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Original Article

Risk Factors Associated with Long COVID Syndrome: A Retrospective Study

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What's Known

- People reporting long-term symptoms associated with COVID-19, (Long COVID Syndrome), have complained of various problems, including respiratory, cardiovascular, musculoskeletal, and neurological problems. However, the extent and characteristics of such post-acute phase lingering symptoms are not clear yet.

What's New

- Long COVID syndrome (LCS) is a frequent and significant and at times, disabling condition. In this large population-based study, we reported that LCS has significant associations with sex (more observed in women), respiratory symptoms at the onset, and the severity of the illness (length of hospital stay).

Abstract

Background: Recently, people have recognized the post-acute phase symptoms of the COVID-19. We investigated the long-term symptoms associated with COVID-19, (Long COVID Syndrome), and the risk factors associated with it.

Methods: This was a retrospective observational study. All the consecutive adult patients referred to the healthcare facilities anywhere in Fars province from 19 February 2020 until 20 November 2020 were included. All the patients had a confirmed COVID-19 diagnosis. In a phone call to the patients, at least three months after their discharge from the hospital, we obtained their current information. The IBM SPSS Statistics (version 25.0) was used. Pearson Chi square, Fisher's exact test, *t* test, and binary logistic regression analysis model were employed. A P value of less than 0.05 was considered to be significant.

Results: In total, 4,681 patients were studied, 2915 of whom (62.3%) reported symptoms. The most common symptoms of long COVID syndrome were fatigue, exercise intolerance, walking intolerance, muscle pain, and shortness of breath. Women were more likely to experience long-term COVID syndrome than men (Odds Ratio: 1,268; 95% Confidence Interval: 1,122-1,432; P=0.0001), which was significant. Presentation with respiratory problems at the onset of illness was also significantly associated with long COVID syndrome (Odds Ratio: 1.425; 95% Confidence Interval: 1.177-1.724; P=0.0001). A shorter length of hospital stay was inversely associated with long COVID syndrome (Odds Ratio: 0.953; 95% Confidence Interval: 0.941-0.965; P=0.0001).

Conclusion: Long COVID syndrome is a frequent and disabling condition and has significant associations with sex (female), respiratory symptoms at the onset, and the severity of the illness.

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Keywords ● COVID-19 ● Medicine ● SARS-CoV-2 ● Viruses

Introduction

It has been more than a year since the start of the coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory syndrome (SARS)-coronavirus-2 (SARS-CoV-2). During the early stages of the pandemic, people were mainly concerned with its fatality, and later on, everybody noticed the psychosocial consequences of the pandemic. More recently, people have recognized the post-acute phase lingering symptoms of the disease.[1, 2] Many COVID-19 survivors have reported a

variety of persistent signs and symptoms after the acute phase of the illness.[3]

Although there is no universally accepted terminology and definition for this condition, some authors have considered the persistence of symptoms (fatigue, breathlessness, cough, joint pain, chest pain, muscle aches, headache, and several others, which could not be attributed to any other cause) beyond two weeks for mild disease, beyond four weeks for moderate to severe illness, and beyond six weeks for critically ill patients as "long COVID syndrome" (LCS).[4] The National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) have jointly developed the following definitions: a. ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks and b. post-COVID-19 syndrome: signs and symptoms developed during or after an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained through an alternative diagnosis.[5]

The etiology and the biological underpinnings of LCS are not clear yet. However, SARS-CoV-2 invades many tissues and has multi-organ and multi-system impacts.[6] In addition, the persistence of viremia and psychological factors may also contribute to the development of LCS.[7,8] People reporting long-term symptoms associated with COVID-19 have complained of various problems, including respiratory, cardiovascular, musculoskeletal, and neurological problems.[9-12] Meanwhile, the extent, characteristics, and the associated factors of such post-acute phase lingering symptoms are not entirely clear yet.

In the current population-based study, we investigated the full spectrum of symptoms of patients suffering from LCS (based on the literature review and consultations with experts in the field). We also examined the chronicity of the symptoms to add to the existing literature. Finally, we scrutinized the potential risk factors associated with the development of LCS in a large cohort of patients with documented COVID-19 to add to the existing literature.

Methods

Participants

In this retrospective, uncontrolled, and observational cohort work, all the consecutive adult patients, 18 years or older, were referred and admitted to healthcare facilities (55 centers) throughout Fars province (located in the South of Iran with a population of 4,851,000 people) from February19, 2020 to November 20, 2020. The Shiraz University of Medical Sciences Institutional Review Board approved this study (IR.SUMS.Rec.1399.022). All the participants consented orally: (We conduct the research to investigate the lingering symptoms of the COVID-19. Do you agree to participate in this study and answer our questions over the phone?).

All the patients had a confirmed COVID-19 diagnosis with a positive result on Real-Time polymerase chain reaction (PCR) testing of nasopharyngeal and oropharyngeal samples. All the samples were taken at the emergency room.

Data Collection

For each patient, admitted with a diagnosis of COVID-19, the following data were collected at the emergency room by the admitting physician and entered into a database (on admission): age, sex, presence of fever, cough, respiratory distress, muscle pain, change in mental status, loss of smell, dizziness, headache, abdominal pain, nausea, vomiting, and anorexia. Other collected data included: PCR test results and admission to a hospital ward [COVID-specific ward, intensive care unit (ICU), or others]. Underlying chronic health problems such as renal, liver, cardiac, or neurological, and diabetes mellitus (DM), cancer, hypertension (HTN), and pulmonary disorders were also collected (self-declared). No data were available about the hospital course of the patients (laboratory test results, management, complications). However, the outcome was also recorded in the database, as dead or discharged. The diagnosis dates of the patients were from 19 February 19, 2020 to November 20, 2020. In a telephone conversation with the discharged patients, made by the last 12 authors, at least three months after their illness (from March 1 to 14, 2021), we investigated their current health status and obtained their information, if they agreed to participate and answer the questions (consented orally: We are conducting research to investigate the lingering symptoms of the COVID-19. Do you agree to participate in this study and answer our questions over the phone?). We randomly selected every other adult patient in our database (alternate patients in the database sorted by their phone numbers). If someone did not answer, in the second attempt, we selected the previous patient in the list, who was skipped initially, because of not responding. Figure 1 illustrates the inclusion process of the participants.

A data gathering form (appendix 1) was specifically designed for the purpose of data collection, and all the team members were instructed by the first author, on how to inquire the data consistently and in the same manner.

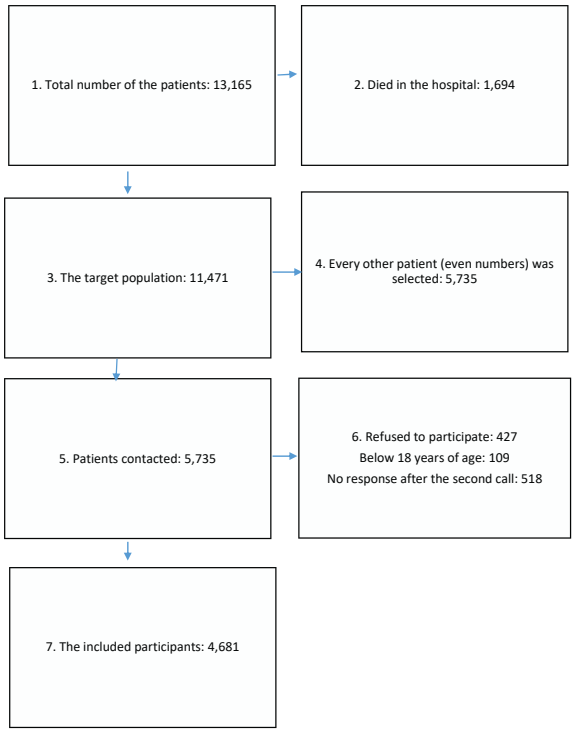

Figure 1: The figure shows the recruitment process of the study.

The first part of the form (eight questions) collected the demographic data and some confirmatory data (date of admission and underlying disorders before COVID-19) to cross-check with the primary database. In the second part (28 questions), we asked if the patient had noticed any problems (cough, fatigue, muscle or joint pain, and headache), or was suffering from any conditions (chronic problems) in the prior week compared with their pre-COVID-19 conditions (any symptoms, complaints, or problems that they did not have before their COVID-19 diagnosis, but appeared after the illness and specifically during the past seven days). The survey was designed and developed as follows: We conducted a literature review and numerous interviews with other participants. We developed the items and conducted an expert validation to assess the clarity and relevance of the items with regard to the construct of interest. For the purpose of this study, we defined LCS as any symptoms, complaints, or problems that the patients did not experience before their COVID-19 diagnosis, but have persistently had during the seven days prior to the follow-up. We specifically asked their complaints during the past seven days in order to minimize the risk of recall bias. Since our work was a retrospective inquiry, we did not study the starting date of the symptoms/problems. We also asked the severity of their complaints (1. Mild and tolerable; 2. Moderate; 3. Severe and disabling). In the third part of the questionnaire (five questions), we asked the patients to compare their current status (on five items) with their pre-COVID-19 status based on a Likert scale (1. Much worse; 2. Somewhat worse; 3. The same as before; 4; Somewhat better; 5. Much better). The following were also asked: 1. ability to perform the activity of daily living; 2. concentration and mind workability ; 3. studying and reading ability; 4. quality of life; 5. hope for the future.

Statistical Analyses

The SPSS Statistics (IBM Corp., USA, version 25.0) was used. We arbitrarily categorized the patients into two groups (to investigate the longevity and chronicity of the symptoms): a. Group 1: a phone call from three to six months after being diagnosed with COVID-19; b. Group 2: a phone call from six to 12 months after the illness. Values were presented as mean±SD for continuous variables and as the number (percent) of subjects for categorical variables. Based on the previous studies, the following variables were selected as the risk factors potentially associated with long COVID syndrome: sex (men and women), age (mean±SD), length of hospital stay (mean±SD), respiratory problems at the onset, neurological problems at the onset, gastrointestinal problems at the onset, pre-existing chronic medical problems, and ICU admission. Pearson Chi square, Fisher's exact test, *t* test, Bonferroni correction test, and binary logistic regression analysis model were employed for statistical analyses, then significant variables from univariate analyses were entered into the logistic regression analysis model. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A P value (two-sided) of less than 0.05 was considered to be significant.

Results

General Characteristic of the Patients

Since the start of the pandemic until November 20, 2020, 13,165 patients with confirmed COVID-19 were referred to 55 healthcare facilities in Fars province; 1694 people died (case fatality rate: 12.8%) and 11,471 individuals (adults and children) were discharged from the hospitals. In the follow-up phase of this study, 4,681 adult patients discharged from the hospitals agreed to participate; 427 people (8.4%) of those, who were contacted refused to participate in this study (figure 1). The respondents included: 2634 patients (56%) and 2047 family members/care-givers (44%). The participants included 2478 men (52.9%) and 2203 women (47.1%), and their mean age was 52±15 years.

Clinical Characteristics of the Patients

Manifestations of COVID-19 on admission were as follows: respiratory/pulmonary in 4182 (89.3%) [hypoxemia (SpO2<93% by Pulse Oximeter reading) in 56.6%, respiratory distress in 54.1%, cough in 52.8%, and chest pain in 5%]; neurological in 818 (17.5%) [headache in 14.1%, loss of smell in 2.2%, change in mental status in 1.7%, loss of taste in 1.1%]; and gastrointestinal (GI) in 731 (15.6%) patients [nausea in 8.6%, vomiting in 5.1%, diarrhea in 4,9%, and abdominal pain in 3.2%]. Several patients had non-specific manifestations [fever in 41%, myalgia in 39.5%, anorexia in 10.9%, and dizziness in 4%]. A minority [482 (10.3%)] of the patients needed ICU admission. Duration of the hospital stay was as short as a few hours (in eight patients) to as long as 112 days, two months or more in eight patients, (mean±SD: 7±6 days). In addition, 1766 patients (37.7%) had pre-existing chronic medical conditions (19.9% HTN, 16.1% DM, 10.6% cardiac problems, 2.6% asthma, 1.9% renal problems, 1.5% other pulmonary disorders, and 1.2% cancer).

Long COVID Manifestations

We called 1996 (42.6%) patients, diagnosed with COVID-19 six to 12 months prior, and 2685 (57.4%) people with the infection three to six months prior. In total, 2915 (62.3%) people reported symptoms/complaints, 1774 (66%) had shorter follow-ups and 1141 (57%) with longer follow-ups (P=0.0001) had long-lasting problems. Table 1 represents the symptoms/complaints of the patients in these two groups. In general, all the symptoms/complaints were reported by both groups; however, some of the symptoms/complaints were significantly less frequent in those with an infection for a longer time (weakness, muscle pain, fatigue, sleep difficulty, palpitation, cough, brain fog, exercise, and walking intolerance). Table 2 shows the severity of the reported symptoms/complaints. While most of the symptoms/complaints were rated as mild and tolerable by the participants, a minority of the patients reported severe and disabling problems. There were no significant differences between the two groups of the patients (those diagnosed with COVID-19 from the previous six to 12 months versus people with the infection from the previous three to six months) with respect to the severity of the symptoms of LCS (table 3). Other reported chronic problems (not mentioned in the tables) included: Hair loss in 102 (2%), new-onset DM in 18, new-onset HTN in 11, loss of libido in two, and new-onset chronic renal failure in one patient.

Factors Associated with Long COVID Syndrome

Table 4 reveals the factors associated with

Table 1: Long COVID symptoms/complaints

Clinical Manifestations	3-6 months follow-up, N=2685 **n (%)**	**6-12 months follow-up, N=1996 n (%)**	**P value**
Weakness	543 (20%)	278 (14%)	0.0001
Muscle pain	562 (21%)	291 (15%)	0.0001
Joint pain	491 (18%)	296 (15%)	0.002
Fatigue	847 (32%)	493 (25%)	0.0001
Sleep difficulty	453 (17%)	254 (13%)	0.0001
Shortness of breath	563 (21%)	347 (17%)	0.003
Chest pain	303 (11%)	175 (9%)	0.005
Palpitation	304 (11%)	166 (8%)	0.001
Cough	272 (10%)	139 (7%)	0.0001
Excess sputum	171 (6%)	123 (6%)	0.808
Loss of smell	123 (5%)	92 (5%)	0.944
Loss of taste	78 (3%)	54 (3%)	0.722
Sore throat	124 (5%)	74 (4%)	0.142
Headache	316 (12%)	207 (10%)	0.146
Dizziness	205 (8%)	125 (6%)	0.083
Brain fog	319 (12%)	161 (8%)	0.0001
Excess sweating	232 (9%)	149 (7%)	0.160
Exercise intolerance	694 (26%)	396 (20%)	0.0001
Walking intolerance	587 (22%)	315 (16%)	0.0001
Diarrhea	73 (3%)	42 (2%)	0.214
Abdominal pain	88 (3%)	56 (3%)	0.393
Anorexia	104 (4%)	65 (3%)	0.303
Weight loss	251 (9%)	130 (7%)	0.001
Weight gain	147 (5%)	101 (5%)	0.598

After Bonferroni correction, the significant P value is at <0.002

Table 2: The severity of the reported symptoms/complaints of long COVID syndrome

Clinical Manifestations	Mild and Tolerable n (%)	Moderate n(%)	Severe and Incapacitating n (%)	Missing data
Weakness	552 (67%)	179 (22%)	89 (11%)	15
Muscle pain	551 (65%)	191 (23%)	106 (12%)	11
Joint pain	447 (57%)	228 (29%)	110 (14%)	13
Fatigue	900 (67%)	316 (24%)	117 (9%)	12
Sleep difficulty	397 (56%)	192 (27%)	117 (17%)	10
Shortness of breath	646 (71%)	194 (22%)	66 (7%)	12
Chest pain	346 (73%)	111 (23%)	20 (4%)	10
Palpitation	328 (70%)	107 (23%)	31 (7%)	10
Cough	312 (77%)	74 (18%)	22 (5%)	13
Excess sputum	192 (66%)	71 (24%)	29 (10%)	11
Loss of smell	135 (63%)	43 (20%)	37 (17%)	11
Loss of taste	75 (57%)	38 (29%)	18 (14%)	13
Sore throat	171 (86%)	25 (13%)	2 (1%)	12
Headache	327 (63%)	133 (25%)	62 (12%)	14
Dizziness	251 (76%)	56 (17%)	22 (7%)	14
Brain fog	306 (64%)	129 (27%)	45 (9%)	18
Excess sweating	205 (54%)	114 (30%)	62 (16%)	19
Exercise intolerance	600 (55%)	321 (29%)	169 (16%)	12
Walking intolerance	469 (53%)	271 (30%)	153 (17%)	23
Diarrhea	88 (79%)	16 (14%)	8 (7%)	26
Abdominal pain	97 (67%)	33 (23%)	14 (10%)	22
Anorexia	107 (64%)	43 (26%)	18 (10%)	23

1766 patients did not have long COVID syndrome

Table 3: Severe symptoms/complaints of the long COVID syndrome

Clinical Manifestations	3-6 months follow-up, N=2685	6-12 months follow-up, N=1996	P value
Weakness	56 (2%)	33 (1.7%)	0.614
Muscle pain	68 (2.5%)	38 (1.9%)	0.920
Joint pain	65 (2.5%)	45 (2.3%)	0.618
Fatigue	74 (2.8%)	43 (2.2%)	0.825
Sleep difficulty	86 (3.2%)	31 (1.6%)	0.045
Shortness of breath	44 (1.6%)	22 (1.1%)	0.408
Chest pain	13 (0.5%)	7 (0.4%)	0.971
Palpitation	16 (0.6%)	15 (0.8%)	0.294
Cough	10 (0.4%)	12 (0.6%)	0.030
Excess sputum	19 (0.7%)	10 (0.5%)	0.188
Loss of smell	21 (0.8%)	16 (0.8%)	0.136
Loss of taste	11 (0.4%)	7 (0.4%)	0.014
Sore throat	1 (0.03%)	1 (0.05%)	0.891
Headache	40 (1.5%)	22 (1.1%)	0.156
Dizziness	15 (0.6%)	7 (0.4%)	0.740
Brain fog	32 (1.2%)	13 (0.7%)	0.639
Excess sweating	35 (1.3%)	27 (1.4%)	0.185
Exercise intolerance	120 (4.5%)	49 (2.5%)	0.093
Walking intolerance	110 (4.1%)	43 (2.2%)	0.118
Diarrhea	6 (0.2%)	2 (0.1%)	0.719
Abdominal pain	11 (0.4%)	3 (0.2%)	0.309
Anorexia	11 (0.4%)	7 (0.4%)	0.881

After Bonferroni correction, the significant P value is at 0.002

any reported long COVID symptoms/complaints. Long-term COVID symptoms/complaints were significantly more frequent in women, those with respiratory problems at the onset of infection, those admitted to the ICU, and those with longer hospital stays. We included these variables in a regression analysis model. Women had LCS more frequently than men (OR: 1.268; 95% CI: 1.122-1.432; P=0.0001). Presentation with respiratory problems at the onset was also significantly associated with having LCS (OR: 1.425; 95% CI: 1.177-1.724; P=0.0001).

Table 4: Factors in association with reporting any long COVID symptoms/complaints in univariate analysis

Clinical Characteristics	Long COVID syndrome, N=2915	No chronic symptoms, N=1766	P value
Sex (Female:Male)	1430:1485 (ratio: 0.96)	773:993 (ratio: 0.78)	0.0001
Age (mean±SD), years	52±15	52±16	0.470
Length of hospital stay (mean±SD), days	7.7±6.8	6.1±5.3	0.0001
Respiratory problems at onset	2647 (91%)	1535 (87%)	0.0001
Neurological problems at onset	520 (18%)	298 (17%)	0.405
Gastrointestinal problems at onset	455 (16%)	276 (16%)	0.835
Pre-existing chronic medical problems	1105 (38%)	661 (37%)	0.756
ICU admission	344 (12%)	138 (8%)	0.0001

Finally, a shorter length of hospital stay was inversely correlated with having LCS (OR: 0.953; 95% CI: 0.941 to 0.965; P=0.0001). The ICU admission was not significant (P=0.169).

The Big Picture

The patients rated the following items over the past week compared with that of before their COVID-19, as shown in table 5 (ability to do routine and normal tasks; ability to concentrate and think; ability to study; overall quality of life; hope for the future). In the next step, we categorized the above items as worse (much worse+somewhat worse) versus not (the same+somewhat better+much better), and we evaluated the associations among these variables and reported LCS. Table 6 demonstrates the results of these analyses. The patients with chronic symptoms/complaints (LCS) reported a worse status on all the items.

Discussion

Herein, we observed that long COVID syndrome is a frequent and disabling condition and found that more than six in 10 patients with COVID-19, who required hospitalization, had long-lasting symptoms/complaints of LCS. The demographic characteristics of our patients (age, sex, length of hospital stay, and the need for ICU admission) were comparable with those from other studies.[13-16] This suggests that our data could be generalized to other populations. Reports of long-lasting COVID-19 symptoms, the so-called "long COVID syndrome (LCS)", are rising very fast and more should be known about its prevalence and the associated risk factors.[13] In a previous study of 4,182 patients with COVID-19, the individuals self-reported their symptoms prospectively in the COVID symptom study application. A total of 558 (13.3%) participants reported symptoms lasting ≥28 days, 189 (4.5%) for ≥8 weeks, and 95 (2.3%) reported symptoms for ≥12 weeks.[13] In another study of 384 patients (mean age 59.9 years; 62% male) followed for a median of 54 days post-discharge, 53% of the patients reported persistent breathlessness, 34% had cough, and 69% reported fatigue.[14] In a study of 478 patients, 244 patients (51%) declared at least one symptom that did not exist

Table 5: How would you rate the following items over the past week compared with that before your COVID-19?

Change of the following items	Much worse n (%)	Somewhat worse n (%)	The same as before n (%)	Somewhat better n (%)	Much better n (%)	Missing data
Ability to do routine and normal tasks	205 (4.4%)	758 (16.3%)	3619 (77.9%)	57 (1.2%)	8 (0.2%)	34
Ability to concentrate and think	117 (2.5%)	634 (13.6%)	3869 (83.3%)	22 (0.5%)	4 (0.1%)	35
Ability to study	90 (1.9%)	427 (9.2%)	4097 (88.2%)	30 (0.6%)	3 (0.1%)	34
Overall quality of life	168 (3.6%)	634 (13.6%)	3781 (81.4%)	54 (1.2%)	9 (0.2%)	35
Hope for the future	176 (3.8%)	480 (10.3%)	3886 (83.7%)	75 (1.6%)	25 (0.5%)	39

Table 6: How would you rate the following items over the past week compared with that before your COVID-19?

Rated worse on the following items	Long COVID syndrome, N=2915	No chronic symptoms, N=1766	P value
Ability to do routine and normal tasks	904 (31%)	59 (3%)	0.0001
Ability to concentrate and think	701 (24%)	50 (3%)	0.0001
Ability to study	477 (16%)	40 (2%)	0.0001
Overall quality of life	765 (26%)	37 (2%)	0.0001
Hope for the future	611 (21%)	45 (3%)	0.0001

After Bonferroni correction, the significant P value is at <0.01

before COVID-19: Fatigue was reported by 31%, cognitive symptoms were observed in 21%, and new-onset dyspnea was reported in 16%.[16] The difference in the methodology may explain the various rates of LCS reported in these studies, while active inquiry suggests a prevalence of more than 50%, observed in our study and the reports by Morin and others, Mandal and colleagues, and Jacobson and others, passive inquiry suggests a much lower prevalence.[14, 16, 17] It is likely that the passive inquiry of the symptoms in people with no LCS (with no fatigue, brain fog), the designed app was used more frequently.[13]

The most common symptoms of LCS in our study were fatigue (tiredness), exercise intolerance, walking intolerance, muscle pain, shortness of breath, and weakness (loss of stamina). Fortunately, most of these symptoms resolved in numerous people over time. Unfortunately, all of these symptoms lasted for many months (more than six months) in a substantial number of people. Many of the observed symptoms in our study were consistent with those from previous studies.[13, 14, 18, 19] Meanwhile, we also reported some intriguing symptoms (e.g., palpitation, GI problems, and weight change) that have less often been recognized before.

In the current study, we observed that the female sex, initial respiratory symptoms, and prolonged hospitalization were significantly associated with experiencing LCS. In a previous study, LCS was more likely correlated with increasing age, body mass index, and female sex. Experiencing more than five symptoms during the first week of illness was also associated with LCS (Odds Ratio:3.53).[13] In another study of 134 patients, 86% of the participants reported at least one residual symptom at the follow-up. The presence of symptoms at the follow-up was not related to the severity of the acute COVID-19 illness. Women were significantly more likely to report residual symptoms.[15] In a study of 599 patients, female sex, a proportional increase in the number of symptoms at the onset of COVID-19, and ICU admission were all the independent risk factors for the post-COVID-19 syndrome.[20] The reproduced observation that female sex is more often associated with LCS is intriguing and should be further explored in future studies. Analysis of the pathophysiological drivers underlying the female sex as a risk factor for LCS is a critical next step.

Our observation that prolonged hospitalization was significantly associated with experiencing LCS and the observations by Sudre and colleagues and Peghin and others[13, 20] that experiencing more symptoms during the first week of illness was associated with LCS may suggest that a more severe COVID-19 at presentation is a significant risk factor for experiencing LCS. However, the study by Sykes and others did not reach this conclusion.[15] Speculatively, we can hypothesize that a more severe COVID-19 is a risk factor for LCS on account of two possibilities: first, severe COVID-19 causes a more severe immune response and cytokine storm and consequently more organ damages (brain, lungs, heart).[12, 21, 22] Second, severe COVID-19 is usually aggressively treated with more medications, corticosteroids and is more often associated with iatrogenic harm, due to intubation or nosocomial infections, with long-lasting sequelae. Therefore, it is reasonable to assume that LCS is a biological phenomenon. Evidence suggests that sustained endotheliopathy is common in convalescent COVID-19, which may lead to long COVID pathogenesis. Other possible mechanisms of LCS may include an elevated inflammatory state, cerebrovascular changes, peripheral organ damage, and dysfunction.[23-25] It is also plausible to assume that LCS is the result of psychosocial consequences of COVID-19, at least to some extent and in some patients.[26] While we could not establish a cause and effect relationship, we observed that LCS is significantly associated with the impaired daily activity and quality of life of the patients. These speculations should be explored in future studies.

A major limitation of this study is that the data set is entirely based on a phone consultation with no clinical, psychological, or paraclinical evaluations. Additionally, we likely have missed some patients with a negative PCR test result, who were diagnosed based on the typical clinical and radiological signs of COVID-19. In addition, the data on LCS were not collected prospectively, and we could not provide the information on their temporal relationship (start date) with the illness (COVID-19), and the course of the LCS symptoms/problems based on the current study. Moreover, we did not evaluate the asymptomatic infections and those with a mild illness in this study. Furthermore, we did not perform validity and reliability testing of our questionnaire formally. Finally, our findings were limited by the absence of a control group and pre-COVID assessments in this cohort. On the other hand, the strengths of our study include a large sample size, a comprehensive data collection form, and quality assessment of the symptoms (self-declared).

Conclusion

Long COVID syndrome is a frequent and

significant and at times, disabling condition. In this large population-based study, we report that LCS has significant associations with sex (women), respiratory symptoms at the onset, and the severity of the illness (length of hospital stay). The scientific community should investigate the pathophysiology of this condition to discover the biological underpinnings of LCS.

Conflict of Interest: None declared.

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