COVID-19 patients at referral to hospital during the first peak of disease: Common clinical findings including myalgia and fatigue

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Abstract

The wide range of manifestations and clinical symptoms of COVID-19 has made it a unique disease. Investigating the epidemiology of different clinical manifestations of this disease in patients referred to medical centers is one of the most effective steps in adopting a suitable diagnostic and treatment approach. These findings also provide a basis for comparing the evolution of the virus and its clinical manifestations over time and at different peaks of the disease. Therefore, the present study was aimed at investigating common clinical findings at the time of referral in patients with COVID-19 in Afzalipour Hospital, Kerman, during the first peak of the disease. This descriptive-analytical cross-sectional study was performed on hospitalized patients diagnosed with COVID-19, between March 2020 and June 2020. The patients were included in the study by census method, and the research variables related to demographic indicators, disease course and clinical symptoms were extracted from the patients' medical records, and then subjected to statistical analysis. In this study, a total of 210 patients were examined, consisted mainly of male patients (59.5%). The mean age was found to be 53.95 ± 19.55 years. Also, 20.3% of patients needed admission in the intensive care unit. In addition, 1% of patients were infected in February 2020, 24% in March 2020, 47.4% in April 2020 and 27.4% in May 2020. The mean onset of symptoms until hospitalization was also found as 6.51 days. The most common clinical symptoms included shortness of breath (75.7%), dry cough (52.9%), fever (50.5%), myalgia (45.7%) and fatigue (41.9%). Fever at admission time was significantly more common in ages less than 50 years (p=0.034). Our study showed that the most common clinical symptoms were shortness of breath, dry cough, fever, myalgia and fatigue. No statistically significant difference was found in common symptoms between men and women. Among the common clinical symptoms, only fever at admission time was observed to be significantly higher in those under 50 years of age.

Key Words: COVID-19, clinical symptoms, Kerman, Iran.

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Corona virus disease 2019 (COVID-19) appeared on December 31, 2019 in Wuhan, China and is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from the family of Betacoronavirus genus, and has subsequently developed into a public health emergency in a short time.[1-3] Coronaviruses are a group of viruses that have caused a wide range of diseases, including Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).[4,5] SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus with a length of 30kb.[6-9] Compared with SARS-CoV and MERS-CoV, SARS-CoV-2 was spared rapidly and resulted in much higher number of deaths, e.g., over 5.35 million deaths by December 20, 2021. Although the main way of transmission of SARS-CoV-2 virus has been known to be through respiratory droplets and aerosols generated during coughing or sneezing,[10] various evidences indicate the possibility of transmission of this virus through fecal-oral route as well.[11-13] The identification of the virus in the urine and feces of patients indicates the ability of SARS-CoV-2 in infecting multiple systems including the digestive and urinary systems.[14] Although the pathophysiology of

disease is not exactly known, studies showed that SARS-CoV-2 is capable of binding to the host's receptor, including the human angiotensin-converting enzyme 2 (ACE2) receptor, and enters the cell through spike glycoproteins.[15]

ACE2 receptors are mainly expressed in several organs, including digestive tracts, lungs, kidney tubule epithelium, brain, liver and heart.[16] After entering the cell, the replication of the virus causes the release of cytokines and inflammatory factors, causing the symptoms of this disease.[17] Clinical symptoms of COVID-19 are described to vary from mild or moderate flu-like symptoms to severe pneumonia.[17,18] Classic patients of acute COVID-19 disease are characterized by symptoms of respiratory system infection (including fever, dry cough, and shortness of breath), fever and gastrointestinal problems.[19,20]

A wide range of other symptoms, such as headache, confusion, weakness and lethargy, nausea, vomiting, chills, sore throat insomnia, palpitations, chronic rhinitis, dysgeusia, have been documented as persistent COVID-19 symptoms.[21-23] In addition to the respiratory system, evidences indicate the involvement of the human gastrointestinal tract in the COVID-19 disease, when viral nucleocapsid proteins have been observed in the cytoplasm of gastric, duodenal, and rectal glandular epithelial cells.[24]

The tendency of the SARS-CoV-2 virus to the gastrointestinal tract has been reported to such an extent that some reports have stated that diarrhea appears as the first symptom before respiratory symptoms occur in about 10 to 20% of patients with CCOVID-19 and gastrointestinal symptoms appear predominantly in COVID-19 patients without respiratory symptoms as well.[25,26] The involvement of the digestive system in the disease of COVID-19, not only is capable of causing common manifestations such as diarrhea, anorexia, nausea and vomiting, but also results in some other manifestations,[27] among which gastrointestinal bleeding is one of the sporadic presentations.[28,29] In addition to these manifestations, prothrombic coagulation disorders and thromboembolisms are now known as fatal complications in patients with COVID-19 disease, resulting in high morbidity and mortality. Pulmonary embolism is the most important thromboembolic event in COVID-19 disease, which is caused by increased coagulability and the occurrence of thrombosis and blockage of pulmonary vessels.[30] One of the causes of this complication is the increase of venous thromboses in critically ill patients due to long-term hospitalization, lack of anti-coagulant drugs, and the occurrence of immunothrombosis due to the pathogenesis of the disease.[31,32] Among other manifestations, skin involvement including urticarial lesions, erythematous rashes, maculopapular and vesicular rashs and hair loss (in the form of telogen effluvium) have been reported.[33]

In addition to the acute manifestations of the disease, there are several evidences showing the sub-acute and long-term effects of the COVID-19 disease, which can affect several organs.[34] Initial reports mentioned symptoms such as fatigue, shortness of breath, chest pain, arthralgia, cognitive impairment, and loss of quality of life as long-term symptoms after getting COVID-19.[35,36] These studies found cell damage caused by SARS-CoV-2 invasion, immune system response and production of inflammatory cytokines, as well as creating a hypercoagulable state to be responsible for these long-term symptoms.[37,38] Investigating the clinical features of this disease in patients referred to medical centers is one of the effective steps for a more accurate diagnosis. Therefore, we report here results describing the common clinical features at the time of admission from a cross-sectional study of patients treated for COVID-19 in Afzalipour Hospital in Kerman city, during the first peak of the disease.

Materials and Methods

This descriptive and analytical cross-sectional study was conducted on hospitalized patients diagnosed with COVID-19 in Afzalipour Hospital, Kerman. The study was approved by the research ethics committee of Kerman University of Medical Sciences with ID IR.KMU.REC.1399.002. Access to clinical records was made after obtaining the necessary permits. Patients' identities were kept confidential when reporting the results.

Table 1. *Frequency distribution of vital signs at admission of the studied patients.*

Variable		Frequency percent
Breathing rate (breaths per minute)	less than 21	69.6
	Greater than or equal to 21	30.4
Number of heartbeats (beats per minute)	Less than 100	66.1
	Greater than or equal to 100	33.9
Cytolic blood pressure (mm of mercury)	Less than 100	5.6
	100 to 140	76.8
	Greater than 140	17.6

Table 2. *Frequency distribution of clinical symptoms of patients with Covid-19.*

CLINICAL SYMPTOMS	FREQUENCY	PERCENT
Fever being hospitalization	106	50/5
Fever during hospitalization	20	9/5
Rrunny nose	6	2/9
Dry cough	111	52/9
Productive cough	23	11/0
Shortness of breath	159	75/7
Pleuritic pain	6	2/9
Diarrhea	21	10/0
Nausea and vomiting	40	19/0
Sore throat	33	15/7
Headache	44	21/0
Ttiredness	88	41/9
Myalgia	95	45/7
Shivering	56	26/7
Sweating	16	7/6
Hoarseness	7	3/3
Hemoptysis	7	3/3
Stomach ache	7	3/3
Feeling of pressure in the chest	45	21/4
Anorexia	54	25/7

Inclusion criteria included:

1. Confirming the diagnosis of COVID-19 based on a positive PCR test or CT scan findings 2. Hospitalization at Afzalipour Hospital in Kerman between March 2018 and May 2019.

Exclusion criteria were:

1. Deficiency of more than 70% of the studied variables.

The current study was carried out by census method and all patients who met the inclusion and exclusion criteria of the study were examined. The data was collected by an information collection checklist in which the demographic variables of the patients and the variables related to the course of the disease extracted from the medical records were recorded.

After making the necessary administrative arrangements and obtaining the baseline permit upon arrival, the baseline heart rate, the number of days of hospitalization in the intensive care unit (ICU) and the baseline clinical symptoms (i.e., fever, runny nose, cough, shortness of breath, pleuritic pain, diarrhea, nausea and vomiting, sore throat, headache, fatigue, myalgia, chills, etc.). The collected data were then statistically analyzed to describe the frequency of the most common clinical findings and compare them according to the characteristics of the patients. The collected data were statistically analyzed using IBM SPSS version 26.0 for Windows. In order to describe the research data, descriptive statistics indicators including frequency, percentage, mean and standard deviation were used. Chi-square test was applied to compare clinical symptoms according to patients' characteristics. A p-value < 0.05 was considered to be statistically significant.

Results

In this study, a total of 210 patients were examined. The study population consisted of 59.5% men and 40.5% women. The mean age of the patients was found to be 53.95 ± 19.55, ranging from 3 to 91 years. The mean and standard deviation of the number of days from the onset of symptoms to hospitalization in the research sample were 6.51 and 6.34 days, respectively, ranging from 0 to 32 days. In terms of the time of infection of the examined patients during the emergence of the COVID-19 pandemic, 1% of the patients had symptoms in February 2020, 24% in March 2020, 47.4% in April 2020 and 27.4% in May 2020. Based on the recorded data, 48.6% of the patients had evidence of COVID-19 involvement in chest CT scan and 54.8% had a positive PCR test (Chart 2). Furthermore, 20.3% of the investigated patients needed hospitalization in the ICU, while 79.7% were only hospitalized (Chart 4-4). In addition, the mean and standard deviation of the duration of hospitalization in ICU were found to be equal to 7.54 and 6.35 days, respectively. Table 1 shows the frequency of vital signs before hospitalization. As shown, 30.4% of patients had tachypnea on admission followed by 33.9% tachycardia. Additionally, 5.6% of the patients had a systolic blood pressure of less than 100 and 17.6% had a systolic blood pressure of more than 140. Table 2 shows the frequency of clinical symptoms of patients with Covid-19. As shown, the most common clinical symptoms were dyspnea (75.7%), followed by dry cough (52.9%), hospitalization fever (50.5%), myalgia (45.7%) and fatigue (41.9%). Symptoms such as runny nose (2.9%), pleuritic pain (2.9%), hemoptysis (3.3%), abdominal pain (3.3%) and hoarseness (3.3%) were less common reported symptoms.

Our results revealed that fever at hospitalization time was more common in men (54.4%) than in women (44.7%).

Table 3. *Comparison of common clinical symptoms of examined patients according to gender.*

Clinical symptoms	sex	Frequency	Percent	p-value
Shortness of breath	Female	66	77.6	0.590
	Male	93	74.4	
Dry cough	Female	46	54.1	0.763
	Male	65	52.0	
Fever during hospitalization	Female	38	44.7	0.168
	Male	68	54.4	
Myalgia	Female	44	51.8	0.147
	Male	52	41.6	
Tiredness	Female	41	48.2	0.125
	Male	47	37.6	

Furthermore, myalgia was more common in women (51.8%) than men (41.6%). Fatigue was also reported in women (48.2%) more than men (37.6%), while the prevalence of shortness of breath and dry cough was almost similar between the two sexes. However, the statistical comparison using the chi-square test demonstrated that the difference in common symptoms between men and women was not statistically significant ($p<0.05$) (Table 3).

Comparison of the most common clinical symptoms of patients according to age showed that shortness of breath was more common in patients over 50 years of age than in patients under 50 years of age (81.1% vs. 70.6%), while fever at hospitalization time in patients under 50 years of age was more common in patients under 50 years of age (51.2 %) compared to those over 50 years old (45.9%). Myalgia was more common in people under 50 years old (54.1%) than in subjects over 50 years. Chi-square test revealed that the difference between age groups was statistically significant regarding fever at hospitalization time ($p=0.034$), but not in other variables ($p>0.05$; Table 4).

Discussion

The results of the present study are in line with an extensive international literature.[1-64] Across the globe, COVID-19 disease patients present with a wide range a broad spectrum of manifestations. These manifestations ranged from symptoms caused by the involvement of the respiratory system, such as cough and shortness of breath, to manifestations caused by the involvement of other body systems, such as skin involvement and hair loss, gastrointestinal bleeding, cardiovascular complications, etc. Epidemiological examination of the clinical findings of patients with COVID-19 at any point in time and geographical area is one of great importance in the accurate and timely diagnosis of the disease. Therefore, this cross-sectional study aimed at examining the characteristics and clinical findings of patients treated for COVID-19 in Afzalipour Hospital in Kerman city, during the first peak of the disease. The findings of our study showed that the majority of hospitalized patients during the first peak of the COVID-19 disease were men (59.5%). This finding is in line with previous studies conducted in the world and Iran.[39-42]

Table 4. *Comparison of common clinical symptoms of examined patients according to age.*

Clinical symptoms	Age	Frequency	Percent	p-value
Shortness of breath	Less than 50 years	60	70.6	0.086
	More than 50 years	90	81.1	
Dry cough	Less than 50 years	49	57.6	0.452
	More than 50 years	58	52.3	
Fever during hospitalization	Less than 50 years	52	61.2	0.034
	More than 50 years	51	45.9	
Myalgia	Less than 50 years	46	54.1	0.131
	More than 50 years	48	43.2	
Ttiredness	Less than 50 years	36	42.4	0.802
	More than 50 years	49	44.1	

It seems that the male sex is more at risk of being hospitalized due to COVID-19. In this regard, some studies have presented hypotheses about the role of gender in COVID-19 pandemic. One of these hypotheses deals with the role of the ACE2 receptor, which is one of the main receptors of the SARS-CoV-2 virus. This receptor is encoded by a gene on the X chromosome and its expression is reduced by estrogen. Therefore, some researchers have attributed to this receptor the greater vulnerability of male patients.[43] Some researchers have also mentioned the protective role of estrogen hormone against underlying diseases in women as the reason for fewer hospitalizations of women, especially at younger ages. Other studies reported that more interferon production from plasmacytoid cells in women compared to men, as one of the reasons for less hospitalization of women.[43,44] On the other hand, a stronger immune inflammatory response to the SARS-CoV-2 virus in men could be another reason.[45] While a meta-analysis study examining more than three million patients, did not show gender difference in COVID-19, men had approximately 3- and 1.4-times odds of admission to the ICU and death, respectively, indicating greater vulnerability of males.[46]

Regarding age susceptibility, our study shows that the average age of hospitalized patients was approximately 54 years. This finding is consistent with many similar studies where the average age of patients requiring hospitalization is over 50 years. For example, two studies in Iran have reported the average age of patients to be 53.75 and 60 years.[42,47] De Souza et al. (2020)[40] reported in their study in Brazil that 65.5% of patients with COVID-19 were over 50 years old. In justifying these findings, the researchers are of the opinion that aging is associated with dysfunction of the immune system and the creation of a chronic pro-inflammatory state in the body, and on the other hand, sexual protective hormones, which have an anti-inflammatory function by nature, are decreasing with increasing age, leading to an increase in susceptibility to disease.[45,48] In addition, the increase of underlying diseases in older age makes people more susceptible to infectious diseases.[45]

The examination of the most common clinical symptoms at the time of presentation in patients with COVID-19 showed that shortness of breath (75.7%) and cough (52.9%) were the most common clinical findings in the patients referred during the first peak of the disease in Afzalipour Hospital, Kerman, Iran. These results are in line with those of Goyal and colleagues (2020)[49] in the United States of America, who showed that cough (79.7%) and shortness of breath (56.5%) were among the most common clinical symptoms of patients with COVID-19. In the initial investigations in China, Huang and Xu (2020)[1] reported that cough was one of the most common findings in patients (about 80% of hospitalized patients showed this as their main symptom)[1,50] In a systematic review at the beginning of the COVID-19 pandemic, others demonstrated that cough was one of the common symptoms of the disease (54.52%).[50,51] All these findings indicated that the respiratory system was the main target of the SARS-CoV-2 virus in the dominant variant of the first peak of COVID-19, resulting in respiratory manifestations. These findings are also related to the transmission of the virus through respiratory droplets, and coughing as a reflex to remove secretions from the airways has been one of the most effective ways to transmit the disease. The high prevalence of shortness of breath is related to the involvement of the lung parenchyma and the greater severity of the disease. Radiological findings such as consolidation and ground-glass opacities, especially in the periphery of the lung, were also effective indicators in the diagnosis of the disease in the first peak of the disease, suggesting the involvement of the lung parenchyma. Therefore, in the clinical examination, attention should be paid to increase in breathing rate, the use of secondary respiratory muscles, voice tremors, weakening of breathing sounds, or muffled chest sounds.

In the present study, fever (50.5%) was the third most common clinical symptom in COVID-19 hospitalized patients, in agreement with a systematic review stating that fever (58.66%) was the most common clinical finding in patients with COVID-19.[51] Fever was also a common clinical symptom (79.6%) in the study of De Souza et al. (2020).[40]

Studies in Iran have also considered fever as one of the common clinical symptoms at the time of hospitalization.[41,47,52] It should be taken into consideartion that although fever is one of the common clinical symptoms of patients, the absence of fever in the initial screening does not rule out the disease. For example, Guan et al. (2020)[53] showed that only 42.8% of patients had fever at admission, while 88.7% developed fever during hospitalization. Our study reveal that fever at admmission was significantly higher in patients under 50 years of age (61.2%) than in patients over 50 years of age (45.9%). This point indicates that fever may be a less common manifestation of the disease at older ages due to the weakening of the immune system and the presence of underlying diseases related to immunodeficiency. This group of patients needs more attention to other clinical symptoms in the absence of fever.

Other common clinical findings in our study were myalgia (45.7%) and fatigue (41.9%), in agreement with other studies. For instance, Javanian et al. (2020)[52] found in Babol city, north of Iran, that fatigue (77%) and myalgia (50%) were among the most common clinical symptoms of patients with COVID-19. In the study by Sobhani et al. (2020)[47] in Mashhad city, Northeast of Iran myalgia was reported in 31.3% of cases and in the study by Shahriarirad et al. (2020)[42] in Tehran, fatigue was reported in 66.4% of cases. Mechanistically, fatigue and myalgia reflect the generalized inflammation and cytokine response during infection. During COVID-19 disease, cell damage increases the level of lactate, decreases cellular pH and the oxygen transport capacity of erythrocytes is disturbed. Due to the expression of

ACE2 receptors in the skeletal muscle system, this system is also subject to involvment with the virus and will be associated with an increase in creatine kinase. Furthermore, the body is in a condition of hypoxia and acidosis due to respiratory involvement. All conditions that may cause of fatigue and myalgia in COVID-19.

Although clinical findings such as anorexia (25.7%), sore throat (15.7%), nausea and vomiting (19%), headache (21%) and diarrhea (10%) were less common in our study, many studies also reported different prevalence for these less common symptoms. Goyal et al. (2020)[49] in the United States of America reported a lower prevalence of gastrointestinal symptoms such as nausea and vomiting (19.1%) and diarrhea (23.7%) compared to other symptoms at the beginning of the pandemic. In the study of Javanian et al. (2020)[52] the prevalence of diarrhea was 14%. All together, these findings demonstrate that respiratory symptoms and non-specific symptoms such as fatigue and myalgia, were more prevalent at the beginning of the COVID-19 pandemic.

In conclusion, we showed that 59.5% of hospitalized patients during the first peak of the COVID-19 disease were men, and that the average age of the patients was 53.95 years. There was no gender difference in common symptoms, while fever at admission time was significantly higher in those under 50 years of age. The most common clinical symptoms included shortness of breath (75.7%), dry cough (52.9%), fever (50.5%), myalgia (45.7%) and fatigue (41.9%).

Of course, future cross-sectional studies will be needed to compare the clinical manifestations during subsequent spikes related to different variants of SARS-CoV-2.

List of acronyms

ACE2 - angiotensin-converting enzyme 2
COVID-19 – Corona virus disease 2019
MERS - Middle East Respiratory Syndrome
SARS - Severe Acute Respiratory Syndrome
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

Contributions of Authors

Study conception and design: AH, AS, FS; Data collection: EA; Data analysis and interpretation: AH, AS, FS; Drafting of the article: AS.

All authors participated in critical revision of the manuscript.

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Conflict of Interest

The authors declare no conflict of interests.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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