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CLINICAL BEHAVIOUR AND THERAPEUTIC RESPONSES OF PATIENTS ON REGULAR HEMODIALYSIS ADMITTED WITH COVID 19 IN A TERTIARY CARE HOSPITAL

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ABSTRACT

The novel coronavirus illness (COVID-19) is quickly expanding, posing significant difficulties for patients with hemodialysis maintenance. The clinical manifestations and consequences of COVID-19-treated ESRD patients are presented here.

Methods

ESRD individuals treated with COVID-19 were studied in a retrospective cohort research at Dr. Ziauddin Hospital North Nazimabad in Karachi, Pakistan, between June 2020 and March 2021.

Findings

The ESRD group had lesser symptoms than others. Shortness of breath, fever, and cough were common symptoms, with statistically significant p values (p.007, p.001, and p.033, respectively). Lower median hemoglobin count (10 vs. 12.4; p0.001) and significantly higher inflammatory markers, such as d-dimer and serum ferritin levels (2922 vs. 1275; p.001, 2681 vs. 754; p.001, respectively), were found in the ESRD group. The median lymphocyte count was lower and inflammatory markers, such as C-reactive protein, ferritin, and lactate dehydrogenase, were greater in dying ESRD patients; however, none of these differences were statistically significant. The majority of the patients in the ESRD cohort were admitted with no oxygen requirements. Discharge, expiry, need for ICU hospitalization and invasive assisted ventilation remained statistically non-significant between the two groups. On Kaplan-Meier analysis, patients in ESRD cohort were discharged earlier (5.12 vs. 7.13 days; Log Rank p.013), had lower survival (3.75 vs. 7.29 days; Log Rank p.005). The ESRD cohort, on the other hand, required ICU admission much sooner after the beginning of symptoms. (4.8 vs. 8.13 days; Log Rank p.020).

Conclusion
Symptoms were milder in the ESRD cohort. Results across ESRD versus non-ESRD groups were, however, virtually identical.

Keywords: End-stage renal disease; Maintenance hemodialysis; COVID-19; ICU; Mechanical ventilation; Expired.

INTRODUCTION

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a novel coronavirus that causes a human disease known as coronavirus disease 2019 (COVID-19). COVID-19 has been confirmed in approximately 200 million people around the world. There are many cases where the disease is self-limiting, ranging from asymptomatic to mild to moderate disease. About 5 percent of patients require assisted ventilation due to respiratory failure, and less than 20 percent require supplemental oxygen[1-3]. When the immune system is overreacting, it can cause a cytokine storm, worsening pulmonary symptoms and potentially resulting in death[4, 5]. An increased risk of death is associated with older age, male gender, and prior medical illness like diabetes, cardiac events, obstructive pulmonary disease (COPD), or a presence of malignancy[6, 7]. Even after accounting for age, race, and diabetes, the end-stage renal disease (ESRD) population had a higher annual mortality rate than the general population. Compared to the general population, annual mortality from sepsis is 30–45 times greater in the dialysis group[8]. A recent study identified a link between seasonal change in all-cause deaths among individuals with ESRD and community influenza-like illness, with increased mortality of 1100 fatalities per year in the ESRD population[9]. The virus's direct impact and an excessive immune response have been associated with COVID-19-related disease[10]. Because of this, the reduced immune response in ESRD may offer protection from the cytokine storm associated with severe COVID19 infection. Patients with COVID-19 had lower levels of inflammation cytokines than those in other dialysis patients, according to the paper published by Ma and colleagues[11]. One other thing to keep in mind is that dialysis patients have a lower angiotensin-converting enzyme 2 (ACE2)[12, 13]. As ACE2 is a receptor for the new coronavirus CoV-2[14], decreased activity may reduce the severity of sickness. On the other hand, patients undergoing dialysis might be more vulnerable to COVID-19 due to enhanced transmission of the virus in dialysis facilities and a decreased ability to fight infection[15, 16]. Patients with chronic kidney disease may be affected by this virus in a currently unknown way[17-19]. Dialysis facilities are more susceptible to disease transmission because of their complex logistics[20].Research published in the United States (US) showed that 59 people with end-stage renal disease (ESRD) had poor outcomes, with 18 (31 percent) dying overall and 6 (75 percent) dying in mechanically ventilated patients[21].Additionally, some researches have revealed that participants with severe COVID-19 disease and known kidney disease have poor outcomes, especially for patients on regular dialysis; however, the study size of the sample was small, and most excluded comparator populations in these investigations[16, 22-25].Among individuals hospitalized with COVID-19, we looked at the outcomes of patients with and without the end-stage renal disease (ESRD).

MATERIAL AND METHODS

From April 2020 to March 2021, a retrospective cohort study was conducted at Dr. Ziauddin Hospital North Nazimabad, a tertiary care hospital in Karachi, Pakistan, to study the clinical manifestations and outcomes of patients with ESRD who were admitted with COVID-19.

The rapid antigen assay, polymerase chain reaction (PCR) on a nasopharyngeal swab, and radiological imaging features compatible with COVID-19 pneumonia were the diagnostic procedures used to identify COVID-19 in this study. Patients who were at least 18 years old and had been diagnosed with COVID-19 were eligible for participation in the research.Besides, patients on maintenance hemodialysis were patients of primary interest. Therefore, patients with a history of acute kidney injury or an estimated glomerular filtration rate less than 60ml/min/1.73 m^2, not requiring maintenance dialysis, were excluded from the study. We also excluded patients with incomplete

medical records, patients who received intubated from other hospitals, as well as patients who died, were left against medical advice, or required mechanical ventilatory support within the first day of hospitalization.

Procedure

The Ethical Review Committee of the institution gave its approval to the study. Patients were begun on the standard of care treatment, including low molecular weight heparin, supplementary oxygen, and steroids, per the institutional protocol. Steroids were administered as methylprednisolone or dexamethasone for seven to ten days (or until hospital discharge). Patients were also given remdesivir as a 200mg loading dose, followed by 100mg once daily for four days, if they presented within ten days of the onset of their first symptom. As there were no clear recommendations on the use of Remdesivir in patients with creatinine clearance of less than 30, its use in this population was on the decision of attending physician according to institutional protocols. A stat dose of 8 mg/kg, or two doses, if necessary, of tocilizumab, was administered intravenously or162mgsubcutaneouslyin each thigh according to national recommendations.

Data Collection

The electronic medical records of all COVID-19 patients admitted throughout the research were extracted. The sociodemographic, comorbidities, clinical characteristics, radiological findings, laboratory data, and clinical outcomes of the patients were all collected. A manual inspection of the charts was also done to confirm that the data was valid. One thousand one hundred eightyeight electronic charts were examined, with 1012 patients included and 176 patients eliminated. Eleven patients were excluded due to acute kidney injury; twenty-nine patients were excluded due to chronic kidney disease; two patients were excluded because they were mechanically ventilated from another hospital, and eighty-two patients were excluded because they died or were left against medical advice or were intubated within 24 hours of admission.Besides, we excluded fifty-two patients due to incomplete medical records. The outcome variables were recovery, the requirement for intensive care hospitalization, the necessity for mechanical ventilation, and mortality.

Statistical Analysis

The baseline features of the individuals, such as demographics, laboratory data, and admission status, were compared. For categorical variables, Pearson's Chi-square test or Fisher's exact test were used to computing and compare frequencies and percentages. The median and inter-quartile range for continuous variables were calculated and compared using the Mann-Whitney U test. From the commencement of symptoms until discharge, ICU stays, aided mechanical breathing, and death, the Kaplan-Meier curve was used to calculate survival. The duration from hospitalization to death, ICU admission, and the use of invasive mechanical ventilation were all compared using the Cox regression analysis with a 95 percent confidence interval. IBM SPSS Version 26 was used to analyze the data, and a P-value of 0.05 was utilized to determine statistical significance.

RESULT*S*

One thousand and twelve patients meeting inclusion were entered into the analysis fig-1.
Demographic characteristics are shown in table-1.

	Total	ESRD N (55)	Non-ESRD N (957)	P-Value
Number of patients (percentage)				
Age (mean ± SD)		61.36 (11.56)	58.41 (14.23)	.048
Gender				

Male	661	31 (56.4)	630 (65.8)	.100
Female	351	24 (43.6)	327 (34.2)	
Comorbidities				
Diabetes mellitus	539	37 (67.3)	502 (52.5)	.022
Hypertension	585	46 (83.6)	539 (56.3)	<.001
Chronic liver disease	21	2 (3.6)	19 (2.0)	.318
Asthma or COPD	65	2 (3.6)	63 (6.6)	.298
Ischemic heart disease	179	18 (32.7)	161 (16.8)	.004
Tobacco use	65	5 (9.1)	60 (6.3)	.275
Symptoms				
Fever	844	34 (61.8)	810 (84.6)	<.001
Cough	643	28 (50.9)	615 (64.3)	.033
Shortness of breath	825	37 (67.3)	788 (82.3)	.007
Gastrointestinal Symptoms	222	7 (12.7)	215 (22.5)	.057
Lethargy	461	29 (52.7)	432 (45.1)	.169
Anosmia	134	2 (12.5)	132 (13.8)	.618
Altered level of consciousness	113	3 (18.8)	110 (11.5)	.282
Radiological findings				
Bilateral Infiltrates	700	11 (68.8)	689 (72.0)	.481
Peripheral Infiltrates	634	9 (56.3)	625 (65.3)	.306
Consolidation	308	3 (18.8)	305 (31.9)	.201
Ground glass opacities	219	5 (31.3)	214 (22.4)	.281
Treatment				
Tocilizumab	243	5 (9.1)	238 (24.9)	<.001
Remdesivir	444	17 (30.9)	427 (44.6)	.031
Steroids				
Dexamethasone	428	25 (45.5)	403 (42.1)	<.001
Methylprednisolone	570	16 (29.1)	554 (57.9)	

Table 1: Demographics

Abbreviations: ESRD: End-stage renal disease, SD: standard deviation, COPD: chronic obstructive pulmonary disease.

The mean age of patients in the ESRD group was significantly higher than in another group with statistical significance (p 0.048). There was no difference in gender in study groups. Hypertension, followed by diabetes and ischemic cardiac disease, was the common comorbid condition in our study population. These conditions were significantly common in the ESRD group with significant p values (p <.001; p.022; p.004, respectively). Shortness of breath, fever, and cough were the most typical symptoms; all were more prevalent in the non-ESRD group with statistically significant p values (p.007; p<.001; p.033 respectively). Common radiological findings included bilateral infiltrates, peripheral infiltrates, consolidation, and ground-glass opacity. There was no significant difference in radiological findings between the study groups. A Higher number of patients in the non-ESRD group

received methylprednisolone, tocilizumab, and remdesivir. Baseline laboratory parameters are shown in table-2.

	ESRD N (55)	Non-ESRD N (957)	P-Value
	Median (IQR)		
Hemoglobin (g/dL)	10 (8.80-11.30)	12.40 (11.0-13.60)	<.001
White Blood Cells (x 10^9/L)	10.40 (6.50-13.80)	10.50 (7.40-14.88)	.347
Lymphocyte (%)	8 (5-17)	10 (5-16)	.460
Neutrophils (%)	85 (74-91)	84 (76-90)	.287
Alanine aminotransferase (U/L)	19 (14.0-56.50)	36 (24-61)	.005
Aspartate aminotransferase ST (U/L)	44 (24.50-79.50)	43 (30-70)	.573
Gamma-Glutamyl transferase (IU/L)	35 (22.50-67)	54 (29-98)	.010
C-reactive protein (mg/L)	79.60 (40.20-205.25)	101 (41.03-197.0)	.631
Lactate Dehydrogenase (U/L)	481 (352.75-651)	429 (314-598.50)	.220
D-dimer (ng/mL FEU)	2922 (1313.5-10232.5)	1275 (658.3-4409.5)	.001
Procalcitonin (ng/mL)	2.360 (.936-7.070)	.340 (.127-.965)	<.001
Pro-BNP (pg/mL)	1909 (450-25770.5)	500 (154.5-1464.5)	.021
Ferritin (µg/L)	2681 (1424.5-6269.0)	754 (400-1442)	<.001

Table 2: Baseline Blood Counts and Biochemical Markers
Abbreviations: ESRD: End stage renal disease, BNP: B-type natriuretic peptide, FEU: fibrinogen-equivalent units, IQR: interquartile range.

Participants in the ESRD cohort had significantly lower median hemoglobin count (10 vs. 12.4; p <0.001). There was no significant difference in white cell count, neutrophils, and lymphocytes. Alanine aminotransferase and gamma-glutamyl transferase were significantly lower in the ESRD group (19 vs. 36; p.005, 35 vs. 54; p.010, respectively. Among inflammatory markers, d-dimer and serum ferritin levels were significantly higher in the ESRD cohort (2922 vs. 1275; p.001, 2681 vs. 754; p <.001, respectively). Comparing of markers between dying and surviving patients of ESRD are shown in table-3.

	Expired N (12)	Not-expired N (37)	P-Value
	Median (IQR)		
Lymphocyte (%)	6 (4-9.5)	11 (5-19)	.086
C-reactive protein (mg/L)	138 (68.80-187.46)	59.67 (32.91-210)	.222
Lactate Dehydrogenase (U/L)	534.5 (431-712.5)	454 (329.5-642.5)	.293
D-dimer (ng/mL FEU)	2910 (1352.25-8232)	2922 (1293-11005)	.891
Ferritin (µg/L)	3859 (1653-13663)	2433 (1397-5345.5)	.266

Table 3: Markers according to survival
Abbreviations: IQR: interquartile range, FEU: fibrinogen-equivalent units.

Median lymphocyte count was lower in patients who ultimately expired than those who survived, although values were not statistically significant. Inflammatory markers, i.e., ferritin, C-reactive protein, and lactate dehydrogenase, were raised in patients who expired than those who survived, but none had a significant p-value. However, d-dimer levels were identical between surviving and expired patients. Oxygen requirements of patients on admission are shown in table-4.

	Total	ESRD N (55)	Non-ESRD N (957)	P-Value
Number of patients (percentage)				
Room air	59	26 (47.3)	33 (3.4)	<.001
Oxygen flow rate <5L/min	192	7 (12.7)	185 (19.3)	
Oxygen flow rate 5-10L/min	236	7 (12.7)	229 (23.9)	
Oxygen flow rate >10L/min	277	4 (7.3)	273 (28.5)	
Non-invasive ventilation	248	11 (20)	237 (24.8)	

Table 4: Status of patients on admission
Abbreviations: L/min: liter per minute, ESRD: End-stage renal disease.

Most of the patients in the ESRD cohort were admitted with no oxygen requirements. While patients requiring less than 5-liter oxygen or those who needed non-invasive ventilation on admission were no differences between groups. Contrary to that, more patients were admitted in the non-ESRD group who needed oxygen from 5 to 10 liter or over 10 liters. The outcome of patients is shown in table-5
.

Clinical Outcome	Total	ESRD N (55)	Non-ESRD N (957)	P-Value
		Number of patients (percentage)		
Discharged	650	37 (67.3)	613 (64.1)	.371
Expired	266	12 (21.8)	254 (26.5)	.274
ICU admission	172	9 (16.4)	163 (17)	.537
Invasive mechanical ventilation	92	6 (10.9)	86 (9)	.383

Table 5: Outcome of Patients
Abbreviations: ICU: intensive care unit, ESRD: End-stage renal disease.

A slightly higher percentage of participants in the cohort group were discharged than the nonESRD group, but no statistical significance. Contrary to that, ESRD participants had a little lower mortality than non-ESRD patients, again with no statistical difference. However, both study groups required invasive mechanical ventilation and admission to the critical care unit identically.

On Kaplan-Meier analysis fig-2, patients in ESRD were discharged earlier than another group with a significant p-value (5.12 vs. 7.13 days; Log Rank p.013). Similarly, patients in the ESRD group had lower survival than the non-ESRD group (3.75 vs. 7.29 days; Log Rank p.005).However, even though the ESRD group required more critical care unit admissions and invasive mechanical ventilation, no statistical significance was found (1.88 vs. 2.79 days; Log Rank p.422; 1.6 vs. 3.77 days; Log Rank p.153 respectively). In contrast, the time from symptom onset to need for ICU admission was significantly shorter in the ESRD cohort compared to nonESRD (4.8 vs. 8.13 days; Log Rank p.020).

According to the Unadjusted Cox Regression Model, patients in the ESRD group had a significantly reduced risk of mortality (HR .460, 95% CI .256-.829, p.010).Similarly, individuals with ESRD had a lower likelihood of needing to be hospitalized to a critical care unit and assisted invasive mechanical ventilation, with no statistically significant p values (HR .781, 95% CI .383-1.592, p.496, HR .564, 95% CI .227-1.403, p.218).

DISCUSSION

The fundamental aim of this report is to provide comprehensive details regarding COVID-19infected individuals on regular hemodialysis, including clinical profile, laboratory reports, drug treatments, radiological findings, and clinical outcomes. Unfortunately, literature is scarce in this population.

Our ESRD cohort had milder early clinical signs than the overall population, with lower rates of fever (61.8 vs. 84.6%), shortness of breath (67.3 vs. 82.3%), and cough (50.9 vs. 64.3%) (50.9 percent vs. 64.3 percent)[26]. Comparable findings were seen by Wang et al. and Yiqiong et al.[11, 27]in maintenance hemodialysis patients, which suggest that immune system malfunction may be a factor in maintenance hemodialysis patients[11]. Similarly, one report from Spain found milder symptoms in patients on maintenance dialysis compared with the other patients[28].However, lethargy was slightly more common in this study in the ESRD group than the non-ESRD group, which contradicted the findings of M. Goicoechea et al., who reported lethargy more prevalent in the general population[28]. Similarly, this cohort reported that almost half of our ESRD population had no oxygen requirements on admission; a finding again contradicting findings of M. Goicoechea et al. They reported a significant number of patients had a baseline peripheral oxygen saturation of less than 95%. (61 percent).The rightward change of the hemoglobinoxygen dissociation curve in maintenance dialysis patients was cited by M. Goicoechea et al. as the reason for these observations[29].According to previously published data, the vast majority of people (68.8%) had or progressed to bilateral pneumonia with the typical radiographic appearance[28, 30, 31].

We discovered that 12 of the 55 ESRD patients hospitalized with COVID-19 infection died (21.8 percent). A slightly higher mortality rate than prior Chinese cohorts. According to Wuhan University data, of thirty-seven COVID-19–positive hemodialysis patients, six (16.2%) expired[32].According to another report by Li et al., the study included sixty-six individuals with provenand twenty-four with probable COVID-19. There were 13.3 percent of patients who died(12 of 90)[33].In contrast to these findings, some researchers have discovered a greater fatality rate. In Spain, Goicoechea et al. published the research results, including thirtysixhemodialysis individuals who had had COVID-19, eleven of which had expired (30.6 percent)[28]. In Italy, the Brescia Renal COVID Task Force documented 24 deaths (42.1 percent) among 57 patients[34]. Our findings conflict with those of previous studies and those of European centers and new single-center statistics from the United States[21, 35].

It has been discovered that COVID-19 severity is linked to inflammatory markers, such as serum ferritin[36, 37].According to JH Ng et al. colleagues, ferritin levels were greater in individuals who expired than in those who survived in the ESRD group[35]. This conclusion is consistent with the current investigation findings, which showed that ESRD individuals who expired had higher levels of ferritin, lactate dehydrogenase, and C-reactive protein than those who lived. The limited sample size may be to contribute the statistically insignificant difference.One study found that a 200 percent increase in serum ferritin could be a helpful screening biomarker for dialysis patients infected with COVID-19[38].

Furthermore, this cohort reported that 16.4 percent of the ESRD group needed intensive care unit admission; although the need for critical care unit admission remained identical to the non-ESRD group, findings were still very high compared to results of a study from China which reported no

COVID-19 pneumonia-related ICU hospitalization or mortality in hemodialysis individuals[11]. Similarly, the need for invasive mechanical ventilation was observed in 10.9 percent of patients in this study, findings closely related to the results of Valeri AM et al., who reported that 14% of ESRD patients needed invasive mechanical ventilation[21]. Valeri AM et al. reported another finding identical to this cohort's conclusions. Time from admission to need for invasive mechanical ventilation was 1.5 days compared to 1.6 days observed in this cohort in ESRD patients. In contrast to these findings, another study showed a higher need for mechanical ventilation; however, rates of mechanical ventilation were similar across the ESRD and nonESRD groups (89 (21.2 percent) vs. 2076 (20.6 percent), respectively)[35].The time from symptom onset to need for ICU admission in maintenance dialysis patients was 4.8 days, a finding consistent with published literature. Flythe JE et al. reported that, on average, it took four days for maintenance dialysis patients to get into the ICU after experiencing symptoms because of COVID-19, seven days for non-dialysis dependent CKD patients, as well as seven days for individuals without pre-existing CKD[39].

Retrospective design, lack of randomized control group, single-center experience, a small proportion of ESRD patients, and reliance on computerized records rather than direct patient history are some of the study's primary limitations. Another significant drawback of this study is the existence of potential confounding factors that could significantly impact the results.

Thisstudyfound that COVID-19 symptoms in patients with end-stage renal disease (ESRD) were milder than those in non-ESRD patients. Lymphopenia, raised ferritin, C-reactive protein, and lactate dehydrogenasewere found in patients with end-stage renal disease (ESRD). Mortality, ICU admission, and mechanical ventilation were not statistically different. The outcomes of ESRD patients in COVID-19 need to be studied in more intensive care units with larger sample sizes, a higher ethnic and socioeconomic diversity.

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