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, MD, PhD[1,2], Delphine BACHELET, PhD[3,4], Marine LIVROZET, MD[5], Minerva CERVANTES-GONZALEZ, MD, PhD[1,2,4], POISSY Julien, MD, PhD[6], François GOEHRINGER[7], Charlotte SALMON GANDONNIERE, MD, PhD[8], Mylène MAILLET[9], Firouzé BANI-SADR, MD, PhD[10], Guillaume MARTIN-BLONDEL, MD, PhD[11], Pierre TATTEVIN, MD, PhD[12], LAUNAY Odile, MD, PhD[13], Laure SURGERS, MD, PhD[14], Emmanuel DUDOIGNON, MD[15], Geoffroy LIEGEON, MD[16], David ZUCMAN MD, PhD[17], Cédric JOSEPH, MD[18], Eric SENNEVILLE, MD, PhD[19], Cécile YELNIK, MD,[20], Pierre-Marie ROGER, MD, PhD[21], Karine FAURE, MD, PhD[22], Marie GOUSSEFF, MD[23], André CABIE[24], Xavier DUVAL, MD, PhD[1,3], Catherine CHIROUZE, MD, PhD[25], Cédric LAOUENAN, MD, PhD[1,3,4], for the French COVID cohort study group and the French COVID cohort investigators group*

[1] Université Paris Cité, INSERM, IAME UMR 1137, Paris, France.

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

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

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

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

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

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

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

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

[10] CHU Reims, Service des Maladies Infectieuses et TFranceles, Reims, France

[11] CHU de Toulouse, Service des Maladies Infectieuses et Tropicales & Institut Toulousain des Maladies Infectieuses et Inflammatoires (Infinit) INSERM UMR1291 - CNRS UFrance, Toulouse, France.

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

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

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

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

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

[17] Service de Médecine Interne, Foch Hospital, Suresnes, France.

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

[19] Department of Infectious Diseases, Tourcoing Hospital, France.

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

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

[22] Service de Maladies Infectieuses, CHU, 59045 Lille, France.

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

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

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

Corresponding authors: Cédric LAOUENAN

e-mail: cedric.laouenan@inserm.fr

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

Word count: abstract 272 words ; text 2597 words.

Abstract

Objectives

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

Methods

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

Results

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

Conclusions

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

Introduction

Clinical presentation of SARS-CoV-2 infection ranges from asymptomatic cases to severe distress respiratory syndrome. When symptomatic, the acute phase commonly features cough, dyspnea, flu-like symptoms, myalgia, joint pain, gastro-intestinal symptoms and anosmia/ageusia (1). Several studies have reported the persistence of COVID-related symptoms following acute phase. In 2021, WHO has developed a clinical definition of post-COVID condition(2). According this definition, the proportion of patients experiencing at least one persistent post-acute COVID-19 symptom (PACS) reaches 66% at two months, 53% at four months and 32% at seven months post-infection in outpatients (3–5), and rises up to 62 to 68% at six months post-infection in patients hospitalized during the acute phase (6,7). It was shown that ICU stay (with or without COVID-19) was associated with worse long-term outcome (8).

Few data are available after 12 months post-infection with design heterogeneity (7,9–11). In the Chinese cohort with a 12-month follow-up as well as in the study performed in France with a six-month follow-up (6,7), female gender was associated with the persistence of PACS. Furthermore, it is known that, at the same age, women report poorer health than men in subjective health assessments, generally and in the COVID-19 specific setting (12–15).Therefore, to add relevant evidence to the current literature we report results stratified by gender from a large national multicentre cohort where COVID-19 patients were followed prospectively from hospital admission up to 12 months regardless development of PACS or not.

Patients and methods

Study oversight and data collection

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

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

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

Study definitions and outcomes

At each visit, the following ten COVID-19 symptoms were collected (fatigue, dyspnea at rest, joint pain, myalgia, headache, rhinorrhoea, cough, sore throat, ageusia and anosmia). In addition, a physical exam and a 6-minute walking test (6MWT) were performed.

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

Statistical analysis

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

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

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

Results

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

Global population

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

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

Results according to gender

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

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

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

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

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

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

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

Discussion

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

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

presentation and the presence of anxiety which may be associated with increased health seeking behavior at M12 in this population. Our results at M6 were in keeping with those reported in a Chinese cohort of hospitalized COVID-19 patients; however, the proportion of individuals with ≥1 symptom and the proportion of those still on sick leave at M12 were lower in the Chinese cohort than in ours (7). Of note, median age in the Chinese cohort was 59 years versus 61 in ours, and the proportion of women was higher in the Chinese cohort (47%) than in ours (34%). In addition, if 88% of participants were indeed back to work at M12 visit in the Chinese cohort, it is important to emphasize that 24% did not return to pre-COVID-19 level of work (7). Interestingly, our results favorably compared with those reported in Dutch ICU patients at M12 post admission (8).

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

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

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

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

Conflict of Interest

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

Funding

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

Acknowledgment

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

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

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

References

1. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 22 mai 2020;369:m1985.

2. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021 [Internet]. [cité 8 févr 2022]. Disponible sur: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

3. Petersen MS, Kristiansen MF, Hanusson KD, Danielsen ME, Á Steig B, Gaini S, et al. Long COVID in the Faroe Islands: A Longitudinal Study Among Nonhospitalized Patients. Clin Infect Dis. 6 déc 2021;73(11):e4058-63.

4. Nehme M, Braillard O, Chappuis F, Courvoisier DS, Guessous I, CoviCare Study Team. Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in an Outpatient Setting. Ann Intern Med. sept 2021;174(9):1252-60.

5. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. févr 2021;27(2):258-63.

6. Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentré F, Bachelet D, et al. Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. Clin Microbiol Infect. juill 2021;27(7):1041.e1-1041.e4.

7. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 28 août 2021;398(10302):747-58.

8. Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, et al. Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19. JAMA. 8 févr 2022;327(6):559-65.

9. Kim Y, Bitna-Ha, Kim SW, Chang HH, Kwon KT, Bae S, et al. Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea. BMC Infectious Diseases. 27 janv 2022;22(1):93.

10. Rivera-Izquierdo M, Láinez-Ramos-Bossini AJ, de Alba IGF, Ortiz-González-Serna R, Serrano-Ortiz Á, Fernández-Martínez NF, et al. Long COVID 12 months after discharge: persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised due to other causes-a multicentre cohort study. BMC Med. 23 févr 2022;20(1):92.

11. Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. Clin Infect Dis. 9 avr 2022;74(7):1191-8.

12. Otten D, Tibubos AN, Schomerus G, Brähler E, Binder H, Kruse J, et al. Similarities and Differences of Mental Health in Women and Men: A Systematic Review of Findings in Three Large German Cohorts. Front Public Health. 2021;9:553071.

13. Tibubos AN, Otten D, Zöller D, Binder H, Wild PS, Fleischer T, et al. Bidimensional structure and measurement equivalence of the Patient Health Questionnaire-9: sex-sensitive assessment of depressive symptoms in three representative German cohort studies. BMC Psychiatry. 5 mai 2021;21(1):238.

14. Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun. oct 2021;97:328-48.

15. Wang Y, Kala MP, Jafar TH. Factors associated with psychological distress during the coronavirus disease 2019 (COVID-19) pandemic on the predominantly general population: A systematic review and meta-analysis. PLoS One. 2020;15(12):e0244630.

16. Yazdanpanah Y, French COVID cohort investigators and study group. Impact on disease mortality of clinical, biological, and virological characteristics at hospital admission and overtime in COVID-19 patients. J Med Virol. avr 2021;93(4):2149-59.

17. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 9 sept 2020;370:m3339.

18. Turan Z, Topaloglu M, Ozyemisci Taskiran O. Medical Research Council-sumscore: a tool for evaluating muscle weakness in patients with post-intensive care syndrome. Crit Care. 18 sept 2020;24(1):562.

19. Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 31 déc 2021;144(12):3576-88.

20. Gouraud C, Bottemanne H, Lahlou-Laforêt K, Blanchard A, Günther S, Batti SE, et al. Association Between Psychological Distress, Cognitive Complaints, and Neuropsychological Status After a Severe COVID-19 Episode: A Cross-Sectional Study. Front Psychiatry. 2021;12:725861.

21. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med. sept 2021;18(9):e1003773.

22. Hirschenberger M, Hunszinger V, Sparrer KMJ. Implications of Innate Immunity in Post-Acute Sequelae of Non-Persistent Viral Infections. Cells. 19 août 2021;10(8):2134.

23. Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. Front Immunol. 2021;12:686029.

24. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. Nature. mars 2021;591(7851):639-44.

25. Cheung CCL, Goh D, Lim X, Tien TZ, Lim JCT, Lee JN, et al. Residual SARS-CoV-2 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-19. Gut. janv 2022;71(1):226-9.

26. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. Lancet. 17 mars 2007;369(9565):946-55.

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

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]	54			
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]	82			
None		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)

[a] Comorbidities were defined using the Charlson comorbidity index, with the addition of clinician-defined obesity.

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

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

		Missing	<3 symptoms at M12	≥3 symptoms at M12	Bivariate analysis[a] OR [95%CI]	p-value	Multivariate analysis[b] 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 M12
423 [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

Figure legends

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

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

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

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