Original Article

Acute kidney Injury in Egyptian Children during COVID-19 Pandemic: A Single Center Study

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ABSTRACT

Introduction: Acute kidney injury (AKI) has emerged as a common complication of COVID-19 pandemic affecting (17 - 37 %) hospitalized patients. But it is not clear whether COVID-19 influenced the epidemiology of AKI irrespective of the infectious status or not.
Aim of the study: To cover AKI patterns during the pandemic.
Methods: This retrospective cohort study was conducted on 50 pediatric patients diagnosed as AKI according to the p-RIFLE criteria, who were admitted at the Nephrology Unit, Pediatric Department, Tanta University Hospitals between January 2020 and June 2023. These patients were subjected to full history taking, full examination and laboratory investigations including (CBC, serum creatinine, urea, D-dimer, CRP, LDH, COVID-19 PCR), renal biopsy and radiological investigations (CT chest, MRI brain).
Results: Among the studied patients, the average age was 5.5 years, with a male-to-female ratio (1.7:1.0). 70% of AKI patients required renal replacement therapy; the survival rate was 86%. At discharge, a significant improvement was noted in serum creatinine, hemoglobin, and platelet counts ($p < 0.001$). The median age of deceased patients (14%) was significantly lower (1.0 years) compared to survivors (7.0 years). Elevated D-dimer levels were observed in 100% of deceased patients, correlating with worse outcomes.
Conclusions: This study revealed a significant increase in AKI incidence between pediatric patients during the COVID-19 pandemic, with poor outcomes in young female children (<5yrs) who had higher D-dimer levels.
Keywords: Acute renal injury (AKI), Egyptian children, COVID -19.

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INTRODUCTION

Acute kidney injury (AKI) is a sudden decline of kidney function that includes both structural damage and impairment. It is classified as pre-renal, renal, and post-renal depending on the mechanism that causes the injury: decreased renal perfusion, direct renal tissue injury, or obstruction of urinary system.[1] AKI is a diverse group of disorders with a common definition and severity classification including, The Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) and AKI Network (AKIN) criteria and studies on risk linkages which are considered the foundations for KDIGO definition and staging. [2, 3]

Corona virus spread from 2019 to 2022, with a pandemic declared in March 2020. Virus effects range from mild respiratory symptoms to multi organ failure and a high mortality rate.[4] The clinical course of coronavirus disease (COVID-19) in children has been described as generally benign until recently, it has been shown that a fraction of children infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can develop multisystem inflammatory syndrome in children (MIS-C), which is characterized by systemic hyper inflammation, fever, and multisystem organ failure. [5]

The actual pathogenic mechanism driving COVID-19 disease renal involvement remains unknown, however, it may be due to one of these mechanisms: **The first mechanism** could be directly by the initial role of the virus on the angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed by several types of human cells such as alveolar epithelial cells (the main target), bronchiolar epithelial cells and lung vascular cells including endothelium and arterial smooth muscle cells. In addition to lungs, ACE2 receptors are expressed in organs such as heart (myocardial cells) and kidney (proximal and distal tubular cells, visceral and parietal epithelial cells of renal tissue glomerulus, as well as interlobular artery components smooth muscle cells and endothelium).[6] Kidney cells also express trans membrane protease serine 2 (TMPRSS2); an enzyme that proteolytically cleaves ACE2 and is essential for the viral entry.[7]

The second mechanism by which Covid-19 can affect the kidney through the immune system. A cytokine storm that follows a viral infection is another method that can affect the kidney both directly and indirectly by causing sepsis, shock, hypoxia, and rhabdomyolysis.

The third mechanism is the development of micro thrombi in Covid19 patients, which can result in acute ischemia and AKI (TMA). [8]

METHODS

This retrospective cohort study was conducted on 50 pediatric patients diagnosed with AKI according to the p-RIFLE criteria **Table 1**, who were admitted to the Nephrology Unit, Pediatric Department, Tanta University Hospitals. we excluded patients with CKD stage V and patients with ESRD on regular hemodialysis.

All the patients were subjected to the following: complete history taking including age, sex, and family history. Clinical manifestations: AKI manifestations (changes in the color and amount of urine, signs of uremic encephalopathy, and volume overload) and

manifestations suspecting COVID-19 infection. Clinical examination including vital signs, systematic examination including (cardiovascular system, respiratory system, gastrointestinal and central nervous system).

Laboratory investigations were done including complete blood count (CBC), serum creatinine and Blood urea nitrogen (BUN), C-reactive protein (CRP), serum Na and k, arterial blood gases, urine analysis, serum lactic dehydrogenase (LDH), D-dimer, liver enzymes, COVID-19 PCR and renal biopsy. Imaging was done including CT Chest brain CT, and MRI.

Statistical analysis

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using numbers and percentages. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative parametric data were described using range (minimum and maximum), meaning, and standard deviation. Quantitative non-parametric data was presented as median and interquartile range (IQR). The significance of the results obtained was judged at the 5% level. The tests used were Chi-square test, Fisher's Exact Student t-test, Mann Whitney test, Paired t-test, Wilcoxon signed ranks test.

Table 1: Pediatric RIFLE criteria of AKI. [33]

Pediatric RIFLE	S. Creatinine	Urine output
Risk	GFR decreased >25%	UO<0.5 ml/kg/hr For 8 hours
Injury	GFR decreased >50%	UO<0.5 ml/kg/hr For 12 hours
Failure	GFR decreased >75%	UO<0.3 ml/kg/hr For 24 hours Or Anuria for >12 hr
Loss End-stage	Persistent failure > 4 weeks Persistent failure > 3 months	

GFR: glomerular filtration rate, UO : urine output

RESULTS

This study consisted of 54.0% males (27 patients) and 46.0% females (23 patients), yielding a male-to-female ratio of 1.17:1.0, their ages ranged from 1 to 16 years, with a median age of 6.5 years. 16.0% of patients have a history of chronic glomerulonephritis. The median hospital stay was 6 weeks, and 40.0% of patients required ICU admission. **Table 2.**

All patients exhibited renal manifestations. Specifically, edema was observed in 35 patients (70%), oliguria was noted in 20 patients (40%), and hypertension was present in 15 patients (30%). Gastrointestinal manifestations were prevalent in 38 patients (76%), with diarrhea affecting 25 patients (50%), vomiting occurring in 20 patients (40%), and abdominal pain reported in 12 patients (24%). Fever was recorded in 34 patients (68%), while respiratory manifestations were observed in 26 patients (52%). Neurological manifestations were noted in 19 patients (38%), with 12 patients (24%) having convulsions and 10 patients (20%) developed disturbed consciousness level (DCL). **Table 2.**

The most common cause of AKI was hemolytic uremic syndrome HUS (50%), 18 patients (36%) had diarrhea-positive (HUS), while 7 patients (14%) had diarrhea-negative (HUS). Followed by post-infectious AKI (28%), additionally, 8 patients (16%) had AKI on top of chronic

glomerulonephritis, and 3 patients (6%) presented with acute tubular necrosis. **Figure 1**.

The initial laboratory data at admission revealed severe anemia, thrombocytopenia, and leukocytosis with elevated reticulocytes and schistocytes. There was significant renal impairment (median creatinine 4.0 mg/dl), elevated liver enzymes (ALT median 33.0 U/l, AST median 38.5 U/l), and elevated inflammatory markers (D-dimer median 2.50 mg/dl, CRP median 6.0 mg/dl, LDH median of 300.0 U/L). Potassium levels were within the normal range (median 4.0 mmol/l), while sodium levels were at the lower limit of normal (median 132.5 mmol/l) (dilutional hyponatremia). There was a marked improvement in laboratory parameters from the initial presentation to discharge among the patients studied. Specifically, both urea and creatinine levels significantly decreased, ($p< 0.001$). The increase in hemoglobin levels ($p = 0.008$) and platelet counts ($p < 0.001$), total leukocyte count (TLC) showed a significant decrease from an initial mean of 13.14 ± 7.89 c/mm³ to 7.19 ± 2.07 c/mm³ at discharge ($p < 0.001$), decrease in reticulocyte counts ($p < 0.001$). Sodium levels also showed a significant rise ($p < 0.001$), while potassium levels remained stable ($p = 0.762$). Furthermore, there is a significant decrease in liver enzymes (ALT and AST). Notably, D-dimer levels exhibited a remarkable reduction ($p < 0.001$). **Table 3**

The majority of patients (90%) tested negative for COVID-19 PCR, inspite of having definite manifestations of COVID-19. while a smaller proportion (10%) tested positive. Thus PCR has low specificity.

Among studied patients who had MRI brains, 8% exhibited findings consistent with (PRES) and another 8% showed normal results. Additionally, brain edema was observed in 6% of patients. For CT chest imaging, 76% of patients did not undergo the procedure, while 8% were classified as CORAD 3, 10% as CORAD 4-5, and 6% exhibited pulmonary edema. **Table 4**

Renal biopsy findings in the studied patients showed thrombotic microangiopathy as the predominant pathology (32.0%), with acute tubular injury observed in 14.0% of patients and crescentic glomerulonephritis in 8.0%. **Table 4** Only 50% of patients did renal biopsy due to limitations in doing the maneuver.

The treatment lines of the studied patients revealed that the majority required plasma transfusion (74.0%) and renal replacement therapy (70.0%), with notable use of antihypertensive drugs (30.0%), antiepileptic drugs (24.0%), and a small percentage receiving eculizumab (6.0%) and requiring CRRT sessions (4.0%). **Table 5**

The survival rate was 86%, while 14% of the patients unfortunately passed away during their hospital stay. Among the patients studied 10% developed CKD and 4% progressed to ESRD. **Table 5**

Among the 7 patients who died, the median age was 1.0 years (IQR: 1.0–10.0), with a mean hospitalization time of 10.80 days (SD: 3.24). The majority of the patients were female (85.7%), with a male-to-female ratio of 1:6. The median weight was 10.0 kg (IQR: 9.0–35.0) and the mean height was 114.1 cm (SD: 17.28). Diagnoses included diarrhea-positive HUS (14%), diarrhea-negative HUS (28%), MIS-C (28%), and AKI with chronic glomerulonephritis (28%). Two patients

(28%) had a positive PCR for COVID-19. All patients received renal replacement therapy and plasma transfusions, while 71% underwent PRBC transfusions. Treatment included antihypertensive drugs (28%), antiepileptics (57%), and plasmapheresis (57%). The causes of death were pulmonary hemorrhage (28%), pulmonary edema due to volume overload (28%), CNS symptoms in atypical HUS (14%), and sepsis related to MIS-C (28%). **Table 6**

There were significant differences in demographic data between patients who survived and those who are deceased. There was a notable predominance of female patients among those who died, with a female-to-male ratio indicating a higher mortality risk in females (85.7% vs. 14.3% for males). The median age of deceased patients (1.0 years) was significantly lower than that of survivors (7.0 years). Additionally, deceased patients had lower median weights (10 kg vs. 27.0 kg) and the mean height of deceased patients (114.1 cm) was significantly lower than that of survivors (127.8 cm). **Table 7**

Significant associations were noticed between mortality outcomes and elevated D-dimer, LDH, and CRP levels, indicating their potential roles as biomarkers for severity in pediatric patients with acute kidney injury, while lymphopenia and COVID-19 PCR results do not show a strong correlation with mortality. **Table 8**

Table 2: Demographics of the patients studied (n = 50).

Data	N0. % 50. (100%)
Min. – Max.	1.0 – 16.0
Median (IQR)	6.50 (1.90 – 12.0)
Sex (N %)	
Male	27 (54.0%)
Female	23 (46.0%)
M: F ratio	1.17: 1.0
Weight (kg)	
Min. – Max.	9.0 – 65.0
Median (IQR)	22.50 (12.0 – 38.0)
Height (cm)	
Min. – Max.	97.0 – 157.0
Median (IQR)	129.0 (110.0 – 140.0)
History of renal diseases	
Chronic glomerulonephritis	8 (16.0%)
Hospital stays (weeks)	
Min. – Max.	1.0 – 10.0
Median (IQR)	6.0(4.0 – 7.0)
Critical cases (ICU admission)	20 (40.0 %)
Clinical manifestations, n (%)	
1. Renal	**50(100%)**
▪ Edema	35(70%)
▪ Oliguria	20(40%)
▪ HTN	15(30%)
2. GIT manifestation	38(76%)
▪ Diarrhea	25(50%)
▪ vomiting	20(40%)
▪ Abdominal pain	12(24%)
3. Fever	34(68%)
4. Respiratory manifestation	26(52%)
5. Neurological	19(38%)
▪ convulsions	12(24%)
▪ DCL	10(20%)

IQR: Inter quartile range, ICU: Intensive care unit, DCL: disturbed conscious level, HTN: hypertension

Table 3: Laboratory data of patients at initial presentation and discharge.

Laboratory data	At initial presentation	At discharge		*P*
Hgb(g/dl)				
Min. – Max.	3.40 – 13.20	8.20 – 14.0	t= 2.786*	0.008
Mean ± SD.	8.63 ± 1.94	9.74 ± 1.29		
Platelets (c/mm3)				
Min. – Max.	56.0 – 440.0	87.0 – 500.0	Z= 3.532*	<0.001*
Mean ± SD.	145.7 ± 85.69	212.51 ± 101.22		
Total Leucocytic Count (c/mm3)				
Min. – Max.	2.70 – 33.80	4.0 – 11.30	Z= 4.166*	<0.001*
Mean ± SD.	13.14 ± 7.89	7.19 ± 2.07		
Reticulocytes %				
Min. – Max.	2.0 – 15.60	0.16 – 2.10	Z= 5.712*	<0.001*
Median (IQR)	4.05 (3.30 – 5.50)	0.80(0.50 – 1.0)		
Urea (mg/dl)				
Min. – Max.	54.0 – 345.0	16.0 – 67.0	Z= 5.712*	<0.001*
Median (IQR)	150.0 (112.0 – 240.0)	42.0(27.50 – 55.0)		
Creatinine (mg/dl)				
Min. – Max.	1.20 – 12.50	0.27 – 2.0	Z= 5.712*	<0.001*
Median (IQR)	4.0 (2.70 – 5.70)	0.70(0.50 – 0.80)		
Sodium (mmol/l)				
Min. – Max.	120.0 – 145.0	130.0 – 145.0	t= 6.162*	<0.001*
Median (IQR)	132.5 (127.0 – 135.0)	137.0 (133.50–140.0)		
Potassium (mmol/l)				
Min. – Max.	2.0 – 6.70	3.66 – 6.0	t= 0.304	0.762
Median (IQR)	4.0 (3.38 – 4.75)	4.0 (3.90 – 4.40)		
ALT (U/l)				
Min. – Max.	11.0 – 465.0	16.0 – 77.0	Z= 2.545*	0.011*
Median (IQR)	33.0 (22.0 – 65.0)	30.0 (23.0 – 33.5)		
AST(U/l)				
Min. – Max.	12.0 – 3900.0	18.0 – 56.0	Z= 3.304*	0.001*
Median (IQR)	38.50 (28.0 – 88.0)	33.0 (28.5 – 40.0)		
D dimer (mg/dl)				
Min. – Max.	0.20 – 23.0	0.10 – 10.0	Z= 5.579*	<0.001*
Median (IQR)	2.50 (1.40 – 6.38)	0.50 (0.25 – 0.55)		
LDH (U/L)				
Min. – Max.	200.0-1161.0	150.0-250.0		
Median (IQR)	300.0(270.0- 370.0)	205.0(180.0-250.0)	Z= 5.516	<0.001*
Arterial Blood Gases				
pH				
Min. – Max.	7.10-7.50	7.35-7.46		
Mean ± SD.	7.31±.09	7.44±.03	t= -0.954	<0.001*
HCO3 (mEq/L)				
Min. – Max.	5.9-22.6	21.0-28.0		
Mean ± SD.	13.7±4.0	22.4±2.1	t= -13.863	<0.001*
PaCO2 (mmHg)				
Min. – Max.	12.0-37.0	30.0-45.0		
Mean ± SD.	23.8±6.1	39.7±3.7	t= -14.754	<0.001*

IQR: Inter quartile range. Z: Wilcoxon signed ranks test, t: Student t-test Paired T-test. p: p-value for comparing between initial laboratory data and laboratory data at discharge. *: Statistically significant at $p \leq 0.05$.

Table 4: Radiological investigation and renal biopsy findings of the patients studied.

	No.%
MRI brain	
Not done	39(78.0%)
Normal	4(8.0%)
PRES (posterior reversible encephalopathy)	4(8.0%)
Brain edema	3(6.0%)
CT chest	
Not done	38(76.0%)
CORAD 3	4(8.0%)
CORAD 4-5	5(10.0%)
Pulmonary edema	3(6.0%)
Renal biopsy	
Renal biopsy	27(54.0%)
Thrombotic microangiopathy	16(32.0%)
Acute tubular necrosis	7(14.0%)
Crescentic Glomerulonephritis	4(8.0%)

CORAD: COVID-19 Reporting and Data system scoring.

Table 5: Treatment and outcome of patients

	No. %
Treatment	
Plasma transfusion	**37 (74.0%)**
Renal replacement therapy	**35 (70.0%)**
Hemodialysis	33 (66.0%)
CRRT	2 (4.0%)
PRBCs transfusion	**28 (56.0%)**
Anti-hypertensive drugs	**15 (30.0%)**
Anti-epileptic drugs	**12 (24.0%)**
Plasmapheresis	**12 (24.0%)**
Steroids	**10 (20.0%)**
Eculizumab	**3 (6.0%)**
Outcome	
Survival	**43 (86.0%)**
Complete recovery	36 (72.0%)
CKD	5 (10.0%)
ESRD	2 (4.0%)
Mortality	**7 (14.0%)**

CRRT; continuous renal replacement therapy, PRBCs: packed red blood cells, CKD: Chronic kidney disease, ESRD: End stage renal disease.

Table 6: Morality data (n=7).

Age in years median) IQR)	1.0(1.0-10.0)
Time in days (mean±SD.)	10.80±3.24
Sex (N. %)	
Males	1(14.3%)
Females	6(85.7%)
Male/female ratio	1: 6
Weight in kg	
(median) IQR)	10.0(9.0-35.0)
Height in cm	
(mean ± SD.)	114.1 ± 17.28
Diagnosis (N. %):	
Diarrhea positive HUS	1(14%)
Diarrhea negative HUS	2(28%)
MIS-C	2(28%)
AKI on top of chronic glomerulonephritis	2(28%)
PCR for COVID (N. %):	
Positive	2(28%)
Negative	5(71%)
Treatment (N. %):	
Renal replacement therapy	7(100%)
PRBCs transfusion	5(71%)
Plasma transfusion	7(100%)
Antihypertensive drugs	2(28%)
Antiepileptics	4(57%)
Plasmapheresis	4(57%)
Cause of death (N. %):	
Pulmonary hemorrhage	2(28%)
Pulmonary edema (volume overload)	2(28%)
CNS symptoms in atypical HUS	1(14%)
Sepsis (MIS-C)	2(28%)

MIS-C: Multisystem inflammatory syndrome in children, HUS: hemolytic uremic syndrome.

Table 7: Comparison between survived & deceased patients according to demographics data.

	Survived (n = 43)		Deceased (n = 7)		Test of Sign	P
	No.	%	No.	%		
Sex						
Male	26	60.5	1	14.3	$\chi2$= 5.168*	FEp =0.039*
Female	17	39.5	6	85.7		
Age (years)						
Median (IQR)	7.0(2.0-12.0)		1.0(1.0-10.0)		U= 64.0*	0.014*
Weight (kg)						
Median (IQR)	27.0(12.0-43.0)		10.0(9.0-35.0)		U= 82.500	0.056
Height (cm)						
Mean ± SD.	127.8 ± 16.46		114.1 ± 17.28		t= 2.029*	0.048*

SD: Standard deviation, U: Mann Whitney test, t: Student t-test,$\chi2$: Chi-square test, FE: Fisher Exact
p: p-value for comparing between No and Yes, *: Statistically significant at $p \leq 0.05$.

Table 8: Comparison between survived and deceased patients according to biomarkers and clinical variables.

	Survived (n = 43)		Deceased (n = 7)		□□	FEp
	No.	%	No.	%		
D -dimer						
Elevated	24	55.8	7	100.0	4.989*	0.035*
Not elevated	19	44.2	0	0.0		
LDH						
Elevated	4	9.3	6	85.7	21.968*	<0.001*
Not elevated	39	90.7	1	14.3		
CRP						
Positive	19	44.2	7	100.0	7.513*	0.010*
Negative	24	55.8	0	0.0		
Lymphopenia						
Positive	28	65.1	4	57.1	0.166	0.692
Negative	15	34.9	3	42.9		
PCR for COVID						
Positive	3	7.0	2	28.6	3.119	0.138
Negative	40	93.0	5	71.4		

χ2: Chi-square test, FE: Fisher Exact, p: p-value for comparing between No and Yes. *: Statistically significant at p ≤ 0.05.

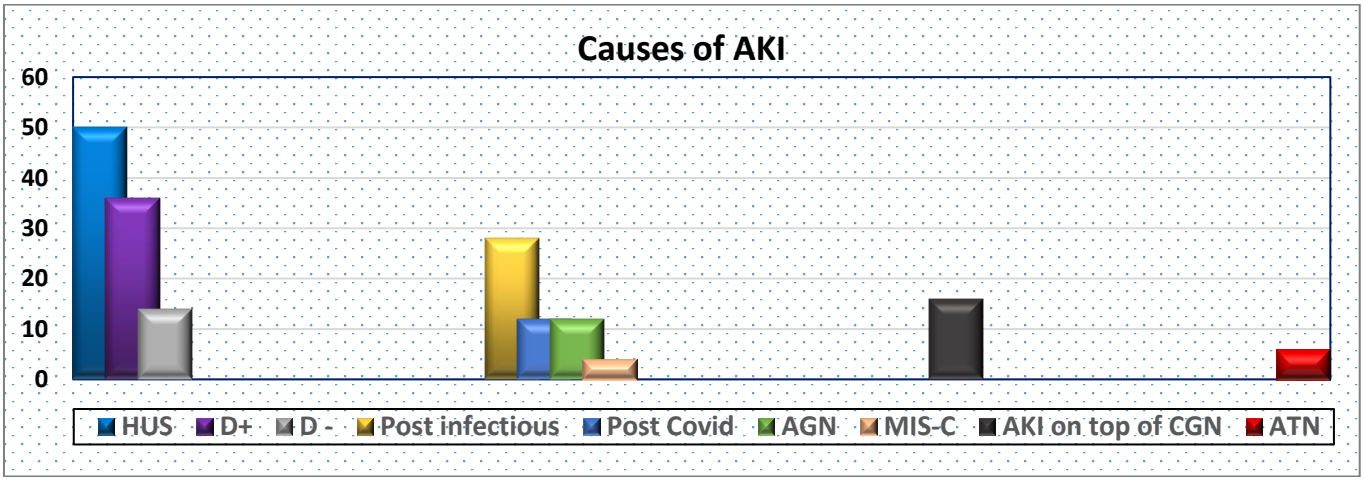

Figure 1: Causes of AKI.

DISCUSSION

The COVID-19 pandemic has had profound effects on kidney health, with acute kidney injury (AKI) emerging as a significant complication among hospitalized patients. AKI, associated with increased mortality, has been exacerbated by COVID-19 due to factors like hemodynamic instability, inflammatory responses, coagulation abnormalities, and potential direct viral impacts on the kidneys. [9]

The pandemic caused widespread disruptions in healthcare systems, affecting the management of both COVID-19 and other conditions. This includes alterations in the care of non-COVID-19 patients, potentially influencing the outcomes of kidney-related diseases, including AKI. [9]

In this present study, 54% of the patients were males and 46% were females, resulting in a male-to-female ratio of 1.17:1.0 the ages of the patients ranged from 1 to 16 years, which is consistent with the findings of Wasiu A. Olowu,[10] who reported the age of their populations at presentation was ranging from 0.05 to 16 years. The male-to-female ratio in their study varied from 1.38 to 2.5:1.0.[10] Similarly, Anirban et al.[11] who observed a male-to-female ratio of 1.07:1.0 in their studied patients. [11]

The median length of hospital stay for the studied patients was 6 weeks (42 days),

with a range of 1 to 10 weeks. In contrast, Chisavu et al.[12] who reported an average hospitalization period of 20.9 ± 19.3 days among 2,194 confirmed acute kidney injury (AKI) cases from July 1, 2014, to December 31, 2021. This indicates that the patients studied had a significantly longer median stay compared to the average duration reported by Chisavu et al. [12]

In this study, gastrointestinal manifestations represented 76% of the patients, and diarrhea was observed in 25 children, accounting for 50% of the study population. Findings can be attributed to the fact that the majority of our patients were associated with hemolytic uremic syndrome (HUS). Typical cases of HUS often present with diarrhea, while atypical cases primarily manifest with abdominal pain. Fever was prevalent in 68% of the children studied, indicating a significant systemic response to the underlying infection. Respiratory manifestations were noted in 52% of the patients.

Neurological manifestations were observed in 38% of our patients studied. This finding can be justified by the fact that approximately 30% of hemolytic uremic syndrome (HUS) cases present neurological symptoms at initial diagnosis. These neurological complications may be related to multiple factors such as hypertension, uremic encephalopathy, and disturbances of electrolyte levels. [13]

Regarding the prevalence of causes of acute kidney injury (AKI), the most common cause among our patients was hemolytic uremic syndrome (HUS), accounting for 50% of cases, followed by post-infection causes at 28%. AKI occurring on top of chronic glomerulonephritis was identified in 16% of the patients, while acute tubular necrosis was the least common cause, representing only 6% of the total. This aligns with the findings of Keenswijk et al.[14], who reported that diarrhea-associated hemolytic uremic syndrome (D+HUS) was the most frequent cause of AKI in their Belgian cohort, accounting for 20.3% of their patients. This can be explained by the etiology of AKI varies widely according to age, geographic region, and clinical setting. [14]

This is in variance with the study performed by Krishnamurthy et al.[15], who found that the common etiologies in their Southern India study were infections (62.9%), acute glomerulonephritis (7.6%), snake envenomation (5.7%), hemolytic uremic syndrome (3.8%), and congestive cardiac failures (3.8%). [15]

Nonetheless, a study conducted in Nigeria identified the leading causes of AKI, which accounted for 80.0% of all etiologies are nephrotoxins (29.0%), infections (20.0%), intravascular volume depletion (17.9%), and glomerular disease (13.1%). [10]

This can be explained by the epidemiology of pediatric acute kidney injury which differs significantly between developed and developing countries due to various factors. In developed countries, there is a higher incidence of AKI related to surgeries and the use of nephrotoxic medications. In contrast, developing countries see infectious diseases, such as diarrhea, and sepsis, as more common causes of AKI, largely due to higher rates of childhood infections.

In this study, hemolytic uremic syndrome (HUS) accounted for 50% of our patients. Of these, 18 patients had diarrhea-positive HUS, while 7 were diagnosed with atypical HUS (aHUS). This prevalence is notably higher than reported in a previous cohort study that

was conducted at our center, which examined 68 children with HUS from January 2009 to January 2019, before the COVID-19 pandemic. In that study, 63 patients had diarrhea-positive HUS, and 5 patients had atypical HUS. The increase in atypical HUS cases during the pandemic can be attributed to several mechanisms; viral trigger COVID-19 can induce a strong inflammatory response that activates the complement system, endothelial damage caused by the virus that promotes thrombotic microangiopathy and immune dysregulation leads to immune system disruptions, increasing susceptibility to complement-mediated disorders. [16, 17]

The initial laboratory findings revealed severe anemia, thrombocytopenia, significantly elevated serum creatinine, urea, liver enzymes, and inflammatory markers (LDH, D-dimer, CRP) with electrolyte disturbance. In this study, serum creatinine values were the main parameter for the diagnosis of AKI, there were higher values of serum creatinine, serum urea, initially at admission in agreement with Yang et al.[18], who found that 50% of the patients with AKI already had a high rate of serum creatinine at the time of admission. [18]

Regarding the hemoglobin level, and platelet count in our present study, it was noticed that their values were significantly lower initially at admission while total leukocyte count was significantly higher in commitment with a higher level of initial serum creatinine. This agrees with Cheng et al.[19] who showed patients with high basal serum creatinine had a higher leukocyte count and a lower count of lymphocytes and platelets.

Moreover, looking again at the kidney function, we found that sCr levels at discharge were slightly higher in patients hospitalized during the COVID-19 period. That is like Chan et al.[20] reported Patients hospitalized during COVID-19 period with AKI showed higher sCr levels.

This observation deserves specific consideration since it could potentially impact long-term kidney function, suggesting that patients discharged in the COVID-19 period may need more intensive kidney follow-up to reduce the risk of future CKD development.

Since the onset of the COVID-19 pandemic, there has been an increased demand for chest CT scans with CORAD (COVID-19 Reporting and Data System) scoring to assess pulmonary involvement in affected patients. In our study, 11 of the studied patients underwent CT chest scans, revealing abnormalities in 14% of cases. These findings included ground glass opacities, consolidations, and pleural effusions. Our findings are consistent with a study by Wang X et al.[21], which investigated CT chest findings in COVID-19 patients with acute kidney injury (AKI). Wang X et al.[21] reported similar radiological manifestations, such as patchy infiltrations, consolidations, and pleural effusions, highlighting the broad spectrum of pulmonary abnormalities seen in severe cases of COVID-19. [21]

Among our studied AKI patients who underwent MRI brain imaging, 4 patients exhibited MRI findings consistent with posterior reversible encephalopathy Syndrome (PRES) and 3 patients presented with brain edema, explained by endothelial dysfunction in the setting of COVID-19 could have contributed to PRES. SARS-CoV-2 binds directly to the angiotensin-converting enzyme 2 (ACE2) receptors. This binding may cause an increase in blood pressure along with weakening of

the endothelial layer leading to a weakened blood-brain barrier, which may result in dysfunction of the brain's autoregulation of cerebral circulation.[22]

In this study, 9 patients exhibited pulmonary findings on CT chest, but COVID-19 PCR was positive in only 5 of these cases. This discrepancy showed that the PCR test had a specificity of 60%, highlighting its potential limitations in accurately detecting COVID-19.

Renal biopsy was performed on a total of 27 patients to evaluate the underlying pathology of AKI. Thrombotic microangiopathy was the most common histopathological finding, observed in 32% of cases (n=16), acute tubular injury was noted in 14% of the biopsied patients (n=7). Crescentic glomerulonephritis was identified in 8% of the biopsied patients (n=4).These results agree with Hafez et al.[23], who reported that children with unexplained acute kidney injury, acute tubular necrosis, crescentic glomerulonephritis, and diarrhea-associated HUS represent a considerable percentage of renal injury. There were limitations for us to obtain renal biopsies in fact of thrombocytopenia in cases of diarrhea-positive HUS and the clinical manifestations were obvious to obtain the diagnosis.[23]

In this cohort study, 56% of patients received packed red blood cells transfusions due to severe anemia associated with ongoing hemolysis, characterized by hemoglobin levels below 8 g/dL during the active phase of the disease. Transfusions were administered according to our center protocols, aiming to stabilize hemoglobin levels above 10 g/dL and effectively manage complications of anemia. Current transfusion guidelines, including those discussed by Kaplan et al.[24], recommend initiating PRBC transfusions when hemoglobin levels drop below 6.0 g/dL, with a targeted maintenance level of approximately 7 g/dL to optimize tissue oxygenation and reduce the risk of symptomatic anemia and thrombosis. [24]

Fresh frozen plasma was used in 74 % of our studied patient's patients. FFP administration was associated with positive outcomes in our AKI patients.[25] In this study, plasmapheresis was employed for all 7 patients diagnosed with atypical hemolytic uremic syndrome (HUS), 2 patients with multi-inflammatory syndrome in children (MICS), and 3 patients presenting with post-infectious (AKI). Additionally, pulse steroid therapy at a dosage of 30 mg/kg/day was administered to 10 patients.

In this study, 30% of patients received antihypertensive drugs to manage elevated blood pressure. Additionally, 24% of these patients were prescribed anti-epileptic drugs to address neurological manifestations and seizures observed during their hospitalization.

Eculizumab was administered to 3 patients diagnosed with recurrent atypical HUS. Meanwhile, 70% of our study cohort required hemodialysis, peritoneal dialysis is unavailable at our facility, and due to the high cost of continuous renal replacement therapy (CRRT) sessions, even with insurance coverage, its utilization was restricted. In agreement with Anirban et al.[11] found that around 65% of their studied patients required dialysis support. [11]

Regarding the outcome, renal recovery has been described as a post-AKI nadir serum creatinine of less than 2 mg/dL, a nadir serum creatinine that is less than 1.15x, 1.25x, or 1.5x baseline,

A creatinine that is within 0.3 mg/dL of baseline, no longer requiring renal replacement therapy (RRT), or no longer meeting any AKI criteria.[26].

In this present study, the survival rate was 86%, with 10% of patients experiencing residual renal impairment and an in-hospital mortality rate of 14%. This aligns closely with findings from Kari et al.[27], who also conducted their study during the pandemic and reported that 9% of their study population developed residual renal impairment upon discharge. The mechanisms underlying how acute kidney injury (AKI) increases the risk of chronic kidney disease (CKD), end-stage renal disease (ESRD), and other adverse outcomes remain unclear. [27]

Supporting our findings, Meena et al.[28] reported a pooled mortality rate of 11% in studied children with AKI from March 2012 to January 2022.[28] Similarly, Hessey et al.[29] examined 2033 pediatric ICU admissions and observed that 92.5% of patients with AKI recovered renal function, defined as discharge creatinine < 1.5 times baseline. However, a lower recovery rate of 75.9% was noted when recovery was defined as discharge creatinine < 1.15 times baseline. [29]

COVID-19 AKI is associated with significantly increased mortality. In addition, many patients do not recover normal kidney function after AKI, and a follow-up study of hospitalized COVID patients showed decreased kidney function at 6 months in 35%, even in some with unrecognized kidney involvement during hospitalization. From 5% to 45% of COVID-19 ICU patients required dialysis management, with continuous renal replacement therapy (continuous venovenous hemofiltration, CVVH) being used most.[30]

After analysis of hospitalization outcomes, we observed a notable increase in ICU admissions, accompanied by a significant prolongation of hospital stays and an increase in in-hospital mortality. This trend parallels findings by Esposito et al.[9], who reported higher rates of ICU admissions and longer hospital stays during the COVID-19 period compared to the pre-COVID-19 era. [9]

There was a higher mortality rate in females (85.7% vs. 14.3% for males). Additionally, the median age of deceased patients was significantly lower by 1.0 years, compared to 7.0 years for survivors. Furthermore, deceased patients exhibited lower median weights (10.0 kg vs. 27.0 kg) and lower mean heights (114.1 cm vs. 127.8 cm) compared to their surviving counterparts. In agreement with Abdelnabi HH et al.[16], who reported a high moralitiy rate in their studied HUS young females (<5 years). [16]

The leading causes of death were pulmonary hemorrhage, pulmonary edema and sepsis. This study identified significant associations between mortality outcomes and elevated levels of D-dimer, lactate dehydrogenase (LDH), and C-reactive protein (CRP) in pediatric patients with acute kidney injury (AKI). In contrast, we found no strong correlation between lymphopenia and COVID-19 PCR results with mortality. As well, El Kassas M et al.[31], who aimed to assess the characterization of COVID-19 infection among the Egyptian population. They demonstrated that N/T ratio and CRP act together as an integrated panel to diagnose symptomatic COVID-19 infection and correlate directly with case severity. Moreover, Ahmed HM et al.[32], found that high CRP>5 mg/dl was detected in 100% of patients. Anemia, leukocytosis,

and lymphopenia were frequently observed.

CONCLUSIONS

During COVID-19 pandemic, increased AKI incidence between children, mostly due to HUS and post-infectious glomerulonephritis. There was a higher need for hemodialysis and continuous renal replacement therapy (CRRT) during the pandemic. The duration of hospital stays for AKI patients was prolonged during the pandemic. Younger ages and female sex were associated with high mortality rates. Elevated levels of D-dimer and lactate dehydrogenase (LDH) were strongly correlated with increased mortality.

LIMITATIONS OF THE STUDY

Single-center study, retrospective, small study size, short duration. No AKI comparator group in pre COVID -19 pandemic period.

ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2	***HTN***	Hypertension
AKI	Acute Kidney Injury Network	***ICU***	Intensive care unit
AKIN	Acute Kidney Injury Network	***KIDGO***	Kidney Disease Improving Global Outcomes
AGN	Acute Glomerulonephritis	***MIS-C***	Multisystem Inflammatory Syndrome in Children
ATN	Acute Tubular Necrosis	***MRI***	Magnetic Resonance Imaging
CRP	C-Reactive Protein	***PLT***	Platelet
CRRT	Continuous Renal Replacement Therapy	***PRES***	Posterior Reversible Encephalopathy Syndrome
CORAD	COVID-19 Reporting and Data System scoring	***PRBCS***	Packed red blood cells
CKD	Chronic kidney disease	***RIFLE***	Risk, Injury, Failure, Loss, End-Stage Renal Disease
CNS	Central nervous system	***SARS-COV-2***	Severe Acute Respiratory Syndrome Coronavirus 2
DCL	Disturbed Conscious Level	***SCr***	Serum Creatinine
ESRD	End stage renal disease	***TMPRSS2***	Trans Membrane Protease Serine 2
FFP	Fresh frozen plasma	***TMA***	Thrombotic microangiopathy
GFR	Glomerular filtration rate	***UO***	Urine output
HUS	Hemolytic Uremic Syndrome		

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STATEMENTS

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This study was approved by the Ethics Committee of Faculty of medicine, Tanta University, with the ethics code 3626. Also, written informed consent was obtained from the parent of the participating children.

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"Not applicable"

Availability of data and material
"Available for your request, anytime"

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