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Follow-up of adults with non-critical COVID-19 two months after symptoms' onset

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Abstract

Objectives

To describe the clinical evolution and predictors of symptom persistence during 2-month follow-up in adults with non-critical COVID-19.

Descriptive clinical follow-up (days 7, 30 [D30] and 60 [D60]) of 150 patients with non-critical COVID-19 confirmed by RT-PCR at Tours University Hospital from March 17 to June 3, 2020, including demographic, clinical and laboratory data collected from the electronic medical records and by phone call. Persisting symptoms were defined by the presence at D30 or D60 of at least one of the following: weight loss ≥ 5%, severe dyspnea or asthenia, chest pain, palpitations, anosmia/ageusia, headache, cutaneous signs, arthralgia, myalgia, digestive disorders, fever or sick leave.

Results

At D30, 68% (n=103/150) of patients presented at least one symptom and 66% (n=86/130) at D60, mainly anosmia/ageusia: (59% (n=89/150) at symptom onset, 28% (n=40/150) at D30 and 23% (n=29/130) at D60). Dyspnea concerned 36.7% (n=55/150) patients at D30 and 30% 130) at D60. Half of the patients (n=74/150) at D30 and 40% (n=52/130) at D

asthenia. Persistent symptoms at D60 were significantly associated with age 40 to 60 years old, hospital admission and abnormal auscultation at symptom onset. At D30, severe COVID-19 and/or dyspnea at symptom onset were additional factors associated with persistent symptoms.

Conclusions

Up to 2 months after symptom onset, two thirds of adults with non-critical COVID-19 had complaints, mainly anosmia/ageusia, dyspnea or asthenia. A prolonged medical follow-up of patients with COVID-19 seems essential, whatever the initial clinical presentation.

Introduction

The most frequent symptoms of COVID-19 at disease onset are cough, fever, asthenia, myalgia, and altered smell or taste, including anosmia/ageusia. Respiratory distress can occur, mostly between 7 to 10 days after symptom onset (1, 2, 3, 4).

Recent studies investigating predictors of poor prognosis at an early stage identified potential risk factors for severe COVID-19 (1,5,6). One recent study in Italy by Carfi *et al.* described persistent symptoms after hospitalization for COVID-19 (7). Such evidence has not been reported for mild to moderate COVID-19. Our objective was to describe the clinical evolution and predictors of symptom persistence at D30 and D60 in patients with initial non-critical COVID-19. The aim was to highlight the initial key symptoms of COVID-19 to alert practitioners and patients of the risk of longer symptom duration in individuals with non-critical COVID-19.

Materials and methods

Study design and population

This epidemiological study, based on a prospective follow-up, was carried out in our academic university hospital from March 17 to June 3, 2020. Inclusion criteria were: every adult patients (≥18 years old) with a confirmed diagnosis of COVID-19 (positive RT-PCR for SARS-CoV-2), and medical care in our hospital either in hospitalization or after consultation at the hospital's outpatient clinical evaluation center (OCEC). The OCEC has been developed to avoid consultation with the general practitioner (GP) or visit at the emergency department to reduce the risk of cross-transmission. The OCEC allowed 1) diagnosing COVID-19 by an RT-PCR test for SARS-CoV-2 with a nasopharyngeal swab; 2) assessing the risk of critical illness/deterioration and the need for surveillance; and 3) eventually proposing hospital admission to monitor the

. Non-inclusion criteria were: patients deceased or admitted to the ICU (cons d a

disease according to the WHO guidance for clinical management of COVID- ,

residents of retirement/nursery homes or long-term care facilities, patients transferred to another healthcare facility (i.e., other hospital, rehabilitation institution, retirement home), those unable to answer a phone questionnaire, and lost-to-follow-up patients at D30.

The infectious diseases (ID) unit was in charge of the outpatient follow-up with confirmed COVID-19 but non-critical disease. Patients with or without clinical signs of pneumonia but without need for oxygen therapy were defined as having mild/moderate COVID-19. Patients with signs of pneumonia requiring oxygen therapy but not needing ICU admission were defined as having severe COVID-19, according to the WHO definition (8). The ID unit assessed these patients' clinical presentation at week one (day 7: D7), 1 month (day 30: D30) and 2 months (day 60: D60) after symptom onset by using a specific case report form (CRF) they developed. The phone interviews were conducted with a clinical decision algorithm to guide care advice messages, triage (evaluation of life-threatening conditions, especially at D7), and screening for COVID-19 symptom persistence or emergence. Baseline characteristics were retrospectively collected from patients' electronic medical records.

Outcome

Persisting symptoms at D30 or D60 were defined as the presence of at least one of the following: weight loss ≥ 5%, grade 2-4 dyspnea according to the modified Medical Research Council (mMRC) scale(9), asthenia grade 3 or 4 according the World Health Organization (WHO) performance status classification(10), persisting chest pain, palpitations, anosmia/ageusia, headache, cutaneous signs (free description), arthralgia, myalgia, persisting digestive disorders (i.e. diarrhea, vomiting, pain), fever (>38°C temperature) or sick leave.

Demographic and initial clinical and laboratory data were collected from patients' electronic medical records (consultation or hospitalization). The relevant comorbidities were those considered at high risk for severe COVID-19 (i.e., obesity [body mass index > 30 kg/m^2], chronic respiratory disease, dialysis, heart failure or previous cardiovascular event, liver cirrhosis, insulin-dependent diabetes, immunosuppression, pregnancy) (11).

The follow-up information was collected by phone at D7, D30 and D60 with use of the specific standardized CRF:

- Day 7, after symptom onset, by phone call for an outpatient or from the electronic medical record for an inpatient: dyspnea, fever, weight loss, chest pain, influenza-like symptoms (headache, asthenia, myalgia), digestive disorders (i.e., diarrhea, vomiting), anosmia and ısia (supplementary material S1).

and D60, after symptom onset, COVID-19 evolution was tracked by use of a fic

standardized CRF (supplementary material S2) by phone call: persistence or emergence of sick leave, general condition (worse, same or better than before COVID-19), dyspnea using the mMRC scale, chest pain and triggering factor, palpitations, anosmia and ageusia on an analog scale (from 0, total anosmia/ageusia to 10, normal) at the worse moment of the disease and at 1-month follow-up, headache, asthenia (WHO), temperature >38°C, myalgia, arthralgia, digestive disorders (i.e., diarrhea, vomiting, pain) and cutaneous signs (supplementary material S2). Each symptom was considered only if not existing before the disease.

For a few clinical variables with a high proportion of missing data, physicians manually reviewed patient charts. Missing data concerned 0 to 29% of the data according to the variables at symptom onset, mainly for dyspnea, chest pain and abnormal auscultation. At D30 and D60, there were few missing data, except for weight evolution (57% and 33% missing data at D30 and D60, respectively).

Statistical analyses

Descriptive statistics included frequency analyses (percentages) for categorical variables and mean (standard deviation [SD]) for quantitative variables. To identify predictors of clinical symptom persistence at D30 and D60, we used comparative analyses with chi-square test or Fisher test for categorical variables or Student *t* test or Mann-Whitney test for quantitative variables. On bivariate analysis, odds ratios along with their 95% confidence intervals (95% CIs) were calculated using logistic regression modelling. Analyses were done using SAS Enterprise Guide 71 64-bit (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant. All tests were two-sided.

All patients were informed of the potential reuse of their data for research purposes and could refuse to participate. This study was registered (no.2020_049) in the teaching hospital register of processing operations performed with personal data, as advised by the French authority *Commission Nationale de l'Informatique et des Libertés* (CNIL). We also had the approval of the local ethics committee in human research (no.2020_039).

Results

Over the first 6 weeks of the epidemic, 293 patients presented to our hospital, as in- or outpatients with RT-PCR-confirmed COVID-19. After excluding 64 ICU patients, 36 residents of nursery home or long-term facilities or patients transferred to another healthcare facility, 24 lost-w-up at D30 and 19 deaths, we finally included 150 patients with non-critical COVID-19 tation. Between D30 and D60, 20 more patients were lost-to-follow-up (Figu

Figure 1

Figure 1 Flow chart. *OCEC: outpatient clinical evaluation center.

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The male/female ratio was 0.79 (females 56%, n=84/150); the mean age was 49 ± 15 years. More than half of the patients (54%, n=80/150) had at least one comorbid condition and half were healthcare professionals (n=75/150). Despite the 20 patients lost-to-follow-up, demographic characteristics at D30 and D60 were similar (supplementary material S3).

The most common symptoms at disease onset were flu-like symptoms (87%, n=129/150), anosmia/ageusia (59%, n=89/150) and fever (51%, n=76/150) (Table I).

Table 1 Patient symptoms at COVID-19 onset and at day 30 (D30) and 60 (D60).

	Onset n=150		D30 n=150		D60 n=130	
Fever (>38°C temperature)	76	(51.4)	5	(3.6)	0	(0.0)
Dyspnea/shortness of breath[a]	49	(42.2)	16	(10.7)	10	(7.7)
Chest pain	15	(14.0)	27	(18.0)	17	(13.1)
Abnormal auscultation	46	(39.3)	-		-	
Flu-like symptoms[b]	129	(87.2)	54	(36.0)	28	(21.5)
Digestive disorders[c]	48	(33.1)	26	(17.3)	15	(11.5)
Including diarrhea[d]	44	(91.7)	13	(50.0)	5	(33.3)
Weight, mean ± SD	78.0 ± 19.4		77.2 ± 20.2		75.6 ± 18.0	
Weightloss ≥ 5%	-		13	(15.9)	15	(17.2)
Anosmia/ageusia	89	(59.3)	40	(27.8)	29	(22.7)

a grade 2-4 dyspnea according the modified Medical Research Council scale.

b myalgia, headache and/or asthenia.

c digestive disorders (i.e., diarrhea, vomiting).

d denominator is digestive disorders.

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For the follow-up at D30 and D60, phone calls were performed at a mean of 32.7 ± 2.5 days (range 27 to 37) and 59.7 ±1.7 (range 57 to 67) after symptom onset. At D30, 103/150 (68%) patients reported at least one symptom as compared with 86/130 (66%) at D60 (Table II). However, each symptom was less frequently reported at D60 than D30, except for arthralgia. At 6% (n=73/150) of patients felt still sick or in a worse clinical condition than at D-
versus 37% (n=48/130) at D60.

Table 2 Patient characteristics at days 30 (D30) and 60 (D60) after symptom onset for patients with ≥ 1 persisting symptom

Patients	Total		≥1 persisting symptom at			
			D30 (n=150)			D6(
	N	%	N	%	P value[a]	N
	150	100	103	68		86
Female	84	56.0	59	57.3	0.6	48.(
Age (years)						
<30	16	10.7	7	6.8		4
30-39	32	21.3	21	20.4		19
40-49	27	18.0	24	23.3		23
					0.06	
60-69	19	12.7	11	10.7		10

a compared to patients without persisting symptom.

b i.e., obesity (body mass index > 30 kg/m2), chronic respiratory disease, dialysis, heart failure or previous cardiovascular event, liver cirrhosis, insulin-dependent diabetes, immunosuppression, pregnancy.

c cough, sneeze and/or rhinitis.

d myalgia, headache and/or asthenia.

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The most frequent symptom reported at D30 and D60 was anosmia/ageusia (Table I). On an analog scale (from 0, total anosmia/ageusia to 10,normal), at the worse moment of the disease, the mean anosmia and ageusia scores were 1.5 ± 2.1 (range 0 to 8) and 1.9 ± 2.5 (range 0 to 8), respectively; at D30, the mean scores were 7 ± 2.9 (range 0 to 10) and 7.7 ± 2.3 (range 0 to 10); and at D60, they were 7.1 ± 2.3 (range 0 to 10) and 8.3 ± 1.6 (range 5 to 10), respectively.

Persisting symptoms at D30 were significantly associated with hospital admission at symptom onset, initial clinical presentation, dyspnea and abnormal auscultation (Figure 2). Persisting clinical symptoms at D30 were associated with age class 40-60 years old but not pre-existing comorbid conditions. At D60, the associations remained for hospital admission and abnormal auscultation at symptom onset as well as the same age class 40-60 years old.

Figure 2

Figure 2 Predictors of persistent COVID-19 symptoms.

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Discussion

This study showed that the medium-term course of 150 patients with mild or moderate COVID-19 was unfavorable: two-thirds of patients still reported symptoms at D30 and D60 and more than

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prolonged symptoms were significantly associated with age 15 to 39 years old, hospital admission at symptom onset, severe COVID-19, and dyspnea or abnormal auscultation.

The main strength of our study was a well-documented prospective follow-up of patients with a non-critical COVID-19 presentation at the early stage and D30 and D60. Indeed, the recent international literature has provided evidence of the clinical presentation and evolution of COVID-19 patients(2,12–15) but mainly regarding the most severe cases in ICUs and predictors of the initial deterioration. The WHO has stated that median time from illness onset to recovery(16) is about 2 weeks for mild cases and 3 to 6 weeks with severe or critical disease. Small-scale studies in Wuhan, China showed that survivors continued to have poor lung and heart function (1).

The initial clinical presentation for patients with mild or moderate COVID-19 (frequent respiratory -like symptoms) was similar from previous studies (17,18) including patients with more clinical presentation at symptom onset described in New York, UK or Italy. H er,

patients included in our study were younger (mean age 49, vs 62 to 73 years in severe cases) (13, 14, 15), and health professionals were overrepresented because of the national recommendations at this date and their prioritizing access to diagnostic tests (19).

For patients with mild or moderate COVID-19, different symptoms such as anosmia/ageusia, myalgia or headache persisted. In a recent study, Lechien et al.(17) reported persistent olfactory dysfunction in 37.5% of patients at least 7 days after the end of mild to moderate COVID-19. The precise mechanism of this symptom is unknown. Patients should be informed of this anomaly and be referred to a specialist.

In our study, at D30, half of the patients still felt sick or in a worse clinical condition than before symptom onset, and 7% reported severe asthenia (3.1% at D60). One-third of the patients had dyspnea and approximately one-sixth had chest pain. This situation is particularly frightening for patients. Rigorous studies with chest explorations seem necessary. Indeed, the evaluation at D30 and D60 was declarative over a phone call, without available physical, biological or imaging assessment. We controlled this potential reporting bias using standardized questionnaires administrated by trained investigators (supplementary data S1 and S2). However, subjective complaints are worth the attention and focus of the medical community and need to be taken into account in the medical care. Moreover, several infectious diseases such as primary cytomegalovirus or Epstein-Barr virus infection are known to be associated with persistent symptoms, without necessarily any obvious anomaly on physical examination (20, 21, 22).

Heavy inflammatory response associated with symptomatic COVID-19 could promote such prolonged convalescence and persisting symptoms. Some authors also suggest the possibility of

psychological disorders have already been shown after acute respiratory distress syndrome (25,26). This hypothesis could not be detailed in our study due to the lack of a reproducible psychological assessment, but should probably be explored.

We found prolonged symptoms significantly associated in bivariate analysis with age 40 to 60 years old, hospital admission at symptom onset, severe COVID-19, and dyspnea or abnormal auscultation. As patients' baseline characteristics were partially retrospectively collected, data for potentially contributive factors were missing, preventing multivariate modelling, as the main contributive factors in bivariate analysis (dyspnea, abnormal auscultation) had up to 29% of missing data. However, the findings of the bivariate analysis were clinically relevant. The smoking status was not available, it would have been interesting to look for an association with duration of symptoms (especially anosmia/ageusia or chronic dyspnea).

With this observational study allowing the prospective follow-up of 150 patients with non-critical COVID-19, we were able to assess the evolution of the disease and demonstrate that even the mildest presentation was associated with medium-term symptoms requiring follow-up. Thus, the COVID-19 pandemic will involve a care burden long after its end.

Conflict of Interest Disclosures

None reported.

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Contribution

- Conceptualization: Claudia Carvalho-Schneider, Louis Bernard, Emilie Beaufils
- Methodology: Emeline Laurent, Leslie Grammatico-Guillon
- Formal Analysis: Emeline Laurent, Leslie Grammatico-Guillon, Claudia Carvalho-Schneider
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- Writing – Review & Editing: Claudia Carvalho-Schneider, Emeline Laurent, Adrien Lemaignen, Emilie Beaufils, Céline Bourbao-Tournois, SaïdLaribi, Thomas Flament, Nicole Ferreira-Maldent, Franck Bruyère, Karl Stefic, Catherine Gaudy-Graffin, Leslie Grammatico-Guillon, Louis Bernard

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- Supervision: Louis Bernard, Claudia Carvalho-Schneider

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The following are the Supplementary data to this article:

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Figure 1

Figure 2

Figure 1 Flow chart. *OC...

Figure 2 Predictors of per...

Tables

Table 1 : Patient symptoms at COVID-19 onset and at day 30 (D30) and 60 (D60).

Table 2 : Patient characteristics at days 30 (D30) and 60 (D60) after symptom onset for patients with ≥ 1 persisting symptom

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