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Research note

Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort

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ABSTRACT

Objectives: Persistent COVID-19 symptoms have been reported up to 3 months after hospital discharge. Little is known on the frequency and the nature of persistent symptoms beyond 3 months. Here we have assessed, in the longitudinal prospective French COVID-19 cohort, symptoms that persisted 6 months after admission for COVID-19.

Methods: Hospitalized patients with virologically confirmed COVID-19 were enrolled. Follow-up was planned with a physician's visit at month (M)3 and M6 after admission. Associations between persistence of symptoms at M6 and clinical characteristics at admission were assessed through bivariate and multivariate logistic regression.

Results: M6 data were available for 1137 participants. Median age was 61 years (IQR 51–71) and 288 (29%, 95% CI 26–32%) were admitted to intensive care unit (ICU) during the acute phase. Six hundred and fifty-five (68%, 95% CI 65–71%) and 639 (60%, 95% CI 57–63%) participants had at least one symptom at M3 and M6 visit, respectively, mostly fatigue, dyspnoea, joint pain and myalgia. At M6, 255 (24%, 95% CI 21–27%) of participants had three or more persistent symptoms. The presence of three or more symptoms at M6 was independently associated with female gender (adjusted odds ratio (aOR) 2.40, 95% CI 1.75–3.30), having three or more symptoms at admission (aOR 2.04, 95% CI 1.45–2.89) and ICU admission/transfer during acute phase (aOR 1.55, 95% CI 1.09–2.18), but not significantly with age or having two or more comorbidities. One hundred and twenty-five (29%, 95% CI 25–34%) of those who initially had a professional occupation were not back to work at M6.

Discussion: A fourth of individuals admitted to hospital for COVID-19 still had three or more persistent symptoms at M6. Longitudinal follow-up of individuals with severe COVID-19 is warranted to better understand the pathophysiology underlying this long-term persistence. **Jade Ghosn, Clin Microbiol Infect 2021;27:1041.e1–1041.e4**

Introduction

Clinical presentation of SARS-CoV-2 ranges from asymptomatic cases to severe distress respiratory syndrome. When symptomatic, the acute phase commonly features cough, dyspnoea, flu-like symptoms, joint pain, gastrointestinal symptoms and anosmia/ageusia [1]. In France, 83% of patients admitted to hospital for severe

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or critical COVID-19 were alive at Day 60 after admission [2]. Progresses have been made in treating the acute phase of COVID-19. Recently, persistent COVID-19 symptoms have been reported up to 3 months after discharge [3,4]. Very little is known on the frequency and the nature of persistent symptoms beyond three months. Here we assessed, in the longitudinal prospective French COVID cohort, symptoms that persisted 6 months after admission for COVID-19.

Materials and methods

The design of the cohort has been described elsewhere [2]. Briefly, hospitalized patients with a virologically confirmed COVID-19 were enrolled (French COVID cohort, registered in clinicaltrials.gov NCT04262921). The study was conducted with the understanding and the consent of each participant or its surrogate.

Table 1
Characteristics at hospital admission and clinical symptoms at 6 months follow-up of 1137 patients enrolled in the French COVID cohort

Characteristics	Value	Missing
At hospital admission		
Age, years, median (IQR)	61 (51; 71)	7
Female sex, *n*/total n (%)	424/1136 (37)	1
Ethnic group, *n*/total *n* (%)		286
Arab, *n*/total *n* (%)	72/851 (8)	
African, *n*/total *n* (%)	82/851 (10)	
Asian, *n*/total *n* (%)	12/851 (1)	
Latin American, *n*/total *n* (%)	8/851 (1)	
Caucasian, *n*/total *n* (%)	641/851 (75)	
Other, *n*/total *n* (%)	36/851 (4)	
Smoking history, *n*/total *n* (%)		176
Never smoked	625/961 (65)	
Former smoker	280/961 (29)	
Current smoker	56/961 (6)	
Days since symptom onset, Median (IQR)	194 (188; 205)	93
Comorbidities, *n*/total *n* (%)		
Chronic cardiac disease (not hypertension)	195/1060 (18)	77
Hypertension	405/1058 (38)	79
Chronic kidney disease	72/1062 (7)	75
Malignant neoplasm	77/1059 (7)	78
Moderate or severe liver disease	10/1062 (1)	75
Obesity (clinician definition)	230/1049 (22)	88
Chronic pulmonary disease (not asthma)	101/1062 (10)	75
Diabetes (type 1 and 2)	206/1062 (19)	75
No of comorbidities, *n*/total *n* (%)[a]		72
0	309/1065 (29)	
1	314/1065 (29)	
≥2	442/1065 (42)	
Symptoms, *n*/total *n* (%)[b]		92
None	56/1045 (5)	
1–2	337/1045 (32)	
≥3	652/1045 (62)	
Follow-up during hospitalisation		
Intensive care unit during acute phase	288/999 (29)	138
Oxygen therapy, *n*/total *n* (%)	728/1011 (72)	126
Non-invasive ventilation (e.g. BIPAP (Bilevel Positive Airway Pressure), CPAP (Continuous Positive Airway Pressure)), *n*/total *n* (%)	153/996 (15)	141
Pharmacological treatment during acute COVID-19		
Antiviral agent, *n*/total *n* (%)	219/1005 (22)	132
Hydroxychloroquine, *n*/total *n* (%)	161/977 (16)	160
Antibiotic, *n*/total *n* (%)	645/1010 (64)	127
Immunomodulator (e.g. anti-interleukin 6), *n*/total *n* (%)	24/965 (2)	172
Corticosteroid – *n*/total *n* (%)	179/999 (18)	138
Length of hospital stay, median (IQR), days	9 (5; 15)	157
Follow-up after discharge		
Days since symptom onset and M6 visit, median (IQR)	194 (188; 205)	93
Days since hospital discharge and M6 visit, median (IQR)	177 (168; 186)	147
If applicable, back to work at M6 visit- *n*/total *n* (%)	304/429 (71)	221
Persistent symptoms 3 months after hospital admission, *n*/total *n* (%)[b]		180
None	302/957 (32)	
1–2	398/957 (42)	
≥3	257/957 (27)	
Persistent symptoms 6 months after hospital admission, *n*/total *n* (%)[b]		69
None	429/1068 (40)	
1–2	384/1068 (36)	
≥3	255/1068 (24)	

[a] Comorbidities were defined using the Charlson comorbidity index, with the addition of clinician-defined obesity.
[b] Number of symptoms among: fatigue, dyspnoea, joint pain, myalgia, headache, rhinorrhoea, cough, sore throat, ageusia and anosmia.

Ethics approval was obtained from the French Ethic Committee CPP-Ile-de-France VI (ID-RCB: 2020-A00256-33). Follow-up was planned with a physician's visit at month (M) 3 and M6 after admission. Comorbidities were assessed according to the 4C mortality score [5]. The following ten COVID-19 symptoms were systematically collected: fatigue, dyspnoea, joint pain, myalgia, headache, rhinorrhoea, cough, sore throat, ageusia and anosmia. Associations between persistence of symptoms at M6 (defined by the presence of three or more symptoms at M6) and baseline clinical characteristics were assessed through bivariate logistic regressions. Variables with less than 10% of missing values and with $p < 0.25$ in bivariate analysis were tested in a multivariate analysis. The variable selection was performed using a stepwise backward multivariate logistic regression with a p value cut-off point of 0.05. Two-way interactions between risk factors kept in the multivariate analysis were tested. Prevalence of symptoms are given with their 95% CI, estimated by using the exact Clopper–Pearson method. Correlations among each symptoms at admission and 6 months follow-up were assessed through Pearson correlation coefficient. We compared the baseline characteristics (age, gender, symptoms at admission, intensive care unit during acute phase) between patients who attended the M6 visit to the eligible patients who did not (excluding deceased patients) using a chi-squared test. We computed the observed proportion of three or more persistent symptoms at M6 and its 95% CI according to each combination of the risk factors found in the multivariate model to impute patients without M6 visit. Therefore, as a sensitivity analysis, we obtained three estimations of the proportion of patients with three or more persistent symptoms on the overall population of eligible patients for the M6 visit using three imputations: the mean proportion and the proportions from the lower bound and the upper bound of the 95% CI.

Results

We focused on participants enrolled between 24 January and 10 April 2020, in order to allow for a 6-month follow-up. Out of the 2858 participants enrolled during this period, 292 died (10%) during initial hospitalization, 29 died (1%) between hospital discharge and M6, 35 withdrew their consent and two did not attend M6 visit according to investigator's decision. By 9 December 2020, M6 data were available for 1137 participants from 63 centres. Their baseline characteristics are summarized in Table 1. Re-hospitalisation had occurred in 20 patients (2%) at M6. Six hundred and fifty-five (68%, 95% CI 65–71%) and 639 (60%, 95% CI 57–63%) participants had at least one symptom at M3 and M6 visit, respectively (Fig. 1), mostly fatigue, dyspnoea, joint pain and myalgia. At M6, these four most frequent symptoms, were all significantly correlated (Fig. S1), and were also correlated at admission, even if it was less than at M6. Globally, the symptoms at M6 were not or hardly correlated with symptoms at admission. At M6, 255 (24%, 95% CI 21–27%) participants had three or more persistent symptoms. Persistence of anosmia and/or ageusia at M6 was evidenced in 79 participants (7%, 95% CI 6–9%). One hundred and twenty-five (29%, 95% CI 25–34%)

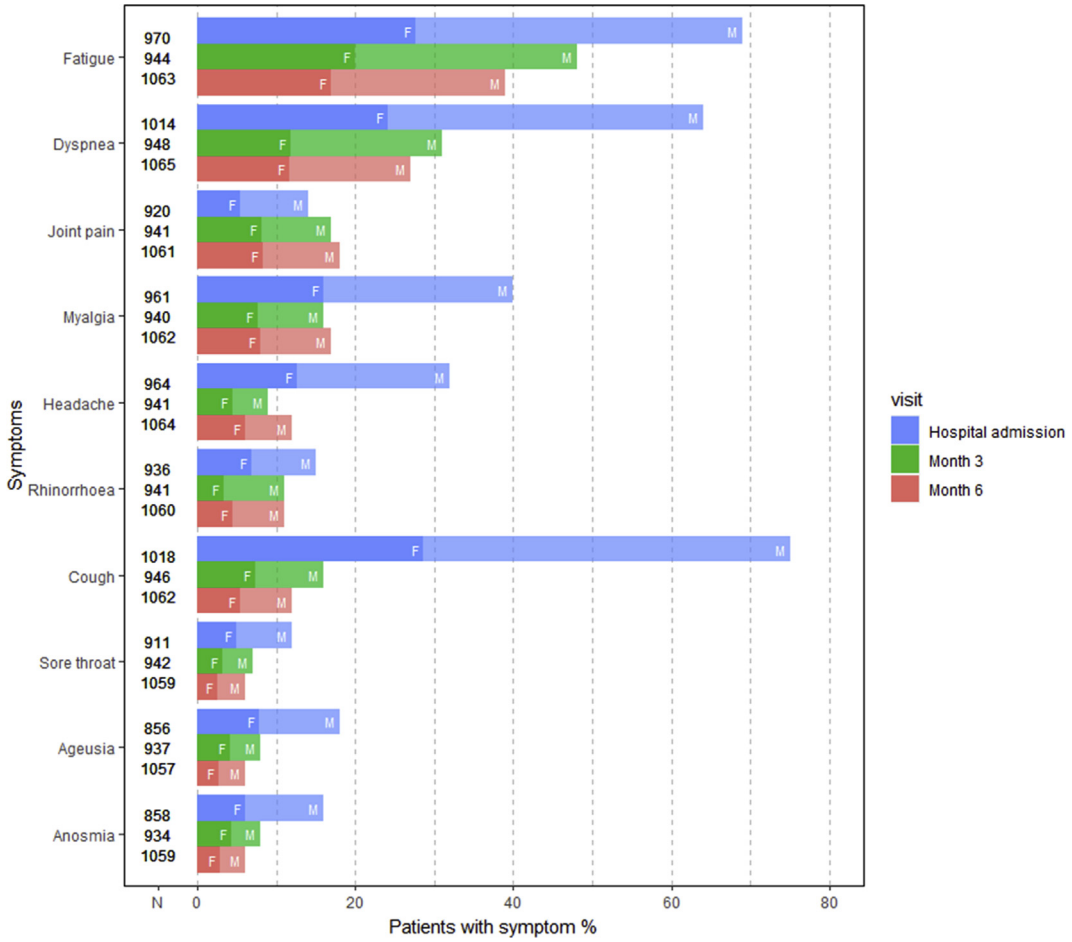

Fig. 1. COVID-19 related symptoms during the acute phase and during follow-up visits according to sex, of 1137 patients enrolled in the French COVID cohort. N, number of patients with data for each symptom at each visit; M, male; F, female.

of those who initially had a professional occupation were not back to work at M6.

In bivariate analysis (Table S1), presence of three or more symptoms at M6 was associated with female gender (OR 2.01, 95% CI 1.51–2.68) and having three or more symptoms at admission (OR 1.99, 95% CI 1.44–2.78), but not significantly with age, ICU admission/transfer during acute phase or having two or more comorbidities. In multivariate analysis (Table S1), presence of three or more symptoms at M6 was associated with female gender (adjusted odds ratio (aOR) 2.40, 95% CI 1.75–3.30), having three or more symptoms at admission (aOR 2.04, 95% CI 1.45–2.89), and ICU admission/transfer during acute phase (aOR 1.55, 95% CI 1.09–2.18). There was no significant two-way interaction among those factors. The observed proportions (and their 95% CI) of three or more persistent symptoms at M6 for each of the eight combinations of the three risk factors are reported in Fig. S2. These proportions ranged between 12% in patients with no risk factor (male, fewer than three symptoms at admission, not admitted/transferred to ICU) to 43% in those with all three risk factors (female, three or more symptoms at admission, admitted/transferred to ICU). In the sensitivity analysis, we obtained three estimations of the proportion of three or more persistent symptoms at M6 among all eligible patients for the M6 visit: the mean proportion was 24% (95% CI 22–26), the proportion from the lower bound of the 95% CI was 20%, and the imputed proportion from the upper bound of the 95% CI was 29%.

Comparing the 1137 patients who attended the M6 visit to the 1587 eligible patients who did not, no statistically significant difference were found except for reporting three or more symptoms at admission. Less patients who did not attend the M6 visit had three or more symptoms at admission (56% versus 62%, $p < 0.001$) (Table S2).

Discussion

Here we show that 60% of individuals admitted to hospital for COVID-19 still complain of one or more symptom 6 months after admission. A fourth of the participants had three or more persistent symptoms at M6. In addition, our data suggest that symptoms still present at M3 are lingering up to M6, and there is little improvement at M6 when compared with M3. These symptoms had disabling consequences since a third of those who had a professional occupation were not back to work at M6. The association between the persistence of symptoms at M6 with gender and clinical presentation during the acute phase (having three or more symptoms at admission and ICU admission/transfer) suggests an intrinsic role of the virus itself and the initial severity of the disease. Of note, ICU admission/transfer during acute phase was not significantly associated in the bivariate analysis, but in multivariate analysis. This is due to strong association between gender and ICU admission/transfer, men being more admitted or transferred to ICU during the acute phase but reported less symptoms at M6 than women.

One limitation of the study could be that reported symptoms severity was not assessed. However, symptoms were collected by a physician and not through self-reports, so we can assume that only significant symptoms were reported. Additionally, many eligible patients for these analyses were lost to follow-up (not reachable or refused to attend follow-up visits), this might be a potential risk of bias if patients who attended the M6 visit were more likely to be more symptomatic. Comparing baseline characteristics between patients who attended the M6 visit and eligible patients who did not (excluding deceased patients), no statistically significant difference were found except for reporting three or more symptoms at admission. The sensitivity analysis (with imputation of patients without M6 visit) was consistent with the main analysis, and confirms that around one fourth of patients has three or more persistent symptoms at M6. Of course this approach, which take into account the differences on the distribution of risk factors, assumes that there is no specific selection bias, i.e., it assumes that patients without visit behave as those with a visit according to the combination of risk factors. Of note, scheduling follow-up hospital visits in this time of saturation of the healthcare system was challenging.

Longitudinal follow-up of individuals with severe COVID-19 is warranted to precisely determine the nature and frequency of persistent COVID-19 symptoms and to better understand the pathophysiology underlying this long-term persistence.

Transparency declaration

C.L., D.B., O.E., L.P., P.L.T. report no conflict of interest. J.G. reports personal fees from Merck, grants and personal fees from ViiV Healthcare, grants and personal fees from Gilead Sciences, personal fees from Roche, personal fees from AstraZeneca, personal fees from Janssen, outside the submitted work. F.M. reports grants from Sanofi, grants and personal fees from Da Volterra, outside the submitted work. The French COVID cohort is funded by the REACTing (REsearch & ACtion emergING infectious diseases) consortium and by a grant of the French Ministry of Health (PHRC no. 20-0424). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author contributions

Dr Laouénan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.03.012.

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