



BRIEF REPORT

Excess of Post-Acute Sequelae of COVID-19 After the First Wave of the Pandemic

Marc Scherlinger · Cédric Lemogne · Renaud Felten ·

Jean Sibilia

Received: July 7, 2022 / Accepted: September 8, 2022
© The Author(s) 2022

ABSTRACT

Introduction: To compare the time distribution of initial COVID-19 among patients with self-reported post-acute sequelae of COVID-19 (PASC).

Methods: We compared the distribution of the date of the reported initial COVID-19 among

patients with self-reported PASC and the COVID-19 cases in France between the first wave (January 1–May 11, 2020) and the later period (May 12, 2020–June 30, 2021) using the chi-squared test. COVID-19 cases in France were assessed using previous modeling of COVID-19 burden in France for the first time period, and positive RT-PCR testing for the second time period.

Results: The study included 567 individuals with PASC (median age 44, [IQR 37–50]; 83.4% women). A total of 293 (51.7%) patients reported an initial COVID-19 infection during the first period while 272 (48%) reported it during

Renaud Felten and Jean Sibilia contributed equally.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40121-022-00698-6>.

M. Scherlinger (✉) · R. Felten · J. Sibilia
Rheumatology Department, CHRU de Strasbourg,
Centre National de Référence des Maladies Auto-
Immunes et Systémiques Rares, Est/Sud-Ouest
(RESO), 1 Avenue Molière, 67098 Strasbourg Cedex,
France
e-mail: marc.scherlinger@chru-strasbourg.fr

M. Scherlinger
Division of Rheumatology and Clinical
Immunology, Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MA 02115, USA

C. Lemogne
Université Paris Cité, INSERM U1266, Institut de
Psychiatrie et Neurosciences de Paris, F-75014 Paris,
France

C. Lemogne
Service de Psychiatrie de l'adulte, AP-HP, Hôpital
Hôtel-Dieu, F-75004 Paris, France

R. Felten
IBMC, CNRS, UPR3572 Strasbourg, France

M. Scherlinger · J. Sibilia
Laboratoire d'ImmunoRhumatologie Moléculaire,
Institut National de la Santé Et de la Recherche
Médicale (INSERM) UMR_S 1109, Institut
Thématique Interdisciplinaire (ITI) de Médecine de
Précision de Strasbourg, Transplantex NG, Faculté
de Médecine, Fédération Hospitalo-Universitaire
OMICARE, Fédération de Médecine Translationnelle
de Strasbourg (FMTS), Université de Strasbourg,
Strasbourg, France

the later period (missing data, $n = 2$; 0.3%). Patients with PASC were 82% more likely to report initial COVID-19 during the first pandemic wave than afterward (OR 1.82, 95% CI [1.55–2.15]; $p < 0.0001$).

Conclusions: The incidence of self-reported PASC wave was significantly higher when initial COVID-19 happened during the first pandemic wave than afterward, suggesting the importance of non-viral factors in PASC development.

Keywords: COVID-19; LongCOVID; Post-acute sequelae of COVID-19; Stress

Key Summary Points

In France, patients with post-acute sequelae of COVID-19 (PASC) were 82% more likely to report an initial infection during the first pandemic wave, and aggregated around the lockdown announcement.

Viral factors (i.e. variants) or prior vaccination were unlikely to explain the observed differences in PASC incidence considering the study period.

We hypothesize that the stress induced by the first wave of the pandemic may have fostered the onset or chronicization of symptoms in a subset of patients with PASC.

INTRODUCTION

SARS-CoV-2 has infected hundreds of millions of people since the beginning of the pandemic in early 2020, resulting in the death of millions. Among a proportion of convalescent individuals, a condition called post-acute sequelae of COVID-19 (PASC) or long COVID has emerged. Since then, the medical and scientific community has been working together with patient associations to define PASC and identify mechanisms underlying its pathogenesis [1, 2]. Several studies have shed some light on the

potential role of central nervous system invasion by SARS-CoV-2 [3], autoimmunity/dysregulated inflammation [4], or metabolic abnormalities in the pathogenesis of PASC [1, 5]. Additionally and in similitude with other chronic diseases, associated mental health disorders such as depression and anxiety have been described in PASC and may affect its prognosis [6].

In our PASC clinic, we were surprised that the majority of patients reported the date of their initial COVID-19 with a perfect precision, although it happened months to years earlier. Moreover, we were struck by the high proportion of patients reporting an initial COVID-19 infection during the first wave. Should it be substantiated, this observation would inform research into the causes of PASC, orientating toward factors that differentiate the first wave from subsequent waves.

The aim of this study was to evaluate if the incidence PASC was uniformly distributed between the first COVID-19 pandemic wave and the later time period, up to June 2021.

METHODS

Study Population

We evaluated a population of individuals with self-reported PASC included in a study conducted in August 2021 assessing the effect of SARS-CoV-2 vaccination on their symptom [7]. The patients were recruited through social media (Twitter, LinkedIn, Facebook) and with the help of a French association of patients with PASC (#AprèsJ20 Covid Long France). Although the study was conducted before the publication of the clinical definition of the post COVID-19 condition by the World Health Organization (WHO) [8], we used a similar definition. All patients gave informed consent and the study was approved by an independent ethics committee (CE-2021-106).

Incidence of COVID-19 in France

During the first wave, SARS-CoV-2 RT-PCRs were not widely available and cannot be used to evaluate COVID-19 incidence. We therefore used a nationwide model conducted by the Pasteur Institute which took into account the number of hospitalizations and deaths due to COVID-19 to infer the number of cases in France [9]. By May 11, 2020, 5.3% of the French population was estimated to have been infected since the beginning of the pandemic. For the later period (May 12, 2020–June 30, 2021), we used widely available data of positive SARS-CoV-2 RT-PCR tests (Our World in Data [10], Supplementary File 1) as a surrogate for new COVID-19 cases.

Statistical Analysis

Quantitative data are given as median with interquartile range (IQR) and qualitative data as percentages. The odds ratio (OR) for the risk of development of PASC after COVID-19 reported during or after the first period was calculated using the chi-squared test. A *p* value less than 0.05 was considered statistically significant. The analysis was conducted using STATA MP 13.0 (STATA CORP, USA).

RESULTS

The study included 567 French individuals with self-reported PASC. The median age was 44 years (IQR 37–50) and 83.4% were female. Other demographic and clinical characteristics can be found in Table 1. A total of 293 (51.7%) patients reported an initial COVID-19 infection during the January 1–May 11, 2020 period while 272 (48%) reported it during the May 12, 2020–June 30, 2021 period (missing infection date, *n* = 2 [0.3%]). In total 6.6% of patients reported being hospitalized for COVID-19 without difference between the first and second time period (8.1% vs. 5.1%, respectively; *p* = 0.15). In accordance with our hypothesis that SARS-CoV-2 RT-PCR is not a good surrogate for COVID-19 evaluation during the first wave,

Table 1 Characteristics of the analysis population

	PASC population (<i>n</i> = 565)
Female sex, % (<i>n</i>)	83.4% (471)
Age, mean (SD)	43.3 (10.0)
COVID-19 severity, % (<i>n</i>)	
Ambulatory	94.9% (536)
Need for oxygen therapy	4.4% (25)
Intensive care hospitalization	0.7% (4)
Confirmed COVID-19, % (<i>n</i>)	64.4% (364)
Positive RT-PCR	45% (254)
Positive lung CT	22.7% (128)
Positive serology	32.6% (183)
Positive antigen test	8.7% (49)
Number of persisting symptoms, mean (SD)	12.1 (3.9)
Reported symptom, % (<i>n</i>)	
Fatigue	96.5% (445)
Brain fog	87.1% (492)
Headaches	70.8% (400)
Irritability	62.8% (355)
Sleeping issues	70.3% (397)
Thoracic pain/oppression	62.8% (355)
Shortness of breath	81.8% (462)
Cough	32.9% (186)
Palpitations	65.8% (372)
Muscle pain	77% (435)
Arthralgia	67.6% (382)
Paresthesia/tingling	58.6% (331)
Anosmia/ageusia	37.7% (213)
Abdominal pain	54.7% (309)
Diarrhea	42.7% (241)
Spontaneous ecchymosis	27.8% (157)
Pruritus	32% (181)
Fever/shivering	30% (226)

Table 1 continued

	PASC population (<i>n</i> = 565)
Professional activity	
Unchanged	45% (254)
Adapted to PASC	17.9% (101)
Interrupted	37.1% (210)

RT-PCR was performed in 22.2% of patients during the first period (65/293) compared to 85.3% (232/272) during the later period ($p < 0.0001$). Instead, we used a previously published estimation that 5.3% of the French population (67 millions; $N = 3,551,000$ cases) had been infected with SARS-CoV-2 as of May 11, 2020 [9]. Between May 12, 2020 and June 30, 2021, a total of 6,007,213 COVID-19 cases were diagnosed using RT-PCR (Our World in Data; Supplementary File 1).

We plotted the date of initial COVID-19 of our population study (red dots) together with the incident COVID-19 cases in France (blue dots; Fig. 1). The risk to self-report PASC was 82% higher (odds ratio 1.82, 95% CI [1.55–2.15], $p < 0.0001$) if the initial COVID-19 happened during the first wave than afterward. In contrast to the modeling of COVID-19 cases during the first wave, the number of COVID-19 cases diagnosed using PCR (second period) did not include asymptomatic cases, which were reported to account for 20–25% of cases in France during the same period [11]. We therefore conducted a sensitivity analysis taking into account different percentages of asymptomatic COVID-19 (missed by PCR) for the second period and computed the corresponding odds ratio which ranged from 1.91 [1.62–2.26] to 2.28 [1.93–2.69] (Table 2; data in Supplementary File 2). Strikingly, the maximal incidence of initial COVID-19 in individuals with self-reported PASC aggregated around the date of the presidential speech announcing the lockdown in France (March 16, 2020; Supplementary File 2).

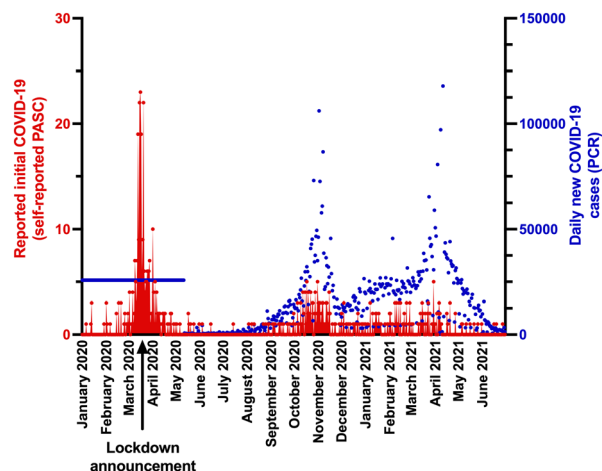


Fig. 1 Distribution of initial COVID-19 in patients with self-reported PASC compared to the incidence of new COVID-19 cases in France. Concerning the incidence of COVID-19 during the first wave, only the mean number of cases is shown since their distribution was not modeled (straight blue line instead of a Gaussian curve). The lockdown was announced by an unprecedented presidential address on March 16, 2020

DISCUSSION

In the present ancillary study, we show that French patients with self-reported PASC were significantly more likely to report an initial COVID-19 infection during the first pandemic wave than afterward.

Several hypotheses may concur to explain time differences in the incidence of PASC. First, it is possible that viral factors (i.e., viral variants) may impact the risk of subsequent PASC. Data from the UK Office of National Statistics (ONS) suggest that the Omicron variant, which appeared after the study period, is linked to a 49.7% lower risk of PASC development [12]. Variant studies conducted in France indicate that the alpha variant became highly prevalent in early 2021 (after the second wave, Fig. 1) [13], suggesting that viral factors cannot fully explain these observed differences. Second, the vaccination against SARS-CoV-2 may decrease the risk of PASC, and observational data from the ONS indicate a 41.1% risk reduction among double vaccinated patients [14]. However, vaccination cannot explain the observed differences in our analysis since none of the included

Table 2 Sensitivity analysis taking into account asymptomatic COVID-19 cases undiagnosed by PCR during the second time period

% of asymptomatic cases	0	5	10	15	20	25
Diagnosed COVID-19 cases during time period 2	6,007,213	6,307,590	6,607,949	6,908,306	7,208,653	7,509,076
Odds ratio to report PASC after COVID-19 during the first wave [95% CI]	1.82 [1.55–2.15]	1.91 [1.62–2.26]	2.00 [1.70–2.36]	2.10 [1.78–2.47]	2.19 [1.85–2.58]	2.28 [1.93–2.69]

individuals had been vaccinated before developing PASC. Finally, the first wave was arguably the most stressful period of the pandemic, considering uncertainties surrounding the emergence of a previously unknown virus, its lethality, and the lack of testing capacities and prevention strategies (i.e., masks). The related anxiety may have catalyzed the onset or persistence of PASC. Supporting this hypothesis, a recent study identified that self-reported previous infection was associated with several PASC symptoms regardless of SARS-CoV-2 serology test results [15]. A recent study conducting multimodal evaluation of self-referred adults with a history of COVID-19 found that anxiety was associated with the reporting of symptoms consistent with PASC while the immunologic, virologic, and cardiopulmonary studies were inconclusive in differentiating individuals with PASC and those without PASC [16]. The underlying mechanisms are likely diverse including a nocebo effect through increased attention toward bodily sensations, incorrect causal attribution of new symptoms to PASC, or chronicization of physical symptoms, either related to SARS-CoV-2 or not, through negative conditioning [17] and avoidant behavior. These mechanisms may result in the persistence of functional somatic disorders after an acute medical episode, such as a viral infection [18, 19]. Furthermore, stress-related disorders are known to be associated with the development of a wide range of conditions including autoimmune [20] and cardiovascular diseases [21]. Finally, anxiety may participate in a “false admittance” of PASC without any previous

SARS-CoV-2 infection. Overall, the links between anxiety and PASC deserve further study.

Our study has some limitations. First, we included patients with self-reported and not medically confirmed PASC, and 35.6% of the patients did not have virological confirmation of the initial COVID-19. However, considering that the clinical definition of PASC is permissive (i.e., no need for virological diagnosis), and that patients reporting an alternative diagnosis were excluded, we believe that the included population satisfies the WHO post-COVID condition definition [8]. Second, the study population was recruited through social media, which may not represent the diversity of patients with PASC. However, PASC is characterized by a structured and supportive patient community, and the recruitment was conducted with the help of one patient association (#AprèsJ20 Covid Long France), promoting a wider recruitment. Therefore, this population is likely to be representative of at least one important subgroup of patients seeking medical advice for PASC. Importantly, 27 patients with PASC (4.8%) reported an initial COVID-19 infection during the January–February 2020 time period, at which point very few cases had been reported in France [22], shedding doubt on the fact that the reported viral infections were COVID-19. Finally, 64 patients (11.3% of the population; 21.8% of those reporting COVID-19 during the first wave) indicated a COVID-19-like illness on the days surrounding the first wave presidential address (March 15–17). This address was unprecedented in the lives of most adults in

France in regards to the uncertainties evoked and the wording used (“We are at war, at war against the virus”). However, while the stress induced by this address may have taken its toll, it may also have induced a recall bias which could explain the aggregations of reported COVID-19 cases around it.

In conclusion, we show that a majority of patients with self-reported PASC report an initial COVID-19 infection during the first wave of the pandemic, supporting the potential role of non-viral factors in the onset of PASC. Further studies in other countries and populations will need to confirm these preliminary findings.

ACKNOWLEDGEMENTS

We thank the association #Après-J20 Covid Long France for advertising the initial study among its members. CL is supported by a grant “AAP Covid long 2022-1” from the Agence nationale de recherches sur le sida et les hépatites virales (ANRS)/Maladies infectieuses émergentes.

Funding. No funding or sponsorship was received for this study or publication of this article. The journal’s Rapid Service Fee was funded by the authors.

Authors Contributions. Marc Scherlinger, Renaud Felten and Jean Sibia conceptualized the study. Marc Scherlinger and Renaud Felten designed the questionnaire. Marc Scherlinger analyzed the data. Marc Scherlinger and Renaud Felten wrote the first draft. Cédric Lemogne and Jean Sibia made significant contributions in the writing and the discussion of the results. All the authors approved the latest version of the manuscript.

Disclosures. Marc Scherlinger received speaker honoraria from Sandoz, Amgen and Nordic Pharma. Cédric Lemogne received consulting and speaking honoraria from Lundbeck and Otsuka pharmaceutical. Renaud Felten received speaking honoraria from Abbvie, BMS, Janssen, Lilly, Nordic Pharma, Novartis, Medac,

MSD, Pfizer, Sanofi, UCB and travel grant from Abbvie, Galapagos, Janssen, Novartis and UCB. Jean Sibia received research grants (unrelated to this work) from Pfizer, BMS, Roche, MSD. JS received speaker honoraria from Roche, Chugai, Bristol-Myers Squibb, UCB, GSK, LFB, Actelion, Pfizer, MSD, Novartis, Amgen, Abbvie, Sandoz, Gilead, Lilly, Sanofi Genzyme, Janssen, Mylan, Galapagos, Sobi.

Compliance with Ethics Guidelines. All patients gave informed consent and the study was approved by an independent ethics committee (CE-2021–106). The study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

Open Access. This article is licensed under a Creative Commons Attribution-Non-Commercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185:881-895.e20.

2. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27:601–15.
3. de Melo GD, Lazarini F, Levallois S, et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. *Sci Transl Med*. 2021;13:eabf8396.
4. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol*. 2022;23:210–6.
5. Montefusco L, Ben Nasr M, D’Addio F, et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat Metab*. 2021;3:774–85.
6. Scherlinger M, Felten R, Gallais F, et al. Refining “long-COVID” by a prospective multimodal evaluation of patients with long-term symptoms attributed to SARS-CoV-2 infection. *Infect Dis Ther*. 2021;10:1747–63.
7. Scherlinger M, Pijnenburg L, Chatelus E, et al. Effect of SARS-CoV-2 vaccination on symptoms from post-acute sequelae of COVID-19: results from the nationwide VAXILONG study. *Vaccines*. 2022;10:46.
8. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1. Accessed 18 May 2022.
9. Salje H, Kiem CT, Lefrancq N, et al. Estimating the burden of SARS-CoV-2 in France. *Science*. 2020;369:208–11.
10. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). *Our World in Data*. 2020. <https://ourworldindata.org/covid-cases>. Accessed 23 Nov 2021.
11. Pullano G, Di Domenico L, Sabbatini CE, et al. Underdetection of cases of COVID-19 in France threatens epidemic control. *Nature*. 2021;590:134–9.
12. Self-reported long COVID after infection with the Omicron variant in the UK - Office for National Statistics. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/selfreportedlongcovidafterinfectionwiththeomicronvariant/6may2022>. Accessed 14 May 2022.
13. Roquebert B, Haim-Boukobza S, Trombert-Paolantoni S, et al. SARS-CoV-2 variants of concern are associated with lower RT-PCR amplification cycles between January and March 2021 in France. *Int J Infect Dis*. 2021;113:12–4.
14. Self-reported long COVID after two doses of a coronavirus (COVID-19) vaccine in the UK - Office for National Statistics. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/selfreportedlongcovidaftertwodosesofacoronaviruscovid19vaccineintheuk/26january2022>. Accessed 14 May 2022.
15. Matta J, Wiernik E, Robineau O, et al. Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic. *JAMA Intern Med*. 2022;182:19–25.
16. Sneller MC, Liang CJ, Marques AR, et al. A longitudinal study of COVID-19 sequelae and immunity: baseline findings. *Ann Intern Med*. 2022;175:969–79.
17. Van den Bergh O, Stegen K, Van de Woestijne KP. Learning to have psychosomatic complaints: conditioning of respiratory behavior and somatic complaints in psychosomatic patients. *Psychosom Med*. 1997;59:13–23.
18. Henningsen P, Gündel H, Kop WJ, et al. Persistent physical symptoms as perceptual dysregulation: a neuropsychobehavioral model and its clinical implications. *Psychosom Med*. 2018;80:422–31.
19. Kachaner A, Lemogne C, Dave J, Ranque B, de Broucker T, Meppiel E. Somatic symptom disorder in patients with post-COVID-19 neurological symptoms: a preliminary report from the somatic study (Somatic Symptom Disorder Triggered by COVID-19). *J Neurol Neurosurg Psychiatry*. 2022. <https://doi.org/10.1136/jnnp-2021-327899>.
20. Song H, Fang F, Tomasson G, et al. Association of stress-related disorders with subsequent autoimmune disease. *JAMA*. 2018;319:2388–400.
21. Song H, Fang F, Arnberg FK, et al. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. *BMJ*. 2019;365:11255.
22. Spiteri G, Fielding J, Diercke M, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. *Euro Surveill*. 2020;25:2000178.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.