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## 1 **Long-term persistence of symptoms of dyspnoea in COVID-19 patients**

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15

### 16 *To the Editor*

17 Even after recovering from the acute phase of COVID-19, patients may report the persistence  
18 of symptoms that have become known as ‘long COVID’ ([Akbarialiabad et al., 2021](#)). In one  
19 meta-analysis of nine studies conducted on 1,816 patients between three weeks and three  
20 months after discharge from hospital, the persistence of dyspnoea, chest pain and a cough  
21 affected 37%, 16% and 14% of patients, respectively ([Cares-Marambio et al., 2021](#)). These  
22 proportions gradually decrease with follow-up time. In a cross-sectional study conducted on  
23 574 patients eight months after recovery, dyspnoea was the most frequent sequelae affecting  
24 29% of patients ([Zheng. et al., 2021](#)). In one prospective cohort study conducted on 588

25 COVID-19 patients, 14% of patients reported dyspnoea at eight months of follow-up (Soraas  
26 *et al.*, 2021). In this study, we aim to estimate the rate of persistent dyspnoea in French  
27 COVID-19 patients, as evaluated at least six months of follow-up and to investigate the risk  
28 factors for this persistence.

29 We identified confirmed COVID-19 patients who reported dyspnoea during the acute phase  
30 of the disease from among a cohort of 3,737 patients tested at our institute between 3 March  
31 and 27 April 2020 (Lagier *et al.*, 2020). Patients with pre-existing chronic respiratory diseases  
32 and chronic heart disease were excluded from this analysis. Information on demographics,  
33 comorbidities, and acute symptoms were retrieved from medical files.

34 The selected patients were interviewed by telephone and asked to complete a questionnaire on  
35 possible persistent dyspnoea. Statistical analysis was performed by R 3.6.1 software (R Core  
36 team. R: A language and environment for statistical computing. R Foundation for Statistical  
37 Computing, Vienna, Austria, 2020. URL: <http://www.r-project.org>). Multiple logistic  
38 regression model were applied to explore the association between patient characteristics and  
39 dyspnoea at the acute phase and at the follow-up time. Variables with  $p$ -values  $< 0.2$  in the  
40 univariable analysis were included in the multivariable analysis. Of the 3,737 COVID-19  
41 patients, 3,222 had no known chronic respiratory disease and/or chronic heart disease at the  
42 time of inclusion and 880/3,222 (27.3%) reported dyspnoea at the acute phase of COVID-19.  
43 Being female or obese and consulting six or more days after the onset of symptoms were  
44 independently associated with dyspnoea. Patients with dyspnoea at admission were more  
45 likely to receive oxygen therapy. In univariate analysis, hypoxaemia, oxygen saturation  
46  $\leq 94\%$ , C-reactive protein  $>5$  mg/L, neutrophils  $>7.5$  Giga/L, eosinophils  $<0.1$  Giga/L,  
47 lymphocyte  $<1$  Giga/L associated with dyspnoea, but a multivariate analysis was not  
48 conducted due to a high proportion of missing information. (Table 1). Of 880 patients, we  
49 randomly selected 838 patients for the telephone interview. Among them, 496/838 (59.2%)

50 answered the questionnaire and 342/838 (40.8%) were lost to follow-up. Patients who  
51 responded were significantly less likely to report hypertension, to present severe symptoms, to  
52 require oxygen upon inclusion, to undergo prolonged hospitalisation and had lower rates of  
53 mortality, as compared with all patients reporting dyspnoea at inclusion ([Supplementary](#)  
54 [Table 1](#))

55 Among these 496 patients, 123 (24.8%) reported persistent dyspnoea. The duration between  
56 the onset of symptoms and the interview was  $44.0 \pm 10.3$  weeks, ranging from 31.6 to 63.1  
57 weeks. Being aged  $\geq 45$  years old and consulting early during the acute phase (less than six  
58 days after the onset of symptoms) were independently associated with persistent dyspnoea  
59 ([Table 2](#)).

60 Lung damage in COVID-19 patients could be explained by various underlying mechanisms,  
61 including viral and immune-mediated implications ([Liu et al., 2020](#)), which could cause the  
62 persistence of dyspnoea. Dyspnoea is, by nature, a highly subjective experience. Women are  
63 more prone to suffer dyspnoea, possibly due to a decreased surface area for pulmonary gas  
64 exchange relative to lung size-matched men ([Cory et al., 2015](#)). People who are obese have a  
65 decreased functional residual capacity and expiration reserve volume ([Parameswaran et al.,](#)  
66 [2006](#)). Therefore, it is not surprising that female and obese COVID-19 patients had a higher  
67 risk for dyspnoea at admission. We observed that dyspnoea was more frequent in patients  
68 consulting more than six days after the onset of symptoms, suggesting that it takes a few days  
69 for the virus to provoke such symptoms. The association with a high viral load upon  
70 admission suggests a direct cytopathic effect of viruses on lung tissue.

71 The association of symptom persistence with being older may suggest a lower capacity of cell  
72 regeneration due to ageing. We have no hypothesis, however, to explain why early  
73 consultation was associated with the persistence of dyspnoea.

74 The use of the telephone interview has some limitations, including the lack of respiratory  
75 functional tests to quantify dyspnoea levels and a lack of information about smoking status. In  
76 addition, patients lost to follow-up could potentially include a high proportion of patients who  
77 fully recovered their respiratory function. Despite these limitations, our study underlined the  
78 high prevalence of the persistence of dyspnoea (24.8%) in COVID-19 patients and its  
79 association with older age. Further investigation with a clinical evaluation of respiratory  
80 function over time is required in these patients.

81 **Ethical approval:**

82 This study was approved by the Comité de Protection des Personnes Nord Ouest II (No. 2021-  
83 A01183-33) on 22/07/2021.

84 **Consent for publication**

85 All authors gave their consent for publication.

86 **Availability of data and materials**

87 All the data for this study will be made available upon reasonable request to the  
88 corresponding author.

89 **Funding**

90 None declared

91 **Conflict of interest**

92 None declared.

93 **Author contributions:**

94 Philippe Gautret and Didier Raoult devised the project, the main conceptual ideas. Nhu Ngoc  
95 Nguyen, Jean Christophe Lagier, Matthieu Million, Thi Loi Dao, Line Meddeb collected the  
96 data. Van Tuan Hoang and Nhu Ngoc Nguyen analyzed and interpreted data. Nhu Ngoc  
97 Nguyen and Philippe Gautret wrote the manuscript. All authors reviewed and approved the  
98 final version of the manuscript.

99 Philippe Gautret is the guarantor for this work.

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109 **Table 1.** Risk factors for dyspnoea during the acute phase (n=3,222)

		No dyspnoea (n=2,342) %	Dyspnoea (n=880) %	Univariate analysis OR [95% CI] p-value	Multivariate analysis** OR [95% CI] p-value
	Mean ± SD	43.6 ± 15.8	43.7 ± 15.5		
	Range	18–96	18–94		
Age	< 45 (n=1,720)	1,255 (53.6)	465 (52.8)	ref	
	≥ 45 (n=1,502)	1,087 (46.4)	415 (47.2)	1.03 [0.88–1.21] 0.71	
Sex	Male (n=1,464)	1,107 (47.3)	357 (40.6)	ref	ref
	Females (n=1,758)	1,235 (52.7)	523 (59.4)	1.31 [1.12–1.54] <b>0.0007</b>	1.38 [1.17–1.61] <b>0.0001</b>
<b>Chronic conditions</b>					
Hypertension	No (n=2,845)	2,080 (88.8)	765 (86.9)	ref	
	Yes (n=377)	262 (11.2)	115 (13.1)	1.19 [0.94–1.52] <b>0.14</b>	
Diabetes	No (n=2999)	2179 (93.0)	820 (93.2)	ref	
	Yes (n=223)	163 (7.0)	60 (6.8)	0.98 [0.71–1.34] 0.89	
Cancer	No (n=3,138)	2,280 (97.4)	858 (97.5)	ref	
	Yes (n=84)	62 (2.6)	22 (2.5)	0.94 [0.55–1.56] 0.81	
Obesity	No (n=2,882)	2,124 (90.7)	758 (86.1)	ref	ref
	Yes (n=340)	218 (9.3)	122 (13.9)	1.57 [1.23–1.99] <b>0.0002</b>	1.45 [1.13–1.84] <b>0.003</b>
<b>Co-medications</b>					
Beta blockers	No (n=3,141)	2,285 (97.6)	856 (97.3)	ref	ref
	Yes (n=81)	57 (2.4)	24 (2.7)	1.12 [0.66–1.85] 0.63	
Dihydropyridine	No (n=3,117)	2,269 (96.9)	848 (96.4)	ref	
	Yes(n=105)	73	32	1.17	

		(3.1)	(3.6)	[0.74–1.82] 0.46	
Angiotensin-converting enzyme inhibitors	No (n=3,197)	2,325 (99.3)	872 (99.1)	ref	
	Yes (n=25)	17 (0.7)	8 (0.9)	1.25 [0.47–3.08] 0.59	
Angiotensin II receptor blocker	No (n=3,107)	2,258 (96.4)	849 (96.5)	ref	
	Yes (n=115)	84 (3.6)	31 (3.5)	0.98 [0.62–1.51] 0.93	
Metformin	No (n=3,125)	2,273 (97.1)	852 (96.8)	ref	
	Yes (n=97)	69 (2.9)	28 (3.2)	1.08 [0.67–1.72] 0.72	
Fenofibrate	No (n=3,203)	2,329 (99.4)	874 (99.3)	ref	
	Yes (n=19)	13 (0.6)	6 (0.7)	1.23 [0.38–3.48] 0.68	
Statin	No (n=3,154)	2,290 (97.8)	864 (98.2)	ref	
	Yes (n=68)	52 (2.2)	16 (1.8)	0.82 [0.43–1.46] 0.48	
<b>COVID-19 status at inclusion</b>					
Time between onset of COVID symptoms and admission	< 6 days(n=1,599)	1,239 (52.9)	360 (40.9)	ref	ref
	≥ 6 days (n=1,623)	1,103 (47.1)	520 (52.1)	1.62 [1.38–1.90] <b>&lt;0.0001</b>	1.51 [1.28–1.77] <b>&lt;0.0001</b>
NEWS Score 2	Low (n=3,017)	2,216 (94.6)	801 (91.0)	ref	
	Medium (n=125)	89 (3.8)	36 (4.1)	1.12 [0.75–1.66] 0.58	
	High (n=80)	37 (1.6)	43 (4.9)	3.22 [2.06–5.03] <b>&lt;0.0001</b>	
Oxygen	No (n=3,034)	2,256 (96.3)	778 (88.4)	ref	
	Yes (n=188)	86 (3.7)	102 (11.6)	3.44 [2.52–4.69] <b>&lt;0.0001</b>	3.13 [2.31–4.25] <b>&lt;0.0001</b>
Oxygen saturation (SpO2) %*	>94% (n=2,754)	1,968 (96.1)	786 (92.4)	ref	
	≤ 94% (n=145)	80	65	2.03	



		(3.9)	(7.6)	[1.43–2.89] <b>&lt;0.0001</b>
Chest Computed Tomography*	Normal (n=509)	370 (32.2)	139 (26.8)	ref
	Limit (n=756)	542 (47.1)	214 (41.3)	1.05 [0.82-1.35] 0.69
	Intermediate (n=329)	203 (17.7)	216 (24.3)	1.65 [1.23-2.22] 0.001
	Severe (n=74)	35 (3.0)	39 (7.6)	2.97 [1.81-4.87] <0.01
C-reactive protein*	≤ 5mg/L (n=1,466)	1,093 (63.2)	373 (56.1)	ref
	>5mg/L(n=929)	637 (36.8)	292 (43.9)	1.34 [1.12-1.62] <b>0.001</b>
Neutrophils*	≤ 7.5 Giga/L (n=2,604)	1,894 (97.8)	710 (96.5)	ref
	>7.5 Giga/L (n=68)	42 (2.2)	26 (3.5)	1.65 [0.96-2.78] <b>0.046</b>
Eosinophils*	≥0.1 Giga/L (n=684)	520 (26.9)	164 (22.3)	ref
	<0.1 Giga/L (n=1,988)	1,416 (73.1)	572 (77.7)	1.28 [1.04-1.58] <b>0.015</b>
Lymphocytes*	≥ 1 Giga/L (n=2,370)	1,731 (89.4)	639 (86.8)	ref
	< 1 Giga/L (n=302)	205 (10.6)	97 (13.2)	1.28 [0.98-1.67] 0.06
D-Dimer*	≤ 0.5 µg/ml (n=335)	227 (58.7)	108 (57.8)	ref
	>0.5µg/ml (n=239)	160 (41.3)	79 (42.3)	1.04 [0.72-1.50] 0.84
Fibrinogen*	≤ 4g/L (n=290)	216 (46.2)	74 (35.2)	ref
	>4 g/L (n=388)	252 (53.8)	136 (64.8)	1.58 [1.11-2.24] 0.008
PCR Ct value < 16 at admission*	No (n=2,460)	1,773 (93.3)	687 (94.9)	ref
	Yes (n=164)	127 (6.7)	37 (5.1)	0.75 [0.50–1.11]

- 110 NEW Score 2: National Early Warning Score
- 111 \*Oxygen saturation, Chest Computed Tomography, C-reactive protein, neutrophil, eosinophil,
- 112 lymphocyte, D-Dimer, Fibrinogen and Ct <16 were not included in the multivariate due to
- 113 >5% missing data
- 114 \*\*only significant results are presented in the multivariate analysis

115 **Table 2.** Risk factors for dyspnoea at follow-up (n=469)

		No dyspnoea persistence (n=373) %	Dyspnoea persistence (n=123) %	Univariate analysis OR [95% CI] p-value	Multivariate analysis** OR [95% CI] p-value
	Mean ± SD	41.0 ±13.4	43.6 ± 12.8		
	Range	18–89	20–72		
Age	< 45 (n=285)	226 (60.6)	59 (48.0)	ref	
	≥ 45 (n=211)	147 (39.4)	64 (52)	1.67 (1.08–2.57)	1.74 [1.15–2.63]
				<b>0.01</b>	<b>0.009</b>
Sex	Male (n=176)	138 (37.0)	38 (30.9)	ref	
	Females (n=320)	235 (63.0)	85 (69.1)	1.31 [0.83–2.09]	0.22
<b>Chronic conditions</b>					
Hypertension	No (n=451)	343 (92.0)	108 (87.8)	ref	
	Yes (n=45)	30 (8.0)	15 (12.2)	1.59 [0.76–3.18]	<b>0.16</b>
Diabetes	No (n=471)	353 (94.6)	118 (95.9)	ref	
	Yes (n=25)	20 (5.4)	5 (4.1)	0.75 [0.21–2.11]	0.57
Cancer	No (n=483)	362 (97.1)	121 (98.4)	ref	
	Yes (n=13)	11 (2.9)	2 (1.6)	0.54 [0.06–2.55]	0.43
Obesity	No (n=431)	327 (87.7)	104 (84.6)	ref	
	Yes (n=65)	46 (12.3)	19 (15.5)	1.29 [0.69–2.38]	0.37
<b>Co-medications</b>					
Beta blockers	No (n=486)	367 (98.4)	119 (96.8)	ref	ref
	Yes (n=10)	6	4	2.05	

		(1.6)	(3.3)	[0.42–8.82]	
				0.26	
Dihydropyridine	No (n=487)	365 (97.9)	122 (99.2)	ref	
	Yes(n=9)	8 (2.1)	1 (0.8)	0.37 [0.008–2.84]	0.34
Angiotensin- converting enzyme inhibitors	No (n=493)	372 (99.7)	121 (98.4)	ref	
	Yes (n=3)	1 (0.3)	2 (1.6)	6.15 [0.31– 363.66]	<b>0.09</b>
Angiotensin II receptor blocker	No (n=484)	364 (97.6)	120 (97.6)	ref	
	Yes (n=12)	9 (2.4)	3 (2.4)	1.01 [0.17–4.14]	0.99
Metformin	No (n=487)	366 (98.1)	121 (98.4)	ref	
	Yes (n=9)	7 (1.9)	2 (1.6)	0.86 [0.09–4.62]	0.86
Fenofibrate	No (n=493)	371 (99.5)	122 (99.2)	ref	
	Yes (n=3)	2 (0.5)	1 (0.8)	1.52 [0.03–29.42]	0.73
<b>COVID-19 status at inclusion</b>					
Time between onset of COVID symptoms and admission	< 6 days(n=207)	146 (39.1)	61 (49.6)	ref	ref
	≥ 6 days (n=289)	227 (60.9)	62 (50.4)	0.65 [0.42–1.01]	0.65 [0.43–0.99]
				<b>0.04</b>	<b>0.045</b>
NEWS Score 2	Low (n=473)	357 (95.7)	116 (94.3)	ref	
	Medium (n=13)	9 (2.4)	4 (3.3)	1.37 [0.41–4.52]	
	High (n=10)	7 (1.9)	3 (2.4)	0.61 1.32 [0.33–5.18]	0.69
Oxygen	No (n=467)	353	114	ref	

		(94.6)	(92.7)	
	Yes (n=29)	20 (5.4)	9 (7.3)	1.39 [0.54–3.31] 0.42
Saturation oxygen (SpO2) %	> 94% (n=453)	335 (93.3)	118 (97.5)	ref
	≤94% (n=27)	24 (6.7)	3 (2.5)	0.35 [0.07–1.20] 0.08
Chest Computed Tomography*	Normal (n=74)	55 (29.9)	19 (27.9)	ref
	Limit (n=105)	77 (41.9)	28 (41.2)	1.05 [0.53-2.07] 0.88
	Intermediate (n=58)	40 (21.7)	18 (26.5)	1.30 [0.61-2.79] 0.50
	Severe (n=15)	12 (6.5)	3 (4.4)	0.72 [0.18-2.84] 0.64
C-reactive protein*	≤ 5mg/L (n=219)	162 (60.0)	57 (62.6)	ref
	>5mg/L (n=142)	108 (40.0)	34 (37.4)	0.89 [0.53-1.50] 0.66
Neutrophil*	≤ 7.5 Giga/L (n=407)	300 (97.1)	107 (100.0)	ref
	>7.5 Giga/L (n=9)	9 (2.9)	0 (0.0)	0.00 [0.00-1.21] 0.07
Eosinophil*	≥0.1 Giga/L (n=96)	82 (26.5)	14 (13.1)	ref
	<0.1 Giga/L (n=320)	227 (73.5)	93 (86.9)	2.40 [1.27-4.81] <b>0.004</b>
Lymphocyte*	≥ 1 Giga/L (n=376)	281 (90.0)	95 (88.8)	ref
	< 1 Giga/L (n=40)	28 (9.1)	12 (11.2)	1.27 [0.56-1.69] 0.51
D-Dimer*	≤ 0.5 µg/ml (n=71)	51 (73.9)	20 (60.6)	ref
	>0.5µg/ml (n=31)	18 (26.1)	13 (39.4)	1.84 [0.69-4.84]

				0.17	
		≤ 4g/L (n=36)	28 (40.6)	8 (30.8)	ref
Fibrinogen*		>4 g/L (n=59)	41 (59.4)	18 (69.2)	1.54 [0.54-4.66]
					0.38
PCR Ct value < 16 at admission*	No (n=396)		297 (93.7)	99 (95.2)	ref
	Yes (n=25)		20 (6.3)	5 (4.8)	0.75 [0.21-2.13]
					0.57
Viral shedding ≥ 10 days*	No (n=285)		220 (89.8)	65 (83.3)	ref
	Yes (n=38)		25 (10.2)	13 (11.7)	1.76 [0.78-3.81]
					0.12
Hospitalisation ≥ 10 days	No (n=485)		366 (98.1)	119 (97.6)	ref
	Yes (n=10)		7 (1.9)	3 (2.5)	1.32 [0.22-5.88]
					0.69
Transfer to the ICU	No (n=485)		364 (97.6)	121 (98.4)	ref
	Yes (n=11)		9 (2.4)	2 (1.6)	0.69 [0.07-3.29]
					0.61
Hydroxychloroquine + azithromycin ≥ 3 days	No (n= 46)		35 (9.4)	11 (8.9)	ref
	Yes (n= 450)		338 (90.6)	112 (01.1)	1.05 [0.50-2.38]
					0.88

116 NEW Score 2: National Early Warning Score

117 \*Chest Computed Tomography, C-reactive protein, neutrophil, eosinophil, lymphocytes, D-

118 Dimer, Fibrinogen, Ct < 16 and viral shedding were not included in the multivariate due to

119 >5% missing data

120 \*\*only significant results are presented in the multivariate analysis

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