a pandemic disease in 2020, with multisystem involvement and high renal morbidity during the acute phase. Some affected patients began to present new or persistent symptoms in a condition known as Long COVID. The study aimed to evaluate renal function using clinical and laboratory findings, and to establish the frequency and staging of renal function decline in Long COVID patients, as well as the associated factors.

Methods This is a cross-sectional observational study that selected participants from a Long COVID clinical care program between 2020 and 2022.

Results A total of 246 patients were selected for this study, and renal function decline was found in 83 (33.7%). Patients over 60 years (29.6%) and those who developed glycaemic alterations (41.8%) exhibited a higher prevalence of renal outcomes in long COVID. Some laboratory test as LDH levels and glycated hemoglobin seems to have a statistic relation with a decrease in renal function ($p < 0.05$).

Conclusion A decline in renal function was common in patients with Long COVID in this study, and older age and glycaemic alterations were relevant to this condition. Some laboratory markers can be used to predict this outcome.

Keywords Long COVID, Renal function, Acute kidney injury, Laboratory markers

Introduction

In 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of coronavirus disease 2019 (COVID-19) [1, 2]. In March 2020, the World Health Organization (WHO) officially declared it a pandemic [3]. COVID-19 has a major impact on the respiratory system, with symptoms of flu-like illness that can progress to progressive respiratory infection, acute respiratory distress syndrome, and death. However, the disease can compromise other organs and systems such as the kidneys, leading to different clinical behaviours, laboratory findings, and sequelae [4, 5].

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Acute Kidney injury in COVID-19 is present in 0.5–15% of the affected population, with 20–50% of patients requiring admission to the intensive care unit (ICU), and approximately 6% needing renal replacement therapy [6–8]. Acute Kidney injury is characterised by a sudden decline in renal function, leading to the accumulation of nitrogenous wastes, hydroelectrolytic disorders, and urine abnormalities, and is associated with poor clinical outcomes and increased mortality in COVID-19 [6, 9].

Additionally, a portion of the population affected by COVID-19 manifests signs and symptoms that persist for more than four weeks or even new symptoms that emerge. According to the definition by the National Institute for Health and Care Excellence (NICE), this condition, which cannot be explained by other causes, is termed Long COVID [10–13]. Long COVID is considered a multisystemic condition, with more than 200 symptoms described, with neuromuscular and respiratory being the most common, affecting the health and quality of life of patients [10, 11].

In COVID-19, kidney injury occurs through multiple mechanisms influenced by individual factors such as age and comorbidities, as well as factors like direct viral injury, inflammatory state, hypercoagulability, states of shock and hypovolemia, endothelial micro- and macrovascular injury, nephrotoxic drugs, and rhabdomyolysis [14].

Kidney injury resulting from COVID-19 can lead to sequelae of varying degrees in Long COVID, which are potentially irreversible [15, 16]. In the context of Long COVID, the risk of renal outcomes increases with the severity of the acute infection [17]. The possibility of developing metabolic syndromes, such as the onset of diabetes mellitus (DM) and systemic arterial hypertension (SAH), has also been described. These conditions may further contribute to the development of a decrease in renal function, given the strong association with these comorbidities [18].

By the end of 2022, more than 861,000 cases of COVID-19 were recorded in Pará. According to estimates by the WHO, approximately 10–20% of the infected population develops some type of sequelae. Therefore, the number of affected people who may need care for long COVID is worrying and further overloads the weakened public health system in the Amazon region [19]. The lack of data and dissemination of the possibility of renal sequelae are worrying factors locally and worldwide [20].

According to studies by the National Kidney Foundation Harris Poll, only 17% of Americans are aware of the risk of renal complications; therefore, limited information is available on renal sequelae in patients with Long COVID, resulting in delays in proper diagnosis and treatment [16].

Therefore, this study aimed to evaluate renal function using clinical and laboratory findings, and to establish the frequency and staging of renal function decline in Long COVID patients, as well as the associated factors.

Methods

Study design and ethical approval

This observational, cross-sectional study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was approved by the Research Ethics Committee of the State University of Pará (UEPA) (Opinion No. 4.252.664) and was carried out in accordance with the principles of the Declaration of Helsinki between August 2020 and June 2022, involving data on renal function markers, clinical, and laboratory parameters in patients with Long COVID. All participants signed an informed consent form (ICF).

Sampling and study groups

We included a total of 246 patients in the study with the aim of evaluating renal function alongside clinical and laboratory findings in Long COVID. The sample ($n = 246$) consisted of adults (≥ 18 years) who voluntarily enrolled in the Long COVID clinical follow-up programme at the State University of Pará (UEPA), located in the municipality of Belém. Participants were selected through convenience sampling.

As an inclusion criterion, the diagnosis of Long COVID was defined as follows: (1) acute symptoms compatible with COVID-19, not attributable to other diseases; (2) COVID-19 confirmed by viral detection through quantitative reverse transcription polymerase chain reaction (RT-qPCR); and (3) at least one symptom of Long COVID lasting for a minimum of 4 weeks after the onset of symptoms (e.g., fatigue, chest pain, shortness of breath, chronic cough, headache, palpitations, loss of smell or taste, brain fog, muscle pain, and dizziness), according to NICE. Following this stage, laboratory tests were conducted.

From an initial population of 265 individuals, a total of 19 were excluded (Fig. 1), including those with reported chronic renal disease. The remaining 246 patients were divided into groups based on the following criteria: 'decline in renal function in Long COVID (according to the CKD-EPI equation)' (Fig. 1).

Clinical assessment

A clinical assessment was conducted at the Respiratory Diseases Outpatient Clinic of the Physiotherapy and Occupational Therapy Unit – UEPA/Specialised Rehabilitation Centre. Study participants were evaluated at a single time point and designated according to the duration of Long COVID from 0 to 3 months, 3 to 6 months,

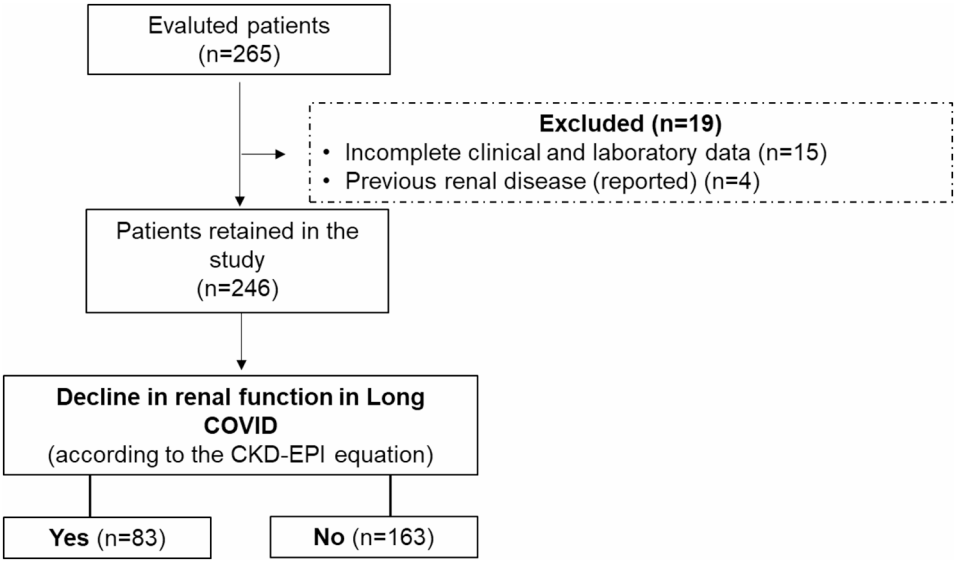

Fig. 1 Flowchart of patient recruitment in the study. Created with Lucidhart.com (www.lucidchart.com)

6 to 12 months, and 12 to 24 months (time from symptom onset to the time of data collection).

Information was gathered from interviews with each participant by completing a specific protocol form (Supplementary Table 1), which included general details such as: sex, age, pre-existing comorbidities, smoking status, ACE inhibitors/ARB use, hospitalisation due to COVID-19, symptoms during Long COVID, and time of Long COVID.

Definition of renal function

Renal function refers to the ability of the kidneys to maintain the body's equilibrium by excreting waste products and toxins, regulating extracellular fluid volume, serum osmolality, electrolyte concentrations, and producing hormones. In this context, the estimated glomerular filtration rate (eGFR) is one of the primary indicators of renal function [21].

According to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, renal function decline refers to a reduction in the kidneys' ability to perform their functions and urinary abnormalities such as proteinuria may also be present.

A decline in renal function can be assessed by the estimated glomerular filtration rate (eGFR) using the CKD-EPI equation, and classified according to the Kidney Disease: Improving Global Outcomes criteria for renal disease stage: stage 1 (G1): GFR ≥ 90 ml/min, Stage 2 (G2): GFR ≥ 60 and ≤ 89 ml/min, Stage 3 (G3): GFR ≥ 30 and ≤ 59 ml/min, Stage 4 (G4): GFR ≥ 15 and ≤ 29 ml/min, and Stage 5 (G5):GFR < 15 ml/min.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is a formula used to estimate GFR. Therefore, for standardisation of GFR assessment, we utilised the CKD-EPI equation, which employs sex, age, and serum creatinine levels as the primary variables to determine eGFR.

In this study, serum creatinine dosage was the option for assessing GFR, although it has a low sensitivity for detecting less advanced degrees of renal function loss.

The formula proposed by Levey et al. [21] is as follows:

$$\boldsymbol{CKD-EPI\ creatinine-based}:$$

$$141\ x\ min?\left(\frac{serum\ creatinine}{k},1\right)^{a}\ x\ \left(\frac{serum\ creatinine}{k},1\right)^{-1,209}$$

$$x\ 0{,}993^{age}\ [x\ 1{,}018\ \ (if\ woman)]\ [x\ 1{,}159\ \ (if\ black)]\ ,$$

where k is 0.7 for women and 0.9 for men, α is − 0.329 for women and − 0.411 for men, min is minimum serum creatinine/k or 1, and max is maximum serum creatinine/k or 1.

Laboratory data

The collected laboratory data broadly evaluated the patient`s health with immunological profiles, inflammatory markers, lipid profile, and above all, urea and creatinine levels for better evaluation of renal function, as well as urine tests with active urinary sediment. Blood collection was performed at a single time point, following the clinical evaluation conducted at UEPA.

Blood samples were collected from patients who had fasted for at least 8 h. This collection consisted of puncturing the peripheral vessel with a needle and collecting samples in 3 ml Vacuette tubes (Greiner Bio-One, Kremsmunster, Austria). Three blood tubes were collected from each patient as follows: (a) tubes containing

the anticoagulant ethylenedi-aminetetraacetic acid for analysis of whole blood, (b) tubes containing separator gel and clot activator for serum analysis, and (c) tubes with citrate for performing coagulation tests. The respective reagent manufacturers adopted standard reference ranges for the tests mentioned above (Supplementary Table2). Urinalysis was performed using a single morning urine sample and analysed using reagent strips and microscopy, through the urine analysis test (EAS).

Statistical analysis

After data collection, an electronic spreadsheet was created to store the data using Microsoft Excel® Software. For the descriptive representation of the data, tables, and graphs were created using Microsoft Excel® Software, representing the mean (standard deviation), median (amplitude interquartile) and minimum and maximum of numerical variables. Categorical variables are presented as absolute and relative percentage frequencies. Data analysis was performed using the Jamovi 2.3.24 program. For all analyses, a significance level of 5% was used (p-value < 0.05).

To identify significant difference (p-value < 0.05) between the median age (years), erythrocyte sedimentation rate, ferritin, albumin, creatine phosphokinase, lactic dehydrogenase, pyocytes, haemoglobin, red blood cells, glucose, glycated haemoglobin, and body mass index (BMI) were evaluated for the presence or absence of renal alteration. The t-student test was used when the data presented normal distribution and the Mann–Whitney test when the assumptions of normality were violated by the Shapiro-Wilk test.

The Yates-corrected Chi-square test was used to compare the proportion of female sex, age (> 60 years), DM, SAH, use of ACEI/ARB variables, hospitalisation, ICU or ward admission, long COVID symptoms, renal function markers, protein C reagent positivity, time of long COVID evaluation, and proteinuria due to the presence or absence of renal alteration.

To determine associations, logistic regression was performed, including all independent variables with a p-value < 0.2 in the bivariate analyses, aiming to differentiate explanatory variables from confounding factors influencing the outcome (Supplementary Table 3).

Table 1 Profile of participants with Long COVID

Variable	*n* = 246	%
Sex		
Female	155	64.01
Male	91	35.99
Age		
> 18 and < 60 years old	174	70.37
> 60 years old	72	29.63
Previous comorbidity		
SAH	88	35.77
Diabetes mellitus	32	13.01
CVD	19	7.72
Previous lung disease	16	6.50
Smoking		
No	182	73.98
Yes	9	3.66
Former smoking	55	22.36
ACE inhibitors/ARB use	**75**	**30.49**
Hospitalisation with COVID-19	**79**	**32.11**
ICU	9	3.66
Clinical of Long COVID (Symptoms)		
Respiratory	110	44.72
Post SAH	90	36.59
Neurological	84	34.15
Muscular	61	24.80
Cardiovascular	55	22.36
Otorhinolaryngological	34	13.82
Renal	25	10.16
Osteoarticular	20	8.13
Gastrointestinal	16	6.50
Dermatological	12	4.88
Psychiatric	11	4.47
Time of Long COVID, months		
0 and 3	59	23.98
> 3 and < 6	59	23.98
> 6 and < 12	60	24.40
> 12 and < 24	68	27.64

SAH, systemic arterial hypertension; CVD, cardiovascular disease; ACE inhibitors, Angiotensin-Converting Enzyme Inhibitors; ARB: angiotensin 2 receptor blockers; ICU, intensive care unit

Results

Of the 246 patients with Long COVID, the majority were female, and approximately one-third were over 60 years old. Diabetes mellitus (DM) and systemic arterial hypertension (SAH) were the most common comorbidities, reported by 32 (13.01%) and 88 (35.77%) patients, respectively. Only 75 patients reported prior use of ACE inhibitors or ARBs, and the mean BMI was 29.24 kg/m², indicating a prevalence of overweight. Only 79 patients required hospitalisation for the treatment of COVID-19, with just nine admitted to the ICU. The main symptoms reported in Long COVID were respiratory symptoms (44.72%) and systemic arterial hypertension (36.59%). Approximately 27.64% of patients experienced Long COVID for 12 to 24 months (Table 1).

In the analysis of the population according to different staging groups (G1-G4) in long COVID, despite differences when considering sex and whether the patient was hospitalised for COVID-19, no significant data were found regarding the incidence of renal function decline between these groups (Fig. 2/a; b).

Laboratory findings of patients with Long COVID demonstrate that, regarding haemoglobin, 109 (44.3%)

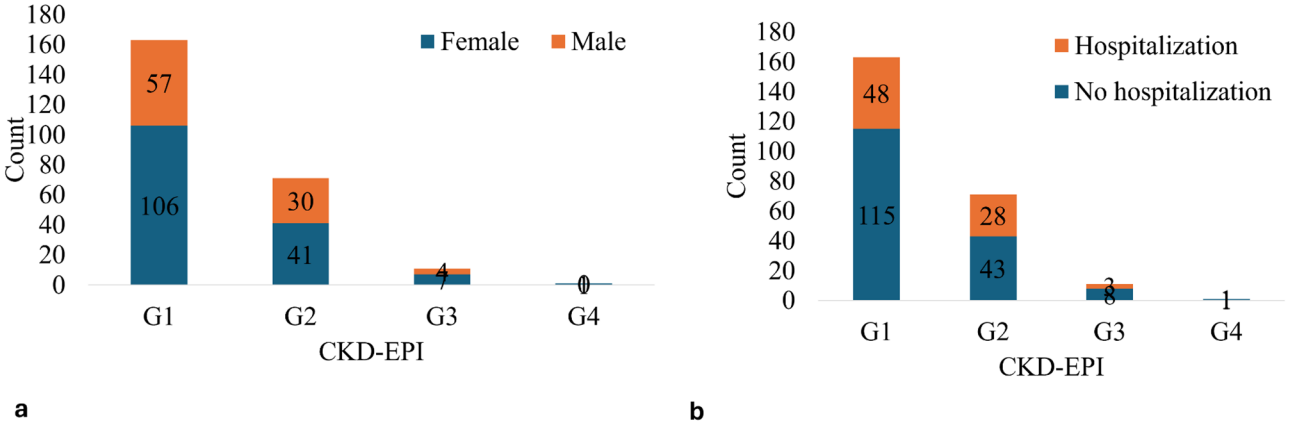

Fig. 2 Identification in absolute numbers and percentage of glomerular filtration rate (GFR) stratification separated by sex (**a**) and hospitalisation for COVID-19 (**b**) at onset according to the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). G1: GFR ≥ 90 ml/min; G2 GFR ≥ 60 and ≤ 89 ml/min; G3 ≥ 30 and ≤ 59 ml/min; G4 ≥ 15 and ≤ 29 ml/min; and G5 < 15 ml/min

Table 2 Laboratory variables in patients assessed with long COVID

Variable	*n* = 246	%
HB > 13.5 g/dl*	109	44.3
Glucose > 100 mg/dl	103	41.87
Positive CRP**	35	14.23
Total Cholesterol > 200 mg/dl	120	48.78
HDL > 50 mg/dl	89	36.18
TG > 150 mg/dl	104	42.28
Urinalysis		
Proteins urine		
0	233	94.72
1	5	2.03
2	6	2.44
3	2	0.81
HB urine		
0	229	93.09
1	10	4.07
2	4	1.63
3	3	1.22
Glucose urine		
0	228	92.68
1	2	0.81
2	1	0.41
3	12	4.88
4	3	1.22
GFR < 90 ml/min	**83**	**33.74**
Glycated Hb %		
Normal	66	35.11
Prediabetes	65	34.57
Diabetes	57	30.32

* The cut-off point for Hb was defined according to the laboratory guidelines, following the manufacturer's specifications; **Qualitative sample (inflammatory marker) - negative referene value; HB, Hemoglobin; HDL, high density lipoproteins; LDL, low density lipoproteins; GFR, glomerular filtration rate

had values above the cut-off (13.5 g/dL), indicating no anaemia. Concerning metabolic issues, 103 (41.87%) patients had high fasting glycaemia, and of the 188 participants whose glycated haemoglobin markers were analysed, 122 (64.89%) showed alterations, of which 65 (34.57%) met the criteria for pre-diabetes/glucose intolerance and 57 (30.32%) were suggestive of diabetes mellitus according to WHO criteria [22] (Table 2).

Among the groups with or without decline in renal funtion in Long COVID, no significant differences were observed in the clinical and laboratory data, except for patients over 60 years old, who had a higher frequency of decline in renal funtion compared to the group with normal renal function (45.68% vs. 21.6%; $p = 0.00$) (Table 3). A trend towards low albumin levels was also observed in the group with a decline in renal function (median 3.9; AIQ 0.5), as well as higher levels of LDH (median 321.5; AIQ 115.250) and glycated haemoglobin (median 6.0; AIQ 1.000) when compared to the group with normal renal function (Table 4).

Discussion/Conclusion

SARS-CoV-2 infection is now recognised not only as a respiratory tract condition but also as a multiorgan syndrome that commonly leads to renal outcomes [23]. The persistence of symptoms after the acute phase of COVID-19 can lead to potential sequelae in various organs and systems, referred to as Long COVID [11, 24]. Data on renal outcomes in patients with Long COVID remain scarce and require further study [20].

Our study included 246 patients (155 women, 174 aged 18–59 years). Seventy-nine required hospitalisations during the acute phase of COVID-19; however, they demonstrated no differences in renal outcomes. The most frequently reported symptoms in long COVID include neurological, Post SAH, muscular, and respiratory symptoms.

Table 3 Comparison of renal outcomes with clinical characteristics in the study population

Variable	Without decline in renal function, *n* = 163, n(%)	With decline in renal function, *n* = 83, n(%)	*p*-value
Female sex	106 (65)	49 (59)	0.43*
Age (> 60 years)	35 (21.60)	37 (45.68)	0.00*
Previous comorbidity			
DM	21 (12.8)	11 (13.2)	0.99*
SAH	56 (34.4)	34 (40.9)	0.38*
CVD	12 (7.3)	7 (8.4)	0.96*
ACE inhibitors/ARB use	**44 (26.9)**	**31 (37.3)**	**0.12***
Hospitalisation with COVID-19	**48 (29.4)**	**31 (37.3)**	**0.26***
in ICU	5 (3.1)	4 (4.8)	0.49**
in the ward	43 (26.4)	27 (32.5)	0.33*
Symptoms attributable to renal injury α	**14 (8.6)**	**11 (13.2)**	**0.35***
Time of Long COVID, months			**0.20****
0 and 3	45 (27.6)	14 (16.8)	
> 3 and < 6	37 (22.7)	23 (27.7)	
> 6 and < 12	46 (28.2)	22 (26.5)	
> 12 and < 24	35 (21.5)	24 (28.9)	
Proteinuria			**0.55****
0	154 (94.5)	79 (95.2)	
1	4 (2.4)	1 (1.2)	
2	3 (1.8)	3 (3.6)	
3	2 (1.2)	0 (0)	

*Chi-square test

**Fisher's exact test

α Alteration in urine (appearance or quantity), edema, and development of hypertension. DM, diabetes mellitus; SAH, systemic arterial hypertension; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ICU, intensive care unit; COVID, coronavirus disease 2019

Table 4 Comparison of renal outcomes with laboratory results in the study population

Variable	Without decline in renal function, *n*=163		With decline in renal function, *n*=83		*p*-value
	Median	AIQ	Median	AIQ	
ESR, mm	31	(32.500)	34	(32.000)	0.749*
Ferritin, mg	134	(192.250)	130	(124.000)	0.594*
Albumin, g/Dl	4.2	(0,7)	3.9	(0.5)	0.053*
CPK, U/L	81.5	(63.500)	88.5	(84.000)	0.247*
LDH, U/L	309	(90.000)	321.5	(115.250)	0.036*
Pyoc	3	92.000)	3	(2.500)	0.589*
Hb[a], g/dl	13.2	(1.23)	13.3	(1,49)	0.552**
Hcs	0	(2.000)	0	(2.500)	0.762*
Glucose, mg/dl	0	(0)	0	(0)	0.995*
Glycated Hb,	5.9	(1.300)	6.2	(1.000)	0.049*
BMI	28	(7.500)	28	(6.000)	0.149*

[a]Mean (standard deviation)

*Mann–Whitney

**Student's t-test

AIQ, amplitude interquartile; ESR, erythrocyte sedimentation rate; CPK, creatine phosphokinase; LDH, lactic dehydrogenase; PYoc, pyoctes; Hb, haemoglobin; hcs, hemaceas; HbGly, glycated haemoglobin; BMI, body mass index

Furthermore, regarding the presence of comorbidities, we identified 32 patients with a previous diagnosis of DM and 88 patients with SAH; 100 patients had a BMI of > 30 kg/m^2. Alterations in renal function through eGFR and urine abnormalities were identified in 83 patients with long COVID, with a statistically significant relationship observed in patients aged over 60 years. Findings related to changes in urinary sediment alone such as proteinuria were present in less than 7% of the patients.

Evidence in the literature demonstrates that renal outcomes can persist for more than 12 months in Long COVID [10, 25]. This perspective supports the findings of this study, in which a decline in renal function was present at all evaluated time points in Long COVID.

These data demonstrate the potential of renal sequelae developed by patients with long COVID, known to have a multifactorial cause related to the maintenance of inflammatory factors, intrinsic tubular damage, and incomplete resolution of the condition, causing an impact on morbidity and the health system, considering the increase in number of patients with chronic non-communicable diseases such as Chronic Kidney Disease [26–28].

A statistically significant relationship between changes in renal function in Long COVID and patients aged over 60 was demonstrated using eGFR, which is consistent with studies on Long COVID [29]. Of the 83 patients who had renal function decline in Long COVID, 71 had a eGFR between < 90 ml/min and ≥ 60 ml/min. What the literature brings so far regarding long COVID is the perpetuation of changes compatible with a decline in eGFR, with the most frequent range being G2 [25] consistent with our findings.

In the literature, DM and SAH were also the most reported comorbidities in individuals who developed long COVID, and the development of these conditions was also identified in some previously healthy patients with long COVID [27, 30]. This perspective is worrisome because hyperglycemia is known to cause renal damage and complications, with genetic, hemodynamic, and metabolic factors related to its pathophysiology [31, 32]. Regarding BMI, the association between obesity and severe cases of COVID-19 in the acute phase is well known; therefore, obesity has a greater potential for sequelae and the development of long COVID [33].

Laboratory data from patients with Long COVID revealed a significant relationship between LDH levels, albumin levels, glycated haemoglobin levels and decline in renal function. These aspects suggest possible associations already identified in other studies, indicating that

LDH levels are closely related to inflammation and hypercoagulable states [28, 35]. Evidence points to a tendency towards lower serum albumin levels in Long COVID due to cellular hypercatabolism, which leads to a reduction in circulating albumin levels [34].

The higher levels of glycated haemoglobin in this study are consistent with data in the literature, as several studies have demonstrated an increased incidence of DM in the long COVID [35–37]. This is concerning because of the high incidence of this disease worldwide and its impact on healthcare systems [38, 39].

As for the use of medications, 75 patients used medications such as ACE inhibitors and ARBs. The possibility of worse clinical and renal outcomes in patients using these medications has been described in the literature because of the suspicion of positive regulation of ACE2 and the consequent increase in viral load [26, 40]. This would also influence the production of angiotensin 1–7, which has antagonistic actions on angiotensin II, such as vasodilation and antiproliferative actions [41]. However, in our study, this association was not observed, which is in line with recent findings in the literature [41–43].

This study has some limitations. The availability of information such as the previous renal function of these patients and details regarding hospitalisation, considering the need for ventilatory support, drugs used, and even the development of AKI, makes it difficult to understand the process of renal illness. The follow-up of these patients for a longer period could provide greater support for assessing the evolution of renal function in patients with long COVID.

However, our data are highly valuable to the medical and scientific community, as they allowed us to identify which patients with Long COVID are at risk of developing renal outcomes for a prolonged period after the acute phase of the disease. The elderly population and those with glycaemic alterations have been identified as being at a greater risk of developing such alterations, and monitoring of renal function should be more comprehensive in such individuals. Therefore, further studies are warranted.

Renal outcomes in patients with Long COVID in this study were observed in one-third of the population studied, with no significant differences between groups with comorbidities, use of medications such as ACE inhibitors and ARBs, need for hospitalisation, or even the time elapsed since the acute phase, indicating that renal function decline can persist for more than 12 months after contact with SARS-CoV-2. Moreover, the elderly population and those who developed glycemic alterations were at a greater risk of a decline in renal function with long COVID. Therefore, we must be attentive to laboratory findings related to renal outcomes such as LDH, glycated hemoglobin, and serum albumin levels.

The lack of similar investigations in the Amazon region emphasises the importance of this study. These findings reinforce the need to establish programs that include renal evaluation in the follow-up of patients with long COVID, in a more comprehensive way, because even young patients without previous comorbidities, presents with increased risk of renal function decline, end-stage renal disease and major adverse renal events. Thus, the implementation of therapeutic measures and health strategies aimed at reducing the medium and long-term impacts of the COVID-19 pandemic on the health of the population in the Amazon region and worldwide may be related to better prognoses.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10355-7.

Supplementary Material 1

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Conceptualization, G.M.C.C.A., I.G.V., R.N.R.R. and P.D.L.L.; methodology, G.M.C.C.A., I.G.V., R.N.R.R. and P.D.L.L.; formal analysis and investigation, G.M.C.C.A. and L.F.M.F.; resources, J.R.S. and L.F.M.F.; data curation, G.M.C.C.A., S.S.X., L.F.M.F. and P.D.L.L.; writing—original draft preparation, G.M.C.C.A; validation, J.R.S., J.A.S.Q., L.F.M.F. and P.D.L.L.; writing—review and editing, G.M.C.C.A., E.C.R.C, D.C.M, J.R.S., J.A.S.Q., L.F.M.F. and P.D.L.L.; visualization, supervision and project administration, J.A.S.Q., L.F.M.F and P.D.L.L.; funding acquisition, L.F.M.F. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data supporting the findings of this study are available upon request to the corresponding author (PDLdL or LFMF). The data are not publicly available due to containing information that could compromise the privacy of research participants.E-mail: PDLdL (patricia.lima@uepa.br); LFMF (fabiofalcao@uepa.br).

Declarations

Institutional review board statement and informed consent statement
The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the State University of Pará (protocol code no. 4.252.664 / 1 September 2020) for human studies. Written informed consent has been obtained from the patients to publish this paper.

Consent for publication
All authors have read and agreed to the published version of the manuscript.

Competing interests
The authors declare no competing interests.

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