Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome?

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Take-home message

Previously hospitalised and non-hospitalised COVID-19 patients can still have multiple persistent symptoms three months after the onset of infection-related symptoms. This provides the first evidence for a 'post-COVID-19 syndrome'.

ABSTRACT

Background: Many patients with COVID-19 do not require hospitalization, let alone have undergone COVID-19 testing. There is anecdotal evidence that patients with 'mild' COVID-19 may complain about persistent symptoms, even weeks after the infection. This suggests that symptoms during the infection may not resolve spontaneously. The objective of this study was to assess whether multiple relevant symptoms recover following the onset of symptoms in hospitalized and non-hospitalized patients with COVID-19.

Methods: 2113 members of two Facebook groups for coronavirus patients with persistent complaints in The Netherlands and Belgium, and from a panel of people who registered at a website of the Lung Foundation Netherlands, were assessed for demographics, pre-existing comorbidities, health status, date of symptoms onset, COVID-19 diagnosis, healthcare utilization, and the presence of 29 symptoms at the time of the onset of symptoms (retrospectively) and at follow-up (79±17 days after symptoms onset).

Results: 112 hospitalized patients and 2001 non-hospitalized patients (confirmed COVID-19, n=345; symptom-based COVID-19, n=882; and suspected COVID-19, n=774) were analysed. The median number of symptoms during the infection reduced significantly over time (14 (11-17) *versus* 6 (4-9), *p* <0.001). Fatigue and dyspnoea were the most prevalent symptoms during the infection and at follow-up (fatigue: 95% *versus* 87%; dyspnoea: 90% *versus* 71%).

Conclusion: In previously hospitalized and non-hospitalized patients with confirmed or suspected COVID-19, multiple symptoms are present about three months after symptoms onset. This suggests the presence of a 'post-COVID-19 syndrome' and highlights the unmet healthcare needs in a subgroup of patients with 'mild' or 'severe' COVID-19.

BACKGROUND

Over the last months, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has been confirmed in millions of people around the world [1], resulting in hospitalization in thousands of cases. Multiple symptoms like fever, cough, fatigue, dyspnoea, headache, diarrhoea, nausea and vomiting, have been reported during the hospital stay [2, 3]. About 60 days after onset of the first COVID-19 symptom, only 13% of the previously hospitalized COVID-19 patients were completely free of any COVID-19-related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more [4].

Next to the hospitalized patients with 'severe' coronavirus disease 2019 (COVID-19), millions of people have most probably been infected with SARS-CoV-2 without formal COVID-19 testing and/or medical treatment in the hospital [5, 6]. Indeed, COVID-19 testing capacity was not available for patients who initially were considered to have mild signs and symptoms. These patients are classified as having 'mild' COVID-19 as they only require home care and the infection is expected to resolve [7, 8]. Then again, patients with the so-called 'mild' COVID-19 may still complain about persistent symptoms, even weeks after the onset of symptoms. To date, however, only anecdotal evidence is available [9, 10].

This study assessed whether or not multiple relevant symptoms recover following the onset of symptoms in hospitalized and non-hospitalised COVID-19 patients.

METHODS

Study design and participants

Between June 4 and June 11 2020, members of two Facebook groups for coronavirus patients with persistent complaints in The Netherlands (~11000 members; '*Corona ervaringen en langdurige klachten!*') [11] and Flanders (Belgium, ~1200 members; '*Corona patiënten met langdurige klachten (Vlaanderen)*') [12], and to a panel of ~1200 people who registered at a website of the Lung Foundation Netherlands (*www.coronalongplein.nl*) for additional information on coronavirus were invited to complete an online survey. The medical ethics committee of

Maastricht University stated that the Medical Research Involving Human Subjects Act (WMO) does not apply for this study and that an official approval of this study by the committee was not required (METC2020-1978). The medical ethics committee of Hasselt University formally judged and also approved the study (MEC2020/041). All respondents gave digital informed consent at the start of the questionnaire. Without the informed consent, the remaining questionnaire could not be completed.

Measures

Besides some general questions about demographics, pre-existing comorbidities, self-reported health status (good/moderate/poor) before the onset of symptoms as well as at follow-up (i.e., at the time of completing the questionnaires) , date of onset of symptoms, and COVID-19 diagnosis (please see below), healthcare care utilization during/after the infection (e.g., general practitioner/physiotherapist/medical specialist/psychologist/dietician/nurse/occupational therapist), respondents were asked about the presence (yes/no) of symptoms at the time of infection (retrospectively) and at the time of completing the questionnaires ('symptoms at follow-up'). Scientists (with a background in rehabilitation sciences, psychology, sociology and pulmonology), methodologists, healthcare professionals (elderly care specialist, pulmonologists) and COVID-19 patients from the two Facebook groups were closely involved in putting together the list of 29 symptoms that were studied [2, 3, 13, 14]: increased body temperature (37.0-37.9 °C), fever (body temperature ≥38.0 °C), cough, mucus, nose cold, sneezing, dyspnoea, sore throat, fatigue, muscle pain, joint pain, anosmia, ageusia, headache, dizziness, diarrhoea, nausea, vomiting, red spots on toes/feet, pain/burning feeling in the lungs, ear pain, chest tightness, pain between shoulder blades, heart palpitations, increased resting heart rate, eye problems, sudden loss of body weight, burning feeling in the trachea, and heat flushes. Moreover, there was the option of an open text field to add other symptoms. These data contained many different symptoms, including loss of concentration and cognitive function, chills, rashes, and sleeping problems. However, these 'other' symptoms were not analysed in detail due the large

heterogeneity. The proportion of patients selecting 'yes' per symptom was calculated, including 'other' if selected. The whole sample was analysed. Moreover, patients were analysed after stratification in four groups: 1) hospitalized with confirmed COVID-19 (regular ward, no admission to intensive care unit (ICU)); 2) non-hospitalized with confirmed COVID-19 (based on reverse transcription polymerase chain reaction (RT-PCR) test and/or computed tomography (CT) scan of the thorax); 3) non-hospitalized with symptom-based COVID-19 (based on symptoms by doctor, no formal COVID-19 testing); and 4) non-hospitalized with suspected COVID-19 (no COVID-19 testing, no symptom-based diagnosis by doctor).

Statistical analysis

Statistical analyses and visualization were conducted using SPSS v25.0 (IBM Corp., Armonk, NY, USA), Graphpad Prism 8.3.5. (GraphPad Software, La Jolla, CA, USA), and SankeyMATIC (http://sankeymatic.com/build/). Data were presented as mean ± standard deviation (SD), median and interquartile range (IQR) or frequency and proportion, as appropriate. Between group analyses were performed with the Chi square test or Kruskal Wallis H test. Differences within groups were evaluated with the Wilcoxon Signed Rank test. Subsequently, post-hoc analyses were performed with a Bonferroni correction for multiple comparisons. Multiple regression analysis was performed to predict the number of symptoms at follow-up from age, self-reported health status before the onset of symptoms, self-reported pre-existing comorbidities, and number of symptoms during the infection. *A priori*, the level of significance was set at 0.05.

RESULTS

Demographic and clinical characteristics

In total, 2159 people responded to the online questionnaire (estimated response rate: 16%). Respondents who were admitted to ICU (n=15) were excluded from the analyses. Additionally, 31 respondents were removed before the start of the analyses due to missing data (e.g., no gender reported or not willing to report, n=9), an onset of symptoms before January 1 2020 (the first official confirmed case of COVID-19 in The Netherlands was on February 28, and in Belgium on

February 4, n=8), or reporting that the onset of symptoms was less than three weeks ago (n=14).

Finally, the data of 2113 respondents (85% women, median age: 47 (39-54) years, median body mass index (body weight in kilograms divided by squared height in meters, BMI): 25 (23-29) kg/m^2) were used for further analyses.

Hundred-and-twelve patients were previously hospitalized, and 2001 were non-hospitalized (confirmed COVID-19, n=345; symptom-based COVID-19, n=882; and suspected COVID-19, n=774). Table 1 summarizes the clinical characteristics of the whole sample and of the four groups. The proportion of women and the proportion of patients without pre-existing comorbidities were lower in the hospitalized sample, which was older and had a higher BMI compared to the three non-hospitalized groups. Furthermore, a significantly higher proportion of hospitalized patients received care by a medical specialist, physiotherapist, psychologist, dietician, and nurse.

	Whole sample (n=2113)	Hospitalized (n=112)	Non-hospitalized (confirmed COVID-19) (n=345)	Non-hospitalized (symptom-based COVID-19) (n=882)	Non-hospitalized (suspected COVID-19) (n=774)	p-value
Women, n (%)	1803 (85.3)	78 (69.6)	314 (91.0)	774 (87.8)	637 (82.3)	<0.001
Age, years	47.0 (39.0-54.0)	53.0 (46.3-60.0)	47.0 (37.0-53.5)	46.0 (38.0-53.0)	47.0 (39.0-54.0)	<0.001
BMI, kg/m^2	25.2 (22.6-28.8)	26.9 (24.5-30.9)	26.0 (23.2-29.4)	25.0 (22.3-28.7)	24.9 (22.5-28.4)	<0.001
Self-reported pre-existing comorbidities, n (%)						
None	1293 (61.2)	51 (45.5)	225 (65.2)	523 (59.3)	494 (63.8)	0.007
1 comorbidity	541 (25.6)	40 (35.7)	77 (22.3)	240 (27.2)	184 (23.8)	
≥2 comorbidities	279 (13.2)	21 (18.8)	43 (12.5)	119 (13.5)	96 (12.4)	
Self-reported health status before the onset of symptoms, n (%)						
Good	1799 (85.1)	88 (78.6)	316 (91.6)	743 (84.2)	652 (84.2)	0.011
Moderate	301 (14.2)	23 (20.5)	27 (7.8)	134 (15.2)	117 (15.1)	
Poor	13 (0.6)	1 (0.9)	2 (0.6)	5 (0.6)	5 (0.6)	
Received health care during/after the onset of symptoms, n (%)						
General practitioner	1285 (60.8)	62 (55.4)	191 (55.4)	584 (66.2)	448 (57.9)	<0.001
Physiotherapist	432 (20.4)	42 (37.5)	74 (21.4)	214 (24.3)	102 (13.2)	<0.001
Medical specialist	366 (17.3)	49 (43.8)	68 (19.7)	153 (17.3)	96 (12.4)	<0.001

Psychologist	112 (5.3)	16 (14.3)	23 (6.7)	42 (4.8)	31 (4.0)	<0.001
Dietician	78 (3.7)	17 (15.2)	15 (4.3)	34 (3.9)	12 (1.6)	<0.001
Nurse	63 (3.0)	16 (14.3)	10 (2.9)	25 (2.8)	12 (1.6)	<0.001
Occupational therapist	25 (1.2)	2 (1.8)	5 (1.4)	15 (1.7)	3 (0.4)	0.080

Abbreviations: BMI = Body Mass Index; n = number

Symptoms during the infection

Patients reported a median number of 14 (11-17) symptoms, and 97% of the respondents had more than five symptoms (Figure 1). The difference in median number of symptoms per subgroup was small but significant, being highest in non-hospitalized patients with a symptom-based diagnosis (Table 2). Fatigue (94.9%) and dyspnoea (89.5%) were by far the most prevalent symptoms in all the four groups.

	Whole sample (n=2113)	Hospitalized (n=112)	Non-hospitalized (confirmed COVID-19) (n=345)	Non-hospitalized (symptom-based COVID-19) (n=882)	Non-hospitalized (suspected COVID-19) (n=774)	*p*-value
Number of symptoms, median (IQR)	14.0 (11.0-17.0)	14.0 (9.3-17.0)	14.0 (11.0-18.0)	14.0 (11.0-18.0)	13.0 (10.0-17.0)	<0.001
Symptoms, n (%)						
Fatigue	2006 (94.9)	104 (92.9)	324 (93.9)	847 (96.0)	731 (94.4)	0.226
Dyspnoea	1892 (89.5)	100 (89.3)	300 (87.0)	827 (93.8)	665 (85.9)	<0.001
Headache	1605 (76.0)	80 (71.4)	273 (79.1)	682 (77.3)	570 (73.6)	0.097
Chest tightness	1588 (75.2)	68 (60.7)	248 (71.9)	709 (80.4)	563 (72.7)	<0.001
Cough	1438 (68.1)	89 (79.5)	235 (68.1)	620 (70.3)	494 (63.8)	0.002
Muscle pain	1367 (64.7)	60 (53.6)	245 (71.0)	578 (65.5)	484 (62.5)	0.003
Sore throat	1309 (61.9)	49 (43.8)	188 (54.5)	564 (63.9)	508 (65.6)	<0.001
Increased body temp. (37.0-37.9 °C)	1293 (61.2)	44 (39.3)	189 (54.8)	571 (64.7)	489 (63.2)	<0.001
Pain between shoulder blades	1289 (61.0)	53 (47.3)	216 (62.6)	584 (66.2)	436 (56.3)	<0.001
Pain/burning feeling in lungs	1279 (60.5)	53 (47.3)	178 (51.6)	587 (66.6)	461 (59.6)	<0.001
Heart palpitations	1159 (54.9)	44 (39.3)	191 (55.4)	521 (59.1)	403 (52.1)	<0.001
Increased resting HR	1154 (54.6)	58 (51.8)	199 (57.7)	519 (58.8)	378 (48.8)	<0.001
Dizziness	1091 (51.6)	46 (41.1)	171 (49.6)	490 (55.6)	384 (49.6)	0.006
Nose cold	928 (43.9)	38 (33.9)	169 (49.0)	363 (41.2)	358 (46.3)	0.006
Burning feeling in the trachea	927 (43.9)	37 (33.0)	121 (35.1)	428 (48.5)	341 (44.1)	<0.001
Fever (body temp. ≥38.0 °C)	903 (42.7)	94 (83.9)	178 (51.6)	380 (43.1)	251 (32.4)	<0.001

Ageusia	893 (42.3)	73 (65.2)	218 (63.2)	350 (39.7)	252 (32.6)	<0.001
Diarrhoea	869 (41.1)	49 (43.8)	150 (43.5)	374 (42.4)	296 (38.2)	0.225
Anosmia	839 (39.7)	67 (59.8)	223 (64.6)	308 (34.9)	241 (31.1)	<0.001
Joint pain	808 (38.2)	37 (33.0)	151 (43.8)	340 (38.5)	280 (36.2)	0.066
Nausea	772 (36.5)	51 (45.5)	124 (35.9)	341 (38.7)	256 (33.1)	0.021
Mucus	764 (36.2)	42 (37.5)	107 (31.0)	328 (37.2)	287 (37.1)	0.193
Sneezing	667 (31.6)	27 (24.1)	123 (35.7)	274 (31.1)	243 (31.4)	0.129
Heat flushes	548 (25.9)	18 (16.1)	90 (26.1)	224 (25.4)	216 (27.9)	0.061
Eye problems	542 (25.7)	20 (17.9)	76 (22.0)	245 (27.8)	201 (26.0)	0.045
Ear pain	459 (21.7)	12 (10.7)	74 (21.4)	210 (23.8)	163 (21.1)	0.015
Sudden loss of BW	388 (18.4)	42 (37.5)	81 (23.5)	165 (18.7)	100 (12.9)	<0.001
Vomiting	191 (9.0)	24 (21.4)	41 (11.9)	76 (8.6)	50 (6.5)	<0.001
Red spots on toes/feet	118 (5.6)	9 (8.0)	15 (4.3)	50 (5.7)	44 (5.7)	0.512
Others	623 (29.5)	19 (17.0)	87 (25.2)	284 (32.2)	233 (30.1)	0.002

Abbreviations: n = number; IQR = Interquartile range; temp. = temperature; HR = heart rate; BW = body weight

[Insert Figure 1]

Symptoms at follow-up

Following a mean period of 79±17 days (= the time between the onset of the first symptoms and completing the questionnaire), the number of symptoms reduced significantly. Indeed, there was a median change of -7 (-10 to -4) symptoms per respondent (p<0.001; Figure 1). The difference in median change of symptoms per subgroup was small but significant, being the highest in non-hospitalized patients with confirmed COVID-19 compared to hospitalized, non-hospitalized symptom-based COVID-19, and non-hospitalized suspected-based COVID-19 diagnosis (respectively -7 (-10 to -5) *versus* -7 (-9 to -5), -7 (-10 to -4), and -6 (-9 to -4); p<0.001). Still, fatigue and dyspnoea were the two most prevalent symptoms (Figure 2); only 0.7% of the respondents were symptom free 79 days after the infection; and 2% of the respondents had an increase compared to the number of symptoms during the infection (Figure 1). Moreover, self-reported health status at follow-up was significantly worse compared to before the infection (p<0.001; Figure 3). The multiple regression model including age, self-reported health-status before the onset of symptoms, self-reported pre-existing comorbidities, and the number of symptoms during the infection, statistically significantly predicted the number of symptoms at follow-up $F(4, 2108) = 293.818$, p<0.001 (adjusted $R^2 = 0.357$). Of the independent variables, the number of

symptoms during the infection was responsible for the largest unique contribution (Beta = 0.58, p<0.001).

[Insert Figure 2]

[Insert Figure 3]

DISCUSSION

This is the first study to report that there is only a partial recovery in symptoms about three months after the onset of symptoms in a survey of a large sample of previously hospitalized and non-hospitalized patients with confirmed or suspected COVID-19. Indeed, the median number of symptoms is still high three months after the onset of symptoms in hospitalized and non-hospitalized patients. Moreover, only a very small proportion of respondents is free of symptoms. This is remarkable for a sample with a median age of 47 years, of which most reported a good health status before the infection and the majority used medical and/or allied health care during/after the infection.

A list of twenty-nine symptoms was completed in a large sample of hospitalized and non-hospitalized patients (and for the non-hospitalized patients: confirmed or suspected COVID-19). This makes the current dataset unique and allows to get a first detailed insight in the presence of symptoms about three months after the onset of symptoms in previously hospitalized and non-hospitalized COVID-19 patients. A median of seven symptoms per patient is reported, of which fatigue and dyspnoea are still very common, also in the non-hospitalized patients. Carfi and colleagues reported also fatigue and dyspnoea about 60 days after the onset of COVID-related symptoms in previously hospitalized COVID-19 patients [4]. This is also in line with findings in other post-viral/infectious syndromes [15-18] and findings from critically ill (non-COVID) patients that have been discharged from the ICU, who still experience a wide array of symptoms months after the hospitalization, also called the post-ICU syndrome [19].

The current study excluded patients who were admitted to the ICU. Therefore, the current findings are the first indications of a 'post-COVID-19 syndrome' in a subgroup of patients, since the symptoms are still present about three months after their onset despite receiving usual care. Nonetheless, only 36% of the variance in symptom burden at follow-up could be explained by the age of the participants, self-reported health status before the onset of symptoms, self-reported pre-existing comorbidities, and the number of symptoms during the infection. This provides a clear rationale for additional assessment of the underlying physical, emotional, cognitive and social factors by a multidisciplinary team, which is needed to better understand the persistence of these symptoms and to identify possible traits for pharmacological and non-pharmacological treatment [20, 21]. Previously, interventions for chronic fatigue syndrome or post-viral fatigue were developed [22]. Whether or not these interventions are effective post-COVID-19 remains unknown [23]. Moreover, to date remains unknown whether and to what extent symptom burden post-COVID-19 is comparable with symptom burden in other post(-respiratory)-infectious syndromes. Indeed, it is important to note that in contrast to other post(-respiratory)-infectious syndromes a large array of atypical symptoms such as diarrhoea, heart palpitations, headache, ageusia, anosmia, fever/increased body temperature etc., are reported months after the infection.

The authors emphasize that readers have to be cautious with the external validity of the current findings, as mostly women responded, whom are more likely to present themselves with symptoms than men [24]. Moreover, only COVID-19 patients from Facebook groups with persistent symptoms and who registered on www.coronalongplein.nl were included in the study. This most probably resulted in an overestimation of the true symptom burden in the non-hospitalised group of COVID-19 patients. Then again, the hospitalized group is older, has more comorbidities, higher BMI and higher proportion males than the non-hospitalized groups, which is in line with previous findings [25]. So, the current study should mostly be used to create broad awareness amongst healthcare professionals, employers, insurers and society at large about the

fact that there are most probably thousands of patients with so-called 'mild' COVID-19 who do not all recover fully about three months following the onset of symptoms. Getting these issues out into the open is an important first step as patients with 'mild' COVID-19 got little guidance and were often abandoned to their fate in comparison to hospitalized patients. By that patients will feel understood and get recognition (by friends, relatives, employers, and healthcare professionals) on the one hand, and healthcare professionals will be informed about the large heterogeneity and possible long-term presence of symptoms associated to this novel virus which is also prevalent in patients with 'mild' COVID-19, on the other hand. The size of this persistent symptomatic group of 'mild' COVID-19 remains to be determined, as well as their symptom trajectory over time. In addition, the current study indicates that in a subgroup of patients with 'severe' COVID-19 (e.g., those who were hospitalized) also a symptom burden persists in the months after the onset of symptoms this is in line with recent findings in hospitalized patients [4]. Taken the abovementioned limitations into consideration, the current data are still eye-opening, as most respondents stated that their general health was good before the infection, and now this is only true for a minority. To conclude, the current results emphasize the presence of multiple symptoms and, in turn, unmet healthcare needs of this large sample of hospitalized and non-hospitalized patients with confirmed or suspected COVID-19 about three months after the infection. The phenomenon that symptoms still persist months after the infection suggests the presence of a 'post-COVID-19 syndrome'.

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AUTHOR CONTRIBUTIONS

YMJG and MVH were co-first authors. YMJG, MVH, JD, AWV, RM, FVCM, SHW were responsible for the data collection. MAS is the principal investigator of this trial. YMJG, MVH, DAJ, MAS drafted the manuscript. All authors critically reviewed and revised the manuscript.

CONFLICT OF INTEREST

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Legend Figure 1. Prevalence and change in the total number of symptoms during and three months after infection. The width of lines in figure are proportional for the flow rate.

Legend Figure 2. Prevalence of symptoms during the infection and at follow-up (79 days later). Abbreviations: temp. = temperature; BW = body weight; HR = heart rate.

Legend Figure 3. Prevalence and change in self-reported health status during and three months after the infection. The width of lines in figure are proportional for the flow rate.

0.8%			0.0%
8.3%			0.5%
			3.0%
29.2%			14.2%
37.0%			41.5%
21.7%			40.2%
2.9%			0.7%

During the infection

At follow-up (79 days later)

0 symptoms   1-5 symptoms   6-10 symptoms   11-15 symptoms   16-20 symptoms   21-25 symptoms   26-30 symptoms

0.6%		28.6%
14.2%		
85.1%		64.2%
		7.2%

Before the infection

At follow-up (79 days later)

Good health status

Moderate health status

Poor health status