Postdischarge rheumatic and musculoskeletal symptoms following hospitalization for COVID-19: prospective follow-up by phone interviews

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Abstract
To describe the rheumatic and musculoskeletal symptoms at hospitalization as well as their persistence/severity after discharge with coronavirus disease 2019 (COVID-19) and to identify whether age, sex, body mass index (BMI), and length of hospital stay are associated with persistence of these symptoms. In this single-center cohort study, comprising 300 participants, two phone interviews were conducted (2-week and 1-month after hospitalization) and symptoms were queried with a standardized form. This form included musculoskeletal symptoms and other COVID-19 symptoms. Considering all symptoms (musculoskeletal and other), 100.0%, 86.7%, and 72.0% of patients reported one or more symptoms, at hospitalization, 2-week, and 1-month, respectively. Considering only musculoskeletal symptoms, 92.3%, 72.7%, and 56.3% of patients reported any musculoskeletal symptom at hospitalization, 2-week, and 1-month, respectively. The musculoskeletal symptoms were fatigue (44.3% of patients reported), back pain (22.7%), arthralgia (22.0%), myalgia (21.0%), low back pain (16.3%), and neck pain (10.3%); the other symptoms were shortness of breath (26.3%), loss of taste (15.0%), cough (14.0%), loss of smell (12.3%), loss of appetite (10.3%), headache (8.7%), sore throat (3.0%), diarrhea (1.3%), dizziness (1.3%), and fever (0.3%) at 1-month. Increasing BMI was associated with higher odds of persistence of fatigue (OR: 1.08, 1.03 to 1.13), myalgia (OR: 1.08, 1.01 to 1.14), and arthralgia (OR: 1.07, 1.02 to 1.14, \( p = 0.012 \)) at 1-month. Nearly three-quarters reported one or more symptoms, with more than half of patients reported any musculoskeletal symptom at 1 month. The most common musculoskeletal symptom was fatigue, followed by back pain, arthralgia, myalgia, low back pain, and neck pain. The persistence of fatigue, myalgia, and arthralgia was related to BMI. The study results increase our understanding of the spectrum of COVID-19, which, in turn, may lead to more efficient and better care for COVID-19 survivors.

Keywords COVID-19 · Post-Acute Sequelae of SARS-CoV-2 infection (PASC) · Fatigue · Myalgia · Arthralgia · Pain · Rheumatic symptoms · Musculoskeletal symptoms

Introduction
The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes a disease named coronavirus disease 2019 (COVID-19), emerged in China in December 2019 [1, 2]. Its rapid worldwide spread leading to an unexpected pandemic has challenged as a global health threat and considerably impacted nearly all aspects of the life of individuals as well as healthcare systems [3–8]. Globally, over 114 million confirmed cases with more than 2.5 million deaths from COVID-19 have been documented as of March 2021 [9].

The initial symptoms of COVID-19 have been well documented. In a report among 373,883 COVID-19 cases with known symptom status, cough, fever, myalgia, headache,
shortness of breath, sore throat, diarrhea, nausea/vomiting, loss of smell or taste, abdominal pain, and runny nose were described in the descending order of frequency [10]. Furthermore, a meta-analysis addressing the rheumatic manifestations of COVID-19 found a pooled estimation of 19% for myalgia and 32% for fatigue as an initial symptom of COVID-19 [11]. However, these studies investigated rheumatic and musculoskeletal symptoms only as of the presence/absence of fatigue, myalgia, and arthralgia.

To the knowledge of the authors, information on detailed documentation of rheumatic and musculoskeletal symptoms at hospitalization as well as their severity/persistence after discharge with COVID-19 is scarce [12–17]. More granular data for rheumatic and musculoskeletal symptoms would increase our understanding of the spectrum of COVID-19, which, in turn, leads to more efficient and better care for COVID-19 survivors. The aim of the present study, therefore, was to describe postdischarge rheumatic and musculoskeletal symptoms following hospitalization for COVID-19 and to identify whether age, sex, body mass index (BMI), and length of hospital stay are associated with the persistence of these symptoms.

**Methods**

**Study design**

The study was a single-center cohort study with prospective follow-up by phone interviews. It was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was granted by the institutional ethics committee. Informed verbal consent was obtained from all participants by phone before proceeding to the survey.

**Study setting**

The study was performed at Gulhane Training and Research Hospital, a Tertiary Hospital.

**Participants**

Participants who were between 18 and 70 years of age, and discharged following hospitalization for COVID-19 between November 18, 2020, and January 30, 2021, were eligible for inclusion. Participants who received intensive care unit (ICU) care at any time during the hospitalization were excluded.

**Data collection**

A total of two phone interviews were conducted (2-week and 1-month after hospitalization). Demographic and baseline characteristics (including age, sex, height, weight, educational level, employment status, comorbidities), initial symptoms at hospitalization (musculoskeletal and others), and length of hospital stay were queried and obtained at the 2-week phone survey. Symptoms of 2-week and 1-month were queried and obtained at 2-week and 1-month phone survey, respectively, with a standardized form. This form included musculoskeletal symptoms (fatigue, myalgia, low back pain, back pain, and neck pain) and other COVID-19 symptoms (fever, cough, loss of appetite, shortness of breath, diarrhea, sore throat, headache, dizziness, loss of taste, and loss of smell). The severity of each musculoskeletal and other COVID-19 symptom was queried with a five-level Likert scale (i.e. none; mild; moderate; severe; and very severe).

**Statistical methods**

The characteristics were analyzed with descriptive statistics, and presented as mean and standard deviation for continuous variables and as frequency and percentage for categorical variables. Generalized estimating equations with a binary logistic model was used to assess the association of age, sex, BMI, and length of hospital stay with the presence of fatigue, myalgia, and arthralgia at 1 month. The sample size was calculated according to the formula provided elsewhere [18]: the number of independent variables was 4, it was estimated a total of 300 participants are needed. All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp.). A two-tailed p value <0.05 was considered statistically significant. The presentation of statistical results was informed by the recent review [19].

**Results**

The demographic and clinical characteristics of the study population comprising 300 participants are presented in Table 1. The majority were male (60%), the mean age was 53 years, 65% had at least one comorbidity, and the mean length of hospital stay was 8 days.

At hospitalization, all patients reported one or more symptoms, with 92.3% reported any musculoskeletal symptom and 98.7% reported any other COVID-19 symptom. The musculoskeletal symptoms were fatigue (87.3% of patients reported), myalgia (63.3%), arthralgia (59.3%), back pain (54.0%), low back pain (44.7%), and neck pain (26.7%); the other COVID-19 symptoms were shortness of breath (76.7%), loss of appetite (71.7%), cough (67.7%), fever (65.3%), loss of taste (53.0%), loss of smell (43.3%), headache (39.3%), sore throat (30.3%), diarrhea (21.3%), and dizziness (3.7%), in the descending order of frequency (Fig. 1,
Myalgia and arthralgia were reported mostly as widespread than local; if these were local the most frequent regions were lower leg and knee, respectively (Table 3).

At 2-week, 86.7% reported one or more symptoms, with 72.7% reported any musculoskeletal symptom and 72.3% reported any other COVID-19 symptom. The musculoskeletal symptoms were fatigue (64.0% of patients reported), myalgia (36.7%), arthralgia (35.0%), back pain (32.3%), low back pain (24.3%), and neck pain (15.7%); the other COVID-19 symptoms were shortness of breath (37.7%), loss of taste (31.3%), loss of appetite (30.0%), loss of smell (27.0%), cough (26.0%), headache (16.7%), sore throat (6.3%), fever (4.0%), diarrhea (4.0%), and dizziness (2.0%), in the descending order of frequency (Fig. 1, Table 2).

At 1-month, 72.0% reported one or more symptoms, with 56.3% reported any musculoskeletal symptom and 51.0% reported any other COVID-19 symptom. The musculoskeletal symptoms were fatigue (44.3% of patients reported), back pain (22.7%), arthralgia (22.0%), myalgia (21.0%), low back pain (16.3%), and neck pain (10.3%); the other COVID-19 symptoms were shortness of breath (37.7%), loss of taste (31.3%), loss of appetite (30.0%), loss of smell (27.0%), cough (26.0%), headache (16.7%), sore throat (6.3%), fever (4.0%), diarrhea (4.0%), and dizziness (2.0%), in the descending order of frequency (Fig. 1, Table 2).

The severity of musculoskeletal and other COVID-19 symptoms at hospitalization, 2-week, and 1-month is detailed in Table 4.

After adjusting for other variables, neither age, nor sex, nor the length of hospital stay was associated with higher odds of persistence of fatigue, myalgia, and arthralgia at 1 month. After adjusting for age, sex, and length of hospital stay, increasing BMI was associated with higher odds of the persistence of fatigue (odds ratio (OR) with 95% confidence interval: 1.08, 1.03 to 1.13, \( p = 0.003 \)), myalgia (OR: 1.08, 1.01 to 1.14, \( p = 0.015 \)), and arthralgia (OR: 1.07, 1.02 to 1.14, \( p = 0.012 \)) at 1 month (Table 5).

**Discussion**

The study found that nearly three-quarters of patients reported one or more symptoms, with more than half of patients reported any musculoskeletal symptom at 1 month. The most common musculoskeletal symptom was fatigue (nearly half of patients), followed by back pain (≈two in five), arthralgia (≈two in five), myalgia (≈two in five), low back pain, and neck pain; the most common other COVID-19 symptom was shortness of breath (≈a quarter of patients), followed by loss of taste, cough, loss of smell, loss of appetite, headache, sore throat, diarrhea, dizziness, and fever at 1 month. In addition, increasing BMI was associated with higher odds of the persistence of fatigue, myalgia, and arthralgia at 1 month; however, no association was found between age/sex/length of hospital stay and persistence of these symptoms.

The available information on the persistence of rheumatic and musculoskeletal symptoms after discharge with COVID-19 is scarce (Table 6) [12–15]. Carfi et al. analyzed 143 patients with a mean of 36 days after discharge.
They found that 87.4% reported persistence of at least 1 symptom, particularly fatigue (53.1%), shortness of breath (43.4%), and joint pain, (27.3%) [12]. Garrigues et al. surveyed 120 patients (96 ward patients and 24 intensive care patients) by phone, and found the most frequently reported persistent symptoms being fatigue (54.2%), and shortness of breath (39.6%) among ward patients [13].
### Table 4 Severity of hospitalization and postdischarge symptoms

| Characteristic | Hospitalization | 2 weeks | 1 month |
|---------------|----------------|---------|---------|
| Fatigue       |                |         |         |
| None          | 38 (12.7)      | 108 (36.0) | 167 (55.7) |
| Mild          | 40 (13.3)      | 68 (22.7) | 93 (31.0) |
| Moderate      | 62 (20.7)      | 56 (18.7) | 30 (10.0) |
| Severe        | 47 (15.7)      | 32 (10.7) | 9 (3.0) |
| Very severe   | 113 (37.7)     | 36 (12.0) | 1 (0.3) |
| Myalgia       |                |         |         |
| None          | 110 (36.7)     | 190 (63.3) | 237 (79.0) |
| Mild          | 21 (7.0)       | 46 (15.3) | 45 (15.0) |
| Moderate      | 60 (20.0)      | 36 (12.0) | 12 (4.0) |
| Severe        | 33 (11.0)      | 6 (2.0)  | 3 (1.0) |
| Very severe   | 76 (25.3)      | 22 (7.3)  | 3 (1.0) |
| Arthralgia    |                |         |         |
| None          | 122 (40.7)     | 195 (65.0) | 234 (78.0) |
| Mild          | 26 (8.7)       | 36 (12.0) | 46 (15.3) |
| Moderate      | 54 (18.0)      | 38 (12.7) | 15 (5.0) |
| Severe        | 29 (9.7)       | 10 (3.3)  | 3 (1.0) |
| Very severe   | 69 (23.0)      | 21 (7.0)  | 2 (0.7) |
| Low back pain |                |         |         |
| None          | 166 (55.3)     | 227 (75.7) | 251 (83.7) |
| Mild          | 19 (6.3)       | 31 (10.3) | 35 (11.7) |
| Moderate      | 30 (10.0)      | 19 (6.3)  | 10 (3.3) |
| Severe        | 25 (8.3)       | 7 (2.3)   | 2 (0.7) |
| Very severe   | 60 (20.0)      | 16 (5.3)  | 2 (0.7) |
| Back pain     |                |         |         |
| None          | 138 (46.0)     | 203 (67.7) | 232 (77.3) |
| Mild          | 32 (10.7)      | 43 (14.3) | 55 (18.3) |
| Moderate      | 42 (14.0)      | 24 (8.0)  | 9 (3.0) |
| Severe        | 31 (10.3)      | 10 (3.3)  | 2 (0.7) |
| Very severe   | 57 (19.0)      | 20 (6.7)  | 2 (0.7) |
| Neck pain     |                |         |         |
| None          | 220 (73.3)     | 253 (84.3) | 269 (89.7) |
| Mild          | 13 (4.3)       | 23 (7.7)  | 23 (7.7) |
| Moderate      | 23 (7.7)       | 12 (4.0)  | 5 (1.7) |
| Severe        | 19 (6.3)       | 4 (1.3)   | 1 (0.3) |
| Very severe   | 25 (8.3)       | 8 (2.7)   | 2 (0.7) |
| Fever         |                |         |         |
| None          | 104 (34.7)     | 288 (96.0) | 299 (99.7) |
| Mild          | 53 (17.7)      | 4 (1.3)   | 1 (0.3) |
| Moderate      | 63 (21.0)      | 6 (2.0)   | –       |
| Severe        | 56 (18.7)      | 1 (0.3)   | –       |
| Very severe   | 24 (8.0)       | 1 (0.3)   | –       |
| Cough         |                |         |         |
| None          | 97 (32.3)      | 222 (74.0) | 258 (86.0) |
| Mild          | 72 (24.0)      | 35 (11.7) | 32 (10.7) |
| Moderate      | 37 (12.3)      | 24 (8.0)  | 9 (3.0) |
| Severe        | 34 (11.3)      | 13 (4.3)  | 1 (0.3) |
| Very severe   | 60 (20.0)      | 6 (2.0)   | –       |
| Loss of appetite |           |         |         |
| None          | 85 (28.3)      | 210 (70.0) | 269 (89.7) |

(continued)

| Characteristic | Hospitalization | 2 weeks | 1 month |
|---------------|----------------|---------|---------|
| Myalgia       |                |         |         |
| Present       | 190 (63.3)     | 269 (89.7) |
| Widespread    | 120 (40.0)     | –       | –       |

(continued)
another phone survey, Halpin et al. analyzed postdischarge symptoms in 100 participants (68 ward patients and 32 intensive care patients). Fatigue was the most common reported symptom by 60.3% followed by shortness of breath by 42.6% in the ward group [14]. Arnold et al. analyzed 110 patients (both ward and intensive care patients) and found that 73.6% of patients reported at least one ongoing symptom with 39.1% shortness of breath, 39.1% fatigue, and 22.7% myalgia [15]. Interestingly, in each study, the most common two persistent symptoms were fatigue (39%–60%) and shortness of breath (39%–43%) [12–15]; the present results (the most common fatigue by 44% followed by shortness of breath by 26%) are consistent with those of the previous studies. In addition, the present study provides information on the persistence of other musculoskeletal symptoms: back pain, arthralgia, and myalgia each was present in two-fifths of patients, and a less frequently low back pain and neck pain were persisted. Regarding the other COVID-19 symptoms, loss of taste, cough, loss of smell, and loss of appetite each was persisted in at least one-tenth of patients. The wide spectrum of persistent symptoms requires multidisciplinary care for discharged survivors. Considering the relatively high frequency of rheumatic and musculoskeletal symptoms, rheumatologists should be involved in multidisciplinary teams caring for COVID-19 survivors.

A meta-analysis addressing the association of obesity and COVID-19 showed individuals with obesity were more at risk for COVID-19 positive, hospitalization, intensive care admission, and mortality [20]. The severity of COVID-19 in obese patients has been attributed to metabolic dysfunction, immune response impairments, adipose inflammation, and decreased lung function [20, 21]. Furthermore, in a phone survey study investigating the persistent symptoms 14–21 days after testing among the 274 symptomatic outpatients (not hospitalized), obesity was associated with not returning to the usual health [22]. In the present study, increasing BMI was associated with higher odds of the persistence of fatigue, myalgia, and arthralgia in hospitalized COVID-19 patients.

Several mechanisms have been proposed for rheumatic and musculoskeletal symptoms in COVID-19 [23–27]. The acute rheumatic and musculoskeletal symptoms of COVID-19 (i.e. myalgia, fatigue, arthralgia) have been widely attributed to immune response and pro-inflammatory cytokines generated after infection [23–27]. Beyond systemic immune response/inflammation, a direct invasion/
injury of musculoskeletal cells by SARS-CoV-2 through the angiotensin-converting enzyme 2 (ACE2) receptor is the other proposed hypothesis [23–27]. Future studies aimed at elucidating the mechanisms underlying the persistent symptoms are needed.

## Limitations

The present study has some limitations. The main limitation was that it had no control group of patients hospitalized for conditions other than COVID-19. A design with a control group would have managed to allow a better interpretation of the present results. Moreover, it included patients who were hospitalized for COVID-19; therefore, the results cannot be generalized to nonhospitalized patients. Also, as COVID-19 patients who have more comorbid conditions have higher odds of hospitalization [10, 28, 29], these comorbidities might have influenced the results observed in the present study as confounding factors. Furthermore, the study design does not allow interpreting the causality between BMI and persistence of fatigue, myalgia, and arthralgia. Despite these limitations, this study provides detailed data on persistence and risk factors of rheumatic and musculoskeletal symptoms after discharge with COVID-19. This information may lead to better address/care for the persistent rheumatic and musculoskeletal symptoms in COVID-19 survivors.

### Table 6 Frequency of postdischarge symptoms in the literature

| Country        | Carfi et al. [12]† | Garrigues et al. [13]† | Halpin et al. [14]† | Arnold et al. [15]‡ | Present study* |
|----------------|--------------------|------------------------|--------------------|--------------------|---------------|
| Number of total patients | Italy              | France                 | UK                 | UK                 | Turkey        |
|                | 143                | 120                    | 100                | 110                | 300           |
| Number of ward patients | 125 (87.4%)        | 96 (80.0%)             | 68 (68.0%)         | N/A                | 300 (100.0%)  |
| Number of intensive care patients | 18 (12.6%)         | 24 (20.0%)             | 32 (32.0%)         | N/A                | 0             |
| Days after hospital admission | N/A               | 111                    | N/A                | 83                 | 30            |
| Days after discharge | 36                 | N/A                    | 48                 | N/A                | N/A           |
| Age, years     | 56.5 ± 14.6        | 64.1 ± 16.1            | 70.5 (20–93)       | 60 (44–76)         | 52.8 ± 12.0   |
| Female sex     | 53 (37.1%)         | 40 (41.7%)             | 33 (48.5%)         | 42 (38.2%)         | 121 (40.3%)   |
| Any symptom    | 87.4%              | N/A                    | 73.6%              | 72.0%              |               |
| Any musculoskeletal symptom | N/A               | N/A                    | N/A                | N/A                | 56.3%         |
| Fatigue        | 53.1%              | 54.2%                  | 60.3%              | 39.1%              | 44.3%         |
| Myalgia        | N/A§               | N/A                    | N/A                | 22.7%              | 21.0%         |
| Arthralgia     | 27.3%              | N/A                    | N/A                | 4.5%               | 22.0%         |
| Low back pain  | N/A                | N/A                    | N/A                | N/A                | 16.3%         |
| Back pain      | N/A                | N/A                    | N/A                | N/A                | 22.7%         |
| Neck pain      | N/A                | N/A                    | N/A                | N/A                | 10.3%         |
| Any other symptom | N/A               | N/A                    | N/A                | N/A                | 51.0%         |
| Fever          | N/A                | N/A                    | N/A                | 0.9%               | 0.3%          |
| Cough          | N/A§               | 14.6%                  | N/A§               | 11.8%              | 14.0%         |
| Loss of appetite | N/A§              | N/A                    | N/A                | N/A                | 10.3%         |
| Shortness of breath | 43.4%             | 39.6%                  | 42.6%              | 39.1%              | 26.3%         |
| Diarrhea       | N/A§               | N/A                    | N/A                | 0.9%               | 1.3%          |
| Sore throat    | N/A§               | N/A                    | N/A                | N/A                | 3.0%          |
| Headache       | N/A§               | N/A                    | N/A                | 1.8%               | 8.7%          |
| Dizziness      | N/A                | N/A                    | N/A                | N/A                | 1.3%          |
| Loss of taste  | N/A§               | 9.4%                   | N/A                | N/A                | 15.0%         |
| Loss of smell  | N/A                | 14.6%                  | N/A                | 11.8%              | 12.3%         |

The data are frequency, frequency (percentage), mean, median, mean ± standard deviation, median (range) or median (interquartiles)

N/A not available

†1-month data are presented for symptoms

‡The data were presented among total patients (both ward and intensive care)

§The data were presented among ward patients

*The data were presented as a bar chart; therefore, exact value could not be obtained
Conclusion

Nearly three-quarters of patients reported one or more symptoms, with more than half of patients, who were hospitalized for COVID-19, reported any musculoskeletal symptom at 1 month. The most common musculoskeletal symptom was fatigue, followed by back pain, arthralgia, myalgia, low back pain, and neck pain at 1-month. The persistence of fatigue, myalgia, and arthralgia was related to BMI. The study results increase our understanding of the spectrum of COVID-19, which, in turn, may lead to more efficient and better care for COVID-19 survivors.

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Declarations

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Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval The ethical approval for the study was granted by the Ethics Committee of the Gulhane Scientific Researches, University of Health Sciences (No: 2020-403).

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