

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

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### ▶ To cite this version:

Nhu Ngoc Nguyen, van Thuan Hoang, Thi Loi Dao, Line Meddeb, Jean-Christophe Lagier, et al.. Long-term persistence of symptoms of dyspnoea in COVID-19 patients. International Journal of Infectious Diseases, 2022, 115, pp.17-23. 10.1016/j.ijid.2021.11.035 . hal-03663035

# HAL Id: hal-03663035 https://amu.hal.science/hal-03663035

Submitted on 8 Jan 2024

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1	Long-term persistence of symptoms of dyspnoea in COVID-19 patients
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1.4	
14	Keywords: SARS-CoV-2; COVID-19; dyspnoea; long COVID
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

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

We identified confirmed COVID-19 patients who reported dyspnoea during the acute phase of the disease from among a cohort of 3,737 patients tested at our institute between 3 March and 27 April 2020 (Lagier *et al.*, 2020). Patients with pre-existing chronic respiratory diseases and chronic heart disease were excluded from this analysis. Information on demographics, 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 dyspnoea at the acute phase and at the follow-up time. Variables with p-values < 0.2 in the 39 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 ≤94%, C-reactive protein >5 mg/L, neutrophils >7.5 Giga/L, eosinophils <0.1 Giga/L, 46 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%) answered the questionnaire and 342/838 (40.8%) were lost to follow-up. Patients who responded were significantly less likely to report hypertension, to present severe symptoms, to require oxygen upon inclusion, to undergo prolonged hospitalisation and had lower rates of mortality, as compared with all patients reporting dyspnoea at inclusion (Supplementary Table 1)

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

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

All the data for this study will be made available upon reasonable request to thecorresponding 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.

### 100 Acknowledgements

101 Our thanks go to Yolande Obadia and all the doctors who volunteered to recruit patients by 102 telephone interview at the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection, 103 including Pierre Bares, Robert Barrus, Souad Benali, Marc Benoit, Dominique Blanc, 104 Christine Carissimi, Denis Charpin, Jean Delmont, Patricia Enel, Charbelle Ezzedine, Pascale 105 Fournier, Marguerite François, Katell Guillon, Guy Marmottant, Marie-Christine Manca-106 Pelissier, Isabelle Pinot, Nicole Quintana Benyahya, Robert Loi, Dominique Ricci Cagnol, 107 Nicole Sarles-Philip, Catherine Tamalet, Jean-Michel Vassault, Marie-Pierre Vergobbi, and 108 Nicole Veschi

		No dyspnoea (n=2,342) %	Dyspnoea (n=880) %	Univariate analysis OR [95%CI] p-value	Multivariate analysis** OR [95%CI] p-value
	Mean $\pm$ SD	$43.6 \pm 15.8$	$43.7 \pm 15.5$		
	Range	18-96	18–94	f	
Δge	< 45 (n=1,720)	1,255	403	rei	
nge		(55.0)	(32.8)	1.03	
	$\geq$ 45 (n=1,502)	1,087	415	[0.88–1.21]	
	_ 、 , ,	(46.4)	(47.2)	0.71	
	Male $(n-1.464)$	1,107	357	ref	ref
	Wide (11–1,404)	(47.3)	(40.6)		
Sex		1,235	523	1.31	1.38
	Females $(n=1,758)$	(52.7)	(59.4)	[1.12–1.54]	[1.17 - 1.61]
Chronic condition	ne			0.0007	0.0001
Chrome condition	18	2 080	765	ref	
	No (n=2,845)	(88.8)	(86.9)	101	
Hypertension		(0010)	115	1.19	
<i>J</i> 1	Yes (n=377)	262	$\begin{array}{c}115\\(12,1)\end{array}$	[0.94–1.52]	
		(11.2)	(15.1)	0.14	
	No (n=2999)	2179	820	ref	
	100 (II-2))))	(93.0)	(93.2)		
Diabetes	Yes (n=223)	162	60	0.98	
		(7.0)	(6.8)	[0.71–1.34]	
		(7.0)	(0.8)	0.89	
		2,280	858	ref	
	No (n=3,138)	(97.4)	(97.5)		
Cancer		67	22	0.94	
	Yes (n=84)	(2.6)	(2.5)	[0.55–1.56]	
		(2.0)	(2.3)	0.81	
	No (n=2,882)	2,124	758	ref	ref
Obasity		(90.7)	(86.1)	1 57	1 45
Obesity	Ves(n-340)	218	122	1.37 [1.23_1.99]	1.45 [1 13_1 84]
	1 es (11=340)	(9.3)	(13.9)	0.0002	0.003
<b>Co-medications</b>					
	$N_{0}$ (n 2 1 1 1)	2,285	856	ref	ref
	100 (n=3,141)	(97.6)	(97.3)		
Beta blockers		57	24	1.12	
	Yes (n=81)	(2.4)	(2.7)	[0.66–1.85]	
		2.2(0	040	0.63	
Dihudronumiding	No (n=3,117)	2,269	848 (06 4)	ref	
Dinyaropyriaine	Ves(n-105)	(90.9)	(90.4)	1 17	
	103(11-103)	15	54	1.1/	

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

		(3.1)	(3.6)	[0.74–1.82] 0.46	
Angiotensin-	No (n=3,197)	2,325 (99.3)	872 (99.1)	ref	
enzyme inhibitors	Yes (n=25)	17 (0.7)	8 (0.9)	1.25 [0.47–3.08] 0.59	
Angiotensin II	No (n=3,107)	2,258 (96.4)	849 (96.5)	ref	
receptor blocker	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	
	No (n=3,203)	2,329 (99.4)	874 (99.3)	ref	
Fenofibrate	Yes (n=19)	13 (0.6)	6 (0.7)	1.23 [0.38–3.48] 0.68	
	No (n=3,154)	2,290 (97.8)	864 (98.2)	ref	
Statin	Yes (n=68)	52 (2.2)	16 (1.8)	0.82 [0.43–1.46] 0.48	
COVID-19 status	at inclusion				
Time between	< 6 days(n=1,599)	1,239 (52.9)	360 (40.9)	ref	ref
symptoms and admission	$\geq$ 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>
	Low (n=3,017)	2,216 (94.6)	801 (91.0)	ref	
NEWS Score 2	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>0.0001</b>	
	No (n=3,034)	2,256 (96.3)	778 (88.4)	ref	
Oxygen	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>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>	
	Normal (n=509)	370 (32.2)	139 (26.8)	ref	
Chest Computed	Limit (n=756)	542 (47.1)	214 (41.3))	1.05 [0.82-1.35] 0.69	
Tomography	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	$\leq$ 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>	
	$\leq$ 7.5 Giga/L (n=2,604)	1,894 (97.8)	710 (96.5)	ref	
Neutrophils*	>7.5 Giga/L (n=68)	42 (2.2)	26 (3.5)	1.65 [0.96-2.78] <b>0.046</b>	
	≥0.1 Giga/L (n=684)	520 (26.9)	164 (22.3)	ref	
Eosinophils*	<0.1 Giga/L (n=1,988)	1,416 (73.1)	572 (77.7)	1.28 [1.04-1.58] <b>0.015</b>	
	$\geq$ 1 Giga/L (n=2,370)	1,731 (89.4)	639 (86.8)	ref	
Lymphocytes*	< 1 Giga/L (n=302)	205 (10.6)	97 (13.2)	1.28 [0.98-1.67] 0.06	
	$\leq 0.5 \ \mu g/ml$ (n=335)	227 (58.7)	108 (57.8)	ref	
D-Dimer*	>0.5µg/ml (n=239)	160 (41.3)	79 (42.3)	1.04 [0.72-1.50] 0.84	
	$\leq$ 4g/L (n=290)	216 (46.2)	74 (35.2)	ref	
Fibrinogen*	>4 g/L (n=388)	252 (53.8)	136 (64.8)	1.58 [1.11-2.24] 0.008	
PCR Ct value <	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

		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	$43.6 \pm 12.8$	<b>r</b>	L
	Range	18–89	20–72		
	< 45 (n=285)	226	59	ref	
Age	· · · · ·	(60.6)	(48.0)		
C	$\geq$ 45 (n=211)	147	64	1.67	1.74
		(39.4)	(52)	(1.08 - 2.57)	[1.15-2.63]
				0.01	0.009
	Male (n=176)	138	38	ref	
		(37.0)	(30.9)		
Sex	Females	235	85	1.31	
	(n=320)	(63.0)	(69.1)	[0.83-2.09]	
				0.22	
Chronic conditions					
	No (n=451)	343	108	ref	
		(92.0)	(87.8)		
Hypertension	Yes (n=45)	30	15	1.59	
		(8.0)	(12.2)	[0.76–3.18]	
		(0.0)	(12.2)	0.16	
Diabetes	No (n=471)	353	118	ref	
		(94.6)	(95.9)		
	Yes (n=25)	20	5	0.75	
		(5.4)	(4.1)	[0.21–2.11]	
				0.57	
	No (n=483)	362	121	ref	
G		(97.1)	(98.4)	0.54	
Cancer	$\mathbf{X}$ (12)	11	2	0.54	
	Yes $(n=13)$	(2.9)	(1.6)	[0.06-2.55]	
	NT ( 421)	207	104	0.43	
	No (n=431)	327	104	ref	
		(87.7)	(84.6)	1.20	
Obesity	$\mathbf{V}_{ac}$ $(r, (5))$	46	19	1.29	
	1  es (m=03)	(12.3)	(15.5)	[0.09-2.38]	
Co-modications				0.37	
		367	110	rof	rof
Beta blockers	ta blockers No (n=486)	(98.4)	(96.8)	101	101
Deta UIUCKEIS	$\operatorname{Yes}(n-10)$	6	(90.0) <u>4</u>	2.05	
	103 (11-10)	0	-7	2.05	

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

		(1.6)	(3.3)	[0.42-8.82]	
				0.26	
	$N_{c}$ (r. 497)	365	122	ref	
	No $(n=487)$	(97.9)	(99.2)		
Dihydropyridine		0	1	0.37	
	Yes(n=9)	8		[0.008-2.84]	
		(2.1)	(0.8)	0.34	
		372	121	c	
	No (n=493)	(99.7)	(98.4)	ref	
Angiotensin-				6.15	
converting enzyme		1	2	[0.31–	
inhibitors	Yes $(n=3)$	(0.3)	(1.6)	363.66]	
				0.09	
		364	120		
	No (n=484)	(97.6)	(97.6)	ref	
Angiotensin II			. ,	1.01	
receptor blocker	Yes (n=12)	9	3	[0.17-4.14]	
		(2.4)	(2.4)	0.99	
		366	121	ref	
	No (n=487)	(98.1)	(98.4)		
Metformin	Yes (n=9)			0.86	
		7	2	[0.09-4.62]	
		(1.9)	(1.6)	0.86	
		371	122	ref	
	No (n=493)	(99 5)	(99.2)	101	
Fenofibrate		()).0)	()).2)	1.52	
i enomerate	Ves(n-3)	2	1	[0 03-29 42]	
	<b>10</b> 5 (II-5)	(0.5)	(0.8)	0.73	
COVID-19 status at i	inclusion			0.75	
	$\leq 6 \text{ days}(n-207)$	146	61	ref	ref
Time between onset	$(0 \text{ days}(\Pi - 207))$	(39.1)	(49.6)	101	101
of COVID	> 6  days	(37.1)	(49.0)	0.65	0.65
symptoms and	$\frac{2}{(n-280)}$	227	62	[0.03]	[0.05 [0.43_0.00]
admission	(11-20))	(60.9)	(50.4)	0.42	0.045
		357	116	ref	0.045
	Low (n=473)	(95 7)	(9/13)	ICI	
		(95.7)	(94.3)	1 27	
	Modium $(n-12)$	9	4	1.37 [0.41.4.52]	
NEWS Score 2	Medium (n=15)	(2.4)	(3.3)	[0.41 - 4.32]	
		7		0.01	
	High (n=10)	(1.0)	3	1.32	
		(1.9)	(2.4)	[0.33 - 3.18]	
		252	114	0.09	
Oxygen	1NO(n=40/)	333	114	rer	

		(94.6)	(92.7)		
		20	0	1.39	
	Yes (n=29)	20	9	[0.54-3.31]	
		(5.4)	(7.3)	0.42	
		335	118	ref	
	> 94% (n=453)	(93.3)	(97.5)		
Saturation oxygen		(2000)	(2.1.2)	0.35	
(SpO2) %	<0.4% (n-27)	24	3	[0.07, 1.20]	
	294% (II-27)	(6.7)	(2.5)	0.08	
		55	10	0.08	
	Normal (n=74)	55	19	rei	
	. ,	(29.9)	(27.9)		
		77	28	1.05	
	Limit (n=105)	(41.9)	(41.2)	[0.53-2.07]	
Chast Computed		(41.9)	(41.2)	0.88	
Tana ang hat	T 4 1' 4	40	10	1.30	
Tomography*	Intermediate	40	18	[0.61-2.79]	
	(n=58)	(21.7)	(26.5)	0.50	
				0.72	
	Severe $(n-15)$	12	3	[0 18-2 84]	
	Severe (II=15)	(6.5)	(4.4)	0.64	
				0.04	
	$\leq$ 5mg/L	162	57	rei	
	(n=219)	(60.0)	(62.6)		
C-reactive protein*	>5mg/I	109	24	0.89	
	(n-1/2)	(40.0)	(37.4)	[0.53-1.50]	
	(11-142)	(40.0)	(37.4)	0.66	
	≤ 7.5 Giga/L	300	107	ref	
	(n=407)	(97.1)	(100.0)		
Neutrophil*			. , ,	0.00	
1	>7.5 Giga/L	9	0	[0.00-1.21]	
	(n=9)	(2.9)	(0.0)	0.07	
	NO 1 Char /I	82	14	rof	
	$\geq 0.1 \text{ Glga/L}$	02	14	Iei	
<b>D</b> · 1·1•	(11=90)	(26.5)	(13.1)	2 40	
Eosinophil*	<0.1 Giga/L	227	93	2.40	
	(n=320)	(73.5)	(86.9)	[1.27-4.81]	
	(11 0 2 0)	(1010)	(000)	0.004	
	≥1 Giga/L	281	95	ref	
	(n=376)	(90.0)	(88.8)		
Lymphocyte*	< 1 Gigo/I	28	12	1.27	
	(n-40)	(9.1)	(11.2)	[0.56-1.69]	
	(11-40)	(9.1)	(11.2)	0.51	
	$\leq 0.5 \ \mu g/ml$	51	20	ref	
D Dimor*	(n=71)	(73.9)	(60.6)		
D-Dimer.	>0.5µg/ml	18	13	1.84	
	(n=31)	(26.1)	(39.4)	[0.69-4.84]	

$\begin{array}{c ccccccccccccccccccccccccccccccccccc$					0.17	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		$\leq 4g/L$	28	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         ref           Yes (n=25)         20         5         0.75 (6.3)         0.75           Viral shedding ≥ 10 days*         No (n=285)         220         65         ref           Viral shedding ≥ 10 days*         No (n=285)         220         65         ref           Viral shedding ≥ 10 days*         No (n=285)         220         65         ref           No (n=285)         25         13         1.76 (10.2)         11.7)         0.12           Hospitalisation ≥ 10 days         No (n=485)         366 (98.1)         119         ref           Yes (n=10)         7         3         1.32 (1.9)         2.5)         0.69           Transfer to the ICU         Yes (n=11)         9         2         0.69           Yes (n=11)         9         2         0.69           Yes (n=45)         35         11         ref           Hydroxychloroquine + azithromycin ≥ 3 days         No (n=46)         35         11         ref           90.60         (01.1)         0.88         0.59 <t< td=""><td></td><td>(n=36)</td><td>(40.6)</td><td>(30.8)</td><td></td><td></td></t<>		(n=36)	(40.6)	(30.8)		
$\frac{54 \text{ gyL}}{(n=59)} = (59.4) = (69.2) = (0.544.66]$ $(9.59.4) = (69.2) = (0.544.66]$ $(0.57 + 4.66]$ $(0.57 + 4.66]$ $(0.57 + 4.66]$ $(0.57 + 6.6]$ $(0.$	Fibrinogen*	N 4 /T	4.1	10	1.54	
$\frac{(11-39)}{(12-39)} = \frac{(39,4)}{(39,4)} = \frac{(69,2)}{(69,2)} = \frac{0.38}{0.38}$ PCR Ct value < 16 at admission* $\frac{12}{12} = \frac{10}{12} = \frac$		>4 g/L	41	10	[0.54-4.66]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		(11-39)	(39.4)	(69.2)	0.38	
PCR Ct value < 16 at admission*       ING (n=356)       (93.7)       (95.2)         Yes (n=25)       20       5       0.75         Viral shedding ≥ 10 days*       No (n=285)       220       65       ref         Viral shedding ≥ 10 days*       Yes (n=38)       25       13       1.76         No (n=485)       25       13       1.76         No (n=485)       366       119       ref         Hospitalisation ≥ 10 days       No (n=485)       366       119       ref         No (n=485)       364       121       ref         Pres (n=10)       7       3       [0.22-5.88]         No (n=485)       364       121       ref         Pres (n=11)       9       2       0.69         Yes (n=11)       9       2       0.69         Yes (n=11)       9       2       0.69         Hydroxychloroquine       No (n=46)       35       11       ref         Hydroxychloroquine       No (n=46)       35       11       ref         Hydroxychloroquine       Yes (n=450)       338       112       1.05         (0.6)       (01.1)       0.88       98       98		$N_{c}$ (r. 206)	297	99	ref	-
at admission*       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 (89.8)       ref         Viral shedding ≥ 10 days*       Yes (n=38)       25 (10.2)       1.76 (11.7)       1.76 0.12         Hospitalisation ≥ 10 days       No (n=485)       366 (98.1)       119 (97.6)       ref         Hospitalisation ≥ 10 days       Yes (n=10)       7 (1.9)       3 (2.5)       1.32 [0.22-5.88]         Transfer to the ICU       Yes (n=10)       364 (97.6)       121 (98.4)       ref         Transfer to the ICU       Yes (n=11)       9 (2.4)       2 (1.6)       0.69 (0.07-3.29]         Hydroxychloroquine + azithromycin ≥ 3 days       No (n=46)       35 (90.6)       11 (0.11)       ref         Yes (n=450)       338 (90.6)       112 (0.11)       1.05 (0.50-2.38]	PCR Ct value < 16	No (n=390)	(93.7)	(95.2)		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	at admission*		20	5	0.75	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		Yes (n=25)	20	$\mathbf{J}$	[0.21-2.13]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			(0.3)	(4.8)	0.57	
Viral shedding $\geq 10$ days*Yes (n=38)(89.8) (10.2)(83.3)Yes (n=38) $25$ (10.2)13 (11.7) $1.76$ (0.78–3.81) 0.12Hospitalisation $\geq 10$ daysNo (n=485) $366$ (98.1)119 (97.6)Hospitalisation $\geq 10$ daysYes (n=10)7 (1.9)3 (2.5) $1.32$ (0.22–5.88] 0.69Transfer to the ICU Yes (n=11)9 (2.4)2 (97.6)0.69 (98.4)Hydroxychloroquine + azithromycin $\geq 3$ daysNo (n=46) $35$ (9.4)11 refHydroxychloroquine + azithromycin $\geq 3$ daysNo (n=450) $338$ (90.6)112 (0.11)		$N_{c}$ (r. 295)	220	65	ref	
Viral shedding ≥ 10 days*       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         Hospitalisation ≥ 10 days       Yes (n=10)       7 (1.9)       3 (2.5)       1.32 (0.22–5.88]         Transfer to the ICU       Yes (n=11)       9 (2.4)       2 (1.6)       0.69 (98.4)         Transfer to the ICU       Yes (n=11)       9 (2.4)       2 (1.6)       0.69 (0.61         Hydroxychloroquine + azithromycin ≥ 3 days       No (n=46)       35 (9.4)       11 (9.4)       ref         Hydroxychloroquine + azithromycin ≥ 3 days       Yes (n=450)       338 (90.6)       112 (0.11)       1.05 (0.50–2.38]		NO (n=285)	(89.8)	(83.3)		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Viral shedding $\geq 10$	Yes (n=38)	25	12	1.76	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	days*		25	15	[0.78–3.81]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			(10.2)	(11.7)	0.12	
Hospitalisation $\geq 10$ daysNo (n=485)(98.1)(97.6)Hospitalisation $\geq 10$ daysYes (n=10)731.32 [0.22-5.88] 0.69Yes (n=10)73[0.22-5.88] 0.69Transfer to the ICUNo (n=485)364121refYes (n=11)920.69 [0.07-3.29] 0.61HydroxychloroquineNo (n=46)3511refHydroxychloroquineNo (n=46)3511ref+ azithromycin $\geq 3$ daysYes (n=450)3381121.05 [0.50-2.38] 0.61		$N_{a}$ (r. 495)	366	119	ref	
Hospitalisation $\geq 10$ Yes (n=10) $7$ $3$ $1.32$ daysYes (n=10) $7$ $3$ $[0.22-5.88]$ $0.69$ $0.69$ Transfer to the ICUYes (n=450) $364$ $121$ refYes (n=11) $9$ $2$ $0.69$ $(2.4)$ $(1.6)$ $[0.07-3.29]$ $(2.4)$ $(1.6)$ $0.61$ HydroxychloroquineNo (n=46) $35$ $11$ $+$ azithromycin $\geq 3$ Yes (n=450) $338$ $112$ $1.05$ $(90.6)$ $(01.1)$ $0.88$	Hamitalization > 10	No (n=485)	(98.1)	(97.6)		
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Hospitalisation $\geq 10$		7	2	1.32	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	days	Yes (n=10)	(1.0)	3 (2.5)	[0.22–5.88]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			(1.9)	(2.5)	0.69	
No (n=485)(97.6)(98.4)Transfer to the ICUYes (n=11)920.69Yes (n=11)92[0.07-3.29](2.4)(1.6)0.61HydroxychloroquineNo (n=46)3511ref+ azithromycin $\geq 3$ Yes (n=450)3381121.05(90.6)(01.1)0.88		N. (. 495)	364	121	ref	
Transfer to the ICU Yes (n=11)9 (2.4)2 (1.6)0.69 [0.07-3.29] 0.61Hydroxychloroquine + azithromycin $\geq 3$ daysNo (n=46)35 (9.4)11 (8.9)ref (9.4)338 (90.6)112 (01.1)1.05 [0.50-2.38] 0.89		No (n=485)	(97.6)	(98.4)		
Yes (n=11)92 $[0.07-3.29]$ 0.61HydroxychloroquineNo (n=46) $35$ 11ref+ azithromycin $\geq 3$ daysYes (n=450) $338$ $112$ $1.05$ $(90.6)$ $(01.1)$ $0.88$	Transfer to the ICU		0	2	0.69	
(2.4)       (1.6)       0.61         Hydroxychloroquine       No (n= 46) $35$ 11       ref         + azithromycin $\ge 3$ (9.4)       (8.9)       1.05         days       Yes (n= 450) $338$ 112       [0.50-2.38]         (90.6)       (01.1)       0.88		Yes (n=11)	9		[0.07-3.29]	
HydroxychloroquineNo (n= 46) $35$ 11ref+ azithromycin $\geq 3$ (9.4)(8.9)1.05daysYes (n= 450) $338$ 112[0.50-2.38](90.6)(01.1)0.88			(2.4)	(1.0)	0.61	
HydroxychloroquineNo (n= 40) $(9.4)$ $(8.9)$ + azithromycin $\geq 3$ 3381121.05daysYes (n= 450)338(01.1) $[0.50-2.38]$		$\mathbf{N}_{\mathbf{a}}$ (r. 46)	35	11	ref	
+ azithromycin $\geq 3$ days3381121.05(90.6)(01.1)(0.50-2.38)	Hydroxychloroquine	No $(n = 46)$	(9.4)	(8.9)		
days Yes (n=450) $\begin{array}{c} 338 \\ (90.6) \\ \end{array} \begin{array}{c} 112 \\ (01.1) \\ \end{array} \begin{array}{c} [0.50-2.38] \\ 0.88 \end{array}$	+ azithromycin $\geq 3$		229	110	1.05	
(90.6) (01.1)	days	Yes (n= 450)	338	(01.1)	[0.50-2.38]	
0.00	2		(90.6)		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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