Potential factors related to post-COVID-19 persistent symptoms; Khorshid COVID cohort study

Introduction

Recently, with the increase in the number of hospitalized severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) cases (1), new problems appeared in the light of following up of patients after recovery (2,3). The high proportion of COVID-19 survivors discharged from the hospital might experience persistent constitutional and respiratory post-discharge symptoms and abnormal radiological outcomes (2,4). Fatigue, dyspnea and psychotic symptoms were the most prevalent symptoms after discharge from the hospital (5,6).

Recognize the nature of remaining symptoms after recovery helps healthcare services to plan the rehabilitation needs in survivors of COVID-19 infection. However, there is limited comprehensive information regarding the prevalence and factors contributing to the remaining symptoms after discharge from the hospital, and their association with the patient's characteristics (7).

Key point

This study highlighted the emergency need for management of persistent symptoms, in particular, cough, dyspnea, fatigue, and weight loss and their modifiable related factors in order to control post-discharge COVID-19 infection.

Objectives

We aimed to assess the patients' characteristics and the prevalence of COVID-19 symptoms at admission and four weeks after recovery to recognize the potential factors related to the persistent symptoms.
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Patients and Methods

Data extraction

The following information of confirmed COVID-19 patients (≥18 years old) was extracted from the Khoshid COVID Cohort (KCC) study, from February 2020 to April 2020 (3). All adult patients who had coronavirus symptoms with typical CT scan lesions or positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) responses were selected by the census method and enrolled in this study. We excluded recorded data about death cases and patients who refused to participate. The disease was defined as severe if the respiratory frequency was more than 30 breaths per minute or blood oxygen saturation was less than 88%. We considered other cases as non-severe COVID-19 patients. Besides collecting some general information about demographics, pre-existing co-morbidities, date of onset of symptoms, and COVID-19 diagnosis, additional follow-up information concerning the presence of post-discharge persistent symptoms was collected at the first and fourth week by two trained physicians using a short phone questionnaire.

Statistical analysis

We performed the χ² test for categorical data and Fisher's exact test for continuous variables to compare the variables regarding illness severity (severe, non-severe). The categorical data differences between paired samples were estimated using McNamara's test. A value of P<0.05 was considered statistically significant. Association between the persistence symptoms and other characteristics of patients was estimated by generalized estimating equation analysis through the four-week follow-up. Two repeated measurements of each patient (the first and fourth weeks after discharge) were accounted for an exchangeable correlation structure and robust variance estimation.

Results

Of 1350 inpatients, characteristics of 876 recovered COVID-19 patients were evaluated, of whom the information of 10 patients who died and 58 cases who denied to follow-up was excluded from the study. In total, 808 patients completed the first week of follow-up and 806 patients remained to the fourth week. The median age in non-severe and severe patients were 55 years (44-66), and 63 years (53-73), respectively (P<0.001). Around 58.9% of all patients were male (Table 1). The time from illness onset to visit hospital ranged from 4-10 days, and the median range of CT score was 10 (6-13). The ratio of severe cases of COVID-19 under active quarantine was more than non-severe patients (P=0.09). The median levels of C-reactive protein (CRP) at admission were 29 (13-53) mg/L. Most patients had at least two pre-existing co-morbidities previously (median [IQR], 2 (1-4).

Symptoms at admission

There was no significant difference in respiratory symptoms between severe and non-severe subgroups of COVID-19 infection (Figure 1A, B). The most prevalent impaired outcomes were cough (76%), fever (70.6), dyspnea (65%), and fatigue (57%).

Symptoms at follow-up

In the first week of follow-up, the most reported symptoms were chest pain (78.6%), cough (25.2%), and dyspnea (20.6%). Inversely, cough (P<0.001), chest pain (P<0.006), and anosmia (P<0.045) were significantly more prevalent in non-severe patients than those in severe ones. Besides, all patients had more complaints of chest pain in the first week compared with admission, 48.6% in the first week versus 35% at admission. However, the sore throat symptom disappeared entirely in all cases (Figure 1A, B).

After four weeks, the presence of dyspnea persisted in approximately 15% of non-severe cases and it increased in patients who experienced severe COVID-19 disease over time (2%). Moreover, most post-discharge patients had complaints of chest pain in the first (41% in severe and 52% in non-severe, P<0.006) and fourth weeks follow-up (20% in severe and 12% in non-sever patients, P<0.001). After four weeks, there were non-significant differences in severe and non-severe COVID-19 patients regarding dyspnea, 20.6% and 14.86%, respectively (P=0.056). There were no significant variances concerning fatigue in severe and non-severe post-discharge individuals throughout the first week, 10.2% and 12.2%, respectively (P=0.429). The gastrointestinal disorder symptoms had low-prevalence during the follow-up. Inversely, anosmia appeared in the fourth week of follow-up in severe (4.4%) and non-sever patients (5%).

Prediction of COVID-19 persistent symptoms risk

Besides, older age (odds ratio [OR]: 1.02; 95% CI: 1.019-1.045, P<0.0001), male gender (OR: 1.32; 95% CI: 1.034-1.705, P=0.02), administration of hydroxychloroquine (OR, 1.35; 95% CI, 1.056-1.738, P=0.017), and more interval time to visit hospital (OR: 2.31; 95% CI, 2.02-2.55, P<0.0001) increased the risk of the persistent respiratory symptoms. However, there was no association between the results of CT score or disease severity and the risk of remaining symptoms. The length of hospital stay and hydroxychloroquine administration significantly decreased the risk of remaining constitutional symptoms (OR: 0.96; 95% CI: 0.937-0.987 and OR: 0.74; 95% CI: 0.56-0.99, all P<0.05, respectively). Interestingly, laboratory tests, including CRP, neutrophil-to-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), levels, did not relate to the risk of persistent symptoms.

Discussion

Our findings indicated that as per previous study, cough, dyspnea and chest pain are the most frequent respiratory
Table 1. Baseline demographic and clinical characteristics of COVID-19 inpatients on admission and 1st and 4th weeks after discharge

|                      | All cases (N = 808) | Non-Severe (546, 67.6%) | Severe (262, 32.4%) | P value |
|----------------------|---------------------|-------------------------|---------------------|---------|
| **Age, Median (IQR) years** | 58 (46-69)          | 55 (44-66)              | 63 (51-73)          | <0.001  |
| **Age groups (y), No. (%)** |                     |                         |                     |         |
| 20-44                | 175 (21.7%)         | 145 (26.5%)             | 30 (11.45%)         |         |
| 45-64                | 372 (46%)           | 254 (46.5%)             | 118 (45.03%)        |         |
| ≥65                  | 261 (32.3%)         | 147 (26.92%)            | 114 (43.51%)        |         |
| **Male, No. (%)**    | 476 (58.9%)         | 320 (58.60%)            | 156 (59.54%)        | 0.801   |
| **Travel to high risk place** | 128 (15.8%)        | 92 (16.8%)              | 36 (13.74%)         | 0.253   |
| **Quarantine n (%)** | 685 (84.8%)         | 455 (83.3%)             | 230 (86.78%)        | 0.09    |
| **Days from illness onset to visit hospital** | 7 (4-10)            | 7 (4-10)                | 7 (4-10)            | 0.550   |
| **Upper respiratory symptom** |                   |                         |                     |         |
| On admit             | 263 (32.5%)         | 363 (66.4%)             | 193 (73.66%)        |         |
| 1st week*            | 10 (1.2%)           | 6 (1.1%)                | 4 (1.52%)           | 0.737   |
| 4th week**           | 605 (74.8%)         | 422 (77.28%)            | 183 (66.84%)        | 0.005   |
| **Lower respiratory symptom** |                  |                         |                     |         |
| On admit             | 724 (89.6%)         | 494 (90.47%)            | 230 (87.78%)        | 0.044   |
| 1st week             | 570 (70.54%)        | 408 (74.72%)            | 162 (61.83%)        | <0.001  |
| 4th week             | 260 (32.17%)        | 160 (29.30%)            | 100 (38.16%)        | 0.023   |
| **Constitutional symptom** |                 |                         |                     |         |
| On admit             | 766 (94.8%)         | 516 (94.50%)            | 250 (95.41%)        | 0.445   |
| 1st week             | 176 (21.7%)         | 114 (20.87%)            | 62 (23.66%)         | 0.472   |
| 4th week             | 195 (24.13%)        | 130 (23.80%)            | 65 (24.80%)         | 0.901   |
| **Gastrointestinal symptom** |                |                         |                     |         |
| On admit             | 453 (56.06%)        | 309 (56.59%)            | 144 (54.96%)        | 0.425   |
| 1st week             | 49 (6.0%)           | 34 (6.22%)              | 15 (5.72%)          | 0.718   |
| 4th week             | 25 (3.09%)          | 17 (3.1%)               | 8 (3.05%)           | 0.917   |
| **Neurologic symptom** |                    |                         |                     |         |
| On admit             | 364 (45.04%)        | 273 (50.0%)             | 91 (34.73%)         | <0.001  |
| 1st week             | 29 (3.58%)          | 25 (4.57%)              | 4 (1.52%)           | 0.025   |
| 4th week             | 40 (4.95%)          | 26 (4.76%)              | 14 (5.34%)          | 0.779   |
| **Mortality at 4th week** | 16 (1.98%)         | 3 (0.5)                 | 13 (4.96%)          | <0.001  |

*p1st week after follow up; **4th week after follow up.

Prolonged symptoms of COVID-19 infection (2). Although the post-discharge chest pain can be associated with several conditions (including tracheitis, pleuritis, pericarditis, GERD (gastroesophageal reflux disease), and musculoskeletal disorders) (8, 9), in some cases, there is no particular reason describing this condition.

Concerning post-discharge fatigue, some studies recently indicated that chronic fatigue syndrome could be as a long-term adverse effect of COVID-19 and caused by neurological exhaustion (10,11). Regarding anosmia manifestation after four weeks, we hypothesized that it could be a delayed symptom of COVID-19 infection, recognized as a hallmark of COVID-19 (12). This symptom may indicate the neuroinvasion of COVID-19 that could result in chronic neurodegenerative disease along with hospitalization in high-risk patients due to the exacerbated cytokines release and neuroinflammation (13). The relationship between prolonged respiratory symptoms and protease inhibitors-based regimens indicated before (14). It seems that patients with more length of hospital stay had lower chances of having persistent constitutional post-discharge symptoms. Nevertheless, owing to coronavirus conflicting outcomes and limited data about post-discharge symptoms, we could not precisely realize the results underlying this condition.

**Conclusion**

This observational study points out the emergency need to cure and manage persistent symptoms, in particular cough, dyspnea, fatigue, and weight loss and their
modifiable related factors, including hydroxychloroquine-based treatments, and the interval time from illness onset to visit the hospital, in order to control post-discharge COVID-19 infection in all patients.

Limitations of the study
Our study has some limitations. Our survey does not include post-discharge pulmonary function tests. Moreover, our analysis relied on the follow-up information of self-reported questionnaires, which may subject to self-reporting and responding bias. We also specifically studied the experience of hospitalized people. Therefore, the community-based study should be designed to assess post-discharge symptoms of Covid-19 patients in the community.

Authors’ Contribution
Conceptualization: RS, NSM
Methodology: RS, ZN, MK ZKK, MN, AT, NSH, MM and NS
Validation: RS, NSM,
Formal analysis: RS, NSM
Investigation: RS,
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Figure 1. (A) Clinical characteristics of non-severe patients at admission, first and fourth weeks after discharge. B) Clinical characteristics of severe patients at admission, first and fourth weeks after discharge.

Data curation: RS, MD, MB and NS
Writing—original draft: RS, NSM
Writing—review and editing: RS, NSM
Visualization: MD, MB
Supervision: RS, ZN, MK ZKK, MN, AT, NSH, MM and NS.
Project administration: RS, NSM.

Conflicts of interest
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study (IR.MUI.MED.REC.1399.680). Accordingly, written informed consent was obtained from all the respondents at the start of the study. This study was extracted from the internal medicine residency thesis of Zahra Khani Khoozani at Isfahan University of Medical Sciences (Proposal #399637). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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