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

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Abstract

Introduction: Recently, a high percentage of post-discharge patients have reported persistent symptoms after COVID-19 recovery. However, there is limited comprehensive information regarding nature's symptoms and association with potential factors.
Objectives: We aimed to assess the inpatients' 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.
Patients and Methods: We assessed the medical information of 262 severe and 546 non-severe COVID-19 inpatients at admission, and during the first and four weeks after post-discharge from the Khorshid COVID Cohort (KCC) study.
Results: Cough, dyspnea, and fatigue were the most reported symptoms at admission, and continuously were declined over the time (all $P<0.01$). However, the complaint of weight loss was increased during follow-up ($P=0.01$). Older age ($P<0.0001$), male gender ($P=0.02$), administration of hydroxychloroquine ($P=0.017$), and the interval time from illness onset to visit hospital ($P<0.0001$) augmented the remaining respiratory symptoms risk. Additionally, more length of hospital stay correlated to the lower risk of persistent constitutional symptoms ($P<0.05$).
Conclusion: This study points out the greater rehabilitation needs and management of persistent symptoms, in particular cough, dyspnea, fatigue and weight loss, and their related factors

Introduction

Recently, with the increase in the number of hospitalization of 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).

Objectives

We aimed to assess the patients' characteristics and the prevalence of COVID-19 symptoms during care at the hospital and four weeks after recovery to recognize the potential

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.

factors related to the persistent symptoms.

Patients and Methods

Data extraction

The following information of confirmed COVID-19 patients (≥18 years old) was extracted from the Khorshid 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.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study. The institutional ethical committee of Isfahan University of Medical Sciences approved all study protocols (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).

Statistical analysis

We performed the χ^2 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

Table 1. Baseline demographic and clinical characteristics of COVID-19 inpatients on admission and 1st and 4th weeks after discharge

| | All cases (N = 808) | Severity | | P value |
		Non-Severe 546 (67.6%)	Severe 262 (32.4%)	
Age, Median (IQR) years	58 (46-69)	55 (44-66)	63 (53-73)	<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 (87.78%)	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 (.54)	13 (4.96%)	<0.001

*1st week after follow up; **4th week after follow up.

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: 9.37-9.87 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 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
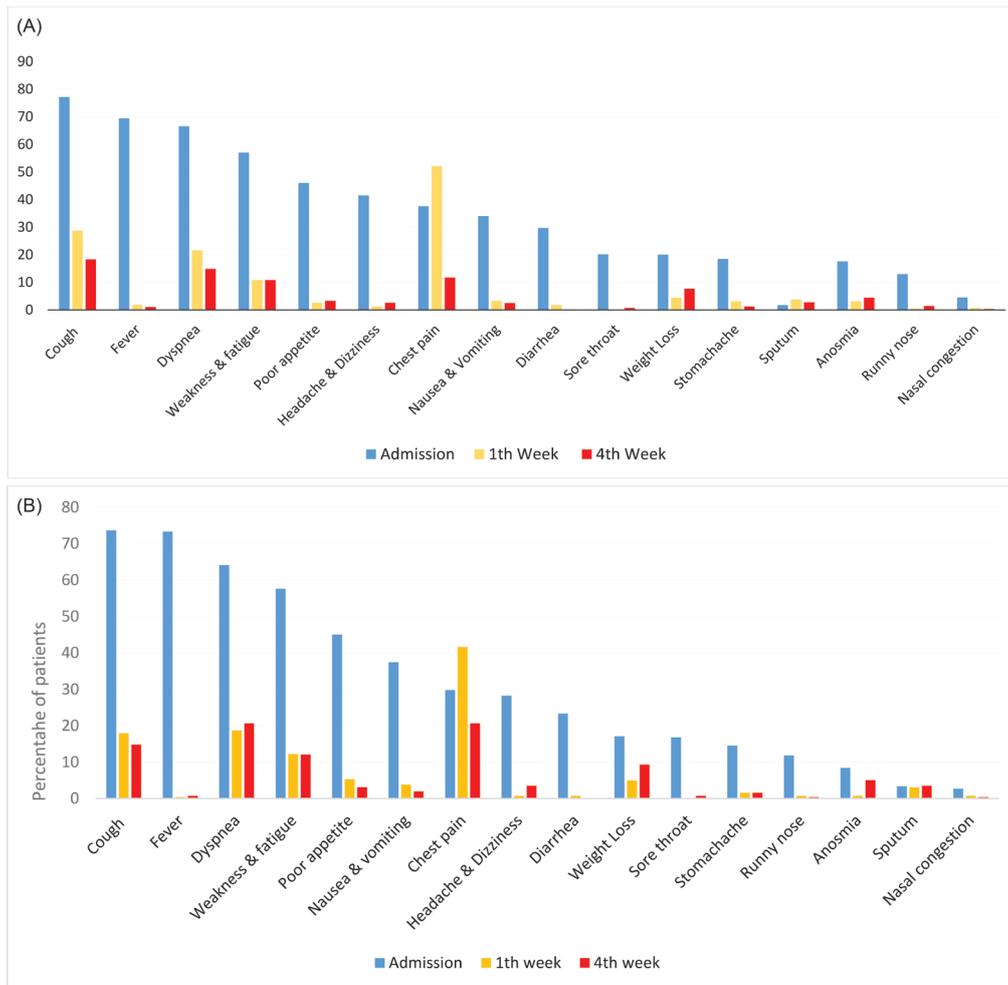
(A)

(B)

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.

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

RS is the principal investigator of the study. RS, ZN, MK ZK, MN, AG, AT, NSH, MM and NS were included in preparing the concept and design. RS, MD, MB and NS revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

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

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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