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1 **Number of initial symptoms is more related to long COVID-**
2 **19 than acute severity of infection: a prospective cohort of**
3 **hospitalized patients.**

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13

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Introduction

28 Post-COVID-19 symptoms experienced by many survivors after infection have a
29 further devastating effect. Reports of risk factor of long COVID-19 are rising but data
30 including reliable assessment of persistent symptoms by structured face to face follow up
31 visit are scarce (Halpinet al. 2021). Here we report a study assessing post-COVID-19
32 associated risk factors in hospitalized patients including those requiring ICU four months
33 after admission. We provide also data about objective measures of COVID-19 severity e.g.,
34 oxygen requirement, inflammatory biomarkers and radiological findings.

35

Methods

36 We conducted a prospective cohort study of hospitalized patients with COVID-19,
37 discharged from the Amiens Picardie University Hospital, France, from 2nd February 2020 to
38 28th December 2020. SARS-CoV-2 infection was confirmed by polymerase chain reaction
39 (PCR) in nasopharyngeal swab. Clinical, biological, radiological and hospitalization data were
40 collected from hospital medical records. All patients were assessed by trained physicians
41 during a face-to-face structured follow-up visits and asked about a list of post-COVID
42 symptoms. Clinical examination, blood analysis and lung CT-scan was also performed during
43 this dedicated visit. Long Covid was considered in patients exhibited post-COVID persistent
44 symptoms 4 months after the hospital admission. Multivariable adjusted logistic regression
45 models were constructed to identify clinical and hospitalization variables associated with
46 post-COVID-19 syndrome in a stepwise manner and Poisson regression to identify those
47 associated with the number of persistent symptoms. All tests were two-sided, and a p-value
48 less than 0.05 was considered statistically significant. For this study we used data from
49 SEQCOV cohort, the study protocol was approved by institutional review board and CHU
50 Amiens-Picardie ethics committee (PI2018_843_0049).

Results

51

52 From 586 discharged patients, a total of 316 patients achieved a four-month
53 structured follow up visit. Patients with follow up evaluation conducted in other hospital or
54 declined (n=138), died (n=34) or with missing data (n=98) were excluded. Two hundred and
55 one (63.6%) of patients had at least one symptom at the follow-up.

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

65 In univariate analysis, women had significantly increased risk (OR = 1.89 95% CI [1.16-
66 3.03], p=0.01) than men. Patient with hypertension (OR = 1.64 95% CI [1.04-2.61], p=0.04)
67 experienced persistent symptoms more frequently. The number of initial symptoms (OR =
68 1.27 95% CI [1.12-1.45], p<0.001) or patient with five or more initial symptoms showed
69 greater risk for long-COVID-19 (OR = 2.47 95%CI [1.12-3.03]).

70 In multivariate logistic regression, female sex (OR = 1.94 95% CI [1.17-3.22], p=0.01)
71 hypertension (OR = 2.01 95% CI [1.22-3.31], p<0.01) and the number of initial symptoms (OR
72 = 1.35 95% CI [1.17-1.54], p<0.001) remained significantly associated with persistent
73 symptoms (supplementary Table 1). Similarly, in multivariate Poisson regression, the number
74 of persistent symptoms was significantly associated with the number of initial symptoms

75 (adjusted incidence rate ratios, aIRR = 1.16 95% CI [1.11-1.22], p<0.001) as well as female sex
76 (aIRR = 1.56 95% CI [1.29-1.87], p<0.001), hypertension (aIRR = 1.23 95% CI [1.02-1.50],
77 p=0.03) and length of stay in hospital (aIRR = 1.01 95% CI [1.005-1.017], p<0.001)

78 **Discussion**

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

82 Our study is in line with reports suggesting that the prevalence of long covid is higher in
83 women compared with men (Bai et al. 2021; Blomberg et al. 2021; Carvalho et al. 2021;
84 Huang et al. 2020; Munblit et al. 2021; Wynberg et al. 2021). After detailed analysis of
85 comorbidities we showed that hypertension was the most significant risk factor for long
86 COVID-19. Number of initial symptoms had already been described as risk factor of
87 persistent symptoms, in ambulatory (Sudre et al. 2021), and in hospitalized patient
88 (Fernández-de-Las-Peñas et al. 2021; Peghin et al. 2021), results that are confirmed here in
89 this large prospective cohort. Interestingly, severity of acute COVID-19 infection evaluated
90 by oxygen requirement, inflammatory response, or CT-scan findings was not associated with
91 persistent symptoms. Our study suggest that long-term burden of COVID-19 involve multiple
92 non-respiratory symptoms, and was not associated with acute severity or related post-
93 intensive care syndrome. Strengths of this study are the completeness of data including
94 objective markers of disease severity and reliable symptoms collection by face-to-face
95 interview during medical assessment. Our study included sufficient severe forms of COVID-
96 19 with more than a third of ICU admission's cases, and infectious or thrombotic
97 complications. This study has several limitations: first, only hospitalized patient alive at
98 follow up were analysed and we might not have captured enough discharged patients;

99 second, we performed follow-up visits in a single university center, results might not reflect
100 all hospitalized patient.

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

103 **Ethical Approval:**

104 This Research was approved by the Ethics Review committee of the CHU AMIENS-Picardie.

105 **Declaration of Competing Interest:**

106 The authors declare no conflict of interest

107 **Funding source statement:**

108 None

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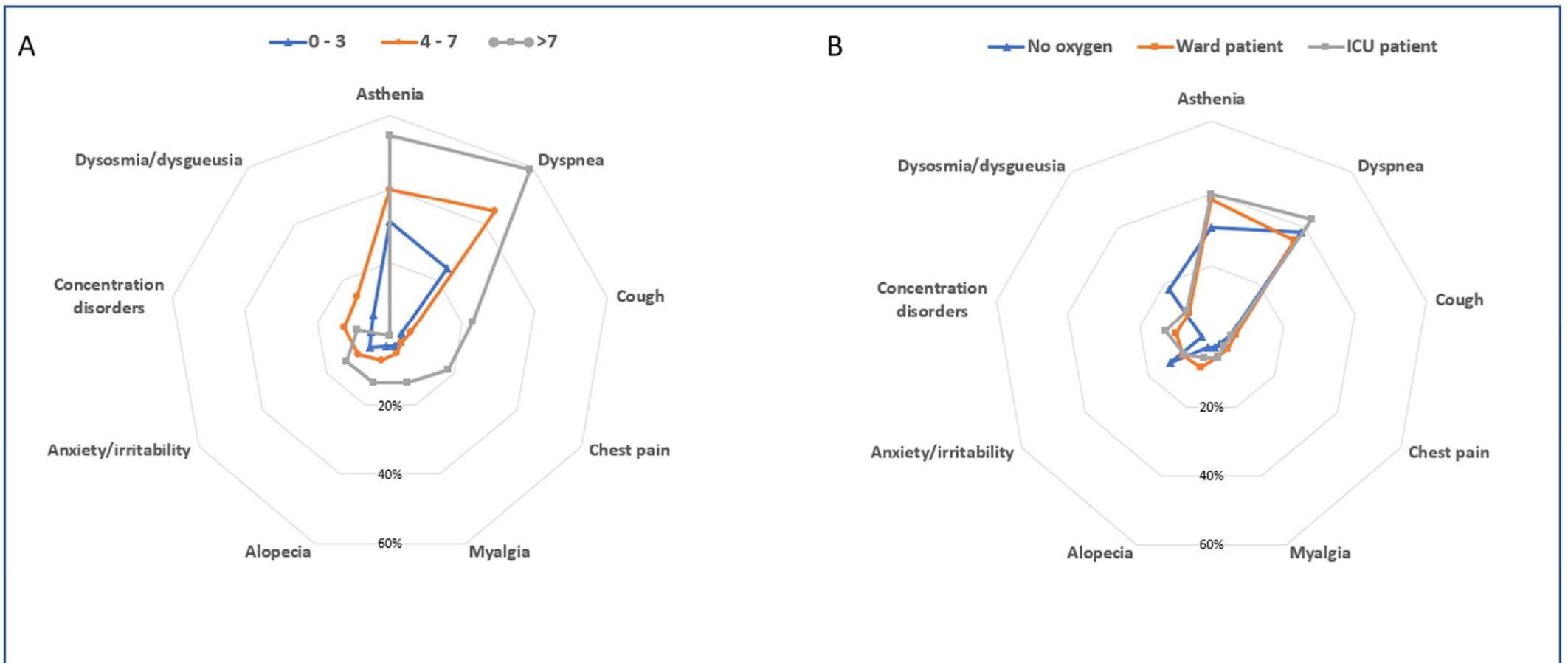


Figure1: Prevalence of persistent symptoms.

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)

	Overall (n=316)	No persistent symptoms (n=115)	Persistent symptoms (n=201)	p-value
Characteristics				
Age (years)	64.1 ± 14.3	64.7 ± 13.7	63.8 ± 14.7	0.62
>65 years old	156 (49.4)	60 (52.2)	96 (47.8)	0.45
Female	129 (40.8)	36 (31.3)	93(46.3)	0.01
Body Mass Index (kg/m ²)	30.27 ± 6.6	29.9 ± 7.0	30.4 ± 6.2	0.45
Obesity >30 kg/m ²	147 (47)	48 (42.5)	99 (49.5)	0.23
Comorbidities				
Hypertension	165 (52.2)	51 (44.3)	114 (56.7)	0.03
Diabetes	85 (26.9)	34 (29.6)	51 (25.4)	0.42
Smoking	119 (37.7)	48 (41.7)	71 (35.3)	0.28
Chronic cardiovascular disease	97 (30.7)	38 (30.0)	59 (29.4)	0.49
Chronic lung disease	68 (21.5)	26 (22.6)	42 (20.9)	0.72
Chronic kidney failure	17 (5.4)	7 (6.1)	10 (5.0)	0.67
Neoplasia	12 (3.8)	5 (4.3)	7 (3.5)	0.70
Other (pregnancy, hepatic or neurologic diseases, immunocompromised)	57 (18.0)	15 (13.0)	42 (20.9)	0.11
<u>Number of comorbidities</u>	2 (1-3)	2 (0-3)	2 (1-3)	0.62
0	67 (21.2)	30 (26.1)	37 (18.4)	0.27
1 or 2	134 (42.4)	46 (40)	88 (43.8)	-
3 or more	115 (36.4)	39 (33.9)	76 (37.8)	-
Chronic treatments				
Corticosteroids	17 (5.4)	6 (5.2)	11 (5.5)	0.92
Immunosuppressive therapy	21 (6.6)	11 (9.6)	10 (5.0)	0.12
ACE inhibitors	68 (21.5)	29 (25.2)	39 (19.4)	0.23
ARB	41 (13)	11 (9.6)	30 (14.9)	0.17
Beta-blocker	66 (20.9)	20 (17.4)	46 (22.9)	0.25
Metformin	50 (15.8)	21 (18.3)	29 (14.4)	0.37
Disease severity				
<u>Numbers of initial symptoms</u>	5 (3-6)	4 (3-5)	5 (4-6)	0.006
0-4	145 (45.9)	69 (60)	50 (24.9)	<0.001
5 or more	171 (54.1)	46 (40)	151 (75.1)	<0.001
ICU admission	115 (36.4)	41 (35.7)	74 (36.8)	0.84
<u>Oxygen requirement</u>				
None	39 (12.3)	17 (14.8)	22 (10.9)	0.38
O ₂ <4l/min	135 (42.7)	47 (40.9)	88 (43.8)	0.57
O ₂ >4l/min	50 (15.8)	22 (19.0)	28 (12.4)	0.23
HFNC or NIV	38 (12.0)	16 (13.7)	22 (10.9)	0.45
IMV	53 (16.8)	13 (11.3)	40 (19.9)	0.05
<u>Laboratory results</u>				
Nadir lymphocyte (/mm ³)	804 ± 385	795 ± 395	814 ± 379	0.68
Lymphopenia <750/mm ³	158 (50.9)	63 (55.3)	95 (48.5)	0.25
CRP max (mg/L)	140 ± 94	139 ± 94	142 ± 96	0.76
CRP > 150mg/L	122 (39.1)	44 (38.9)	78 (39.2)	0.96
<u>Lung parenchymal involvement at CT-scan</u>				0.46
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)	
Clinical course				
<u>Length of stay in hospital in days (IQR)</u>	10 (6-19)	11 (6-16)	10 (6-21)	0.84
1-6	88 (27.8)	35 (30.4)	53 (26.4)	0.44
7 or more	228 (72.2)	80 (69.6)	148 (73.3)	-
Infectious complications	57 (18)	17 (14.8)	40 (19.9)	0.26
Thrombotic complications	23 (7.3)	8 (7.0)	15 (7.5)	0.87
Follow-up				
Time from symptom onset to follow up in days,	121 (109-139)	121 (110-137)	120 (109-140)	0.78

Time from hospitalization admission to follow up (days)	115 (103-130)	115 (104-130)	114 (102-131)	0.48
<u>Persisting symptoms:</u>				
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)	
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)	
<u>Lung parenchymal involvement at CT-scan</u> ♂				
No parenchymal abnormalities	122 (40.7)	48 (43.2)	74 (39.2)	0.33
<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	<0.001
HAD-D score	5.2 ± 5.1	2.8 ± 3.5	6.4 ± 5.4	<0.001

Table 1: Demographic and clinical characteristics of enrolled patients according to persistent COVID symptoms.

Abbreviations are: ACE: Angiotensin Convertase Enzyme; ARB: angiotensin II Receptor Blocker, ICU: Intensive Care Unit, CRP: C-reactive protein, HNF: High Flow Nasal Cannula for oxygen therapy, IMV: invasive mechanical ventilation. ♂: 300 patients. HAD: Hospital Anxiety and Depression Scale a subscale score (A or D) ≥11 denotes anxiety or depression
Quantitative variables are presented as mean ± standard deviation or median (interquartile Range), categorical variables are presented as absolute numbers (percentages).