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Prevalence, clinical course and outcomes of COVID-19 in peritoneal dialysis (PD) patients: a single-center experience

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Abstract

Introduction There are limited data on the effects of COVID-19 on peritoneal dialysis (PD) patients. This study aimed to describe the impact of COVID-19 on the PD population.

Methods A monocentric retrospective observational study was conducted on 146 consecutive PD patients followed from January 2020 to March 2022 at the University Hospital of Modena, Italy.

Results Twenty-seven (18.4%) PD patients experienced 29 episodes of SARS-CoV-2 infection, corresponding to an incidence rate of 0.16 episodes/patient-year.

Median age of COVID-19 patients was 60.4 (interquartile range [IQR] 50.2–66.5) years. In unvaccinated patients (n. 9), COVID-19 was always symptomatic and manifested with fever (100%) and cough (77.7%). COVID-19 caused hospital admission of three (33.3%) patients and two (22.2%) died of septic shock.

COVID-19 was symptomatic in 83.3% of vaccinated subjects (n.18) and manifested with fever (61.1%) and cough (55.6%). Hospital admission occurred in 27.8% of the subjects but all were discharged home.

Median SARS-CoV-2 shedding was 32 and 26 days in the unvaccinated and vaccinated groups, respectively. At the end of the follow-up, COVID-19 triggered the shift from PD to HD in two subjects without affecting the residual renal function of the remaining patients. Overall, COVID-19 caused an excess death of 22.2%. COVID-19 vaccination refusal accounted for only 1.6% in this cohort of patients.

Conclusion COVID-19 incident rate was 0.16 episodes/patient-year in the PD population. About one-third of the patients were hospitalized for severe infection. Fatal outcome occurred in two (7.4%) unvaccinated patients. A low vaccination refusal rate was observed in this population.

Keywords COVID-19 · Peritoneal dialysis · Vaccine · Mortality · SARS-COV-2 · Virus shedding · Dialysis · Vaccine acceptance · Vaccine hesitancy · Hospitalization · Hemodialysis · Residual renal function · Ultrafiltration

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Introduction

A great amount of information has been divulged on the epidemiology and outcome of COVID-19 in patients with end-stage renal disease (ESRD). The majority of the studies have been conducted in patients on maintenance hemodialysis (HD) and kidney transplant recipients. Both groups have been exposed to the dire consequences of COVID-19, especially during the pre-vaccination period [1–4]. Published data reported that hospitalization rate of symptomatic patients on HD varied from 35 to 88.2% and COVID-19 was associated with a case-fatality rate up to 47% [5]. In the meantime, kidney transplant recipients experienced a poor outcome during COVID-19 pandemic. Results from the ERA-EDTA registry showed that mortality risk in this group of patients was even 1.28 times higher than in matched dialysis patients [1]. Based on these data, there is consensus that COVID-19 has substantially affected mortality in patients receiving kidney replacement therapy given their burden of comorbidities and vulnerability to infectious diseases [6, 7]. Yet, there are limited data, essentially case series, on the epidemiology, clinical course, and outcomes of COVID-19 among peritoneal dialysis (PD) patients. The information on this group of subjects has been principally extrapolated from aggregated data including a much higher percentage of HD patients [1]. As a result, the impact of COVID-19 is unclear in this subset of the dialysis population. According to the ERA-EDTA registry data, patients on PD were less likely to be affected by COVID-19 compared to HD patients [1]. Sachdeva et al [8] documented that SARS-CoV-2 infection was essentially transmitted among household members as PD patients are less exposed to the risk of nosocomial transmission than in-center HD patients [9]. After more than 2 years since the spread of SARS-CoV-2 infection worldwide, we conducted a study to evaluate the impact of SARS-CoV-2 in vaccinated and unvaccinated patients on PD in terms of prevalence, clinical manifestations and outcomes. We also provided a comparison of PD with the hemodialysis (HD) population in order to better understand the effects of COVID-19 in ESRD patients on different dialysis modalities.

Materials and methods

We conducted a single-center retrospective analysis of 146 consecutive PD patients followed at the University Hospital of Modena (Italy) during the COVID-19 pandemic. All patients with a COVID-19 diagnosis from January 30, 2020 (first case of documented COVID-19 in Italy) to

March 31, 2022, were enrolled in the study. Patients with multiple episodes of COVID-19 were counted one time and were enrolled in the dataset at the time of the first diagnosis of SARS-CoV-2 infection.

The diagnosis of COVID-19 was performed through RT-PCR nasopharyngeal swab in all symptomatic PD patients and contacts of infected subjects. The time elapsed from the diagnosis of COVID-19 to the first negative nasopharyngeal RT-PCR test was referred to as "SARS-CoV-2 shedding". Theoretically, the disappearance of viral RNA on the nasal mucosa coincided with the clearance of the infection. According to our protocol, RT-PCR test was performed weekly in all COVID-19 patients after an overall improving course of COVID-19. Since caught, anosmia and ageusia may persist for weeks or months after recovery, the timing for RT-PCR was not delayed in presence of these symptoms. RT-PCR nasopharyngeal swab was generally postponed in case of fever, diarrhea, sore throat and extreme fatigue.

Eligibility for re-entering to the kidney transplant waiting list after COVID-19 required a second negative RT-PCR nasopharyngeal swab.

In our center, RT-PCR was not performed as universal screening during the scheduled in-office visits. To avoid heterogeneity arising from different diagnostic tests used to end the isolation of COVID-19 patients, the results of the antigen tests were not taken into account in the calculation of the viral shedding.

The estimation of "episodes of COVID-19 per patient-year" referred to the number of incident cases with COVID-19 divided by the amount of person-time at risk from the start of the period of observation.

According to the local policy, hospitalization of patients with COVID-19 occurred only for subjects with moderate or severe symptomatic illness. Moderate COVID-19 included patients with evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) $\geq$ 94% on room air at sea level whereas severe illness indicates individuals who have: i) SpO2 < 94% on room air at sea level, ii) a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO$_2$/FiO$_2$) < 300 mm Hg, iii) a respiratory rate > 30 breaths/min, iv) lung infiltrates > 50% [10]. All hospitalized patients with COVID-19 continued PD treatment with the assistance of PD nurses. The shift from PD dialysis to HD was provided for clinical reasons, namely, in cases of ultrafiltration failure and/or inadequate dialysis treatment.

In our center, patients on dialysis received mRNA vaccines since March 2021. PD population was subdivided into two groups: unvaccinated and vaccinated patients. The term "unvaccinated" refers primarily to patients who contracted the infection before the availability of mRNA vaccine whereas the term "vaccinated" refers to patients who completed the vaccination cycle according to the

international guidelines of that period. The "unvaccinated group" included also patients with COVID-19 who denied anti-SARS-CoV-2 vaccination. From the start of the study, 21 patients dropped out of PD before the start of the vaccination campaign in Italy. As a result, 125 PD patients were invited for COVID-19 vaccination from March 2021 to the end of the study. The rate of vaccine refusal coincided with the number of patients who denied vaccination from the start of the vaccination campaign.

Residual renal function (RRF) and dialysis adequacy were evaluated before and after COVID-19 to verify any changes in kidney function and peritoneum caused by COVID-19. RRF was defined as the average of 24-h clearance of urea and creatinine. Ultrafiltration (UF) coincided with the sum of fluids removed by PD on 24-h period. A weekly Kt/V of 2.1 was considered an adequate target for blood purification in our PD patients.

Patients on chronic HD were enrolled in the study to evaluate differences between PD and HD patients with COVID-19. From January 30, 2020 to March 31, 2022, 279 patients on HD were enrolled in the study. The diagnosis of COVID-19 and termination of isolation were performed by RT-PCR assay. This group of patients underwent universal screening with a rapid antigen test from January 2021. During the vaccination era (from March 2021), 174 HD patients were invited to receive mRNA vaccination.

This study has been approved by the local Ethical Committee of Emilia Romagna (n. 839/2020/OSS/AOUMO SIRER ID 692).

Statistical analysis

Appropriate statistical tests were used to verify the normality of the data. Non-normally distributed variables were compared using the Mann–Whitney U test and expressed as the median and interquartile range (IQR). Wilcoxon signed-rank test was used to evaluate differences in terms of renal function and dialysis adequacy on two dependent samples measured pre- and post-SAR-CoV-2 infection.

Categorical variables were compared using the chi-square or Fisher exact test when frequencies were less than 5% and expressed as frequencies and percentages. Poisson's 95% confidence interval (CI) was calculated for the incidence rate of COVID-19 in dialysis patients.

Excess mortality estimated the number of deaths potentially related to COVID-19. Excess deaths estimated the difference between the observed numbers of deaths during

COVID-19 pandemic and the expected numbers of deaths in the same periods without COVID-19.

A p-value < 0.05 was considered statistically significant. Statistical analysis was conducted using IBM SPSS® Statistics 23 (SPSS Inc., Armonk, NY, USA).

Results

During the pandemic, 27 out of 146 patients experienced 29 episodes of SARS-CoV-2 infection. Characteristics of PD patients are shown in Table 1. Median age of these patients was 60 (IQR, 50.2–66.5) years. This group of patients was characterized by a predominance of males (74%). The percentage of patients on automated peritoneal dialysis (APD) accounted for 69.4%. COVID-19 occurred after a median of 0.9 (IQR, 0.7–2.4) years from the start of PD. The illness was symptomatic in most patients (88.9%) and required hospital admission for 30.8% of the infected patients. Two patients (7.4%) died during the early stage of COVID-19 pandemic, causing an excess death of 22.2% in the PD population compared to previous periods. Two patients manifested hesitancy toward COVID-19 vaccination until the end of the study. Thus, the prevalence of patients who refused vaccination since March 2021 (beginning of vaccination in Italy) accounted for 1.6% (2 out of 125 patients).

The median post-COVID-19 follow-up of PD patients was 2.7 (IQR, 1.6–6.4) months. The rate of COVID-19 in our PD population was 0.16 (95%CI 0.11–0.23) episodes per patient-year. The COVID-19 dynamic was heterogenous during the pandemic with an increase in COVID-19 cases in the late phase of the observation period. The incidence rate of COVID-19 cases in the vaccination era (0.21 [95%CI 0.13–0.33] episodes per patient-year) was higher than in the pre-vaccination period (0.11 [95%CI 0.05–0.21] episodes per patient-year), but this difference failed to reach statistical significance ($p = 0.09$). Furthermore, COVID-19 was more common during the autumn–winter season (86.2%) than the spring–summer one (13.8%) (Fig. 1).

The study also evaluated the impact of COVID-19 on kidney function and PD performance. The results showed that RRF, 24-h urinary output, peritoneal ultrafiltration and weekly Kt/V remained unchanged pre- and post-COVID-19. (Table 2).

Given the different spectrum of clinical manifestations and outcomes between vaccinated and unvaccinated patients, our population was subdivided according to their vaccination status.

Table 1 Demographic and clinical characteristics of patients on peritoneal dialysis with COVID-19

Variables	All (n. 27)	Unvaccinated patients (n. 9)	Vaccinated patients (n.18)	p-value
Age (IQR), yr	60 (50.2–66.5)	55 (52–65)	64.3 (57–75.1)	0.35
Male, n. (%)	20 (74)	8 (88.9)	12 (66.7)	0.29
Dialysis vintage (IQR), yr	0.9 (0.7–2.4)	1.2 (0.5–2.9)	1.4(0.7–2.1)	1.76
CAPD, n. (%)	8 (29.6)	2 (33.3)	7 (38.9)	0.41
Immunosuppressive therapy, n. (%)	8 (29.6)	1 (16.7)	5 (27.7)	0.13
Weekly Kt/V	2 (1.8–2.4)	1.9 (1.6–2)	2 (1.9–2.7	0.09
Etiology of ESRD, n. (%)				0.43
Hypertensive nephropathy	8 (22.2)	4 (44.4)	4 (22.2)	
Diabetic nephropathy	5 (11.1)	2 (22.2)	3 (16.7)	
IgA nephropathy	4 (7.4)	1 (11.1)	3 (16.7)	
Lupus nephritis	2 (7.4)	0 (0)	2 (11.1)	
Others	8 (37)	2 (22.2)	6 (33.3)	
Comorbidities, n. (%)				
Diabetes	10 (37)	3 (33.3)	7 (38.9)	1
CVD	8 (29.6)	4 (44.4)	6 (33.3)	0.69
Obesity	8 (29.6)	2 (22.2)	6 (33.3)	1
Cancer	5 (18.5)	2 (22.2)	3 (16.7)	1
Asymptomatic, n. (%)	3 (11.1)	0 (0)	3 (16.6)	1
Symptoms, n. (%)				
Cough	17 (63)	7 (77.7)	10 (55.6)	0.4
Fever	20 (74.1)	9 (100)	11 (61.1)	1
Dyspnea	7 (25.9)	3 (33.3)	4 (22.2)	1
Oxygen therapy, n. (%)	7 (25.9)	3 (33.3)	4 (22.2)	1
Viral shedding (IQR), day	26 (16.7–34.2)	26 (15–35)	29 (19–34)	0.73
Switch to HD, n. (%)	2 (7.4)	2 (22.2)	0 (0)	0.1
Hospitalization, n. (%)	8 (30.8)	3 (33.3)	5 (27.8)	1
Hospital length of stay (IQR), day	14.5 (10.5–11.5)	11 (9–19)	17 (12–19)	0.89
ICU-admission, n. (%)	0 (0)	0 (0)	0 (0)	NA
Death, n. (%)	2 (7.4)	2 (22.2)	0 (0)	0.11

CAPD continuous ambulatory peritoneal dialysis, *CVD* cardiovascular disease, *ESRD* end-stage renal disease, *HD* hemodialysis, *IQR* interquartile range

Unvaccinated patients

SARS-CoV-2 infection occurred in nine (33.3%) unvaccinated PD patients. Median age was 55 (IQR, 52–65) years and male were 88.9%. The infection was symptomatic in all patients. Fever (100%) and cough (77.7%) were the most common symptoms. Viral shedding, traced with RT-PCR nasopharyngeal swabs, lasted 26 (IQR, 15–35) days.

COVID-19 caused hospital admission of three (33.3%) patients. During hospitalization two patients (22.2%) switched from PD to HD for ultrafiltration failure. One patient died soon after the switch to HD for septic shock with multiorgan failure (MOF) whereas the other patient continued on HD until the end of the follow-up. A second unvaccinated patient died of septic shock due COVID-19. Median age of these two patients was 65 years and both were affected by cardiovascular disease.

Vaccinated patients

Eighteen PD patients (66.7%) contracted the infection after a complete cycle of anti-SARS-CoV-2 vaccination.

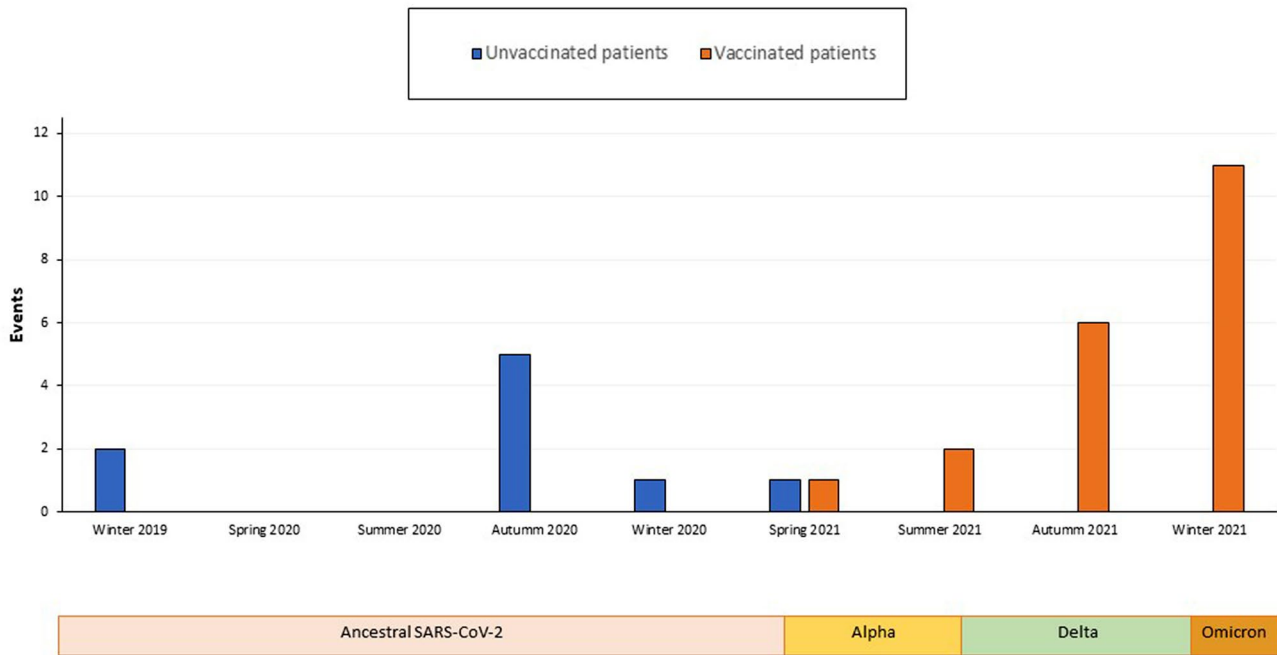The median age of these patients was 64.3 (IQR, 57–75.1) years. Males were 66.7% of the patients.

Fig. 1 Distribution of COVID-19 cases in our cohort of patients onPD according to the diffusion of SARS-CoV-2 variants of concern across the national territory[27]

Table 2 Kidney function and PD performance pre- and post-COVID-19

All patients ($n.=27$)	Pre-COVID-19	Post-COVID-19	*p* value
UF (IQR), ml	400 (175–600)	450 (100–900)	0.42
24-h urine output (IQR), ml	1800 (900–2000)	1500 (850–2000)	0.19
RRF (IQR), ml/min	4.1 (3.2–6.8)	3.7 (1.7–5.5)	0.07
Kt/V (IQR)	2 (1.9–2.3)	1.9 (1.6–2.1)	0.07
Unvaccinated patients ($n.=9$)			
UF (IQR), ml	400 (250–1250)	600 (200–1600)	0.14
24-h urine output (IQR), ml	2000 (800–2300)	1500 (900–2000)	0.07
RRF (IQR), ml/min	3.5 (2.6–5.1)	2.5 (1.2–4.2)	0.22
Kt/V (IQR)	2 (1.6–2.1)	1.9 (1.4–2)	0.068
Vaccinated patients ($n.=18$)			
UF (IQR), ml	400 (112–487)	400 (100–600)	0.95
24-h urine output (IQR), ml	1750 (800–1950)	1500 (700–2000)	0.81
RRF (IQR), ml/min	4.7 (3.9–7.5)	4 (1.8–7.2)	0.24
Kt/V (IQR)	2 (1.9–2.5)	1.9 (1.7–2.2)	0.18

IQR denotes interquartile range, *RRF* Residual renal function, *UF* ultrafiltration

The infection was symptomatic in 83.4% of subjects. The main symptoms were fever (61.1%) and cough (55.6%). Hospital admission occurred in 27.8% of them. All hospitalized patients were successfully treated with casirivimab + imdevimab ($n=3$) or sotrovimab ($n=2$) and dismissed home afterward. In this group of patients, shedding of SARS-CoV-2 lasted 32 (IQR, 12–36) days.

Comparison between vaccinated and unvaccinated PD patients

There were no differences between vaccinated and unvaccinated patients in terms of baseline characteristics, etiology of CKD and comorbidities (Table 1). It is worth noting that all unvaccinated patients became symptomatic

after SARS-CoV-2 infection, whereas 16.6% of vaccinated patients remained asymptomatic after COVID-19 diagnosis. As expected, a higher rate of symptoms, such as cough, fever and dyspnea, were experienced in the unvaccinated patients without reaching statistical significance. Concerning hospital admission, no statistically significant differences were noted between the two groups. Viral shedding was also similar in the two groups ($p = 0.73$). The prolonged positivity was particularly harmful to patients on the waiting list for kidney transplantation, as they remained inactive on the waiting list for kidney transplantation for 44 (IQR, 42–54) days.

Comparison between PD and HD patients with COVID-19

During the same period of observation, 87 out of 279 HD patients contracted COVID-19. Median age of HD patients with COVID-19 was higher (66.7 vs 60 years) (IQR, 53.3–81.9) than PD patients, but this difference was not significant ($p = 0.15$). Gender was similar between the two cohorts of patients ($p = 0.25$). The overall incidence rate of COVID-19 in the HD population [0.17 (95%CI 0.13–0.20) episodes per patient-year] was similar to the incidence rate in the PD cohort ($p = 0.9$). In parallel, the incidence rate of COVID-19 cases among HD patients in the pre-vaccination (0.14 [95%CI 0.1–0.19]) and vaccination periods (0.23 [95%CI 0.17–0.31]) did not differ from those of patients receiving PD. A significant difference was noted in the epidemiology of COVID-19 in HD population. The incident rate of this illness was indeed significantly higher after vaccination ($p = 0.02$).

Overall, HD patients with COVID-19 experienced a similar rate of hospitalization ($p = 0.64$) but had a higher rate of death compared to PD patients ($p = 0.03$) (Supplementary Table 1). Subgroup analysis by vaccination status did not reveal any differences between HD and PD patients in hospitalization and mortality rate. The administration of the vaccine significantly improved the clearance of the virus in HD population by reducing the shedding of the virus from the nasal mucosa (28 vs 44 days) ($p = 0.001$).

The inactivation on the waiting list was similar between HD and PD populations (44 vs 39 days, $p = 0.56$). Lastly, the rate of vaccine refusal was lower among PD patients (1.6 vs 3.4%) but this difference did not achieve statistical significance ($p = 0.47$).

Discussion

The scarce information published on PD patients during the COVID-19 pandemic creates uncertainty on the outcome of this population once infected with SARS-CoV-2.

It is widely known that PD patients are less exposed to the risk of infectious disease transmission compared to in-center HD patients as home dialysis reduces the risk of virus transmission from healthcare workers and patients. However, the great burden of comorbidities of PD patients may lead these patients to experience the same clinical vulnerabilities as those receiving HD.

One-fifth of PD patients followed at our facility contracted COVID-19 during the period of observation. The overall incidence rate of SARS-CoV-2 infection accounted for an incidence rate of 0.16 episodes per patient-year, which is generally comparable or slightly lower than the rate of peritonitis in centers of excellence [11–13]. However, our findings confirmed that COVID-19 adversely affected patients on chronic PD as hospitalization for severe symptoms occurred in one-third of patients. All subjects admitted to the hospital required oxygen therapy for hypoxemia due to pneumonia. The course of the disease was extremely severe only in two unvaccinated patients who died of MOF during the first wave of COVID-19, before the vaccination campaign. Consequentially, COVID-19 caused an excess death of 22.2% in our population since the start of COVID-19 pandemic. COVID-19 also triggered the shift from PD to HD in two overhydrated hospitalized subjects with respiratory distress. Given the vast array of COVID-19-related complications, including acute [14] and chronic kidney injury [15] and potential SARS-CoC-2 invasion of the peritoneal membrane [16], we investigated the impact of COVID-19 on kidney function and PD performance. We documented that RRF, 24-h urinary output, peritoneal ultrafiltration and weekly Kt/V resulted unaffected by COVID-19 both in unvaccinated and vaccinated patients.

The advent of COVID-19 vaccination has been a pragmatic shift for the outcome of COVID-19 in patients on renal replacement therapy [17]. mRNA vaccines provided a high degree of protection against severe illness and death in immunocompetent people [10]. For this reason, COVID-19 vaccination has been prioritized for the dialysis population, as they are at high risk for adverse outcomes including death [5, 10, 18]. In our study, vaccination showed a tendency to provide clinically valid protection against severe COVID-19. Patients who underwent vaccination experienced a lower rate of COVID-19 symptoms (cough, fever and dyspnea), despite a higher rate of older and immunosuppressed patients in the vaccinated group. The rate of hospitalization and length of stay remained similar to unvaccinated subjects, but no one died of the severe consequences of this illness.

The findings of this study pointed out that adhesion to COVID-19 vaccination was substantial in our population. Only 1.6% of the PD patients expressed vaccine hesitancy until the end of the follow-up. A higher rate, albeit not statistically significant, has been found in our HD population,

where it accounted for 3.4%. In parallel, high rates of vaccine hesitancy have been observed in 150 HD facilities in the United States (20%) [19] and in four HD facilities in Europe (11.3%) [11]. The question that arises is why PD patients have such a low rate of vaccine hesitancy than HD counterparts? Likely a better understanding of own health status and a high level of accountability in PD patients may explain a higher rate of COVID-19 vaccine acceptance in this population [20]. Another hypothesis may be the exclusion of vulnerable and marginalized patients from PD treatment. There is indeed evidence that sociodemographic factors such as a low household income and a low level of education are associated with a high level of vaccine hesitancy [21–23].

We also explored the effect of COVID-19 vaccine on the viral shedding measured by RT-PCR nasopharyngeal swab. The duration of the viral shedding was similar between vaccinated and unvaccinated PD patients. In particular, we did not observe any reduction of viral shedding in the vaccinated patient and reinfected patients. Although it is widely known that viral shedding does not equal infectivity, this problem temporarily affects the eligibility of patients on the waiting list for kidney transplantation. Indeed, PD and HD subjects with COVID-19 remained inactive on the waiting list for kidney transplantation for a median of 44 (42–54) and 39 (28–38) days, respectively.

Lastly, we noted that the number of episodes of SARS-CoV-2 infection rose principally after the vaccination and during the autumn and winter seasons. The increased number of COVID-19 cases after vaccination was more pronounced in HD than in PD. This was likely due to the spread of SARS-CoV-2 Omicron variants through Italy from November 2021 [24]. This strain, more transmissible than the ancestral and Alpha strain, is able to drive repeated infections in humans [25]. With regard to the influence of seasonal factors on the spread of SARS-CoV-2, our date confirmed the increased transmissibility of the virus in cold conditions [26]. However, the seasonability of the virus needs to be confirmed, given the recent steep rise of COVID-19 cases despite warm temperatures throughout Europe and Asia.

Three main limitations of this study must be highlighted. First, the small sample size of the unvaccinated group limits a proper comparison with the vaccinated counterpart. Second, the outcomes of our patients were not correlated to the level of neutralizing antibodies, which were unavailable at the time of the study. As a result, we are unaware of the rate of unresponsive patients to vaccination. Lastly, the representativeness of the sample affects the generalizability of our results. Nevertheless, our study is one of the few experiences reporting the outcome of this "forgotten" group of dialysis patients during COVID-19 pandemic.

Conclusion

Patients on chronic PD experienced the negative effects of COVID-19. Despite effective vaccination, one-third of the PD population required hospital admission for lung pneumonia. However, the disease had a severe prognosis only in two unvaccinated patients. Similar to HD patients, all survivors receiving PD showed long-term viral shedding when measured by RT-PCR nasopharyngeal swab. Lastly, a low rate of vaccine hesitancy was found in the PD population compared to the data extrapolated from HD patients.

Declarations

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