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Original article

Symptoms of Long-COVID 1-Year after a COVID-19 outbreak among sailors on a French aircraft carrier



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ABSTRACT

Objectives: While persistent symptoms have been reported after the coronavirus disease-2019 (COVID-19), long-term data on outpatients with mild COVID-19 are lacking. The objective was to describe symptoms persisting for 12 months.

Methods: This prospective cohort study on 1767 sailors of an aircraft carrier in which a Covid-19 outbreak occurred during a mission in April 2020 described predefined self-reported symptoms of Long-COVID at 6, 9 and 12 months. Logistic-regression analyses were used to identify correlates for Long-COVID at months 6, 9 and 12.

Results: Among the 641 participants, 619 (35%) completed at least one follow-up questionnaire (413 COVID-positive and 206 COVID-negative). Symptoms of Long-COVID were reported by 53.7%, 55.2% and 54.3% of COVID-positive participants vs 31.2%, 23.3% and 40.0% in COVID-negative patients, at 6 ($p < .002$), 9 ($p < .002$) and 12 months ($p = .13$), respectively. The most frequent symptoms reported were concentration and memory difficulties, asthenia and sleep disorders.

Conclusion: In this study more than half of COVID-positive outpatients reported persistent symptoms up to 12 months post-quarantine. These findings suggests that all patients, including those with mild disease, can be affected by Long-COVID. A lack of difference at 12 months with COVID-negative patients prompts caution. The symptoms of Long-COVID are so non-specific that they may be viewed as the consequence of multiple intercurrent factors.

1. Introduction

Since 1 December 2019, the date of the first identified coronavirus disease-2019 (COVID-19) case, successive pandemic waves have occurred as variants have emerged, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) infection has caused 523 million cases and 6.3 million deaths worldwide [1,2]. Although the symptoms of the acute phase are now well-known and the sub-

ject of numerous publications, the long-term consequences of COVID-19 on health remain poorly elucidated, especially for mild-moderate COVID-19 [3,4]. Several commercialized vaccines have enabled significant reductions of severe COVID-19 and its associated mortality rates. However, their efficacy diminishes over time and with the emergence of SARS-CoV2 variants [5,6].

The term "Long-COVID" was first used on social media by participants suffering from symptoms persisting after the acute phase of the infection [7]. Then, in late 2020, it was adopted by the medical community, with several editorials describing persistent symptoms and the need for real-life studies on the existence of Long-COVID [8]. The UK National Institute for Health Care and Excellence (NICE) distinguishes persistent COVID-19 (COVID symptoms persisting or appearing 4 to 12 weeks after acute

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infection) from post-COVID syndrome (unexplained COVID symptoms persisting or appearing beyond 12 weeks: post-acute phase) [9]. Long-COVID is defined as the persistence or appearance of signs or symptoms more than 4 weeks after acute COVID-symptom onset. That definition encompasses the so-called post-COVID syndrome and persistent COVID. Long-term COVID manifestations are the subject of many debates in different published reports [10–13]. The majority of these studies concerned hospitalized participants and were conducted over less than 4 months. Little information is available concerning non-hospitalized participants and, to our knowledge, up until now, no study has observed the evolution of Long-COVID over time [8].

In spring 2020, during a mission at sea, the Charles de Gaulle aircraft carrier (AC-CDG) experienced a COVID-19 outbreak [14]. At its return to base, the 1767 sailors were quarantined for 15 days, and twice subjected to reverse transcriptase-polymerase chain reaction tests for SARS-CoV2. Among them, 1236 (almost 70%) tested positive and 27 required hospitalization [15]. A cohort study was undertaken to determine the frequency of clinical and psychological sequelae in the entire AC-CDG population, regardless of their SARS-CoV2-infection status, during one year following the on-board outbreak. Long-term follow-up of this cohort enabled an evolutionary description over time of the outpatients' Long-COVID symptoms.

2. Methods

2.1. Study design

This prospective, longitudinal COV-PA study has followed the AC-CDG cohort of sailors since April 2020. After the on-board outbreak, participants enrolled after an inclusion visit received electronic questionnaires 6-, 9- and 12 months post-quarantine. This report is written according to the STROBE guideline for cohort studies. All data were collected in the context of standard care from completely anonymized files, in accordance with French and European laws, including General Data Protection Regulation. All participants were informed and provided written consent for use of their data. The COV-PA study was approved by the regional Research Ethics Committee on December 7, 2020 (IDRCB 2020-A02397-32).

2.2. Participants and exposure

All AC-CDG personnel on-board during the outbreak were asked to participate in this follow-up cohort. This population was identified from information available during initial management of the outbreak and quarantine upon return to base. Individuals who did not respond to at least 2 follow-up questionnaires were excluded from the analyses. Participants were divided into 2 groups according to their COVID-19 status during the outbreak.

The COVID-positive group was constituted by two subgroups: biological-confirmed COVID-19 (positive RT-PCR at any time during the 2-week quarantine or positive serology at the end of quarantine), and probable-COVID (participants with specific symptoms (ageusia and/or anosmia, or at least 3 symptoms associated with COVID-19, according to the CDC criteria), despite negative RT-PCR and serology).

SARS-CoV2-infection negativity (by RT-PCR and serology test) of the COVID-negative group was documented during the outbreak and quarantine period.

The participants in the COVID-positive group were classified as having asymptomatic, mild, moderate or severe COVID-19 based on National Institutes of Health guidelines [16]. The same electronic questionnaire was sent to participants 6, 9 and 12 month

post- quarantine. It comprised 110 questions, requiring about 40 minutes (mean) to complete. The first part concerned pre-defined general and physical symptoms, modified athletic or professional (fitness, work restrictions) capacities. The second part consisted of standardized questionnaires on potential psychological sequelae. Due to French military recommendations, all sailors received an injection of RNA vaccine in January 2021, i.e. 9 months after the epidemic.

2.3. Outcomes

The primary outcome measure was the presence (whatever the severity) of at least one Long-COVID symptoms at 6, 9 or 12 months. Long-COVID is defined as the persistence or appearance of signs or symptoms more than 4 weeks after acute COVID onset and a priori not linked to another disease. The symptoms retained in the literature include: fatigue, dyspnea, cough, thoracic pain, palpitations, trouble concentrating and brain fog, difficulty finding one's words, headaches, paresthesia, loss of smell/adulterated sense of smell (anosmia) and/or taste (ageusia), tinnitus, vertigo, difficulty swallowing, muscle, tendon and/or joint aches, sleep disorders (notably insomnia), irritability, anxiety, abdominal pain, nausea, diarrhea, loss of or no appetite, itching, urticaria, pseudo-chilblains, fever and chills.

We compared the frequency of these events between COVID-positive and COVID-negative groups over the pre-designated time.

The secondary outcomes were analysis of each symptom according to its initial status vis-à-vis SARS-CoV2 infection and its evolution over time. Long-COVID occurrence was compared according to sociodemographic status and COVID-19 severity. The subjects' psychological state and its evolution over time was assessed with validated scales. Depression and anxiety were assessed at months 6, 9 and 12 by Hospital Anxiety Depression Scale (HAD)-Depression and -Anxiety (cut-off at 11 for each component). The Rivermead head injury follow-up questionnaire assesses post-concussion syndrome. A score above 30 indicates an impact on social participation, lifestyle, and psychosocial functioning. Post-traumatic Stress Disorder Check List Scale for DSM-5 (PCL-5) assesses the post-traumatic syndrome (cut-off > 34). Injustice Experience Questionnaire (IEQ) measures feeling of injustice (cut-off > 30). Memory and cognitive difficulties were evaluated with the Subjective Memory Complaints Questionnaire (SMCQ, cut-off > 3). Another objective was to determine whether being convinced of having had COVID-19 regardless of actual COVID-19 status was a factor associated with Long-COVID. Finally, the impact of Long-COVID on (a) fitness to perform professional duties by according to the military general practitioner and (b) the young sailors' athletic capacities was explored.

2.4. Data extraction

All data were extracted from medical records by centrally trained research staff using a standardized data-collection form. Participants received an e-mail with a link to a secure internet site (accessible by mobile phone, tablet or computer) that would enable them to complete the questionnaire. Their responses were automatically entered into the electronic case-report form (eCRF). The questionnaire link was sent at a date set at the end of the AC-CDG sailors' COVID-19 quarantine (1 May 2020). A weekly e-mail reminder was sent and, after 3 such messages, the research staff called the participant to encourage him/her to complete the questionnaire. Investigators entered into the eCRF the information collected during the telephone call.

2.5. Statistical analyses

The study population's sociodemographic and behavior variables and symptoms were described. Long-COVID frequencies at months 6, 9 and 12 were compared. Sociodemographic variables, mental health outcomes and athletic capacities were compared between COVID-positive and COVID-negative groups. Comparisons of qualitative variables used 2-sided Fisher's exact tests; those of quantitative variables used Kruskal-Wallis rank tests. Univariate logistic-regression analyses assessed Long-COVID status at months 6, 9 and 12, to determine odds ratios (OR [95% confidence interval (CI)]). Lastly, multivariate analyses were performed at each follow-up to compute adjusted odds ratios (ORa). All correlates with a p -value ≤ 0.2 in univariate analyses were included in the initial models. Variables from the final models were selected using backward stepwise procedures (likelihood ratio test). All analyses were computed with Stata software version 14 (StataCorp, College Station, Texas). $P \leq 0.05$ defined significance for all the analyses.

3. Results

Among the 1767 AC-CDG sailors, 641 participants agreed to participate in this follow-up study. Among them, 22 (3.4%) did not complete any questionnaire despite the scheduled reminders. Among the 619 responders, 413 (66.7%) sailors had developed SARS-CoV-2 infections during the on-board outbreak and were included in the COVID-positive group; 206 (33.3%) without SARS-CoV-2 infection were assigned to the COVID-negative group. As shown in Table 1, the 2 groups were comparable for gender, mean

body mass index (BMI), medical history, athletic capacities and tobacco and alcohol consumption. Mean age was slightly higher in the COVID-positive group (31.7 vs 29.1 – $p = 0.006$). Among the 413 COVID-positive participants, 27 (6.5%) had required hospitalization and oxygen therapy, including one admitted to intensive care unit for high-flow oxygen therapy. During the acute phase of the SARS-CoV-2 infection, the most frequent reported symptoms were asthenia (61.5%), muscle aches (57.4%), anosmia (54.9%), ageusia (47.9%) and dyspnea (45.4%).

According to the data from the initial outbreak investigation (1568 sailors included) the median age of the crew was 29 (interquartile range (IQR): 24–36), distribution that appears similar to that of the present sample (median age: 29; IQR: 23–37). The present sample was also comparable with the rest from the crew in terms of gender (13.2% of women vs 15.4% – $P = 0.39$) and COVID-19 prevalence (66.7% vs 68.6% – $P = 0.44$) [17].

3.1. Primary outcome

At follow-up, despite several electronic and telephone reminders, not all of the participants responded to the questionnaires. In the COVID-positive group, 211/413 (48.9%) responded at 6 months, and 136 (32.9%) and 154 (37.3%) at 9 and 12 months, respectively. Response rates were significantly lower in the COVID-negative group (30.1%, 15.1% and 21.8% at 6, 9 and 12 months, respectively – $P < 0.001$). While gender did not significantly vary in responders at different follow-up times, mean respondent age increased in groups responding at months 9 and 12, and COVID-19 prevalence was significantly higher in respondents at each follow-up time than at inclusion (Table 2). As a result,

Table 1
Characteristics of Participants According to Positive or Negative SARS-CoV-2 RT-PCR Result.

Characteristic	COVID+, n/N (%) (N = 413)	COVID-, n/N (N = 206)	P
Age, mean	31.7 [404 responders]	29.1 [199]	0.006
Body mass index, mean	24.6 [395 responders]	24.3 [199]	0.77
Gender			0.50
Female	45/404 (11.1)	26/199 (13.1)	
Male	359/404 (88.9)	173/199 (86.9)	
Medical history			
Cardiovascular	6/258 (2.3)	1/75 (1.3)	1.0
Respiratory	17/258 (6.6)	4/75 (5.3)	1.0
Neurological	3/258 (1.2)	1/75 (1.3)	1.0
Ear, nose & throat	10/258 (3.9)	5/75 (6.7)	0.34
Dermatological	11/258 (4.3)	4/75 (5.3)	0.75
Psychological	32/258 (12.4)	9/75 (12.0)	1.0
Athletic activities (h/week)	4.6 [203 responders]	3.9 [56]	0.87
Active smoker, %	49/259 (18.9)	22/76 (29.0)	0.08
Alcohol intake (glasses/week)	3.6 [188 responders]	4.0 [49]	0.56
Severity of COVID-19, n (%)			
Asymptomatic	30/413 (7.3)		
Mild	356/413 (86.2)		
Moderate	26/413 (6.3)		
Severe	1/413 (0.2)		
Type of COVID-19, n (%)			
Confirmed-COVID	405/413 (98.1)		
Probable-COVID	8/413 (1.9)		
Main symptoms, n (%)			
Asthenia	158/257 (61.5)		
Muscle aches	147/257 (57.2)		
Anosmia	141/257 (54.9)		
Ageusia	123/257 (47.9)		
Dyspnea	116/257 (45.1)		
Cough	103/257 (40.1)		
Fever	84/257 (32.7)		
Rhinorrhea	76/257 (29.6)		
Digestive disorders	50/257 (19.5)		
Chest pain	48/257 (18.7)		
Palpitations	34/257 (13.2)		

Table 2

Variations in respondent characteristics at different times of follow-up.

Characteristics	Inclusion (n = 619) % [95%CI]	Month 6 (n = 264) % [95%CI]	Month 9 (n = 167) % [95%CI]	Month 12 (n = 199) % [95%CI]
Women	11.8 [9.4–14.6]	12.4 [8.8–17.1]	12.5 [8.2–18.7]	14.1 [9.8–19.8]
COVID-19 positive	66.7 [62.9–70.3]	76.5 [71.0–81.3]	81.4 [74.7–86.7]	77.4 [71.0–82.7]
Age (mean [95%CI])	30.8 [30.1–31.6]	32.5 [31.3–33.6]	34.3 [32.9–35.7]	33.8 [32.5–35.1]

Table 3

Evolution of Self-Reported Long-COVID Symptoms over 1 Year of Follow-Up According to Initial SARS-CoV-2 Status.

Symptom	Month 6			Month 9			Month 12		
	COVID+ No. (%)	COVID– No. (%)	P	COVID+ No. (%)	COVID– No. (%)	P	COVID+ No. (%)	COVID– No. (%)	P
Long-COVID	108/201 (53.7)	19/61 (31.2)	0.002	74/134 (55.2)	7/30 (23.3)	0.002	83/153 (54.3)	18/45 (40.0)	0.13
Difficulty concentrating	53/190 (27.9)	12/55 (21.8)	0.27	37/131 (28.2)	2/27 (7.4)	0.026	46/143 (32.9)	5/40 (12.5)	0.016
Asthenia	43/201 (21.4)	6/61 (9.8)	0.06	35/134 (26.1)	3/30 (10.0)	0.09	30/153 (19.6)	7/45 (15.6)	0.67
Sleep disorder	40/201 (19.9)	6/61 (9.8)	0.08	34/134 (25.4)	2/30 (6.7)	0.03	41/153 (26.8)	8/45 (17.8)	0.25
Headaches	28/201 (13.9)	4/61 (6.6)	0.18	15/134 (11.2)	1/30 (3.3)	0.31	21/152 (13.8)	6/45 (13.3)	1
Cough	19/201 (9.5)	3/61 (4.9)	0.43	15/134 (11.2)	0/30 (0.0)	0.08	14/153 (9.2)	6/45 (13.3)	0.41
Anosmia	18/201 (9.0)	1/61 (1.6)	0.09	12/134 (9.0)	0/30 (0.0)	0.13	11/151 (7.3)	1/44 (2.3)	0.31
Pruritis	18/201 (9.0)	2/61 (3.3)	0.18	9/134 (6.7)	3/30 (10.0)	0.46	13/151 (8.6)	2/45 (4.4)	0.53
Anxiety	13/196 (6.6)	4/57 (7.0)	1	6/133 (4.5)	1/29 (3.5)	1	8/150 (5.3)	2/44 (4.6)	1
Dyspnea	12/201 (6.0)	0/61 (0.0)	0.07	7/134 (5.2)	0/30 (0.0)	0.35	6/153 (3.9)	2/45 (4.4)	1
Digestive disorders	12/201 (6.0)	2/461 (3.3)	0.53	7/134 (5.2)	0/30 (0.0)	0.35	8/152 (5.3)	0/45 (0.0)	0.20
Chest pain	7/32 (21.9)	–	–	4/27 (14.8)	–	–	3/29 (10.3)	–	–
Ageusia	5/201 (2.5)	0/61 (0.0)	0.59	3/134 (2.2)	0/30 (0.0)	1	3/151 (2.0)	1/44 (2.3)	1
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Number of symptoms	1.40 (1.72)	0.67 (1.29)	0.002	1.43 (1.70)	0.43 (0.97)	0.002	1.41 (1.84)	0.93 (1.64)	0.008

SD: standard deviation.

Table 4

Univariable Analysis Identification of Factors Associated with Long COVID-19.

Factor	6 months		9 months		12 months	
	OR (95% CI) n = 249	P	OR (95% CI) n = 158	P	OR (95% CI) n = 191	P
Age, y				<0.0001		
<30	1.00	–	1.00	–	1.00	–
≥ 30	1.27 (0.77–2.12)	0.35	1.67 (0.86–3.26)	0.13	1.56 (0.86–2.82)	0.14
Gender						
Male	1.00	–	1.00	–	1.00	–
Female	1.15 (0.54–2.43)	0.72	1.26 (0.63–3.23)	0.63	1.22 (0.54–2.23)	0.63
Body mass index						
<30	1.00	–	1.00	–	1.00	–
≥30	0.92 (0.32–2.63)	0.88	0.85 (0.25–2.89)	0.79	1.17 (0.35–3.99)	0.80
Smoking status						
Never-Former	1.00	–	1.00	–	1.00	–
Current	0.99 (0.56–1.75)	0.98	0.42 (0.19–0.94)	0.03	0.73 (0.36–1.46)	0.37
Initial COVID status						
COVID-negative	1.00	–	1.00	–	1.00	–
COVID-positive	2.57 (1.40–4.72)	0.002	4.05 (1.63–10.09)	0.003	1.78 (0.90–3.50)	0.10
COVID Severity						
Outpatient (asymptomatic/mild)	1.00	–	1.00	–	1.00	–
Inpatient (moderate/severe)	2.55 (0.88–7.39)	0.09	4.11 (1.12–15.11)	0.03	3.64 (0.98–13.51)	0.05
COVID form						
Asymptomatic	1.00	–	1.00	–	1.00	–
Symptomatic	17.26 (3.93–75.87)	0.0001	7.89 (1.65–37.67)	0.01	4.35 (1.33–14.26)	0.015
Thinks had COVID	2.24 (1.29–3.87)	0.004	3.37 (1.59–7.13)	0.001	3.15 (1.61–6.13)	0.001

COVID-positive persons were overrepresented compared with the rest of the crew [17].

At least one Long-COVID symptom was self-reported by COVID-positive group participants at months 6 (53.7%), 9 (55.2%) and 12 (54.3%). While significantly more COVID-positive participants had at least one Long-COVID symptom at 6 ($P < .002$) and 9 months ($P < .002$) than in the COVID-negative group, the difference was no longer significant at 12 months ($P = .13$). The number of Long-COVID symptoms reported was also significantly higher in the COVID-positive group at months 6 and 9 only (Table 3).

3.2. Secondary outcomes

The most frequently reported Long-COVID symptoms were concentration and memory difficulties (brain fog), asthenia, sleep disorders and headaches (Table 3). In contrast, typical COVID-19 symptoms, such as ageusia or anosmia, were much less common. Significant differences between the COVID-positive and COVID-negative groups were found for brain fog and sleep disorders at 9 months, but only brain fog differed at 12 months.

Univariate analysis identified some factors associated with developing Long-COVID (Table 4): COVID-positive status at inclu-

sion, severity of the SARS-CoV2 infection, symptomatic COVID-19 and being convinced of having had COVID-19 regardless of initial status. COVID-positive status at inclusion was significantly associated with Long-COVID at months 6 (OR: 2.57 [95% CI: 1.40–4.72]) and 9 (OR: 4.05 [95% CI: 1.63–10.09]). Participants with moderate or severe forms (inpatients) had a greater probability of having Long-COVID at 9 months (OR: 4.11 [95% CI: 1.12–15.11]). This heightened risk was not found at 6 and 12 months. Symptomatic SARS-CoV-2 infection was a significant risk factor for the follow-up period as a whole. Being convinced that one had had COVID-19 was also associated with the risk of developing Long-COVID symptoms (OR: 2.24, 3.37 and 3.15 at 6, 9 and 12 months, respectively). Age, gender, BMI and smoking status were not significantly associated with developing Long-COVID, with the exception of a lower risk at 9 months for current smokers (OR: 0.42 [95% CI: 0.19–0.94]). OR could not be calculated for anxiety and depression, these symptoms being observed exclusively in the Long-COVID group at all follow-up times, with the exception of depressive symptoms at month 12 (non-significant relationship; (OR: 4.95 [95% CI: 0.57–43.16])).

Only COVID-19 at inclusion remained significantly associated with Long-COVID at months 6 (ORa: 3.29[95% CI: 1.63–6.63] – $P = 0.001$) and 9 (ORa: 4.72 [95% CI: 1.61–13.87] – $P = 0.005$) in multivariate analyses. At month 12, the only significant correlate was being convinced of having had COVID-19 (ORa: 3.17 [95% CI: 1.57–6.39] – $P = 0.001$). Two non-significant variables were also retained in the final model at month 9: tobacco use (ORa: 0.43 [95% CI: 0.18–1.04] – $P = 0.06$) and being aged 30 or more (ORa: 1.74 [95% CI: 0.83–3.64] – $P = 0.14$).

Regarding the impact on performance, SARS-CoV-2-infected participants showed a significantly higher probability of feeling a diminution of their athletic abilities up to 9 months (35.2% [71/202 responders] vs 11.3% [7/62 responders] – $P < .001$ at month 6 and 35.3% [48/136 responders] vs 12.9% [4/31 responders] – $P < .02$ at month 9). By 1 year, the difference had disappeared

(32.5% in COVID-positive group vs 22.2% – $P = 0.20$). All personnel were considered fit-to-work at each time of follow-up, with no restrictions imposed.

Table 5 summarizes HAD-Depression and -Anxiety, PCL-5, Rivermead, SMCQ and IEQ scale scores. Only SMCQ differed significantly between COVID-positive and COVID-negative groups at 9 (28.2% vs 7.4%, $P < .03$) and 12 months (32.2% vs 12.5%, $P < .02$).

4. Discussion

To the best of our knowledge, no other cohort study has examined the real-life temporal evolution of Long-COVID over 1 year in such a large and successively questioned population. Even though COVID-19 is being better and better described, Long-COVID remains poorly studied in populations of young adults, without comorbidities, who developed mild forms of COVID-19. In addition, unlike other studies using a paired controlled population, our population of strictly comparable individuals who had lived under the same conditions as documented COVID-positive participants, but for whom it was proven that they persistently remained SARS-CoV-2-negative during the on-board outbreak, represented an exceptional opportunity to compare the two groups' symptoms and evolution.

Approximately half of the COVID-positive participants enrolled in this study had at least one Long-COVID symptom at 6, 9 and 12 months of follow-up. That rate does not seem to have declined over time. The reported Long-COVID rate ranged from 10% to 90%, depending on the acute-COVID infection severity, follow-up time, and participant comorbidities [8,11,18–21]. A significant link was found between confirmed COVID-19 and at least one Long-COVID symptom 6- and 9-months post-infection, but by 12 months, it had disappeared. That loss could be explained by the very non-specific symptoms of Long-COVID reported by participants who never had COVID-19, a hypothesis supported by the **33% of Long-COVID symptoms** described at 12 months by individuals never infected by SARS-CoV2.

The Long-COVID symptoms reported by our COVID-19 participants were predominantly neurocognitive, such as diminished ability to concentrate and memory difficulties at 9 and 12 months (confirmed by SMCQ and Rivermead scores), sleep disorders at 9 months and anosmia at 6 months [10,11,18,21]. While these findings are similar to the others published, they highlight the fact that the symptoms can arise in a much younger, healthy cohort. In contrast, dyspnea and headaches, at times reported as being associated with COVID-19, were not found in our study [11,18,21,22].

The mechanism of neuropsychological manifestations of Long-COVID has not yet been clearly elucidated. However, SARS-CoV2's ability to easily cross the blood-brain barrier has been shown in animals [23]. Indeed, the recent comparison of the ^{18}F FDG-positron-emission tomography scans of Long-COVID participants and healthy subjects showed the former to have hypermetabolism in certain brain regions, notably the olfactory bulb or hippocampus, which could explain the memory and concentration difficulties (brain fog), anosmia and sleep disorders [24].

The main risk factor for developing Long-COVID at months 6 and 9 in multivariate analysis was initial SARS-CoV2 infection. Unlike previous studies, gender, age and comorbidities were not associated with the occurrence of Long-COVID, which might be explained by the predominantly young male population without comorbidities enrolled in the cohort [18,25–29]. Results recently published in *JAMA Internal Medicine* demonstrated a psychological component in Long-COVID, i.e., that being convinced of having had COVID-19 despite persistent negativity was significantly associated with development of Long-COVID symptoms [11]. This is in line with the present study which found, in multivariate analysis

Table 5
Standardized Psychological Test Results According to Initial SARS-CoV-2 Status.

Score	COVID+, n/N (%)	COVID–, n/N (%)	P
HAD-Depression ^a			
Month 6	5/196 (2.6)	1/57 (1.8)	1
Month 9	3/133 (2.3)	0/29 (0.0)	1
Month 12	3/149 (2.0)	3/44 (6.8)	0.13
HAD-Anxiety ^b			
Month 6	13/196 (6.6)	4/57 (7.0)	1
Month 9	6/133 (4.5)	1/29 (3.5)	1
Month 12	8/150 (5.3)	2/44 (4.6)	1
PCL-5 ^c			
Month 6	39/193 (20.2)	9/55 (16.4)	0.70
Month 9	20/131 (15.3)	3/27 (11.1)	0.77
Month 12	20/144 (13.9)	5/40 (12.5)	1
SMCQ ^d			
Month 6	53/190 (27.9)	12/55 (21.8)	0.49
Month 9	37/131 (28.2)	2/27 (7.4)	0.03
Month 12	46/143 (32.2)	5/40 (12.5)	0.02
Rivermead ^e			
Month 6	6/190 (3.2)	1/55 (1.8)	1
Month 9	7/158 (5.3)	0/27 (0.0)	0.60
Month 12	7/142 (4.9)	1/40 (2.5)	0.69
IEQ ^f			
Month 6	3/190 (1.6)	0/55 (0.0)	1
Month 9	3/131 (2.3)	0/27 (0.0)	1
Month 12	1/142 (0.7)	0/40	1

^a Hospital Anxiety Depression-Depression score > 11.

^b Hospital Anxiety Depression-Anxiety score > 11.

^c Post-traumatic Stress Disorder Check List Scale for DSM-5 score > 34.

^d Subjective Memory Complaints Questionnaire score > 3.

^e Rivermead head injury follow-up questionnaire score > 30.

^f Injustice Experience Questionnaire (IEQ) score > 30.

at 12 months, a significant relationship between being convinced of having had COVID-19 and Long-COVID occurrence, while association with confirmed COVID history remained, but was no longer significant. Lastly, unlike what has been reported, regarding the impact of COVID-19 on work or physical performances, even though 50% of our participants reported Long-COVID symptoms, while 30% had the clear impression of diminished athletic capacities, all of our SARS-CoV2-infected sailors were deemed fit to work, with no restrictions and compared to controls, during the 12 months of follow-up [13].

5. Study limitations

Only 641 out of 1767 (36%) sailors agreed to participate. However, sample characteristics at inclusion were similar to the rest of the crew in terms of gender, age and initial COVID-19 prevalence, suggesting a limited selection bias. The main limitation of this study is the lost-to-follow-up rate (171/641, 26.7%) which can be explained, in part, by our sailors' deployment in missions at sea without internet access during the 12 months of follow-up, and this was quite close to that previously reported data [18]. Hence, COVID-19 prevalence was higher at follow-up than at inclusion, suggesting better implication of participants than in controls. This limitation may artificially overestimate the Long-COVID rate but should have a limited impact with regard to Long-COVID correlates. Even if the results of the present study are in accordance with previous literature, the above-mentioned limitations prompt us to interpret these results with caution. The self-reporting in questionnaires and absence of open responses could lead to a loss of information affecting the search for specific symptoms. In addition, Long-COVID symptoms, recognized only after the beginning of the study (joint or muscle aches/pain, prolonged fever...) were not considered [30,31]. Finally, it is important to remember that our study population comprised healthy young individuals, mostly male, meaning that extrapolation of outcomes to the general population should be carried out with due caution.

6. Conclusion

Based on the first year of follow-up of our cohort, the results demonstrated that 50% of our COVID-positive young participants presented symptoms of Long-COVID, mainly neurocognitive. Lack of difference at 12 months with COVID-negative participants prompts caution. The symptoms of Long-COVID are so non-specific that they may be the consequence of multiple intercurrent factors. Symptoms of Long-COVID 12 months after an infection should not be systematically attributed to COVID-19 and differential diagnoses are required. Nevertheless, our findings suggest that a non-negligible proportion of patients can develop a Long-COVID syndrome, even after mild disease. At present, at a time when European nations are lifting public health restrictions because the majority of their populations are vaccinated, limiting the numbers of persons developing Long-COVID must remain a priority, especially because its very long-term consequences remain unknown.

7. Funding statement

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8. Ethics statement

All data were collected in the context of standard care from completely anonymized files, in accordance with French and Euro-

pean laws, including General Data Protection Regulation. All participants were informed and provided written consent for use of their data. The COV-PA study was approved by the regional Research Ethics Committee on December 7, 2020 (IDRCB 2020-A02397-32).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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