



HAL
open science

Prevalence of Post-Acute COVID-19 Symptoms Twelve Months after Hospitalisation in Participants Retained in Follow-up: Analyses Stratified by Gender from a Large Prospective Cohort

Jade Ghosn, Delphine Bachelet, Marine Livrozet, Minerva Cervantes-Gonzalez, Julien Poissy, François Goehringer, Charlotte Salmon Gandonniere, Mylène Maillet, Firouzé Bani-Sadr, Guillaume Martin-Blondel, et al.

► To cite this version:

Jade Ghosn, Delphine Bachelet, Marine Livrozet, Minerva Cervantes-Gonzalez, Julien Poissy, et al.. Prevalence of Post-Acute COVID-19 Symptoms Twelve Months after Hospitalisation in Participants Retained in Follow-up: Analyses Stratified by Gender from a Large Prospective Cohort. *Clinical Microbiology and Infection*, 2023, 29 (2), pp.254.e7-254.e13. 10.1016/j.cmi.2022.08.028 . hal-03801797

HAL Id: hal-03801797

<https://u-picardie.hal.science/hal-03801797>

Submitted on 21 Feb 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution-NonCommercial 4.0 International License

1 **Prevalence of post-acute COVID-19 symptoms twelve months after hospitalisation in**
2 **participants retained in follow-up: analyses stratified by gender from a large prospective**
3 **cohort**

4
5
6 Jade GHOSN, MD, PhD^{1,2}, Delphine BACHELET, PhD^{3,4}, Marine LIVROZET, MD⁵, Minerva
7 CERVANTES-GONZALEZ, MD, PhD^{1,2,4}, POISSY Julien, MD, PhD⁶, François
8 GOEHRINGER⁷, Charlotte SALMON GANDONNIERE, MD, PhD⁸, Mylène MAILLET⁹,
9 Firouzé BANI-SADR, MD, PhD¹⁰, Guillaume MARTIN-BLONDEL, MD, PhD¹¹, Pierre
10 TATTEVIN, MD, PhD¹², LAUNAY Odile, MD, PhD¹³, Laure SURGERS, MD, PhD¹⁴,
11 Emmanuel DUDOIGNON, MD¹⁵, Geoffroy LIEGEON, MD¹⁶, David ZUCMAN MD, PhD¹⁷,
12 Cédric JOSEPH, MD¹⁸, Eric SENNEVILLE, MD, PhD¹⁹, Cécile YELNIK, MD,²⁰ Pierre-
13 Marie ROGER, MD, PhD²¹, Karine FAURE, MD, PhD²², Marie GOUSSEFF, MD²³, André
14 CABIE²⁴, Xavier DUVAL, MD, PhD^{1,3}, Catherine CHIROUZE, MD, PhD²⁵, Cédric
15 LAOUENAN, MD, PhD^{1,3,4}, for the French COVID cohort study group and the French COVID
16 cohort investigators group*

17
18 ¹ Université Paris Cité, INSERM, IAME UMR 1137, Paris, France.

19 ² AP-HP.Nord, Hôpital Bichat, Department of Infectious and Tropical Diseases, Paris, France.

20 ³ INSERM, Centre d'Investigation clinique 1425, Hôpital Bichat, Paris, France.

21 ⁴ AP-HP.Nord, Hôpital Bichat, Department of Epidemiology Biostatistics and Clinical
22 Research, Paris, France.

23 ⁵ Université Paris Cité, INSERM, PARCC, Paris, France and CIC1418 and DMU CARTE, AP-
24 HP, Hôpital Européen Georges-Pompidou, Paris, France.

25 ⁶ Université de Lille, Inserm U1285, CHU Lille, Pôle de réanimation, CNRS, UMR 8576 -
26 UGSF - Unité de Glycobiologie Structurale et Fonctionnelle, F-59000, Lille, France.

27 ⁷ Department of Infectious Diseases, CHRU-Nancy, Université de Lorraine, Nancy, France.

28 ⁸ Médecine Intensive Réanimation, INSERM CIC 1415, CRICS-TriGGERSep network, CHRU
29 de Tours, Tours, France.

30 ⁹ Infectious Diseases, Annecy Genevois Hospital Centre, Epagny Metz-Tessy, Rhône-Alpes,
31 France.

32 ¹⁰ CHU Reims, Service des Maladies Infectieuses et TFranceles, Reims, France

33 ¹¹ CHU de Toulouse, Service des Maladies Infectieuses et Tropicales & Institut Toulousain des
34 Maladies Infectieuses et Inflammatoires (Infini) INSERM UMR1291 - CNRS UFrance,
35 Toulouse, France.

36 ¹² Hôpital Pontchaillou, Maladies Infectieuses et Réanimation, CHU Rennes, France.

37 ¹³ Université Paris Cité, CIC Cochin-Pasteur; AP-HP, Hôpital Cochin; INSERM CIC1417,
38 Paris, France.

39 ¹⁴ AP-HP, Hôpital Saint-Antoine, Infectious and Tropical Diseases Department, Paris, France

40 ¹⁵ AP-HP.Nord, Hôpital Saint-Louis, Service d'anesthésie-réanimation-CTB, DMU
41 PARABOL, Université Paris Cité, Paris, France

42 ¹⁶ AP-HP.Nord, Hôpital Saint-Louis, Service des Maladies Infectieuses et Tropicales,
43 Université de Paris, Paris, France

44 ¹⁷ Service de Médecine Interne, Foch Hospital, Suresnes, France.

45 ¹⁸ CHU Amiens-Picardie, Service des Maladies Infectieuses et Tropicales, and EA 4294, AGIR,
46 Jules Verne Picardy University, Amiens, France.

47 ¹⁹ Department of Infectious Diseases, Tourcoing Hospital, France.

48 ²⁰ CHU Lille, Département de Médecine Interne et Immunologie Clinique, France.

49 ²¹ Centre Hospitalier Universitaire de Guadeloupe, UMR 1058 Pathogenesis and Control of
50 Chronic and Emerging Infections, Guadeloupe, France.

51 ²² Service de Maladies Infectieuses, CHU, 59045 Lille, France.

52 ²³ Service de Médecine Interne, Maladies Infectieuses et Hématologie, Centre Hospitalier
53 Bretagne Atlantique, Vannes, France.

54 ²⁴ Université des Antilles, CHU de Martinique, Fort-de-France, Martinique, France.

55 ²⁵ CHU Besançon, Service de Maladie Infectieuses et Tropicales, Besançon, France.

56

57 **Corresponding authors:** Cédric LAOUEANAN

58 e-mail: cedric.laouenan@inserm.fr

59

60 *Membership of the French COVID cohort study and the French COVID cohort investigators
61 groups is provided in the Supplementary Material.

62

63 **Word count: abstract 272 words ; text 2597 words.**

64 Abstract

65

66 Objectives

67 Persistent post-acute COVID-19 symptom (PACS) have been reported up to 6-months (M6)
68 after hospital discharge. Here we assessed, in the longitudinal prospective national French
69 COVID cohort, symptoms that persisted 12-months (M12) after admission for COVID-19.

70

71 Methods

72 Hospitalized patients with a virologically-confirmed COVID-19 were enrolled. Follow-up was
73 planned until M12 post-admission. Associations between persistence of ≥ 3 PACS at M12 and
74 clinical characteristics at admission were assessed through logistic regression according to
75 gender.

76

77 Results

78 We focused on participants enrolled between January 24th and July 15th 2020, in order to
79 allow M12 follow-up. M12 data were available for 737 participants. Median age was 61
80 years, 475 (64%) were men and 242/647 (37%) were admitted to ICU during the acute phase.
81 At M12, 194/710 (27%) of participants had ≥ 3 persistent PACS, mostly fatigue, dyspnea and
82 joint pain. Among those who had a professional occupation before the acute phase 91/339
83 (27%) were still on sick leave at M12. Presence of ≥ 3 persistent PACS was associated with
84 female gender, both anxiety and depression, impaired health-related quality of life (HRQL)
85 and mMRC scale < 57 . Compared to men, women more often reported presence of ≥ 3 persistent
86 PACS (98/253, 39% vs 96/457, 21%), depression and anxiety (18/152, 12% vs 17/268, 6% and
87 33/156, 21% vs 26/264, 10%, respectively), impaired physical HRQL (76/141, 54% vs
88 120/261, 46%). Women had less often returned to work than men (77/116, 66% vs 171/223,
89 77%).

90

91 Conclusions

92 A fourth of individuals admitted to hospital for COVID-19 still had ≥ 3 persistent PACS at M12
93 post-discharge. Women reported more often ≥ 3 persistent PACS, suffered more from anxiety
94 and depression, and had less often returned to work than men.

95 **Introduction**

96 Clinical presentation of SARS-CoV-2 infection ranges from asymptomatic cases to severe
97 distress respiratory syndrome. When symptomatic, the acute phase commonly features cough,
98 dyspnea, flu-like symptoms, myalgia, joint pain, gastro-intestinal symptoms and
99 anosmia/ageusia (1). Several studies have reported the persistence of COVID-related symptoms
100 following acute phase. In 2021, WHO has developed a clinical definition of post-COVID
101 condition(2). According this definition, the proportion of patients experiencing at least one
102 persistent post-acute COVID-19 symptom (PACS) reaches 66% at two months, 53% at
103 four months and 32% at seven months post-infection in outpatients (3–5), and rises up to
104 62 to 68% at six months post-infection in patients hospitalized during the acute phase (6,7).
105 It was shown that ICU stay (with or without COVID-19) was associated with worse long-
106 term outcome (8).
107 Few data are available after 12 months post-infection with design heterogeneity (7,9–11).
108 In the Chinese cohort with a 12-month follow-up as well as in the study performed in
109 France with a six-month follow-up (6,7), female gender was associated with the persistence
110 of PACS. Furthermore, it is known that, at the same age, women report poorer health than
111 men in subjective health assessments, generally and in the COVID-19 specific setting (12–
112 15).Therefore, to add relevant evidence to the current literature we report results stratified
113 by gender from a large national multicentre cohort where COVID-19 patients were
114 followed prospectively from hospital admission up to 12 months regardless development
115 of PACS or not.

116

117 **Patients and methods**

118 **Study oversight and data collection**

119 The design of this national multicentre prospective cohort (French COVID Cohort) has
120 been described elsewhere (16). Briefly, hospitalized patients with a virologically confirmed
121 COVID-19 were enrolled in the cohort (registered in clinicaltrials.gov NCT04262921); ethics
122 approval was obtained from the French Ethic Committee CPP-Ile-de-France-VI (ID-RCB:
123 2020-A00256-33). Patients were co-included in the European H2020 ORCHESTRA
124 project.

125 Follow-up was planned with a physician's visit at month (M)3, M6 and M12 after hospital
126 admission. Comorbidities were assessed according to the 4C Mortality Score (17).

127 We asked every center to check the French register of deceased persons
128 (<https://arbre.app/en/insee>) in order to have the vital status (causes of death was not available)
129 of those who did not attend follow-up visits.

130

131 **Study definitions and outcomes**

132 At each visit, the following ten COVID-19 symptoms were collected (fatigue, dyspnea at
133 rest, joint pain, myalgia, headache, rhinorrhoea, cough, sore throat, ageusia and anosmia).

134 In addition, a physical exam and a 6-minute walking test (6MWT) were performed.

135 At M12 visit, a measure of the functional independence using the modified Rankin scale
136 (mRS) (0 indicates no symptoms, 5 severe disability) and an assessment of muscle strength
137 of each limb using the modified Medical Muscle Research council Scale (mMRC) (score
138 from 0 to 60) were also performed (18). Patients were also interviewed on health-related
139 quality of life (HRQL) with the 12-items Short Form Health Survey (SF-12) and on their
140 psychological distress (Health Anxiety Depression Scale, HADS). For SF-12, an individual
141 was defined as having an impaired physical (or mental) HRQL if his Physical (or Mental)
142 Component Summary (was lower than the 25th percentile of the distribution in the general
143 French population of the same age and gender. HADS is divided into anxiety (HADS-A)
144 and depression subscale (HADS-D). Each HADS item was scored on a 4-point Likert scale
145 with higher scores indicating more severe anxiety/depression. Scores ≥ 11 indicated
146 abnormal levels.

147

148 **Statistical analysis**

149 All analyses were stratified by gender. Associations between presence of PACS at M12
150 (defined by the presence of ≥ 3 of the ten COVID-19 symptoms) and baseline characteristics
151 were assessed through bivariate logistic regressions. The final multivariate models were
152 developed by starting with a model that included all covariates with $< 10\%$ of missing
153 values and $p < 0.20$ and then excluding variables that did not improve the overall fit as
154 measured by the $-2\log$ likelihood ratio test.

155 Prevalence of symptoms are given with their 95% CI (exact Clopper-Pearson method). For
156 patients who have both evaluation at M6 and M12, we compared the proportion of each
157 symptom through McNemar paired tests. We compared the baseline characteristics between
158 alive patients who attended the M12 visit to the eligible patients who did not (excluding
159 deceased patients) using a chi-square test. We computed the observed proportion of ≥ 3 PACS
160 and its 95% CI according to each combination of the risk factors found in the multivariate model

161 to impute patients without M12 visit. Finally, separately in women and men, as a sensitivity
162 analysis, we obtained three estimations of the proportion of patients with ≥ 3 persistent PACS
163 on the overall population of eligible patients for the M12 visit using three imputations: the mean
164 proportion and proportions from the lower and the upper bound of the 95%CI. All tests were
165 2-sided and analyses were performed with R software.

166

167 **Results**

168 We focused on participants enrolled between January 24th and July 15th 2020, in order to
169 allow for a 12-month follow-up. Out of the 3426 participants enrolled during this period,
170 391 died (11%) during initial hospitalization, 67 died (2%) between hospital discharge and
171 M12. By September 2021, M12 data were available for 737 patients. The baseline and M12
172 characteristics for the 737 patients (262 women and 475 men), are summarized in **Table 1**.

173

174 ***Global population***

175 At M12 visit, 194/710 (27%, 95%CI: 24-31%) participants had ≥ 3 persistent PACS. Fatigue
176 (327/705, 46%, 95%CI: 43-50%), dyspnea (235/704, 33%, 95%CI: 30-37%) and joint pain
177 (146/703, 21%, 95%CI: 17-24%) were the 3 most frequently reported symptoms
178 individually or in combination. Women reported myalgia frequently in addition to latter 3
179 symptoms (**eFigure 1**). Pulmonary auscultation was reported as “normal” in 507/634
180 patients (87%, 95%CI: 83-89%). In those with abnormal pulmonary auscultation, persistent
181 crackles were reported in 19/74 (26%) and wheezing in 10/74 (14%) cases, respectively.
182 The median percentage of predicted value of the 6MWT was 88% (IQR: 74;100) for the
183 163 patients who did this test. Of note, this was lower in the 61 patients who reported
184 dyspnea compared to those who did not (85% [IQR: 71;99] vs. 95% [IQR: 76;101],
185 $p=0.04$). When focusing on dyspnea at rest, persistent dyspnea at M12 was reported in 187/578
186 (32%) of the subset of individuals with no pulmonary chronic condition. Globally, the
187 presence of ≥ 3 persistent PACS was associated with female gender (data not shown because
188 all analysis were presented by gender), both anxiety and depression, impaired HRQL
189 (physical and mental), mRS ≥ 2 (**Supplementary Table 1**). Anxiety at M12 was associated
190 with female gender (OR=2.46, 95%CI: 1.41-4.32), not getting back to work (OR=2.72,
191 95%CI: 1.17-6.27) and dyspnea (OR=3.49, 95%CI: 1.98-6.27) (**Supplementary Table 2**).
192 Six hundred and sixty-three patients attended both M6 and M12 visits. Between the two
193 visits, there was no global evolution of the frequency of the ten PACS except for

194 rhinorrhoea and cough that were more often reported at M12 in women only (**Figure 1**).
195 Some patients reported an onset of symptoms at M12 compared to M6: 95/339 (28%,
196 95%CI: 33-46%) patients who did not have fatigue at M6 reported fatigue at M12, 101/425
197 (24%, 95%CI: 20-28%) for dyspnea and 81/490 (17%, 95%CI: 13-20%) for joint pain.

198

199 ***Results according to gender***

200 Compared to men, women more often reported the presence of ≥ 3 persistent PACS (98/253,
201 39%, 95%CI: 33-45% vs. 96/455, 21%, 95%CI: 17-25%), depression and anxiety
202 (respectively, 18/152, 12%, 95%CI: 7-18% vs. 17/268, 6%, 95%CI: 4-10% and 33/156,
203 21%, 95%CI: 15-28% vs. 26/264, 10%, 95%CI: 7-14%), an altered physical HRQL
204 (76/141, 54% vs. 120/261, 46%, 95%CI: 40-52%), and a mRS ≥ 2 (respectively, 45/170,
205 26%, 95%CI: 20-34% vs. 59/310, 19%, 95%CI: 15-24%). For those who previously had
206 an occupation, women were more often on sick leave than men (39/116, 34%, 95%CI: 25-
207 43% vs. 52/223, 23%, 95%CI: 18-29%).

208 In women, factors associated with the presence of ≥ 3 persistent PACS at M12 were age < 65
209 years (aOR=1.8, 95%CI: 1.0-3.2) and having ≥ 3 symptoms at admission during the acute
210 phase (aOR=2.2, 95%CI: 1.3-3.9). For men, only hospitalization in ICU and use of oxygen
211 during the acute phase were significant factors (respectively OR=3.1, 95%CI: 1.4-7.9 and
212 OR=2.7, 95%CI: 1.2-7.0) (**Table 2**).

213 The observed proportions of ≥ 3 persistent PACS at M12 for each of the combinations of
214 risk factors are reported in **efigure 2**. In women, these proportions ranged between 22%
215 with no risk factor (age ≥ 65 years, < 3 symptoms at admission) to 53% in those with both
216 risk factors. In men, these proportions ranged between 10% with no risk factor (no oxygen,
217 no invasive ventilation, no ICU stay) to 23% in those with both risk factors.

218

219 ***Comparison between eligible participants who attended M12 visit and those who did not,*** 220 ***and sensitivity analysis on all eligible participants***

221 Comparing the 737 patients who attended the M12 visit to the 2231 eligible patients who did
222 not, significant differences were found for admitted/transferred to ICU. Patients who attended
223 the M12 visit had been more often admitted/transferred to ICU (242/654, 37% versus 581/1937,
224 30%; $p < 0.001$) (**Table 3**).

225 In the sensitivity analysis, we obtained three estimations of the proportion of ≥ 3 persistent
226 PACS among all eligible patients for the M12 visit. In women, the mean proportion was
227 39% (95%CI: 36-41), the imputed proportion from the lower bound of the 95%CI was

228 33%, and the imputed proportion from the upper bound of the 95%CI was 46%. In men,
229 these proportions were 21% (95%CI: 19-23), 17% and 25%, respectively.

230

231 **Discussion**

232 Epidemiology and natural history of PACS are poorly understood. PACS subtypes are
233 widely distributed and cover exercise intolerance, pain syndromes, cognition, mood and
234 sleep disorders, and dysautonomia (19). In this large national prospective cohort of patients
235 hospitalized for confirmed COVID-19 during the acute phase, with 12-month follow-up
236 after hospital discharge, a fourth of the participants reported the presence of ≥ 3 persistent
237 PACS. The prevalence of PACS in our cohort is probably overestimated given the high
238 proportion of participants not retained in follow-up, and given the fact that those still
239 attending follow-up visits might be more prone to complain from PACS than those who
240 did not attend. In addition, there was no change between M6 and M12 globally but in a
241 same individual, some symptoms that were not reported at M6 could arise at M12. As these
242 signs are very unspecific, it is disputable whether they are linked with COVID-19. For
243 example, the 28% of people with fatigue at M12 among those who did not at M6 may not be
244 related to acute infection one-year-ago. Furthermore, 20% of participants stated that they had
245 not regained full independence at M12. These symptoms had disabling consequences since
246 a fourth of those who had a professional occupation before COVID-19 was still on sick
247 leave at M12.

248 It has been previously shown that women reported symptoms more frequently than men,
249 generally and in the COVID-19 setting (12–15), therefore, we chose to stratify our analyses
250 according to gender. Indeed, factors associated with the presence of PACS at M12 were
251 different according to gender. In men, admission/transfer to ICU and oxygen therapy were
252 associated with the presence of ≥ 3 PACS at M12, suggesting a potential role of the initial
253 severity of the disease in the persistence of symptoms. This could also suggest a role of the
254 antiviral adaptive response, or of the innate immune response. However, in women, the
255 persistence of ≥ 3 PACS at M12 was associated with having ≥ 3 symptoms at admission and
256 with younger age. Also, women reported more often anxiety and depression than men.
257 Recently, it has been shown that cognitive complaints at one month after a hospitalization for
258 COVID-19 were associated with psychological distress, independently of objective
259 neuropsychological status (20). We show that women are more likely to present to health care
260 clinics with symptoms post discharge. Increase presentation is associated with severity of initial

261 presentation and the presence of anxiety which may be associated with increased health seeking
262 behavior at M12 in this population. Our results at M6 were in keeping with those reported in a
263 Chinese cohort of hospitalized COVID-19 patients; however, the proportion of individuals with
264 ≥ 1 symptom and the proportion of those still on sick leave at M12 were lower in the Chinese
265 cohort than in ours (7). Of note, median age in the Chinese cohort was 59 years versus 61 in
266 ours, and the proportion of women was higher in the Chinese cohort (47%) than in ours (34%).
267 In addition, if 88% of participants were indeed back to work at M12 visit in the Chinese cohort,
268 it is important to emphasize that 24% did not return to pre-COVID-19 level of work (7).

269 Interestingly, our results favorably compared with those reported in Dutch ICU patients at M12
270 post admission (8).

271 The proportion of patients still complaining from PACS at M6 post COVID-19 (6) was
272 higher than that reported in matched patients who had influenza (21). The pathophysiology
273 underlying these persistent or fluctuant PACS long after the acute phase is still unknown.
274 Chronic inflammation, initial cytokine storm, residual virus in lungs post recovery,
275 activation of the complement system, microthrombi and macrothrombi formation have
276 been suggested as potential causes for these persistent symptoms (22,23). In our series,
277 21% of participants had a mRS ≥ 2 , and the percentage of predicted value of the 6MWT
278 was lower in the 61 patients who reported dyspnea compared to those who did not. CRP,
279 however, was low in all participants, but this marker might not be a good marker of
280 prolonged/chronic inflammation. Also, no samples for identification of residual viral
281 persistence were obtained. Indeed, a few studies reported detection of viral proteins and
282 RNA in various tissues, by *in situ* methods, months after infection (24,25). Chronic distress
283 can also be associated with chronic inflammation (26).

284 Our study had several limitations. First, the severity of PACS was not assessed. Indeed, in
285 our cohort at M6, when focusing on self-reported symptoms (and not symptoms reported
286 by the physician), the proportion of reported symptoms was roughly the same but most
287 symptoms were grade 1 (27). Second, is the potential bias in patients who attended M12
288 follow-up, such patients being more prone to be more symptomatic and thus, continue to
289 seek medical care, than those who have completely recovered. Indeed, patients who did not
290 attend the M12 visit had been less admitted/transferred to ICU than those who did attend,
291 these characteristics being less frequently associated with persistent PACS far from the
292 acute episode. This limitation might explain in part the differences between our results and
293 those of the Chinese cohort in which the number of participants attending M6 and M12
294 visits was similar, whereas the number of those attending M12 visit in our cohort was not

295 only lower than expected regarding the total number of eligible patients, but also lower
296 than those who attended M6 visit. We performed a sensitivity analysis by computing the
297 observed proportion of ≥ 3 PACS at M12 according to each combination of the risk factors found
298 in the multivariate model to impute patients without M12 visit. However, this approach, which
299 takes into account the differences on the distribution of risk factors, assumes that there is
300 no specific selection bias, i.e., it assumes that patients without visit behave as those with a
301 visit according to the combination of risk factors. Of note, scheduling follow-up hospital
302 visits in this time of saturation of the healthcare system was challenging. Third, we did not
303 have the health status (HRQL, anxiety and depression) of patients before acute infection.
304 Finally, the impact of vaccines, treatment and less virulent strains (such as Omicron
305 variant) is unknown.

306 In conclusion, longitudinal follow-up of individuals with severe COVID-19 is warranted
307 to precisely determine the nature and frequency of persistent PACS, with self-reported
308 online or telephone assessments to reduce the number of patients lost to follow-up, with
309 additional questionnaires to address somatic symptom disorders, and to better understand
310 the pathophysiology underlying this long-term persistence.

311 Conflict of Interest

312 Authors report no conflict of interest except JG who reports personal fees from Merck, grants
313 and personal fees from ViiV healthcare, grants and personal fees from Gilead Sciences,
314 personal fees from Roche, personal fees from AstraZeneca, personal fees from Janssen, outside
315 the submitted work.

316 Funding

317 The French COVID cohort is funded by the REACTing (REsearch & ACtion emergING
318 infectious diseases) consortium, by a grant of the French Ministry of Health (PHRC n°20-0424),
319 and by the ORCHESTRA project which has received funding from the European Union's
320 Horizon 2020 research and innovation program under grant agreement N°101016167. The
321 funders had no role in the design and conduct of the study; collection, management, analysis,
322 and interpretation of the data; preparation, review, or approval of the manuscript; and decision
323 to submit the manuscript for publication.

324

325 Acknowledgment

326 **Author Contributions:** Dr Laouéan had full access to all of the data in the study and take
327 responsibility for the integrity of the data and the accuracy of the data analysis.

328 **Group Information:** The members of the French COVID cohort study and investigators
329 groups are provided in Supplementary Material.

330 **Additional Information:** The study included a scientific advisory board composed of
331 Dominique COSTAGLIOLA, Astrid VABRET, Hervé RAOUL and Laurence WEISS.

332 **References**

- 333 1. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features
334 of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical
335 Characterisation Protocol: prospective observational cohort study. *BMJ*. 22 mai
336 2020;369:m1985.
- 337 2. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October
338 2021 [Internet]. [cité 8 févr 2022]. Disponible sur: [https://www.who.int/publications-detail-
339 redirect/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1](https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1)
- 340 3. Petersen MS, Kristiansen MF, Hanusson KD, Danielsen ME, Á Steig B, Gaini S, et al. Long
341 COVID in the Faroe Islands: A Longitudinal Study Among Nonhospitalized Patients. *Clin
342 Infect Dis*. 6 déc 2021;73(11):e4058-63.
- 343 4. Nehme M, Braillard O, Chappuis F, Courvoisier DS, Guessous I, CoviCare Study Team.
344 Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic
345 COVID-19 in an Outpatient Setting. *Ann Intern Med*. sept 2021;174(9):1252-60.
- 346 5. Carvalho-Schneider C, Laurent E, Lemaigen A, Beaufils E, Bourbao-Tournois C, Laribi
347 S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset.
348 *Clin Microbiol Infect*. févr 2021;27(2):258-63.
- 349 6. Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentré F, Bachelet D, et al. Persistent
350 COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a
351 large prospective cohort. *Clin Microbiol Infect*. juill 2021;27(7):1041.e1-1041.e4.
- 352 7. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital
353 survivors with COVID-19: a longitudinal cohort study. *Lancet*. 28 août
354 2021;398(10302):747-58.
- 355 8. Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, et al.
356 Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit
357 Treatment for COVID-19. *JAMA*. 8 févr 2022;327(6):559-65.
- 358 9. Kim Y, Bitna-Ha, Kim SW, Chang HH, Kwon KT, Bae S, et al. Post-acute COVID-19
359 syndrome in patients after 12 months from COVID-19 infection in Korea. *BMC Infectious
360 Diseases*. 27 janv 2022;22(1):93.
- 361 10. Rivera-Izquierdo M, Láinez-Ramos-Bossini AJ, de Alba IGF, Ortiz-González-Serna R,
362 Serrano-Ortiz Á, Fernández-Martínez NF, et al. Long COVID 12 months after discharge:
363 persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised
364 due to other causes-a multicentre cohort study. *BMC Med*. 23 févr 2022;20(1):92.
- 365 11. Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, et al. Persistent
366 Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A
367 Prospective Cohort Study. *Clin Infect Dis*. 9 avr 2022;74(7):1191-8.
- 368 12. Otten D, Tibubos AN, Schomerus G, Brähler E, Binder H, Kruse J, et al. Similarities and
369 Differences of Mental Health in Women and Men: A Systematic Review of Findings in
370 Three Large German Cohorts. *Front Public Health*. 2021;9:553071.

- 371 13. Tibubos AN, Otten D, Zöller D, Binder H, Wild PS, Fleischer T, et al. Bidimensional
372 structure and measurement equivalence of the Patient Health Questionnaire-9: sex-sensitive
373 assessment of depressive symptoms in three representative German cohort studies. *BMC*
374 *Psychiatry*. 5 mai 2021;21(1):238.
- 375 14. Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae
376 of COVID-19 - A systematic review. *Brain Behav Immun*. oct 2021;97:328-48.
- 377 15. Wang Y, Kala MP, Jafar TH. Factors associated with psychological distress during the
378 coronavirus disease 2019 (COVID-19) pandemic on the predominantly general population:
379 A systematic review and meta-analysis. *PLoS One*. 2020;15(12):e0244630.
- 380 16. Yazdanpanah Y, French COVID cohort investigators and study group. Impact on disease
381 mortality of clinical, biological, and virological characteristics at hospital admission and
382 overtime in COVID-19 patients. *J Med Virol*. avr 2021;93(4):2149-59.
- 383 17. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of
384 patients admitted to hospital with covid-19 using the ISARIC WHO Clinical
385 Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ*. 9
386 sept 2020;370:m3339.
- 387 18. Turan Z, Topaloglu M, Ozyemisci Taskiran O. Medical Research Council-sumscore: a tool
388 for evaluating muscle weakness in patients with post-intensive care syndrome. *Crit Care*.
389 18 sept 2020;24(1):562.
- 390 19. Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19:
391 potential mechanisms of disease. *Brain*. 31 déc 2021;144(12):3576-88.
- 392 20. Gouraud C, Bottemanne H, Lahlou-Laforêt K, Blanchard A, Günther S, Batti SE, et al.
393 Association Between Psychological Distress, Cognitive Complaints, and
394 Neuropsychological Status After a Severe COVID-19 Episode: A Cross-Sectional Study.
395 *Front Psychiatry*. 2021;12:725861.
- 396 21. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-
397 occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study
398 of 273,618 survivors of COVID-19. *PLoS Med*. sept 2021;18(9):e1003773.
- 399 22. Hirschenberger M, Hunszinger V, Sparrer KMJ. Implications of Innate Immunity in Post-
400 Acute Sequelae of Non-Persistent Viral Infections. *Cells*. 19 août 2021;10(8):2134.
- 401 23. Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the Mystery
402 Surrounding Post-Acute Sequelae of COVID-19. *Front Immunol*. 2021;12:686029.
- 403 24. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of
404 antibody immunity to SARS-CoV-2. *Nature*. mars 2021;591(7851):639-44.
- 405 25. Cheung CCL, Goh D, Lim X, Tien TZ, Lim JCT, Lee JN, et al. Residual SARS-CoV-2
406 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-
407 19. *Gut*. janv 2022;71(1):226-9.
- 408 26. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. *Lancet*.
409 17 mars 2007;369(9565):946-55.

- 410 27. Eloy P, Tardivon C, Martin-Blondel G, Isnard M, Turnier PL, Marechal ML, et al. Severity
411 of self-reported symptoms and psychological burden 6-months after hospital admission for
412 COVID-19: a prospective cohort study. *Int J Infect Dis.* 11 sept 2021;112:247-53.

413

Journal Pre-proof

414 **Table 1.** Characteristics at hospital admission and clinical symptoms at 12 months follow-up
 415 of 737 patients enrolled in the French COVID cohort

Characteristics	Missing	All N=737	Women N=262	Men N=475
At hospital admission				
Age - Median [IQR] – years	0	61 [52; 70]	60 [51; 70]	61 [52; 70]
Age <65 years - no/total no (%)	0	437/737 (59)	155/262 (59)	282/475 (59)
Comorbidities - no/total no (%)				
Chronic cardiac disease (not hypertension)	58	108/679 (16)	31/248 (12)	77/431 (18)
Hypertension	72	258/665 (39)	86/243 (35)	172/422 (41)
Chronic kidney disease	55	55/682 (8)	11/248 (4)	44/434 (10)
Malignant neoplasm	57	46/680 (7)	15/248 (6)	31/432 (7)
Moderate or severe liver disease	70	7/667 (1)	1/244 (0)	6/423 (1)
Obesity (clinician definition)	71	139/666 (21)	63/240 (26)	76/426 (18)
Chronic pulmonary disease (not asthma)	55	78/682 (11)	22/248 (9)	56/434 (13)
Diabetes (type 1 and 2)	67	129/670 (19)	43/245 (18)	86/425 (20)
No of comorbidities - no/total no (%) ^a				
0		188/683 (28)	72/249 (29)	116/434 (27)
1		202/683 (30)	78/249 (31)	124/434 (29)
≥2		293/683 (43)	99/249 (40)	194/434 (45)
Symptoms - no/total no (%) ^b				
None	82	39/655 (6)	19/241 (8)	20/414 (5)
1-2		250/655 (38)	86/241 (36)	164/414 (40)
≥3		366/655 (56)	136/241 (56)	230/414 (56)
Management during hospitalisation				
ICU during acute phase	90	242/647 (37)	63/234 (27)	179/412 (43)
Oxygen therapy - no/total no (%)	105	482/632 (76)	165/234 (71)	317/398 (80)
Non-invasive ventilation (e.g. BIPAP, CPAP) - no/total no (%)	115	126/622 (20)	43/233 (18)	83/389 (21)
Pharmacological treatment during acute COVID-19 - no/total no (%)				
Antiviral agent	104	178/633 (28)	56/234 (24)	122/399 (31)
Hydroxychloroquine	129	106/608 (17)	37/222 (17)	69/386 (18)
Immunomodulator (for example anti-IL6)	146	17/591 (3)	2/219 (1)	15/372 (4)
Corticosteroids	98	142/639 (22)	48/238 (20)	94/401 (23)
Length of hospital stay - Median [IQR] - d	77	9 [5; 17]	8 [5; 13]	11 [6; 19]
M12 follow-up after discharge				
Days from symptom onset to M12 visit - Median [IQR] – d	55	391 [374; 419]	391 [374; 415]	392 [373; 420]
Days from discharge to M12 visit - Median [IQR] – d	56	370 [352; 398]	371 [355; 395]	368 [350; 400]
Six-minute walk test (6MWT) done at M12 visit - no/total no (%)	195	264/542 (49)	75/189 (40)	187/351 (53)
Distance walked in % - Median [IQR]	570	88 [74; 100]	85 [75; 100]	94 [74; 100]

Medical Research Council Scale <48 at M12 visit - no/total no (%)	253	8/484 (2)	3/168 (2)	5/316 (2)
Simplified Modified Rankin Scale at M12 visit - no/total no (%)	257			
0 - No symptoms		242/480 (50)	76/170 (45)	166/310 (54)
1 - No significant disability		134/480 (28)	49/170 (29)	85/310 (27)
2 - Slight disability		79/480 (16)	34/170 (20)	45/310 (15)
3 - Moderate disability		22/480 (5)	10/170 (6)	12/310 (4)
4 - Moderately severe disability		2/480 (0)	1/170 (1)	1/310 (0)
5 - Severe disability		1/480 (0)	0/170 (0)	1/310 (0)
HADS - no/total no (%)	317			
Anxiety score ≥ 11		59/420 (14)	33/156 (21)	26/264 (10)
Depression score ≥ 11		35/420 (8)	18/152 (12)	17/268 (6)
SF-12 - no/total no (%)	335			
Impaired physical HRQL		196/402 (49)	76/141 (54)	120/261 (46)
Impaired mental HRQL		126/402 (31)	45/141 (32)	81/261 (31)
If applicable, back to work at M12 - no/total no (%)	398	248/339 (73)	77/116 (66)	171/223 (77)
CRP at M12 visit - Median [IQR] – mg/L	323	3 [1; 4]	3 [2; 7]	2 [1; 4]
Persistent PACS 12 months after hospital admission - no/total no (%) ^b	27			
None		236/710 (33)	62/253 (25)	174/457(38)
1-2		280/710 (39)	93/253 (37)	187/457 (41)
≥ 3		194/710 (27)	98/253 (39)	96/457 (21)

416 ^a Comorbidities were defined using the Charlson comorbidity index, with the addition of clinician-
417 defined obesity.

418 ^b Number of symptoms among: fatigue, dyspnea, joint pain, myalgia, headache, rhinorrhoea, cough,
419 sore throat, ageusia and anosmia.

420 **Table 2.** Univariate and multivariate association analyses with 3 or more symptoms at M12 visit separately in women and in men

	Missing	<3 symptoms at M12	≥3 symptoms at M12	Bivariate analysis ^a		Multivariate analysis ^b		
				OR [95% CI]	p-value	aOR [95% CI]	p-value	
Women	Age <65 years, n (%)	0	83 (54%)	67 (68%)	1.87 [1.11; 3.21]	0.020	1.79 [1.03; 3.15]	0.042
	≥3 symptoms at admission, n (%)	19	69 (49%)	64 (69%)	2.30 [1.34; 4.02]	0.003	2.21 [1.28; 3.89]	0.005
	≥2 comorbidities, n (%)	11	54 (37%)	41 (43%)	1.31 [0.77; 2.22]	0.32		
	Antiviral agent, n (%)	26	37 (27%)	17 (19%)	0.63 [0.32; 1.19]	0.16		
	Corticosteroids, n (%)	22	28 (20%)	18 (20%)	0.99 [0.50; 1.90]	0.97		
	ICU/non invasive ventilation/oxygen	31						
	No		34 (25%)	26 (30%)	1 reference			
	Oxygen only (no ICU, no ventilation)		58 (43%)	33 (38%)	0.74 [0.38; 1.45]	0.38		
ICU or non invasive ventilation		42 (31%)	29 (33%)	0.90 [0.45; 1.81]	0.77			
Men	Age <65 years, n (%)	0	213 (59%)	58 (60%)	1.06 [0.67; 1.69]	0.80		
	≥3 symptoms at admission, n (%)	56	170 (54%)	51 (60%)	1.27 [0.78; 2.08]	0.34		
	≥2 comorbidities, n (%)	37	144 (44%)	40 (46%)	1.11 [0.69; 1.78]	0.68		
	Antiviral agent, n (%)	73	84 (28%)	31 (37%)	1.46 [0.87; 2.41]	0.15		
	Corticosteroids, n (%)	71	64 (21%)	23 (27%)	1.39 [0.79; 2.40]	0.24		
	ICU/non invasive ventilation/oxygen	70						
	No		63 (21%)	7 (9%)	1 reference		1 reference	
	Oxygen only (no ICU, no ventilation)		98 (32%)	30 (37%)	2.77 [1.25; 7.03]	0.019	2.70 [1.17; 7.02]	0.028
ICU or non invasive ventilation		143 (47%)	44 (54%)	2.76 [1.20; 7.16]	0.024	3.08 [1.38; 7.85]	0.010	

421 OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval

422 ^a Women: n=253, 155 with <3 symptoms at M12 and 98 with ≥3 symptoms at M12. Men: n=457, 361 with <3 symptoms at M12 and 96 with ≥3 symptoms at M12423 ^b Women: n=234, 141 with <3 symptoms at M12 and 93 with ≥3 symptoms at M12. Men: n=385, 304 with <3 symptoms at M12 and 81 with ≥3 symptoms at M12

424 **Table 3.** Comparison between patients included in the analyses and patients not deceased who
 425 did not attend M12 visit
 426

	Included in the analyses (N=737)	Not included in the analyses (N=2231)	p-value*
Age ≥ 65 years	300 (41%)	973 (44%)	0.12
Female gender	262 (36%)	852 (39%)	0.13
≥ 3 symptoms at admission	366 (56%)	1116 (57%)	0.65
Intensive care unit during acute phase	242 (37%)	581 (30%)	<0.001
≥ 2 comorbidities	293 (43%)	947 (45%)	0.24

* chi-square test

427

428 **Figure legends**

429 **Figure 1:** COVID-19 related symptoms during the acute phase and during follow-up visits of
430 patients with M6 and M12 visits for women (n=235) and for men (n=428) enrolled in the French
431 COVID cohort

432

433 **Note: McNemar paired tests (M6 vs M12) for each symptom among women and men:**

434 Women: fatigue (p=1, N=213), dyspnea (p=0.11, N=215), joint pain (p=0.11, N=215), myalgia (p=0.37,
435 N=209), cough (p=0.007, N=211), headache (p=1, N=206), rhinorrhoea (p=0.026, N=210), ageusia
436 (p=0.45, N=205), anosmia (p=0.40, N=205), sore throat (p=0.40, N=209).

437 Men: fatigue (p=0.31, N=385), dyspnea (p=0.29, N=385), joint pain (p=0.22, N=381), myalgia (p=1,
438 N=381), cough (p=0.55, N=384), headache (p=0.090, N=382), rhinorrhoea (p=0.093, N=379), ageusia
439 (p=0.82, N=383), anosmia (p=0.65, N=382), sore throat (p=0.45, N=384).

