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Original Article

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Clinical Characteristics and Short-Term Outcomes of ESKD Patients Undergoing Hemodialysis with COVID-19 Infection in Madurai, South India

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ABSTRACT

Objective: Novel coronavirus disease-19 is spreading rapidly, and therefore, optimal management of the disease in end-stage kidney disease patients requiring hemodialysis is not fully explained. We report the clinical characteristics and the short-term outcomes in patients with end-stage renal disease who require hospitalization for coronavirus disease-19 and who underwent hemodialysis.

Methods: In this retrospective, observational, single-center study, we analyzed the clinical course and outcomes of 116 consecutive end-stage kidney disease patients hospitalized with laboratory-confirmed coronavirus disease-19 who underwent at least 1 hemodialysis session in our hospital between June 26 and August 10, 2020. Baseline clinical features, laboratory data, and treatment given were compared between survivors and non-survivors to identify risk factors associated with mortality.

Results: Among the 116 patients who were enrolled in our study, males constituted 81% (n = 94). Many had underlying comorbidities, of which hypertension (90.4%) was the most common. The most common symptoms were fever (76.1%), dyspnoea (61.2%), cough (58.6%), and diarrhea (18.1%). In total, 66.4% of patients had arteriovenous fistula or grafts. Inflammatory markers like C-reactive protein and serum ferritin were significantly higher in non-survivors group. Multivariate logistic regression analysis revealed that dialysis vintage less than 6 months was the most important predictor for mortality. Mortality was 27.5% in our cohort.

Conclusion: Mortality among hospitalized end-stage kidney disease patients who underwent hemodialysis was higher when compared to the general population. The presence of comorbid conditions like hypertension, diabetes mellitus, and pre-existing pulmonary disease had a poor prognosis. Patients having central venous catheters as their dialysis access had a poor prognosis. Dialysis vintage less than 6 months was the most important predictor of mortality.

Keywords: COVID-19, ESKD, hemodialysis, mortality

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INTRODUCTION

The novel coronavirus disease-19 (COVID-19) is caused by a completely unique severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in China in December 2019. Since then, it has affected immeasurable people within the world.[1,2] Severe infections can lead to multisystem disorders. Clinical presentation can vary from an asymptomatic or very mild course to severe involvement with unilateral or bilateral pneumonia (approximately 15%) that may cause acute respiratory distress that needs ventilatory support within the intensive care unit (ICU; 3%-5%). Sometimes in severe cases, a robust inflammatory reaction resulting in a cytokine storm will worsen respiratory symptoms, which can cause death.[3] Factors related to a poor prognosis include advanced age, male sex, and

previous comorbidity, particularly cardiovascular events, diabetes mellitus, chronic obstructive pulmonary disease, or a history of cancer.[4,5]

The impact of this virus on patients with chronic kidney disease (CKD) is not clearly understood. Due to the increased age and comorbidity of those patients, mortality could be higher than that in the general population, especially in patients on dialysis therapy.[3] Although various preventive measures have been advised to forestall the spread of this infection, the particular characteristics of this disease on end-stage kidney disease (ESKD) patients remain not fully understood.

The objective of this study is to describe the clinical characteristics and the short-term outcomes in end-stage renal disease who require hospitalization for COVID-19 and who underwent hemodialysis (HD).

METHODS

Study Population

Study population included 116 consecutive ESKD patients hospitalized with laboratory-confirmed COVID-19 who underwent at least 1 HD in our hospital between June 26 and August 10, 2020. Informed consent was obtained from those patients who were willing to enroll in our study. The study was approved by the Institutional Ethical Committee of Madurai Medical College, Tamil Nadu. Patients were required to have either a positive nasopharyngeal swab for SARS-CoV-2 by reverse transcriptase method or computerized tomography (CT) chest suggestive of COVID-19 (CORADS 4-6). Those patients who were hemodynamically unstable for dialysis or those who were not consenting to the study were excluded.

As per institutional protocol, all patients with COVID-19 requiring kidney replacement therapy were admitted irrespective of symptomatology. Routine laboratory parameters that were measured on admission included a complete blood count and serum biochemistry (including electrolytes, C-reactive protein (CRP), and ferritin). All patients underwent chest imaging by CT.

MAIN POINTS

- The mortality among end stage kidney disease patients hospitalised with COVID-19 infection is higher when compared to the general population.
- Comorbidities like diabetes mellitus and pre existing pulmonary disease were associated with poor prognosis.
- Presence of central venous catheter for hemodialysis , higher lung involvement in radiological imaging and higher level of inflammatory markers were associated with poor prognosis.
- Dialysis vintage less than 6 months was found to be the most important predictor of mortality.

Due to logistical limitations, pre-determined schedules could not be followed and HD was performed at the discretion of the treating physician based on clinical and laboratory indications. Preference was given to those patients who were having hypoxia or having uremic symptoms. Dialyzer and blood tubings were discarded after a single use. The ultrafiltration rates were set according to individual needs. According to the outcome, patients were divided into survivors and non-survivors groups.

Statistical Analysis

The statistical analysis was carried out in SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and MS-Excel (2019 version, Miscrosoft, Washington, USA). Initially, the empirical data were verified for the normality assumptions using Shapiro–Wilk test. Almost all the empirical data of variables satisfied the normality assumptions. Therefore, parametric statistical tests are performed to analyze the data. Chi-square/Fisher's exact test was used to find the association between categorical data, whereas an independent sample *t*-test was used to find the difference between 2 groups with respect to continuous variable. Multivariate logistic regression model was used to find the association between symptoms, comorbidities, and survival status of patients. In this model, the independent variables that were independently associated with mortality of patients were applied. Backward selection logit model was used to find the most predominant factor that is associated with mortality. In the statistical model, we included the following independent variables: age, dialysis vintage, hypertension, and diabetes mellitus. Kaplan–Meier test is used for comparing the survival pattern of the patients who are alive and the patients who are expired based on the duration of hospital stay and severity of the disease.

RESULTS

The clinical characteristics of the cohort are shown in Table 1. In this study, 116 consecutive ESKD patients hospitalized with laboratory-confirmed COVID-19 who underwent at least 1 HD were included. Males constituted 81% of the study population, and there was no significant difference in age and sex among survivors and non-survivors .The dialysis vintage was significantly less in non-survivors (0.44 ± 0.99 years). The mean duration of CKD was significantly less in non-survivors (0.79 ± 1.32 years). The common comorbidities were hypertension (90.4%), diabetes mellitus (48.3%), coronary artery disease (24.1%), and pre-existing pulmonary disease (8.6%). When considering the comorbidity status of the patients, there was a significant difference in the proportion of patients who had hypertension ($P < .05$), diabetes mellitus ($P < .05$), and pre-existing pulmonary diseases ($P < .05$) among survivors and non-survivors. However, survivors and non-survivors were similar with respect to the proportion of patients who had coronary artery disease. Patients having arteriovenous fistula or graft comprised of about 66.4%. In total, 19.8% patients were newly inducted for HD using a central venous catheter and 13.8% of patients were already on the central venous catheter.

Table 1. Baseline Characteristics and Treatment Variables Compared Between Survivors and Non-survivors

Variables	Survivors (*N* = 84)	Non-survivors (*N* = 32)	*P*
Age (in years)			.067
<39	16 (19.0)	6 (18.8)	
40-59	51 (60.7)	13 (40.6)	
>60	17 (20.2)	13 (40.6)	
Male	69 (82.1)	25 (78.1)	.622
Comorbidities			
Hypertension	81 (87.6)	23 (71.9)	.001
Diabetes mellitus	35 (41.7)	21 (65.6)	.021
Coronary artery disease	18 (21.4)	10 (31.2)	.269
Pulmonary disease	4 (4.8)	6 (18.8)	.026
Dialysis vintage (in years)	1.32 ± 0.89	0.44 ± 0.99	.001
Duration of CKD (in years)	2.72 ± 1.98	0.79 ± 1.32	.001
Symptoms			
Fever	57 (67.9)	32 (100.0)	.001
Cough	39 (46.4)	29 (90.6)	.001
Breathlessness	39 (46.4)	32 (100.0)	.001
Diarrhea	2 (2.4)	19 (59.4)	.001
Time from symptom onset to hospital admission	3.62 ± 1.17	5.13 ± 0.91	.001
SPO2 at admission	93.35 ± 4.01	83.66 ± 3.69	.001
No. of hemodialysis done	2.12 ± 1.05	2.09 ± 1.40	.926
Central venous catheter	14 (16.7)	25 (78.1)	.001
New induction of hemodialysis	7 (8.3)	16 (50.0)	.001

The most common symptoms at initial presentation were fever (76.1%), dyspnoea (61.2%), cough (58.6%), and diarrhea (18.1%). The time from symptom onset to hospital admission and lung involvement was significantly more in non-survivors ($P < .01$).

Biochemical parameters (Table 2) including hemoglobin, total leukocyte count, neutrophil–lymphocyte ratio, urea, and creatinine were significantly increased in non-survivors group. Patients who expired had significant hyperglycemia ($P < .05$), hyponatremia ($P < .01$), and elevated serum potassium levels ($P < .01$). Significant elevation of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were observed in non-survivors group. Inflammatory markers, CRP, and ferritin were significantly increased in non-survivors group ($P < .01$). CT of the chest was done for all admitted patients. The percentage of lung involved was significantly higher in non-survivors group (P value <.01).

Patients were treated with hydroxy chloroquine, azithromycin, steroids, and remdesvir. The difference in number of HD done in survivors and non-survivors groups was not statistically significant. The use of central venous catheter and the new induction of HD were associated with poor prognosis.

The log-rank test clearly reveals that there was a significant variation in the survival pattern of the mild-disease patients and severe-disease patients. The length of the hospital stay was less for mild-disease patients and their probability of survival was high, whereas the length of the hospital stay was more for severe-disease patients and their probability of survival was gradually decreased.

A multivariate logistic regression analysis was performed (Table 3), including all variables that were found to be predictors of mortality. It showed that dialysis vintage less than 6 months was the most important predictor for mortality.

DISCUSSION

Patients with advanced age and with comorbid conditions such as diabetes, pulmonary disease, and cardiovascular disease are at the highest risk of severe manifestations of COVID-19.[6] Due to the immunocompromised nature of ESKD and the high comorbid disease burden seen in patients with kidney failure,

Table 2. Laboratory Parameter Compared Between Survivors and Non-survivors

Variables	Survivors (*N* = 84)	Non-survivors (*N* = 32)	*P*
Hemoglobin (g/dL)	8.02 ± 1.25	8.90 ± 1.77	.013
Total leucocyte count	6033.33 ± 2366.75	14143.75 ± 8881.44	.001
Neutrophil–lymphocyte ratio	6.07 ± 3.21	10.46 ± 3.29	.001
Platelets (in lakhs/mL)	2.26 ± 0.56	2.04 ± 0.90	.211
Urea (mg/dL)	151.92 ± 52.98	212.75 ± 53.13	.001
Creatinine (mg/dL)	10.34 ± 3.09	13.46 ± 3.98	.001
Random blood sugar	152.52 ± 44.36	205.06 ± 111.24	.014
Sodium (meq/L)	132.43 ± 5.98	128.53 ± 7.65	.005
Potassium (mmol/L)	4.38 ± 0.84	5.82 ± 0.86	.001
Bilirubin (mg/dL)	0.73 ± 0.69	1.59 ± 2.62	.077
SGOT (U/L)	23.00 ± 13.91	63.72 ± 70.32	.003
SGPT (U/L)	26.99 ± 19.18	65.41 ± 65.89	.003
ALP (U/L)	65.32 ± 30.79	127.28 ± 88.69	.001
CRP (mg/L)	40.49 ± 43.16	78.82 ± 89.16	.002
Ferritin (ng/mL)	550.77 ± 246.32	934.97 ± 307.87	.001
Percentage of lung involvement in CT chest	19.12 ± 15.88	56.56 ± 6.15	.001

ALP, alkaline phosphatase; CRP, C-reactive protein; CT, computerized tomography; SGOT, serum glutamic oxaloasetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Table 3. Multivariate Logistic Regression Analysis of the Association Between Mortality and Various Characteristics

	OR	95% CI for OR		*P*
		Lower	Upper	
Model 1				
Age	1.024	0.978	1.072	.306
Dialysis vintage (>6 months)	0.069	0.022	0.214	.001
Hypertension (yes)	0.327	0.059	1.814	.201
Diabetes mellitus (yes)	1.294	0.432	3.876	.645
Constant	1.025			.986
Model 2				
Age	1.027	0.982	1.073	.242
Dialysis vintage (>6 months)	0.065	0.021	0.198	.001
Hypertension (yes)	0.323	0.058	1.790	.196
Constant	1.072			.962
Model 3				
Dialysis vintage (>6 months)	0.066	0.022	0.200	.001
Hypertension (yes)	0.291	0.053	1.581	.153
Constant	4.500			.054
Model 4				
Dialysis vintage (>6 months)	0.050	0.018	0.143	.001
Constant	1.733			.090

The first model and the second model explained around 46% (pseudo R^2; 0.464) variations due to the predictors. However, the largest *P*-value of diabetes mellitus (DM) indicated that DM was the least important factor. Hence, DM was eliminated from the second model. Similarly, age and hypertension were the least important factors in model 2 and model 3, respectively. Therefore, they were eliminated from the final model. The final model showed the only 1 most important predictor "dialysis vintage ($P < .05$), which was associated with mortality. The odds ratio for dialysis vintage > 6 months was less than 1 (OR = 0.050), which meant that the odds of mortality were high among the patients with dialysis vintage < 6 months compared to dialysis vintage > 6 months.

patients with ESKD are more vulnerable.[7] Our study describes the clinical characteristics and the short-term outcome of 116 ESKD patients who underwent HD and was hospitalized due to COVID-19 infection in our institution.

Similar to the previously published reports, we observed that diabetes mellitus, hypertension, and pre-existing pulmonary diseases were associated with poor prognosis.[8-10]

In our cohort, the most common symptoms at presentation were fever (77%), breathlessness (61.2%), cough (58.6%), and diarrhea (18.1%). This result was consistent with similar findings in maintenance HD patients with COVID-19 infection reported by Goicoechea et al[3] and Fisher et al[11] in their respective studies. Patients in non-survivors group were having significantly lower oxygen saturation at presentation when compared to the survivors group (83.6% vs. 93.3%). The percentage of lung involved in CT chest was significantly higher in non-survivors group (56.5% vs. 19.1%). In many patients, CT chest findings had overlapping features of pulmonary congestion and covid pneumonia. Both of these features would have contributed to the poor oxygen saturation and need for respiratory support.

According to Goicoechea et al[3], longer dialysis vintage was associated with poor prognosis, but in our study, multivariate logistic regression analysis showed that dialysis vintage less than 6 months was the most important predictor for mortality. This may be due to various factors like lack of permanent access for HD, underlying central venous catheter sepsis, poor compliance

for HD treatment by patients who were recently started on maintenance HD.

Inflammatory markers like mean total count, neutrophil–lymphocyte ratio, CRP, and ferritin were significantly higher in non-survivors group. A sudden immune response leading to cytokine storm is one of the proposed mechanism of SARS CoV-2 causing severe illness and death .The mean serum potassium levels were also found to be significantly elevated in non-survivors group, which may be due to the increased time gap from symptom onset to admission leading to longer dialysis-free period. Hyponatremia was more pronounced in non-survivors group ($P < .01$), which may be due to the fluid overload status or gastrointestinal symptoms like diarrhea and vomiting. Previous studies have shown that COVID-19 infection worsens glycemic control in diabetes. Similarly, findings from our cohort also show significantly elevated blood sugar in non-survivors group. Treatment with steroids will further worsen the glycemic status and may lead to diabetic ketoacidosis, which may be detrimental to the patient.

The number of HD done in survivors and non-survivors groups did not differ significantly. But the presence of central venous catheter as HD access was found to have poor outcome. Those patients who were newly inducted on HD were also associated with poor outcome. Factors like sepsis, pneumonia, and diabetic ketoacidosis may have precipitated further worsening of renal function, which led to the initiation of HD. Moreover due to the strict covid screening protocols in many HD centers around us, patients who were on maintenance HD were referred earlier to our center before worsening of symptoms.

Our data suggest that mortality is higher (27%) in ESKD patients on HD when compared to the general population (1.4%-8%). Mortality rate in our center was similar to other previously published reports on HD in COVID-19 patients around the world.[3,11-14] The causes of death in our patients were respiratory failure 38% (n = 12) (Figure 1), sepsis 32% (n = 10), diabetic ketoacidosis 9% (n = 3), pulmonary oedema 9% (n = 3), uremic encephalopathy 6% (n = 2), and sudden cardiac arrest 6% (n = 2). These data contrast with the Wuhan cohort,[15] in which the main cause of death was a cardiovascular event, and also the Spanish cohort[3] where the main cause of death was COVID-19 pneumonia.

Our study has few limitations. First, as the follow-up of discharged patients was not available, long-term damage and prognosis of HD patients with novel COVID-19 infection could not be assessed. Second, patients who were too ill for HD or those who died before the initiation of HD were not included. Our study's strengths include its relatively large sample size to date of hospitalized ESKD patients with COVID-19 and that patients were referred from different dialysis center over a wide area.

In conclusion, the mortality in ESKD patients on HD admitted with COVID-19 is alarmingly high. The symptoms like fever, cough, and breathlessness in maintenance HD patient may indicate COVID-19 infection and prompt the initiation of treatment for the infection together with providing adequate HD that may decrease the mortality. As dialysis vintage less than 6 months was found to be the most important predictor of mortality, special emphasis should be given to those patients who are recently initiated on HD. Further studies are required to assess the long-term impact of COVID-19 infection in ESKD patients.

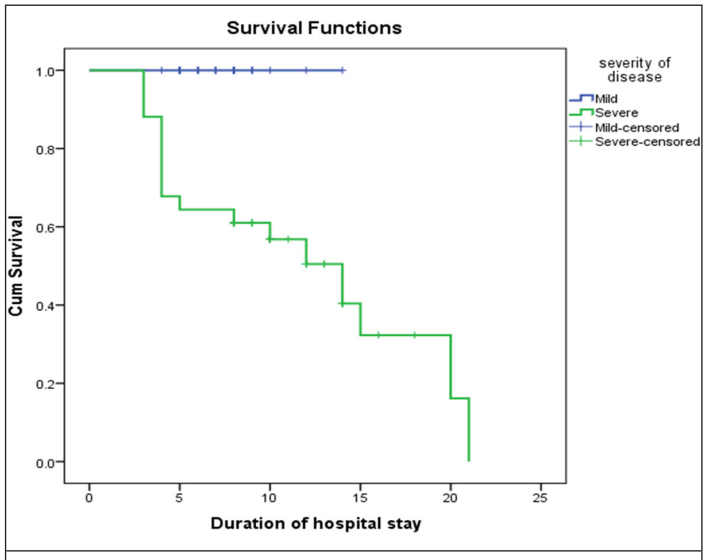

Figure 1. Kaplan–Meier survival curves. Mild disease-respiratory tract symptoms without hypoxia. Severe disease-respiratory tract symptoms with hypoxia.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Ethical Committee of Madurai Medical College, Tamil Nadu (Approval Date: June 13 , 2020; Approval Number: CDSCO: Reg no.ECR/1365/Inst/TN/2020).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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