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SARS-CoV-2 infection in dialysis patients in northern Italy: a single-centre experience

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ABSTRACT

Background. Dialysis patients are considered at high risk for COVID-19 and the infection can easily spread in dialysis units.

Methods. We conducted an observational single-centre cohort study to describe clinical characteristics, treatments and outcomes of dialysis patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We tested patients who presented symptoms or had contact with a confirmed case. We enrolled 15 patients positive for SARS-CoV-2.

Results. We tested 37 of 306 dialysis patients. Patients with SARS-CoV-2 infection were older (mean age 75.96 ± 11.09 years) and all had comorbidities. At presentation, most had interstitial infiltrates on chest X-ray, three-quarters had leucopenia and none had respiratory insufficiency. During follow-up, there was an increase in serum C-reactive protein and interleukin-6. Eighty percent of patients received supplemental oxygen; none received non-invasive ventilation, one was intubated. Most patients (80%) were treated with oral hydroxychloroquine for a median time of 6.5 days [interquartile range (IQR) 5–14.5] and 40% received azithromycin; two patients received a short course of antivirals and one received a single dose of tocilizumab. Only two patients did not require hospitalization. Of the nine survivors, eight still tested positive for SARS-CoV-2 a median of 19 days (IQR 9.25–23) after diagnosis. Six patients died (case fatality rate 40%) a median of 5.5 days (IQR 1.75–9.75) after diagnosis. The main reported cause of death was respiratory failure related to COVID-19 (five patients).

Conclusions. We report a single-centre experience of SARS-CoV-2 infection in dialysis patients. The disease showed a high case fatality rate and most patients required hospitalization. Survivors show prolonged viral shedding.

Keywords: COVID-19, dialysis, SARS-CoV-2

INTRODUCTION

In late December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a novel pathogen causing serious pneumonia cases; it was later named coronavirus disease 2019 (COVID-19) in Wuhan, China [1]. Since then, the infection has demonstrated an extremely rapid global spread, with a devastating evolution in northern Italy. There, several simultaneous clusters developed with a substantial number of critically ill patients and a very high case fatality rate, especially among the elderly and those with comorbidities [2].

Haemodialysis (HD) and peritoneal dialysis (PD) patients are very susceptible to transmission of communicable diseases. Patients undergoing HD travel several times per week to the dialysis unit to receive treatment and are in contact with other patients and with the hospital staff. Moreover, dialysis patients often present a relevant burden of comorbidities (among others, a high prevalence of diabetes and cardiovascular disease) and the immune system has been reported to be dysfunctional in end-stage renal disease [3]. For these reasons, they are considered at high risk for contracting SARS-CoV-2 infection and for developing complications related to COVID-19 [4]. Despite several position papers that have been recently published to provide information regarding transmission reduction in HD facilities [4–8], at present, scant information is available regarding clinical course, management and prognosis of SARS-CoV-2 infection in dialysis patients. One case series from Wuhan, China, described 37 cases among HD patients in one centre, with 16.1% prevalence and six deaths (corresponding to 16% of SARS-CoV-2-positive patients). Mentioned causes of death were apparently unrelated to the infection (mainly cardiovascular and cerebrovascular disease or hyperkalaemia). Of note, during the same period, the authors report only one death among SARS-CoV-2negative dialysis patients [9].

The aim of this report is to describe demographic and clinical characteristics, laboratory and imaging findings, clinical course, treatments and outcomes in dialysis patients with SARS-CoV-2 infection in the Nephrology and Dialysis Unit at the 'Azienda Ospedaliero-Universitaria di Modena', Modena, Italy.

MATERIALS AND METHODS

We designed an observational, retrospective and prospective cohort study to assess clinical characteristics, treatments and outcomes of dialysis patients with SARS-CoV-2 infection. The primary objective was to describe the evolution of SARS-CoV-2 infection in dialysis patients in terms of clinical and laboratory data, treatments and outcomes. As a secondary objective, we divided patients into those who died and those who survived and compared clinical and laboratory characteristics between groups. We included dialysis patients who were diagnosed with SARS-CoV-2 infection or developed COVID-19 pneumonia and were followed at the Nephrology and Dialysis Unit or were hospitalized at the 'Policlinico' Hospital of the 'Azienda Ospedaliero-Universitaria di Modena', Modena, Italy. According to the World Health Organization guidance [10], laboratory confirmation for SARS-CoV-2 infection was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction assay of nasal and oropharyngeal swabs. Only laboratory-confirmed cases were included. COVID-19 was defined as SARS-CoV-2 infection plus clinical and radiological evidence of pneumonia. The study was approved by the ethical committee 'Comitato Etico dell'Area Vasta Emilia Nord' of the 'Azienda Ospedaliero-Universitaria di Modena' (protocol

number AOU 0010159/20); informed consent was waived. We collected demographic data, information of clinical symptoms and signs at presentation, laboratory and radiologic results, treatments and outcomes through hospital medical charts. All laboratory tests and radiological studies were performed at the discretion of the treating physician. Descriptive statistics were used to summarize the data. Continuous data were reported as median and interquartile range (IQR) or mean and standard deviation (SD), as appropriate; categorical variables were reported as number and percentage. Data were compared with Student's t-test, Mann–Whitney test and Fisher's exact test as appropriate. Statistical analysis was performed with GraphPad Prism version 6.01 (GraphPad Software, San Diego, CA, USA).

RESULTS

During the study period, our centre offered dialysis care to 235 patients on chronic HD and 71 on PD. Our tertiary-level hospital also functioned as a hub for dialysis patients coming from peripheral dialysis units in the province who needed specialist care.

We report the clinical data of dialysis patients in follow-up at our centre who tested positive for SARS-CoV-2 infection from 27 February to 7 April 2020. During this period, a total of 37 diagnostic swabs were performed in dialysis patients; we tested patients who presented with symptoms (mainly fever and cough) or who had contact with a confirmed case.

Since the beginning of the SARS-CoV-2 epidemic in northern Italy, appropriate screening and containment measures were instituted at our centre. Specifically, regular triage for HD patients before every dialysis session (or every visit for PD patients) was performed by a trained nurse to exclude symptoms consistent with the infection. If the patient was considered suspect, adequate precautions were undertaken and a diagnostic swab collected. HD patients who were known to be positive or were highly suspected were dialyzed in a separate room. Hospitalized patients underwent the same diagnostic procedure and were isolated in a dedicated single room, receiving dialysis there.

Fourteen patients (12 HD and 2 PD patients), corresponding to 38% of the tested patients and 5% of total dialysis patients, tested positive. An additional case coming from a peripheral dialysis unit and hospitalized in our institution was added to our cohort. Most patients [13/15 (87%)] developed COVID-19. None of our patients had a history of travel outside the province in the last 14 days. Five patients had been in contact with a patient with SARS-CoV-2 infection (three during a previous or current hospitalization, two at home). The median follow-up in our cohort was 10 days (IQR 6–23).

The demographic and clinical characteristics of the patients at the time of diagnosis of SARS-CoV-2 infection are detailed in Table 1. The mean age of patients was 75.96 ± 11.09 years, 87% were male and the median dialysis vintage was 3.95 years (IQR 0.44–6.24). All patients had comorbidities; the most significant ones were diabetes, hypertension, cardiovascular disease and obesity. Of note, none of our patients was receiving renin–angiotensin–aldosterone system inhibitors. Most HD patients (7/12) were treated with haemodiafiltration. The most common symptoms at presentation were fever (67%) and cough (73%); body temperature was often only mildly elevated (four patients had a temperature >37.5°C) and a minority of patients showed signs of respiratory distress.

Laboratory and radiological data from our patients at presentation are reported in Table 2. Notably, no patients had

Table 1. Clinical characteristics of the patients at the time of diagnosis

Characteristics	Patients (N = 15)
Age (years), mean (SD)	75.96 (11.09)
Sex, *n* (%)	
Male	13 (87)
Female	2 (13)
Body mass index, mean (SD)	25.18 (4)
Coexisting disorder, *n* (%)	15 (100)
Diabetes mellitus	8 (53)
Arterial hypertension	14 (93)
Cardiovascular disease	7 (47)
Obesity	4 (27)
Others	14 (93)
Symptoms, *n* (%)	
Fever	10 (67)
Cough	11 (73)
Dyspnoea	5 (33)
Asthenia	7 (47)
Myalgia	3 (20)
Gastrointestinal symptoms	0 (0)
Vital signs at first evaluation, mean (SD)	
Temperature >37.5°C	4 (27)
Heart rate >100 bpm	0 (0)
Respiratory rate >20/min	4 (27)
Mean arterial pressure (mmHg)	91.84 (13)

Table 2. Laboratory and radiological findings at presentation and evolution of laboratory parameters during follow-up

Laboratory and radiological findings	At presentation	During follow-up
Parameter	Patients (*n* = 15)	Patients (*n* = 15)
pO_2 (mmHg)		
Median (IQR)	72.75 (64.25–84.83)	59 (50.75–76.5)[a]
<60 mmHg, *n* (%)	0 (0)	6 (40)
pO_2:FIO_2		
Median (IQR)	337.5 (293.5–371.5)	262 (85–352.5)[a]
<200, *n* (%)	0 (0)	5 (33.33)
White blood cell count, $n/\mu L$		
Median (IQR)	5570 (4800–6930)	5570 (4490–6630)[b]
Distribution, *n* (%)		
>10.000/μL	1 (6.67)	
<4000/μL	1 (6.67)	1 (6.67)[b]
Lymphocyte count, $n/\mu L$		
Median (IQR)	870 (565–1115)	610 (530–1020)[b]
<1500/μL, *n* (%)	11 (73.33)	11 (73.33)[b]
Lactate dehydrogenase (U/L), median (IQR)	480 (408–498)	540 (426–907)[c]
D-dimer (ng/L), median (IQR)	1330 (960–3830)	1620 (960–3980)[c]
Platelets ($n/\mu L$), median (IQR)	170 (110–230)	155 (109–230)[b]
C-reactive protein (mg/dL), median (IQR)	2.8 (1.7–6.1)	12.4 (4.8–25.4)[c]
Procalcitonin (ng/mL), median (IQR)	0.95 (0.625–2.125)	
IL-6 (pg/mL), median (IQR)	167.4 (106.3–332.8)	269.8 (148.2–1843)[c]
Chest X-ray, *n* (%)	12 (80)	
No relevant alterations	2 (13.33)	
Interstitial infiltrates	8 (53.33)	
Lobar of multifocal consolidation	6 (40)	
Pleural effusion	3 (20)	
Chest CT scan, *n* (%)	1 (6.67)	

[a]Lowest values.
[b]Nadir levels
[c]Zenith levels.

respiratory insufficiency, as defined by a partial pressure of oxygen (pO_2) <60 mmHg or a pO_2:fraction of inspired oxygen (FIO_2) ratio <200. The most relevant laboratory alteration was lymphocytopaenia, present in roughly three-quarters of cases. The majority of patients showed alterations on chest X-rays, the most common being interstitial infiltrates. During follow-up, patients showed a deterioration of respiratory function, with ~30% of them developing at least moderate respiratory insufficiency (pO_2:FIO_2 <200). The presence of lymphocytopaenia was always confirmed and we observed an expected and marked increase in C-reactive protein (CRP) and interleukin-6 (IL-6) levels. Laboratory findings during follow-up are described in detail in Table 2.

All patients received adequate supportive care at the discretion of the treating physicians. Most patients (80%) received intravenous broad-spectrum antibiotic therapy; two patients (13%) received steroid infusion.

With respect to oxygen treatment, 13 patients (80%) received supplemental oxygen, with a median FIO_2 of 34% (IQR 27–52.5); no patients received non-invasive ventilation and one patient was intubated and died shortly thereafter.

Regarding off-label treatments for COVID-19, most patients [12/15 (80%)] received oral hydroxychloroquine (HCQ) at a median dose of 300 mg/day (IQR 125–400) and for a median time of 6.5 days (IQR 5–14.5). Six patients (40%) received oral azithromycin, always on top of HCQ treatment, at a dose of 500 mg/day for a median time of 5 days. Two patients received darunavir/cobicistat combination for a median time of 2 days. One patient received a single dose (324 mg) of subcutaneous tocilizumab. Six patients (40%) received prophylactic subcutaneous low molecular weight or calcium heparin injections.

Nine patients (60% of the total) required hospital admission and four (27% of the total) were already hospitalized at the time of diagnosis; only one patient with acute respiratory distress syndrome (ARDS) related to COVID-19 was admitted to the intensive care unit (ICU). The median duration of symptoms from diagnosis to hospital admission was 2 days (IQR 0.5–2.5). Only two patients (13% of the total) did not require hospitalization. Of the nine patients who survived the infection, three were discharged from the hospital [after a median time of 18 days (IQR 2–19)], three are still hospitalized, two are being monitored at home and one required hospitalization for other reasons. Interestingly, only this last patient showed evidence of viral clearance (two negative oropharyngeal and nasal swabs 24 h apart) after 21 days from initial detection. All other patients still test positive for SARS-CoV-2 at a median of 19 days (IQR 9.25–23) after diagnosis; of note, five of these patients had a follow-up of >14 days.

Six patients died in our cohort, a median of 5.5 days (IQR 1.75–9.75) after diagnosis. Five of them had respiratory failure or ARDS related to COVID-19 as the main reported cause of death; in one case, the main cause of death was sepsis. Additionally, multiple organ failure was mentioned in one case and cardiac ischaemia was mentioned in another as concurrent causes of death.

Comparisons between patients who died and survived did not show significant differences in demographics, received treatments and clinical and laboratory parameters, apart from serum CRP, which was significantly higher in the patients who died (see Table 3).

DISCUSSION

The world is now facing a pandemic of SARS-CoV-2 infection–causing COVID-19, which is unique in terms of its rapidity of growth and global involvement. Emerging infectious diseases represent an enormous threat of contagion to dialysis patients, who in turn are subjected to frequent in-centre accesses and hospitalizations and can substantially contribute to the spreading of the infection if specific diagnostic and containment manoeuvres are not undertaken.

Clinical course, prognosis and recommended management for dialysis patients who become positive for SARS-CoV-2 are unclear. Moreover, the impact of treatments other than best supportive care in this population has been scarcely reported.

Indeed, dialysis patients were poorly represented in recent case series of COVID-19 patients from the Italian outbreak. A recent study [11] including >1500 patients with severe disease requiring hospitalization in the ICU described only 36 of them as having chronic kidney disease, and the percentage of dialysis patients was not specified.

With respect to the COVID-19 Italian outbreak, Modena province is one of the most involved in the Emilia Romagna region (second most affected in the country), with a reported prevalence of SARS-CoV-2 infection in the population of 0.406% on 9 April 2020 [12]. We believe that our report contributes to describe the situation of dialysis patients with SARS-CoV-2 in a real-world setting, where rapid spreading of the infection is present and urgent action needs to be undertaken.

As a first consideration, the rapid application of containment measures appeared to be effective in limiting diffusion of the infection in our dialysis unit. After >1 month since the beginning of the epidemic in our city, we report only 14 cases among our dialysis patients. Indeed, since a previous report from China described a prevalence of the infection of 16% in an HD unit in Wuhan [9], a greater number of cases could have been expected in an area with rapid disease expansion such as our city. This finding underlines the importance of implementing strict protocols for minimizing risks of transmission in dialysis units, with measures of prevention through active triage of patients before dialysis sessions, protection of personnel and isolation of suspected and confirmed cases.

Notably, most of our patients presented with mild symptoms and none of them had respiratory insufficiency at the first evaluation, despite the disease showing a severe course in many shortly thereafter. Clinicians should be aware that symptoms and signs of SARS-CoV-2 infection can be subtle in the early phases, requiring a high degree of suspicion and imposing logistical challenges in order to isolate suspected cases.

In line with findings described in the non-dialysis population, the majority of our patients with COVID-19 were males of older age and with several comorbidities [13]. Lymphocytopaenia was common at presentation and during follow-up, and the main finding on chest X-ray was the presence of interstitial infiltrate. Most clinical and laboratory data were not different in patients who died compared with survivors. Even if some parameters were notably higher in the non-survivor group (see Table 3), statistical significance was reached only for CRP, likely due to the small number of patients included. We suggest strict monitoring of inflammatory indices in COVID-19 dialysis patients, since they could help identify patients with a poor prognosis.

Several drugs are currently being used off-label for the treatment of COVID-19. Our study was not designed to assess the effect of therapies; nevertheless, we believe it is important to report treatments and their case-by-case effects, as data on dialysis patients are extremely scarce.

There is mounting enthusiasm regarding the use of the antimalarial HCQ against SARS-CoV-2, since a small non-randomized clinical trial from France showed that infected

Table 3. Comparison between patients who died and survived

Parameter	Patients who died ($n = 6$)	Survivors ($n = 9$)	P-value
Age (years), mean (SD)	75.46 (10.04)	76.3 (12.32)	0.89
Dialysis vintage (years)	2.89 (0.14–5.06)	5.71 (1.36–9)	0.22
Sex (% of males)	83.33	88.89	1
Body mass index, mean (SD)	25.55 (4.41)	24.98 (4.08)	0.81
Diabetes (%)	83.33	33.33	0.12
Obesity (%)	33.33	22.22	1
Lowest pO_2 (mmHg)	53 (47.95–104)	60 (54.9–72)	1
Lowest pO_2:FIO_2	100 (50–377.5)	274 (146–300)	0.5
White blood cell count nadir (n/uL)	5655 (5153–8497)	4800 (4375–6305)	0.18
Lymphocyte count nadir (n/uL)	540 (465–2135)	705 (545–995)	0.75
Lactate dehydrogenase zenith (U/L)	548 (444–1383)	532 (421–870)	0.63
D-dimer zenith (ng/L)	1510 (1330–1860)	2445 (892–3965)	1
Platelets nadir (n/uL)	141 (105–247)	166 (107–220)	0.9
C-reactive protein zenith (mg/dL)	26.15 (16.93–34.38)	7.5 (4.35–13.15)	0.02
IL-6 zenith (pg/mL)	470 (355.8–2405)	152.8 (107.9–1241)	0.14
Specific treatments (%)			
Hydroxychloroquine	66.66	88.88	0.52
Azithromycin	33.33	44.44	1
Darunavir/cobicistat	16.66	11.11	1
Heparin	44.44	33.33	1
Tocilizumab	0	11.11	1

Values are expressed as median (IQR) unless stated otherwise.

patients treated with HCQ were more likely to achieve virologic clearance [14]. Despite poor-quality evidence, given the lack of alternative effective treatments, the relatively safe toxicity profile and its wide availability, many centres in Italy have adopted HCQ as a first-line strategy in patients with COVID-19. According to the manufacturer's instructions, there is no dosage adjustment in patients with chronic kidney disease. Nevertheless, renal clearances of the drug account for up to a quarter of the total, and dose reduction should be considered with chronic use. Since treatment was prolonged >7 days in our patients due to limited clinical and virologic response, the dose was reduced (median 300 mg/day) compared with standard treatment. We have not reported side effects of HCQ in our treated dialysis patients until now. A synergistic effect of azithromycin together with HCQ to enhance viral clearance has been reported [14], and azithromycin was prescribed in less than half of our dialysis patients. Since both drugs have been reported to prolong the QT interval, patients should undergo baseline electrocardiogram for corrected QT evaluation and subsequent monitoring during treatment.

The role of antivirals in COVID-19 is controversial. After initial promising results of lopinavir-based combinations [15] in a recently published randomized clinical trial, no benefit was observed with lopinavir–ritonavir treatment beyond standard care [16]. In our institution, lopinavir-based antivirals have been frequently replaced by darunavir-based combinations, according to pharmacy stock availability and considering a similar mechanism of action. The experience with antivirals in our dialysis patients is very limited.

It is currently believed that the severity of pulmonary involvement in SARS-CoV-2 infection is mainly driven by an excessive inflammatory response mounted by the host immune system in response to the pathogen. Indeed, inflammation-related indices have been reported to be higher in patients with COVID-19 pneumonia who develop ARDS compared with those who do not; interestingly, IL-6 was significantly more elevated in these patients [17]. The use of tocilizumab, a humanized monoclonal antibody that competitively inhibits IL-6, is currently being investigated in a multicentre study in Italy [18]. In order to reduce the inflammatory response in the lung, we decided to administer off-label tocilizumab to the youngest of our dialysis patients (50 years old at the time of diagnosis), also supported by high levels of IL-6 in the blood. The patient is currently hospitalized in our service (Day 22), with slowly improving pulmonary function under supplemental oxygen and a progressive reduction of interstitial infiltrates on chest X-ray.

Not surprisingly, most patients in our cohort required hospitalization, often for >2 weeks. Clinicians should consider that hospitalized dialysis patients will need to continue to receive renal replacement treatment in isolation conditions; in our centre, this was most easily achieved by delivering dialysis to the patient's room. Technical and organizational aspects of this procedure should be taken into account in the replanning of nephrology units during the SARS-CoV-2 epidemic.

When to consider a survived patient cured from SARS-CoV-2 infection is of crucial importance. To assess the persistence of viral shedding in positive patients, our local practice is to repeat nasal and oropharyngeal swabs after 14 days from the initial diagnosis. If two consecutive swabs 24 h apart are negative, the patient is considered no longer infectious. In our cohort, survivor patients showed prolonged viral positivity after the resolution of clinical symptoms. Indeed, it was previously observed by Zhou et al. [13] that the median time of viral shedding persistence is 20 days in inpatients with COVID-19. In this cohort,

patients with baseline chronic kidney disease made up only 1% of the subjects (with no information regarding dialysis status) and 10% of all subjects required renal replacement therapy during admission. Moreover, patients with more severe disease in a smaller cohort described by Liu et al. [19] were reported to have a longer course before negativity; unfortunately, no data regarding kidney function are available in this study. We reinforce the concept that strict surveillance and isolation of dialysis patients who survive the disease is of paramount importance beyond the symptomatic period and for >14 days to avoid further contamination of dialysis units.

COVID-19 had a poor prognosis in our infected dialysis patients. While a case fatality rate of 7% (with peaks of 20% in patients >80 years of age) had been reported in Italy in mid-March 2020 [20], in our small cohort of dialysis patients with SARS-CoV-2 infection the case fatality rate is presently 40%. Since dialysis patients are often of older age and with several comorbidities, the infection is expected to have a very severe course. Moreover, for the same reasons, these patients are less likely to benefit from access to the ICU and are less often offered this option, a fact that can contribute to explaining the high number of deaths. In our cohort, only one patient was admitted to the ICU for ARDS related to COVID-19 during the first days of the outbreak in our city. For all the other patients who died, high-intensity care was considered non-beneficial, taking into account the high burden of comorbidities and understanding the importance of advance care planning in the present circumstances [21]. This issue was extensively discussed with patients and with their families whenever possible.

Our study has several limitations. First, it includes a small number of patients, which limits generalizations of our findings. Nevertheless, given the extremely fast growth of the pandemic of SARS-CoV-2 worldwide, we believe it is of paramount importance to report infection rates, management of cases and prognosis in special populations before the results of large clinical trials become available.

Second, due to limited laboratory capacity, screening for SARS-CoV-2 infection is not currently available in our hospital and diagnostic tests are performed only on clinical indication. It is then possible that the diffusion of the infection is undervalued and its severity overestimated in our report, since asymptomatic cases were excluded. In this regard, widespread screening for anti-SARS-CoV-2 antibodies could help in defining a clearer picture. In addition, since treatments against SARS-CoV-2 were administered to our dialysis patients off-label as compassionate use, we are unable to provide definitive data on their efficacy.

In conclusion, we report a single-centre experience of SARS-CoV-2 infection and COVID-19 in dialysis patients. The disease had a very high case fatality rate in our cohort and most patients required hospitalization; survivors showed prolonged viral shedding. Further multicentre studies including a larger number of dialysis patients could contribute to define a more precise case fatality rate, identify clinical and laboratory characteristics associated with poor outcome and describe the role of specific treatments.

AUTHORS' CONTRIBUTIONS

F.F. conceived the study, collected and analysed the data and wrote the manuscript. F.G., M.F. and L.L. collected the data. G.A. and G.M. collected the data and contributed to the analysis. R.M. and G.C. critically revised the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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