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COVID-19 in patients under maintenance hemodialysis; clinical characteristics, laboratory findings and treatments

Ali Hasanvandi¹, Leila Sabetnia², Farzaneh Hematian³, Amir Jamshidnezhad⁴, Leila Kouti^{3*}

¹Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

²Chronic Renal Failure Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

³Department of Clinical Pharmacy, Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

⁴Department of Health Information Technology, Faculty of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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ABSTRACT

Introduction: The patients undergoing maintenance hemodialysis (MHD) who are affected with COVID-19 may be at a higher risk for severe disease and complications. Considering the current COVID-19 pandemic, there is a need for studies investigating the various aspects of COVID-19 in patients with MHD.

Objectives: The present study aimed to identify the risk factors associated with higher COVID-19-related mortality in patients under MHD.

Patients and Methods: The present retrospective study included 90 patients under MHD who were hospitalized with COVID-19 and diagnosed using the reverse transcription polymerase chain reaction (RT-PCR) from March 20, 2020, to December 20, 2020.

Results: The participants' mean age was 57.5±18.61 years, and 49 patients (54.4%) were men. Moreover, 35 patients (38.9%) were expired due to COVID-19. The most common underlying diseases included diabetes mellitus, hypertension and cardiovascular diseases. The patients expired due to COVID-19 had a significantly higher chance of needing oxygen therapy, mechanical ventilation, and intensive care unit admission compared to survived patients. Moreover, a significant negative relationship between mineral-multivitamin supplementation and COVID-19-related mortality was detected. The prevalence of dyspnea was significantly higher in the expired patients compared to survived patients.

Conclusion: The COVID-19 patients under MHD are high-risk for severe disease and mortality. Therefore, hemodialysis centers should establish strict preventive measures.

Implication for health policy/practice/research/medical education:

Maintenance hemodialysis (MHD) could be a risk factor for COVID-19 prognosis partly due to the drug regimen of the patients. In our 90 MHD patients infected with COVID-19 who were treated with seven different drug regimens, we found patients expired due to COVID-19 had a significantly higher chance of needing oxygen therapy, mechanical ventilation, and intensive care unit admission compared to the survived patients.

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Introduction

The coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been spreading globally since December 2019, becoming a threat to global public health (1). At the time of this paper, more than 513.9

million cases of confirmed COVID-19, as well as more than 6.2 million deaths, have been reported globally (2). Initially, it was assumed that COVID-19 was a pulmonary disease. However, involvements of other organs, including kidneys, heart, gastrointestinal tract, blood, liver, and nervous system, have been reported already (3). The

*Corresponding author: Leila Kouti,
Email: leilakouti2@gmail.com, kouti-l@ajum.ac.ir

common causes of death in these patients include acute respiratory distress syndrome (ARDS), heart failure, renal failure, multi-organ failure, and shock (4). Some patients, such as the elderly, those with underlying diseases, and immunocompromised patients are at a higher risk for severe COVID-19 and related mortality (1, 5). According to the previous studies, patients under maintenance hemodialysis (MHD) are more likely to become infected with COVID-19. Moreover, they are at high risk for severe disease and mortality (6). This can be explained by the fact that many of these patients are elderly and have several comorbidities, such as hypertension, diabetes mellitus, and cardiovascular diseases (7). Moreover, they are usually immunocompromised due to the uremic state and chronic inflammation, which renders them more susceptible to severe COVID-19 (6,7). These patients usually have to pay frequent visits to hospitals and are in close contact with the healthcare providers and other patients. Therefore, they have an increased chance of COVID-19 contraction (5).

Despite all the findings regarding the various aspects of COVID-19 in the patients under MHD, many points have not been illustrated yet. Therefore, there is a need for further studies investigating the COVID-19 in patients with MHD.

Objectives

The present multicenter, retrospective observational study aimed to identify the risk factors associated with COVID-19 mortality in the patients under MHD. The authors evaluated the clinical characteristics, laboratory findings, and treatment regimens in the patients under MHD who have been hospitalized due to COVID-19. Moreover, we investigated the chance of hospitalization in the COVID-19 patients under MHD.

Patients and Methods

Study design

Of a total of 1410 patients undergoing MHD in Ahvaz, 123 patients were hospitalized in hospitals due to COVID-19 diagnosed using the reverse transcription polymerase chain reaction (RT-PCR) from March 20, 2020, to December 20, 2020. However, data for 33 patients were incomplete and excluded from the study. Finally, a total of 90 patients were enrolled in the present study. All the study participants were followed until death or discharge, and their demographics, clinical characteristics, laboratory findings, and COVID-19 treatment regimens were recorded. Then, these data were compared between the patients expired due to COVID-19 and those who survived in order to identify the risk factors associated with COVID-19 mortality.

Data collection

The related data, including the demographics, clinical manifestations, underlying diseases, PCR test results, chest CT scan findings, and outcome of the study participants, were extracted from the COVID-19 registry system of the hospitals, which was designed by the Ahvaz Jundishapur University of Medical Sciences. Detailed information on this database has already been published. Afterward, we collected the data regarding the hemodialysis and laboratory results of the patients by referring to hemodialysis centers and referral COVID-19 centers.

Diagnostic criteria

All the patients had undergone RT-PCR testing for SARS-CoV-2 using nasopharyngeal and oropharyngeal samples. Those with at least one positive test were considered confirmed COVID-19 cases and were included in the present study.

Statistical analysis

The quantitative variables were described using the mean and standard deviation, while the qualitative variables were described using the frequency and percentage. Then, the variables were compared between the survived and expired patients. The comparisons were conducted using the T-test for quantitative variables, as well as the chi-square test and Fisher's exact test for qualitative variables. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 25.0 software. A *P* value <0.05 was considered as statistically significant.

Results

Of a total of 1410 patients undergoing MHD in Ahvaz between March 20, 2020, and December 20, 2020, 123 patients were admitted to the hospitals of the city with confirmed COVID-19. However, data for 33 patients were incomplete and excluded from the study. We found the COVID-19-related hospitalization rate was 8.7% in the patients undergoing MHD (Figure 1).

Baseline characteristics

The demographic characteristics of the patients are shown in Table 1. The participants' mean age was 57.5±18.61 years, with the age range of 12-97. Moreover, the mortality rate was 38.9% (n=35) and the mean hospital stay of the survived patients was 9±6.7 days. The most common underlying diseases include hypertension, diabetes mellitus, and cardiovascular diseases. Furthermore, 8 patients had a history of kidney transplantation, one patient had experienced liver transplantation, 2 patients had systemic lupus erythematosus, and 2 patients were affected by rheumatoid arthritis.

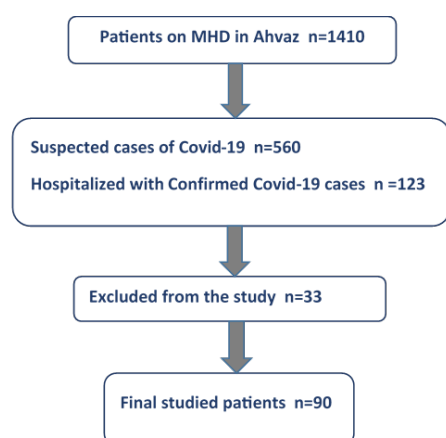


Figure 1. Flowchart showing the study population selection

The treatment regimens and medications of the patients based on their underlying diseases are presented in Table 2.

Clinical and laboratory findings

The clinical and laboratory findings at the time of COVID-19 diagnosis are introduced in Table 3. The most common symptoms were dyspnea, fever, cough and fatigue.

According to our findings, the mean white blood cell (WBC), platelet, and lymphocyte counts of the patients were $8.42 \pm 4.21 \times 10^9/L$, $188.7 \pm 182.0 \times 10^9/L$, and $1.31 \pm 1.3 \times 10^9/L$, respectively. Moreover, 7 patients (7.8%) had leukopenia, 21 (23.3%) had leukocytosis, 25 (27.8%) had thrombocytopenia, and 38 (42.2%) had lymphopenia.

The mean hemoglobin level of the patients was below the normal range, while the mean levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, and C-reactive protein (CRP) were higher than the normal range. Most patients (86.7%) had pulmonary CT findings consistent with COVID-19.

Finally, there was no significant relationship between mortality and clinical or laboratory findings, except for dyspnea. The patients with dyspnea had a significantly higher risk for mortality.

Treatment

The COVID-19 drug regimens are introduced in Table 4. Of a total of 90 patients, 75 (83.3%) received antibiotics during their hospitalization, including cephalosporins (n=45, 50%), meropenem (n=40, 44.4%), vancomycin (n=26, 28.9%), azithromycin (n=15, 16.7%), and other antibiotics (n=12, 13.3%). Moreover, 46 (51.1%) received systemic corticosteroids, while 20 patients (22.2%) received interferon β -1a. Furthermore, 49 patients required oxygen supplementation, 18 patients needed mechanical ventilation, and 21 patients were admitted to the intensive care unit (ICU). According to our findings, the deceased patients had a significantly higher rate of need for oxygen therapy, mechanical ventilation, and ICU admission compared to the survived patients.

Discussion

Considering the novelty of COVID-19 and our limited and unreliable knowledge about this disease, there is a need for more studies on the course of this disease in the patients undergoing MHD in order to provide sufficient and reliable knowledge for clinical practice. The present multicenter and retrospective study investigated the epidemiologic, clinical, and therapeutic data of 90 patients under MHD who were hospitalized due to COVID-19, which was confirmed using the RT-PCR test. The participants' mean age was 57.5 ± 18.6 years, with an age range of 12-97. Moreover, more than 50% of the patients were older than 60, and 54.4% were male patients.

According to our findings, 54.4% of the patients needed oxygen therapy, 23.3% were admitted to ICU, and 20% required mechanical ventilation. The overall mortality rate was 38.9%, while 90.5% and 72.2% of the

Table 1. Baseline characteristics of patients with COVID-19 according to the mortality rate

Characteristics, n (%)	Total (n = 90)	Mortality		P value
		Survivor (n = 55)	Nonsurvivor (n = 35)	
Age (y)	57.5±18.6	55.8±17.3	60.1±20.5	0.317
Sex				
Female	41 (45.6)	19 (34.5)	22 (62.9)	0.01
Male	49 (54.4)	36 (65.5)	13 (37.1)	
Coexisting disorder				
Hypertension	44 (48.9)	25 (45.5)	19 (54.3)	0.517
Diabetes mellitus	41 (45.6)	23 (41.8)	18 (51.4)	0.394
Cardiovascular diseases	30 (33.3)	23 (41.8)	7 (20)	0.040
Organ transplantation	9 (10)	6 (10.9)	3 (8.6)	1.00
Chronic respiratory disease	5 (5.6)	2 (3.6)	3 (8.6)	0.366
Autoimmune disease	4 (4.4)	2 (3.6)	2 (5.7)	0.641

Table 2. Past drug history according to the mortality rate

Past drug history, n (%)	Total (n = 90)	Mortality		P value
		Survivor (n = 55)	Nonsurvivor (n = 35)	
Mineral-multivitamin supplement ^a	46 (51.1)	35 (63.6)	11 (31.4)	0.005
Calcium channel blocker	44 (48.9)	27 (49.1)	17 (48.6)	1.000
Statin	41 (45.5)	25 (45.5)	16 (45.7)	1.000
ASA	40 (44.4)	27 (49.1)	13 (37.1)	0.286
Insulin	40 (44.4)	23 (41.8)	17 (48.6)	0.664
ACEi/ARBs	35 (38.9)	20 (36.4)	15 (42.9)	0.658
Beta blocker	35 (38.9)	24 (40)	13 (37.1)	0.828
Loop deuretic	21 (23.3)	14 (25.5)	7 (20)	0.617
Vasodilator	19 (21.1)	9 (16.4)	10 (28.6)	0.295
Immune-supressive drugs	13 (14.4)	11 (20)	2 (5.7)	0.72
Alfa blocker	12 (13.3)	9 (16.4)	3 (8.6)	0.355

^a All patients used the same brand that each tablet contained: Vitamin B1 (1.5 mg), vitamin B2 (1.7 mg), vitamin B5 (10 mg), vitamin B6 (10 mg), vitamin B12 (6 µg), vitamin E (50 mg), vitamin C (60 mg), biotin (300 µg), zinc oxide (25 mg), nicotinamide (20 mg), folic acid (5 mg).

Table 3. The clinical characteristics and laboratory findings of patients with COVID-19 according to the mortality rate

Characteristics	Total (n = 90)	Mortality		P value
		Survivor (n = 55)	Nonsurvivor (n= 35)	
Symptoms, n (%)				
Dyspnea	58 (64.4)	30 (54.5)	28 (80)	0.023
Fever	44 (48.9)	27 (49.1)	17 (46.8)	1.000
Cough	42 (46.7)	26 (45.7)	16 (45.7)	1.000
Fatigue	31 (34.8)	17 (30.9)	14 (41.2)	0.365
Nausea and vomiting	21 (23.3)	12 (21.8)	9 (25.7)	0.799
Anorexia	18 (20)	12 (21.8)	6 (17.1)	0.788
Myalgia	17 (18.9)	12 (21.8)	5 (14.3)	0.422
Laboratory tests, mean± (SD)				
WBC (10 ⁹ /L)	8.42±4.21	8.2±3.97	8.77±4.61	0.538
Lymphocytes (10 ⁹ /L)	1.31±1.33	1.4±0.74	1.16±0.76	0.151
HB (g/dL)	9.82±9.9	9.84±1.89	9.79±2.35	0.908
PLT (10 ⁹ /L)	188.7±70.43	188.6±70.3	188.8±71.7	0.992
AST (SGOT) (U/L)	61.36±127.1	70.87±158.73	46.52±45.86	0.459
ALT (SGLT) (U/L)	33.30±60.93	40.26±74/86	22.00±23.1	0.251
BUN (mg/dL)	64.78±38.43	58.16±28.82	75.47±48.87	0.067
Creatinine	7.11±6.33	6.71±2.75	7.75±9.61	0.0533
LDH (U/L)	734.32±709.2	679.0±651.0	806.4±787.6	0.522
CRP (mg/L)	37.29±42.36	22.4±21.3	54.88±54.64	0.059
Abnormal Chest CT, n (%)	78 (86.7)	49 (89.1)	29 (82.9)	0.527

LDH level was measured only in 53 patients.

ICU-admitted and mechanically ventilated patients were deceased, respectively. The mean hospital stay was 9±6.7 days for the survived patients.

According to our results, the mean COVID-19-related hospitalization rate of the patients under MHD was 8.7%, which was higher than those of the general population of Ahvaz (0.94%). Therefore, the patients undergoing MHD are at high risk for COVID-19 contraction and severe

disease. This finding can be explained by the frequent visits of these patients to hospitals and their close contact with the healthcare providers and other patients. Therefore, it is necessary to establish strict preventive measures in the hemodialysis centers, including the facemask wearing by all the patients and healthcare providers, repeated RT-PCR testing for the patients under MHD, isolation of the infected patients, and vaccination.

Table 4. The COVID-19 therapeutic interventions according to the mortality rate

Interventions, n (%)	Total (n = 90)	Mortality		P Value
		Survivor (n = 55)	Nonsurvivor (n = 35)	
COVID-19 medication				
Glucocorticoids	46 (51.1)	31 (56.4)	15 (42.9)	0.28
Hydroxychloroquine	34 (38.2)	22 (40.7)	12 (34.3)	0.656
Lopinavir/Ritonavir	23 (25.6)	15 (27.3)	8 (22.9)	0.805
Atazanavir	22 (24.4)	10 (18.2)	12 (34.3)	0.130
Interferon beta-1a	20 (22.2)	7 (12.7)	13 (37.1)	0.09
Azithromycin	15 (16.7)	10 (18.2)	5 (14.3)	0.775
Sofosbuvir/Daclatasvir	7 (7.8)	5 (9.1)	2 (5.7)	0.701
ICU admission	21 (23.3)	2 (3.6)	19 (54.3)	0.001>
Oxygen therapy	49 (54.4)	25 (45.5)	24 (68.6)	0.05
Intubation	18 (20)	5 (9.1)	13 (37.1)	0.002

On the other hand, the COVID-19-related mortality rate of the patients under MHD was 38.9%, four folds higher than that of the non-MHD patients hospitalized due to COVID-19 during the study period in Ahvaz. According to studies, the general mortality rate of the patients hospitalized due to COVID-19 is 11-23% (8), while this range is 16.3%-39.2 in the patients under MHD (6,9). This finding can be explained by the fact that patients under MHD are usually old, immunocompromised, and have various underlying diseases, which can increase the risk of COVID-19-related mortality.

In the present study, the survived patients were younger than the deceased patients. This finding was compatible with other studies reporting advanced age as a risk factor for COVID-19-related mortality (6,10). Moreover, male patients were more than female patients in the present study, which was compatible with other studies reporting that men are more likely to be affected by end-stage renal disease compared to women (11). However, the mortality rate was significantly higher in female patients compared to male patients, which was not compatible with previous studies (8,10,12). According to previous studies, COVID-19-related mortality can be affected by different risk factors, such as age, gender, underlying diseases, and smoking (12). In the present study, the mean age of the male and female patients was 56.2 and 59 years, respectively. On the other hand, 44.9% of male and 53.6% of female patients had two or more underlying diseases, while only one male patient was a smoker.

According to our results, the most common underlying diseases were hypertension, diabetes mellitus, and cardiovascular diseases. However, the prevalence of cardiovascular diseases was significantly higher in the survived patients compared to deceased patients, which was incompatible with previous studies (9,10,12). This difference can be explained by the small sample size of the present study. Moreover, two-thirds of the patients with a

history of organ transplant could survive the COVID-19, which may be due to the use of immunosuppressive drugs, and more studies should be done in this regard.

In the present study, the most common COVID-19 manifestations included dyspnea, fever, cough, and fatigue in order of prevalence, which was compatible with other studies (5,6). Moreover, the prevalence of dyspnea was significantly higher in deceased patients compared to survived patients. According to a recent meta-analysis, fever, cough, and dyspnea were reported to be the risk factors increasing the mortality of the COVID-19 patients under hemodialysis (7). Therefore, it seems that pulmonary manifestations have a prognostic value in the COVID-19 patients under MHD. Thus, the pulmonary CT findings should also be considered to follow the course of COVID-19 in the patients under MHD.

According to our findings, use of mineral-multivitamin supplements was significantly higher in the survived patients compared to deceased patients. However, there was no significant relationship between other medications and mortality. All the patients used the same brand of mineral-multivitamin supplements, which included zinc oxide and vitamins E, C, and B complex. According to evidence, zinc has antioxidant and anti-inflammatory effects. Therefore, it can be helpful for patients under MHD who have a high level of oxidative stress and chronic inflammation (13). Moreover, a randomized, open-labeled study reported that concomitant use of folic acid and vitamin B complex could effectively reduce the plasma levels of total homocysteine and high-sensitivity CRP and increase the plasma albumin levels in patients under hemodialysis. Therefore, such supplementation was helpful in improving the inflammation and nutritional status of the patients (14).

On the other hand, according to reports, many patients under hemodialysis have a lower intake of trace elements and vitamins in their daily diet compared to the

recommended daily allowance (15). Therefore, it seems that micronutrient supplementation in patients under MHD can boost their immune system, increasing their resistance to COVID-19 and other infectious diseases.

The present study did not find a significant relationship between using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and COVID-19-related mortality.

ACEIs and ARBs are widely used for managing hypertension and other cardiovascular diseases. These drugs can increase the angiotensin-converting enzyme 2 (ACE2) expression in human tissues (16). On the other hand, the ACE2 is an auxiliary receptor for the entry of SARS-CoV-2 into the target cells. Therefore, there is a possibility that the use of ACEIs or ARBs can increase the severity and mortality of COVID-19 (17). However, there is not enough evidence to support the discontinuation of these drugs in the patients due to the increased risk of COVID-19 contraction (17-19).

According to a retrospective study in Wuhan, China, on 112 patients with cardiovascular diseases who were infected with COVID-19, the use of ACEIs or ARBs had no significant effect on COVID-19 severity and mortality (20). Moreover, a comprehensive systematic review and meta-analysis by Bavishi et al, which included 31 cohort studies and 87951 patients with COVID-19, reported no significant relationship between treatment with ACEIs or ARBs and COVID-19 severity or mortality (16). Therefore, it is recommended to continue using ACEIs and ARBs in the patients with COVID-19 until further studies are performed.

In the present study, the levels of AST, BUN, creatinine, LDH, and CRP were higher than the normal range, and several patients had lymphopenia. However, there was no significant relationship between COVID-19-related mortality and laboratory variables. These findings were not compatible with several studies reporting a relationship between COVID-19-related mortality and the variables of leukocytosis, lymphopenia, and increased levels of LDH, CRP, procalcitonin, AST, ALT, and BUN (10). Moreover, a study by Wang et al on 136 COVID-19 patients under hemodialysis reported that lymphopenia, prolonged prothrombin time, and elevated LDH were the most common laboratory abnormalities in the patients (1).

According to our results, there was no significant relationship between COVID-19 therapeutic regimens and mortality. The drugs usually used for COVID-19 treatment include antivirals, steroids, cell and gene therapies, and monoclonal antibodies. Numerous ongoing clinical trials are currently being conducted worldwide to investigate the efficacy and safety of various treatment options for COVID-19.

According to evidence, measures such as early diagnosis, isolation, and supportive care of the patients are recommended to prevent the spread of the disease. Moreover, personal protective measures, such as facemask wearing in public places and vaccination, are essential for COVID-19 prevention in high-risk groups, such as the patients under MHD.

Conclusion

According to our results, significant relationships between COVID-19-related mortality and the variables of gender, low oxygen saturation, and cardiovascular diseases was seen. Moreover, the COVID-19 contraction and related mortality were much higher in the patients under MHD compared to the general population. Therefore, hemodialysis centers should establish strict preventive measures.

Limitations of the study

Some limitations of this retrospective observational study are; 1) The time of MHD initiation was not recorded. 2) The data regarding the cause of death and secondary infections were not available. 3) The imaging findings were not analyzed in detail. 4) Moreover, 33 patients were excluded due to incomplete data or failure to continue the treatment. Finally, our sample size was small, which could potentially affect the results. Therefore, there is a need for studies with larger sample sizes in order to generalize the findings of the present study.

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Authors' contribution

AH, LK and LS were the principal investigators of the study. AH, LK, LS, FH and AJ were included in preparing the concept and design. FH and AJ revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur

University of Medical Sciences approved this study (ethical code #IR.AJUMS.REC.1399.800). Accordingly, written informed consent was taken from all participants before any intervention. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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