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Original Article

Renal Complications Due to SARS-CoV-2 Infection in Pediatric Population

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ABSTRACT

Background and Aim: COVID-19 pandemic originated in Wuhan City, China, in 2019. The disease spectrum ranges from asymptomatic to severe respiratory failure leading to death. Although in a lower percentage, pediatric patients also have complications, not only pulmonary but also systemic, affecting other organs. This article aims to study the renal involvement of pediatric patients infected by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

Methods: We designed a retrospective observational cohort study of patients hospitalized in the emergency department and intensive care unit of a tertiary medical facility hospital Infantil de México Federico Gomez in Mexico City, from March 1, 2020, to May 16, 2021. The inclusion criteria included patients younger than 18 years who had a positive Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test or a positive rapid antigen test of nasopharyngeal sample for SARS-CoV-2 at admission.

Results: We included 165 patients, of whom 29(17.6%) patients developed renal complications during hospitalization. In these patients, 12(41.3%) patients developed proteinuria, 10(34.5%) developed any type of Acute Kidney Injury (AKI), i.e., Acute Kidney Injury Network (AKIN-1) in 26.6%, AKIN-2 in 40% and AKIN-3 in 33.3%. Also, 5(17.2%) patients had arterial hypertension, 2(6.9%) required renal replacement therapy, 4(13.8%) had hematuria. Only 1(3.4%) patient had developed rapidly progressive glomerulonephritis.

Conclusion: COVID-19 infection within its spectrum can cause kidney disease; the most common complications are proteinuria and AKI. Older age and admission to the intensive care unit are risk factors for kidney damage.

Keywords: SARS-CoV-2, Kidney disease, Pediatrics, México, Complication

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Introduction

In 2019, a new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in the Wuhan region in China, causing the Coronavirus Disease 2019 (COVID-19), which rapidly spread into a worldwide pandemic [1]. The first reported evidence suggests that COVID-19 has a higher burden on adults who were an exposed group with a higher risk of adverse outcomes and mortality than the younger population [2]. Overall, pediatrics has demonstrated the lowest mortality rates from COVID-19 in several epidemiological reports. A recent systematic review showed that approximately 95% of all pediatric cases tend to develop asymptomatic to mild-moderate clinical patterns with a low risk for hospitalization and the need for mechanical intubation [3]. Nevertheless, the real impact on the pediatric population is related to their susceptibility to diverse extrapulmonary impairments of COVID-19, such as gastrointestinal, cardiovascular, neurological, hematological, and dermatological [4].

A particular impairment is the renal complications described in pediatrics due to SARS-CoV-2 infection. There are still controversies about the physiopathology of renal complications; however, the most supported hypothesis suggests direct virus invasion in renal cells, systemic and local inflammation, activation of procoagulant pathways, and microvascular injury in the renal parenchyma [5]. Recent reports indicate that Acute Kidney Injury (AKI) is one of the most common renal complications associated with SARS-CoV-2 infection. A review of kidney implications in children concluded that AKI was the most common complication in hospitalized patients [6]. A retrospective cohort of hospitalized pediatrics showed that 11.8% of their population developed AKI during hospitalization [7]. Furthermore, other potential renal complications can be attributed to SARS-CoV-2 infection.

The potential renal complications and their associated risk factors can be implied in hospitalized pediatrics. Therefore, we aim to describe the incidence of renal complications (AKI, glomerulopathy, arterial hypertension, and pathological findings in urinalysis) and their associated risk factors in a retrospective cohort of pediatric patients in a tertiary care hospital in Mexico City.

Materials and Methods

Study design

We designed a retrospective observational cohort study of patients hospitalized in the emergency room and the Intensive Care Unit (ICU) from a tertiary medical facility, “Hospital Infantile de México Federico Gomez” in Mexico City, from March 1, 2020, to May 16, 2021. Our inclusion criteria included patients younger than 18 years who had a positive Reverse Transcription-Polymerase chain Reaction (RT-PCR) test or a positive rapid antigen test of a nasopharyngeal sample for SARS-CoV-2 at admission from a laboratory approved by the Institute for Epidemiological Diagnosis and Reference (InDRE). We excluded patients who had incomplete clinical records or were discharged to another hospital center due to lack of follow-up, patients with a renal disease such as nephrotic syndrome, chronic renal disease with or without continuous renal replacement therapy, and hypertension at any stage of diagnosis. Up to the writing of this report, the COVID-19 vaccination policy did not cover the pediatric population in Mexico; therefore, none of our included patients were vaccinated during the study period. This study was approved by the Ethics and Research Committee (HIM2020-031).

Clinical, medical, anthropometric, and biochemical measurements

We extracted patients’ data using their clinical records from this institution. Our demographic variables included age, sex, and state of residency. Relevant clinical variables were previously known, no renal comorbidities and vital signs at admission. Our anthropometric variables were weight, height, and Body Mass Index (BMI) (weight [kg] divided by height [cm^2]). Our biochemical data included urinalysis (proteinuria, hematuria, and abnormalities in the urine sediment) and blood chemistry, which included Blood Urea Nitrogen (BUN), uric acid, creatinine, and electrolytes, such as sodium, potassium, chloride, calcium, magnesium, and phosphorus. To estimate kidney function parameters during hospitalization, we collected biochemical data during hospitalization, three and seven days after hospitalization, and on the last day of hospitalization.

Clinical definitions and outcomes

We defined renal complication as a concept based on the incidence of AKI according to AKIN criteria (AKIN-1 Serum Creatinine [SCr] >0.3 mg/dL or

150%-200% x baseline increase, AKIN-2 SCr 200%-300% x baseline increase, and AKIN-3 ≥300% baseline increase or SCr ≥4 mg/dL [with the acute increase ≥0.5 mg/dL]) [8], new-onset arterial hypertension based on American Academy of Pediatrics (AAP) clinical practice guidelines [9], glomerulopathy with proteinuria, hematuria based on Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the management of glomerular diseases [10], and or use of renal replacement therapy, such as hemodialysis, peritoneal dialysis, and continuous renal replacement therapy during hospitalization.

Statistical analysis

Continuous data are shown as means (standard deviation) or medians (interquartile range) according to their distribution evaluated by the Anderson-Darling normality test. Categorical variables are presented by the absolute frequency with their corresponding absolute percentage. Descriptive characteristics among patients who developed renal complications and those without renal complications during hospitalization were compared using the Student t test or Wilcoxon signed-rank test, which one is appropriate. Categorical variables were compared with the Chi-square test. To evaluate the changes in our included biochemical variables during hospitalization, we used ridgeline plots for the normalized variables to compare their density distribution among follow-ups. To explore the conditions associated with the incidence of renal complications during hospitalization, we fitted Cox proportional hazard regression models to explore the role of demographic, clinical, anthropometric, and biochemical characteristics. Time to event was considered the time from admission to the development of any renal complication during hospitalization. The final models were selected according to the lowest Bayesian Information Criteria (BIC). Variance Inflation Factor (VIF) >5 was considered as a model with multicollinearity in its estimation. All statistical analyses were performed in RStudio (version 4.1). P<0.05 was statistically significant.

Results

Study population

We recorded information from 165 children who had filled our selection criteria. Table 1 presents the complete demographic, renal comorbidities, and baseline laboratory information stratified by patients developing renal complications. We observed a female predominance (50.9%) with Mean±SD age of 8.02±6 years with population range between 6 months and 18 years, and a high proportion of patients from the urban area (81.5%). Intense care admission was registered in 25 (15.15%) of our total studied populations with a median length of 4 days (IQR: 3-7). Lethality was recorded in only 1patient (0.58%) caused by an extensive respiratory failure and mixed shock. The main symptoms presented in our population were fever (55.15%), diarrhea (17.58%), and vomiting (22.42%) (Table 2).

Renal complications during hospitalization

From the total included population, we identified 29 patients (17.6%) who developed renal complications during hospitalization in the emergency room department and intensive care unit. In these patients, 12 (41.3%) developed proteinuria, 10 (34.5%) developed AKI (AKIN-1 in 26.6%, AKIN-2 in 40% and AKIN-3 in 33.3%), 5 (17.2%) had arterial hypertension, 2 (6.9%) required renal replacement therapy, 4 (13.8%) had hematuria, and only 1 (3.4%) developed a rapidly progressive glomerulonephritis. According to our concept of renal complications, 18 (62.1%) had at least 1 of the mentioned complications, 6 (20.7%) had 2 combined complications, and 5 (17.2%) had more than 3 combined complications. We observed that patients who developed renal complications were older (mean age: 10.9±6.2 years), with a higher body mass index (median: 20.3, IQR: 17.1-27.6 kg/m^2), plasmatic creatinine (median: 0.5, IQR: 0.35-0.67 mg/dL) with a range of 0.20 to 3.7 mg/dL at admission, 0.30 to 2.48 mg/dL at three days of admission, 0.48 to 1.9 mg/dL at seven days of admission and 0.44 to 2.1 mg/dL at discharge and calcium levels (median: 8.2, IQR: 7.8-8.9 mg/dL) (Table 1). We observed no differences in symptom presentation between patients with renal complications and those without the event (Table 2).

Biochemical evaluation at follow-up

We analyzed our selected biochemical variables during hospitalization and observed that patients with renal complications had lower levels of serum calcium (P=0.001) compared to patients without any renal complications. At the follow-up, only serum creatinine and potassium showed higher levels after 1 week of hospitalization in patients with renal complications. Finally, all biochemical characteristics were similar among both groups at discharge except for two patients who continued with elevated serum creatinine (Figure 1).

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Table 1. Clinical characteristics in pediatric patients with SARS-CoV-2 infection

Parameters	Total Population (n=165)	With Renal Complication (n=29)	Without Renal Complication (n=136)	P
Age (y) (Mean±SD)	7.75±5.9	10.52±6.29	7.15±5.67	0.009
Female, No. (%)	84(50.91)	17(58.62)	67(49.26)	0.477
Metropolitan area, No. (%)	135(81.82)	23(79.31)	112(82.35)	0.904
Other states, No. (%)	30(18.18)	6(20.69)	24(17.65)	
Body mass index (kg/m^2)	17.31 (14.65-21.3)	20.2848 (16.847-27.548)	17.0381 (14.354-20.789)	0.015
One or more comorbidity, No. (%)	111(67.27)	17(58.62)	94(69.12)	0.381
Asymptomatic, No. (%)	24(14.5)	4(13.79)	20(14.71)	0.812
With ≥1 symptom, No. (%)	141(85.5)	25(86.21)	116(85.29)	0.912
Heart rate (bpm)	125 (100-147)	125 (96-140)	124.5 (100-150)	0.291
Respiratory rate (bpm)	26 (21-36)	30 (23-42)	25.5 (21-36)	0.514
Pulse oximetry (%)	95 (89-96)	92 (86-96)	95 (91.75-97)	0.082
Systolic arterial pressure (mm Hg)	107 (95-118)	109 (98-118)	107 (95-117.25)	0.339
Diastolic arterial pressure (mm Hg)	68 (59-74)	65 (59-72)	68 (59-75)	0.533
Intensive care unit, No. (%)	25(15.15)	11(37.93)	14(10.29)	<0.001
Time in an intensive care unit (d)	4 (3-7)	7 (4-9)	3.5 (2.25-6)	0.038
Uric acid (%)	3.9 (3-5.2)	4.2 (3-6.2)	3.9 (3-5.1)	0.423
Blood urea nitrogen (%)	12 (8.6-16.66)	12 (9.7-17)	11.98 (8.6-16.66)	0.481
Plasmatic creatinine (mg/dL)	0.5 (0.35-0.67)	0.6 (0.38-0.84)	0.48 (0.35-0.633)	0.0603
Sodium (mg/dL)	138 (136-141)	138 (136-141)	139 (136-141)	0.919
Potassium (mg/dL)	4.1 (3.7-4.5)	4.1 (3.8-4.4)	4.1 (3.7-4.5)	0.801
Chloride (mg/dL)	103 (100-105)	103 (101-104)	103 (100-105)	0.950
Phosphorus (mg/dL)	4.4 (3.6-5.2)	4.3 (3.5-5.2)	4.4 (3.6-5.2)	0.897
Calcium (mg/dL)	8.5 (8.1-9.5)	8.3 (7.8-9)	8.6 (8.2-9.6)	0.025
Magnesium (mg/dL)	2.1 (1.9-2.3)	2 (1.8-2.2)	2.1 (1.975-2.3)	0.504

Predictors of renal complications

In the Cox regression model, we found that age (Hazard Ratio [HR]: 1.08, 95% CI: 1.02-1.57, P=0.009) and intensive care unit admission (HR: 3.45, 95% CI: 1.60-7.41, P<0.001) were the conditions associated with the development of any renal complications during hospitalization by adjusting the number of comorbidities and the number of symptoms at baseline (Table 3). Finally, we model the effect of age on the risk of developing any renal complication. We found an exponential growth in the hazard effect of age, in which older pediatrics are at the highest risk for renal complications compared to the youngest (Figure 2).

Discussion

In this work, we performed a retrospective cohort study of 165 hospitalized children with SARS-CoV-2 infection in a tertiary medical hospital in Mexico City. We observed that 17.6% of our study population developed renal complications, in which significant pro-

Table 2. Prevalence of symptoms reported at hospital admission in pediatric patients with SARS-CoV-2 infection

Parameters	No. (%)			P
	Total Population (n=165)	Without Renal Complications (n=136)	With Renal Complications (n=29)	
Cough	36(21.82)	27(19.85)	9(31.03)	0.308
Dyspnea	10(6.06)	7(5.15)	3(10.34)	0.322
Odynophagia	11(6.67)	7(5.15)	4(13.79)	0.179
Respiratory difficulty	11(6.67)	7(5.15)	4(13.79)	0.133
Fever	91(55.15)	74(54.41)	17(58.62)	0.915
Anosmia	1(6.06)	1(5.15)	0(10.34)	0.981
Myalgia,	8(4.85)	8(5.88)	0(0)	0.981
Conjunctivitis	8(4.85)	8(5.88)	0(0)	0.981
Asthenia	17(10.3)	14(10.29)	3(10.34)	0.981
Rhinorrhea	20(12.12)	14(10.29)	6(20.69)	0.389
Nasal congestion	1(0.61)	0(0)	1(3.45)	0.457
Abdominal pain	32(19.39)	28(20.59)	4(13.79)	0.336
Vomiting	37(22.42)	30(22.06)	7(24.14)	0.782
Nausea	8(4.85)	7(5.15)	1(3.45)	0.915
Diarrhea	29(17.58)	25(18.38)	4(13.79)	0.775
Skin manifestations	13(7.88)	11(8.09)	2(6.9)	0.925
Headache	20(12.12)	14(10.29)	6(20.69)	0.389

teinuria and AKI were the most commonly observed events. We detected that pediatrics with renal complications tended to have selected biochemical alterations at admissions, such as higher plasma creatinine and decreased serum calcium. Finally, we found that older age and being hospitalized in an intensive care unit were conditions associated with a higher risk of renal complications. Our findings suggest that renal complications are a relatively frequent manifestation and are associated with a higher risk in older and critically ill pediatrics.

At the beginning of the COVID-19 pandemic in Mexico, the most affected population with severe complications due to SARS-CoV-2 was mostly adult patients. Nevertheless, pediatrics also showed vulnerability in developing complications caused by the disease. In our study, the most common renal complications were proteinuria and AKI. A retrospective study by Basalely et al. reported an incidence of AKI in 8.2% of hospitalized pediatrics [7]. In a recent systematic review conducted by Raina et al., the authors estimated that SARS-CoV-2 infection increases the risk of AKI between 1.3% and 44%, which was consistent with our

Table 3. Cox proportional hazard regression model to evaluate the risk for renal complications

Variables	Z	Hazard Ratio	95% CI	P
Age (y)	2.578	1.08	1.02-1.57	0.009
Intensive Care Unit	3.180	3.45	1.60-7.41	0.001

Adjustment covariates: sex, number of comorbidities, and number of symptoms.

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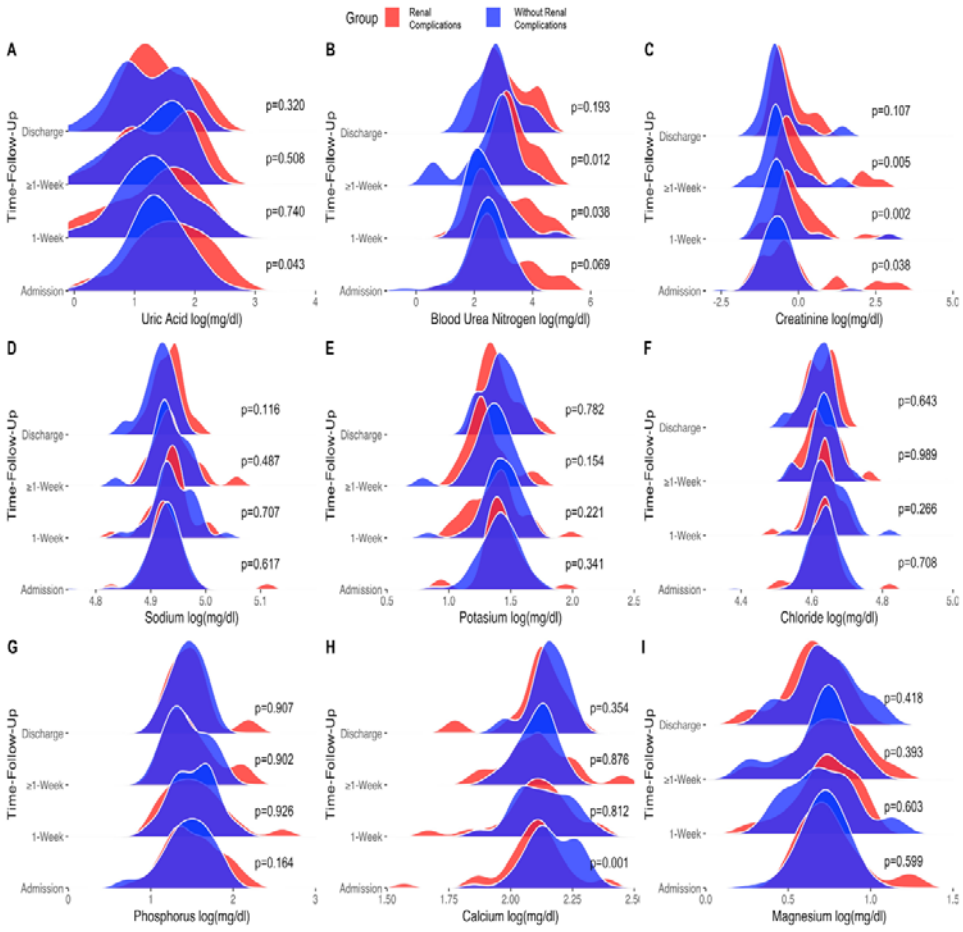

Figure 1. Biochemical characteristics of hospitalized pediatric patients due to COVID-19 stratified by incident renal complications outcome

study, where AKI was reported at 34.5% [8]. The hypothesis that can explain the physiopathology between SARS-CoV-2 infection with renal complications is primarily related to the expression of ACE-2 receptors in the kidney parenchyma affecting tubular epithelial cells and causing loss of brush border and non-isometric vacuolization [11]. Other hypotheses suggest that AKI may be explained by acute tubular necrosis because pediatrics tends to have a high proportion of renal tubular protein in urine protein electrophoresis [12]. Another proposed mechanism for kidney injury can be secondary dehydration caused by extensive volume loss by vomiting, diarrhea, or reduced fluid intake [13]. In our population, these symptoms mainly were reported at admission.

Another finding was proteinuria in 41.3% of cases; the exact mechanism of proteinuria is not well explained. Other studies have shown that proteinuria is higher when measured without dipsticks because it is more sensitive to albuminuria than tubular proteinuria. Also, they found that proteinuria was mainly formed from tubular proteins; this finding can be attributed to the higher expression of ACE-II receptors in tubular cells, which can be directly infected by the SARS-CoV-2 virus, causing damage and necrosis [14]. Our study measured quantitative proteinuria, which may explain its higher incidence. The exact cause of proteinuria needs further investigation. A systematic review showed that patients with proteinuria were at a higher risk of death than patients without proteinuria [15].

A mild clinical course has been reported in the pediatric population with COVID-19 compared to the adult population. We collected routinely recorded biochemical parameters and found that only serum calcium and creatinine showed significant changes at admission. These findings are supported by previous reports, where hypocalcemia is a common finding in hospitalized pediatrics with SARS-CoV-2 infection; other viral infections such as Ebola can cause hypocalcemia. However, it cannot be differentiated whether hypocalcemia is caused by the infection or by kidney injury.

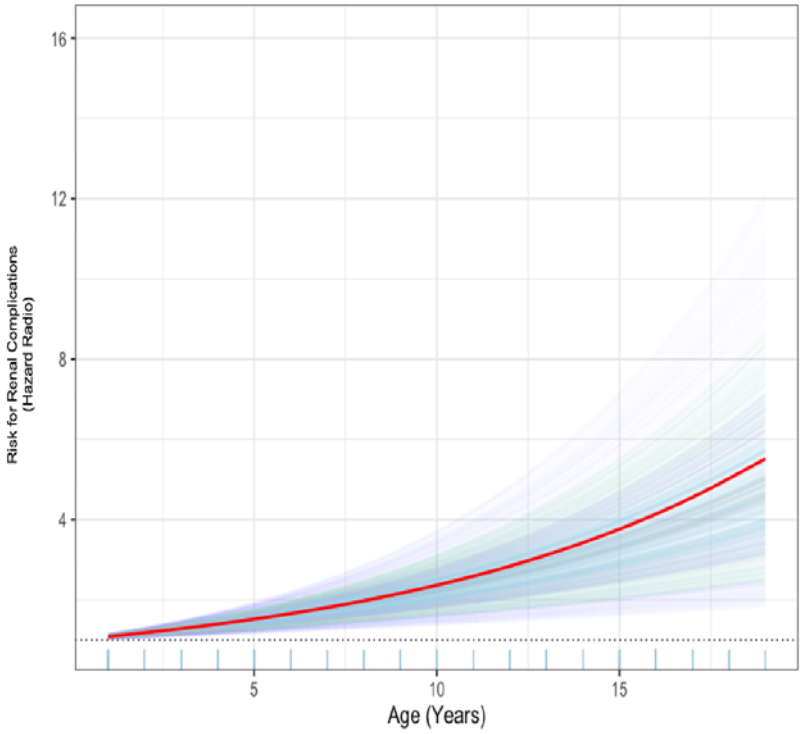

Figure 2. Simulation plot to evaluate the risk for renal complications using age as the main predictor in hospitalized pediatric patients due to COVID-19

Some authors suggested that Parathyroid Hormone (PTH) can be inhibited by proinflammatory cytokines in patients with COVID-19 [16]. This theory cannot explain hypocalcemia in our study because we did not measure the PTH. Nevertheless, as observed in previous reports, certain conditions can exacerbate the risk of severe complications of COVID-19. In our studied population, most of our children had previously reported comorbidities, 13 of 29 children with renal complications showed overweight and obesity with BMI >P85 according to age. Additionally, older pediatrics had the highest risk for renal complications because it could be a link between increased age and the development of chronic comorbidities, which has been proven to be a known risk factor in adults. Some studies have suggested that in children older than 6 years, the risk of adverse outcomes of COVID-19 is higher [17]. We observed that 11 of 29 children with COVID-19 and renal complications developed it during the intensive care unit hospitalization, making it a risk factor for renal complications [18].

Our study suggests possible risk factors associated with SARS-CoV-2 infection and the development of renal complications. We must emphasize that the hospital is a tertiary medical unit and a reference center for children with SARS-CoV-2 infection, which made it possible to conduct this clinical research. On the other hand, we also recognize the limitations. Our sample size is limited to the study period in which we collected our information, which may not reflect the diverse dynamics of SARS-CoV-2 variants in our country. There are different criteria or clinical scales to determine AKI. According to the AKIN criteria, the AKI estimation in our study was done only with serum creatinine without urine output; therefore, the incidence of such kidney involvement can be underestimated.

Conclusion

COVID-19 pandemic is far from over; therefore, it is important to investigate and understand more about this disease. Children have lower complications than adults; nevertheless, it is essential to investigate more how they affect the pediatric population. In our study, the main renal complications in children are proteinuria and AKI, and older age and hospitalization in the intensive care unit are factors predicting renal involvement.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics and Investigation Committee of Hospital Infantil de México (HIM, 2020-031).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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