Delayed Symptoms in Patients Recovered from COVID-19

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Abstract

Background: COVID-19 is a new disease, so we don't know what comes next. Since information on delayed symptoms is limited, this study was conducted to assess the frequency of delayed symptoms in patients with COVID-19.
Methods: This follow-up cross-sectional study was conducted in a referral general hospital in Tehran, Iran from Feb to Apr 2020. Two hundred patients hospitalized for COVID-19 and were discharged were assessed for delayed symptoms 6 wk after discharge.
Results: The mean age of the participants was 55.58±13.52, and 160 (80%) Of them were male. On admission to hospital, patients reported a mean of 5.63±2.88 symptoms per patient, range from 1 to 14 symptoms. Dyspnea was seen in 119 (59.5%) 0f them as the most frequent symptom. Then weakness, myalgia, and shivering were reported with a frequency of 111 (55.5%), 107 (53.5%), and 103 (51.5%), respectively. Six weeks after discharge reassessment was done. None of the patients was readmitted to the hospital. Ninety-four (42%) of them were symptom-free. Fatigue was the most frequent delayed symptom with a frequency of 39 (19.5%), and then dyspnea, weakness, and activity intolerance with a frequency of 37 (18.5%), 36 (18%), and 29 (14.5%) were reported, respectively.
Conclusion: Fatigue, dyspnea, weakness, anxiety, and activity intolerance were most frequent delayed symptoms, respectively. Majority of patient was symptoms free and those with symptom, had mild to moderate symptoms. The importance of symptoms is not fully recognized. Follow up clinics and in some cases rehabilitation programs may be helpful.

Keywords: COVID-19; Fatigue; Activity intolerance; Rehabilitation

Introduction

In late Dec 2019, the first cases of pneumonia were reported in Wuhan, China. On Jan 12, 2020, the WHO temporarily named the new virus as the novel 2019 coronavirus. Then, on Jan 30, 2020, the WHO declared the 2019 new coronavirus epidemic a public health emergency of international concern (1). On Feb 11, 2020, the WHO officially named the disease caused by the new coronavirus COVID-19(2, 3).

Over time, data on the clinical symptoms of COVID-19 increased. Fever, cough, myalgia or fatigue, severe dyspnea and pneumonia are the most common symptoms, while diarrhea, headache, rhinorrhea and sputum production and

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hemoptysis are less common symptoms (4, 5). In severe cases, complications have been seen in the cardiovascular, renal and pulmonary systems (6). Patients with mild symptoms recover after 1 week, while severe alveolar damage and progressive respiratory failure may lead to death (7). However, we do not know if these symptoms will end with discharge or not.

ARDS is the most common pulmonary complication of COVID-19. ARDS has some long-term side effects including, pulmonary function decline, cognitive impairment and memory loss, posttraumatic stress disorder, depression, anxiety, muscle weakness, ambulatory dysfunction, and overall poor quality of life (8). We have a history of long-term complications of SARS coronavirus in 2003. Patients had symptoms of persistent fatigue, diffuse myalgia, weakness, and depression. They had these symptoms for a long time after discharge (9). The data about long-term complications and symptoms of COVID-19 is lacking. Moreover, we do not know that SARS data are reproducible or not?

The disease has different clinical courses from mild to severe (10). Therefore, information on delayed symptoms is limited. This study was conducted to assess the frequency of delayed symptoms in patients with COVID-19.

Materials and Methods

Study design

In a follow-up cross-sectional study that was done from Feb to Apr 2020 in a referral general hospital in Tehran, Iran. This hospital had the highest number of COVID-19 visits in the country. Different range of treatment modalities were used including, antivirals, hemoperfusion, plasma exchange therapy, extracorporeal membrane oxygenation (ECMO), and so on.

Totally 300 patients with COVID-19 hospitalized due to moderate to severe symptoms and were discharged from hospital were recruited. Six weeks after discharge using convenient sampling method Patients were selected. The sample size was calculated using Cochran's formula. For test-

ing the difference between two ratios and taking into account the test power (0.9) and reliability coefficient (0.95), the number 270 people were calculated and by considering a 10% attrition in samples, 300 patients were considered. Inclusion criteria were all hospitalized patients with COVID-19 recovered and then discharged 4wk earlier. These patients also had to be able to communicate. The COVID-19 was confirmed in all cases using the real-time reverse transcriptase PCR of nasal and pharyngeal swab specimen for SARS-CoV2 RNA. These patients were asked to participate in a telephone survey 6 wk after discharge. Patients recovered from COVID-19 6 wk after discharge were included. Moreover, they were able to communicate.

Data collection and variable measurement

The instruments used in the study, contains a two-part questionnaire, one of related to the demographic data and disease history such as (age, gender, education, comorbidities, the number of days of hospitalization, failure of vital organs, consumed drugs and chest computerized tomography (CT) and treatment modalities). Part II; the questionnaire was clinical symptoms that were measured two times: during hospitalization and delayed 6 wk of the discharged, which included general symptoms (fever; headache; weakness and fatigue; muscle pain; and activity intolerance); Gastrointestinal (nausea and vomiting; anorexia; diarrhea; dyspepsia; taste disorder and weight loss); Respiratory symptoms (sneezing; cough; sore throat; sputum and shortness of breath; odor disorder); Psychological symptoms (anxiety; lack of concentration; low mood; irritability and sleep disturbance) and others.

The first part of questionnaire was completed during the arrival of patients to emergency room. The emergency medical specialist assessed the patients sign and symptoms. All treatment modalities and drugs were recorded. Then chest CT scans were analyzed by radiologist and reported data were recorded. The hospital stay time interval was calculated from emergency arrival to discharge.

Six weeks after discharge, the remained symptoms were asked by telephone. First, they asked about general condition. The researcher then reads the symptoms and asks the patient to determine their presence or absence. Finally, they were asked if they have any extra symptoms. After that, patients' questions about issues such as, activity, nutrition, and sexual function were replied. In case of patient request or researcher assessment of the need for a physician visit, planning was done. Moreover, they were informed about symptom management based on the initial assessment.

Statistical methods

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) 19.0 statistical package (Chicago, IL, USA) and a two-side *P*-value more than 0.05 was considered as a statistically significant difference. Categorical variables are presented as frequency rates and percentages, and continuous variables are described using mean ± standard deviation (SD) values. Data analysis was performed using descriptive and inferential statistics (independent t-test, Chi-square, Multinomial logistic regression). The normality of numeric variables was tested using Kolmogorov-Smirnov test. The comparison of demographic characteristics were done by independent t-test for continuous variables and Chi-square test or Fisher's exact test for categorical variables.

A binary regression test was performed to assess relation of basic and demographic data, treatment modalities, chest CT scan findings, and initial symptoms with the delayed symptoms.

Ethics

After getting permissions from the Ethics Committee of Baqiyatallah University of Medical Sciences with code number ID: IR.BMSU.REC.1399.076. In the first step, the research objectives were explained to participants and verbal consent was obtained from them. Besides, the questionnaires were anonymous and kept in a safe place. The participants had the right to withdraw from the study.

Results

Totally 300 participants were invited to participate in the study. Initial data were collected for not all of them, but after 6 wk 80 patients were available to respond to the telephone and 20 patients were not satisfied to participate in the study. Finally, 200 of them were able to complete the follow-up. The mean age of the participants was 55.58±13.52, and 160 (80%) Of them were male. Other demographic and patient characteristics are presented in Table 1.

Table 1: Baseline demographic and clinical characteristics of the Patients Diagnosed with COVID-19

Variables	
Demographic characteristics	
Age (mean ± SD)	55.58±13.52
Gender (male, %)	160 (80)
Body mass index (mean ± SD)	25.93±4.38
Smoking (yes, %)	45(22.5)
Opium history (yes, %)	6 (3)
Hospital stay (mean ± SD)	6.30±3.47
Comorbidities	
Renal diseases (yes, %)	3 (1.5)
Diabetes mellitus (yes, %)	45 (22.5)
Malignancy (yes, %)	7(3.5)
Respiratory disease (yes, %)	29(14.5)
Heart disease (yes, %)	32(16)
Hypertension (yes, %)	48 (24)

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Patients reported a mean of 5.63±2.88 symptoms per patient, range from 1 to 14 symptoms. Dyspnea was seen in 119 (59.5%) 0f them as the most frequent symptom. Then weakness, myalgia, and shivering were reported with a frequency of 111 (55.5%), 107 (53.5%), and 103 (51.5%), respectively. Other symptoms are reported in Table 2.

Table 2: Clinical Symptoms of the Patients Diagnosed with COVID-19

Variables	Admission Frequency (%)	Post-discharge Frequency (%)
Fever	87(43.5)	3(1.5)
Dyspnea	119(59.5)	37(18.5)
Cough	88(44)	23(11.5)
Myalgia	107(53.5)	16(8)
Activity intolerance	21(10.5)	29(14.5)
Fatigue	22(12.5)	39(19.5)
Weakness	111(55.5)	36(18)
Weight loss	13(6.5)	15(7.5)
dizziness	21(10.5)	6(3)
headache	68(34)	7(3.5)
Shivering	103(51.5)	1(0.5)
Otalgia	16(8)	1(0.5)
Sore Throat	31(15.5)	7(3.5)
Sputum	27(13.5)	11(5.5)
Sneezing	1(0.5)	1(0.5)
Rainfall	16(8)	2(1)
Odor disorder	26(13)	13(6.5)
Taste disorder	31(15.5)	8(4)
Nausea	66(33)	3(1.5)
Vomiting	15(7.5)	1(0.5)
Diarrhea	41(20.5)	5(2.5)
Anorexia	19(9.5)	4(2)
Dyspepsia	1(0.5)	2(1)
Anxiety	70(35)	30(15)

Six weeks after discharge from the hospital, patients were asked by telephone about their symptoms. None of the patients was readmitted to the hospital. Most of the symptoms were mild to moderate and were easily managed by patients and their families at home. They experienced a mean of 1.45±2.02 symptoms, range from 0 to 9 symptoms. Ninety-four (42%) of them had no symptoms. Sixteen patients reported more than 5 symptoms. Fatigue was the most frequent symptom with a frequency of 39 (19.5%), and then dyspnea, weakness, and activity intolerance with a frequency of 37 (18.5%), 36 (18%), and 29 (14.5%) were reported respectively. Other data is presented in Table 2.

The binary regression showed that there is no predictive variable for the severity of delayed symptoms based on different variables including demographic data, disease history, admission symptoms, Chest CT scan findings, and the treatment modalities.

Discussion

This study evaluated the frequency of delayed symptoms in patients with COVID-19. The pre-

sent study is innovative because, as far as we know, only limited studies have been done in patients recovered from the novel coronavirus to determine long-term problems and other symptoms.

While a large number of patients who have been facing COVID-19 have fully recovered, a small but substantial number of patients whose symptoms continue for weeks and even months after first recovery are increasingly concerned. According to recent research from King's College London, around five percent of COVID-19 patients experienced long-term symptoms for at least one month or more(11).

Similar to the findings of other studies, most of the patients recovered from COVID-19 and were symptom-free (12), however, even for people who have officially recovered, back to normal may be a long process (13). WHO estimates that for patient in critical condition, it can take 6 wk or longer to fully recover (14). In recent study, patients reported a range from 1 to 14 symptoms at admission time while 6 wk post-discharge, they experienced a range from 0 to 9 symptoms and none of the patients were readmitted to the hospital. In our study, the patients' evaluation took place at least 6 wk after discharge and different results may be reported by changing the time interval.

The most frequent delayed symptom were, fatigue, dyspnea, weakness, anxiety, and Activity intolerance, respectively (from 19.5% to 15%) and the other symptoms were in minimum range (from 1% to 8%).

Fatigue was the most frequent delayed symptom. Prolonged fatigue is well established after other viral infections such as the Epstein-Barr virus, and Post-viral fatigue was also seen in a quarter of those infected with the original SARS virus in Hong Kong in 2003 (15, 16). Fatigue was also evident 4 years after SARS (17). Fatigue was seen in 53.1% of patient with COVID-19 one month after infection (18). Although it's a respiratory illness, we're also thinking about fatigue and mental health (19).

In our study, dyspnea was seen in the patients as the second frequent symptom. COVID-19 often targets the respiratory system, and feeling back to

complete pulmonary recovery may be a long process (20). Moreover, some people are prone to developing cardiomyopathy several weeks after recovering from COVID-19. Therefore, worrying about the dangerous delayed consequences of COVID-19 is a real and important concern (21).

After recovering from a moderate case of COVID-19, expecting prolonged fatigue, cough and even shortness of breath for several weeks after recovery is likely (21). However, within two years after the SARs in 2003 were mostly healed Lung damage and pulmonary function test findings that were evaluated by interstitial changes marked on lung CT scans (22) but recovered patients from the new coronavirus have not followed long enough for respiratory complications. Most of delayed symptoms were mild to moderate and were easily managed by the patients and their families at home. Encouraging the patients to walk, even if at home, can improve general condition (13).

Weakness, anxiety and activity intolerance were reported as other frequent delayed symptoms. "Adult patients may experience difficulties resuming the activities of daily life or struggle to return to work. Moreover, patients may suffer from muscle weakness and chronic pain"(23) .

Neurological and psychological issues in critically ill COVID-19 patients might be seen after discharge. ARDS survivors frequently have increased rates of depression and anxiety, and many experience post-traumatic stress (24). During the SARS outbreak, recovered patients scuffled with psychological distress and stress for at least one year after outbreak. However, it is still too early to assess the psychological effects of patients recovering from COVID- 19. Some studies were showed about two months after infection, was developed some symptoms, including headaches, extreme and chronic fatigue, diarrhea, nausea, tremors, difficulty concentrating, and short-term memory loss (21, 25). People suffering from PICS (post ICU syndrome) may experience anxiety, sleep difficulties, depression, or post-traumatic stress disorder (PTSD) (26). Fear of complications and limited human communication may cause anxiety (27). In some cases PTSD

has been reported. Cognitive decline can be due to the direct pathogenesis of the virus or immune-mediated mechanisms (28).

The binary regression showed that there is no predictive variable for the severity of delayed symptoms based on different variables including demographic data, disease history, admission symptoms, Chest CT scan findings, and the treatment modalities. Although some factors such as older age; and some laboratory factors on admission such as elevated lactate dehydrogenase and C-reactive protein, direct bilirubin, blood urea nitrogen, and lower albumin related to severe COVID-19 (29). This predictor variable investigate for predicting severe COVID-19 in beginning of the disease. However, in our study predictive variable were checked for the severity of delayed symptoms. In addition, the severity of disease was not predictive of delayed symptoms.

Symptoms can be looked at separately and planned, or be seen as a general pathology named fatigue syndrome. Fatigue syndrome is overlap of mood, behavioral, and biological components. This syndrome includes symptoms such as cognitive dysfunction, memory decline, unrefreshing sleep, fatigue, muscle and join pain, and headache (30). Association between this syndrome and infection has previously been reported (31). The cause of the syndrome is not well understood. Some attribute it directly to the virus and the presence of virus DNA, and some attribute it to psychological origin (32, 33). The important points about this syndrome are its long duration and the need for follow-up and intervention.

Hospitals are focusing on the acute phase of the disease while monitoring long-term complications is essential. Most patients need rehabilitation and in most cases, follow-up clinics are needed in problems, such as nutrition consult for taste and odor disturbances, psychological consult for cognitive and behavioral disorders, and rehabilitation for fatigue and activity intolerance. Of course, accurate interventions require accurate identification of pathology.

Limitation

Because COVID-19 is a new disease, so we do not know what comes in next. Moreover, the experience from SARs in 2003 shows that long term complications are common. The time interval from infecting may change the view about residual or long-term symptoms. We evaluated only one hospital. Although the hospital is a referral, but our sample size is small for generalizations. The patients' symptoms are only evaluated based on their report on telephone. A comprehensive physical examination and mental status check could be more useful. Besides, checking the outcomes by relevant questionnaires or tests could improve our insight. For example, physical functioning could be assessed by 6 min walking test. Para clinic testing for long-term complications and organ damage could be used as complementary data. Chest CT scan, liver and renal function test are some examples.

Conclusion

Fatigue, dyspnea, weakness, anxiety, and activity intolerance were most frequent delayed symptoms, respectively. Majority of patient were symptoms free and those with symptom, had mild to moderate symptoms. The importance of symptoms is not fully recognized. Follow up clinics and in some cases, rehabilitation programs may be helpful.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

lah medical science university, for providing data on patients with COVID-19.

Conflicts of interest

The authors declare no conflict of interest

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