The keys to control a COVID-19 outbreak in a haemodialysis unit

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ABSTRACT

Background. The high rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreading represents a challenge to haemodialysis (HD) units. While fast isolation of suspected cases plays an essential role to avoid disease outbreaks, significant rates of asymptomatic cases have recently been described. After detecting an outbreak in one of our HD clinics, wide SARS-CoV-2 screening and segregation of confirmed cases were performed.

Methods. The entire clinic population, 192 patients, underwent testing for SARS-CoV-2 detection by real-time reverse-transcriptase polymerase chain reaction. We used univariate and multivariate logistic regression to define variables involved in SARS-CoV-2 infection in our dialysis unit. Later, we analysed differences between symptomatic and asymptomatic SARS-CoV-2-positive patients.

Results. In total, 22 symptomatic and 14 of the 170 asymptomatic patients had a SARS-CoV-2-positive result. Living in a nursing home/homeless [odds ratio (OR) 3.54; P = 0.026], having been admitted to the reference hospital within the previous 2 weeks (OR 5.19; P = 0.002) and sharing health-care transportation with future symptomatic (OR 3.33; P = 0.013) and asymptomatic (OR 4.73; P = 0.002) positive patients were independent risk factors for a positive test. Nine positive patients (25.7%) remained asymptomatic after a 3-week follow-up. We found no significant differences between symptomatic and asymptomatic SARS-CoV-2-positive patients.

Conclusions. Detection of asymptomatic SARS-CoV-2-positive patients is probably one of the key points to controlling an outbreak in an HD unit. Sharing health-care transportation to the dialysis unit, living in a nursing home and having been admitted to the reference hospital within the previous 2 weeks, are major risk factors for SARS-CoV-2 infection.

Keywords: asymptomatic carriers, COVID-19, dialysis, haemodialysis, outbreak, outcomes, risk factors
INTRODUCTION

The World Health Organization (WHO) characterized coronavirus disease 2019 (COVID-19), the disease caused by the newly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], as a pandemic on 11 March. International guidelines [2, 3] and general and local recommendations [4–6] focus on the importance of hygiene measurements and rapid identification and isolation of COVID-19-positive patients for preventing infection spread. Dialysis patients usually have a high burden of associated comorbidities and are more prone to develop severe complications of the disease. Measures of isolation are of special importance in dialysis units, since many patients need to be repeatedly treated at the same dialysis area and require transportation for at least thrice-weekly treatment. Thus, early identification of COVID-19 cases is highly necessary to cohort them.

The WHO-China Joint Mission on Coronavirus Disease 2019 [7] found that asymptomatic cases were relatively rare on the date of identification and most of them went on to develop the disease. Truly asymptomatic infections were not frequent and did not appear to be a major driver of transmission. However, significant rates of asymptomatic cases have been described by other authors [8–11], and some recent papers [12–17] propose transmission from pre-symptomatic or asymptomatic cases. Although the pre-symptomatic infectious period is not well defined, some preliminary data [18–20] suggest that it might be around 2 days before the onset of symptoms. The presence of asymptomatic or pre-symptomatic contagious patients can be a major epidemiological drawback for COVID-19 spread prevention in dialysis units.

However, scarce information is available about the infection in dialysis patients, and the rate of asymptomatic cases has not been well characterized. Based on data from Wuhan [21] and the first outbreak in Lombardy [5], COVID-19 infection could affect up to 10–30% of dialysis patients.

On 25 February 2020, to minimize the COVID-19 cross-infection risks, strict protocol measures based on international recommendations [4, 22, 23] were implemented in all Fresenius Medical Care (FMC) clinics in Spain as well as in 28 different countries included in the FMC EMEA (Europe, Middle East and Africa) region. Any person with suspected infection was isolated before starting haemodialysis (HD) treatment.

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Despite previous prevention measures, during the second half of March, there was a COVID-19 outbreak in one of our HD clinics. Based on general recommendations, a nasopharyngeal swab SARS-CoV-2 polymerase chain reaction (PCR) testing was performed in all patients of this clinic.

The aim of this study was to analyse possible variables involved in SARS-CoV-2 transmission and the differences between symptomatic and asymptomatic SARS-CoV-2-positive dialysis patients.

MATERIALS AND METHODS

Study population

We present an analytical observational study where a population of 192 end-stage kidney disease patients in HD treatment were tested for SARS-CoV-2 infection. All of them received regular HD treatment in a single centre placed within L’Hospitalet de Llobregat, Barcelona, Spain.

Between 20 and 28 March 2020, a total of 22 (11.5%) patients reported COVID-19-compatible symptoms to the clinical staff and were tested and diagnosed with COVID-19 disease (‘initial screened patients’). After the confirmation of positive results and as part of containment measures, from 30 March to 31 March, the rest of the patients from the centre—170 asymptomatic patients—were also tested by real-time reverse-transcriptase PCR (RT-PCR). Fourteen out of the 170 asymptomatic patients had a SARS-CoV-2-positive result (Figure 1A) and an isolated COVID-19-specific room was created in a different clinic, to which asymptomatic COVID-19-positive patients were transferred. All cases were followed up within 3 weeks after testing.

All patients had previously been informed about data privacy and had provided written informed consent for the use of their data to conduct scientific research. Clinical data were extracted from the European clinical database from FMC (EuCliD).

SARS-CoV-2 tests

Nasopharyngeal swabs were collected by the clinical staff, stored between 2°C and 8°C and processed within 24 h. The specimens corresponding to the initial screened patients were processed, according to their protocol, by the Central Laboratory of Hospital Universitari Bellvitge (Barcelona, Spain). Furthermore, those samples from the rest of the screened patients were managed by Synlab Diagnosticos Globales S.A. (Barcelona, Spain). According to supplier’s availability, two kits were used: ‘TaqMan® 2019-nCoV Assay Kit v2 from Applied Biosystems (ThermoFisher Scientific, Pleasanton, CA, USA) and VIASURE SARS-CoV-2 Real Time PCR Detection Kit (Cerette Biotec, Zaragoza, Spain).

Study variables

Age, gender, Charlson Comorbidity Index, basal (February 2020) laboratory parameters (leucocytes, lymphocytes, sodium, C-reactive protein, ferritin and albumin), concomitant medication (angiotensin-converting enzymes (ACEs), angiotensin II receptor blockers (ARBs) and non-steroidal anti-inflammatory drugs (NSAIDs)), dialysis session details, hydration status measured by Body Composition Monitor (Fresenius Medical Care), symptoms and patients’ outcomes were all extracted from EuCliD.

Kt/V is measured in every dialysis session through the OCM (Online Clearance Monitor). The previous month (February) mean value was calculated. The average of relative overhydration (AvROH) (pre-dialysis minus normohydrated weight and adjusted per extracellular water) was calculated.

The prevalence of COVID-19 infection associated with the patients’ residence area was calculated. We used the data published by the Catalan Quality and Assessment Health Agency (Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQUAS)) [24]. The zip code from each patient’s address was obtained from EuCliD and then matched to the prevalence (rate per 10,000 residents) of COVID-19 infection within that zip code area.

At no point were COVID-19-diagnosed patients receiving dialysis treatment together with the rest of patients in the clinic. However, based on a recent publication [25], we assumed a pre-symptomatic infectious period of 6 days. We registered the patients who had been dialysed by the same nurse, in the same room and in adjacent dialysis machines as a patient who...
developed symptoms within 6 days and was diagnosed with COVID-19.

Information about patients living in nursing homes, those who were attended at the reference hospital for any cause within the previous 2 weeks and patient’s health-care transportation was collected.

All these data were saved in an independent database where the subjects’ identities were anonymized.

Statistical analysis

Data are presented as mean values with standard deviation (SD) for normally distributed variables, medians with interquartile range (25th–75th percentile) for non-normally distributed variables and percentages for categorical variables. Chi-square test, Student’s t-test or Mann–Whitney U test were used for univariate analyses, based on variable characteristics.

First, variables involved in SARS-CoV-2 transmission in our centre were analysed using a univariate approach. Variables that statistically related to transmission in univariate analyses were included in a multivariate logistic regression. Linear relationship between continuous predictors and the logit of the outcome variable and no multi-collinearity (tolerance and variance inflation factor statistics) assumptions were checked.

Later, we analysed the differences between symptomatic and asymptomatic SARS-CoV-2-positive patients to look for variables associated with an asymptomatic infection.

All P-values are two-sided. Statistical significance was set at P < 0.05. Statistical analyses were performed using IBM SPSS statistics version 19 (IBM Corp., Armonk, NY, USA).

RESULTS

This study included 192 chronic dialysis patients from a single FMC centre in Spain. The mean age was 74.3 ± 12.6 years.

A first group of 22 symptomatic patients was initially tested and confirmed as positive for COVID-19 disease. After this finding, the rest of the patients from the clinic, asymptomatic at that moment, were also screened. Fourteen out of 170 asymptomatic patients had a SARS-CoV-2-positive result. One patient was considered as lost to follow-up. Since early April, four patients COVID-positive who remained asymptomatic communicated the appearance of COVID-19 symptoms. However, a group of nine patients remained totally asymptomatic after a follow-up of 21 days. “+, positive population; “, negative population; FUp, follow-up. (B) Cumulative incidence of the number of COVID-19-positive cases along the study.

Differences between SARS-CoV-2-positive and -negative patients

Regarding demographic data, we found no significant differences in age, sex or dialysis vintage between negative and positive SARS-CoV-2 patients. However, while Charlson Comorbidity Index median values resulted identical between both groups of patients, we found that 8.3% of the positive cases presented moderate/severe hepatic disease compared with negative patients, among which only 0.6% presented this comorbidity (P = 0.02). Sodium levels were lower in SARS-CoV-2-positive patients (135.5 ± 3.38 versus 136.89 ± 2.8 mmol/L; P = 0.01) and
they were significantly more overhydrated (13.35 ± 11.77 versus 9.58 ± 8.99; P = 0.03) (Table 1).

Regarding the factors directly related to a social environment shared and/or contact interactions, we found a higher incidence of positive cases in homeless patients or living in nursing homes (25% versus 7.7%; P = 0.006), in patients that had visited a hospital at least 2 weeks prior to being tested (30.6% versus 9%; P = 0.002) and/or had shared health-care transportation with a future symptomatic (41.7% versus 13.5%; P < 0.001) or asymptomatic (36.1% versus 10.3%; P < 0.001) positive patient. On the other hand, the location of the normal area of residence did not determine any significant difference between the positive and negative patients (Table 1).

We found no differences in receiving dialysis in the same room, sharing the same nurse or receiving treatment in adjacent monitors as a future positive (Table 1).

Multivariate logistic regression confirms that sharing health-care transportation with future symptomatic and asymptomatic positive patients, living in a nursing home/homeless and having attended at the hospital in the prior 2 weeks were independent risk factors for getting a positive PCR test (Table 2).

Differences between symptomatic and asymptomatic SARS-CoV-2-positive patients

A total of four patients who were initially asymptomatic developed clinical symptoms related to COVID-19 disease a few days after performance of PCR (0, 2, 2 and 11 days, respectively). These pre-symptomatic patients were then classified as symptomatic for the following analysis. In total, we found that 26 (74.3%) of the positive cases were symptomatic and 9 (25.7%) remained asymptomatic until the end of the 3-week follow-up period (Figure 1A). The frequencies of each symptom are described in Table 3.

We did not find any statistically significant difference among the demographic characteristics, the laboratory parameters or the social environment-related variables analysed between symptomatic and asymptomatic patients (Table 4).

Evolution of the outbreak after the screening

After wide screening and segregation of asymptomatic SARS-CoV-2-positive patients, there was a reduction in the incidence of new cases (18.7%, 95% CI 16.6–20.9 versus 1.3%, 95% CI 1.1–1.5). Only two new patients had been diagnosed with COVID-19 infection, one was a homeless and the other living in a nursing home (Figure 1B).

Seven patients from the COVID-19-positive population died during their hospitalization period [median age 80 (75–85) years; six males and one female].

DISCUSSION

In the present study, we described the incidence, clinical symptoms, risks factors and management of an outbreak of SARS-CoV-2...
Until now, there have been very few reports of SARS-CoV-2 outbreaks in dialysis units to allow us to better manage this situation. The first outbreak in an HD unit in Europe was described in Lombardy (Italy) [5]. In a satellite HD centre, 18 out of 60 treated patients (30%) were diagnosed over 1 week. During this time, the nephrology unit was transformed into an isolation unit and the 18 patients were treated in a small, dedicated dialysis ward set up to deal with the emergency, separated from the main dialysis ward. Despite no universal screening being done, the rigidly implemented isolation measures were effective and no other patient developed a clinical picture thereafter. However, the lack of precise knowledge about the natural history of the disease and the awareness that even nonsymptomatic or oligosymptomatic cases may spread the infection led us to perform screening for all patients once the outbreak appeared.

We investigated risk factors for SARS-CoV-2 infection and inferred that neither demographic nor lab data were associated with risk. Interestingly, positive SARS-CoV-2 patients had lower basal sodium levels and were more overhydrated previously to being infected. The hypothesis that these two factors, aside from social distancing, may in part explain and facilitate the infection has not been reported before, and should be interpreted with caution due to the small sample size.

As expected, by univariate and multivariate regression analysis we found that (i) sharing health-care transportation to the dialysis unit, (ii) living in a nursing home and (iii) having been admitted to the reference hospital within the previous 2 weeks are major risk factors for SARS-CoV-2 infection.

(i) The first result confirmed the recommendation of maintaining social distancing. The CDC Community Mitigation Framework (CDC COVID-19 Response Team) recommends a phased approach to be implemented at the community level, according to its incidence and its severity [26]. This measure means not only a big challenge for our patients, who are unable to ‘stay at home’ because of the need for thrice-weekly treatments, but also for the transportation providers, who had to take extreme precautions to keep at least 2 m distant from patients. The small size of the waiting hall (20 m²) of the dialysis ward probably also contributed to the spread of the infection. Therefore, measures directed at reducing the use of shared transport to the dialysis units (e.g. transfer by families, individual transport by ambulance or taxi) will reduce the spread of infection. Moreover, the Spanish government declared a total lockdown in the country on 15 March, helping to control the spread of infection in the general population.

(ii) Of noteworthy importance is the risk of transmitting infection to the elderly, particularly those over the age of 60 years [27]. One of the most vulnerable and affected populations for the COVID-19 infection in the reported papers [25] has been people living in nursing homes. A high number of deaths among this vulnerable population has been described, related to small outbreaks despite the strict measures implemented by the government [28].

(iii) Patients who visited the reference hospital during the 2 weeks before the PCR test were more likely to become infected, suggesting the importance of considering the hospital as a potential hot spot for COVID-19 [29].

When new respiratory infectious diseases become widespread, such as during the COVID-19 pandemic, health-care

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**Table 2. Multivariate logistic regression for a positive SARS-CoV-2 result**

| Variables | OR     | 95% CI   | P-value |
|-----------|--------|----------|---------|
| Contact(s) in health-care transport shared with a future symptomatic positive | 3.33 | 1.3–8.55 | 0.013 |
| Contact(s) in health-care transport shared with a future asymptomatic positive | 4.73 | 1.74–12.87 | 0.002 |
| Nursing home/homeless | 3.54 | 1.16–10.81 | 0.026 |
| Prior visit(s) to hospital | 5.19 | 1.84–14.66 | 0.002 |
| Overhydration, % | 1.02 | 0.98–1.07 | 0.331 |
| Na⁺, mmol/L | 0.91 | 0.79–1.05 | 0.209 |

**Table 3. Frequencies of symptoms attending to its presence in COVID-19-positive patients**

| Variables | Patients | % |
|-----------|---------|---|
| Asymptomatic | 9/35 | 25.7 |
| Symptomatic | 26/35 | 74.3 |
| Hospitalization | 23/26 | 88.5 |
| Pneumonia | 21/26 | 80.8 |
| Fever >37.5°C | 19/26 | 73.1 |
| Cough | 17/26 | 65.4 |
| General malaise | 13/26 | 50.0 |
| Dyspnea | 11/26 | 42.3 |
| Feverishness | 5/26 | 19.2 |
| Gastrointestinal discomfort | 3/26 | 11.5 |
| ICU requirement | 1/26 | 3.8 |
| Exitus | 7/26 | 26.9 |

Asymptomatic and symptomatic percentages were calculated referred to total COVID-19-positive population. Each symptom percentage represents its frequency referred to the total of COVID-19-positive symptomatic population. ICU, intensive care unit.

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workers’ adherence to infection prevention and control (IPC) guidelines becomes even more important. Houghton et al. [30] highlighted the importance of including all facility staff when implementing the IPC guidelines. Interestingly, there was no transmission from health professionals working at the dialysis unit to patients, since we were not able to find any association between nurses treating positive patients and the spread of infection.

In this outbreak, we observed that 25% of patients on dialysis were asymptomatic carriers of SARS-CoV-2. Despite the prevalence of asymptomatic carriers of SARS-CoV-2 infection has not been well-characterized until now; this figure is much larger than the 1.2% reported from the Chinese CDC [31] in more than 44 000 confirmed cases and it is close to the estimated asymptomatic proportion of 17.9% (95% CI 15.5–20.2) among SARS-CoV-2 cases aboard the Diamond Princess cruise ship in Japan [10]. In a large study to trace close contacts of confirmed cases (206 confirmed cases) in two centres from China, the prevalence of the silent infection of COVID-19 was 5.8% (95% CI 3.4–9.9), and was more likely to occur in young adults without chronic diseases [9].

We did not observe any demographic or clinical data that differentiate asymptomatic from symptomatic patients. In fact, asymptomatic carriers of SARS-CoV-2 infection were old patients (mean age of 76 years) with high comorbidities (median Charlson Comorbidity Index of 4). Thus, there will be individual factors not controlled in this study that will explain why some patients did not experience symptoms.

In summary, we described an outbreak of SARS-CoV-2 infection in an HD unit located in the metropolitan area of Barcelona (Spain). Testing by PCR of nasopharyngeal swabs

| Table 4. Baseline characteristics of COVID-19-positive population |
|---------------------------------------------------------------|
| Variables | Symptomatic n = 26 | Asymptomatic n = 9 | P-value |
| Age, years | 72.35 ± 12.86 | 76.67 ± 13.86 | 0.40 |
| Gender, female | 5 (19.2) | 2 (22.2) | 1.00 |
| Dialysis vintage, months | 29 (9.75–45.75) | 21 (12.5–35.5) | 0.54 |
| Body mass index, kg/m² | 26 (23–28.25) | 26 (24–32) | 0.38 |
| Charlson Comorbidity Index | 3.5 (2–6.25) | 4 (3.5–6.5) | 0.31 |
| Co-existing conditions (%) | | | |
| Coronary artery disease | 0 (0) | 2 (22.2) | 0.06 |
| Congestive heart disease | 7 (26.9) | 2 (22.2) | 1.00 |
| Peripheral vascular disease | 4 (15.4) | 2 (22.2) | 0.64 |
| Cerebrovascular disease | 4 (15.4) | 0 (0) | 0.55 |
| Chronic pulmonary disease | 6 (23.1) | 2 (22.2) | 1.00 |
| Diabetes | 12 (46.2) | 6 (66.7) | 0.44 |
| Hepatic disease | 2 (7.7) | 1 (11.1) | 1.00 |
| Treatments | | | |
| ACEI/ARB | 0 (0) | 1 (11.1) | 0.26 |
| Calcimimetics | 4 (15.4) | 1 (11.1) | 1.00 |
| Vitamin D | 13 (50) | 5 (55.6) | 1.00 |
| NSAIDs | 6 (23.1) | 5 (55.6) | 0.10 |
| Corticoids | 5 (19.2) | 2 (22.2) | 1.00 |
| Statins | 12 (46.2) | 5 (55.6) | 0.71 |
| Body composition | | | |
| AvROH (%) | 12.27 ± 9.09 | 13.51 ± 16.02 | 0.78 |
| Lean Tissue Index, kg/m² | 12.38 ± 3.27 | 12.63 ± 3.3 | 0.84 |
| Fat Tissue Index, kg/m² | 12.55 ± 4.26 | 14.77 ± 7.06 | 0.27 |
| Laboratory values | | | |
| Na⁺, mmol/L | 135.23 ± 3.57 | 136.78 ± 2.33 | 0.24 |
| K⁺, mmol/L | 5.1 ± 0.73 | 4.9 ± 0.6 | 0.45 |
| Leucocytes, no./mm³ | 6600 (5300–8625) | 6100 (4500–8400) | 0.47 |
| Lymphocytes, no./mm³ | 1057.15 (555.35–1467.18) | 992.2 (857.2–1697) | 0.54 |
| Haemoglobin, g/dL | 11.18 ± 1.52 | 10.91 ± 0.86 | 0.62 |
| 25-hydroxyvitamin D, ng/mL | 23.43 ± 10.55 | 23.99 ± 12.21 | 0.90 |
| Ferritin, μg/L | 324.5 (164.75–449.75) | 377 (288.5–590.5) | 0.34 |
| C-reactive protein, mg/L | 6.52 (2.73–14.92) | 8.35 (1.66–14.58) | 0.99 |
| Albumin, g/dL | 4.05 (3.6–4.3) | 3.8 (3.55–4) | 0.18 |
| Dialysis parameters | | | |
| Pre-dialysis systolic blood pressure, mmHg | 142.08 ± 17.76 | 140.56 ± 13.33 | 0.82 |
| Online haemodilatation (%) | 24 (92.3) | 9 (100) | 1.00 |
| Kt/V | 1.71 (1.55–1.99) | 1.62 (1.42–1.87) | 0.32 |

Baseline characteristics: last available data before PCR performance. All laboratory parameters correspond to the previous month measurement, excepting 25-hydroxyvitamin D (6 months). Values are represented as mean ± SD, medians with interquartile range (25th–75th percentile) or n (%).
asymptomatic carriers and enabled them to be properly isolated, leading to control of the spread of infection. The main risk factors for SARS-CoV-2 infection were sharing health-care transportation, living in a nursing home and having been admitted to the reference hospital within the previous 2 weeks. Thus, we recommend screening for SARS-CoV-2 infection for all patients treated in dialysis clinics that suffer an outbreak, in order to mitigate the spread of infection. Of course, accurate and strict implementation of recommended general practices is mandatory to reduce the risk of outbreaks in the first place.

CONFLICT OF INTEREST STATEMENT

None declared.

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