Clinical Kidney Journal, 2021, vol. 14, no. 4, 1222–1228

doi: 10.1093/ckj/sfab019
Advance Access Publication Date: 1 February 2021
Original Article

ORIGINAL ARTICLE

Arterial oxygen saturation and hypoxemia in hemodialysis patients with COVID-19

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ABSTRACT

Background. Maintenance hemodialysis (MHD) patients are particularly vulnerable to coronavirus disease 2019 (COVID-19), a viral disease that may cause interstitial pneumonia, impaired alveolar gas exchange and hypoxemia. We ascertained the time course of intradialytic arterial oxygen saturation (SaO_2) in MHD patients between 4 weeks pre-diagnosis and the week post-diagnosis of COVID-19.

Methods. We conducted a quality improvement project in confirmed COVID-19 in-center MHD patients from 11 dialysis facilities. In patients with an arterio-venous access, SaO_2 was measured 1×/min during dialysis using the Crit-Line monitor (Fresenius Medical Care, Waltham, MA, USA). We extracted demographic, clinical, treatment and laboratory data, and COVID-19-related symptoms from the patients' electronic health records.

Results. Intradialytic SaO_2 was available in 52 patients (29 males; mean ± standard deviation age 66.5 ± 15.7 years) contributing 338 HD treatments. Mean time between onset of symptoms indicative of COVID-19 and diagnosis was 1.1 days (median 0; range 0–9). Prior to COVID-19 diagnosis the rate of HD treatments with hypoxemia, defined as treatment-level average SaO_2 <90%, increased from 2.8% (2–4 weeks pre-diagnosis) to 12.2% (1 week) and 20.7% (3 days pre-diagnosis). Intradialytic O_2 supplementation increased sharply post-diagnosis. Eleven patients died from COVID-19 within 5 weeks. Compared with patients who recovered from COVID-19, demised patients showed a more pronounced decline in SaO_2 prior to COVID-19 diagnosis.

Conclusions. In HD patients, hypoxemia may precede the onset of clinical symptoms and the diagnosis of COVID-19. A steep decline of SaO_2 is associated with poor patient outcomes. Measurements of SaO_2 may aid the pre-symptomatic identification of patients with COVID-19.

Keywords: chronic kidney disease, COVID-19, hemodialysis, hypoxemia, oxygen saturation

Received: 27.10.2020. Editorial decision: 11.1.2021

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INTRODUCTION

The clinical spectrum of coronavirus disease 2019 (COVID-19) varies from asymptomatic to life-threatening, with respiratory and multiorgan failure [1–6]. Older age and comorbidities, including chronic kidney disease and dialysis, are risk factors for adverse outcomes [4, 7].

COVID-19 may cause interstitial pneumonia and impaired gas exchange. Measurement of arterial oxygen saturation (SaO_2) provides an easy-to-use, non-invasive means to assess blood oxygenation. Hypoxemia, conventionally defined as an SaO_2 <90%, is a harbinger of clinical instability and progressive hypoxemia is associated with poor outcomes in patients with pulmonary diseases [8]. SaO_2 is used to evaluate the severity of the COVID-19, although it is not widely applied [5, 9]. In the general population, previous studies reported SaO_2 <90% in around 40% of COVID-19 patients at the time of hospital admission [9, 10]. A retrospective study in 36 hospitalized maintenance hemodialysis (MHD) patients with COVID-19 reported a SaO_2 <95% in 61% of the patients; a report of 23 hospitalized MHD patients with COVID-19 indicated a hypoxemia rate of 16% [11, 12]. However, these studies were focused on hospitalized MHD patients; data are limited on non-hospitalized in-center MHD patients.

In MHD patients with arterio-venous vascular access, the Crit-Line monitor (CLM) affords the opportunity to quasi-continuously measure SaO_2 during HD. The goal of our analysis was to interrogate routinely collected intradialytic SaO_2 data to ascertain the frequency and degree of hypoxemia in COVID-19 MHD patients before and after diagnosis.

MATERIALS AND METHODS

Population

In this quality improvement project, we focus on MHD patients with confirmed COVID-19 dialyzed in 11 US facilities [seven from the Renal Research Institute (RRI); four from Fresenius Kidney Care (FKC)]. We report observations between 1 February and 30 April 2020. In these clinics, the CLM (Fresenius Medical Care, Waltham, MA, USA) is used as standard of care. Only patients with arterio-venous access and eligible SaO_2 measurements (for definition see below) were included in our analysis. We extracted demographic, clinical, treatment-related and laboratory data, and COVID-19-related signs and symptoms from the patients' electronic health records (EHR). The use of supplemental O_2 during dialysis was documented in the EHR. We defined 'silent' hypoxemia as the presence of SaO_2 <90% without administration of supplemental O_2. This quality improvement protocol was approved by corresponding committees and legal and compliance officers. Informed consent was waived.

Screening for and diagnosis of COVID-19

Since 12 March 2020, all in-center MHD patients and clinic staff underwent a systematic screening process prior to admittance to their clinics. They were required to wear gloves and surgical masks while being in the dialysis facility. A trained healthcare worker asked standardized questions regarding recent travel, contact with COVID-19 patients, fever and respiratory symptoms. Body temperature was measured (threshold for a positive test was 37.4°C), and the entrance screening results were documented. Patients who screened negative were admitted to the dialysis facility, where they had again their body temperature measured. Nasopharyngeal or oropharyngeal swabs for reverse transcription polymerase chain reaction (RT-PCR) testing were obtained in patients who presented with any signs and symptoms indicative of COVID-19 or reported a recent exposure to a person with COVID-19. The clinics followed the US Centers for Disease Control and Prevention recommendations for the diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis/screening.html).

Measurement of SaO_2

The CLM is approved by the US Food and Drug Administration for the measurement of hematocrit and O_2 saturation in the extracorporeal circuit. The CLM reports hematocrit and O_2 saturation 1×/min (an example is shown in Supplementary data, Figure S1). Per the manufacturer, the accuracy of SaO_2 measurements is 2%. CLM telemetry readings of SaO_2 were continuously, automatically and securely transferred to either the RRI or FKC data warehouse and were subsequently extracted for joint analysis.

SaO_2 data eligibility

CLM data with the following characteristics were deemed implausible or unreliable and hence excluded: relative blood volume >120% or <60%, SaO_2 >100% or zero, hematocrit levels <15% or >60%, and data points collected before or after dialysis.

Laboratory data

Laboratory measurements (Spectra Laboratories, New Jersey, NJ, USA) were downloaded to the RRI and FKC data warehouses and extracted for subsequent joint analysis.

Statistical analyses

Descriptive statistics comprise mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Average treatment-level SaO_2 was calculated utilizing all eligible measurements. The treatment-level average SaO_2 was then used for further analysis. HD treatments were also characterized by mean treatment-level SaO_2 (≥90% and <90%). We used SaO_2 available up to 4 weeks pre-diagnosis and the week post-diagnosis for this analysis. Additionally, we also examined HD treatments grouped by mean treatment-level SaO_2 (≥90% and <90%) in non-COVID-19 MHD patients.

We report baseline descriptive statistics, group differences [95% confidence intervals (CIs)] in all patients and stratified by survivor status. A baseline period was defined as the time between 4 and 6 weeks before the diagnosis of COVID-19. Next, we report the association between hypoxemia and/or O_2 supplementation with death and hospitalization.

To further assess SaO_2 patterns in relation to outcomes, we used estimates from adaptive spline mixed-effects models [13]. For this analysis, patients were stratified by clinical outcomes into two groups (hospitalization or death; neither of both).

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R 3.4.4 (libraries ggplot2, dplyr and mgcv; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Between February and April 2020, 1166 MHD patients were dialyzed in these 11 facilities. Eighty patients (6.7% of the total population) were diagnosed with COVID-19. Twenty-five of these 80 COVID-19 patients (31.3%) had no arterio-venous vascular access, making a measurement of SaO_2 by CLM impossible; the baseline characteristics of these 25 patients are shown in Supplementary data, Table S1. Three COVID-19 patients (3.8%) lacked eligible CLM measurements. The remaining 52 MHD patients contributed in total 338 HD treatments with eligible SaO_2 recordings. Their age was 66.5 ± 15.7 years, dialysis vintage was 6.9 ± 5.0 years, 44.2% were White, 65.4% males, 81.2% had hypertension, 68.7% diabetes, 31.2% congestive heart failure and 14.6% chronic obstructive pulmonary disease (COPD) (Table 1).

Eleven patients expired from COVID-19 within 5 weeks after diagnosis; their baseline characteristics are compared with those of the 41 COVID-19 recovered patients in Table 1.

COVID-19-related signs and symptoms

Data regarding COVID-19 signs and symptoms were available for 46 of the 52 patients (88.5%). Among those, only one patient was asymptomatic; the remaining patients presented with a variety of symptoms. At presentation, malaise (63%), fever (54%), cough (35%) and shortness of breath (30%) were the most common. Gastrointestinal symptoms were present in five (11%) patients, specifically diarrhea; anosmia or dysgeusia were not reported. Most patients (76.1%) showed first symptoms within 48 h before COVID-19 diagnosis. Naso-pharyngeal swabs for SARS-CoV-2 RT-PCR were collected on average 1.1 days after symptom onset (median 0, range 0–9).

Treatment-level average SaO_2

The weekly distribution of HD treatments stratified by SaO_2 levels in the 4 weeks pre-diagnosis is shown in Figure 1; the day-by-day distribution in the final pre-diagnosis week is shown in Figure 2. Because of its effect on SaO_2, this analysis is limited to SaO_2 recordings from dialysis treatments without the use of supplementary O_2. Prior to COVID-19 diagnosis, the rate of HD treatments with hypoxemia, i.e. an average $SaO_2 < 90\%$ during dialysis, increased from 2.9% (2–4 weeks pre-diagnosis) to 12.2% (1 week) and 21.7% (3 days pre-diagnosis). Six days pre-diagnosis, $SaO_2 \geq 90\%$ was observed in all HD treatments; 3 days later the rate dropped to 83%. In contrast , 4–6 days pre-diagnosis $SaO_2 < 90\%$ was not observed, with a significant increase noted 3 days later (Figure 2). In

Table 1. Patient characteristics at baseline of all patients and stratified by survival status

Variable	Baseline[a]	Recovered	Died	Difference between patients who recovered and passed away [mean (95% CI)]
Number of patients	52	41	11	NA
Demographics				
Age, years	66.5 ± 15.7	63.3 ± 15.4	78.5 ± 10.5	15.2 (7.0 to 23.4)
Males, %	65.4	68	55	13 (−13 to 43)
HD vintage, years	6.9 ± 5.0	6.7 ± 4.9	7.7 ± 5.6	1.0 (−2.4 to 4.5)
White	44	41	55	−14 (−16.0 to 45.0)
Black or African American	37	15	18	3 (−22 to 30.0)
Other	15	44	27	−17 (−22 to 31)
Comorbidities, %				
Hypertension	81	60	86	26 (−49 to 11)
Diabetes mellitus	69	71	90	19 (−5.0 to 50)
Congestive heart failure	31	34	30	−4 (−27 to 30)
COPD	15	14	10	−4 (−58 to 12)
Treatment-related variables				
Treatment time, min	228.7 ± 25.7	210.7 ± 45.3	211.4 ± 37.1	0.7 (−29.2 to 30.6)
IDWG, kg	1.8 ± 1.4	1.4 ± 1.4	1.5 ± 0.9	0.1 (−9.2 to 1.1)
Pre-dialysis weight, kg	84.9 ± 24.3	85.4 ± 25.2	78.5 ± 21.7	−6.9 (−23.6 to 10.0)
Pre-dialysis temperature, °C	36.4 ± 0.3	36.7 ± 0.8	37.2 ± 0.8	0.6 (0.0 to1.1)
Pre-dialysis heart rate, beats/min	79.0 ± 12	82.0 ± 17.7	88.0 ± 19.3	6.0 (−6.3 to 18.3)
Pre-dialysis SBP, mmHg	147.6 ± 25.9	140.3 ± 28.0	152.4 ± 26.4	12.1 (−6.8 to 31.0)
UFV, L	2.0 ± 1.1	1.6 ± 1.0	1.6 ± 1.0	0.0 (−0.7 to 0.7)
UFR, mL/kg/h	6.5 ± 3.7	5.9 ± 4.2	5.5 ± 1.3	0.3 (−2.3 to 3.0)
Intradialytic O_2 saturation, %	95.7 ± 3.5	95.9 ± 2.8	94.5 ± 5.3	−1.3 (−3.8 to 1.1)
Biochemical variables				
Hemoglobin, g/dL	10.8 ± 1.2	10.8 ± 1.3	10.7 ± 0.7	−0.1 (−0.9 to 0.7)
Leukocytes, 1000/μL	7.2 ± 2.4	7.1 ± 2.4	7.4 ± 2.4	0.3 (2.4 to0.8)
Lymphocytes, 1000/μL	19.9 ± 8.4	20.0 ± 9.1	19.4 ± 5.1	−0.6 (−6.7 to 5.5)
Serum albumin, g/dL	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.4	0.0 (−0.2 to 0.3)
Serum sodium, mmol/L	138.5 ± 2.7	138.1 ± 2.6	140.1 ± 2.4	2.0 (0.2 to3.7)
Serum potassium, mmol/L	4.7 ± 0.5	4.6 ± 0.5	4.9 ± 0.5	0.2 (−0.1 to 0.6)
NLR	4.3 ± 2.8	4.5 ± 3.1	3.7 ± 1.5	−0.8 (−2.8 to 1.2)
Serum ferritin, ng/dL	1196 ± 325	1137 ± 487	1110 ± 257	−27 (−335 to 281)

[a]Baseline measurements for both groups were obtained between 30 and 45 days prior to COVID-19 diagnosis. The first available data point during this baseline period was used for analysis.

Data are expressed as mean ± SD, or percentage (%).

SBP: systolic blood pressure; IDWG: interdialytic weight gain; UFV: ultrafiltration volume; UFR: ultrafiltration rate; NLR: neutrophil-to-lymphocyte ratio.

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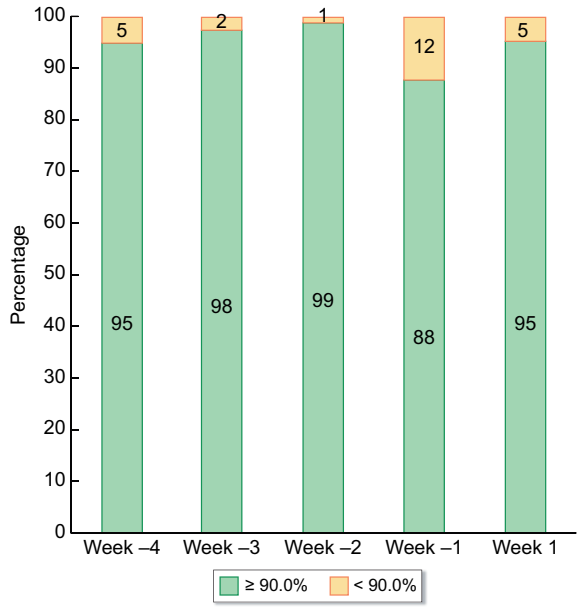

FIGURE 1: Distribution of intradialytic SaO_2 in the 4 weeks before and the week after the COVID-19 diagnosis. During none of these treatments was supplemental O_2 given. The y-axis shows the indicated SaO_2 categories as percentage.

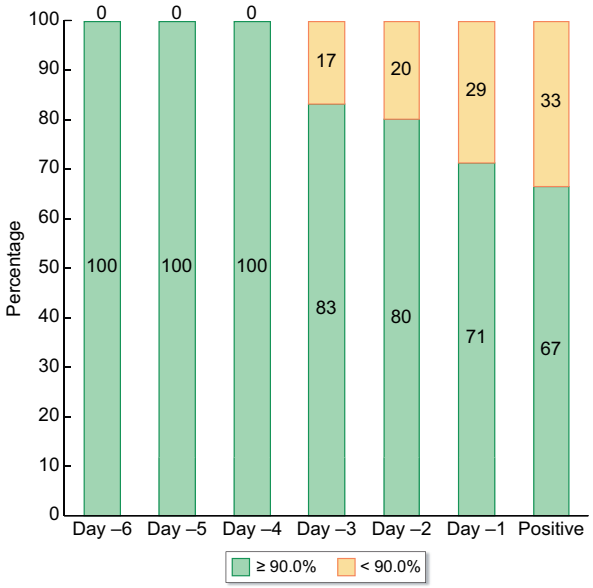

FIGURE 2: Distribution of intradialytic SaO_2 in the 7 days prior to the COVID-19 diagnosis. During none of these treatments was supplemental O_2 was given. The y-axis shows the indicated SaO_2 categories in percentage.

the week following the diagnosis of COVID-19, hypoxemia was present in 5% of the treatments (Figure 1).

Intradialytic SaO_2 in non-COVID-19 patients

In 1567 MHD patients without COVID-19 MHD, the rate of HD treatments with hypoxemia remained <5.5% (Supplementary data, Figure S3).

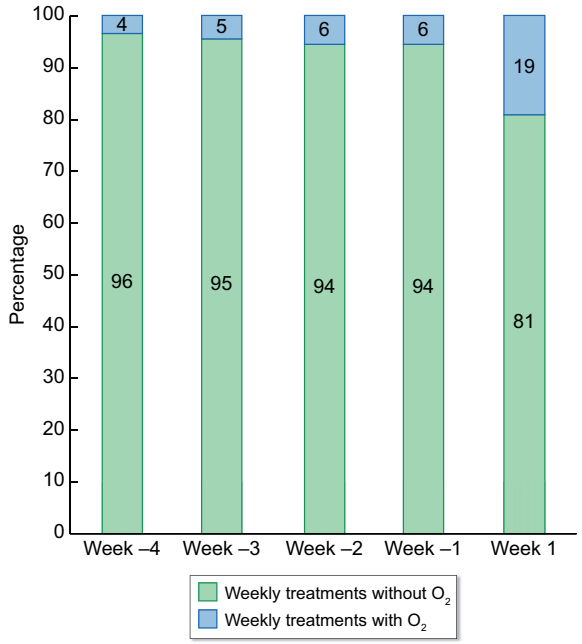

FIGURE 3: Rate of HD treatments with O_2 supplementation in the 4 weeks before and the week after COVID-19 diagnosis. The y-axis shows the indicated categories as percentage.

O_2 supplementation and 'silent' hypoxemia before COVID-19 diagnosis

In the 4 weeks pre-diagnosis, O_2 supplementation was documented in 5% of HD treatments. In the post-diagnosis week, this rate increased to 19% (Figure 3). In the week's pre- and post-diagnosis, we observed seven treatments (10% of all treatments with hypoxemia) with an average intradialytic SaO_2 <90% without a concurrent use of supplemental O_2, indicative of 'silent' hypoxemia. Indication for O_2 supplementation was based on clinical assessment by the clinic staff and was administered exclusively during the in-center dialysis sessions.

Hospitalization and mortality

Patients were followed for up to 5 weeks post-diagnosis. During that period, 11 (21.5%) out of the 52 patients died (Table 1). The mean post-diagnosis survival time was 14 days (range 2–24). Twenty-nine patients were hospitalized, with an average length of hospitalization of 14 days (median 14, range 5–20). All patients who died were hospitalized during the course of the disease. Hospitalization was based on clinical assessment and criteria by the emergency room physician.

Hypoxemia and/or O_2 supplementation was documented in 4 (36%) of 11 patients who died, compared with 7 (17%) of the 41 patients who survived (Table 2). Five (18%) out of 28 patients who were hospitalized were either hypoxemic or required O_2 supplementation (Table 3).

We then stratified patients based on outcome into two groups, i.e. hospitalization and/or death versus non-hospitalized/survival. We analyzed these two groups using adaptive spline mixed-effect models. We analyzed these two groups based on COVID-19 onset of symptoms and on COVID-19 diagnosis. Patients who were hospitalized or passed away showed both a pronounced pre-onset of symptoms and pre-diagnosis SaO_2 decline; this decline was not observed in the non-hospitalized/survival group (Figures 4 and 5).

Table 2. Frequency of hypoxemia and O_2 supplementation during dialysis

Hypoxemia and O_2 supplementation	COVID-19 survival status	
	Died, $n = 11$ (%)	Recovered, $n = 41$ (%)
Either $SaO_2 < 90\%$ or O_2 given; $n = 9$	4 (44)	5 (56)
$SaO_2 \geq 90\%$ and no O_2 given; $n = 43$	7 (16)	36 (84)

Patients were stratified by their survivor status. The percentages are expressed relative to the number of patients per row.

Table 3. Frequency of hypoxemia and O_2 supplementation during dialysis

Hypoxemia and O_2 supplementation	COVID-19 hospitalization	
	Yes, $n = 28$ (%)	No, $n = 24$ (%)
Either $SaO_2 < 90\%$ or O_2 given; $n = 9$	5 (56)	4 (44)
$SaO_2 \geq 90\%$ and no O_2 given; $n = 43$	23 (53)	20 (47)

Patients were stratified by hospitalizationstatus. The percentages are expressed relative to the number of patients per row.

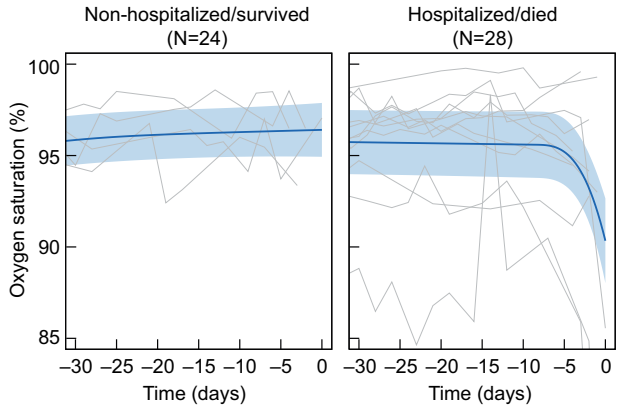

FIGURE 4: SaO_2 prior to COVID-19 onset of symptoms. Patients are stratified by outcomes. Estimates from adaptive spline mixed-effects models (blue line) with 95% CIs (shaded areas) stratified based on the absence (left panel) or presence (right panel) of hospitalization and/or death. Gray lines are a spaghetti plot of individual trajectories. Time zero corresponds to the time of onset of COVID-19 symptoms.

DISCUSSION

In our analysis, we interrogated routinely collected intradialytic SaO_2 data to ascertain the rate and dynamics of hypoxemia in MHD patients with confirmed COVID-19. This is the first report of SaO_2 levels during dialysis in a larger group of in-center MHD patients with COVID-19. The main finding is a rise in intradialytic hypoxemia rate in the days before onset of symptoms and diagnosis of COVID-19. We also corroborated the presence of 'silent' hypoxemia, defined as $SaO_2 < 90\%$ without the use of supplemental O_2.

Hypoxemia results from pathologies that impair pulmonary gas exchange (e.g. pneumonia), respiratory control (e.g. neurological diseases) or ventilation mechanics (e.g. pneumothorax); it may compound tissue hypoxia and organ dysfunction.

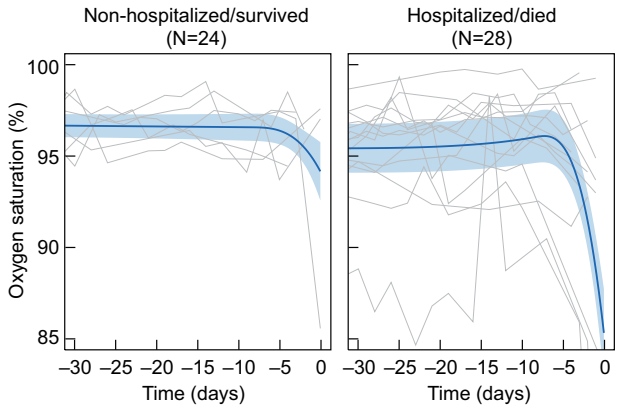

FIGURE 5: SaO_2 prior to COVID-19 diagnosis. Patients are stratified by outcomes. Estimates from adaptive spline mixed-effects models (blue line) with 95% CIs (shaded areas) stratified based on the absence (left panel) or presence (right panel) of hospitalization and/or death. Gray lines are a spaghetti plot of individual trajectories. Time zero corresponds to the time of COVID-19 diagnosis.

Hypoxemia during HD has been well described in the pre-COVID-19 era [14, 15].

In the general population, hypoxemia, usually defined as $SaO_2 < 90\%$, has been described in 9–38% of COVID-19 patients [9, 10, 1]. It is attributed to interstitial pneumonia, reduced alveolar O_2 diffusion, intrapulmonary shunts (V/Q mismatch) and microthrombi [16, 17]. Data on hypoxemia in MHD patients with COVID-19 are scarce. Two reports on MHD patients who had to be hospitalized due to a more severe clinical course of COVID-19 show decreased SaO_2 levels (<95%) and hypoxemia at admission in 16–60% of patients [11, 12]. In our study, patients who were hospitalized and those who expired due to COVID-19 had a higher hypoxemia rate than those who were not hospitalized or expired. Patients who succumbed to COVID-19 infection were older, had more comorbidities and a longer dialysis vintage. These findings corroborated previously reported risk factors for mortality [11, 12, 18]. It is also noticeable that half of our patients with documented hypoxemia or requiring O_2 supplementation during dialysis were hospitalized; almost half of them died from COVID-19.

In our study, malaise and fever were the most common symptoms at presentation, corroborating previous publications [11, 12, 18–20]; on the other hand, we found a lower frequency of cough and shortness of breath compared with other cohorts [12, 20, 21]. Patients showed symptoms on average around 1 day before being tested positive for COVID-19. This brief time period indicates that strict screening procedures implemented in dialysis facilities allow for timely identification and isolation of COVID-19-positive patients. Our results show a sharp decline on SaO_2 levels before any symptoms occurred in those patients who required hospitalization or died.

We observed patients who were hypoxemic with an apparent absence of symptoms, a clinical phenotype called 'silent' hypoxemia [22–24]. The variability in breathing response to hypoxemia, as well as differences in intra-pulmonary shunts early in the course of the disease, have been proposed as explanations of silent hypoxemia [25]. However, its pathophysiology is still poorly understood. Carbon dioxide, the key stimulus of respiratory drive, diffuses roughly 20 times faster than O_2 in liquids. Therefore, in some disease circumstances, O_2 exchange can be compromised before carbon dioxide removal, resulting in hypoxemia without pronounced hypercapnia and hence less

shortness of breath. It is also intriguing to speculate that an infection of the central nervous system by SARS-CoV-2 might play a role.

To the best of our knowledge, this is the first report of intradialytic SaO_2 levels in in-center MHD patients before and shortly after COVID-19 diagnosis and symptoms onset. The strength of this report is the routine, quasi-continuous and automatic documentation of SaO_2 during dialysis, allowing us to interrogate a large number of SaO_2 recordings. We acknowledge that our study has some limitations. We lack objective data such as imaging studies that might have been done outside the dialysis units and could provide useful information on the severity of the disease. Unfortunately, such studies are not available due to healthcare regulations. Lastly, there was relatively brief follow-up after COVID-19 diagnosis. While after May 2020 no new COVID-19 cases were diagnosed in our 11 dialysis, continued vigilance is warranted.

In summary, hypoxemia may precede both the symptoms onset and diagnosis of COVID-19 in MHD patients. Patients with adverse outcomes such as hospitalization or death showed a steeper decline in SaO_2 compared with their fellow patients who had an uncomplicated clinical course. Measurement of SaO_2 may afford nephrologists an opportunity to identify pre-symptomatic COVID-19 patients and alert them to patients at increased risk of adverse outcomes. Informed by the current data, we posit that routine measurement of SaO_2 in MHD patients is a valuable addition to our surveillance armamentarium.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

FUNDING

This work was funded by the Renal Research Institute, a wholly owned subsidiary of Fresenius Medical Care North America and the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK130067.

AUTHORS' CONTRIBUTIONS

P.P., L.M.T.S., X.Y., H.Z., Y.W. and P.K contributed to the design and implementation of the research. X.Y, H.Z, Y.W. and P.W. analyzed the data. P.P., L.M.T.S and J.P.K wrote the manuscript with input from all authors. P.K directed the project. All authors provided critical feedback and helped shape the research, analysis and manuscript.

CONFLICT OF INTEREST STATEMENT

P.P, L.M.T.S, X.Y., H.Z. and P.K. are employees of the RRI, a wholly owned subsidiary of Fresenius Medical Care North America. P.K. holds stock in Fresenius Medical Care North America. The other authors report no financial disclosures.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to company privacy policies. The data will be shared on reasonable request to the corresponding author.

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