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Evaluation of Outcomes of Peritoneal Dialysis Patients in the Post-COVID-19 Period: A National Multicenter Case-Control Study from Turkey

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Abstract

Introduction: There are not enough data on the post-COVID-19 period for peritoneal dialysis (PD) patients affected from COVID-19. We aimed to compare the clinical and laboratory data of PD patients after COVID-19 with a control PD group. ***Methods:*** This study, supported by the Turkish Society of Nephrology, is a national, multicenter retrospective case-control study involving adult PD patients with confirmed COVID-19, using data collected from April 21, 2021, to June 11, 2021. A control PD group was also formed from each PD unit, from patients with similar characteristics but without COVID-19. Patients in the active period of COVID-19 were not included. Data at the end of the first month and within the first 90 days, as well as other outcomes, including mortality, were investigated. ***Results:*** A total of 223 patients (COVID-19 group: 113, control group: 110) from 27 centers were included. The duration of PD in both groups was similar (median [IQR]: 3.0 [1.88–6.0] years and 3.0 [2.0–5.6]), but the patient age in the COVID-19 group was lower than that in the control group (50 [IQR: 40–57] years and 56 [IQR: 46–64] years, $p < 0.001$). PD characteristics and baseline laboratory data were similar in both groups, except serum albumin and hemoglobin levels on day 28, which were significantly lower in the COVID-19 group. In the COVID-19 group, respiratory symptoms, rehospitalization, lower respiratory tract infection, change in PD modality, UF failure, and hypervolemia were significantly higher on the 28th day. There was no significant difference in laboratory parameters at day 90. Only 1 (0.9%) patient in the COVID-19 group died within 90 days. There was no death in the control group. Respiratory symptoms, malnutrition, and hypervolemia were significantly higher at day 90 in the COVID-19 group. ***Conclusion:*** Mortality in the first 90 days after COVID-19 in PD patients with COVID-19 was not different from the control PD group. However, some patients continued to experience significant problems, especially respiratory system symptoms, malnutrition, and hypervolemia.

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Introduction

The presence of comorbidities, including chronic kidney disease, has been reported to be a risk factor for short-term adverse outcomes, such as hospitalization, need for intensive care support, and mortality during the COVID-19 [[1–4]. Among chronic kidney disease patient groups, these outcomes are more pronounced in patients with end-stage kidney disease. However, almost all studies on this subject are related to hemodialysis (HD) patients and included early results (the active period of COVID-19). The European Renal Association COVID-19 Database (ERACODA) showed that the 28-day probability of death in dialysis patients was 25.0% (95% CI: 20.2–30.0%) [5]. In this study, 125 of 4,298 patients were on peritoneal dialysis (PD), and the 28-day probability of death was also 25.0%. Data from New York, USA, showed 28% in-hospital mortality among HD patients [5]. Our group showed that maintenance HD is an independent risk factor for intensive-care-unit (ICU) admission and in-hospital mortality [2, 6]. However, PD had become a

priority since it is an individual treatment at home during the pandemic period and the risk of COVID-19 transmission was lower [7, 8]. In a study that includes historical trends from Medicare and Medicaid data, the initialization rate of PD (against HD) was 24% higher during the pandemic [9]. In a study comparing outcomes of hospitalized PD, HD, and non-uremic control COVID-19 patients, we showed that in-hospital mortality of PD and HD was not significantly different [10].

Nevertheless, there are limited studies on PD patients regarding the COVID-19 outcomes. In a multi-center study by Jiang et al. [11] from Wuhan, China, 8 of 818 patients on PD reported being diagnosed with COVID-19 from January 1, 2020, to April 12, 2020. The incidence rate of symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in this study was 2.44 per 1,000 person-months. In another study from New York, United States, only 2 of 59 patients were on PD [12]. On the other hand, there are not enough published data on the outcomes at the follow-up of PD patients in the post-COVID-19 period. Herein, we aimed to present the outcomes data, including symptoms, rehospitalization, and mortality obtained in the follow-up of PD patients in the immediate post-COVID-19 period for 90 days, and compare them with a control PD group.

Materials and Methods

This retrospective study followed the report Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [13]. Ethics Committee of Health Sciences University Haseki Training and Research Hospital approved this study (#2020-256).

Population and Setting

We conducted a national multicentric retrospective case-control study including PD patients aged 18 years or older who survived after a confirmed COVID-19. The study was unconditionally supported by the Turkish Society of Nephrology. In addition, a control PD group was selected among patients who did not have COVID-19 in the same PD unit. While forming the control group, we tried to include, as far as possible, the next patient who was started PD treatment at the same unit at similar times and did not have COVID-19. We collected data through a Web-based database specifically designed for PD patients. This study was prepared from the data recorded in this database between April 21, 2021, and June 11, 2021. The same project is also collecting data regarding the active COVID-19 phase (the first month of COVID-19) among the PD patients, and another paper prepared from that data related to outcomes of the active COVID-19 patients was also submitted.

This study included patients who had confirmed SARS-CoV-2 infection based on positive reverse transcriptase-polymerase chain reaction (RT-PCR) testing of a nasopharyngeal swab from the main database. Patients in the active period of COVID-19 (SARS-CoV-2 RT-PCR still positive and/or still receiving antiviral treatment for COVID-19). SARS-CoV-2 RT-PCR-negative COVID-19 patients and the patients without 3rd-month outcome data were excluded.

Measurements and Definitions

Demographic data, comorbidities and medications, primary kidney diseases that cause end-stage kidney disease, duration of PD, type of PD modality, residual urine amount, weight, systolic and diastolic blood pressures, Kt/V, and daily ultrafiltration volumes were recorded. Data regarding basic laboratory tests (hemogram, serum creatinine, albumin, CRP, ferritin) at the last monthly routine check before the development of COVID-19 at that PD center were also collected. The same laboratory tests were obtained in the same monthly check for the control group. In addition, we obtained data regarding the presence of pneumonia in computerized chest tomography (CT) for the COVID-19 group and CO-VID-19 treatment, and if hospitalized, hospitalization in ICU, mechanical ventilation, and major treatments in ICU. We classified COVID-19 patients according to the clinical severity of the disease at presentation, in accordance with the Ministry of Health guidelines [14]: Patients with no symptoms and/or detected on screening were classified as asymptomatic disease. If the patient has complaints such as fever and cough but does not have concomitant shortness of breath (there may be an abnormal finding on CT), it was classified as mild disease. If shortness of breath (perhaps with other symptoms) required oxygen delivery presented, it was termed moderate to severe illness. The disease was defined as those with blood arterial oxygen saturation <90% or hemodynamic disorders requiring ICU follow-up despite oxygen support at admission.

Outcomes

We investigated mortality, rehospitalization, the persistence of respiratory symptoms associated with COVID-19, and the development of lower respiratory system infection or peritonitis within the first 30 days and 90 days after diagnosis of COVID-19. For the control group patients, the same endpoints were also questioned during the same period (30 days and 90 days) and compared with the COVID-19 group.

Statistical Analyses

Categorical variables were presented as numbers and percentages, and numeric variables were presented as median and interquartile ranges (25–75%) in descriptive statistics. We determined the variables' normality using visual methods (histograms and probability plots) and Kolmogorov-Smirnov tests. The χ^2 test was used for two or multiple group comparisons of categorical variables, and the independent t test or Mann-Whitney U test was used as appropriate in comparing numerical variables. In the multiple group comparisons, we used the variance (ANOVA) test for numerical variables with normal distribution and the Kruskal-Wallis test for numerical variables that were not normally distributed. We used IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. $p < 0.05$ was accepted as the level of significance.

Table 1. Demographic and baseline laboratory data of patients, comorbidities, and primary kidney disease

	COVID-19 group, N = 113	Control group, N = 110	p value
Demographic data			
Age,* years, median (IQR)	50 (40–57)	56 (46–64)	0.039
Gender, female, n (%)	68/113 (60.2)	62/110 (56.4)	0.564
PD duration, years, median (IQR)	3.0 (1.88–6.0)	3.0 (2.0–5.6)	0.993
BMI, kg/m², median (IQR)	25.1 (23.4–28.7)	25.7 (23.3–29.6)	0.375
Primary kidney disease, n (%)			
Primary glomerulonephritis	15/113 (13.3)	18/110 (16.4)	0.842
Diabetic nephropathy	24/113 (21.2)	19/110 (17.3)	
Hypertensive nephrosclerosis	29/113 (25.7)	31/110 (28.2)	
ADPCKD	10/113 (8.8)	7/110 (6.4)	
Other	35/113 (31.0)	35/110 (31.8)	
Comorbidities, n (%)			
Diabetes mellitus	25/113 (22.1)	23/110 (20.9)	0.825
Hypertension	88/113 (77.9)	93/110 (84.5)	0.203
COPD	3/113 (2.7)	1/110 (0.9)	0.326
Ischemic heart disease	16/113 (14.2)	16/110 (14.5)	0.934
Heart failure	10/113 (8.8)	10/110 (9.1)	0.950
Cerebrovascular disease	6/113 (5.3)	1/110 (0.9)	0.060
Medications, n (%)			
ACE inhibitor*	20/113 (17.7)	34/110 (30.9)	0.021
Angiotensin receptor blocker	27/113 (23.9)	17/110 (15.5)	0.113
Calcium channel blocker	66/113 (58.4)	56/110 (50.9)	0.261
Beta-blocker	54/113 (47.8)	49/110 (44.5)	0.627
Other antihypertensives	25/113 (22.1)	28/110 (25.5)	0.559
Insulin	20/113 (17.7)	18/110 (16.4)	0.791
Oral antidiabetic agents	6/113 (5.3)	5/110 (4.5)	0.792
Statin	10/113 (8.8)	16/110 (14.5)	0.185
Antiaggregant*	40/113 (35.4)	16/110 (14.5)	<0.001
Anticoagulant	8/113 (7.1)	12/110 (10.9)	0.317
Pre-COVID-19 data,[1] median (IQR)			
Systolic blood pressure,* mm Hg	130 (120–150)	140 (130–150)	0.151
Diastolic blood pressure, mm Hg	80 (74–90)	80 (80–90)	0.242
Average dialysate volume, L/day	8 (7.3–9.5)	8 (8–10)	0.314
Average UF, mL/day	1,100 (700–1,500)	1,000 (775–1,500)	0.604
Exchanges, n (pcs/day)	4 (4–4)	4 (4–5)	0.651
Weekly Kt/V (total)	2.12 (1.89–2.58)	2.09 (1.89–2.56)	0.748
Weekly Kt/V (dialysate)	1.8 (1.4–2)	1.79 (1.5–2)	0.560
Daily residual urine, mL/day	775 (200–1,150)	800 (200–1,275)	0.970
Creatinine, mg/dL	7.9 (6.3–10.1)	8.105 (6.32–9.78)	0.325
Parathormone, pg/mL	332 (212–637)	330 (192–523)	0.263
Albumin, g/dL	3.69 (3.3–4)	3.7 (3.4–3.9)	0.205
Ferritin, ng/mL	269 (150–505)	248 (123–500)	0.972
CRP, mg/L	4.5 (2–12.36)	4.0 (2–8.1)	0.404
Hemoglobin, g/dL	10.9 (9.7–12)	11.0 (9.9–12.1)	0.450
Leukocytes, /mm³	7,400 (5,780–8,800)	7,500 (5,800–9,040)	0.444

IQR, interquartile range; ADPCKD, autosomal dominant polycystic kidney disease; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; D/P, dialysate/plasma; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; CRP, C-reactive protein. * p < 0.05 [1] All data were based on the month before the development of COVID-19, in the COVID-19 group, and the same month with the COVID-19 patient in the control group.

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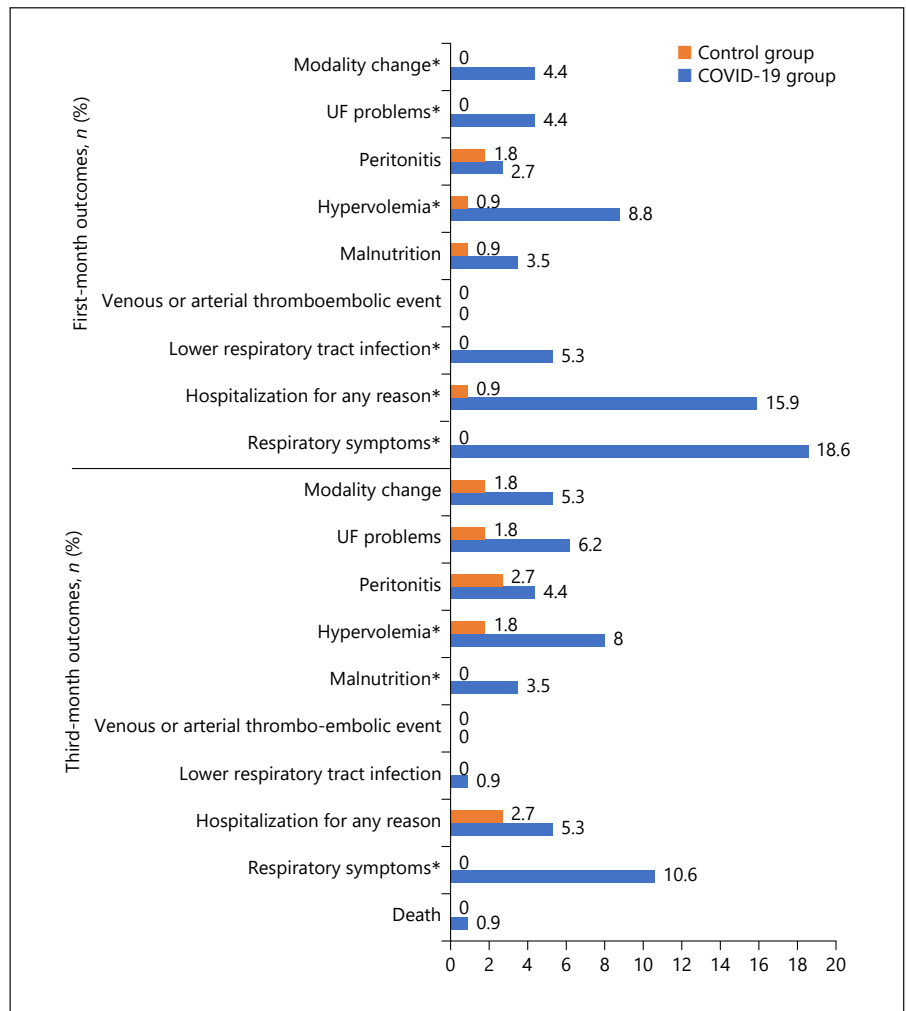
Fig. 1. The clinical outcomes obtained at the first and third months compared by groups (*p < 0.05).

Results

Participants, Demographics, and Baseline Characteristics

The main database had 316 patients from 27 centers in Turkey. We excluded RT-PCR-negatives (20 patients), the patients who died during the active phase of COVID-19 (26 patients), the patients that had no control group from the same center (8 patients), resubmissions (8 patients), the patients with missing main outcome data (14 patients), and the patients with active COVID-19 (17 patients). The remaining 223 patients (113 patients in the COVID-19 group, 110 patients in the control group) were included in this study. Table 1 shows the patients' baseline demographics, comorbidities, PD-related data, and laboratory tests. A comparative presentation of some additional demographic baseline laboratory and PD data and the results of the patients at the first and third months are presented in online

supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000526234). The median age of the COVID-19 group was lower than the control group (median age [IQR]: 50 [40–57] years and 56 [46–64], respectively, $p < 0.001$).

PD-Related Data of the Groups

The laboratory data of the COVID-19 group in the month before the COVID-19 development and the control group in the same month as the COVID-19 patient were almost similar (Table 1). The PD duration, weight, dialysate volume, UF volume, daily exchange number, weekly Kt/V, and daily residual urine volume of both groups were not significantly different. Only D/P creatinine at the 4th hour in the peritoneal equilibrium test was significantly higher in the COVID-19 group. None of the other baseline laboratory values were different between the groups.

Table 2. Comparative presentation of patients' baseline laboratory and PD data at the first and the third months and outcomes

	COVID-19 group, $N = 113$	Control group, $N = 110$	p value
First-month data, median (IQR)			
Weight, kg	71 (61–76)	71 (60–83)	0.398
Systolic blood pressure, mm Hg	130 (120–145)	135 (120–150)	0.350
Diastolic blood pressure, mm Hg	80 (80–95)	80 (76–90)	0.675
Average dialysate volume, L/day	8 (8–9.5)	8 (8–10)	0.231
Average UF, mL/day	1,200 (700–1,500)	1,100 (700–1,600)	0.879
Number of exchanges, pcs/day	4 (4–5)	4 (4–5)	0.451
Daily residual urine, mL/day	750 (200–1,000)	800 (250–1,200)	0.975
Creatinine, mg/dL	7.5 (6.1–10.5)	8,2 (6.2–9,7)	0.762
Albumin,* g/dL	3.5 (3.2–3.9)	3.7 (3.5–3.9)	0.004
Ferritin, ng/mL	329 (161–638)	266 (133–478)	0.194
CRP, mg/L	6.0 (2.35–11.7)	4.4 (2.0–9.1)	0.300
Hemoglobin,* g/dL	10.1 (9.4–11.6)	11.0 (10.1–12.1)	<0.001
Leukocytes, /mm^3	7,040 (5,770–9,070)	7,580 (5,700–9,060)	0.264
First-month outcomes, n/N (%)			
Respiratory symptoms*	21/113 (18.6)	0/110 (0)	<0.001
Hospitalization for any reason*	18/113 (15.9)	1/110 (0.9)	<0.001
Lower respiratory tract infection*	6/113 (5.3)	0/110 (0)	0.014
Venous or arterial thromboembolic event	0/113 (0)	0/110 (0)	–
Malnutrition	4/113 (3.5)	1/110 (0.9)	0.185
Hypervolemia*	10/113 (8.8)	1/110 (0.9)	0.006
Peritonitis	3/113 (2.7)	2/110 (1.8)	0.673
UF problems*	5/113 (4.4)	0/110 (0)	0.026
Modality change*	5/113 (4.4)	0/110 (0)	0.026
Third-month data, median (IQR)			
Weight, kg	71 (62–76)	72 (60–82,4)	0.721
Systolic blood pressure, mm Hg	135 (127–140)	130 (115–140)	0.765
Diastolic blood pressure, mm Hg	80 (80–95)	80 (76–90)	0.082
Average UF, mL/day	1,100 (700–1,500)	1,025 (700–1,500)	0.853
Number of exchanges, pcs/day	4 (4–5)	4 (4–5)	0.617
Daily residual urine, mL/day	750 (200–1,200)	800 (200–1,200)	0.693
Creatinine, mg/dL	8 (6–10.4)	7.9 (6.0–9.8)	0.615
Albumin, g/dL	3.6 (3.2–3.9)	3.7 (3.5–4.0)	0.064
Ferritin, ng/mL	240 (144–456)	246 (121–469)	0.876
CRP, mg/L	3.3 (2.0–9.7)	4.7 (2.7–13.0)	0.081
Hemoglobin, g/dL	10.8 (9.6–11.7)	11.0 (9.8–12.3)	0.144
Leukocytes, /mm^3	7,240 (5,940–9,170)	7,390 (5,910–8,890)	0.296
Third-month outcomes, n/N (%)			
Death	1/113 (0.9)	0/110 (0)	0.323
Respiratory symptoms*	12/113 (10.6)	0/110 (0)	<0.001
Hospitalization for any reason	6/113 (5.3)	3/110 (2.7)	0.327
Lower respiratory tract infection	1/113 (0.9)	0/110 (0)	0.323
Venous or arterial thromboembolic event	0/113 (0)	0/110 (0)	–
Malnutrition*	4/113 (3.5)	0/110 (0)	0.046
Hypervolemia*	9/113 (8.0)	2/110 (1.8)	0.034
Peritonitis	5/113 (4.4)	3/110 (2.7)	0.496
UF failure	7/113 (6.2)	2/110 (1.8)	0.097
Modality change	6/113 (5.3)	2/110 (1.8)	0.161

All data were obtained according to time the diagnosis of COVID-19 in the COVID-19 group and the same month with the COVID-19 patient in the control group. IQR, interquartile range; UF, ultrafiltration; CRP, C-reactive protein. * $p < 0.05$.

The Data regarding COVID-19

Comparing demographics, comorbidities, laboratory and COVID-19 outcome data according to whether CO-VID-19 PD patients are outpatient or inpatient, age, albumin, ferritin, CRP, leukocyte, the rate of multiple bilateral lesions on CT, and the rate of clinically severe disease at admission were significantly higher in hospitalized patients than in outpatients (online suppl. Table 2). We compared the patients' outcomes according to the presence or absence of shortness of breath at the 3rd month; fibrinogen level, the presence of shortness of breath, rehospitalization for any reason, hypervolemia, and UF failure in the 1st month and the presence of hypervolemia and peritonitis the 3rd month were significantly higher in the shortness of breath positive group (online suppl. Table 3).

Outcomes at the 28th Day and between the 28th Day and 90th Day

Significant differences were observed among the groups in terms of the outcomes on the 28th day of the diagnosis of COVID-19 (Table 2; shown in Fig. 1). Among laboratory tests on the 28th day, serum albumin and hemoglobin levels were significantly lower in the COVID-19 group than in the control group. Respiratory symptoms, readmission to hospital for any reason, development of lower respiratory tract infection, change in the PD modality, UF failure, and hypervolemia were significantly higher in the COVID-19 group on the 28th day. Venous or arterial thromboembolic events were not diagnosed in any COVID-19 and control patients. There was no difference in peritonitis rates between the groups.

There was no significant difference in the PD and laboratory parameters assessed on the 90th day. Only 1 (0.9%) patient died from the COVID-19 group between the 28th and 90th days of the diagnosis of COVID-19, but there was no dead in the control group. Respiratory symptoms, malnutrition, and hypervolemia were significantly higher in the COVID-19 group than the control group at the 90th day.

When we compared the baseline laboratory and PD outcome data at the first and third months of the CO-VID-19 patients according to the presence of shortness of breath at the third month (online suppl. Table 3), shortness of breath, rehospitalization, hypervolemia, and UF failure within the first month and hypervolemia and peritonitis rate at the third month were significantly higher in patients with shortness of breath at the third month than patients without shortness of breath.

Discussion

In this multicenter retrospective study involving PD patients recovering from COVID-19 and a control group, we have found no significant 90th-day mortality difference between the groups. Although the mortality of PD patients with COVID-19 was significantly higher than the COVID-19 patients from the general population [15], as far as we know, no study has shown similar mortality after the acute phase of COVID-19 (post-COVID-19 period) than the control counterparts among PD cohort. Hence, our data clearly show no continued increased risk of mortality after COVID-19 in PD.

There were no published studies comparing ongoing COVID-19 symptoms in PD patients in the post-COVID period. We observed that complications such as ongoing respiratory symptoms, readmission to hospital for any reason, development of lower respiratory tract infection, change in the PD modality, UF failure, and hypervolemia were significantly higher in the COVID-19 group in the first month. Recovery time from COVID-19 is variable but usually takes 2 weeks, while those with severe illness can take months [16]. Although most of our patients recovered before the 28th day, respiratory symptoms persisted in 18.6% of patients in the first month and 10.6% in the third month. In our study, hypervolemia and UF failure were also reported more in the patients with persisting shortness of breath. It was not possible to distinguish whether the patients' dyspnea was from post-CO-VID-19 sequelae or hypervolemia due to UF failure; modality change rate was significantly higher in the first month and nonsignificantly higher in the third month. These may be due to changes in peritoneal transport function after COVID-19. There is no study investigating peritoneal transport changes after COVID-19, but there were data regarding the transfer of PD patients to HD during COVID-19. In their study, Jiang et al. [11], in which 8 PD patients were diagnosed with COVID-19, 2 patients died. Median Kt/V, amount of UF, and residual urine volume were found to be lower in these COVID-19 patients. Our data showed that all patients who still had shortness of breath at the 3rd month were in the CO-VID-19 group also shows the fact that these patients continue to have the risk of long-term respiratory failure symptoms. On the other hand, PD patients can sometimes switch to HD during the active period of COVID-19 [11]. However, according to our study, PD patients have not been transferred to HD after COVID-19 follow-ups. This indicates that the persisting respiratory symptoms

or hypervolemia in the post-COVID period are not sufficient to cause a patient's renal replacement type change.

Rehospitalization rates within 28 days and between day 28 and day 90 were significantly higher in the COVID-19 group than in the control group. Rehospitalization rates of PD patients in the post-COVID-19 period have not been previously reported. However, similarly increased readmission or hospitalization rates were published in non-uremic populations [17, 18].

COVID-19 usually causes a hypercoagulable state [19–21]. In our study, there were no patients with venous or arterial thromboembolic events found in either the COVID-19 group or the control group. We were unable to identify any published studies of thrombotic events in PD patients who survived COVID-19. In a study including a median follow-up of 7 months in 185 HD patients, an increase in late thrombotic events in COVID-19 survivors was shown compared to the uninfected cohort (18.5% vs. 1.9%, $p = 0.002$) [22]. However, it may not be appropriate to compare PD patients with HD patients with continuous extracorporeal circulation and rapid fluid withdrawal.

This study has some limitations as it was retrospective, and the groups were not fully randomized. According to 2020 Turkish registry reports, there are 3,387 PD patients [23], and 223 patients registered in this study constitute only 6.6% of the PD patients. However, we collected patient data from different regions and included a control group from each center. Therefore, our results may be considered close to those encountered in real life. We also designed our study with simple randomization to avoid selection bias, making the results more valuable. But some patients who had this condition but discontinued PD before the study due to technical failure or transplantation may not have been included in the study. This may have influenced the selection of control patients. During the pandemic, some PD patients with COVID-19 came consecutively and were enrolled in the COVID-19 group, while sometimes, a candidate patient in the control group had exclusion criteria. For this reason, the numbers of the COVID-19 and control groups could not be precisely equal. In addition, we were unable to use multivariate analyses of risk factors associated with deaths as mortality data from subjects enrolled in this study were very scarce.

In conclusion, the mortality rate in the first and third months after COVID-19 in PD patients with COVID-19 was not different from the control PD group. However, some of these patients continue to experience significant problems, especially respiratory system symptoms.

Therefore, there is a need for studies with a more extended follow-up period and detailed investigations of the findings in PD patients recovering from COVID-19.

Author Contributions

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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