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## Short Communication

# Number of initial symptoms is more related to long COVID-19 than acute severity of infection: a prospective cohort of hospitalized patients

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## ABSTRACT

**Objectives:** Post-COVID-19 symptoms experienced by many survivors have a further devastating effect. This study aimed to analyze the risk factors associated with long COVID-19 in a prospective cohort of hospitalized patients including those requiring intensive care unit (ICU) transfer, taking into account objective measures of COVID-19 severity.

**Methods:** Hospitalized patients with confirmed COVID-19 were enrolled. A structured follow-up visit was performed 4 months after hospital admission. Multivariable adjusted regression models were used to analyse the association between parameters at the acute phase and persistent symptoms.

**Results:** A follow-up visit was performed in 316 patients including 115 (36.4%) discharged from the ICU. Mean age was 64.1 years, and 201 patients (58.3%) were men. Female sex (odds ratio [OR], 1.94; 95% confidence interval [CI], 1.17–3.22;  $P = .01$ ), hypertension (OR, 2.01; 95% CI, 1.22–3.31;  $P < .01$ ), and the number of initial symptoms (NIS) (OR, 1.35; 95% CI, 1.17–1.54;  $P < .001$ ) were significantly associated with long COVID-19. Number of persistent symptoms was significantly associated with NIS (adjusted incidence rate ratio [aIRR], 1.16; 95% CI, 1.11–1.22;  $P < .001$ ), female sex (aIRR, 1.56; 95% CI 1.29–1.87;  $P < .001$ ), hypertension (aIRR, 1.23; 95% CI, 1.02–1.50;  $P = .03$ ), and length of stay in hospital (aIRR, 1.01; 95% CI, 1.005–1.017;  $P < .001$ ).

**Conclusion:** Our study suggested that female sex, hypertension, and NIS had a significant impact on persistent symptoms in hospitalized patients in contrast to severity of acute COVID-19 infection.

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## Introduction

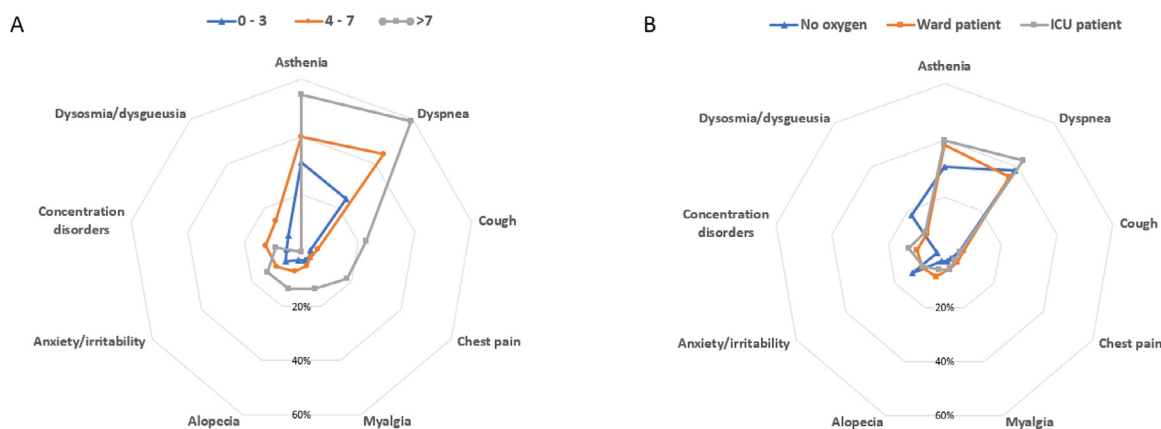
Post-COVID-19 symptoms experienced by many survivors after infection have a further devastating effect. Reports of risk factors of long COVID-19 are rising, but data including reliable assessment of persistent symptoms through structured face-to-face follow-up visits are scarce (Halpin et al., 2021). Here we report a study assessing risk factors associated with post-COVID-19 symptoms in hospitalized patients, including those requiring intensive care unit (ICU) transfer 4 months after admission. We also provide data on

objective measures of COVID-19 severity, for example, oxygen requirement, inflammatory biomarkers, and radiologic findings.

## Methods

We conducted a prospective cohort study of hospitalized patients with COVID-19, discharged from the Amiens-Picardie University Hospital, France, from 2nd February 2020 to 28th December 2020. SARS-CoV-2 infection was confirmed by PCR testing of nasopharyngeal swab. Clinical, biological, radiologic, and hospitalization data were collected from the hospital medical records. All patients were assessed by trained physicians during a face-to-face structured follow-up visit and they were asked about a list of post-COVID-19 symptoms. Clinical examination, blood analysis, and lung

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**Figure 1.** Prevalence of persistent symptoms.

A: Distribution of persistent symptoms according to the number of initial symptoms (0-3: n = 96; 4-7: n = 198; >7: n = 22)

B: Distribution of persistent symptoms according to the severity of acute COVID-19 (no oxygen: n = 39; ward patients: n = 135 patients; ICU patients: n = 142).

Abbreviations: ICU: intensive care unit.

computed tomography (CT) scans were also performed during this dedicated visit. Long COVID-19 was suspected in patients who exhibited persistent post-COVID-19 symptoms 4 months after the hospital admission. Multivariable adjusted logistic regression models were constructed to identify clinical and hospitalization variables associated with post-COVID-19 syndrome in a stepwise manner, and Poisson regression was used to identify variables associated with the number of persistent symptoms. All tests were 2-sided, and a  $P$  value  $<.05$  was considered statistically significant. For this study, we used data from the SEQCOV cohort, and the study protocol was approved by the institutional review board and ethics committee of the CHU Amiens-Picardie (PI2018\_843\_0049).

## Results

From 586 discharged patients, a total of 316 patients attended a structured follow-up visit 4 months after hospital admission. Patients with follow-up evaluation conducted in other hospitals or those who declined (n = 138), died (n = 34), or had missing data (n = 98) were excluded. There were 201 (63.6%) patients who had at least 1 symptom at the follow-up.

The demographic and clinical characteristics of participants are shown in the Table 1. Overall, the mean age was 64 years, with 187 (59%) participants being men. The prevalence of hypertension was higher in patients with long COVID-19, but other comorbidities were not different between the 2 groups. Both patient groups had similar oxygen therapy requirement, admission to ICU, inflammatory markers, and CT-scan abnormalities. Patients reported 5 (interquartile range, 3–6) symptoms at the admission. Hyperthermia (79.1%), cough (70.6%), dyspnea (68%), and myalgia (50.6%) were mainly reported. Participants were assessed a median of 115 days after hospital discharge. The most frequent persistent symptoms were dyspnea (39.2%) and asthenia (37.1%). Distribution of symptoms is shown in the Figure 1.

In univariate analysis, women had significantly higher risk (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.16–3.03;  $P = .01$ ) than men. Patients with hypertension experienced persistent symptoms more frequently (OR, 1.64; 95% CI, 1.04–2.61;  $P = .04$ ). Higher numbers of initial symptoms (OR, 1.27; 95% CI, 1.12–1.45;  $P <.001$ ), especially having 5 or more initial symptoms (OR, 2.47; 95% CI, 1.12–3.03), were associated with greater risk of long COVID-19.

In multivariate logistic regression, female sex (OR, 1.94; 95% CI, 1.17–3.22;  $P = .01$ ), hypertension (OR, 2.01; 95% CI, 1.22–3.31;  $P <.01$ ), and the number of initial symptoms (OR, 1.35; 95% CI,

1.17–1.54;  $P <.001$ ) remained significantly associated with persistent symptoms (Supplementary Table 1). Similarly, in multivariate Poisson regression, the number of persistent symptoms was significantly associated with the number of initial symptoms (adjusted incidence rate ratio [aIRR], 1.16; 95% CI, 1.11–1.22;  $P <.001$ ), female sex (aIRR, 1.56; 95% CI, 1.29–1.87;  $P <.001$ ), hypertension (aIRR, 1.23; 95% CI, 1.02–1.50;  $P = .03$ ), and length of stay in hospital (aIRR, 1.01; 95% CI, 1.005–1.017;  $P <.001$ ).

## Discussion

In our prospective cohort study, female sex, hypertension, and high number of initial symptoms increased the risk of long COVID-19 and the number of persistent symptoms, independently of acute disease severity and clinical course in hospitalized patients.

Our study is in line with reports suggesting that the prevalence of long COVID-19 is higher in women than in men (Bai et al., 2021; Blomberg et al., 2021; Carvalho et al., 2021; Huang et al., 2021; Munblit et al., 2021; Wynberg et al., 2021). After detailed analysis of comorbidities, we showed that hypertension was the most significant risk factor for long COVID-19. Number of initial symptoms had already been described as a risk factor for persistent symptoms in ambulatory (Sudre et al., 2021) and hospitalized patients (Fernández-de-Las-Peñas et al., 2021; Peghin et al., 2021), which is confirmed in this large prospective cohort. Interestingly, severity of acute COVID-19 infection evaluated by oxygen requirement, inflammatory response, or CT-scan findings was not associated with persistent symptoms. Our study suggests that long-term burden of COVID-19 involves multiple nonrespiratory symptoms and these were not associated with acute severity or related post-intensive care syndrome. Strengths of this study are the completeness of data including objective markers of disease severity and reliable symptom collection by face-to-face interview during medical assessment. Our study included sufficient severe forms of COVID-19 with more than a third of ICU admission cases, and infectious or thrombotic complications. This study has several limitations: first, only hospitalized patient alive at follow-up were analysed, and we might not have captured enough discharged patients; second, we performed follow-up visits in a single university center, thus the results might not reflect all hospitalized patients.

Identification of risk factors associated with long COVID-19 could be used to target early intervention and developments to support rehabilitation.

**Table 1**  
Demographic and clinical characteristics of enrolled patients according to persistent COVID-19 symptoms.

Characteristics	Overall (n = 316)	No persistent symptoms (n = 115)	Persistent symptoms (n = 201)	P value
Age (years)	64.1 ± 14.3	64.7 ± 13.7	63.8 ± 14.7	.62
>65	156 (49.4)	60 (52.2)	96 (47.8)	.45
Female	129 (40.8)	36 (31.3)	93 (46.3)	.01
Body mass index (kg/m <sup>2</sup> )	30.27 ± 6.6	29.9 ± 7.0	30.4 ± 6.2	.45
Obesity >30 kg/m <sup>2</sup>	147 (47)	48 (42.5)	99 (49.5)	.23
<b>Comorbidities</b>				
Hypertension	165 (52.2)	51 (44.3)	114 (56.7)	.03
Diabetes	85 (26.9)	34 (29.6)	51 (25.4)	.42
Smoking	119 (37.7)	48 (41.7)	71 (35.3)	.28
Chronic cardiovascular disease	97 (30.7)	38 (30.0)	59 (29.4)	.49
Chronic lung disease	68 (21.5)	26 (22.6)	42 (20.9)	.72
Chronic kidney failure	17 (5.4)	7 (6.1)	10 (5.0)	.67
Neoplasia	12 (3.8)	5 (4.3)	7 (3.5)	.70
Other (pregnancy, hepatic or neurologic diseases, immunocompromised)	57 (18.0)	15 (13.0)	42 (20.9)	.11
<b>Number of comorbidities</b>				
0	2 (1-3)	2 (0-3)	2 (1-3)	.62
1 or 2	67 (21.2)	30 (26.1)	37 (18.4)	.27
3 or more	134 (42.4)	46 (40)	88 (43.8)	-
Chronic treatments	115 (36.4)	39 (33.9)	76 (37.8)	-
Corticosteroids	17 (5.4)	6 (5.2)	11 (5.5)	.92
Immunosuppressive therapy	21 (6.6)	11 (9.6)	10 (5.0)	.12
ACE inhibitors	68 (21.5)	29 (25.2)	39 (19.4)	.23
ARB	41 (13)	11 (9.6)	30 (14.9)	.17
Beta-blocker	66 (20.9)	20 (17.4)	46 (22.9)	.25
Metformin	50 (15.8)	21 (18.3)	29 (14.4)	.37
<b>Disease severity</b>				
Number of initial symptoms	5 (3-6)	4 (3-5)	5 (4-6)	.006
0-4	145 (45.9)	69 (60)	50 (24.9)	<.001
5 or more	171 (54.1)	46 (40)	151 (75.1)	<.001
ICU admission	115 (36.4)	41 (35.7)	74 (36.8)	.84
<b>Oxygen requirement</b>				
None	39 (12.3)	17 (14.8)	22 (10.9)	.38
O <sub>2</sub> <4l/min	135 (42.7)	47 (40.9)	88 (43.8)	.57
O <sub>2</sub> >4l/min	50 (15.8)	22 (19.0)	28 (12.4)	.23
HFNC or NIV	38 (12.0)	16 (13.7)	22 (10.9)	.45
IMV	53 (16.8)	13 (11.3)	40 (19.9)	.05
<b>Laboratory results</b>				
Nadir lymphocyte (/mm <sup>3</sup> )	804 ± 385	795 ± 395	814 ± 379	.68
Lymphopenia <750/mm <sup>3</sup>	158 (50.9)	63 (55.3)	95 (48.5)	.25
CRP max (mg/L)	140 ± 94	139 ± 94	142 ± 96	.76
CRP > 150mg/L	122 (39.1)	44 (38.9)	78 (39.2)	.96
<b>Lung parenchymal involvement at CT scan</b>				
No parenchymal abnormalities	18 (7.1)	10 (10.4)	8 (5.1)	
<25%	95 (37.5)	34 (35.4)	61 (38.9)	
25%-50%	81 (32.0)	30 (31.3)	51 (32.5)	
>50%	59 (23.3)	22 (22.9)	37 (23.6)	
<b>Clinical course</b>				
	10 (6-19)	11 (6-16)	10 (6-21)	.84
<b>Length of stay in hospital in days (IQR)</b>				
1-6	88 (27.8)	35 (30.4)	53 (26.4)	.44
7 or more	228 (72.2)	80 (69.6)	148 (73.3)	-
Infectious complications	57 (18)	17 (14.8)	40 (19.9)	.26
Thrombotic complications	23 (7.3)	8 (7.0)	15 (7.5)	.87
<b>Follow-up</b>				
Time from symptom onset to follow-up (days)	121 (109-139)	121 (110-137)	120 (109-140)	.78
Time from hospital admission to follow-up (days)	115 (103-130)	115 (104-130)	114 (102-131)	.48
<b>Persisting symptoms:</b>				
Asthenia	121 (38.3)		121 (60.2)	
Myalgia	16 (5.1)		16 (8)	
Chest pain	14 (4.4)		14 (7.0)	
Cough	19 (6.0)		19 (9.5)	
Dyspnea	124 (39.2)		124 (61.7)	
Anosmia/dysosmia	20 (6.3)		20 (10.0)	
Ageusia/dysgeusia	15 (4.7)		15 (7.5)	

(continued on next page)

**Table 1** (continued)

Characteristics	Overall (n = 316)	No persistent symptoms (n = 115)	Persistent symptoms (n = 201)	P value
Headache	7 (2.2)		7 (3.5)	
Concentration disorder	32 (10.1)		32 (15.9)	
Anxiety/irritability	29 (9.2)		29 (14.4)	
Alopecia	20 (6.3)		20 (10.0)	
.33				
<u>Lung parenchymal involvement at CTscan<sup>a</sup></u>				
No parenchymal abnormalities	122 (40.7)	48 (43.2)	74 (39.2)	
<25%	127 (42.4)	47 (42.3)	80 (42.3)	
25%–50%	42 (14.0)	15 (13.5)	27 (14.3)	
>50%	9 (3.0)	1 (0.9)	8 (4.2)	
HAD-A score	6.7 ± 4.3	4.7 ± 3.4	7.5 ± 4.3	<.001
HAD-D score	5.2 ± 5.1	2.8 ± 3.5	6.4 ± 5.4	<.001

Quantitative variables are presented as mean ± standard deviation or median (interquartile range); categorical variables are presented as absolute numbers (percentages).

Abbreviations: ACE: angiotensin convertase enzyme; ARB: angiotensin II receptor blocker; CRP: C-reactive protein; CT: computed tomography; HAD: Hospital Anxiety and Depression Scale (a subscale score [A or D] ≥11 denotes anxiety or depression); HNFC: high-flow nasal cannula for oxygen therapy; ICU: intensive care unit; IQR: InterQuartile Range; IMV: invasive mechanical ventilation; NIV: noninvasive ventilation.

<sup>a</sup> A total of 300 patients.

## Disclosures

None.

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## Ethical approval

This research was approved by the ethics review committee of the CHU Amiens-Picardie.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2022.03.006](https://doi.org/10.1016/j.ijid.2022.03.006).

## Declaration of Competing Interest

The authors declare no conflict of interests.

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