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COVID-19 disease in Pakistani children with chronic kidney disease on hemodialysis – a tertiary care experience

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ABSTRACT:

— ***Objective:*** COVID-19 is a novel viral disease caused by SARS-CoV-2 which has rapidly spread throughout the world. We determined the clinical course and outcome of COVID-19 disease in Pakistani children with chronic kidney disease (CKD) on maintenance hemodialysis during the first wave of the pandemic.

— ***Patients and methods:*** The study was conducted in the hemodialysis unit at the University of Child Health Sciences and Children's Hospital, Lahore, Pakistan. Patients of both sexes below 18 years of age on maintenance hemodialysis with COVID-19 disease confirmed by PCR were included. Data were collected regarding underlying etiology of CKD as well as symptomatology, treatment received and outcome of COVID-19 disease.

— ***Results:*** 9 patients were confirmed as COVID-19 positive by PCR – 56% were males with a median age of 11 years. The most common underlying etiology of chronic kidney disease was obstructive uropathy (22.2%) with fever and cough reported to be the most common presenting symptoms. Only 6% of the children had neutropenia while all others had normal white cell count. Radiological findings revealed diffuse inflammatory infiltration of lungs in all the participants with ground-glass haze in 11% of the subjects. The patients were managed with supportive treatment, antimicrobial coverage, and systemic steroids along with oxygen supplementation while mechanical ventilation with inotropic support was required in almost a quarter and bi-level positive airway pressure in 11% of the children.

— ***Conclusions:*** Our study showed that even children in the advanced stages of CKD were at low risk of developing COVID-19 disease. More than 50% of the patients were discharged uneventfully while 20% of the subjects expired due to severe COVID disease.

— ***Keywords:*** COVID-19, Chronic kidney disease, Hemodialysis, Children, Pakistan.

— ***Abbreviations:*** CKD: Chronic kidney disease, COVID-19: Coronavirus disease; PCR: Polymerase chain reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

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INTRODUCTION

Coronavirus 2019 (COVID-19) is a novel viral disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which has rapidly spread throughout the world. Compared with high prevalence and severity of other common viral respiratory infections, the incidence of COVID-19 disease in children is less than 10%[1-7]. Although the epidemiology and reasons for low prevalence are still unknown, a lower ACE2 expression and different immune response to the virus limit the infectivity of SARS-CoV-2 in the pediatric population[8]. Besides the pulmonary involvement, a multisystem inflammatory syndrome has been described in children (MIS-C) related to COVID-19 disease[9-13]. All over the world, children had bad impact on mental and physical health as a consequence of lockdowns, restricted education and limited social interactions[14-17]. The overall childhood mortality due to COVID-19 disease has been reported to be low in England in an analysis by Odd et al[18]. Children with co-morbid conditions such as kidney disease, liver disease, diabetes, neurological, genetic or metabolic conditions, congenital heart disease, asthma and chronic lung disease are more susceptible to COVID-19 disease. Chronic kidney disease (CKD) is seen to be associated with enhanced risk of COVID-19 in adults[19] and has also been reported by Spanish Pediatric Chronic Kidney Registries estimating an incidence of 0.61% for children on treatment for kidney failure[20,21]. The risk of experiencing infections is high in patients on renal replacement therapy because of the (1) compromised immune system due to long-term malnutrition, uremia and/or immune-suppressants (2) frequent exposure to infected healthcare workers in hospital setting (3) close proximity to other patients in a confined unit (4) high risk of cluster infection due to presence of parents/relatives during dialysis treatment and (5) non-compliance with the recommended infection preventive practices[22-24]. Patients with CKD should be counseled to follow standard infection control guidelines and take precautions to minimize risk exposure to the virus. Hospitalization should be considered only according to the clinical condition as these patients can be managed on outpatient basis with close monitoring.

The aim of our study was to determine the clinical course and outcome of COVID-19 disease in Pakistani children with CKD on maintenance hemodialysis during the first wave of pandemic.

PATIENTS AND METHODS

This prospective cross-sectional study was carried out for one month (July 2020) in the hemodialysis unit at The University of Child Health Sciences and Children's Hospital Lahore Pakistan. The approval was obtained from the institutional review board and parental consent was taken for enrollment of the children. All in- and out-patients of both sexes below 18 years of age on maintenance hemodialysis with COVID-19 disease confirmed by polymerase chain reaction (PCR) were included. They were transferred to the designated COVID-19 intensive care unit of the hospital where the dialysis treatment was continued. The data were collected including details of demographics, underlying etiology of renal failure, travel and contact history, severity of symptoms and treatment related to COVID-19 disease, co-morbidities, laboratory tests, radiological findings, management, and outcome. Severe COVID-19 disease was defined as use of mechanical ventilation, multi-organ failure and presence of hypoxia (oxygen saturation <92%). The statistical analysis was performed using the SPSS version 20.0 (IBM, Armonk, NY, USA). The mean standard deviation (SD) or median was used to describe the quantitative variables such as age and duration of treatment while categorical variables such as sex and treatment modality were presented as frequency and percentage. Two-sided *p*-values < 0.05 were considered statistically significant.

RESULTS

After screening a total of 150 children regularly coming to the hemodialysis unit for dialysis treatment, only 9 (6%) patients were found affected with COVID-19 disease confirmed by polymerase chain reaction (PCR) – 5 (56%) were males with a median age of 11 years. History of contact with SARS-CoV-2 infected patients was found in 4 (44.4%) children while travel history was not present. The demographic data, underlying etiology of renal failure, severity of symptoms related to COVID-19 disease and co-morbidities are presented in Table 1, while the chest radiological findings included diffuse infiltration of lungs in all the patients and ground glass haze in 11.1%. The mean duration of illness was 2.56 $\pm$ 2.6 SD while the mean duration of hospital stay was 11.3 $\pm$ 8.4 SD days. Hemodialysis was continued in 4 (44.4%) subjects while 5 (55.6%) children underwent acute peritoneal dialysis for 5 days due to hemodynamic instability. The vascular access used for hemodialysis was a temporary double lumen catheter placed in internal jugular vein in 6 (66.7%) patients while 3 (33.3%) children had a brachiocephalic arteriovenous fistula created on the left arm. The dialysis treatment complications occurring during the study period were intradialytic hypotension (73%), catheter blockade (33.3%), leg cramps (27.8%), seizures (15.4%) and fever after the dialysis treatment session (13.2%). Steroids and anticoagulation were prescribed for COVID-19 disease in 4 (44.4%) patients. The median follow-up was 18 days after the COVID-19 diagnosis was made and the outcome of patients is presented in Figure 1 showing death of patients being due to severity of COVID-19 pneumonia and uncontrolled volume overload as a consequence of uremia in hemodynamically unstable children.

DISCUSSION

Chronic kidney disease is found to be associated with enhanced risk of severe COVID-19 disease in adults while little information is available about pediatric patients[3]. Although the course of disease in children with co-morbidities has not been well described, patients with CKD have been reported with increased infection risk due to abnormal B- and T-cell function and blunted immune

Table 1. Demographic and clinical characteristics of the study population on hemodialysis with COVID-19 disease (n = 9).

Median age	11 years (6-15 years)
Gender	56% males, 44% females
Underlying renal disease	Obstructive uropathy – 22.2% Reflux nephropathy – 22.2% Juvenile nephronophthisis – 11.1% Primary hyperoxaluria – 11.1% Polycystic kidney disease Membranoproliferative glomerulonephritis – 11.1% Unknown – 22.2%
Co-existent cardiac disease	Left ventricular dysfunction (88.9%) Valvular heart disease (33.3%) Pulmonary hypertension (22.2%)
COVID-19 symptoms	Fever (44.4%) Cough (44.4%) Rhinitis Dyspnea (55.6%) Diarrhea (11.1%) Fatigue (55.6%)
Contact exposure	4 (44.4%)
Respiratory support	Mechanical ventilation (22.2%) Bi-level positive airway pressure (11.1%) High flow face mask oxygen (55.6%)

response. Hemodialysis patients represent a high-risk group for SARS-CoV-2 infection due to several reasons which include inability to quarantine due to travelling from home for frequent treatment sessions, transmission of infection within the hospital environment and lack of isolation facilities in the hemodialysis units.

Although little epidemiological data are available, our study performed as a single center experience supports the observation that COVID-19 disease is fortunately uncommon in children with coexisting chronic kidney disease (6%). This could be due to an impaired immune response in the setting of uremia resulting in a less profound cytokine storm**.** This inference is similar to other studies which have also demonstrated a low incidence of COVID-19 disease in children with coexisting diseases[25]. Nicastro et al[26] reported 36 pediatric COVID-19 cases with chronic kidney disease having mild illness requiring no oxygen administration (28 of them under immunosuppressive therapy, including 15 kidney transplant recipients). Spanish trials carried out a large survey comprising of 16 pediatric nephrology centers across 11 countries, indicating that the incidence of symptomatic SARS-CoV-2 infection is as low in pediatric patients with chronic kidney pathologies as in general population[27,28]. The Italian Society of Pediatric Nephrology also conducted a nationwide observational study and identified 70% pediatric population with chronic kidney diseases (1,572 children) – only three patients were found to be tested positive for SARS-CoV-2 with two having mild symptoms (fever and skin rash) while one was asymptomatic[29].

In our study, 6% of patients on regular maintenance hemodialysis were identified to have COVID-19 disease confirmed by PCR – 56% were males with a median age of 11 years. One of the first reported cases of COVID-19 was described by Rawson et al[30] in two pediatric hemodialysis patients aged 13 and 18 years. Schwierzeck et al[31] also reported a nosocomial outbreak of SARS-CoV-2 infection in a pediatric dialysis unit affecting 13 children with an average age of 10 years. A much lower age has been documented in studies from China showing a median age of 3 years in children with COVID disease[32,33]. The most common underlying etiology of chronic kidney disease in our children was obstructive uropathy (22.2%) as compared to 31.3% of patients with renal dysplasia contributing to majority of subjects in a Spanish study[20].

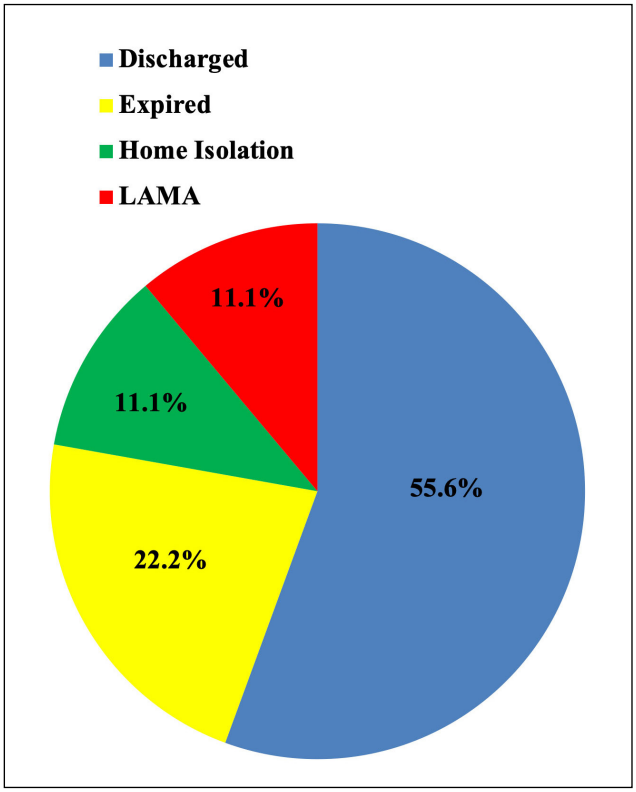

Figure 1. Outcome of nine patients tested positive for SARS-CoV-2 in the hemodialysis unit of University of Child Health Sciences & The Children's Hospital Lahore, Pakistan. (LAMA: Left against medical advice).

Contact with a SARS-CoV-2 infected person is a significant risk factor for COVID-19 disease in children. Almost 50% of our study population had a definite history of contact as compared to other trials by Chaudhry et al[34] and Xia et al[35] who reported positive contacts in 65% and 71% respectively. The clinical presentation of COVID-19 disease in pediatric age group is diverse with a wide spectrum of clinical features and a relatively mild course of illness. Chen et al[36] described fever and dry cough as the main clinical symptoms according to the case definition by the National Clinical Research Center for Child Health, Zhejiang University School of Medicine[36]. Fever and cough have also been narrated to be the most common presenting symptoms in the previously published systematic reviews[37,38] and were also observed in our study in 44.4% of cases. MIS-C has been described as an unusual complication of COVID-19 manifesting as fever, abdominal symptoms, rash, neurological symptoms and conjunctivitis[9,10], but it was not observed in any of our study population.

Laboratory findings in patients with COVID-19 disease have been found to be normal or reduced total leukocyte counts with neutropenia/lymphopenia and/or thrombocytopenia[39-43]. Only 6% of our children had neutropenia while others had normal white cell count which was consistent with the case series of 34 children reported by Wang et al[44] – majority (83%) showed normal leukocyte count and only 3% had neutropenia and lymphopenia. The main radiological features reported by Chen et al[36] were bronchial thickening, ground-glass opacity, and inflammatory lung lesions suggestive of pneumonia. These pulmonary findings were also found by Han et al[45] in asymptomatic patients or those with mild symptoms, suggesting that COVID-19 induces a primary inflammation of lower respiratory tract airways. Our study also revealed diffuse inflammatory infiltration of lungs in all the children while ground-glass haze of lungs was seen in 11% of the subjects. Blondiaux et al[12] described diffuse myocardial edema when cardiac imaging was performed in 4 patients with MIS-C which favored post-infectious myocarditis in children and adolescents with COVID-19. A few cases have been reported with features resembling atypical Kawasaki disease in UK, Italy and USA[13]. None of our subjects developed multisystem inflammatory syndrome but co-existent cardiac disease related to uremia was present in the form of left ventricular dysfunction (89%), valvular heart disease (33%) and pulmonary hypertension (22%).

Our entire study population was managed with supportive treatment, antimicrobial coverage and systemic steroids along with oxygen supplementation while mechanical ventilation and inotropic support were required in 25% and bi-level positive airway pressure in 11% of children. In contrast, Irfan et al[6] managed patients with antibiotics (37%), systemic steroids (19%), mechanical ventilation and inotropes (9%). On the other hand, a Spanish trial[20] administered antiviral treatment and hydroxychloroquine to about one-third of children affected by COVID-19 with chronic kidney disease. The pandemic has resulted in deaths of COVID-19 affected patients on hemodialysis while a few mortalities have been attributed to alterations in hemodialysis therapy regimens[46]. The median follow-up period of 18 days in our study showed that majority of our patients recovered while 20% of deaths occurred secondary to COVID-19 complications (pneumonia and acute respiratory distress syndrome). On the other hand, Odd et al[18] reported an overall low child mortality rate as a consequence of COVID-19 disease, while Plumb et al[24] described encouraging results that none of their study participants experienced any adverse outcomes. A median follow-up of 19 days in another study showed complete clinical recovery in all the patients with no child requiring admission to the pediatric intensive care unit[16].

CONCLUSIONS

This was a single center study performed over one month duration with a short follow-up period which limits the generalizability of the results. Specific treatment options for severe COVID-19 disease like antiviral agents and monoclonal antibodies were not available in our center. However, the University of Child Health Sciences & Children's Hospital Lahore is the largest referral center for pediatric population in Pakistan and provides the first comprehensive picture of children on hemodialysis with COVID-19 disease in the country.

Although the cause is unknown, the incidence of COVID-19 is found to be low in the pediatric population with a benign clinical trend. Our study showed that children in the advanced stages of CKD were at low risk of developing COVID-19 disease with fever, cough and dyspnea being the main presenting symptoms. The most common underlying etiology of CKD was obstructive uropathy and 20% of patients died due to severe pulmonary complications of COVID disease requiring ventilatory support**.** As patients on chronic maintenance hemodialysis are particularly susceptible to infections, infectious disease guidelines should be strictly followed in order to effectively prevent and control the transmission of SARS-CoV-2.

Contributions of Co-authors:
Conception or design – Dr. Samreen Ashraf; Statistical analysis – Dr. Fiaz Bhatti and Dr. Ameenullah; Interpretation of data – Dr. Adeela Chaudhry; Drafting the article or revising it – Dr. Shahida Perveen and Dr. Naureen Akhtar; Providing intellectual content of critical importance to the work described – Dr. Naureen Akhtar; Final approval of the version to be published – Dr. Naureen Akhtar.

Conflict of Interests:
The authors declare that they have no conflicts of interest.

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