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Egyptian Retrospective Multicenter Study: The Interrelationship between COVID-19 Infection and Hemodialysis

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ABSTRACT

Background: Individuals on dialysis are disproportionately affected by corona virus. It is beneficial to compare the general population's and dialysis population's hospitalisation trends during the COVID-19 pandemic.

Objective: To study the clinical presentation of SARS-CoV-2 infection in maintenance hemodialysis patients and identify their clinical sequel and outcomes through comparing the results with non-COVID-19 infection hemodialysis patients, and non-hemodialysis COVID-19 infection patients.

Material and Methods: In this retrospective multicenter study 734 Egyptian patients were recruited. The clinical course and outcomes of hemodialysis patients with confirmed COVID, **(group I)** were compared to non-COVID hemodialysis patients **(group II)**, and non-hemodialysis COVID-19 patients **(group III).**

Results: The most common co-morbidities among **group I** was hypertension (45%), then diabetes mellitus (28.3%). Fever was the most common symptom (84.4 %) followed by dyspnea (46.9%). The cure rate was 84.4% and mortality was (15.6%). 5.3% of patients needed mechanical ventilation and majority were treated according to Egyptian protocol at home (65.3%). Comparison between **(group I)** and **(group II)** revealed that body mass index were significantly higher in **group I** while comparing investigations of both groups revealed that hemoglobin, hematocrit, leucocytes, platelets, ferritin & C-reactive protein showed statistically significant difference. Unexpectedly, although the need for intensive care admission presented more in **group III**, mortality significantly increased among **group I.** Comparing investigations during and after cure there were significant decrease in leucocytes, lymphocytes, and platelets.

Conclusion: Obesity, hypertension and diabetes mellitus are important risk factors among hemodialysis patients with COVID-19 infection. Hemoglobin, hematocrit, leucocytes, platelets, ferritin & C-reactive protein are significant investigations for screening of COVID-19 among them, while WBCs, Lymphocytes, and platelets are considerable for follow-up of cure. Unexpectedly the need for ICU admission presented more in non-hemodialysis patients and mortality significantly increased among hemodialysis group with COVID-19.

Keywords: COVID-19, Hemodialysis, Obesity, Screening, Hypertension, DM.

INTRODUCTION

Infection with the SARS-CoV-2 corona virus first appeared in Wuhan, China in December 2019, and it has since spread quickly around the world [1]. The general public's use of hospitals, and dialysis patients in particular, has been significantly impacted by the COVID-19 pandemic [2].

A single-strain RNA virus called SARS-CoV-2 primarily damages the respiratory system, however severe infections might progress to multisystem diseases. The clinical picture varies greatly, ranging from an asymptomatic or moderate course (up to 80%), to severe involvement with bilateral pneumonia (about 15%), to a very critical illness requiring mechanical ventilation in the intensive care unit ICU (3%–5%) [3]. The best way to handle new COVID-19 is not well understood, and patients on maintenance hemodialysis treatment have even less information than the general public [4]. Patients receiving dialysis may have greater death rates than the general population because of their advanced age and co-morbid conditions. Unfortunately, not only is the infection rate higher among them, but the infection is also more severe, leading to more fatalities. Mortality rates were recorded at a startling incidence of nearly 25% prior to the vaccination distribution [5].

Although there is adequate information to support the implementation of preventative measures in hemodialysis centres to stop the spread of the SARS-CoV-2 virus, the specifics of the illness in this group are yet unknown. There have now only been a few isolated reports made regarding the frequency and outcomes of COVID-19 in hemodialysis patients [6].

The aim of this work was to study the clinical presentation of SARS-CoV-2 infection in maintenance hemodialysis patients and identify their clinical sequel and outcomes through comparing the results with non-COVID-19 infection hemodialysis patients, and non-hemodialysis COVID-19 infection patients.

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MATERIAL AND METHODS

In this retrospective observational multicenter study 734 Egyptian patients in Nasser Institute, Ahmed Maher Teaching Hospital, Electricity Hospital and El Sahel Teaching Hospital were recruited at the period between 6/6/2020 and 25/8/2020.

Adults > 18 years, chronic kidney disease (CKD) patients on regular hemodialysis, were included in this research after taking informed consent, with exclusion of Patients unwilling to participate, those with AKI (acute kidney injury) or advanced malignancy

The dialysis team screened patients for recent exposure to a known COVID-19 patient, travel history to an endemic location, and/or symptoms of cough, dyspnea, fever, sore throat, and unexplained oxygen saturation below 92% to identify those who needed to be tested.

Patients were divided into three groups: Group I included 377 hemodialysis patients who dialyze thrice per week, complained of symptoms of COVID-19 infection, assessed clinically by pulmonologist, and confirmed by polymerase chain reaction (PCR), **Group II** included 237 maintenance hemodialysis non-COVID-19 & **Group III:** included 120 COVID-19 patients without hemodialysis also complained of symptoms of COVID-19 infection, also assessed clinically by pulmonologist, and confirmed by polymerase chain reaction (PCR).

All patients were underwent to the following:

Complete history and clinical examination, laboratory investigations, PCR for COVID-19. Imaging study including CT chest, with detection of the dry weight and height, then BMI was calculated using the formula: BMI= [WT (Kg)/ HT (m^2)]. Normal BMI was defined as less than 25 kg/m^2, overweight as BMI > 25 kg/m^2 and obesity as BMI > 30 kg/m^2 for both men and women [7].

Laboratory investigations included CBC, s. ferritin, CRP, D-dimer, lactate dehydrogenase LDH, liver functions, kidney functions and PCR for COVID-19.

Sysimex XS 500 completed a complete blood analysis to evaluate RBC, WBCs, and platelets. The immune-turbitimetric approach was used on the Cobas311 equipment to measure CRP and albumin. On the Cobas311 equipment, kidney function tests were performed using the standardised Enzymatic FCC-IDMS technique for creatinine and the Urease UV method for urea.

Respiratory samples (nasal/oropharyngeal swabs) positive for SARS-CoV-2 that were obtained under strict aseptic conditions by certified ENT specialist were subjected to real-time fluorescence RT-PCR.

Follow up of patients after eradication of the virus and survival: 14 days from appearance of symptoms with PCR negative and comparing the outcomes with this one month prior the infection regarding clinical assessment and laboratory investigation including serum albumin, CBC, serum ferritin, CRP and D-dimer.

For statistical analysis, demographic, co-morbidity, and clinical data were gathered and tabulated, including emergency department and/or hospitalisation events, death reports, and clinical information.

Ethical approval: General Organization for Teaching Hospitals and Institutes granted clearance with the approval code (HAM 00118) for The Local Ethics Committee. Before being enrolled in the trial, patients who decided to participate signed informed consent forms. The principles outlined in the Helsinki Declaration were followed in conducting the study.

Statistical analysis

Descriptive statistics was presented in frequency tables, means ± standard deviation whenever appropriate. Analytical tests will include Paired t test for comparing values at baseline and during follow up, independent t-test for comparison between two means, Analysis of variance (ANOVA i.e. F test) for comparing the means of more than two groups, and the Chi-Square test when analysing contingency tables. Multivariate analysis was conducted to detect the risk factors. When normal distribution violated (when the distribution of data not follow normal distribution) non-parametric tests was applied.

RESULTS

The current study recruited 734 patients at the period between 6/6/2020 and 25/8/2020. 400 patients [54.5%] were males, and 334 patients [45.5%] were females, with a mean age of 55.8 ± 13.8 years. They were divided in to 3 groups; **group I** (n=377) COVID-19 infected patients on hemodialysis sessions. Another two comparative groups, **group II** non-COVID-19 infected on regular hemodialysis (n=237), and **group III:** non-ESRD patients with COVID-19 infection (n=120).

The most common co-morbidities among **group I** were found to be HTN (45%), followed by DM (28.3%), cardiac disease (15%), liver disease (12.7%) and lung disease (7.6%). Fever was the most common symptom and presented in 84.4%. The second most common symptom was dyspnea (46.9%) followed by cough (46.7%). The cure rate in this group was 84.4% and mortality was (15.6%). 5.3% of patients in this group needed mechanical ventilation and majority of patients were treated according to Egyptian protocol at home (65.3%) as shown in figure (1) & table (1).

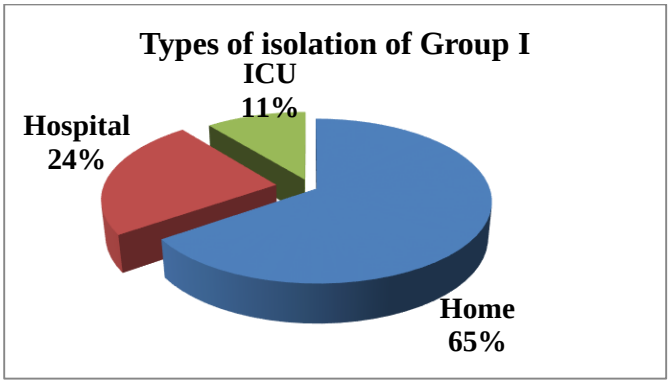

Figure (1): Types of isolation of Group I

Table (1): Demography of group I

Variables	N	M±SD/ Proportion
Age	286	57.39±13
Male	198	52.5%
Female	179	47.5%
BMI	109	28.13±6.5
Comorbidities		
DM	107	28.3%
HTN	170	45%
Cardiac disease	57	15%
Lung disease	29	7.6%
Liver disease	48	12.7%
Immunosuppresive drugs	21	5.6%
Symptoms		
Fever	318	84.4%
Cough	176	46.7%
Dyspnea	177	46.9%
Sore throat	67	17.8%
Diarrhea	47	12.5%
Vomiting	2	0.5%
Abdominal pain	49	13%
Fatigue	128	34%
Skin eruption	33	10.3%
AVF closure	32	10%
Drowsiness	31	9.7%
Confusion	40	10.6%
Myalgia	71	18.8%
Lab investigations		
HB% (g/dL)	231	9.7±1.8
HCT (%)	131	28.3±6.2
WBCs (mcL)	194	8.9±2.2
Lymphocyte	183	1.3±0.3
PLT (mcL)	174	242.49±59.4
Ferritin (ng/ml)	21	823.3±202.8
CRP (mg/L)	34	584.9±144.8
Urea (mg/dl)	42	191.3±45.8
Creatinine (mg/dl)	44	10.7±2.6
Na (mmol/L)	30	136.7±5.6
K (mmol/L)	32	4.8±1.2
AST (U/L)	6	20.5±4.7
ALT (U/L)	5	29±7.1
Glucose (mg/dl)	9	141.9±34.6
INR	6	1±0.07
D-dimer	16	2200±546.2
LDH (U/L)	11	328.8±81.8

Comparing the HD COVID-19 group **(Group I)** with **group II** patients, we discovered no statistically significant variations in demographic data between the two groups, with the exception of body mass index, which was considerably higher in group I (p-value0.003). Also, duration of dialysis, which was significantly higher in **group II** (p-value 0.001). All co-morbidities were more prevalent in **group I** with high statistically significant difference as DM (p-value 0.001), lung diseases (p value 0.0002), liver diseases (p-value 0.0001), cardiac diseases (p-value 0.0002) and malignancy (p-value 0.0001) (Table 2).

Table (2): Comparison of group I and group II

Variables	Group I N=377		Group II N=237		P. Value
	N	M±SD	N	M±SD	
Age	286	57.3±13	152	55.2±14.1	0.113
Male	198	52.5%	133	56.1%	0.38
Female	179	47.5%	104	43.9%	0.38
ight before dialysis	120	82.5±18.6	131	78.6±18.2	0.089
Weight after dialysis	123	76.37±18	163	74.1±18.3	0.2
Duration of dialysis	116	366±3398	284	37.9±53	0.10
Co morbidities					
DM	107	28.3%	40	16.8%	0.001
HTN	170	45%	101	42.6%	0.5
Cardiac disease	57	15%	13	5.5%	0.0002
Lung disease	29	7.6%	3	1.3%	0.0005
Liver disease	48	12.7%	5	2.1%	0.000
Malignancy	24	6.4%	1	0.4%	0.000
Lab investigations					
HB% (g/dL)	231	9.7±1.8	228	10.2±1.9	0.002
HCT (%)	131	28.3±6.2	182	32.2±5.6	0.000
WBCs (mcL)	194	8.9±2.2	229	7.3±1.7	0.0487
PLT (mcL)	174	242.5±59.4	229	216.5±52.7	0.002
Ferritin (ng/ml)	21	823.3±202.8	209	555.6±136.3	0.017
CRP (mg/l)	34	584.9±144.8	4	6.3±1.4	0.013
Blood.urea (mg/dl)	42	191.3±45.8	205	86.1±20.7	0.000
Creatinine (mg/dl	44	10.7±2.6	228	9.8±2.3	0.72
AST (U/L)	6	20.5±4.7	84	15.4±3.7	0.2
ALT (U/L)	5	29±7.1	84	16.2±3.8	0.94

Comparing investigations of **group I** with **group II** revealed that HB%, HCT, WBCs, PLT, ferritin & CRP showed statistically significant difference. Comparing **group I** with **group III** patients we found that there were statistically significant prevalence of HTN, liver disease, lung disease, malignancy, liver diseases among HD population. Fever, cough, dyspnea, chest pain, diarrhea, sore throat, and confusion were presented more in non-hemodialysis group while abdominal pain and fatigue were presented more in hemodialysis group. Unexpectedly need for ICU admission was presented more in non-hemodialysis group. Regarding lab investigations there were statistically significant decrease in HB%, HCT, AST, and ALT among hemodialysis group, and statistically significant increase in platelets, serum ferritin, CRP, urea, creatinine, and d-dimer (Table 3). Mortality significantly increased among hemodialysis group infected with COVID-19 (Figure 2).

Table (3): Comparison between group I and group III

Variables	Group I N=377		Group III N=120		P. Value
	N	M±SD	N	M±SD	
Age	286	57.4±13	120	52.6±15	0.001
Male	198	52.5%	69	57.5%	0.34
Female	179	47.5%	51	42.5%	0.34
Comorbidities					
DM	107	28.3%	57	47.5%	0.000
HTN	170	45%	40	33.3%	0.02
Cardiac disease	57	15%	14	11.7%	0.3
Liver disease	48	12.7%	5	4.2%	0.008
Lung disease	29	7.6%	3	2.5%	0.04
Immunosuppressive drug	21	5.6	1	0.8	0.028
Symptoms					
Fever	318	84.4	109	90.8%	0.07
Cough	176	46.7	96	80%	0.000
Dyspnea	177	46.9	110	91.7%	0.000
Chest pain	0	0%	12	10%	0.000
Diarrhea	47	12.5	45	37.5%	0.000
Abdominal pain	49	13	7	5.8%	0.03
Sore throat	67	17.8	38	31.7%	0.001
Drowsiness	31	9.7	6	5%	0.24
Confusion	40	10.6	29	24.2%	0.000
Anosmia	0	0%	1	0.8%	0.07
Loss of taste	0	0%	2	1.7%	0.012
Fatigue	128	34	39	32.5%	0.7
Need ICU admission	41	10.9%	16	13.3%	0.4
Laboratory investigation results					
HB% (g/dL)	231	9.7±1.8	119	11.2±2.3	0.000
WBCs (mcL)	194	8.9±2.2	120	6.7±1.4	0.001
Lymphocytes	183	1.3±0.3	120	1.2±0.2	0.546
PLT (mcL)	174	242.5±59.4	97	227.7±9	0.19
Ferritin (ng/ml)	21	823.3±202.8	65	520.5±97	0.02
CRP (mg/L)	34	584.9±144.8	67	90.6±5	0.0002
B.urea (mg/dl)	42	191.3±25.8	120	49.7±8.8	0.000
Creatinine (mg/dl)	44	10.7±2.6	120	1.2±0.15	0.000
AST (U/L)	6	20.5±4.7	120	46.6±4.7	0.005
ALT (U/L)	5	29±7.1	69	56.4±9.6	0.04
D.dimer	16	2200±506.2	2	250±53	0.005

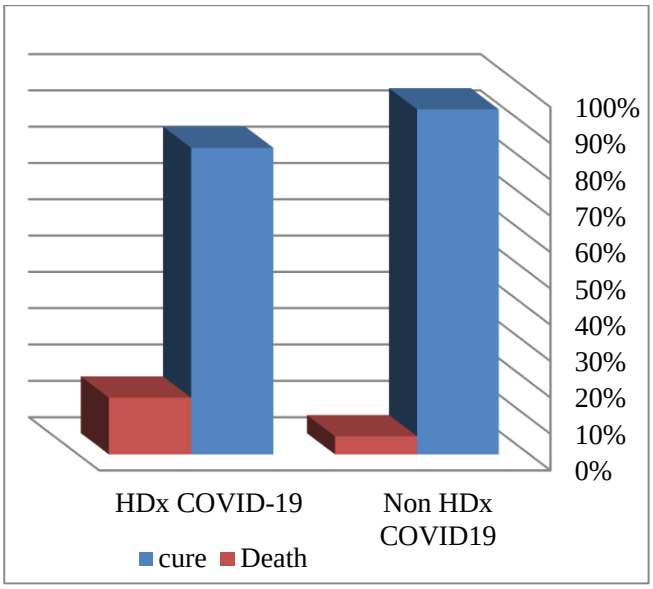

Figure (2): Comparison between outcomes of group I and group III

Studying the effect of COVID-19 on hemodialysis patients by comparing outcomes during and after cure from the infection, we found that there were statistically significant decrease in WBCs, lymphocytes, and platelets during the infection (Table 4).

Table (4): Comparison between laboratory investigations of group I during and after COVID-19 infection

Variables	During M±SD	After M±SD	P. Value
HB% (g/dL)	9.7±1.8	9.8±1.8	0.687
HCT (%)	27.9±6.9	27.3±5.2	0.626
WBCs (mcL)	5.7±1.4	8.9±2.2	0.012
Lymphocytes	1.7±0.4	2.5±0.6	0.001
PLT (mcL)	226.7±56.4	238.3±58.9	0.02
S.Ferritin (ng/ml)	607.5±136.9	500.8±124.8	0.8
CRP (mg/L)	65.7±16.1	60±14.8	0.8
LDH (U/L)	393±9.8	206.5±27.6	0.322
Serum albumin (g/dL)	3.6±0.3	3.5±0.3	0.056
Urea (mg/dl)	120±28.9	130±5.7	0.827
Creatinine (mg/dl)	12.9±1.2	6.9±1.6	0.195

DISCUSSION

COVID-19, a Corona virus illness, was declared a pandemic, with CKD as a major risk factor for morbidity and mortality. Dialysis increases the chance of transmission [8]. In addition, patients on hemodialysis are vulnerable to Covid-19 infection due to associated co-morbidities & insufficient immune system [9]. The prevention and control of COVID-19 in dialysis units is more difficult than in the general population and is particularly problematic due to frequent patient visits and shared use of the dialysis department [10].

The current multi-center study recruited 734 Egyptian patients in the period between 6/6/2020 and 25/7/2020. It described the demographics, clinical and laboratory course of COVID-19 in patients on maintenance dialysis during the recent epidemic in Egypt and compared their outcome to patients on HD NON-covid-19 and to patients with COVID-19 and normal kidney function. The mean age of the study population of the HD COVID-19 group was57.39 ± 13 years, with 52.5% males and 47.5% females. **Vallejos *et al.*** [11] reported that compared to the overall population, dialysis patients with COVID-19 had larger percentages of older age groups and a considerably higher median age (60 versus 37 years). Although this difference was not statistically significant, the sex distribution of dialysis patients with COVID-19 indicated a slightly larger proportion of male individuals. While in **Oruc *et al.*** [12] study, a total of 309 dialysis patients during the COVID-19 pandemic (54.9 ± 15.1 years, 51.6% females, 55.7% HD) were recorded.

In this study, regarding the clinical symptoms in HD COVID-19 patients, fever was the most common symptom and was present in 84.4% the second most common symptom was dyspnea (46.9%) followed by cough (46.7%). This was contrary to data reported by **Xingguo *et al.*** [13] who analyzed the data of 32 hemodialysis patients with COVID-19 including clinical, laboratory & radiological data in Wuhan. They found that fever only recorded 46.875%, which indicated that it was not a specific manifestation of infection in dialysis patients. However, cough discomfort represented 65.625%, but this comes in contact with the study of **Tortonese *et al.*** [14] whose data on 44 patients receiving maintenance dialysis in Paris using COVID-19 showed that the most common first symptoms were fever (79.5%), shortness of breath (29.5%), cough (43.2%), and diarrhoea (13.6%).

To detect the effect of COVID-19 on hemodialysis patients, we compared the HD COVID-19 group with HD non-COVID-19 patients we found that there were no statistically significant differences between the two groups regarding demographic data except for body mass index, which was significantly higher in the HD group with COVID-19 (p-value 0.003) as well as the duration of dialysis which was significantly higher in non HD COVID-19 (p-value 0.001).

In this study, all co-morbidities were more prevalent in group I with a high statistically significant difference as DM (p-value 0.001), lung diseases (p-value 0.0002), liver diseases (p-value 0.0001), cardiac diseases (p-value 0.0002) and malignancy (p-value 0.0001). Although, HTN was the most common co-morbidity in both groups I and II, there was no statistically significant difference between them and this

goes in line with a study done by **Tortonese *et al.*** [14] on hemodialysis patients with COVID-19. They found that co- morbidities included HTN (97.7%), DM (50%), and chronic cardiac disease (38.6%). **Fung and Babik** [15] reported the average age of COVID-19 patients getting maintenance dialysis is 65, and they typically have other co-morbid diseases, including DM, obesity, and dysregulated d immunity, all of which enhance the likelihood of poor results. Studies in China [16], Italy [17], The United Kingdom [18], and New York [19] showed that COVID-19 hemodialysis patients had more severe disease than the overall population. Also, **Hsu *et al.*** [20] found that COVID-19 patients exhibited a greater burden of co-morbidity, including a higher prevalence of cardiovascular disease and DM.

To detect the effect of hemodialysis on COVID patients, our study compared group I HD with COVID and group III COVID patients without HD, there was statistically significant prevalence of HTN, liver disease, lung disease, malignancy, HCV, and HBV infection among HD population. Fever, cough, dyspnea, chest pain, diarrhea, sore throat, and confusion were presented more in non-hemodialysis COVID group, while abdominal pain and fatigue and need for ICU admission were presented more in the hemodialysis group. Regarding laboratory investigations, there was statistically significant increase in platelets, serum ferritin, CRP, urea, creatinine, and D-dimer. Mortality significantly increased among the hemodialysis group infected with COVID-19. **De Meester *et al.*** [21] reported that the frequency of hospitalisation among dialysis patients during the first wave of the COVID-19 pandemic was equivalent to that of the general population. This is different, in particular, from earlier research that showed greater incidence rates among the dialysis group. An interesting exception to this was younger dialysis patients (25–35 years old), who had a hospitalisation rate that was around four times greater than that of the overall populations of similar age group [22]. **Chan *et al.*** [23] found that 122 patients with kidney failure were hospitalised with COVID-19. Patients with kidney failure had a greater frequency of DM (55% VS 43%), and HTN (66% VS 55%) when compared to 610 patients with COVID-19 who did not have kidney failure. There were no appreciable changes in the presenting symptoms and vital signs between patients with and without renal failure, despite the fact that patients with kidney failure had greater inflammatory markers. The ACE2 receptor over-expression in the tubular cells and disturbance of the immune system may explain why COVID-19 patients on dialysis had a considerably higher risk of death [24]. End-stage kidney disease (ESKD) patients are among those most at risk for COVID-19-related hospitalisation, serious illness, and fatality. Clinical observations revealed that hemodialysis patients' death rates were 10- to 20-fold greater than those of the general public [25].

In our study patients group of hemodialysis with COVID-19 infection showed a cure rate of 84.4% and a mortality of 15.6%. Majority of patients were treated according to Egyptian protocol at home (65.25%), hospital admission represented 23.87% but those who needed admission to ICU represented 10.88%, while 5.3% of them needed mechanical ventilation. In comparison with the group of non-hemodialysis infected with COVID-19, the need for ICU admission presented more in the hemodialysis group (13.3% versus 10.9%), and the death rate was more in the hemodialysis group (14% versus 5%). Contrary to our results, **Chan *et al.*** [23] postulated that patients with kidney failure required less intensive care, and there was no change in the requirement for mechanical ventilation or in-hospital mortality. Furthermore, **Ikizler** [26] stated that although COVID-19 infection rates in hemodialysis patients are significantly greater than in other populations, the illness is often less severe and seldom deadly.

However, our findings are consistent with those of a research conducted by **Abreu *et al.*** [27] who found that the incidence, mortality, and fatality rates in the hemodialysis population were eminently higher than the general public. Also, **Osiboguns *et al.*** [28] reported that individuals with kidney disease were 12.53 times more likely to die as a result of COVID-19, while **Valeri *et al.*** [29] reported 31% mortality in hospitalised individuals with renal failure and COVID-19. However, this study was lacking a comparator group. The study by **Ding *et al.*** [30] reported higher death and hospitalisation rates among dialysis patients who had COVID-19. They discovered that the majority of them got their diagnoses made in the hospital when they arrived with a severe COVID-19 clinical picture. The high COVID-19 death rate, which hovers around 20% among maintenance dialysis patients, may be attributed to late presentation and the scarcity of effective treatments [31]. Likewise, COVID-19 patients endure protracted ICU stays, extended periods of ventilator dependency, and related decreased mobility [32].

Researchers are very interested in performing studies on hemodialysis patients who had a full recovery from COVID-19. So in our study, comparing the effect of COVID-19 on patients of maintenance hemodialysis outcomes during and after curing the infection, we found that there were statistically significant decreases in WBCs, lymphocytes, and platelets during the infection. According to **Wang *et al.*** [33] study, 5 instances of hemodialysis patients exposed to COVID-19 experienced lymphopenia following treatment, with a drop in WBC. As we know there is no optimal COVID-19 management till now, and the therapeutic approach still needs significant evidence, particularly for patients on hemodialysis. Therefore, it is essential to limit the short- and long-term risk of hospitalisation among maintenance dialysis patients by preventing

severe COVID-associated illness [34]. Despite the fact that these patients are at high risk, the centres for disease control and prevention's 2022 vaccination guidelines remain ambiguous for patients with advanced CKD, acknowledging that they are at increased risk for poor outcomes but not specifically recommending a 3-dose primary series over a 2-dose vaccination [35].

CONCLUSION

Obesity, hypertension and diabetes mellitus are important risk factors among hemodialysis patients with COVID-19 infection. HB%, HCT, WBCs, PLT, ferritin & CRP are significant investigations for screening of COVID-19 infection among haemodialysis patients, while WBCs, lymphocytes, and platelets are considerable for follow up of cure. Although unexpectedly the need for ICU admission presented more in non-hemodialysis patients, mortality significantly increased among hemodialysis group infected with COVID-19.

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