













Prevalence of renal involvement among pediatric patients hospitalized due to coronavirus disease 2019: A multicenter study

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ABSTRACT

Introduction. Renal involvement among pediatric patients with coronavirus disease 2019 (COVID-19) ranges between 1.2% and 44%. Given the limited information available locally, the primary objective of this study was to estimate the prevalence of renal involvement in our setting.

Population and methods. Cross-sectional study conducted in 13 Argentine sites between March and December 2020. Patients aged 1 month to 18 years hospitalized due to COVID-19 and with at least one measurement of serum creatinine and/or a urinalysis were included. Those with a known kidney disease were excluded. Renal involvement was defined as the presence of acute kidney injury (AKI), proteinuria, hematuria, leukocyturia and/or arterial hypertension (HTN).

Results. Among 528 eligible medical records, 423 patients were included (55.0% were males; median age: 5.3 years). The clinical presentation was asymptomatic in 31%; mild, in 39.7%; moderate, in 23.9%; severe, in 1.2%; critical, in 0.7%; and 3.5% had multisystem inflammatory syndrome in children (MIS-C). Two patients (0.47%) died. The prevalence of renal involvement was 10.8% (95% confidence interval: 8.2–14.2); it was described as leukocyturia (16.9%), proteinuria (16.0%), hematuria (13.2%), HTN (3.7%), and AKI (2.3%). No patient required dialysis. Renal involvement was associated with severe forms of disease ($p < 0.0001$).

Conclusion. The prevalence of renal involvement among pediatric patients hospitalized due to COVID-19 in 13 Argentine sites was 10.8%; severe forms of disease prevailed.

Key words: COVID-19, acute kidney injury, proteinuria, hematuria, child.

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INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative factor of coronavirus disease 2019 (COVID-19), which disseminated worldwide subsequently.¹ Children are less susceptible to severe infection compared to adults; 50% of them are asymptomatic.^{2,3} Although respiratory involvement predominates, from upper respiratory tract catarrh to severe respiratory failure, it can also present with multiorgan failure and develop into multisystem inflammatory syndrome in children (MIS-C).²

The etiopathogenesis of renal involvement is multifactorial; it involves a direct cytopathic effect of the virus on podocytes and tubular epithelial cells, the disruption of the renin-angiotensin-aldosterone axis, and the systemic inflammatory response to infection.⁴ Such complication, especially the development of acute kidney injury (AKI), in pediatric patients hospitalized due to COVID-19 ranges from 1.2% to 44%, depending on the severity of the general clinical picture.⁵⁻¹⁰ Given that there is limited local information about renal involvement,¹¹ we conducted this study with the primary objective of estimating the prevalence of renal involvement among pediatric patients hospitalized due to COVID-19 in our

setting. The secondary objectives of the study were to describe the characteristics of renal involvement and explore the risk factors for its development.

PATIENTS AND METHODS

Multicenter, cross-sectional, and descriptive study carried out in 13 sites from Argentina between March and December 2020. Participating sites were invited to the study via nephrologists members of the Committee of Nephrology of the Sociedad Argentina de Pediatría. Inclusion criteria were the following: patients hospitalized due to confirmed SARS-CoV-2 infection, aged 1 month to 18 years, with at least one serum creatinine measurement and/or urinalysis as requested at the treating physician's discretion. Patients with past and/or current kidney disease not related to COVID-19 (including urinary tract infection) were excluded.

As established by the National Ministry of Health of Argentina, since the onset of the pandemic until June 2020, all patients with COVID-19 were hospitalized, including asymptomatic patients and those who did not meet the clinical criteria. As of June 29th, 2020, hospitalization was restricted to patients who met the clinical criteria for severity and/or had risk factors (including patients younger than 3 months).¹²

Renal involvement was defined as the presence of AKI, pathological proteinuria, hematuria and/or leukocyturia. Although arterial hypertension (HTN) is not always caused by a kidney disease *per se*, it was also considered a manifestation of renal involvement. During hospitalization, the following data were collected from the medical records: age, sex, weight, comorbidities, length of stay in days, clinical severity upon admission (as per the classification of the National Ministry of Health of Argentina),¹² presence of diarrhea and/or vomiting, blood pressure, admission to the intensive care unit (ICU), inotrope requirement, and MIS-C. In addition, baseline serum levels of urea, creatinine, blood count, electrolytes, transaminases, glucose, albumin, and C-reactive protein (CRP) and the latest available creatinine level were recorded. Proteinuria, hematuria, and leukocyturia were also recorded. Not all tests were requested in some patients, so the frequency of measurements was also recorded.

The study was approved by the corresponding ethics committees, and they exempted the need of

having an informed consent (PRIISABA registry no.: 1803).

Definitions

SARS-CoV-2 infection: polymerase chain reaction performed on nasopharyngeal aspirates or positive serology (IgM and/or IgG).⁶

The **evidence of renal involvement** was assessed based on the presence or absence of:

- AKI: based on the extent of serum creatinine increased above the upper limit of normal for age; it was classified into stage 1 (1.5 to 1.9 times increase), stage 2 (2 to 2.9 times increase), and stage 3 (≥ 3 times increase).¹³
- Hematuria: > 5 red blood cells per high-power field in centrifuged urine.¹⁴
- Proteinuria: 1 or more crosses in the urine strip or urine protein/creatinine ratio on spot urine sample > 0.2 .¹⁵
- Leukocyturia: ≥ 5 red blood cells per high-power field in centrifuged urine.¹⁶
- HTN: systolic and/or diastolic blood pressure $\geq 95^{\text{th}}$ percentile for age, sex, and height in subjects younger than 16 years and systolic blood pressure between 140 and 159 mmHg and/or diastolic blood pressure between 90 and 99 mmHg in subjects older than 16 years.¹⁷

Based on the **clinical condition upon admission**, patients were classified into:

- Asymptomatic: diagnosed through close contact tracing, no symptoms.¹²
- Mild: patients with respiratory or general non-specific symptoms, without risk factors, no oxygen therapy or parenteral hydration requirement, with normal vital signs.¹²
- Moderate: patients with respiratory distress, who required oxygen therapy and/or parenteral hydration or had mild conditions in a risk group.¹²
- Severe: patients with severe respiratory distress and compensated septic shock.⁸
- Critical: patients with impending acute respiratory failure, decompensated shock or cardiorespiratory arrest.⁸
- MIS-C: children with fever for more than 3 days and 2 of the following: a) skin rash or bilateral conjunctivitis or mucocutaneous inflammation; b) hypotension or shock; c) myocardial dysfunction, pericarditis, valvulitis or coronary artery anomalies; d) coagulopathy; and e) gastrointestinal symptoms, with elevated markers of inflammation.^{18,19}

Associated severity risk factors: prematurity, heart disease, pre-existing respiratory disease, immune compromise, neuromuscular disease, moderate or severe encephalopathy, malnutrition, insulin-dependent diabetes, and sickle cell disease.²⁰

Statistical analysis

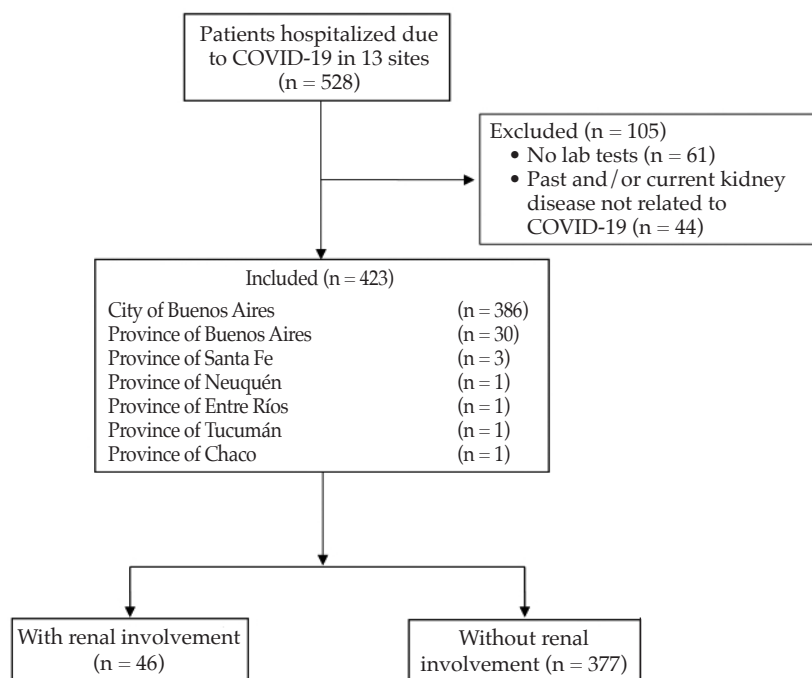
Given that at the time the protocol was developed, this was an emerging disease, with great variability in international data regarding the prevalence of renal involvement added to the limited local information,⁵⁻¹¹ we considered all patients hospitalized due to COVID-19 to be eligible. The prevalence was estimated on the basis of the proportion of participants who had renal involvement out of the total number of participants hospitalized due to COVID-19 during the study period and was expressed as a percentage with its 95% confidence interval (CI).²¹ Quantitative variables were expressed as median (interquartile range) and categorical variables, as frequency of presentation (n) and/or percentage. Patients with or without renal involvement were compared using Fisher's exact test or the χ^2 test (with their corresponding odds ratios [ORs] and 95% CIs) and the Wilcoxon test, as appropriate. The significance level was established at $p < 0.05$. The Statistix 7[®] software was used.

RESULTS

The medical records of 528 children hospitalized in the study period were reviewed; the medical records of 423 patients were included. In this group, 80.3% corresponded to a children's hospital in the City of Buenos Aires (Figure 1). In total, 55.0% (n = 233) of cases were males; participants' median age was 5.3 years (0.8–11.95) and their median weight was 20 kg (9.45–41.7). The clinical presentation was asymptomatic in 31% (n = 131); mild, in 39.7% (n = 168); moderate, in 23.9% (n = 101); severe, in 1.2% (n = 5); critical, in 0.7% (n = 3); and 3.5% (n = 15) developed MIS-C. Twenty-three patients (5.4%) required admission to the ICU and 2 (0.47%) died.

Serum creatinine values were available for 384 out of 423 patients; 9 (2.3%) had AKI (4 in stage 1, 4 in stage 2, and the rest in stage 3). Urinalyses were requested in 106 cases: 18 (16.9%) had leukocyturia, 17 (16.0%) had proteinuria (1 massive proteinuria without nephrotic syndrome), and 14 (13.2%) had microscopic hematuria. Blood pressure was recorded in 81 patients; of these, 3 had sustained HTN (3.7%). Based on these findings, renal involvement was identified in 46 patients (10.8%; 95% CI: 8.2–14.2). Table 1 details renal findings based on clinical severity. Among patients with renal

FIGURE 1. Flow chart of patients



involvement, 26% (n = 12) had comorbidities: 4, respiratory disease (2 asymptomatic cases and 2 moderate cases); 5, immunocompromise (3 moderate cases, 1 severe case, and 1 critical case); and 3, other comorbidities (1 moderate case, 1 severe case, and 1 critical case). No patient required renal replacement therapy. The 2 patients who died developed AKI and had associated diseases (1 had immunocompromise and 1, encephalopathy).

Renal involvement was more common among patients with MIS-C (8/15 versus 38/408, $p < 0.0001$, OR: 11.12, 95% CI: 3.8–32.3); 4 (26.6%) of them developed AKI (Table 1). Lastly, the presence of renal involvement was associated with severe forms of disease (severe + critical + MIS-C) ($p < 0.0001$, OR: 11.74, 95% CI: 4.82–28.6) and with admission to the ICU, inotrope requirement, and the presence of vomiting and/or diarrhea. In association, patients in the renal involvement group showed lower levels of albumin, sodium, potassium, lymphocytes, and a higher level of white blood cells, neutrophils, and CRP (Table 2). In all patients with AKI, creatinine levels returned to normal during hospitalization.

DISCUSSION

The prevalence of renal involvement in our series of patients hospitalized due to COVID-19 was 10.8%; leukocyturia (16.9%) and proteinuria (16%) predominated. Hematuria was observed in 13.2% of cases, and only 2.3% developed AKI. In hospitalized adults, renal involvement was observed in approximately 30% of cases, expressed as proteinuria (40–60%), hematuria (20–40%), leukocyturia (30%), and AKI (15%); 5% required renal replacement therapy.^{22,23} In

pediatrics, in a series of 52 patients, 29% had AKI; 10%, proteinuria; and 23%, hematuria.⁶ However, most pediatric studies focused on assessing only the presence of AKI as an expression of kidney damage.^{5–10}

In one of the first characterizations of the disease, 36 hospitalized children were assessed and none had renal dysfunction.² Subsequently, a study in 238 patients, with only 3 severe cases, recorded this complication in 1.2% of the cases.⁵ In our case series, the prevalence of AKI was low, which is probably also due to the fact that many of our patients were asymptomatic and mild. In contrast, in studies that included severe cases, such prevalence increased to a range from 11.8% to 29%.^{6–9} Moreover, in a study restricted to critically ill children with COVID-19, the prevalence of AKI reached 44%.¹⁰ The worsening of the general condition with the need for admission to the ICU, usually accompanied by hemodynamic instability requiring inotropes, increases the risk for renal involvement, mainly AKI.^{6–10,23–25} In fact, in our series, we also found an association between the presence of severe clinical forms, admission to the ICU, and inotrope support requirement and the development of renal involvement.

In line with this, a high prevalence of renal involvement has also been documented in patients with MIS-C, ranging from 15% to 73%.^{6,7,9,26} This clinical form is characterized by a hyperinflammatory state with multiple organ involvement, so its association with AKI is to be expected.^{7,26} Basaley et al. observed that patients with MIS-C have more than twice the prevalence of AKI than those with COVID-19 without MIS-C (8% versus 18%, respectively),⁹ similar to what

TABLE 1. Description of renal involvement in 46 patients with COVID-19

Type of renal involvement	Number of patients (n = 46)	Severity of COVID-19
Acute kidney injury	7 (15.2%)	1 mild, 2 severe, 1 critical, 3 MIS-C
Proteinuria	8 (17.3%)	1 asymptomatic, 3 mild, 3 moderate, 1 MIS-C
Hematuria	6 (13.0%)	2 asymptomatic, 2 mild, 2 moderate
Leukocyturia	9 (19.5%)	6 asymptomatic, 2 mild, 1 moderate
HTN	1 (2.1%)	1 moderate
Acute kidney injury + HTN	2 (4.3%)	1 critical, 1 MIS-C
Proteinuria + hematuria	4 (8.6%)	1 mild, 2 moderate, 1 MIS-C
Proteinuria + leukocyturia	5 (10.8%)	1 asymptomatic, 2 mild, 2 MIS-C
Hematuria + leukocyturia	4 (8.6%)	1 asymptomatic, 1 mild, 1 moderate, 1 critical

HTN: arterial hypertension, MIS-C: multisystem inflammatory syndrome in children.

occurred in our patients with MIS-C, who had a higher prevalence of renal involvement, including the development of AKI.

Unlike other studies,^{25,27} the presence of comorbidities did not increase the risk for renal involvement, although the 2 deceased patients had previous diseases and AKI. Even though this could be due to the lack of power of this study, in a series of patients with MIS-C, the presence of comorbidities was less frequent than in the control group.²⁸ There was also no evidence of an increased risk for severe forms of COVID-19 in patients with cancer.²⁹ Further studies should clarify these contradictory observations.

Gastrointestinal involvement by SARS-COV-2 is frequent in children, probably because of the high expression of its receptor, angiotensin-converting enzyme 2, in the small intestine

and colon.^{4,30} Children are more prone than adults to gastrointestinal invasion of the virus with risk for dehydration, which predisposes to the development of AKI.^{6,31} In spite of this, and unlike our study, other authors found no association between the presence of vomiting and/or diarrhea and this complication, which could be due to early detection and correction of dehydration to prevent kidney damage.^{8,9}

According to the consensus by the Acute Disease Quality Initiative (ADQI) working group,²³ the predictors for developing AKI upon hospitalization are the following: COVID-19 severity, severe respiratory involvement, diarrhea, leukocytosis, lymphopenia, elevated inflammatory markers, hypovolemia, elevated viremia, rhabdomyolysis, and treatment with angiotensin-converting enzyme 2 inhibitors,

TABLE 2. Demographic, clinical, and laboratory factors associated with renal involvement in children with COVID-19

Variable	Without renal involvement (n = 377)	With renal involvement (n = 46)	p value
Demographic data			
Age (years)	5.2 (0.8–12.15)	6.4 (2.5–11.9)	0.32
Sex (female/male)	168/209	22/24	0.67
Weight (kg)	19 (9–41)	28 (13.2–45)	0.1
Clinical condition upon admission			
Asymptomatic, mild or moderate versus severe, critical or with MIS-C	366/11	34/12	< 0.0001
Length of stay (days)	8 (5–9)	8 (6–12)	0.14
Comorbidities	96	12	0.92
Diarrhea and/or vomiting	52	15	0.001
Admission to the intensive care unit	10	13	< 0.0001
Inotropes	6	4	0.015
Laboratory data upon admission			
Hemoglobin (g/dL) (331/42)	12.5 (11.5–17)	12 (10.5–13.3)	0.17
White blood cells (/mm ³) (330/42)	6655 (5190–8775)	8400 (6322.5–11 700)	0.007
Neutrophils (%) (327/41)	40 (25–53)	51 (31.2–74.2)	0.003
Lymphocytes (%) (326/41)	46 (34.4–64)	36 (17–57)	0.007
Platelets (/mm ³) (330/42)	258 000 (215 500–322 500)	243 500 (191 150–334 500)	0.58
Blood glucose level (mg/dL) (318/38)	90 (83/101)	93.5 (86/109.2)	0.15
GOT (IU/L) (282/36)	30 (20.7–44)	28.5 (19.2–41.5)	0.66
GPT (IU/L) (302/39)	18 (12–26)	19 (12–28)	0.72
Sodium (mEq/L) (92/21)	138 (136–140)	134 (131–138)	0.002
Potassium (mEq/L) (91/20)	4 (3.8–4.4)	3.7 (3.3–4.2)	0.01
Urea (mg/dL) (337/41)	21 (16–29)	23 (18–30)	0.38
Creatinine (mg/dL) (327/40)	0.39 (0.29–0.52)	0.46 (0.33–0.55)	0.12
Albumin (mg/dL) (304/38)	4.48 (4.2–4.7)	4.2 (3.5–4.5)	0.001
CRP (mg/dL) (270/35)	1.05 (0.3–4.7)	15 (0.4–48)	0.001

MIS-C: multisystem inflammatory syndrome in children, GOT: glutamic-oxaloacetic transaminase;

GPT: glutamic-pyruvic transaminase; CRP: C-reactive protein.

In the *Variable* column, the number of data available per group is indicated between parentheses (without renal involvement or with renal involvement).

Quantitative data are described as median (interquartile range), whereas categorical data, as frequency (n).

statins, corticosteroids, or non-steroidal anti-inflammatory drugs. The first seven are consistent with our results. The association between renal involvement and hypoalbuminemia, lymphopenia, and leukocytosis was reported in different studies.^{2,9,32} Hypoalbuminemia could be due to an increase in capillary permeability due to systemic inflammation that would also produce alterations in white blood cells. Elevated CRP, a known marker of inflammation, would also be related to disease severity.³²

COVID-19 in children has a favorable course, with a mortality rate of less than 1%;^{2,3} in our series, it was 0.47%. In relation to renal involvement, all patients in this study with AKI reached normal creatinine levels during hospitalization. Furthermore, as previously reported, in a subgroup of these patients from one of the participating sites, in whom resolution of urinary findings had not been documented, complete remission was noted in most cases at 3-month follow-up.¹¹ Furthermore, the absence of progression to chronic kidney disease in patients with AKI associated with MIS-C has been recently observed.³³

Although the number of patients studied is relatively large and we assessed renal involvement in a comprehensive manner, without restricting to AKI, as most studies do, several limitations should be noted. In relation to the operative definition of renal involvement, it is worth mentioning that in order to increase case detection we included the finding of low-grade proteinuria, which could be due to other clinical conditions (e.g., fever), and leukocyturia, which, although it usually reflects involvement of the urinary tract, has also been described in patients with renal parenchymal disease, such as AKI of different causes and tubulointerstitial nephritis associated with COVID-19.^{34,35} In addition, urinary tract infection was ruled out in all cases.

In addition, although this is a multicenter study, the representativeness of the sample may have been affected because it did not cover the entire country and 80% of the cases came from a single site. Finally, the hospitalization of all children at the beginning of the pandemic, while allowing assessment of renal involvement in many asymptomatic or mild patients, may have been responsible for a lower prevalence of renal involvement than in studies that included mainly severe cases.⁶⁻¹⁰ In turn, such disparate inclusion of cases, as well as the lack of many laboratory

measurements and blood pressure records, may not only have influenced the prevalence observed, but also limits the assessment of the risk factors associated with renal involvement, so this analysis should be considered exploratory and interpreted with caution.

CONCLUSION

The prevalence of renal involvement among pediatric patients hospitalized due to COVID-19 in Argentine sites was 10.8%; it prevailed in severe forms of COVID-19. It is worth noting that it is necessary to manage renal function in patients hospitalized due to COVID-19. ■

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