Long COVID in the Faroe Islands - a longitudinal study among non-hospitalized patients

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Summary: It might take months for COVID-19 symptoms to resolve, even among non-hospitalized persons with milder illness course in the acute phase.

Abstract

Background:

Little is known about long-term recovery from COVID-19 disease, especially in non-hospitalized individuals. In this longitudinal study we present symptoms registered during the acute phase as well as long COVID, i.e. long-lasting COVID-19 symptoms, in patients from the Faroe Islands.

Methods

All consecutive patients with confirmed RT-PCR testing from April to June 2020 were invited to participate in this study for the assessment of long COVID. Demographic and clinical characteristics and self-reported acute and persistent symptoms were assessed using a standardized detailed questionnaire administered at enrollment and at repeated phone interviews in the period 22th April to Aug 16th.

Results

Of the 180 participants (96.3% of the 187 eligible COVID-19 patients), 53.1% reported persistence of at least one symptom after a mean of 125 days after symptoms onset, 33.3% reported one or two symptoms and 19.4% three or more symptoms. At the last follow-up, 46.7% were asymptomatic compared with 4.4 % during the acute phase. The most prevalent persistent symptoms were fatigue, loss of smell and taste, and arthralgias.

Conclusions

Our results show that it might take months for symptoms to resolve, even among non-hospitalized persons with mild illness course in the acute phase. Continued monitoring for long COVID is needed.

Key words: COVID-19; persistent symptoms; longitudinal study; Faroe Islands

Introduction

The literature on the inpatient course of illness of coronavirus disease 2019 (COVID-19) has rapidly grown over the past several months[1]; however, little is known about the long-term recovery from COVID-19 in non-hospitalized individuals. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that mainly affects the respiratory system, causing for example, interstitial pneumonia and acute respiratory distress syndrome[2]. However, the clinical long-term consequences after recovery of acute COVID-19 is uncertain, and most studies have focused on severe patients in hospital settings. Very few studies have prospectively assessed persistence of symptoms in COVID-19 patients, or long COVID, the term recently proposed in Nature[3]. As of yet there is no consensus on the terminology surrounding "long COVID", but long COVID simply refers to a lengthy period of illness, without making assumptions on the underlying cause. An Italian study found that in patients discharged from the hospital after recovery from COVID-19, 87.4% reported persistence of at least one symptom, particularly fatigue and dyspnea[4], while a Chinese longitudinal study reported that 49.6% of recovered patients had one or more common symptoms, including physical decline, fatigue, and myalgia three months after discharge[5]. The majority of COVID-19 patients are, however, not hospitalized, and it is necessary to quantify and characterize long COVID in those not hospitalized to get the full picture of the public health challenge imposed by the pandemic.

In the Faroe Islands, the first point of evidence found that 89% of patients with COVID-19 presented with symptoms (Kristiansen et al. under peer review); the most prevalent symptoms were fever, headache and cough. Furthermore, the intensive testing regime in the Faroe Islands implies that the number of unregistered patients is probably very low[6] which makes this an opportune setting for investigating persistence of symptoms among initially mild patients of COVID-19. Therefore, we performed this longitudinal study

with the aim to describe symptoms in the acute phase and especially long COVID in mainly non-hospitalized patients from the Faroe Islands.

Methods

All consecutive patients diagnosed with COVID-19 confirmed by RT-PCR testing of an oropharyngeal swab between 3 March and 22 April 2020 were invited to participate in the study. A task force consisting of medical doctors was established under the Ministry of Health in response to COVID-19, to monitor all isolated diagnosed COVID-19 patients, and their quarantined contacts. The task force recorded baseline symptoms as well as date of onset, date of recovery, and hospitalization. All diagnosed patients were asked permission to be contacted by the research team, with the purpose of assessing persistent symptoms of disease.

Upon acceptance, data on specific symptoms potentially associated with COVID-19 were obtained using a detailed standardized questionnaire administered at enrollment, and subsequently repeated through phone interviews, to evaluate any persistent symptoms. The number of interviews was dependent on how long symptoms persisted, and the time from onset of symptoms to first interview. Time from the acute phase to first interview varied mainly due to a workload at times higher than projected among the interviewers. However, all patients received a minimum of two follow-up calls. If a participant reported symptoms to have ceased at an assessment or reported symptoms to be stable at two consecutive assessment occasions, and more than two months had passed since the acute phase, the follow-up was terminated. Patients were asked to retrospectively recall the presence or absence of symptoms during the acute phase of COVID-19 and whether each symptom persisted at the time of the phone interview. The symptoms could be rated as mild, moderate, or severe. With small children (0-15 years), the parents were asked to estimate their

children's symptoms. In addition, basic background information was collected, such as education, smoking, self-rated health, medication use, and chronic diseases. The fatigue impact scale was used to ask patients to score their fatigue. It is a self-reported questionnaire that consists of 8 items, each describing one possible experience of fatigue. Individuals were asked to rate the extent to which fatigue has been a problem for them in regard to each of these items, on a scale ranging from 0 (no problem) to 4 (extreme problem)[7].

The Faroese Ethics Committee and Data Protection Agency have approved this study. Data collection began on 21 April and ended in August 2020, and informed consent was obtained from all participants.

Statistics

Descriptive results are presented with mean and standard deviations (SD) for continuous variables and with number and percentages for categorical variables. We used the χ^2 test, Fisher's exact test, or Mann-Whitney U test to compare groups, e.g., individuals with and without persistent symptoms, age groups etc. where appropriate. Of note, age was divided into the following age groups: 0-17, 18-34, 35-49, 50 to 66, and 67+years. ANOVA test was used to compare normally distributed variables such as mean number of symptoms. All analyses were performed using SPSS version 25. P (two-tailed) < 0.05 was considered statistically significant.

Results

A total of 187 patients were potentially eligible for the follow-up assessment; five individuals (3%) did not wish to participate, and two were not reached (1%). Thus, 180 individuals were included in the study. The mean (SD, range) age was 39.9 (19.4, 0-93), and 98 (54%) were women. Only eight individuals were hospitalized. The mean length of hospital stay was two

days (range 0-11 days). The median age of hospitalized patients was 57 (range 37-92). Seven of the eight admitted patients had one or more comorbidities, such as hypertension, emphysema, asthma, ulcerative colitis, diabetes, and cardiovascular disease (Kristiansen et al. under peer review). No fatalities have occurred. The characteristics of the study population are summarized in table 1.

A total of 98 (55%) patients received one follow-up phone interview, i.e. besides the baseline interview, 32% (n=57) two, 8% (n=14) three and 1 % (n=2) four follow-up calls. The mean (SD, range) number of days from onset of symptoms to first follow-up was 93 days (42, 42-140) and from onset of COVID-19 symptoms to last follow-up was 125 days (18, 45-215).

During the acute phase of COVID-19, 4.4% (n=8) were asymptomatic and 7.2% (n=13) reported one or two symptoms while more than 30% had nine or more symptoms (table 2). At the last follow up 46.7% (n=84) were asymptomatic, while 33.3% (n=60) reported 1 or 2 symptoms, and 19.4% (n=35) 3 or more symptoms. The most prevalent symptoms during the acute phase were fatigue, fever, headache, chills, and loss of smell and taste, while the

most persistent symptoms were fatigue, loss of smell and taste, and arthralgias (figure 1). The same symptoms, apart from fever and chills, were reported as the most common severe symptoms reported during acute COVID-19 disease, while the most persisting severe symptoms at last follow-up (n=15) were fatigue, loss of smell and taste, and arthralgias (figure 2). Of the 172 that reported symptoms at baseline, 93 reported at least one persistent symptom at last follow-up. It was particularly those who reported higher number of symptoms during the acute phase that experienced persistent symptoms or long COVID at last follow-up. Paired data in relation to the most prevalent symptoms (loss of smell and taste, fatigue and headache) from the acute phase and the last follow-up show that 43 (24.3%)

reported loss of smell at last follow-up point among the patients who had symptoms in acute phase, 89 (50.3%) loss of taste, 43 (23.9%) fatigue and 11 (6.2 %) headache (table 3). Of note, 1% did not report these symptoms in the acute phase but reported symptoms at the last follow-up. Among those experiencing fatigue during the acute phase (n=127) and at the last follow up (n=53), the fatigue impact scale score was in mean (SD) 1.8 (1.1) and 1.2 (1.0), respectively. None of the participants reported fever or any signs or symptoms of acute illness at the follow-up.

Age-stratified analysis revealed a statistically significant difference in occurrence and number of symptoms between different age groups. During the acute COVID-19 phase an overall difference in the presence of symptoms across age groups (yes/no) ($p<0.0001$) was observed, with a significantly higher proportion reporting any symptom in the age groups from 18 to 66 years, compared with the youngest and the oldest ($p= 0.01$ - $p=0.005$) (Supplementary Fig 1). The youngest age group (0-17 years) reported significantly fewer symptoms, compared with age groups 35-49 ($p=0.03$) and 50-67 ($p=0.03$), but comparable symptoms with the oldest age group (67+). Otherwise, there were no differences across age groups in the presence, the amount, or regarding severity of symptoms (Supplementary Fig. 1 and 2).

At the follow-up, symptoms persisted significantly more frequently among individuals in the age group 50-66 compared with the youngest groups (0-17 years, $p=0.003$; 18-34 years, $p=0.001$), but not with the two other groups. There was no difference regarding the presence or severity of persistent symptoms, but symptoms seemed to be more persistent with increasing age (Supplementary Fig. 3).

No differences were found in presence or severity of symptoms with regard to hospitalization, sex, smoking, self-reported medication use, or chronic diseases overall, or for

each of the most prevalent diseases (hypertension, asthma, hypercholesterolemia, or diabetes type 2) (data not shown).

Discussion

In this study, we followed 180 individuals after recovery from active COVID-19 for the assessment of long COVID. In the study population, 53.1% reported persistence of at least one symptom after a mean of 125 days, in particular fatigue, loss of smell and taste, and arthralgia. Most studies to date have focused on symptoms duration and clinical outcomes in adults hospitalized with severe COVID-19[4, 5, 8, 9]. Our results show that it might take months for symptoms to resolve, and for patients to return to normal health, even among non-hospitalized patients. More than half of the participants reported symptoms for a period of 125 days after active disease, with variable severity; 8.9% reported severe persistent symptoms. Further, analyzing paired data revealed that loss of smell and fatigue was the symptom that most patients reported both during the acute COVID-19 phase and the last follow-up.

An Italian study (n=147) assessed persistent symptoms in patients discharged from hospital after recovery from COVID-19 and found that after a mean of 60.3 days, 87.4% reported persistence of at least 1 symptom, particularly fatigue and dyspnea[4]. In our study sample the occurrence of persistent symptoms is somewhat lower (53.1%), which might be expected due to longer follow-up and since our sample represents all COVID-19 disease courses, i.e. mild, moderate, severe disease, and only 8 hospitalized patients. Another longitudinal study from China (n=538) reported that 49.6% of recovered patients who had been hospitalized had one or more common symptoms, including physical decline, fatigue,

and myalgia three months after discharge[5]. This result is more in line with our estimate of 53.1%, despite that our study almost entirely included non-hospitalized patients; only eight patients have been hospitalized. Thus, our results reveal that long COVID with variable severity occur in a high proportion of individuals affected by COVID-19, even among those with mild disease courses in the acute phase.

No gender difference was observed in prevalence of acute or long-term symptoms, and similarly symptom occurrence did not vary according to pre-existing chronic disease, smoking status, or medication use. This stands somewhat in contrast to other studies[5], but may reflect differences in the study samples. Our study sample consists of relatively young COVID-19 patients with generally mild courses. On the other hand, low statistical power might explain that we are not able to substantiate any differences according to sex or morbidity.

Age, however, seems to play a role in the symptom presentation. The middle-aged individuals seem most affected in the acute phase with the highest occurrence of presenting with symptoms, the highest mean number of symptoms, and the highest frequency of severe symptoms (Supplementary Fig. 3). However, in the post COVID-19 period, a tendency of relatively more persistent symptoms with increasing age was observed. The difference between the proportion reporting any symptom diminished with age from 51% reduction among the youngest age group to 17% among the oldest. Thus, the symptoms, although at a lower prevalence, seem to be more persistent among the oldest age group.

Studies from other countries have shown varying proportions of asymptomatic patients ranging from 7-52 %[10-13]. During the acute phase, 11.2% reported to be asymptomatic (Kristiansen et al, under review), while our retrospective assessment found that

only 4.4%, in fact, were asymptomatic. The lower percentage of asymptomatic individuals can be explained by a more thorough questionnaire at the follow-up than during the acute phase, leading to a higher likeliness of reporting some symptoms in milder patients. The list of symptoms was expanded in this project as new knowledge emerged regarding possible COVID-19 related symptoms. Another explanation of the differing proportion of asymptomatic patients between this study and other studies might be misclassification of symptoms in previous reports, categorizing COVID-19 patients as asymptomatic patients, when they actually were pre-symptomatic.

The study has several strengths. It is a population-based study including 96% of all Faroese COVID-19 patients from the first outbreak, careful recording of symptoms with follow-up performed by medical doctors in a standardized manner to monitor long COVID and a high participation rate limiting any selection bias of more or less severe patients. Compared to other studies that have looked at hospitalized patients, we consider it a strength that our study includes almost entirely non-hospitalized patients, i.e. the most common course of COVID-19, with both mild, moderate, and severe patients. However, there are some limitations including lack of information on medical history before acute COVID-19 illness and a lack of objective assessment of symptom severity. However, the participants were giving the possibility to rate their symptoms as none, mild, moderate, or severe. The symptoms and severity are self-reported, which may have led to both under- and overestimation and recall bias may also have occurred. However, due to the public awareness around COVID-19, recall bias may have posed less of a problem in later interviews.

Conclusion

Our results show it might take months for symptoms to resolve, even among non-hospitalized persons with milder illness course in the acute phase. The most persistent symptoms reported were fatigue, loss of smell and taste, and arthralgia. Studying the symptoms of COVID-19 and long COVID is critical for understanding the full natural history of the disease, accurately predicting the disease's cumulative impact beyond hospitalization and mortality and continues monitoring for long COVID is needed. Our results highlight the need to quantify long COVID properly and accurately to create better guidance on how to improve investigation in patients with enduring symptoms. To further study long COVID in Faroese patients, a comprehensive medical assessment with detailed history and physical examination is now offered to all study participants.

Acknowledgments

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Conflict of interest

None

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Figure legends

Figure 1. Prevalence of COVID-19 symptoms (percentages) during the acute phase (orange bars) and at last follow-up (blue bars) in COVID-19 patients from the first wave in the Faroe Islands (n=180).

Figure 2. Prevalence of self-reported severity (mild, moderate and severe) of COVID-19 symptoms during the acute phase (upper panel), and at last follow-up (lower panel) in COVID-19 patients from the first wave in the Faroe Islands.

Table 1. Demographic and clinical characteristics of COVID-19 patients in the Faroe Islands (n=180)

Women, n (%)	98 (54.4)		
Age (years), mean CSD), range	39.9 (19.4), 0-93	Daily medication use, n (%)	62 (35)
Age distribution, n (%)		Self-reported diseases, n (%)	
0-17	21 (11.7)	Anxiety	1 (0.8)
18-34	57 (31.7)	Asthma	16 (11.8)
35-49	39 (21.7)	Myocardial infarction	3 (2.2)
50-66	45 (25.0)	Carnitine transporter defect	2 (1.5)
67+	18 (10.0)	Ulcerative colitis	4 (3.0)
School, n (%)		Cerebral haemorrhage	3 (2.2)
Currently in primary school	20 (11.2)	Heart failure	1 (0.8)
7 years or less	9 (5.0)	Hypertension	27 (19.4)
8-9 year	8 (4.5)	Hypercholesterolemia	8 (6.0)
10-11 year	49 (27.4)	Hyperthyroidism	1 (0.8)
Upper secondary school	93 (52.0)	Cancer	4 (3.0)

Completed education, n (%)		Chronic bronchitis, COPD	3 (2.3)
Apprentice-/preliminary business college/business college	21 (17.4)	Hypothyroidism	7 (5.1)
Other vocational education	16 (13.2)	Arthritis	3 (2.3)
Shorter education (<3 years)	10 (8.3)	Psoriasis	4 (3.0)
Middle education (3-4 years)	54 (44.6)	Diabetes, type 1	1 (0.8)
Longer education (> 4 years)	20 (16.5)	Diabetes, type 2	5 (3.7)
Smoking status, n (%)			
Active smoker	34 (19.3)		
Occasional smoker	5 (2.8)		
Former smoker	41 (23.3)		
Never smoker	96 (54.6)		

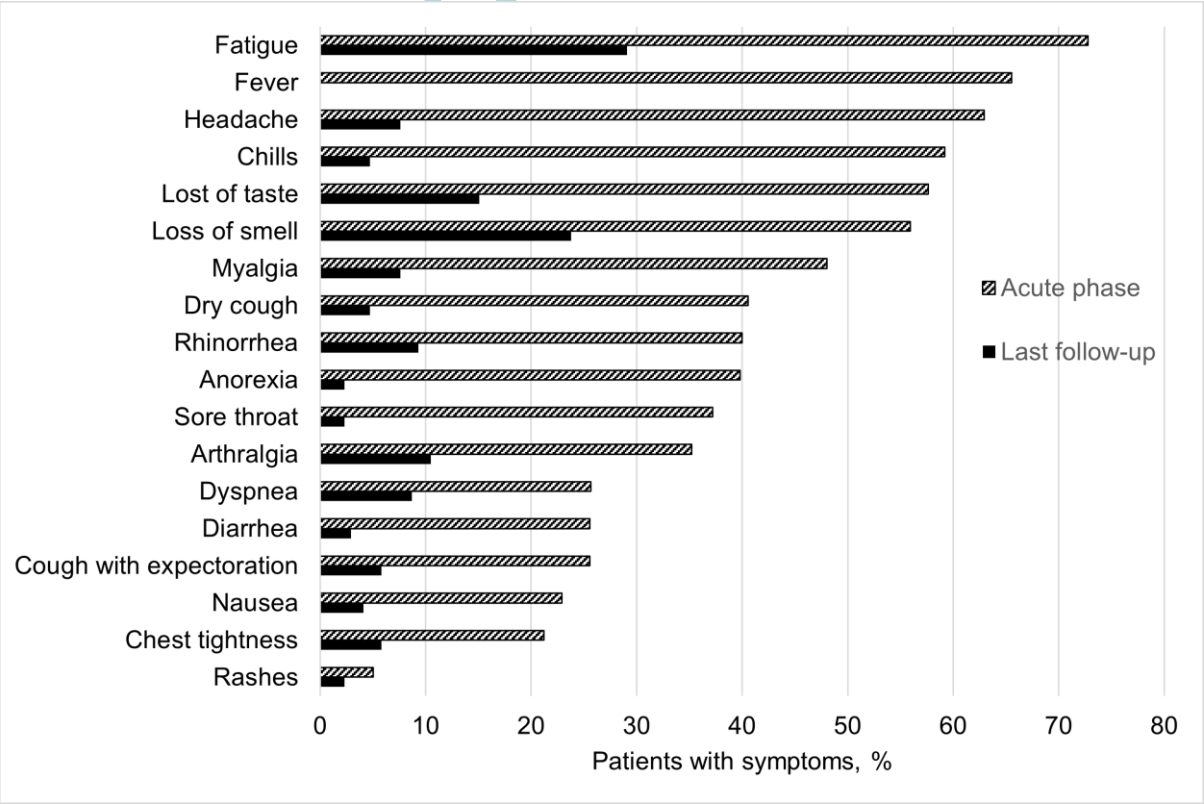
Table 2: Symptoms during acute COVID-19 phase and symptoms at last post COVID19 follow-up in Faroese COVID-19 patients

	Acute COVID-19 phase	Last post COVID-19 follow-up
Symptoms, n (%)	172 (95.6)	95 (53.1)
Mild, n (%)	145 (80.6)	80 (44.1)
Moderate, n (%)	142 (78.9)	42 (23.3)
Severe, n (%)	145 (80.5)	17 (9.4)
Number of symptoms, n (%)	8 (4.4)	84 (46.7)
1-2	13 (7.2)	59 (33)
3-5	43 (23.9)	25 (14.0)
6-8	44 (24.4)	9 (5.0)
9-12	48 (26.7)	2 (1.1)
13+	10 (5.5)	0
Number of symptoms, mean (SD)	7.7 (3.6)	2.7 (2.3)
Mild symptoms, mean (SD)	3.1 (1.9)	1.9 (1.3)
Medium symptoms, mean (SD)	2.8 (1.6)	2.0 (1.3)
Severe symptoms, mean (SD)	3.3 (2.2)	1.8 (1.1)

Table 3. Paired data on the most prevalent symptoms (headage, loss of smell and taste and fatigue) among Faroese COVID-19 patients' symptoms during acute COVID-19 phase and last post COVID-19 follow-up.

	Loss of smell, n (%)	Loss of taste, n (%)	Fatigue, n (%)	Headage , n (%)
No symptoms at acute phase or last follow-up	75 (41.47)	72 (40.0)	47 (26.1)	64 (35.6)
No symptoms at acute phase but at baseline	3 (1.7)	3 (1.7)	2 (1.1)	2 (1.1)
Symptoms at acute phase but not last follow-up	56 (31.1)	73 (40.6)	88 (48.9)	101 (56.1)
Symptoms at acute phase and at last follow-up	43 (23.9)	29 (16.1)	43 (23.9)	13 (7.2)

Figure 1


Fatigue
Fever
Headache
Chills
Lost of taste
Loss of smell
Myalgia
Dry cough
Rhinorrhea
Anorexia
Sore throat
Arthralgia
Dyspnea
Diarrhea
Cough with expectoration
Nausea
Chest tightness
Rashes
Acute phase
Last follow-up
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10
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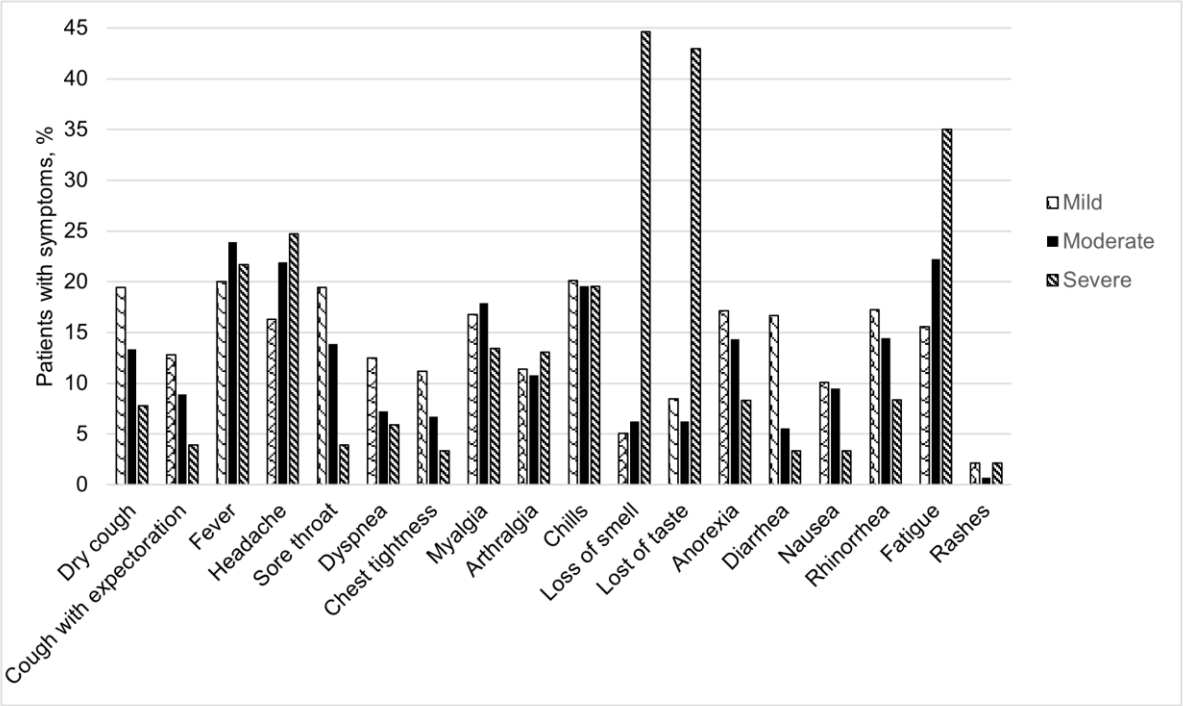
30
40
50
60
70
80
Patients with symptoms, %

Figure 2


Patients with symptoms, %
45
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15
10
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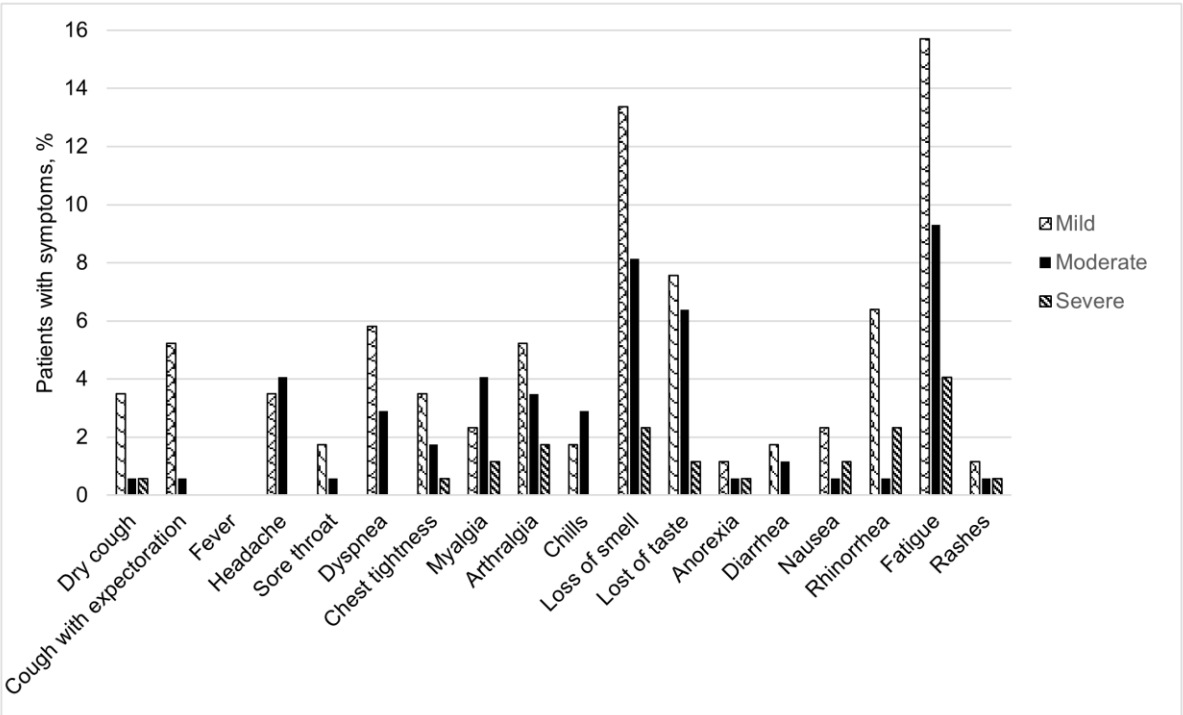
Dry cough
Cough with expectoration
Fever
Headache
Sore throat
Dyspnea
Chest tightness
Myalgia
Arthralgia
Chills
Loss of smell
Lost of taste
Anorexia
Diarrhea
Nausea
Rhinorrhea
Fatigue
Rashes
Mild
Moderate
Severe


Patients with symptoms, %
16
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Dry cough
Cough with expectoration
Fever
Headache
Sore throat
Dyspnea
Chest tightness
Myalgia
Arthralgia
Chills
Loss of smell
Lost of taste
Anorexia
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Fatigue
Rashes
Mild
Moderate
Severe