

Clinical characteristics and symptoms of patients with the recurrence of COVID-19 and underlying disease in Taleghani and Valiasr hospitals in Khuzestan, Iran

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Abstract

Due to the widespread prevalence of coronavirus disease 2019 (COVID-19) in the world, especially in Iran, this study attempted to evaluate risk factors associated with the recurrent of COVID-19 patients in healthcare centers of Khuzestan province. This study was conducted on patients admitted to Taleghani and Valiasr hospitals, with positive COVID-19 real-time-polymerase chain reaction (RT-PCR), from 20 February 2020 to 19 January 2021. Meanwhile, 398 cases with the recurrent of COVID-19 were included. Investigations were conducted as follows, demographic characteristics, clinical signs and symptoms, and underlying disease, history of ICU hospitalization, international travel, and contacts with foreign nationals and mortality. The collected data were recorded by laboratory experts. Out of 398 patients, 251 (63.07%) were male, and 147 (36.93%) were female. The average age was 49.39 years old. None of the patients were hospitalized in ICU. Most patients were in 30-40 years (24.37%). International travelling and contact with foreigners was observed in only 25 (6.28%) cases. The most underlying diseases were hypertension and diabetes. In this study, the number of patients who died was 253 (63.57%). Due to the severe symptoms and higher mortality among COVID-19 recurrent patients with underlying disease, it is recommended to give more attention to COVID-19 recurrent patients with underlying diseases such as diabetes and hypertension. Presenting the results of this study to health-care systems might help a better understanding of risk-factors associated with the recurrent COVID-19 disease, leading to a better control and management of this patients.

Keywords: COVID-19, SARS-CoV-2, Clinical characteristics, Recurrence, Iran

1. Introduction

Coronavirus disease 2019 (COVID-19), a severe respiratory infection syndrome, is the new coronavirus disease that appeared in 2019 in Wuhan, Hubei province, China caused by severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2). This infection is highly contagious and spreads rapidly among human through direct transmission and it is spreading throughout the world [1-3]. Due to the worldwide spread of this disease, the World Health

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Organization (WHO) declared COVID-19 as an extensive pandemic to cause over a thousand sufferers and deaths daily [4]. SARS-CoV-2 is a zoonotic virus. However, the origin of COVID-19 which is a big puzzle, is more likely to be transferred from bats to human.

Coronaviruses are enveloped with helical symmetry, positive single-stranded RNA and have the largest genome in RNA viruses [5-7]. SARS-CoV-2 is involved in beta coronavirus due to its structural and genetic similarity [1]. According to the recent research, SARS-CoV and SARS-CoV-2 conjugate with ACE2 receptors on the lung epithelial membrane and enters the cell thereafter replicates and results in downregulation of these receptors. The physiological function of these receptors is to degrade angiotensin II. It binds to angiotensin converting enzyme 2 (ACE-2) receptor through its spike glycoprotein on the envelope. The mechanisms of attachment and entry of SARS-CoV-2 into the host cells is similar to other SARS-CoV [1]. *ACE-2* gene is expressed in the lung, kidney, heart, testis, thyroid, and intestine [8], which is a 60 nm round or oval protein [3, 9].

COVID-19 causes acute pneumonia, and it can also affect other organs of the body, however the mortality is mostly due to severe lung involvement [8, 10, 11]. Despite prolongation of the COVID-19 pandemic, no definitive cure is found until now. Direct contact and respiratory droplets are the essential routes to transfer SARS-CoV-2 [12]. The quarantine criteria were considered e.g. stay at home, physical distancing, wearing masks and gloves, etc. [13]. It commonly infects adolescents and adults, but it also affects children and infants [14]. Studies showed that adult and elderlies are more vulnerable to COVID-19 while children are often asymptomatic [15] because they are less exposed to this infection and do not use cigarettes as an underlying cause [16].

Patients with COVID-19 often refer to medical centers with symptoms of common cold, dry cough, high fever and shortness of breath. The clinical symptoms of the disease appear in less than a week and worsen over time [5]. Most patients are adults, and the highest mortality is in patients with the underlying disease, for example, lung failure, diabetes, etc. [9]. Men are more susceptible to this disease than women due to genetics, hormonal, social, and occupational reasons. Besides, they refer to medical centers too late. Many primary and recurrent cases of COVID-19 have been reported from most countries,

while the number of recurrent cases is increasing [17, 18]. The main reason of this recurrence is not clear yet [19]. Khuzestan province, in the south of Iran has the most suffers of COVID-19 also many cases have been seen with the recurrence of COVID-19.

Recurrence of the COVID-19 spread among residents of Khuzestan, but no information was evaluated about these patients. Due to lack of recorded knowledge about patients with the recurrence of COVID-19, this study aimed to identify possible associations between demographic data, clinical signs and symptoms, history of ICU hospitalization, traveling abroad, contacts with foreign nationals, and any other underlying disease, and mortality in patients with the recurrent COVID-19.

2. Materials and Methods

2.1 Study design

A descriptive cross-sectional study was conducted on 398 patients admitted to Taleghani and Valiasr hospitals in Khuzestan, during 20 February 2020 to 19 January 2021. The patients referred with recurrent COVID-19 symptoms, 14-20 days after a complete course of treatment and release (These drugs and therapeutic agents include antiviral agents: remdesivir, hydroxychloroquine, chloroquine, lopinavir and oseltamivir, and supporting agents: Ascorbic acid, Azithromycin and Corticosteroids). Informed consent was obtained from all individual participants included in the study. Noted that, none of the patients in this study receive vaccine.

2.2 Upper respiratory tract samples collection and transfer method

According to Centers for Disease Control and Prevention (CDC) guidelines, two types of synthetic fiber swabs (Dacron and rayon) can be used for SARS-CoV-2 diagnosis, and cotton swab do not recommend [20]. The first swab for nasopharyngeal was deeply inserted into one nostril and rotated for many times, so the tip of the swab was placed into the sterile vial, consisting of TRIS-EDTA (0.5 mm) and pH=8, then should be refrigerated until ready to transfer to lab [20]. The second swab for throat insert into mouth, for getting a good sample and not affected by anything the swab do not touch to the teeth, gums and tongue. Then the tip of the swab was placed into the same vial as described above [21]. Throat and nasal swab samples were used for real-time-polymerase chain reaction

(RT-PCR) as a qualitative detection. All cases were hospitalized and confirmed with SARS-CoV-2 by RT-PCR, as a gold standard for definitive diagnosis based on common WHO guidance [22].

2.3 RNA extraction and cDNA synthesis

The samples were treated with chloroform then centrifuged, so protein extracted and removed. Thereafter, isopropanol was added to solution to harvest the RNA. The RNA purity was determined with agarose gel electrophoresis. Converting RNA into DNA, we used Bio fact cDNA kit (Daejeon, South Korea).

2.4 Real-time PCR

For detection of SARS-CoV-2 in samples, real-time RCR analysis was performed in Taleghani and Valiasr hospitals in Khuzestan, Iran. About 5-10 ng cDNA and 2X real-time PCR master mix (SYBR Green I; BIOFACT, South Korea) were used. Incubation in one cycle 95°C for 10 min, 40 cycles at 95°C for 30s, 55°C for 30s and 72°C for 30s was done, and the melting curve was between 95°C and 60°C for 10 s and 1 min, respectively. To demonstrate there is no contamination between samples, we used a negative control in real-time PCR.

All medical data of patient were recorded and analyzed. The recorded data consists of clinical signs

and symptoms of disease, diagnostic tests, age, sex, ICU hospitalization, and international travel history, contacts with foreign nationals, underlying diseases and mortality in patients with the COVID-19. The needed information was recorded by the group of a nurse, a physician, a laboratory expert and a radiologist. Laboratory tests such as biological and hematological parameters were evaluated to detect disease progression and treatment responses. Clinical laboratory tests as well as clinical sign and symptoms were identified and recorded during hospital stay. Diabetes, hypertension, cardiovascular, lung disease and kidney disease were diagnosed and confirmed by a physician.

3. Results

A total of 398 patients with the recurrent COVID-19 were included in this study. SARS-CoV-2 infection was confirmed by RT-PCR assay in all patients. Among the identified patients, 251 (63.07%) and 147 (36.93%) cases were males and females, respectively.

The patients had a wide range of age from 2 to 93 years with the median age 49.39 years. The data showed that there is no sharp difference in median age between males (49.28%) and females (49.58%). The majority of patients were 30-40 years old (24.37%), while only 1.6% of patients were children and adolescent (1-20 years old), (Figure 1).

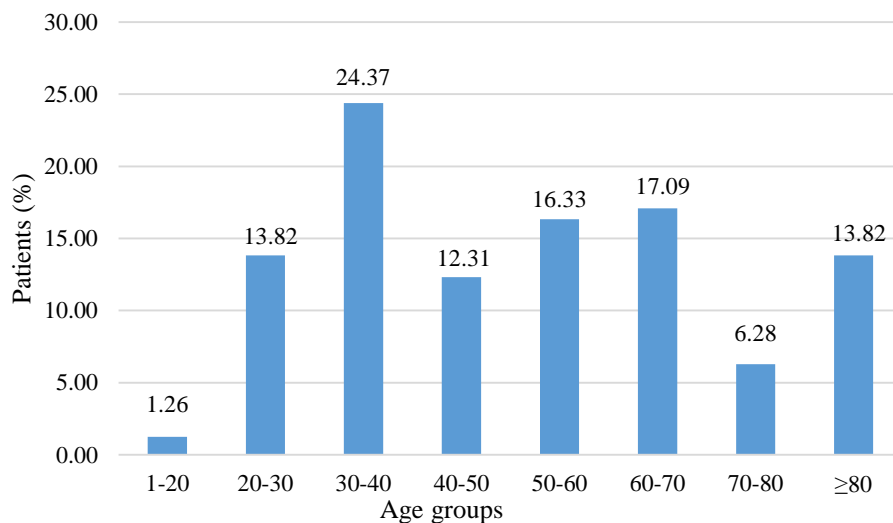


Figure 1. Distribution of patients based on different age groups. The age of patients ranges from 1 to 93 years old. The minimum and the maximum number of recurrent COVID-19 patients were categorized in 1-20 (1.26%) and 30-40 (24.37%) age groups.

The estimated mean period between symptoms onset and hospitalization was 2-7 days. None of the patients were hospitalized in ICU. Among COVID-19 patients, only 25 (6.28%) cases had international travelling and contact with foreign national history.

The clinical signs and symptoms of the recurrent COVID-19 patient outcomes are briefed in Table1. The most common symptoms in these patients were fever, dry cough and dyspnea 140 (35.18%), fever and dry cough 81 (20.35%), fever, dry cough and angina 19 (4.77%), dyspnea 17 (4.27%), dry cough 14 (3.52%), fever, chills and dyspnea 10 (2.51%), dry cough and angina 10 (2.51%), pseudo-influenza 10 (2.51%), fever and myalgia 10 (2.51%), dry cough and chest pain 9 (2.26%), fever 5 (1.26%), fever, stomach pain and nausea 5 (1.26%), fever, dyspnea and fatigue 5 (1.26%), dry cough, headache and diarrhea 5 (1.26%), dry cough, muscle weakness and faintness 5 (1.26%), dry cough and angina 5 (1.26%), chills 5 (1.26%), anosmia, fever and severe myalgia 4 (1.01%), fever, headache, sweating and lack of appetite 4 (1.01%), fever, dry cough and headache 4 (1.01%), dry cough and myalgia 4 (1.01%), fever, dry cough and abdominal pain 4 (1.01%), loss of smell and taste 4 (1.01%).

All patients with the recurrent COVID-19 suffered from underlying diseases. The most prevalent underlying disease were diabetes with 241 (60.55%) cases and hypertension with 97 (24.37%) cases. Other

underlying disease such as cardiovascular, lung and kidney diseases were in low incidence, Figure 2. The number of patients who died was 253 (63.57%) and the major reason of death was respiratory failure owing to diffuse alveolar damage.

4. Discussion

COVID-19 disease has revealed a global distribution caused by SARS-CoV-2 and it is very contagious with large-scale transmission in humans, specifically in patients with underlying diseases. Current study focused on assessment of sign and symptoms, demographic data and risk factors associated with COVID-19 among patients.

Most patients were males (63%), implicating men are more exposed to COVID-19 infection. Thus, social and economic conditions in a community might differently affect the immune response in both male and female which shows the result in the incidence of COVID-19. The adaptive immune system in females act stronger with a large number of CD4+ T cells, CD8+ T cells and immunoglobulin producing B cells[23]. In males, B cells decreases along with age subsequently causes the immune system aging and induces infection [24]. Also, the X chromosome consists of the immune system associated genes [25] and affects IFN production [26, 27]. Also, high level of *estrogen concentration results in IFN production.*

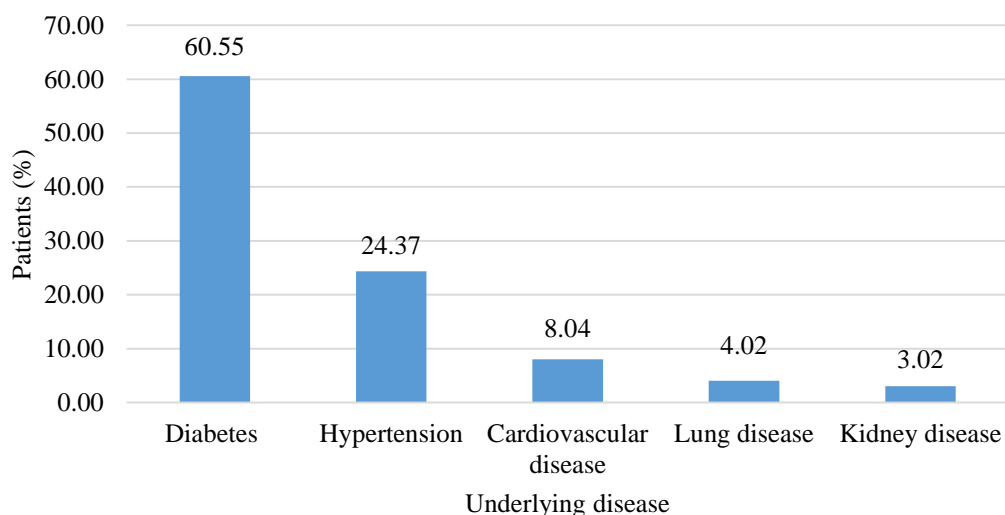


Figure 2. Underlying diseases in COVID-19 recurrent patients. Among hospitalized patients with the recurrent COVID-19, diabetes, hypertension, cardiovascular disease, lung disease and kidney disease were common underlying disease. The most and least common underlying diseases were diabetes 241 (60.55%) and kidney disease 12 (3.02%), respectively.

Table 1. Signs and symptoms in COVID-19 recurrent patients

Signs and symptoms	No (%)
Fever, Dry cough, Dyspnea	140 (35.18%)
Fever, Dry cough	81 (20.35%)
Fever, Dry cough, Angina	19 (4.77%)
Dyspnea	17 (4.27%)
Dry cough	14 (3.52%)
Fever, Shake, Dyspnea	10 (2.51%)
Dry cough , Angina	10 (2.51%)
Pseudo-influenza	10 (2.51%)
Fever, Myalgia	10 (2.51%)
Dry cough , Chest pain	9 (2.26%)
Fever	5 (1.26%)
Fever, Stomach pain, Nausea	5 (1.26%)
Fever, Dyspnea, Fatigue	5 (1.26%)
Dry cough, Headache, Diarrhea	5 (1.26%)
Dry cough, Muscular weakness, Faintness	5 (1.26%)
Dry cough, Angina	5 (1.26%)
Shake	5 (1.26%)
Anosmia, Fever, Severe myalgia	4 (1.01%)
Fever, Headache, Sweating, Inappetence	4 (1.01%)
Fever, Dry cough, Headache	4 (1.01%)
Dry cough, Myalgia	4 (1.01%)
Fever, Dry cough, Abdominal pain	4 (1.01%)
Loss of smell and taste	4 (1.01%)

Thus, both X chromosome and high concentration of estrogen strengthens the immune system in females [28, 29]. An immune response enhancing factor in women is the estradiol hormone, which decreases expression of ACE2 receptors that are used by SARS-CoV-2 for entry to the cell, the ACE2 receptor gene is located on chromosome X [30, 31].

Based on the finding, the mean age of identified patients was 49.39 years while the average age of COVID-19 patients in the USA was 63 years [32] and in China was 45 and 56 years in two different researches [33]. In the present study, most patients were in 30-40 years while in the US the age of 20-49 years were most patients of COVID-19 that this age group distributed SARA-CoV-2 [34].

Symptoms of the disease usually begin with shortness of breath, in some cases a mild illness may occur, and in severe cases the disease may lead to hospitalization. In this study, the mean duration of clinical symptoms to hospitalization was 2-7 days.

Symptomatic patients were powerfully capable to transmit the infection to susceptible individuals.

In the present study none of 398 patients were transferred to the ICU, while in another study, carried out by Abolfathi et al. in 2020, among 85% of identifying patients who were living in town and could be more exposed to the virus, 15% were hospitalized in the ICU [35]. Similar to our study, Yang and et al. reported that none of 149 patients were hospitalized [33].

The most common symptoms in patients identified in this study were fever, dry cough, and dyspnea, which were in accordance with recent researches [36], while only four of the participants in this study reported loss of smell and taste. Other symptoms in our study for example angina, shake, pseudo-influenza, myalgia, stomach pain, nausea, fatigue, headache, diarrhea, muscular weakness, anosmia, sweat, inappetence and abdominal pain have been seeing.

Recurrence of symptoms after completion of treatment for COVID-19 with nirmatrelvir-ritonavir (Paxlovid) is increasingly recognized. In a cohort study, researchers sought to determine how often symptoms of COVID-19 recur if left untreated. The biological basis of this phenomenon is unclear and may be multifactorial, including rapid clearance of nirmatrelvir with delayed immune responses or possible development of drug resistance. The contribution of treatment to symptom recurrence must be distinguished from symptom recurrence that may occur during the natural history of COVID-19. Results in individuals with untreated COVID-19 suggest that recurrent symptoms are more common among those who initially recover. It is common, but these recurring symptoms do not indicate progression to severe COVID-19 [37].

In another study, 33 patients with recurrent COVID-19 and positive PCR were described. Recurrence is associated with work as a health care professional, blood type A, and a low IgG response to infection. Evidence from differential viral sequencing between first and second episodes supports de novo reinfection. Recurrent episodes with a fatal infection were more severe [38].

Studies showed that one of the most significant risk factors in COVID-19 recurrence is underlying diseases such as diabetes that exacerbates the disease fatality [39]. In patients with diabetes, high levels of glucose increases the growth and proliferation of the SARS-CoV-2 [40]. Also, another high-risk group for COVID-19 is hypertension patients, the reason is unknown [41]. Our study showed that a large number of patients with COVID-19 recurrence (60.55%) were diabetic. Thus, after that diabetes, hypertension was the most prevalent underlying disease, among patients (24.37%). This finding is similar to that of studies by Richardson et al. from USA [32] and Zhou et al. from China [42].

According to the findings, only 25 (6.28%) of 398 patients had travelled abroad and had a direct contact with foreigners.

Mortality in COVID-19 recurrence is due to severe lung involvement, underlying diseases or etc. In the present study, the mortality rate among 398 patients with the recurrent disease of COVID-19 was reported 253 (63.57%). While Wang et al. in 2020 in China and Richardson et al. in 2020 in the USA the mortality rate were reported 4.3% and 88.1%, respectively [32, 43].

In this study more severe symptoms and higher mortality in COVID-19 recurrent patients with underlying disease were noted. According to the obtained results, it is recommended to give more attention to COVID-19 recurrent patients with underlying diseases such as diabetes and hypertension. Presenting the results of this study to healthcare staff might help a better understanding of risk-factors associated with the recurrent COVID-19 disease, leading to a better control and management of this patients.

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Authors' contributions

NGF, SM, SS: design of study. NGF, SM, SS, MB, SK, ZRA: acquisition of data. NGF, SM, FRA, AS, FM: evaluation of data, preparation of the manuscript. NGF, SM, SS, MB: assessment of data. All authors read and approved the final manuscript.

Conflicts of interest

The authors have declared that no competing interests exist. All authors have approved this manuscript.

Ethical declarations

The study protocol was approved by the medical ethics committee of Abadan faculty of Medical Sciences (IR.ABADANUMS.REC.1400.055), and written informed consent was obtained from all the patients.

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