



ORIGINAL ARTICLE

Long-term impact of COVID-19 among maintenance haemodialysis patients

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ABSTRACT

Background. Maintenance haemodialysis (MHD) patients have a high risk of initial mortality from coronavirus disease 2019 (COVID-19). However, long-term consequences of this disease in the MHD population are poorly described. We report the clinical presentation, outcome and long-term follow-up of MHD patients affected by COVID-19 in a multicentric cohort from the Paris, France area.

Methods. We conducted a retrospective analysis of clinical presentation and long-term follow-up of MHD patients affected by COVID-19 in 19 MHD centres in the Paris, France area.

Results. In this cohort of 248 patients with an initial mortality rate of 18%, age, comorbidities, dyspnoea and previous immunosuppressive treatment were associated with death at <30 days. Among the 203 surviving patients following the acute phase, long-term follow-up (median 180 days) was available for 189 (93%) patients. Major adverse events occurred in 30 (16%) patients during follow-up, including 12 deaths (6%) after a median of 78 days from onset of symptoms. Overall, cardiovascular events, infections and gastrointestinal bleeding were the main major adverse events. Post-COVID-19 cachexia was observed in 25/189 (13%) patients. Lower initial albuminaemia was significantly associated with this cachexia. No reinfection with severe acute respiratory syndrome coronavirus 2 was observed.

Conclusions. This work demonstrates the long-term consequences of COVID-19 in MHD patients, highlighting both initial and long-term severity of the disease, including severe cachexia.

Keywords: cachexia, COVID-19, haemodialysis, long-term follow-up, mortality, nutritional status, SARS-CoV-2

INTRODUCTION

A new type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in December 2019, causing coronavirus disease 2019 (COVID-19), which rapidly spread to a global public health emergency [1, 2]. Maintenance haemodialysis (MHD) patients have a high risk of initial mortality from the disease [3–6]. Additionally, COVID-19 is also associated with long-term deleterious symptoms in survivors [7]. This 'long-COVID' syndrome notably includes persistent dyspnoea, fatigue and muscle weakness, although the exact spectrum of this syndrome remains debated [7, 8]. The description of long-term follow-up in MHD patients who survived COVID-19 has not been reported to date.

In this study we report the clinical presentation, outcomes and long-term follow-up of a multicentre cohort of MHD patients presenting with COVID-19 between February and May 2020 in the Paris, France area.

MATERIALS AND METHODS

Population

All adult patients on MHD for >1 month and diagnosed with COVID-19 between 1 February and 1 May 2020 from 19 different centres (17 private practice and 2 academic) were included in this HD-CovIDF cohort. Overall, 1790 patients are managed in these facilities. COVID-19 diagnosis was made in presence of SARS-CoV-2 RNA detected by real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab specimens or imaging findings indicative of COVID-19.

Relevant clinical, laboratory and outcome data were retrospectively reported. Data were recorded at diagnosis when available or during follow-up. Management of patients [including renin-angiotensin system (RAS) blockade discontinuation or not] was performed according to the judgement of the treating physician. Previous immunosuppressive treatment included

ongoing use of steroids, biotherapy and chemotherapies. The clinical outcomes were monitored up to 30 September 2020.

SARS-CoV-2 serologic assays were performed using the Abbot SARS-CoV-2 immunoglobulin G (IgG) assay [targeting the nucleocapsid (NC) antigen] using an Architect system and the Ortho Clinical Diagnostics Vitros IgG assay (targeting the spike antigen).

We defined post-COVID-19 cachexia by non-oedematous weight loss >10% at the last follow-up and/or extreme muscle weakness [9, 10]. Major adverse events included cardiovascular events (myocardial infarction, stroke, acute peripheral artery disease, pulmonary embolism or cardiac arrest) or severe infections needing hospitalization or prolonged antibiotherapy or other events requiring hospitalization. Severe forms of COVID-19 were defined according to the need for oxygen therapy.

Data collection was declared to the French Commission Nationale de l'Informatique et des Libertés (registration 2218583). This protocol was submitted for the approbation of the Paris Centre Institutional Review Board. Oral consent for this retrospective study was obtained from all patients or next of kin in case of death.

Statistical analysis

Categorical variables are presented as number (percentage) and quantitative variables as mean [standard deviation (SD)]. All statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria). Univariate analyses were adjusted for multiple comparisons and conducted using robust tests accounting for rare events. Spearman rank correlation coefficients, Welch t-tests, White corrected one-way analysis of variance (ANOVA), chi-square and Fisher's exact tests were used when appropriate, depending on the nature of the dependent and independent variables. The predictor for initial COVID-19 mortality and hospitalization was

previously discussed [11]. Detailed statistical analyses are provided in [Supplementary Methods](#).

RESULTS

Patient presentation and initial outcome

A total of 248 consecutive patients were included. A previous report described the initial evolution and treatment impact of these patients [12]. Given an overall population of 1790 patients managed in the 19 centres, the proportion of patients diagnosed with COVID-19 was 13.8%. Patients were mostly men [$n = 165$ (67%)], with a mean age of 67 ± 27 years and a mean MHD vintage of 5 ± 5 years. The most frequent comorbidities included hypertension [94% ($n = 232$)], diabetes [59% ($n = 147$)], history of coronary disease [30% ($n = 74$)] and cardiac failure [16% ($n = 40$)]. Of the 248 patients, COVID-19 was detected by real-time RT-PCR in 88% of cases ($n = 196$). The hospitalization rate was 58% ($n = 145$), after a mean of 3.5 ± 6 days after the first symptoms. The most frequent presenting features were fever [$n = 152$ (61%)], cough [$n = 122$ (49%)] and fatigue [$n = 101$ (40%)], with 29 patients being asymptomatic (11%).

The mean levels of haemoglobin, lymphocyte count and C-reactive protein were 10.7 ± 1.8 g/dL, 915 ± 1046 /mm³ and 92 ± 98 mg/L, respectively. Chest computed tomography (CT) was performed in 62% of cases ($n = 153$). Detailed patient characteristics are provided in [Table 1](#).

Hospital admission was associated with a history of hypertension, previous immunosuppressive treatment and the presence of cough and confusion ([Supplementary data, Table S1](#)).

Treatments and initial outcome have been previously reported [12]. Most hospitalized patients received oxygen therapy [$n = 114$ (79%)]. A total of 14% ($n = 20$) of patients required intensive care unit hospitalization. Acute respiratory distress syndrome requiring invasive mechanical ventilation was observed in 9% of patients ($n = 13$). Overall, initial mortality (<30 days) was 18% ($n = 45$) after a mean of 14 days (median 9 days) since the onset of symptoms ([Supplementary data, Figure S1](#)). Characteristics of survivors and non-survivors (<30 days) are detailed in [Supplementary data, Table S2](#), and the predictors of mortality have been previously reported, including the favourable effect of previous RAS blockers [12] in this cohort.

Long-term follow-up

Among the 203 surviving patients after the acute phase, follow-up to Month 6 was available for 189 (93%) patients. Major adverse events occurred in 30 (16%) patients during follow-up and 12/189 died (6% of the whole population) after a median of 78 days post-diagnosis ([Supplementary data, Figure S1](#)). Characteristics of overall 6-month survivors and non-survivors are presented in [Supplementary data, Table S3](#). No impact of RAS blockade was detected in overall mortality. Cardiovascular events ($n = 3$), severe infections ($n = 3$) and cachexia ($n = 3$) were the main causes of long-term (>30 days) death ([Table 2](#)). Overall, cardiovascular events, infections and gastrointestinal bleeding were the main major adverse events ([Table 2](#)). Causes of death (<30 days and long-term death) are presented in [Supplementary data, Table S4](#).

After controlling for multiple comparisons, no predictors were significantly associated with major adverse events during the follow-up. However, older age [$t(14.35) = -2.59$, $P = 0.021$, P -corrected = 0.100; $d = 0.64$], lower albumin levels at the time of

diagnosis [$t(5.95) = 4.97$, $P = 0.003$, P -corrected = 0.066; $d = 1.67$], a history of peripheral artery disease [odds ratio (OR) 4.64, $P = 0.020$, P -corrected = 0.100] and chronic heart failure (OR 3.88, $P = 0.050$, P -corrected = 0.178) presented trends of association with long-term death ([Table 3](#)). Notably, sex, underlying nephropathy and immunosuppression did not impact the risk of long-term death. None of the 19 patients presenting with an asymptomatic COVID infection died, but this association did not reach statistical significance ($P = 1$) and the severity of the initial presentation was not a significant predictor of fatality ($P = 0.771$). No patient developed *de novo* autoimmune disease or flare of an underlying autoimmune disease. One patient with heart transplant presented acute rejection.

Repeat SARS-CoV-2 RT-PCR was performed in 61 patients for reinfection suspicion during follow-up. Only 2/61 (3%) RT-PCRs was positive, which were performed <2 months after initial diagnosis, suggesting these positive results might be persistent viral detection of the initial infection. Repeat serological assays evaluating anti-NC or anti-spike antibodies until Month 6 post-infection were available in 65 patients, as previously reported [13]. Among them, 5/65 patients had no initial seroconversion. Among 60 patients with initial seroconversion, a progressive decline in antibody titres was observed. Moreover, 15/60 (25%) patients had a negative anti-NC titre at Month 6. However, only 3/60 (5%) patients had both negative anti-NC and anti-spike antibodies. Cellular immunity was not evaluated in these patients. No symptomatic reinfection was observed in these patients.

Overall, post-COVID-19 cachexia was seen in 25 patients (13.2%), defined as a loss of >10% of dry weight [$n = 16$ (8.5%)] or extreme muscle weakness [$n = 9$ (4.8%)]. After multiple testing correction, low initial albuminaemia remained a significant predictor of cachexia [$t(16.87) = 4.91$, $P = 0.005$; $d = 1.39$] (see [Supplementary data, Table S5](#)).

DISCUSSION

We report the long-term follow-up of a large series of MHD patients affected by COVID-19. In our cohort, the mortality rate at <30 days was 18%, which is in line with previously reported cohorts of MHD patients [3, 4, 11]. Notably, hospitalized patients with comorbidities represent the majority of observed death at <30 days. We previously reported the deleterious role of previous immunosuppression in initial mortality in this cohort [12]. Moreover, in this cohort including both ambulatory and hospitalized MHD patients, exposure to RAS blockers was associated with a 50% reduction of initial mortality risk, after propensity score weighting. However, the role of RAS blockers in initial COVID-19 evolution of MHD patients remains debated [14]. Interestingly, recent data suggest that previous exposure to RAS blockers may limit the risk of hospitalization secondary to COVID-19 in ambulatory hypertensive patients [15]. However, RAS blockade was not associated with overall mortality after long-term follow-up in this cohort.

This work provides original information regarding long-term follow-up after COVID-19 in MHD patients. We show that 6-month mortality affects 6% of initial survivor patients after a median of 78 days. This is much higher than recently described in the non-MHD population (1.3%) [7] but is in line with the annual survival proportions of HD patients in France [16]. Actually, according to recent data from the Paris region [17], after the peak mortality of HD patients observed in early 2021, the 2020 6-month mortality appears similar to that observed in 2018 and 2019. Causes of death mainly included cardiovascular and

Table 1. Demographics, comorbidities and presentation of the HD-CovIDF cohort

Characteristics	Overall (N = 248)	Hospitalized [n = 145 (58%)]	Outpatients [n = 103 (42%)]	Adjusted P-value
Age (years), mean (SD)	67 (27)	69 (27)	64 (25)	0.04
Sex (male), n (%)	165 (67)	98 (68)	67 (65)	0.9
Duration of HD (years), mean (SD)	5 (4)	5 (4)	4 (4)	0.8
Nephropathy, n (%)				0.99
Vascular and/or diabetes	181 (73)	107 (74)	74 (72)	–
Interstitial disease	6 (2)	3 (2)	3 (3)	–
Glomerular disease	32 (13)	20 (14)	12 (12)	–
Polycystic kidney	12 (5)	6 (4)	6 (6)	–
Other	17 (7)	9 (6)	8 (8)	–
Comorbidities, n (%)				
Hypertension	232 (94)	139 (96)	93(90)	0.2
Diabetes	147 (59)	92 (64)	55 (52)	0.3
Cardiac failure	40 (16)	27 (19)	13 (13)	0.4
Coronary disease	74 (30)	49 (34)	25 (24)	0.3
Chronic respiratory failure	11 (4)	9 (6)	2 (2)	0.3
COPD/asthma	27 (11)	16 (11)	11 (11)	1
Previous renal transplant	21 (8)	15 (10)	6 (6)	0.3
Immunosuppressive therapy	24 (10)	21(14)	3 (3)	0.01
HIV	8 (3)	4 (3)	4 (4)	0.8
Cancer <5 years	23 (9)	15 (10)	8 (8)	0.7
Obesity (BMI ≥30 kg/m ²)	60 (24)	32 (22)	28 (27)	0.7
Smoker (active)	22 (9)	9 (6)	13 (13)	0.3
Previous RAS blockers	96 (39)	56(39)	40 (39)	1
Home (versus facility) living	199 (80)	104 (72)	95(92)	0.04
Presentation				
Positive RT-PCR n (%) ^a	196 (79)	121 (84)	75 (73)	0.02
Duration between onset of symptoms and PCR (days), mean (SD)	2.9 (5)	4 (6)	2 (3)	0.02
Fever, n (%)	152 (61)	98 (67)	54 (52)	0.07
Cough, n (%)	122 (49)	92 (63)	30 (29)	<0.001
Fatigue, n (%)	101 (40)	71 (48)	30 (29)	0.013
Myalgia, n (%)	37 (14)	24 (16)	13 (12)	0.013
Diarrhoea, n (%)	29 (11)	15 (10)	14 (13)	0.7
Dyspnoea, n (%)	76 (30)	64 (44)	12 (11)	<0.001
Headache, n (%)	18 (7)	13 (8)	5 (4)	0.4
Sore throat, n (%)	4 (1)	2 (1)	2 (1)	1
Anosmia, n (%)	10 (4)	7 (4)	3 (2)	0.9
Thoracic imaging (CT scan), n (%)	153 (62)	109 (76)	44 (43)	0.097
Moderate infiltrate, n (%) among those with a CT	64 (27)	38 (26)	26 (25)	–
Large infiltrate, n (%) among those with a CT	28 (11)	23 (15)	5 (4)	–
Severe infiltrate, n (%) among those with a CT	25 (10)	21 (15)	4 (4)	–
Blood tests				
Haemoglobin (g/dL), mean (SD)	10.7 (1.8)	10.7 (1.8)	10.70 (1.8)	0.98
White blood cell count (mm ³), mean (SD), mm ³	5659 (2806)	5841 (3003)	5391 (2481)	0.4
Neutrophils (mm ³), mean (SD)	4182 (2618)	4508 (2853)	3720 (2174)	0.08
Lymphocytes (mm ³), mean (SD)	915 (1046)	750 (396)	1152 (1538)	0.02

Table 1. (continued)

Characteristics	Overall (N = 248)	Hospitalized [n = 145 (58%)]	Outpatients [n = 103 (42%)]	Adjusted P-value
Platelets (mm ³), mean (SD)	200 380 (186 624)	183 265 (77 003)	225 591 (277 216)	0.2
CRP (mg/L), mean (SD)	92 (98)	115 (109)	60 (69)	<0.001
Procalcitonin (ng/mL), mean (SD)	18 (79)	24 (96)	7 (31)	0.4
Prothrombin time/control (%), mean (SD)	80 (18)	79 (20)	84 (11)	0.4
Fibrinogen (g/L), mean (SD)	4.9 (1.8)	5.2 (1.9)	4.4 (1.3)	0.2
Ferritin (µg/L), mean (SD)	1036 (1150)	1247 (1332)	755 (774)	0.07
D-dimers (µg/L), mean (SD)	3144 (3395)	3435 (3547)	1351 (1318)	0.3
Albumin (g/L), mean (SD)	31.5 (5.4)	31 (6)	32 (4.3)	0.4

^aA total of 30 (12%) and 22 (8%) patients had negative and non-available RT-PCR, respectively. Bold values indicate statistical significance.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HIV, human immunodeficiency virus.

Table 2. Long-term adverse events (between 30 days and last follow-up)

Data	Values
Follow-up	
Follow-up (days), median (IQR)	180 (16)
Facility living after COVID-19 acute phase, n (%)	13 (6.9)
Kidney transplantation after COVID-19, n (%)	4 (2.1)
Death, n (%)	12 (6.3)
Time from diagnosis to death (days), median (IQR)	78 (70)
Causes of death, n (%)	
Cardiovascular event	3 (1.5)
Infection	3 (1.5)
Post-COVID-19 cachexia	3 (1.5)
Metastatic cancer	1
Unknown	2
Major adverse events, n (%)	
Cardiovascular events	11 (5)
Myocardial infarction	2 (1.1)
Stroke	2 (1.1)
Acute peripheral artery disease	1 (0.5)
Cardiac arrest	5 (2.1)
Pulmonary embolism	1 (0.5)
Infections	14 (7.4)
Gastro intestinal bleeding	3 (3.1)
Acute pancreatitis	1 (0.5)
Macroscopic haematuria	1 (0.5)
Loss of weight >5%	40 (21.2)
Post-COVID-19 cachexia	25 (13.2)
Loss of weight >10%	16 (8.5)
Extreme muscle weakness	9 (4.8)

infectious diseases, which are also the main aetiologies of death in non-COVID HD patients. We did not detect any case of SARS-CoV-2 symptomatic reinfection in this cohort, suggesting that such cases remain rare even in the dialysis population. Of note, no systematic screening of SARS-CoV-2 RT-PCR was performed in our cohort following the acute phase, so we cannot rule out possible asymptomatic reinfections. Moreover, long-term serological evaluation in 65 patients with positive initial serology showed that most patients retained detectable humoral immunity against SARS-CoV-2 until 6 months after initial infection

[13]. These results suggest that HD patients have long-term immunity against SARS-CoV-2 and a low risk of symptomatic reinfection after 6 months of follow-up.

Lastly, in this survivor population we identified post-COVID-19 cachexia in 13% of patients, which included patients with very severe weight loss (>10% after 6 months). We used the threshold of >10% dry weight loss after 6 months of follow-up to stratify patients with an unambiguous marker of cachexia [9, 10, 18], given the previously identified role of nutritional status in the prognosis of MHD patients [10]. A recent study of 6-month consequences in patients hospitalized for COVID-19 identified fatigue or muscle weakness in 63% of patients, together with sleep disorders, anxiety and impaired pulmonary diffusion capacities [7]. The more severe long-term symptoms were observed especially in the most severe symptomatic forms of COVID-19. Although the incidence of these symptoms is unknown in the MHD population and warrants further studies, our report shows that MHD patients may also present with severe long-term consequences of COVID-19. Conversely, we did not detect any impact of initial severity, age, sex or comorbidities on the risk of developing post-COVID-19 cachexia. The only identified risk factor of post-COVID-19 cachexia was initial albumin level, which could be explained by the association between initial albumin and underlying nutritional status of MHD patients [10].

Our work has several limitations, including the retrospective nature, which could introduce a selection bias towards patients with more severe evolution, and imposes stronger corrections on the results of the tests, which could lead to false negatives. Moreover, asymptomatic SARS-CoV-2-infected patients were not systematically screened, so the overall initial and long-term severity of COVID-19 in MHD patients could be overestimated. However, the detailed characteristics and long-term follow-up of these 248 patients from both academic and private centres allow a representative description of the disease in a large population of MHD patients.

In conclusion, this work describes the deleterious consequences of COVID-19 in MHD patients, highlighting the initial and long-term severity of the disease in this population, including a high rate of severe cachexia.

Table 3. Initial characteristics of long-term (>30 days) survivor and non-survivor patients

	All (N = 189)	Survivor (n = 177)	Non-survivor (n = 12)	Adjusted P-value
Epidemiological data				
Age (years), mean (SD)	65.44 (15.20)	64.91 (15.34)	73.35 (10.56)	0.100
Sex (male), n (%)	127 (67.2)	119 (67.2)	8 (66.7)	1
Nephropathy, n (%)				
Polycystic kidney	8 (4.2)	7 (4.0)	1 (8.3)	–
Vascular and/or diabetes	137 (72.5)	127 (71.8)	10 (83.3)	–
Glomerular disease	26 (13.8)	26 (14.7)	0 (0.0)	–
Interstitial disease	13 (6.9)	12 (6.8)	1 (8.3)	–
Other	5 (2.6)	5 (2.8)	0 (0.0)	–
Candidate for kidney transplantation, n (%)	98 (51.9)	94 (53.1)	4 (33.3)	0.352
Former kidney transplantation, n (%)	13 (6.9)	12 (6.8)	1 (8.3)	1
HD vintage (years), mean (SD)	4.43 (4.38)	4.26 (3.81)	6.85 (9.30)	1
Comorbidities, n (%)				
Diabetes	109 (57.7)	101 (57.1)	8 (66.7)	1
Hypertension	176 (93.1)	166 (93.8)	10 (83.3)	0.904
Chronic heart failure	24 (12.7)	20 (11.3)	4 (33.3)	0.178
Peripheral artery disease	61 (32.3)	53 (29.9)	8 (66.7)	0.100
Coronary artery disease	53 (28.0)	47 (26.6)	6 (50.0)	0.297
Chronic respiratory failure	5 (2.6)	4 (2.3)	1 (8.3)	0.784
COPD/asthma	21 (11.1)	18 (10.2)	3 (25.0)	0.673
Immunosuppressive therapy	13 (6.9)	13 (7.3)	0 (0.0)	1
HIV	5 (2.6)	5 (2.8)	0 (0.0)	1
Cancer	16 (8.5)	15 (8.5)	1 (8.3)	1
BMI, mean (SD)	26.28 (5.83)	26.29 (5.89)	26.07 (5.16)	1
Acute phase COVID-19 characteristics				
Clinical severity, n (%)				
Asymptomatic	19 (10.1)	19 (10.7)	0 (0.0)	–
Mild	90 (47.6)	85 (48.0)	5 (41.7)	–
Severe ^a	71 (37.6)	66 (37.3)	5 (41.7)	–
Hospitalization, n (%)	88 (46.6)	81 (45.8)	7 (58.3)	1
Intensive care unit admission, n (%)	11 (5.8)	10 (5.6)	1 (8.3)	1
Blood tests				
Leucocytes (mm ³), mean (SD)	5492.59 (2549.53)	5517.72 (2560.93)	5068.00 (2433.65)	1
Lymphocytes (mm ³), mean (SD)	959.07 (1162.98)	973.85 (1194.42)	715.20 (286.46)	0.478
CRP (mg/L), mean (SD)	80.68 (88.18)	80.46 (90.34)	84.34 (40.47)	1
HS troponin, mean (SD)	163.25 (461.56)	116.60 (174.14)	699.67 (1537.94)	1
Albuminaemia (g/L), mean (SD)	31.72 (5.47)	32.17 (5.31)	25.00 (2.92)	0.066
Thoracic imaging (CT scan), n (%)				
Moderate infiltrate, n (%) among those with CT	50 (26.5)	48 (27.1)	2 (16.7)	–
Large infiltrate, n (%) among those with CT	23 (12.2)	20 (11.3)	3 (25.0)	–
Severe infiltrate, n (%) among those with CT	16 (8.5)	15 (8.5)	1 (8.3)	–

^aSevere COVID-19 was defined as the need for oxygen therapy. Bold values indicate statistical significance.

BMI, body mass index; CRP, C-reactive protein; HS, high sensitivity; HIV, human immunodeficiency syndrome.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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DATA AVAILABILITY STATEMENT

Data are available on reasonable request

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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