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ORIGINAL RESEARCH

Clinical Course and Outcome of ESRD Patients on Maintenance Hemodialysis Infected with COVID-19: A Single-Center Study

Samia Kazmi[1]
Ashar Alam[2]
Beena Salman[2]
Faiza Saeed[2]
Shoukat Memon[2]
Javeria Chughtai[2]
Shahzad Ahmed[2]
Sobia Tariq[2]
Salman Imtiaz[2]

[1]Department of Internal Medicine, The Indus Hospital and Health Network, Karachi, Sindh, Pakistan; [2]Department of Nephrology, The Indus Hospital and Health Network, Karachi, Sindh, Pakistan

Background: In an ESRD subset of patients, COVID-19 infection is associated with increased disease burden and higher mortality rates.

Methods: We conducted a retrospective single-center cohort study in which 43 ESRD patients had a diagnosis of COVID-19. Association of risk factors with mortality was assessed by chi-square test and logistic regression analysis. Data were collected on a structured performa which included variables like age, gender, comorbid conditions, drug history, clinical presentation, hemodynamic status and laboratory parameters. Outcome variables were recovery and death. All patients received standard treatment for COVID-19 according to hospital protocols, along with hemodialysis and continuous renal replacement therapy (CRRT) when needed.

Results: Those most affected were found to be male, 25 (58.1%), while the number of females affected was 18 (41.9%). The most frequent comorbid condition was hypertension (HTN), seen in 35 (81.4%) patients; however, thromboembolic complications were very few in these patients. The mortality rate in our study was 25.6%, and the population most susceptible to poor outcomes in the ESRD subgroup was elderly people (45.5%), while younger patients recovered the most from COVID-19 (53.1%). Hypoalbuminemia, leukocytosis, lymphopenia and raised LDH were also found to be associated with death in ESRD patients suffering from COVID-19 (81.8, 72.7, 100 and 100%, respectively). In multivariate logistic regression analysis, we found that the odds ratio of dying from COVID-19 was 19.5 times higher in patients aged >65 years as compared to patients aged 18–50 years (p=0.039). Similarly, patients with a high TLC were 24.1 times more likely to die than patients with a normal TLC (p=0.008).

Conclusion: In our center, the mortality rate of ESRD patients affected with COVID-19 disease was 25.6%, and older age, leukocytosis, lymphopenia, hypoalbuminemia and high LDH were significantly associated with mortality.

Keywords: ESRD, COVID-19, hemodialysis, Pakistan, CKD, CRRT

Introduction

Since its outbreak, the novel coronavirus disease 2019 (COVID-19) has set unprecedented challenges for the medical community worldwide. Along with varied presentations ranging from asymptomatic disease to multi-organ dysfunction, outcomes also tend to vary in different subsets of patients affected with COVID-19. In the background of pre-existing chronic conditions, COVID-19 is associated with increased disease severity, adding significant morbidity and mortality to such subsets.[1–5]

Correspondence: Samia Kazmi
Department of Internal Medicine, The Indus Hospital and Health Network, Plot C-76, Sector 31/5, Opposite Crossing, Darussalam Society Sector 39 Korangi, Karachi, Sindh, Pakistan
Tel +923061608016
Email samia.kazmi@tih.org.pk

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In a meta-analysis published by Wang et al, which included 34 studies, patients with diabetes, cardiovascular disease (CVD) and chronic kidney disease (CKD) were associated with poor outcomes. Out of the 34 studies included in this meta-analysis, CKD was included as a comorbid condition in 13 studies and was strongly correlated with increased disease severity, with moderate heterogeneity of 38.1%. In a multi-centered French cohort study, clinical outcomes of 2336 patients from 11 dialysis centers were studied. Of 2336 end-stage renal disease (ESRD) patients, 126 tested positive for COVID-19, with 45 patients (36.9%) reaching an end point of critical evolution (transferred to the ICU or died).[6] Additionally, higher rates of in-patient hospital mortality were found in 133 of 149 hospitalized COVID-19 positive ESRD patients, contributing to a 31.7% mortality.[7]

Patients on hemodialysis are recognized by their unique pathophysiology; that is, "reverse epidemiology" for cardiovascular risk factors,[8] worse outcome on normalization of hemoglobin,[9] impaired innate and acquired immune system[10] and an earlier calcification of the blood vessels.[11] This makes them vulnerable to respond to the stress of a new disease like COVID-19, which has a double hazard of a cytopathic and a cytokine release effect. Several studies[12–16] have implicated the vulnerability of ESRD patients diagnosed with COVID-19, highlighting the need for judicious monitoring in such subgroups of patients. Since ESRD patients succumb to fatal outcomes, whether this is due to the presence of other comorbidities, impaired immune response or symptoms at the time of presentation, this validates the need for more research in this area.

In this single-centered retrospective study, we aim to elucidate the clinical characteristics and outcomes of 42 COVID-19 positive ESRD patients admitted to our facility.

Materials and Method

This is a retrospective analysis of COVID-19 patients with a diagnosis of ESRD on maintenance dialysis admitted to Indus Hospital COVID ICU from 15 March 2020 to 30 September 2020. Indus Hospital is one of the largest tertiary care facilities to manage COVID-19 patients. We included patients of more than and equal to 18 years of age with a diagnosis of COVID-19 infection made by nasopharyngeal swab via the reverse transcriptase-polymerase chain reaction (RT-PCR) method. Patients with a history of acute kidney injury (AKI) were excluded. Permission from the institutional ethical review committee was taken prior to the conduction of study. All patient data was treated with confidentiality in accordance with the Declaration of Helsinki. History, clinical examination and laboratory investigations were acquired from the Health Management Information System (HMIS) record of the patients. Data was collected on a structured performa, which included variables like age, gender, comorbid conditions, drug history, clinical presentation, hemodynamic status and laboratory parameters. Outcome variables were recovery and death. All patients received standard treatment for COVID-19 according to hospital protocols, along with hemodialysis and continuous renal replacement therapy (CRRT) when needed.

Statistical Analysis

The data was entered and analyzed in SPSS version 21. Cleaning and coding of data was done prior to analysis. Mean ± STD and median with IQR were computed for continuous data while, for categorical variables, frequency with percentages were measured. At the time of analysis, all continuous variables were categorized according to their normal cutoff values and association of risk factors with outcomes was assessed by applying chi-square tests. The parameters which were found significant in univariate analysis were subjected to multivariate logistic regression analysis and a predicted model was built to establish the effect of risk factors on the death of patients and odds ratios with 95% confidence intervals were obtained. The predicted capacity of the model was checked by omnibus test and pseudo R-squares were obtained (Table 1). A p-value of ≤0.05 was considered significant.

Results

There were 43 patients with a diagnosis of ESRD on maintenance hemodialysis who were infected with COVID-19 at Indus Hospital. Those affected more were found to be males, 25 (58.1%), while number of females

Table 1 Model Summary

	Chi-square	**p-value**
Omnibus test	21.307	<0.001
Hosmer–Lameshow test	3.046	0.803
Pseudo R-square	Cox & Snell	Negalkarke
	0.391	0.575

Table 2 Demographic and Clinical Parameters of Patients, n=43

Variables	n (%)/Mean ± STD
Gender	
Male/female	25 (58.1)/ 18 (41.9)
Age in years	51.4 ± 15.1
Comorbidities	
Diabetes mellitus	14 (32.6)
Hypertension	35 (81.4)
Ischemic heart disease	12 (27.9)
Complications of COVID-19 infection	
Acute coronary syndrome	5 (11.6)
Congestive cardiac failure	5 (11.6)
Peripheral vascular disease	2 (4.7)
Cerebrovascular accident	2 (4.7)
Signs & symptoms	
Anemia	16 (37.2)
Pedal edema	11 (25.6)
Confusion	7 (16.3)
Drowsiness	6 (14)
Periorbital swelling	3 (7)
Fever	3 (7)
Nausea	2 (4.7)
Loss of appetite	2 (4.7)
Volume depletion	1 (2.3)

affected was 18 (41.9%). The mean age was 51.4 ± 15.1 years, with a minimum of 20 years and a maximum of 78 years. The most frequent comorbidity was hypertension (HTN), seen in 35 (81.4%) patients. Anemia was the most common sign in our patients (16, 37%) while fever was a presenting complaint in only 3 (7%) (Table 2). The laboratory parameters are described in Table 3.

Gender was not significantly associated with the outcome of COVID-19 in ESRD patients, although more male than female patients died [8 (72.7%) vs 3 (27.3%), respectively]. On the other hand, different age groups of the patients were found to be significantly associated with outcome (p=0.035): 5 of 11 patients (45.5%) aged more than 65 years died while the maximum number of patients who recovered were in the age group of 18–50 [17 (53.1%)]. No comorbidity was found to be significantly associated with outcome of disease in ESRD patients; however, almost all patients who succumbed to death were hypertensive [10 (90.9%)]. Similarly, the development of complications in COVID-19 showed no significant impact on the death of patients and overall there were very few cardiac and thromboembolic events in ESRD patients who suffered from COVID-19 (Table 4).

For analysis, we categorized our laboratory parameters according to their cutoff values, as described in KDIGO 2012 guidelines for CKD dialysis patients. Among all laboratory parameters, TLC, lymphocyte count, albumin and LDH were found to be significantly associated with outcome of COVID-19 in an ESRD subset of patients. Eight of the 11 (72.7%) patients who died had a high TLC count. Furthermore, all 11 (100%) patients who died had lymphopenia and a raised level of LDH. Similarly, low albumin was also found in 9 of the 11 patients (81.8%) who died. All other markers of disease severity, like CRP, high sensitivity troponin I and ferritin, were also elevated in patients who died but, possibly due to the low sample size, did not achieve a significant level (Table 5).

The statistically significant risk factors for death in COVID-19 patients were further analyzed to calculate the level of effect on outcome by building a multivariate model. Although lymphocyte count and LDH were significant at the univariate stage, in multivariate logistic regression, they could not be included due to zero in one of their categories. Patients aged more than 65 years died 19.5 times more often than did younger patients (18–50 years); p-value 0.039. Likewise, patients with a high TLC died 24.1 times more often than did those with normal TLC; p-value <0.008. On the other hand, the effect of low albumin became insignificant in this model, although the patients with low albumin died 4.2 times more often than patients with normal albumin levels (Table 6).

Discussion

In our study, we examined the clinical characteristics, laboratory parameters and risk factors associated with outcome in ESRD patients. Due to the disturbance in the internal milieu secondary to uremia, dysregulated immune response in the background of inflammation, infections are more prevalent in this cluster of patients.[10] This may result in severe consequences for patients on maintenance dialysis as the likelihood of cross-infections and contamination in dialysis units pertaining to COVID-19 is high. COVID-19 has grave implications for this subgroup, resulting in severity of disease, prolonged hospital stay, increased intensive care unit (ICU) admissions and end outcome of death. Multiple studies conducted to determine the outcome of ESRD patients in COVID-19 have shown high mortality

Table 3 Clinical and Laboratory Parameters of ESRD Patients with COVID-19

Variables	Mean ± STD & Median, IQR	Minimum	Maximum
Weight (kg)	60.7 ±17.5	24	102
Pulse (beats/min)	88.6 ± 13.2 and 86,18	70	123
SBP (mm Hg)	143.4 ± 20.5	100	200
DBP (mm Hg)	79.2 ± 13.1	56	114
RR (breaths/min)	24.6 ± 7.7 and 23,9	12	46
Hemoglobin (g/dl)	11 ± 2.3	6.9	18
Total leucocyte count ($x10^9$/L)	10.6 ± 6.8 and 8.8,8	3.2	30.1
Lymphocyte (%)	15.7 ± 8.4	2.1	31.1
Platelets ($x10^9$/L)	195.6 ± 93.7 and 169,107	95	533
Albumin (g/dl)	3.4 ±0.6 and 3.4,0.9	1.15	4.4
Urea (mg/dl)	101.8 ± 50.1 and 101,60	28	293
Creatinine (mg/dl)	9.2 ± 5.7 and7.9,4.9	3.6	39
Sodium (meq/L)	137.3 ± 4.2	127	145
Potassium (meq/L)	4.7 ±1.2 and 4.4,1.2	3	6.9
Chloride (meq/L)	101.5 ± 5.4 and103,7	86	110
Bicarbonate (meq/L)	17 ± 4.9	5	26
Calcium (mg/dl)	8.2 ± 0.98	6.3	10.6
Phosphorus (mg/dl)	4.9 ±2	0.8	10.5
Uric acid (mg/dl)	6.8 ± 1.5	2.9	9.2
Lactate dehydrogenase (U/L)	960.5 ±3336.4 and 416,255	124	22,289
Troponin I	441.6 ± 828.1 and 89,516	0.03	4675
C reactive protein (mg/L)	116.7 ± 119.7 and 67,187	2.9	438
Ferritin (ng/mL)	2219.7 ± 2581.1 and 1675,317	237	14,442
D-dimer (ng/mL)	645.7 ± 1929 and2.7,456.7	1.4	12,007

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate.

rates in this vulnerable population. In a multi-centered study conducted in Wuhan, 41 of the 131 maintenance hemodialysis patients died, accounting for a 31.29% mortality rate.[14] Additionally, single and multi-center cohort studies conducted in the USA, Spain, Italy and France were also associated with 31.7, 30.5, 52 and 28% mortality rates, respectively.[6,7,15,16] In contrast, Stefan and Mehedinti from Romania reported a mortality rate of 19% in their hemodialysis population.[17] Similarly, a multi-center study from Turkey showed a mortality rate of 16.2%.[18] We found a mortality rate of 25.6% in our study, which is in-between the aforementioned studies. One reason for these differences in mortality in the dialysis population might be an overall difference in COVID-19 mortality rates in these countries within their general population. Another factor could be differences in mean age of the dialysis population in these countries because higher mean age results in higher mortality. Although the mean age of our dialysis population is lower compared to the other studies we discussed above, the mortality in our population is higher as compared with Romania and Turkey. This relatively higher mortality rate might be influenced by the relatively small sample size of

Table 4 Association of Demographic Variables, Comorbidities and Complications with Outcomes of COVID-19

Demographic Variables		Outcome of COVID-19		p-value
		Died, 11 (25.6)	Recovered, 32 (74.4)	
Gender	Male Female	8 (72.7) 3(27.3)	17 (53.1) 15 (46.9)	0.256
Age	18–50 years 51–65 years >65 years	2 (18.2) 4 (36.4) 5 (45.5)	17 (53.1) 11(34.4) 4 (12.5)	0.035
Comorbidities				
Diabetes mellitus		4(36.4)	10 (31.3)	0.755
Hypertension		10(90.9)	25(78.1)	0.347
Ischemic heart disease		5(45.5)	7(21.9)	0.133
Complications of COVID-19				
Acute coronary syndrome		3(27.3)	2(6.3)	0.096
Congestive cardiac failure		3(27.3)	2(6.3)	0.096
Peripheral vascular disease		0(0)	2(6.3)	0.61
Cerebrovascular accident		2(18.2)	0(0)	0.061

our study and whether or not this difference in our cluster of patients has any ethnic, racial or socioeconomic association needs to be determined.

Typically, ESRD patients have co-existent conditions like diabetes, CVD and HTN, which add to their morbidity and are recognized risk factors for COVID-19 disease.[4] In our study, HTN was the most frequent comorbidity, followed by diabetes. In many studies, HTN and diabetes along with CVD are the most prevalent risk factors implicated in COVID-19 disease. We found this association to be accurate in our study as well. However, we did not find their impact on patient outcome to be significant. The most meaningful parameters with respect to patient outcome in our study were age, serum albumin, TLC, lymphocyte count and LDH levels. The population most susceptible to poor outcomes in the ESRD subgroups is elderly people, making this a factor influencing outcome, as we discussed earlier. Early changes in laboratory parameters are predictors of poor outcomes in the non-CKD population; in a meta-analysis of 78 studies, a low lymphocyte count of $<0.8\times10^9$, an LDH over 250 U/L and an increased leukocyte count of $>9.5\times10^9$ were found to be associated with higher mortality.[19] Hypoalbuminemia is recognized as a major risk factor for morbidity and mortality in dialysis patients,[20] and it was also found in our study to be associated with poor outcome in univariate analysis. Low albumin levels may be related to malnutrition–inflammation syndrome, which is also recognized as an important "paradoxical" risk factor for cardiovascular mortality in dialysis patients,[21] or concomitant liver injury observed in critical COVID.[22] Leukocytosis and lymphopenia have both been known to affect outcome in COVID-19 patients. Pertaining to our study, both have been associated with fatal outcomes, which may be utilized as prognostic indicators in COVID-19 disease. Lymphopenia is not only an important marker of severity of viral infection, but also portends the seriousness of an underlying cytokine storm. Various studies support this evidence.[1,2] LDH is a ubiquitous intracellular enzyme, which catalyzes the conversion of pyruvate and lactate. High values can result from multiple-organ injury and decreased oxygenation with upregulation of the glycolytic pathway. We also detected LDH as a poor prognostic marker in our hemodialysis patients. High LDH levels with poor prognosis have also been documented by others.[17,18]

There are a few limitations in our study. Firstly, due to the retrospective nature of the data, laboratory tests like serum ferritin and D-dimers were not done in a specific time frame rather than done when required. Thus, their insignificance in our study related to prognostic factors for in-hospital death should be taken cautiously. Secondly, the study is from a single center and has a small sample size, hence it was difficult to evaluate risk factors for mortality in regression models when they was adjusted for more variables. Lastly, data about procalcitonin is missing therefore it is difficult to elucidate the cause of high TLC.

In summary, the outcomes of ESRD patients at our facility were relatively better compared to other single and multi-center studies done in Western populations and our patients exhibited different clinical characteristics from those of the general population along with variations in laboratory parameters predicting the end point in COVID-19 disease.

Table 5 Association of Laboratory Parameters with Outcome of COVID-19

Variables		Outcome of COVID-19		p-value
		Died, 11 (25.6)	Recovered, 32 (74.4)	
Hemoglobin (g/dl)	<10	3(27.3)	10(31.3)	0.125
	10–12.9	4(36.4)	19(59.4)	
	>12.9	4(36.4)	3(9.4)	
Total leucocyte count (x10^9/L)	Normal	3(29.3)	27(84.4)	<0.001
	High	8(72.7)	5(15.6)	
Lymphocyte count (%)	Normal	0(0)	14(43.8)	0.008
	Low	11(100)	18(56.3)	
Phosphorus (mg/dl)	Normal	4(36.4)	17(35.1)	0.337
	High	7(63.6)	15(46.9)	
Albumin (g/dl)	Normal	2(18.2)	19(59.4)	0.018
	Low	9(81.8)	13(40.6)	
Calcium (mg/dl)	Normal	7(63.6)	19(59.4)	0.803
	Low	4(36.4)	13(40.6)	
Lactate dehydrogenase (U/L)	Normal	0(0)	9(28.1)	0.048
	High	11(100)	23(71.9)	
C reactive protein (mg/L)	Normal	0(0)	6(18.8)	0.178
	High	11(100)	26(81.8)	
Troponin I	Normal	0(0)	0(0)	NA
	High	11(100)	32(100)	
D-dimer(ng/mL)	Normal	5(45.5)	23(71.9)	0.113
	High	6(54.5)	9(28.1)	
Ferritin (ng/mL)	Normal	1(9.1)	4(12.5)	0.999
	High	10(90.9)	28(87.5)	

Table 6 Effect of Variables on Death of ESRD Patients Infected with COVID-19

Variables	Odds Ratio	95% CI Lower-Upper	p-value
Age			
18–50 years	1		
51 −65 years	1.9	0.18–18.6	0.601
>65 years	19.5	1.2–325.9	0.039
High TLC	24.1	2.3–251.8	0.008
Hypoalbuminemia	4.2	0.58–30.5	0.155

Abbreviation: TLC, total leukocyte count.

Disclosure

The authors reported no conflicts of interest for this work.

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