COVID-19 in Children with Chronic Dialysis and Kidney Transplantation

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Abstract

The aim of the study is to present incidence of COVID-19 in children with renal replacement therapy (RRT) and compare the severity and outcomes of the disease between the groups undergoing dialysis and kidney transplantation (KTx). This multicenter observational study was based on data collected from children receiving RRT, either chronic dialysis or KTx, diagnosed with COVID-19. All members of the Istanbul branch of the Turkish Pediatric Nephrology Association were requested to submit all their confirmed COVID-19 cases between April 1 and December 31, 2020. They were also asked to report the number of their prevalent patients on RRT under the age of 20. A total of 46 RRT patients diagnosed with COVID-19 were reported from 12 centers. Of these, 29 were KTx recipients, and 17 were on dialysis. COVID-19 cases represented 9.3% of all prevalent dialysis patients and 9.2% of all prevalent KTx recipients. Twelve KTx recipients (41.4%) and three dialysis patients (17.6%) were asymptomatic (p = 0.12). The hospitalization rate was higher in dialysis patients than KTx recipients (82.4% vs. 27.6%, p = 0.001). Two patients, one in each group, experienced a severe disease course, and only one hemodialysis patient had a critical illness that required mechanical ventilation. Acute kidney injury developed in 36% of KTx recipients, but none required dialysis or lost their graft. In the entire cohort, one patient on hemodialysis with multiple comorbidities died.

Conclusion: Although most of cases were asymptomatic or had a mild disease, children on RRT seem to have an increased risk for COVID-19.

What Is Known

- In adult population, both dialysis patients and kidney transplant recipients are at increased risk for severe illness of COVID-19 and have higher mortality rate.
- Children with kidney transplantation are not at increased risk for COVID-19 and most have mild disease course.
- Data on children on dialysis are scarce.

What Is New

- Children on dialysis and kidney transplantation have an increased risk for COVID-19.
- Children on dialysis and kidney transplantation have similar disease course.
- The mortality risk seems to be higher among children on dialysis than transplant recipients.

Introduction

Currently, the overall mortality rate of COVID-19 is about 2.1% worldwide [1], and this rate varies from country to country, by age, and between specific patient groups. Uremia is a known risk factor for impaired immune function as evidenced by an increased susceptibility to infections [2]. The evidence to date suggests that chronic kidney disease (CKD), especially end-stage kidney disease (ESKD), is

associated with severe illness and a high mortality rate of COVID-19 in the adult population [3]. The mortality rate of COVID-19 rises to 32% in adult patients with ESKD on maintenance dialysis [4-6]. However, the limited available data suggest that COVID-19 is uncommon in children with advanced stages of CKD and the disease has a mild course in children on chronic dialysis [7, 8].

Major concerns remain in the severity of the disease in kidney transplant (KTx) recipients. Early evidence from the adult population showed that KTx recipients are at an increased risk for critical COVID-19 illness, with remarkably high mortality that reaches 28% [9, 10]. The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) registry showed a low absolute risk for COVID-19 in adult KTx recipients but a high attributable mortality rate of 20% [5]. On the other hand, most of the evidence suggests that young KTx recipients are not at high risk for COVID-19 [11] and most children receiving immunosuppressive therapy for kidney disease, including KTx recipients, have a mild disease course during COVID-19 [12].

In Turkey, a nationwide study has shown that the mortality rate is higher in hospitalized COVID-19 patients with stages 3-5 CKD, hemodialysis (HD), and KTx compared with those without kidney disease [13]. In this multicenter study from Istanbul, which is the most crowded city in Turkey, we aimed to present incidence of COVID-19 in children with renal replacement therapy (RRT) and compare the disease course and outcomes between children receiving chronic dialysis and KTx recipients with a functioning graft.

Materials And Methods

This multicenter observational study was based on data collected on children with RRT, either chronic dialysis or KTx, diagnosed with COVID-19. The study was announced in April 2020 following ethical approval (number: 57697, April 29, 2020), and the patient registration form was sent to all members of the Istanbul branch of the Turkish Pediatric Nephrology Association. All members were requested to submit all confirmed cases of COVID-19 (inpatients and outpatients) under the age of 20 years who were on RRT. The data collection was completed on December 31, 2020. A total of 12 pediatric nephrology centers reported their COVID-19 cases during the study period. These centers were also asked to report their prevalent patients with RRT under the age of 20 that they have actively followed up.

Data on anthropometric measurements, primary renal disease, dialysis duration and modality, transplant properties, comorbid conditions, vaccination status for pneumococcus and influenza, and list of medications were obtained from the patient registration forms. Regarding comorbid condition, obesity was defined as a height-specific body mass index greater than 95th percentile according to the national pediatric growth percentiles [14]. Hypertension was defined in patients with an office blood pressure greater than 95th percentile according to age-, sex-, and height-specific normative values in the Fourth Report [15]. Patients receiving antihypertensive medication were also defined as hypertensive.

COVID-19 was diagnosed by laboratory confirmation using the reverse transcriptase-polymerase chain reaction (PCR) or serology tests. The possible source of COVID-19, presenting symptoms, clinical, radiological, and available laboratory findings at the time of diagnosis, drug therapy, and outcomes were

documented. The severity of the disease was classified as mild, moderate, severe, or critical illness [16]. The number of patients with multisystem inflammatory syndrome (MIS-C) was also reported. For the KTx group, serum creatinine level before COVID-19 (baseline), serum creatinine at the diagnosis of COVID-19, and maximum serum creatinine during COVID-19 were noted. Acute kidney injury (AKI) was defined as an increase of serum creatinine by 0.3 mg/dL or 50% from baseline within seven days, according to the Kidney Disease: Improving Global Outcomes (KDIGO) [17].

Statistical analyses were performed using SPSS Version 21.0 (IBM, Armonk, NY, USA). Data were analyzed by descriptive statistics and presented as a mean (± standard deviation), median [(quartile 1 (Q1) – quartile 3 (Q3)], or number (percentage). The two groups were compared using the Mann–Whitney U test or chi-square test. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

A total of 46 cases of RRT diagnosed with COVID-19 were reported from 12 centers between April 1 and December 31, 2020. Of these, 29 were KTx recipients, and 17 were on chronic dialysis [10 HD and 7 peritoneal dialysis (PD)]. The total number of prevalent patients reported by the 12 centers was 314 for KTx and 182 for chronic dialysis. On December 31, COVID-19 cases represented 9.3% of all prevalent dialysis patients and 9.2% of all prevalent KTx recipients (**Fig. 1**). Seventy percent (n = 29) of the patients were diagnosed in the second wave of the pandemic; the remaining were in the first wave.

Clinical course and treatment

There were no differences between dialysis patients and KTx recipients in terms of age, sex, primary renal disease, or comorbid conditions including hypertension and obesity (**Table 1**). Transplant-specific properties are summarized in **Table 2**.

Twelve KTx recipients (41.4%) and three dialysis patients (17.6%) were asymptomatic (p = 0.12). All asymptomatic children were tested due to close contact with a person with confirmed COVID-19. Fever was the most common symptom in dialysis patients (53%); however, it was present in 24% of the KTx recipients (p = 0.06) (**Fig. 2**). Two patients, one in each group, experienced a severe disease course, and only one HD patient had a critical illness that required mechanical ventilation. (**Table 3)**. Abnormal radiological findings at the time of diagnosis were found in 14 out of 34 patients (41.2%). The most common radiological abnormalities were multi-focal consolidation (n = 8) and ground-glass opacification (n = 7). Lymphopenia was present in 41% of the KTx recipients and 62.5% of dialysis patients (p = 0.33).

A total of 22 patients received antiviral treatment, including favipiravir (n = 15) and hydroxychloroquine (n = 7). No side effects were documented in patients who received neither favipiravir nor hydroxychloroquine. Use of antiviral drugs did not differ between dialysis patients and KTx recipients (47% vs. 48%) but antibiotic use was more common in dialysis patients than KTx recipients (47% vs. 14%, p = 0.019). The immunosuppressive treatment was modified in 18 KTx recipients (62%) during COVID-19.

The most common change in immunosuppressive therapy was a discontinuation or dose reduction of mycophenolate (**Table 3**).

Outcomes

The hospitalization rate was significantly higher in dialysis patients compared with KTx recipients (82.4% vs. 27.6%, p = 0.001); however, there was no difference in the median time of hospitalization between the two patient groups [11.5 (4.75 – 16.25) days for dialysis patients vs. 6.5 (5.25 – 21.0) days for KTx recipients, p = 0.87]. In total, three patients were admitted to the ICU due to critical illness (n = 1) and MIS-C (n = 2). One patient died during the study period. This patient was receiving maintenance HD because of ESKD secondary to bacterial sepsis and AKI after bone marrow transplantation due to aplastic anemia. The patient also had an immune deficiency and constrictive pericarditis. The case fatality ratio of COVID-19 was 2.2% among all patients with RRT, and 5.9% among dialysis patients.

Renal outcome in KTx recipients

Two patients had proteinuria, but none had hematuria. There was a significant increase in median serum creatinine from baseline [0.84 (0.67 – 1.10) mg/dL] to peak level [0.95 (0.70 – 1.30) mg/dL] during COVID-19 in 22 KTx recipients who had available data (p = 0.003). Acute kidney injury developed in 8 out of 22 KTx recipients (36%). All had AKI stage 1 with a median increase in serum creatinine of 0.46 (0.30-0.96) mg/dL. There was no difference between the patients with or without AKI in terms of sex, age, comorbidity, medications, or disease severity, or baseline; however, the hospitalization rate was significantly higher in patients with AKI (75%, n = 6) than their counterparts (14%, n = 2) (p = 0.008).

Discussion

This multicenter study consisted of a cohort of children with chronic dialysis and kidney transplantation. This study provided an important opportunity to determine the cumulative incidence of COVID-19 in this specific pediatric patient population and to compare the severity and outcomes of the disease between children on dialysis and KTx recipients. Our results revealed that both children receiving maintenance dialysis and children with a kidney transplant are at increased risk for COVID-19, but most patients in both groups develop mild forms of the disease. It is noteworthy that a high proportion of KTx recipients were asymptomatic. AKI developed in more than one-third of KTx recipients, but none of whom required dialysis or lost their graft. In the entire cohort, one child receiving HD with multiple comorbidities died from COVID-19.

It is challenging to determine and effectively compare the incidence of COVID-19 due to differences in testing strategies between countries and centers and the presence of many asymptomatic cases. The ERA-EDTA registry showed that the incidence of diagnosed COVID-19 was 1.4% in KTx recipients and 2.9% in the dialysis population at the beginning of the pandemic [5]. For children with ESKD (on dialysis or transplanted), the Spanish Pediatric Association estimated an incidence of COVID-19 of 0.61% [8]. Similarly, the Improving Renal Outcome Collaboratives (IROC) registry from the United States reported an

overall incidence of COVID-19 of 0.6% among pediatric KTx recipients and 4.4% among tested KTx recipients during the study period of April to September 2020 [18]. In the present study, among the 182 prevalent children on chronic dialysis across centers in Istanbul, 17 (9.3%) were diagnosed with COVID-19 between April 1 and December 31, 2020. Similar to dialysis patients, the rate of COVID-19 was 9.2% among 384 KTx recipients during the 9-month study period. In contrast to previous reports, our study period included both the first and second waves of the pandemics. Our results also showed that 70% of COVID-19 positive patients were diagnosed between September and December 2020. Considering the overall rate of the disease was 1.2% (1-5%) around the world on the 31st of December, according to the World Health Organization [1], and lower infection rates for children than adults, our result suggests that children with RRT are at increased risk of COVID-19. This high rate of COVID-19 in children with RRT may have resulted from regional factors as well as disease-specific factors. It is known that the uremic milieu and chronic immunosuppression increase infection risk, and patients with RRT have a higher risk of exposure to COVID-19 due to their ongoing clinical care. Moreover, these patients were closely monitored and more frequently tested for COVID-19 due to an enhanced risk of severe disease. The high proportion of asymptomatic cases in our cohort supports this hypothesis. On the other hand, this study was conducted in Istanbul, the most populous city in Turkey and one of the highest-risk cities during the pandemic, contributing to the high rate of COVID-19 in our cohort.

In contrast to adults, a significant number of children with COVID-19 are asymptomatic [14]. Similar to the general pediatric population, the IROC registry reported that 37% of KTx children were asymptomatic [18]. Consistent with this report, our KTx patients developed asymptomatic disease at a rate of 41%. Fever was the most common clinical symptom associated with COVID-19 in dialysis patients, which was present in 53% of this patient population. In accordance with the current result, previous studies have demonstrated that fever accounted for about half of dialysis patients [4, 19]. On the other hand, only one-fourth of our KTx recipients had fever as a presenting symptom. The present study contributes to previous reports indicating that fewer transplant patients may present with fever [9, 20]. Our results also showed that severe respiratory symptoms were uncommon in both groups, and most symptomatic patients had mild forms of the disease. This finding is consistent with previous pediatric studies evaluating children with ESKD, mostly in heterogeneous patient populations [8, 12, 18, 21].

Our study included both outpatients and inpatients with COVID-19. The hospitalization rate among patients on dialysis was much higher than KTx recipients despite their similar disease severity. While less than one-third of KTx recipients were hospitalized, 82% of dialysis patients were admitted to the hospital. A global pediatric study from 30 different countries revealed the hospitalization rate of 60% among 113 children with kidney disease receiving immunosuppressive therapy [12]. In our cohort, the lower rate of hospitalization among the KTx population might have resulted from the greater number of asymptomatic patients. In addition, maybe the patients with a mild disease course were isolated at home since the hospitals were quite full of COVID-19 patients.

Early evidence of the pandemic revealed a high mortality rate of up to 32% in adult dialysis and transplant patients with COVID-19, strongly associated with older age and comorbidities [5, 9, 22-24].

Comparing to adults, the pediatric population had lower rates of COVID-19-associated mortality. According to a multicenter European Study, the reported mortality rate of COVID-19 is 0.7% among the general pediatric population [25]. This rate ranges from 0 to 3.5% in children with coexisting kidney disease [7, 8, 12, 21]. In our cohort of 49 children with RRT, one child on HD died from COVID-19. This case had severe comorbidities such as malignancy and immune deficiency. Our finding contributes additional evidence that patients on dialysis, especially whom with comorbidities, are at high risk of mortality due to COVID-19.

There is limited evidence regarding effective antiviral treatment in children with COVID-19. Approximately half of our patients received antiviral therapy according to the national treatment strategy. Favipiravir was given to two-thirds of these patients, and hydroxychloroquine was given to the remaining one-third. No side effects were observed with either treatment. For KTx recipients, the best strategy for immunosuppressive therapy is still unknown. It is recommended to continue their calcineurin inhibitors and prescribed dose of glucocorticoids and to stop any anti-proliferative drugs [26]. Our analysis showed that anti-proliferative agents were modified in 62% of KTx recipients, which was equally divided between withdrawal and dose reduction of antimetabolites. In addition, tacrolimus dose reduction or discontinuation were done in two cases. None of the patients experienced allograft rejection or AKI requiring dialysis. However, 36% of KTx recipients developed early-stage AKI (stage 1). In accordance with the present result, previous studies have demonstrated that COVID-19 associated AKI develops in 27% to 52% of KTx recipients [22, 23, 27-29]. Taken together, these results highlight the need for caution regarding the increased risk of developing AKI in KTx recipients.

Our study has several limitations. We did not have any control group of the general pediatric population with COVID-19 from Istanbul to compare the infection rate and disease course to minimize regional differences. Another limitation is that we could not obtain any information regarding how many children with RRT were tested for COVID-19. Lastly, some variation may have been introduced due to the multicenter design since individual centers had their own indications for hospitalization and different approaches for the immunosuppressive modifications in KTx recipients.

Conclusion

Although most of our cases were asymptomatic or had a mild disease, children on RRT seem to have an increased risk for COVID-19. Besides, the case-fatality risk is high among HD patients, especially patients with severe comorbidities. Therefore, we think that protective and isolation measures should be continued very carefully in this patient population, and dialysis patients, especially those with comorbidities, should be closely monitored due to their increased mortality risk.

Abbreviations

AKI, acute kidney injury

CKD, Chronic kidney disease

COVID-19, Coronavirus disease 2019

ESKD, End-stage kidney disease

HD, hemodialysis

KTx, Kidney transplant

PCR, Polymerase chain reaction

PD, Peritoneal dialysis

RRT, Renal replacement therapy

Declarations

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Tables

Table 1. Clinical characteristics and demographic information of the patients

	KTx Group n = 29	Dialysis Group n = 17	P value
Age, years	13.3 ± 5.3	12.5 ± 5.3	0.67
Sex (female), n (%)	14 (48)	6 (35)	0.54
RRT duration, months	39.4 ± 40.4	17.3 ± 11.6	0.18
Primary renal disease			0.46
CAKUT	9	7	
Glomerular disease	8	6	
Ciliopathies	8	2	
Cystinosis	2	0	
Others	2	1	
Unknown	0	1	
Comorbid conditions, n (%)			
Hypertension	18 (62)	12 (71)	0.75
Obesity	9 (31)	1 (6)	0.07
Other comorbid conditions	6 (21)	8 (47)	0.10
Pulmonary disease	3	1	
Cardiac problems	1	3	
Malignancies	2	2	
Neurologic problems	0	1	
Esophagus atresia	0	1	
Vaccination status, n (%)			
Pneumococcus	19 (65.5)	11 (65)	1.0
Influenza	11 (38)	3 (18)	0.25

KTx; kidney transplantation, *RRT;* renal replacement therapy, *CAKUT;* congenital anomalies of the kidney and urinary tract.

Table 2. Transplant-specific properties of 29 kidney transplant recipients

Donor type, living /deceased, n (%)	25 (86) / 4 (14)
Number of HLA mismatches*	3.0 (3.0 – 4.0)
Time from transplantation*, months	24.4 (5.2 – 64.8)
Induction therapy, n (%)	
ATG	10 (35)
Basiliximab	14 (48)
None	5 (17)
Maintenance immunosuppression, n (%)	
PRED + TAC + Mycophenolate (MMF/MPA)	25 (86)
PRED + TAC + mTORi	2 (7)
PRED + CsA + MMF	1 (3.5)
TAC + MMF	1 (3.5)

**Data presented as median (Q1 – Q3)*

HLA; human leukocyte antigen, *ATG*; anti-thymocyte globulin, *PRED*; prednisolone, *TAC*; tacrolimus, *MMF*; mycophenolate mofetil, *MPA*; mycophenolate sodium, *mTORi*; the *mammalian target of rapamycin inhibitor, CsA; cyclosporine.*

Table 3. COVID-19 specific features of the patients

	KTx Group n = 29	Dialysis Group n = 17
Diagnosis of COVID-19, n (%)		
Positive PCR test	27 (93)	17 (100)
Positive IgM test	2 (7)	0
Possible source of COVID-19, n (%)		
Household	22 (76)	10 (59)
Healthcare	0 (0)	2 (12)
Unknown	7 (24)	5 (29)
Severity of the disease, n (%)		
Asymptomatic disease	12 (41.4)	3 (17.6)
Mild disease	14 (48.3)	12 (70.6)
Moderate disease	2 (6.9)	0 (0)
Severe disease	1 (3.5)	1 (5.9)
Critical illness	0 (0)	1 (5.9)
Abnormal radiologic findings, n/N (%)	8/19 (42.1)	6/15 (40.0)
Lymphopenia (<1500 cells/μL), n/N (%)	9/22 (40.9)	10/16 (62.5)
Respiratory support, n (%)		
No respiratory support	26 (89.7)	16 (94.1)
Oxygen treatment	3 (10.3)	0
Mechanical ventilation	0	1 (5.9)
Drug treatment, n (%)		
Favipiravir	12 (41)	3 (18)
Hydroxychloroquine	2 (7)	5 (29)
Antibiotics*	4 (14)	8 (47)
Oseltamivir	1 (3)	0 (0)
IVIG	3 (10)	1 (6)
Immunosuppressive modification, n (%)	18 (62)	
Mycophenolate discontinuation	9	

Mycophenolate dose reduction	9	
TAC dose reduction or discontinuation	2	
Increase in steroid dose	4	
Hospitalization, n (%)**	8 (27.6)	14 (82.4)
ICU admission, n (%)	3 (10.3)	1 (5.9)
Outcome, n (%)		
Full recovery	28 (96.6)	16 (94.1)
Chronic pulmonary disease	1 (3.4)	0
Death	0	1 (5.9)

*P = 0.019 and **P = 0.001, other parameters did not differ between the two groups.

KTx; kidney transplantation, *PCR;* polymerase chain reaction, *IVIG;* intravenous immunoglobulin, *TAC; tacrolimus*, *ICU;* intensive care unit

Figures

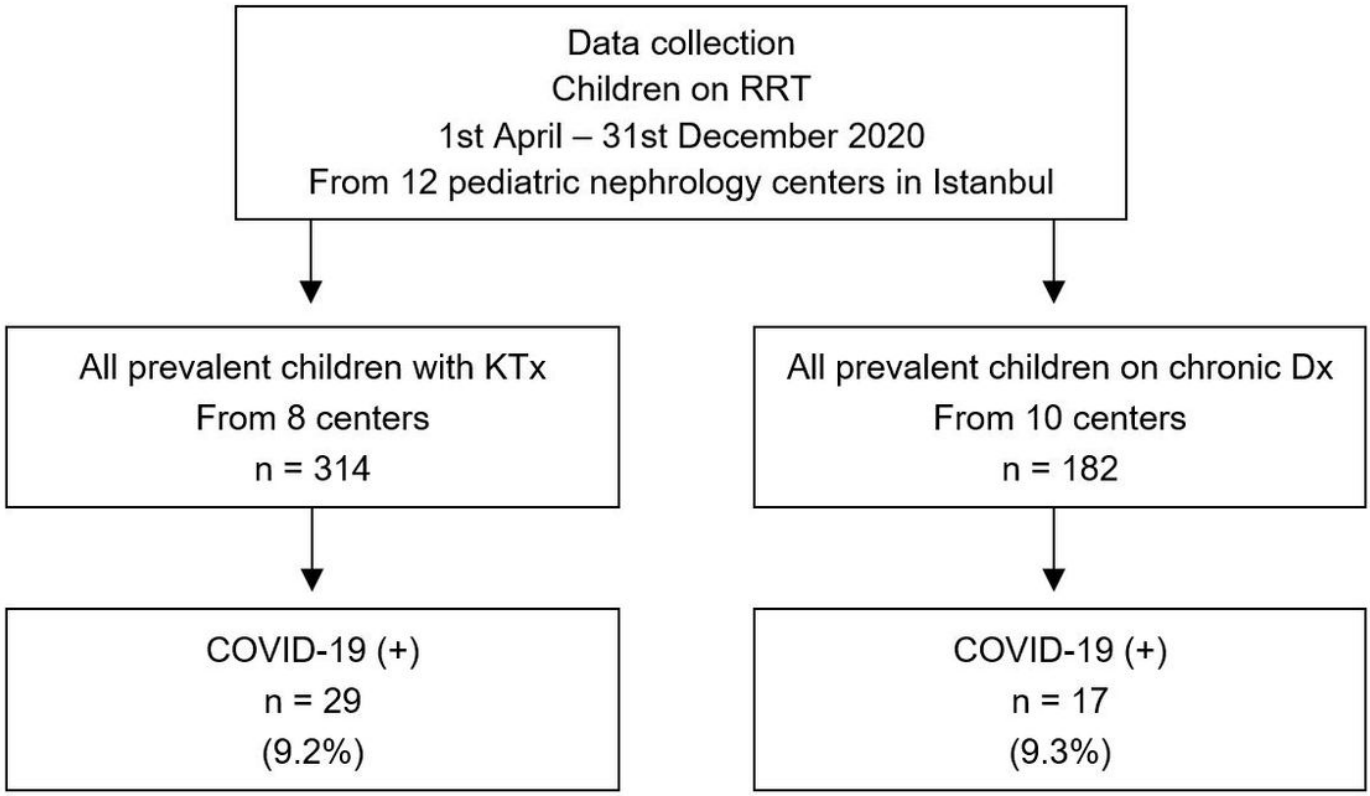

Figure 1

Flowchart of the study population. RRT; renal replacement therapy, KTx; kidney transplantation; Dx, dialysis.

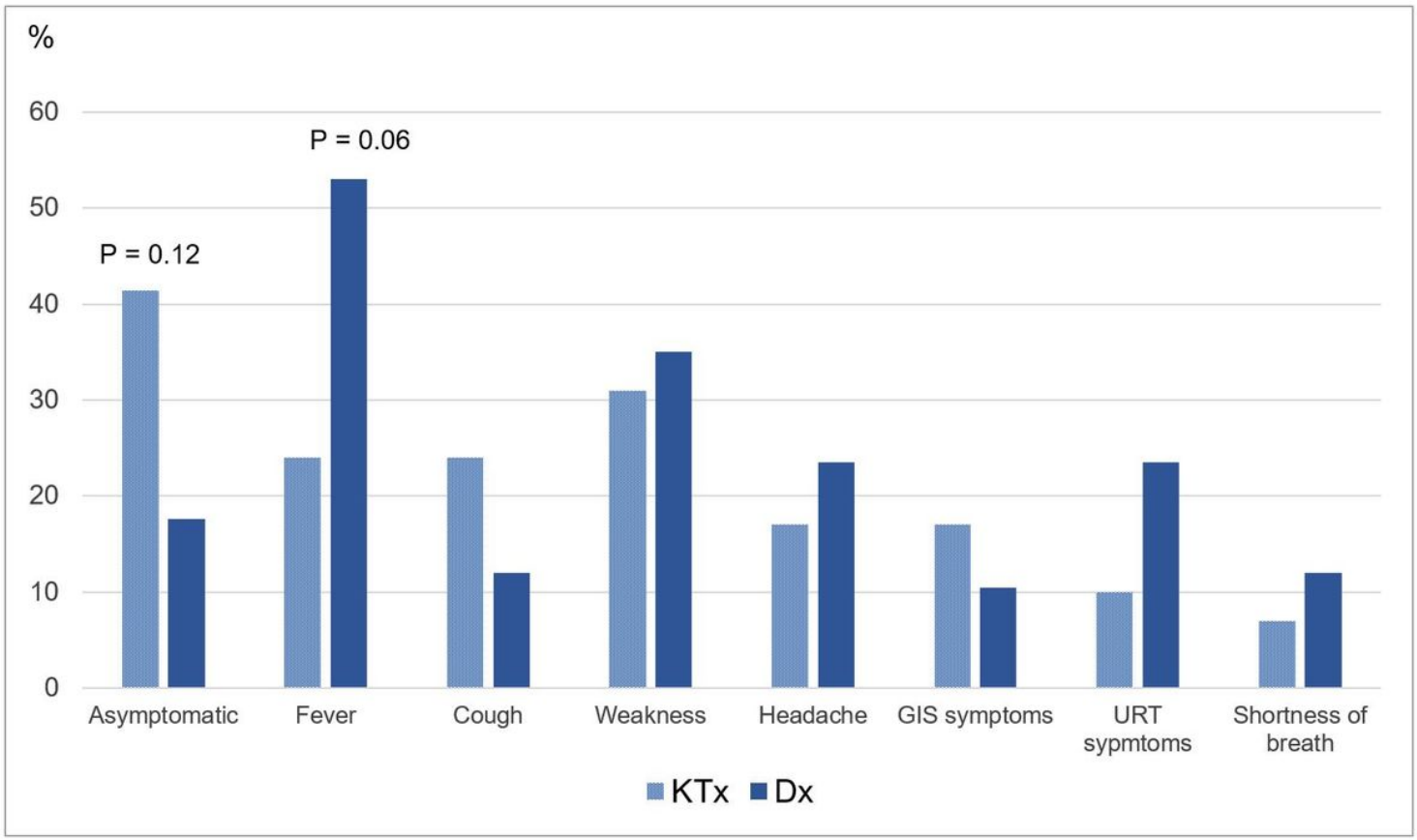

Figure 2

Presenting symptoms of COVID-19 in patients with chronic dialysis (Dx) and kidney transplant (KTx) recipients. GIS; gastrointestinal; URT; upper respiratory tract.