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Prevalence and clinical presentation of COVID-19 infection in hemodialysis patients

Azra Kenarkoohi[1], Maryam Maleki[2*], Bahareh Ghiasi[3*], Elham Bastani[4], Iraj Pakzad[1], Mahtab Bonyadi[5], Amir Abdoli[6], Shahab Falahi[7]

[1]Department of Microbiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[2]Department of Physiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[3]Department of Nephrology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran, Iran
[4]Department of Internal Medicine, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[5]Clinical Research Development, Mostafa Khomeini Hospital, Ilam University of Medical Sciences, Ilam, Iran
[6]Department of Parasitology and Mycology, School of Medicine, Jahrom University of Medical Sciences, Jahrom, Iran
[7]Zoonotic Diseases Research Center, Ilam Ilam University of Medical Sciences, Ilam, Iran

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ABSTRACT

Introduction: Hemodialysis (HD) patients are at increased risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Objectives: The aim of this study was to evaluate the prevalence and clinical symptoms of SARS-CoV-2 infection in HD patients.

Patients and Methods: This is a single-center study conducted at HD center, in Ilam, Iran. The study was included 87 HD patients to be tested. SARS-CoV-2 infection was diagnosed with confirmed test by rRT-PCR (real-time reverse transcription polymerase chain reaction) assay.

Results: Around 35.63% of HD patients were diagnosed as COVID-19 infection; most of them were male (74.4%). Dyspnea (58.1%) and cough (45.2%) were the most common symptoms among HD cases with SARS-CoV-2 infection. Diabetes (16.1%) and hypertension (19.4%) were the most coexisting medical illnesses. About 12.9% of patients needed ICU care. Additionally, 16.1% of our patients died, which all of them were male.

Conclusion: This study showed a high prevalence of COVID-19 among our HD group, accompanied by mild symptoms. The HD population is probably among the most sensitive and high-risk groups for COVID-19 because of advanced age, comorbidities disease, low-immune function and frequent required visits, and patient overload in HD centers. Preventive measures should be taken in order to minimize the virus transmission in dialysis centers.

Implication for health policy/practice/research/medical education:
This study showed high prevalence of COVID-19 among hemodialysis (HD) group, accompanied by mild symptoms. The HD population is probably among the most sensitive and high-risk groups for COVID-19 because of advanced age, comorbidities disease, low-immune function and frequent required visits, and patient congestion in HD centers.

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Introduction

The initial cases of novel coronavirus (SARS-CoV-2) were reported in Wuhan, Hubei province, China in late December 2019 and became a pandemic soon. Coronavirus disease 2019 (COVID-19) has no specific treatment and the infection control is based on disruption of the transmission chain. The virus binds to the ACE2 receptor with an affinity 10 to 15 times greater than SARS-CoV (1), therefore it is much more infectious than SARS-CoV and its high transmittance makes it difficult to control infection.

The main routes for SARS-CoV-2 transmission are close contact exposures and breathe droplets. In addition to transmission through symptomatic patients, transmission

*Corresponding author: Maryam Maleki, Email; Maryammaleki777@yahoo.com, maleki-m@medilam.ac.ir and Bahareh Ghiasi, Email:bahar55gh@yahoo.com, ghiasi-b@medilam.ac.ir

Original Article

from pre-symptomatic and asymptomatic individuals also occurs (2,3). SARS-CoV-2 is also transmitted indoors via airborne (2). Other ways include the fecal-oral route (1). The presence of SARS-CoV-2 has also been reported in the blood sample of a number of SARS-CoV-2 infected patients, but blood may not be a route for transmission (4). If the blood has potential to transmit this virus, hemodialysis (HD) patients are at high-risk groups.

SARS-CoV-2 enters the body via upper respiratory tract and enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor. Then it multiplies and reaches the lungs which include the main target tissue of SARS-CoV-2. The digestive system, kidneys, heart, vascular endothelium, skin, eyes and brain are also affected by the virus. Pulmonary edema, endotheliitis, hypercoagulopathy, thrombosis, diffuse intravascular coagulation, conjunctivitis, encephalitis, encephalopathy, delirium, skin rash may be observed in COVID-19 patients (5). These patients show a heterogeneous spectrum of clinical signs that varies from patient to patient. The major clinical signs in COVID-19 patients include fever fatigue, dry cough, myalgia and dyspnea(6). Headache, dizziness and gastrointestinal signs are less common (6).

Older age, male gender and smoking are risk factors for COVID-19 disease and are associated with disease severity. Comorbidities such as hypertension, cardiovascular disease, diabetes and kidney disease significantly affect the prognosis of the disease and are associated with increased risk of death in COVID -19 patients(7).

Laboratory findings suggest that lymphopenia, neutrophil/lymphocyte ratio (NLR), high levels of C-reactive protein (CRP), LDH, D-dimer and interleukin-6 are as some risk factors for the severity of COVID 19- disease(8).

HD populations are in increased SARS-CoV-2 infection peril for several reasons; higher average age, multiple comorbidities and weak immune system (9). Additionally, staying in the dialysis room for hours and not possibility to stay at home due to their regular need for treatment are as factors that cause increased risk of infection in this group (9). Therefore, the effect of this pandemic on dialysis centers should not be neglected. In this regard, a study in Italy has reported that 55 out of 209 HD patients (with or without symptoms) had SARS infection while a prevalence of 26% was reported (3). Furthermore, in a Chinese study, the prevalence of SARS-CoV-2 was reported to be 16.09% (37 positive cases out of 230 patients) among HD patients and 12.12% among dialysis staff. COVID -19 infection was reported mild in most patients(10).

In the study of Goicoechea et al, the most common symptoms in HD cases with SARS-CoV-2 infection consisted fever, cough, fatigue and gastrointestinal signs, respectively (11).

HD patients are frequently visiting hospitals and HD centers, these centers are crowded and HD patients have to visit even during quarantine, hence they are at high risk for infection by the virus. In general, HD patients need special attention to be monitored during covid-19 pandemic period. Limit studies have been performed to survey prevalence of SARS-CoV-2 among HD patients and at the time of present study, no study has not been performed on the effect of SARS-CoV-2 infection on HD patients in Iran.

Objectives

The present study was conducted to evaluate the prevalence, clinical symptoms and outcome of SARS-CoV-2 infection in HD patients in one HD center, in, Ilam, in the west of Iran.

Patients and Methods

This was a single-center study done at HD center, Mostafa Khomeini hospital, Ilam province, Iran, from April 3, 2020 to July 12, 2020. Around 87 HD patients were enrolled in the study to be tested. SARS-CoV-2 infection was diagnosed with a confirmed test by real time reverse transcription polymerase chain reaction (rRT-PCR) assay via collected oral and nasal swab samples. Within the time of patients screening, all diagnosed infected patients were quarantined, or transferred to a defined hospital based on the government and medical university instructions. All clinical symptoms data were collected from the medical records of the HD patients.

We evaluated and analyzed the medical history, physical examination, demographics, signs and symptoms, from 31 HD patients with confirmed SARS-CoV-2 infection. All data were checked by two physicians.

Virus detecting via rRT-PCR test

Sample collecting from HD cases were done by experts in accordance with safety principles, then under safety conditions the samples were transferred to the special lab for coronavirus in the insulated boxes equipped with cool pack (4°C). A particular primer and probe RT-PCR were utilized to target ORF1ab and nucleoprotein gene (N genes) and detect the viral genomes. In advance to RT-PCR, extraction of viral RNAs from the samples was carried out by a gene All Ribospin™ (Seoul, Korea), and then kept at −20°C to the test operation time. PCR amplifying was done in accordance with Sansure Biotech Inc. kit producer instruction (Changsha, China). For the cycle's threshold (CT) value more than 40, the test result was reported as negative.

First 30 µL Master Mix and then 20 µL of the extracted viral RNA were added into each well. PCR tubes were located in the Mic Real-Time PCR System (Bio Molecular Systems, Australia). The rRT-PCR test was completely performed about 124 minutes and the fluorescent curve was observed to inspect the result. Positive result with a CT value less than 40 confirmed the existence of SARS-CoV-2 RNA.

The LoD of the kit was 200 copies per mL. In each detection run, a negative control was put in order to check any contamination during the rRT-PCR procedure, as well, a positive control applied to observe whether the rRT-PCR method operated properly. To preserve the quality controls from sample collecting to virus detection, all materials were selected disposable, sterile and RNAse/DNAse free in the present study.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Ilam University of Medical Sciences approved this study. The institutional ethical committee at Ilam University of Medical Sciences approved all study protocols (IR.MEDILAM.REC.1399.019). Accordingly, written informed consent was taken from all participants before any intervention.

Data analysis

Continuous measurements and categorical variables were reported as mean and count (%), respectively. SPSS software version 20 was used to analyze data. The significance level was considered less than 0.05.

Results

The study population included 87 HD patients which 31 patients (35.63%) were diagnosed COVID-19 infection with PCR that we included their data to analyze. The mean age of SARS-CoV-2 infected HD patients was 51.72±3.2 years. The youngest was 24, and the oldest was 82 years. Most of the patients were male (24, 74.4% versus 7, 22.6%) (Table 1).

Of the 31 patients, 12 (38.7%) had one or more concurrent medical illnesses. Diabetes 16.1% (n=5) and hypertension 19.4% (n=6) were the most coexisting medical illnesses (Table 1). 83.87% (n=26) were hospitalized, of whom 4 patients (12.9%) needed ICU cares.

The most common symptoms of these patients were dyspnea (58.1%) and cough (45.2%). Most of the patients had a dry cough. The patients' temperature range was 36 to 39.8°C. Only 6(19.4%) patients were febrile (>38°C). Abdominal pain and nausea were less common symptoms. The other signs and symptoms are presented in Table 1. One of the patients just admitted with abdominal pain.

Table 1. Findings of HD patients infected with SARS-CoV-2

Sign (number (%)	Positive	Negative
Fever	6(19.4)	25(80.6)
Cough	14(45.2)	17(54.8)
Dyspnea	18(58.1)	13(41.9)
Sore throat	4(12.9)	27(87.1)
Myalgia	2(6.5)	29(93.5)
Abdominal pain	0	31(100)
Nausea	0	31(100)
Agitation	1 (3.2)	30 (96.8)
Confusion	1 (3.2)	30 (96.8)
ICU	4(12.9)	27(87.1)
Other disease	12 (38.7)	19 (61.3)
Diabetes	5 (16.1)	26 (83.9)
Cardiovascular disease	3 (9.7)	28 (90.3)
High blood pressure	6 (19.4)	25 (80.6)
Obesity	1 (3.2)	30 (96.8)
Liver disease	1 (3.2)	30 (96.8)
Expired patients	5 (16.1)	26 (83.9)

Expired patients

Five (16.1%) of our patients died, and 26 (83.9%) discharged. The mean age of expired patients was 60±6 with a range of (34-78) years. Surprisingly all of them were male. Table 1 summarizes the data from 31 HD patients infected with SARS-CoV-2 infection.

Discussion

COVID-19 epidemic, originated from SARS-CoV-2, has spread in various areas of many countries, all over the world, thereby announced as a pandemic. There are limited reports regard to the influence of COVID-19 epidemic on HD patients. HD group is a different class from the other groups of population since making up a large scale group; receiving concentrated dialysis treat in a large space; compromising the immune system as well as being potential "super-spreaders" when they are infected, regarding their feature, this patients and HD treatment rooms must be given high concern in epidemic control (10).

This study revealed the prevalence of COVID-19 in HD patients at hemodialysis center of Ilam, Iran was very high, almost 36%, since most of this HD patients were male. Yiqiong et al reported that from the onset of outbreak to 12 March, 2020, 18.26% of HD cases (42 of 230) were diagnosed as COVID-19 (10). They showed, the prevalence of COVID-19 was reported about 12.12% among dialysis staff (10). In addition, based on an unpublished finding in HD patients at the dialysis centers in Wuhan up to 10% HD patients has been infected with COVID-19 (12). Another study in the nephrology and dialysis department in a hospital in Lecco Lombardy

province, Italy, showed that 18% of symptomatic HD patients (33 of 188) had been diagnosed as COVID-19 infected via positive nasopharyngeal swabs however, in this study the prevalence of COVID-19 in their entire HD groups was reported as 26%, 55 of 209 (3). In HD centers, the more transmission possibility of SARS-CoV-2 to the medical staff, other patients, and their relatives is resulted from the difficulty in observing the health measures, for instance isolating and social distancing (12). In HD centers, maintain the 2-meter distance is not possible all the time; in addition, many patients hardly bear the facial mask for a long-time, hence SARS-CoV-2 may be revealed with a high prevalence among them, as our study shows. The high incidence of SARS-CoV-2 in the HD population of our study may have other reasons that need to be investigated more precise. For instance, according to the studies, the prevalence may increase based on the special weather of a region and the amount of air pollution and the date of sampling (13). In addition, due to the time it takes from the onset of the disease, as the time progresses, the disease has spread more; therefore the number of carriers and patients has also increased.

In accordance with our results, the other studies reported that male patients were more than female patients. In the dead cases, also men were more than women. In a meta-analysis study, it has been documented that generally 55.9% were male patients (14). Klein et al interpreted that, the results are inconsistent reporting (15). They also have highlighted the difference in mechanisms specially ACE2 expression among genders (15). It has been reported that ACE2 level is different between men and women tissues. It was explained that expression of ACE2 is affected by estrogen and testosterone(16). Klein et al also highlighted antiviral immunity and some gender related characteristic, such as comorbidities associated with both age and race(15). It has been illustrated that inflammatory, antiviral responses, as well as humoral immune at viral infections are greater in female rather than male that leads to better clearance of viral infection such as SARS- CoV-2 (15).

The most common clinical symptoms for infected HD patients at the admission time were dyspnea and cough while only 6(19.4%) patients were febrile (>38°C). According to a meta-analysis study, generally fever (88.7%), cough (57.6%), and dyspnea (45.6%) were the most common clinical symptoms (14). Wang et al stated that the most common clinical signs of HD patients with COVID-19 included diarrhea, fever, fatigue, dyspnea, and abdominal pain. Of our five patients, only one had a dry cough and none of the patients had upper respiratory system signs such as rhinorrhea and sore throat (17). Furthermore, in the study by Ma et al on HD patients (between January 14th to February 17th), it was showed that COVID -19 infection was mild in most of these patients. They observed that the most common clinical symptoms in HD patients were fever (11%), fatigue (8%) cough, chest pain or nausea (3%). Additionally, according to the study by Ma et al no other symptoms in their HD patients were seen (10). Probably fever is not a common symptom, while a study showed low-degree fever (T<38°C) only in 20% of their cases, however another study reported fever in 44% of their cases (18, 19). In fact HD patients with COVID-19 have considerably low-serum levels of inflammatory cytokines than other patients of COVID-19, because of the impairment in immune system and cytokines, thereby HD patients with COVID-19 infection show clinically mild and unlikely rise to severe pneumonia (10). Previously it has been shown that SARS-CoV-2 infection can decline the lymphocytes count in the patients, but in vivo experiments shown the levels of inflammatory cytokines increase considerably cytokine storm might be among the main reasons to worsen the situation and even die (20); this is not expected in dialysis patients due to their special conditions.

In our study of the 31 HD patients, 38.7% had one or more concurrent medical illnesses. Chronic HD patients will be among the high-risk people when facing with SARS-CoV-2 because of their immunosuppressed situation, advanced ages and remarkable comorbidities, specifically heart diseases and diabetes (9). In agreement with this, diabetes and hypertension were the most coexisting medical illnesses among HD patients in the present study. Donoghue et al reported that failing and non-failing human heart don't have difference in ACE2 protein expression rate (21), but a factor that causes heart failure patients be more prone to COVID-19 is higher plasminogen level. Remarkably patients with chronic heart failure have increased levels of urinary plasminogen and plasmin (7). Plasmin can cleave the extracellular S-protein domain of SARS-CoV-2 and enhances its binding to ACE2 receptor in the host body cells, thereby facilitates virus entry to the cell (8). Chen et al have shown that about 30% of people infected with SARS-CoV-2 had hypertension (22). It should be mentioned that increased expression of ACE II in varied cells and organs (particularly at lungs) may lead to an increased risk for SARS-CoV-2 infection (7). Moreover, diabetes patients may receive high amounts of ACE inhibitors and angiotensin receptor blockers because of hypertension and albuminuria, which face with high ACE2 expression (as an adaptive response to the increased levels of angiotensin II and I), while raised ACE2 receptor amount facilitates the entry of SARS-CoV-2 into the cells and results in severe outcomes. Besides diabetic individuals are more prone to be infected

with virus or bacteria than others, mainly because of less robust immune responses (23).

At last, 16.1% of our HD patients with mean age of 60 years old died and all dead patients were male. HD patients are likely at high risk of COVID-19 and its complications, because of being in advanced ages and having multiple comorbid diseases and suppressed immune systems (24). In a joint mission between WHO and China, data showed that patients older than 60 years and those with comorbidities had an elevated chance to experience a severe disease and dying (25).

Conclusion

As our study showed an increased incidence of COVID-19 among HD groups, these patients are probably among the most sensitive and high-risk groups for COVID-19 disease. Preventive actions are required to be taken in order to minimize virus transmission probability in dialysis centers. In this regard, it is necessary to perform routine screening and prevent the spread of infection in dialysis centers by rapid diagnosis and isolation of infected people.

Limitations of the study

CT scan findings of HD patients were not available to us. Despite the participating of all HD patients in this center in the study, the sample size was somewhat small.

Authors' contribution

AK, MM, BG, EB, IP, MB, AA and SF were the main investigators of this study. All authors participated in preparing the final draft and approved the content of the manuscript and confirmed the accuracy and integrity of each part of the work. The authors read and signed the final draft.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. This article does not contain any studies with human participants or animals performed by any of the authors.

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