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Patients with Long COVID continue to experience significant symptoms at 12 months and factors associated with improvement: A prospective cohort study in France (PERSICOR)

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ABSTRACT

Objectives: This study examines long COVID symptoms course over 12 months, their impact on daily life, and associated factors for symptom relief.
Methods: A prospective cohort study included 231 participants with long COVID at 12-month follow-up. Data on characteristics, symptom course, and remission were collected using a questionnaire and a remission scale. Poisson regression models were used to estimate the prevalence rate ratio (PRR) and 95% confidence intervals (CIs) for factors associated with symptom improvement.
Results: Of the 231 participants, 63.2% developed SARS-CoV-2 antibodies before COVID-19 vaccination. At 12 months, only 8.7% (95% CI: 5.4-13.1%) reported complete remission, while 28.6% noted significant improvement. Most symptoms remained prevalent: asthenia (83.1%), neurocognitive/neurological (93.9%), cardiothoracic (77.9%), Musculoskeletal (78.8%). During long COVID, 62.2% stopped working, and only 32.5% resumed full-time professional activities. Presence of SARS-CoV-2 antibodies before vaccination increased the probability of improvement (aPRR: 1.60, $P = 0.028$), while ageusia at initial long COVID phase decreased the probability (aPRR: 0.38, $P = 0.007$).
Conclusions: Long-COVID symptoms persisted in the majority of participants after 12 months, with significant impacts on daily life and work. SARS-CoV-2 antibodies were associated with better prognosis, while persistent ageusia indicated a lower probability of improvement. These findings highlight the need for ongoing support and care for individuals with long COVID.

Introduction

About 15% to 30% of the patients develop long-term symptoms after an acute symptomatic COVID-19 episode [1–3]. In the World Health Organization (WHO) 2021 definition, post-COVID condition is defined as long-lasting symptoms that may or persist from the initial illness or may be of new onset following initial recovery from an acute COVID-19 episode, [4–6]. The lack of virological documentation of SARS-CoV-2 infection does not exclude this diagnosis [4]. These symptoms evolve in fluctuating waves and often get worse following physical or intellectual effort. This condition has been commonly called PACS or long COVID by the patients themselves.

Several factors associated with the occurrence of long-lasting symptoms have been identified [7–9]. Prolonged symptoms are more common in women [7–9] than in men and relatively young

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subjects around the age of 45 [7]. Presenting a high number of symptoms during acute infection appears to increase the risk of long-term symptoms [7,8]. The impact of SARS-CoV-2 antibody levels is controversial. According to varied studies, a high level of antibodies either appears to be protective [7] or, conversely, to be associated with higher persisting symptoms [7,8].

So far, the underlying mechanisms of these symptoms remain unclear: the persistence of viral RNA and/or proteins in tissue reservoirs has been demonstrated for some patients [10–16]. To date, it is not known whether this genetic or protein material persistence corresponds to a replicating virus or not. Such persistence or other potential mechanisms could lead to prolonged cytokines secretion [16] and to coagulation disorders [17] and tissue damage.

The course of long COVID fluctuates over time and usually lasts for months or years. Symptoms generally impact daily life functioning [18]. In comparison with hospitalized patients for whom follow-up data [19] are available, little is known about the long-term course of ambulatory patients with long COVID, the impact of the persistent symptoms on social, family, and work life. Preliminary results obtained suggest that less than 14% of monitored participants are in complete symptomatic remission after 1 year [20].

Our aim was, thus, to describe the 12-month evolution of patients with long COVID followed in an outpatient clinic in Paris, the impact of the symptoms on patients' work lives, and the factors associated with the relief of symptoms.

Patients and methods

Setting

A dedicated long COVID clinic has been operational since May 2020 at Hotel Dieu in Paris, affiliated with the Greater Paris Public Hospital. A team of physicians provided patient care on a rotating basis. Patients received a comprehensive medical evaluation, including physical and biological examinations. A standardized questionnaire gathered baseline data at the initial acute COVID-19 phase, including age, sex, occupation, medical history, physical measurements, symptoms during the initial acute COVID-19 phase, treatment received, duration of symptoms, progression and course of persistent symptoms, medical care and treatments, return to work, and daily activities. SARS-CoV-2 serology tests were routinely conducted, along with SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assays and other bioassays as needed based on the present symptoms.

Ethics approval and consent to participate

Patients attending this consultation were invited to participate in an observational study called PERSICOR previously described [5] if they had the following inclusion criteria: age >18, documented or probable acute infection as defined by WHO COVID-19 case definition [21]; at least two persistent or recurrent symptoms lasting for more than 2 months and occurring in the 3 months following initial COVID infection and absence of another obvious cause of symptoms, a definition corresponding to the WHO post-COVID-19 condition definition [4]. Patients who agreed to be enrolled were asked to give a non-opposition. Ethics approval for PERSICOR study was granted by the local Institutional Review Board of Henri-Mondor Hospital (Ethics Committee number 00011558, Approval number 2020-088).

Definitions (supplementary materials A)

Onset of long COVID symptoms was defined as the period between the first onset of long COVID symptoms after acute episode and the first consultation at the long COVID clinic [4,21].

Strong evidence in favor of SARS-CoV-2 infection was defined by five possibilities: a positive PCR or antigenemia, anosmia or ageusia, typical COVID-19 lesions on chest computed tomography (CT) scan, or a close contact with a confirmed case at acute infection.

A post infection positive SARS-CoV-2 serology was defined as detection of one or more antibodies against SARS-CoV-2 S and/or N proteins at least once before any vaccination. Antibodies to SARS-CoV-2 were detected by an enzyme-linked immunosorbent assay technique in the great majority of cases. Only antibodies detected prior to vaccination and validated on a laboratory chart were considered. If serology was not available on the day of the first consultation, the test was performed in the clinic.

Reinfection was based on a new positive PCR or antigenemia and symptoms in favor of an acute infection, a time interval of at least 3 months, from the first infection.

Assessment

This sub-study was organized with two visits, and at each visit, a specific standardized questionnaire was completed. The first visit was a presential visit (first consultation), and at this visit, data on acute infection and onset of long COVID period were collected. The second visit was done at 12 months $\pm$ 1 month after the first consultation via a presential or via an online questionnaire for those who would not come to the consultation. The second questionnaire assessed evolution of the symptoms, diagnoses performed, treatments received, and impact of long COVID on social, work, and family life. The patients were asked to rate their overall health on a score from 1 to 10 on a post-COVID-19 condition self-assessment scale that was designed by our team and is described in supplementary materials B.

Information on vaccination was obtained through self-reporting at the 12-month visit from the participants and was checked on the French "AllAnticovid" application where all vaccine doses received were mandatory collected at this time.

Participants

To be included in this sub-analysis, participants were selected from the PERSICOR as ambulatory patients with long COVID-19, having their first COVID-19 episode between January 15, 2020, and October 18, 2021. Participants with only suspected initial COVID-19 infection as defined by the WHO COVID-19 case definition were excluded. [21] Those referred to intensive care unit during the acute COVID-19 infection were also excluded, in order to avoid mixing the sequelae of resuscitation and prolonged symptoms of COVID.

Statistical analyses

Quantitative data were presented using mean, median, and interquartile ranges, while qualitative data was expressed as frequency distribution and relative frequency. Proportions' 95% confidence intervals (CIs) were calculated using the Clopper–Pearson interval. Symptoms were categorized into ten main classes: asthenia, neurocognitive/neurological, cardiothoracic (POTS, hyperventilation…), smell and taste, digestive, other ear-nose-throat (ENT) symptoms, fevers/shivering, musculoskeletal, cutaneous-vascular, and ophthalmic symptoms. Symptom assessment was performed at three time points, the acute COVID-19 infection, the first consultation at long COVID-19 clinic, and the 12-month follow-up.

The cumulative percentage of participants reporting symptom remission was calculated using the reverse Kaplan–Meier method. Complete remission was defined as 10. The outcome of interest was to have "a significant improvement of symptoms or complete remission" defined as giving an overall post-COVID self-assessment

Table 1
Patient characteristics and association with significant improvement or complete remission of symptoms at 1 year.

Background characteristics	Sample size n (%) N=231	Significant improvement or complete remission at 1 year (score=8 to 10 on remission scale) n (%) N=86	PRR of having significant improvement or complete remission
Age at initial COVID-19 infection (%)			p=0.716
under 40	65 (28.1%)	23 (35.4%)	1[a]
40 and older	166 (71.9%)	63 (38.0%)	1.07 (0.73-1.57)
Sex (%)			p=0.836
Female	179 (77.5%)	66 (36.9%)	1[a]
Male	52 (22.5%)	20 (38.5%)	1.04 (0.70-1.55)
BMI (%)			p=0.927
BMI<25	162 (70.1%)	60 (37.0%)	1[a]
BMI>=25	69 (29.9%)	26 (37.7%)	1.02 (0.71-1.47)
Occupation (%)			p=0.838
Health and social workers	60 (26.0%)	23 (38.3%)	1[a]
Others	171 (74.0%)	63 (36.8%)	0.96 (0.66-1.41)
Tobacco consumption (%)			p=0.828
No	211 (91.3%)	79 (37.4%)	1[a]
Yes	20 (8.7%)	7 (35.0%)	0.93 (0.51-1.73)
Period of initial COVID-19 infection (%)			p=0.610
Before June 2020	184 (79.7%)	70 (38.0%)	1[a]
After June 2020	47 (20.3%)	16 (34.0%)	0.89 (0.58-1.38)
Atopy/Allergy/Asthma (%)			p=0.894
No	98 (42.4%)	64 (36.4%)	1[a]
Yes	133 (57.6%)	22 (40.0%)	1.02 (0.73-1.44)
Personal or familial autoimmune disease (%)			p=0.631
No	176 (76.2%)	64 (36.4%)	1[a]
Yes	55 (23.8%)	22 (40.0%)	1.10 (0.75-1.62)
Depression, anxiety history (%)			p=0.312
No	174 (75.3%)	68 (39.1%)	1[a]
Yes	57 (24.7%)	18 (31.6%)	0.81 (0.53-1.22)
Hospitalization at initial COVID-19 infection (%)			p=0.067
No	178 (77.1%)	72 (40.4%)	1[a]
Yes	53 (22.9%)	14 (26.4%)	0.65 (0.41-1.03)
Number of symptoms at initial COVID-19 phase (%)			p=0.289
Under 5	111 (48.1%)	38 (34.2%)	1[a]
5 and over	120 (51.9%)	48 (40.0%)	1.17 (0.83-1.64)
SARS-CoV-2 positive serology at least once before vaccination (%)			p=0.005
No	85 (36.8%)	22 (25.9%)	1[a]
Yes	146 (63.2%)	64 (43.8%)	1.67 (1.15-2.49)

BMI: body mass index; CI: confidence interval; PRR: prevalence rate ratio obtained using Poisson regression.
[a] Reference group.
The comparison groups are “significant improvement or complete remission at 12-month” vs “no significant improvement and no remission at 12-month” for each variable. The result gives the prevalence rate ratio to have a significant improvement or a complete remission at 1 year of a category compared to the reference group.

score at 12 months, between 8 and 1. Factors associated with "significant improvement of symptoms or complete remission" at 1 year were studied. The comparison groups are “significant improvement or complete remission at 12 months” vs “no significant improvement and no remission at 12 months” for each variable.

Selected variables included participants' baseline characteristics, types of symptoms at acute infection, at onset of long COVID symptoms as well as SARS-CoV-2 serological results. Prevalence rate ratios (PRR) were calculated using univariate and adjusted multivariate general linear models (Poisson regression), adjusted for age, sex, and hospitalization at acute COVID-19 infection. Multivariable analysis included all covariates with P <0.05 and was adjusted on age, sex, and hospitalization at initial COVID-19 infection. Two sensitivity analyses were performed: one on participants who were not ambulatory non-hospitalized patients with acute infection, and one on patients who had strong evidence of SARS-CoV-2 infection.

The internal reliability of the scale was evaluated using the Cronbach alpha coefficient, and a validation of the convergent was carried out by examining the association of the elements of the scale with the return to work and the resumption of routine domestic activities. Statistical analyses were conducted using SAS (version 9.4) and R (version 4.2.1) software packages.

Results

Population characteristics (Table 1)

Of 307 patients with long COVID included and who reached the one-year follow-up point, 296 were successfully recontacted. Of those contacted, 65 did not participate in the survey, and 231 (78%) completed a 12-month follow-up questionnaire.

Median age was 45 years (interquartile range [IQR]: 38-53), 77.5% were female, 57.6% had a history of atopy, allergy, or asthma, and 24.7% had a history of depression or anxiety prior to the pandemic. Additionally, 23.8% of participants reported an autoimmune disease (personal 17.3% and/or familial 13.8%). Only 53 participants (22.9%) had been hospitalized during their acute infection, and 8 (3.5%) experienced reinfections following their initial COVID-19 episode.

A free interval between acute infection and onset of long COVID was reported for 46%, and the median delay of this free interval was 1.0 months (IQR: 0-2.0).

The median delay from acute infection to first consultation in long COVID clinic was 4.6 months (IQR: 2.2-8.7), and the median delay between the first consultation in long COVID clinic and the 12-month questionnaire was 12.6 months (IQR: 11-13).

Table 2
Evolution of the prevalence of symptoms at the three phases of the study: acute COVID-19 infection, at the initial consultation for long COVID, and the 12-month follow-up after first long COVID consultation.

Symptoms	Initial COVID-19 episode		At first consultation of long COVID -19 phase		One-year follow-up	
	N	% 95% CI	N	% 95% CI	N	% 95% CI
Smell and taste	144	62.3% (55.7-68.6%)	82	35.5% (29.3-42.0%)	92	39.8% (33.5-46.5%)
Other ear-nose-throat	183	79.2% (73.4-84.3%)	53	22.9% (17.7-28.9%)	146	63.2% (56.6-69.4%)
Asthenia	155	67.1% (60.6-73.1%)	178	77.1% (71.1-82.3%)	192	83.1% (77.7-87.7%)
Fevers or shivering	196	84.8% (79.6-89.2%)	39	16.9% (12.3-22.3%)	75	32.5% (26.5-38.9%)
Cardiothoracic	193	83.5% (78.1-88.1%)	187	81.0% (75.3-85.8%)	180	77.9% (72.0-83.1%)
Neurological and neurocognitive	169	73.2% (67.0-78.8%)	193	83.5% (78.1-88.1%)	212	91.8% (87.5-95.0%)
Digestive	86	37.2% (31.0-43.8%)	93	40.3% (33.9-46.9%)	124	53.7% (47.0-60.2%)
Musculoskeletal	86	37.2% (31.0-43.8%)	93	40.3% (33.9-46.9%)	182	78.8% (72.9-83.9%)
Cutaneous and vascular	29	12.6% (8.6-17.5%)	72	31.2% (25.3-37.6%)	142	61.5% (54.9-67.8%)
Ophthalmic	23	11.3% (7.5-16.1%)	48	20.8% (15.7-26.6%)	103	44.6% (38.1-51.2%)

CI, confidence interval; IQR, interquartile range.
Smell and taste disorders: ageusia, anosmia. **Other ear-nose-throat:** tinnitus, vestibular involvement, odynophagia, rhinorrhea, dysphagia or other otorhinolaryngologic disorders. **Cardiothoracic:** dyspnea, cough, thoracic, tightness, tachycardia, bradycardia, or desaturation. **Neurological and neurocognitive disorders:** neurocognitive, sensory disorders, other neurological. **Neurocognitive disorders:** concentration and attention disorders (bradypsychia), immediate memory disorders. **Sensory disorders:** tingling, burning, neurogenic pain or balance disorders, or paresthesia. **Other neurological disorders:** difficulty swallowing, difficulty articulating, urinary retention, thermoregulation disorders, deafness, dysphonia, thermoregulation, insomnia/hypersomnia. **Psychological disorders:** anxiety, emotionality, thymic disorders, mood disorders. **Digestive disorders:** diarrhea, abdominal pains, constipation, gastroparesis, or vomiting/nausea**, Musculoskeletal disorders:** myalgia, muscle weakness, arthralgia, or tenosynovitis. **Cutaneous and vascular disorders:** urticaria, eczema, subcutaneous hematoma, or vascular inflammation. **Ophthalmic disorders:** dry eyes, cloudy vision, conjunctivitis, orbit pain or blurred vision
The symptoms were assessed at trois times points: a free interval between acute infection and onset of long COVID was reported for 46%, and the median delay of this free interval was 1.0 months (IQR: 0-2.0). The median delay from acute infection to first consultation in long COVID clinic was 4.6 months (IQR: 2.2-8.7), and the median delay between the first consultation in long COVID clinic and the 12-month questionnaire was 12.6 months (IQR: 11-13).

SARS-CoV-2 antibodies and vaccination

Overall, 146 (63.2%) tested positive for SARS-CoV-2 antibodies, 83 (35.9%) tested negative, 2 (0.9%) had not taken a test. The median time between acute infection and the serological test was 2.5 months (IQR: 1.9-3.3). It was 2.3 months (IQR: 1.7-3.1) for those with antibodies and 2.7 months (IQR: 2.1-4.1) for those without antibodies. The 1st test was performed for 68.0% of the patients between 0 and <3 months, for 21.2% between 3 and <6 months, for 6.0% between 6 and <9 months, and for 4.8% between 9 and <12 months.

Within the subgroup of 85 participants lacking SARS-CoV-2 antibodies (n = 83) or who had not undergone SARS-CoV-2 serology (n = 2), (71.8%:61/85) presented compelling evidence in favor of an initial SARS infection: 19 had a positive PCR, 48 reported anosmia or ageusia, 13 displayed typical COVID-19 lesions on chest CT scans, and 19 had been in close contact with confirmed cases.

All participants were unvaccinated before acute infection and at enrolment. During the follow-up, 152 (65.8%) received at least one dose of an anti-COVID vaccine among which five participants (3.3%) before their first serology date.

Course of symptoms over time

Table 2 and Figure 1a display the prevalence of various symptoms at the three stages of follow-up: acute infection, onset of long COVID (first consultation in long COVID clinic), and the 1-year follow-up.

During acute infection, 62.3% experienced smell and taste disorders, 79.2% had other ENT disorders 67.1% had fatigue, 84.8% experienced fever or shivering, 83.5% reported cardiothoracic problems, and 73.2% neurological and neurocognitive disorders.

At the first long COVID consultation, fever or shivering decreased to 16.9%, smell and taste disorders decreased to 35.5%, while other ENT disorders affected 58%. Asthenia remained high at 77.1%, and cardiothoracic disorders persisted in 81%, and neurological and neurocognitive issues in 83.5% of cases.

At 12-month follow-up, most symptoms persisted: 32.5% reported occasional fever or shivering, 39.8% reported smell and taste disorders, 63.2% had other ENT disorders, 83.1% experienced asthenia, 77.9% cardiothoracic disorders, and 93.9% neurological and neurocognitive issues.

Figure 1b and supplementary materials D present the prevalence of the symptoms, including sensory impairments, neurological and neurocognitive symptoms, cutaneous-vascular symptoms, and ophthalmic symptoms.

Remission rate and daily life

At the 12-month follow-up, the median of post-COVID-19 condition self-assessment score was 7 (IQR: 6-8). Supplementary materials F provides cumulative percentages of participants reporting complete symptom remission (score at 10). The cumulative percentages of complete remission at 12 months were 8.7% (95% CI: 5.4-13.1%). A significant improvement (score at 8-9) was reported by 28.6% while 62.7% reported minor or no significant improvement in symptoms (score <8). No significant difference in significant improvement was observed when comparing individuals who received or did not receive the vaccine.

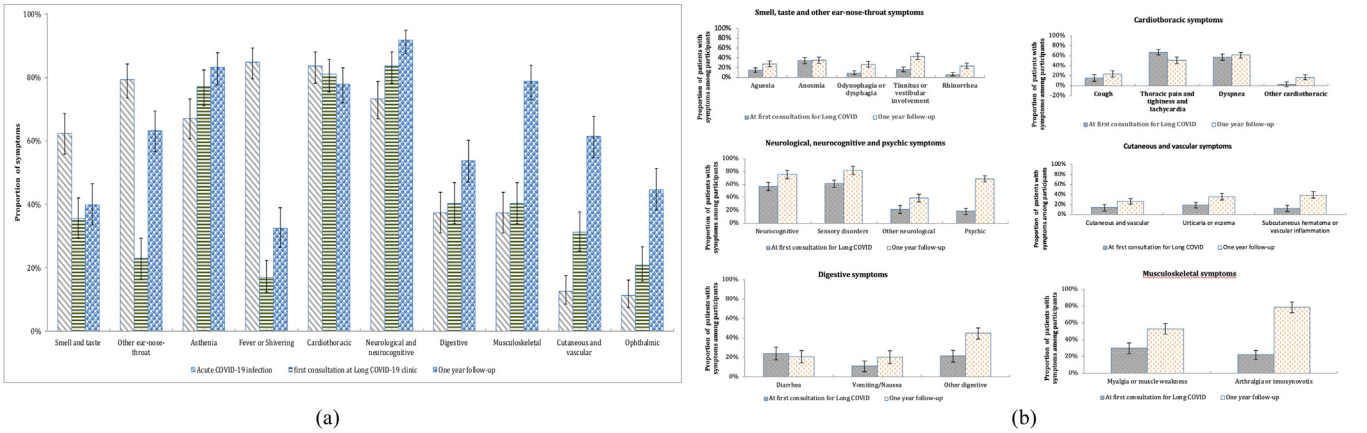
Regarding the impact on daily life (Table 3), 62.2% of participants (120/193) who had been employed before their acute infection had to discontinue their work during long COVID phase. Among those who stopped working, only 66.7% (80/120) resumed their professional activities. Only 58% (47/80) of those who had ceased working were back to full-time employment at 1 year.

Regarding routine domestic activities, 24.7% of participants were able to resume them after 12 months. For sports activities, 29% could engage them without any difficulty. A worrying picture also emerged regarding driving without difficulties (64.5%), reading without difficulties (59.7%).

High internal consistency of the items scale was observed with a Cronbach's alpha coefficient of 0.9594 (P <0.0001), and improvement or complete remission defined by the scale was associated with return to work (relative risk [RR]: 4.02; p<0.0001) or able to resume routine domestic activities scale (RR: 5.67; P <0.0001).

Factors associated with "remission or significant improvement of symptoms"

At the 12-month assessment, 37.2% (95% CI: 31.0-43.8%) of the participants overall noted a remission (8.7%) or a significant



(a) (b)

Figure 1. Evolution of long COVID symptom. (a) Course dynamics of the three phases of the study: initial COVID-19 infection, initial long COVID phase and 1 year follow-up (proportion and 95% confidence interval). (b) Evolution by symptom class: initial long COVID phase and 1 year follow-up (proportion and 95% confidence interval)
Smell and taste disorders: *ageusia, anosmia.* **Other ear-nose-throat:** *tinnitus, vestibular involvement, odynophagia, rhinorrhea, dysphagia or other otorhinolaryngologic disorders.* **Cardiothoracic:** *dyspnea, cough, thoracic pain, tightness, tachycardia, bradycardia, or desaturation.* **Neurological and neurocognitive:** *neurocognitive, sensory disorders, other neurological.* **Neurocognitive:** *concentration and attention disorders (bradypsychia), immediate memory disorders, mood disorders, insomnia/hypersomnia.* **Sensory disorders:** *tingling, burning, neurogenic pain or balance disorders, or paresthesia.* **Other neurological:** *difficulty swallowing, difficulty articulating, urinary retention, thermoregulation disorders, deafness, dysphonia, or thymic disorders.* **Musculoskeletal:** *myalgias, muscle weakness, arthralgias, or tenosynovitis.* **Cutaneous and vascular:** *urticaria, eczema, subcutaneous hematoma, or vascular inflammation.* **Ophthalmic:** *dry eyes, cloudy vision, conjunctivitis, orbital pain, or visual blurring.* **Other cardiothoracic**: *hypertension, orthostatic hypotension, asthma*. **Other digestives**: *constipation, bloating, gastroesophageal reflux.* **Other cutaneous:** *peeling skin, skin rash, hair loss, skin dryness.* **Other neurological:** *difficulty swallowing, difficulty articulating, bladder retention thermoregulation disorders, deafness, dysphonia, thermoregulation.*
The symptoms were assessed at trois times points. A free interval between acute infection and onset of long COVID was reported for 46%, and the median delay of this free interval was 1.0 months (IQR:0-2.0). The median delay from acute infection to first consultation in long COVID clinic was 4.6 months (IQR:2.2-8.7), and the median delay between the first consultation in long COVID clinic and the 12-month questionnaire was 12.6 months (IQR: 11-13).
IQR, interquartile range.

improvement in their general health condition (28.6%) on the remission scale. Table 1 and Figure 2 present the factors associated with such significant improvement of symptoms (scores 8 to 10) in univariate and multivariate analysis.

Univariate analysis (Figure 2a) revealed some symptoms at acute infection such as ageusia, neurocognitive, musculoskeletal, and cutaneous-vascular disorders were linked to reduced improvement (PRRs: 0.45, 0.54, 0.61, 0.48, $P = 0.008$, $P = 0.003$, $P = 0.007$, $P = 0.003$). Conversely, participants who developed SARS-CoV-2 antibodies at least once were more likely to improve (PRR: 1.67, $P = 0.005$).

A sensitivity analysis, limited to participants with strong evidence of initial infection, confirmed that ageusia, neurocognitive, and musculoskeletal symptoms during the onset of long COVID phase were linked to reduced improvement at 12 months (PRRs: 0.41, 0.55, 0.60, $P = 0.007$, $P = 0.002$, $P = 0.006$). In non-hospitalized patients with long COVID, the presence of SARS-CoV-2 antibodies was highly linked to significant improvement at 12 months (PRR 2.25, $P = 0.002$).

In multivariate analysis (Figure 2b), adjusted on age, sex, and hospitalization status at acute infection, participants who had SARS-CoV-2 antibodies at least once before COVID vaccination had a higher probability of significant improvement at 1 year than those who had no SARS-CoV-2 antibodies at any consultation (aPRR: 1.60; 95% CI: 1.05-2.44, $P = 0.028$). Participants who had ageusia at onset of long COVID (aPRR: 0.38; 95% CI: 0.19-0.77, $P = 0.007$) had a lower probability of significant improvement at 1 year than those who did not develop ageusia.

Discussion

Among patients with long COVID, who followed an outpatient clinic for their persistent symptoms, we showed that less than 10% feel in complete remission at 1 year, while about a third have, however, a significant relief of their symptoms. Fatigue and neurocognitive symptoms are the symptoms remaining the most prevalent at 1 year. These persistent symptoms had a severe negative impact on resuming work and everyday activities. Our data also show that having developed SARS-CoV-2 antibodies after infection and prior any vaccination seems to increase the probability of improvement at 12 months follow-up. Persistent ageusia might be on the contrary associated with a less favorable outcome.

Our results are concordant with the Compare e-cohort study showing that at 1 year, 89% of the patients with long COVID still complained of persisting symptoms [20]. The same team has shown that 2 years after symptom onset, most patients continue to improve slowly over time, while 5% have rapid improvement and 4% have a persistent condition [22].

However, no study has yet described in detail the clinical and biological factors linked to symptom remission in patients with long COVID.

In our study, 37% never had detectable antibodies. Several studies have shown that following a minor infection, mostly in children, and despite positive SARS-CoV-2 PCR, a certain percentage of subjects do not develop antibodies or have a rapid decay of SARS-CoV-2 antibodies especially in patients with mild infection [23].

This suggests that one of the mechanisms that could contribute long COVID might be the low capacity to mount an efficacious adaptive immune response. Sensitive humoral and cellular tests would be useful to explore this question, as they could perhaps detect low level responses, however, detectable in these patients. A previous study showed that a low SARS-CoV-2 antibodies level after acute initial COVID infection was a risk factor for the persistence of symptoms [7]. Another study has identified that in patients with long COVID as compared to patients with COVID resolved without sequelae, N-specific CD8+ T cell responses were lower and waning more rapidly at month 4 [23].

Naturally, we may suppose that patients without SARS-CoV-2 antibodies suffered from another disease than COVID-19 [24]. To prevent such possibility, only patients with a documented or probable COVID diagnosis as defined by WHO were included, while those with only had a suspected diagnosis of COVID were excluded.

Moreover, the sensitivity analysis performed in the subgroup of patients with strong arguments for a SARS-CoV-2 infection showed

Table 3
Impact of long-term persistent symptoms on professional and social life, and on daily activities at 1 year.

Activities	Sample size	Percentage (IC 95%)
Professional activities		
Professional activities before acute Covid-19 (n = 231)		
No	38	16.5% (11.9-21.9%)
Yes	193	83.5% (78.1-88.1%)
Work interruption during persistent Covid-19 symptoms (n = 193)[a]		
No	73	37.8% (31.0-45.1%)
Yes	120	62.2% (54.9-69.0%)
Returning to work after stopping (n = 120)[b]		
No	40	33.3% (25.0-42.5%)
Yes	80	66.7% (57.5-75.0%)
Professional activities at one-year follow-up (n = 231)		
No	77	33.3% (27.3-39.8%)
Yes	154	66.7% (60.2-72.7%)
Working part-time at 1 year (n = 154[c])		
Part-time	104	67.5% (59.5-74.8%)
Full-time	50	32.5% (25.2-40.5%)
Domestic and social activities		
Resumption of domestic activities at 1 year (n = 231)		
No	58	25.1% (19.7-31.2%)
Part-time Full-time	116	50.2% (43.6-56.8%)
	57	24.7% (19.3-30.8%)
Sports activities at 1 year (n = 231)		
Unable to exercise	57	24.7% (19.3-30.8%)
Difficult to exercise	98	42.4% (36.0-49.1%)
Possible to do sports	67	29.0% (23.2-35.3%)
Did not try to exercise	9	3.9% (1.8-7.3%)
Ability to drive a car at 1 year (n = 231)		
Unable to do it	57	24.7% (19.3-30.8%)
Difficult to do it	98	42.4% (36.0-49.1%)
Possible to do it	67	29.0% (23.2-35.3%)
Did not try to do it	9	3.9% (1.8-7.3%)
Ability to read at 1 year (n = 231)		
Unable to do it	8	3.5% (1.5-6.7%)
Difficult to do it	74	32.0% (26.1-38.5%)
Possible to do it	138	59.7% (53.1-66.1%)
Did not try to do it	11	4.8% (2.4-8.4%)

[a] Ceasing work among participants engaged in activities before Covid-19
[b] Returning to work among participants who stopped working during the long COVID phase
[c] Rate of return to work among participants employed before Covid-19

similar factors associated with significant improvement or complete symptom remission at 1 year.

This finding reinforces the hypothesis that one of the mechanisms of long COVID could be a reduced capacity of the host to clear the virus leading to viral persistence in reservoirs.

Additionally, we found that persistent ageusia at the onset of long COVID was associated with a poorer prognosis. This finding is not easily explained and requires looking into the pathophysiology of ageusia in COVID-19. We analyzed review articles discussing the hypothetical mechanisms of action of ageusia in patients with COVID-19 [25,26]. Regarding transient ageusia occurring during acute infection, several hypotheses have been made: direct viral neural invasion of olfactory and gustatory nerves, viral cytotoxicity to taste buds, angiotensin II imbalance, pro-inflammatory cytokines, and disturbances in salivary glands and sialic acid [25]. Chronic ageusia, especially when combined with other neurological symptoms, seems to be caused by damage to one or more cranial nerves, to the brainstem, or to the cerebral cortex. The taste nervous system is based on three pairs of cranial nerves: the facial, the glosso-pharyngeal, and the vague nerves. The nerve fibers carried by these nerves all end in the nucleus of the solitary tract, where projections are made towards the thalamus and the insula [27].

We know from studies performed in humans and in SARS-CoV-2-infected hamsters that the areas of the brain the most affected by neuroinflammation during long COVID are the brain stem and adjacent structures (rectal/orbital gyrus, temporal lobes, including amygdala and hippocampus, thalamus, pons/medulla brainstem, insula, and cerebellum) [26–28]. PET-CT scan (18F-fluorodeoxyglucose (FDG)-positron emission tomography) studies have reported hypometabolisms in these regions in patients reporting neurocognitive impairment [26,27]. One of these studies has shown that a significant hypometabolism in the para hippocampal gyri and orbitofrontal cortex in patients with persistent ageusia and anosmia [27–29]. Hence, ageusia might be a proxy for brainstem lesions. We did not find any direct correlation between ageusia and neurocognitive disorders, which may be explained by the very high prevalence of neurocognitive disorders within our population.

The prevalence of depression in our study seems higher than in the general population in France [30]. However, in our study, a previous history of depression or anxiety was not associated with a less favorable outcome ($P = 0.3$).

Our study has some limitations. First, all study participants were all recruited from one long COVID clinic, where they sought ongoing medical care and support for their post-acute COVID-19 symptoms.

This may potentially introduce bias toward people who have more severe, persistent symptoms. On the other hand, recruiting participants from long COVID clinics allowed for comprehensive longitudinal assessment of patients with significant symptom burden over time.

Second, the study faced constraints related to logistics and budget, which restricted the ability to include a larger number of participants. This limitation can impact the statistical power of the study, potentially making it more challenging to detect smaller

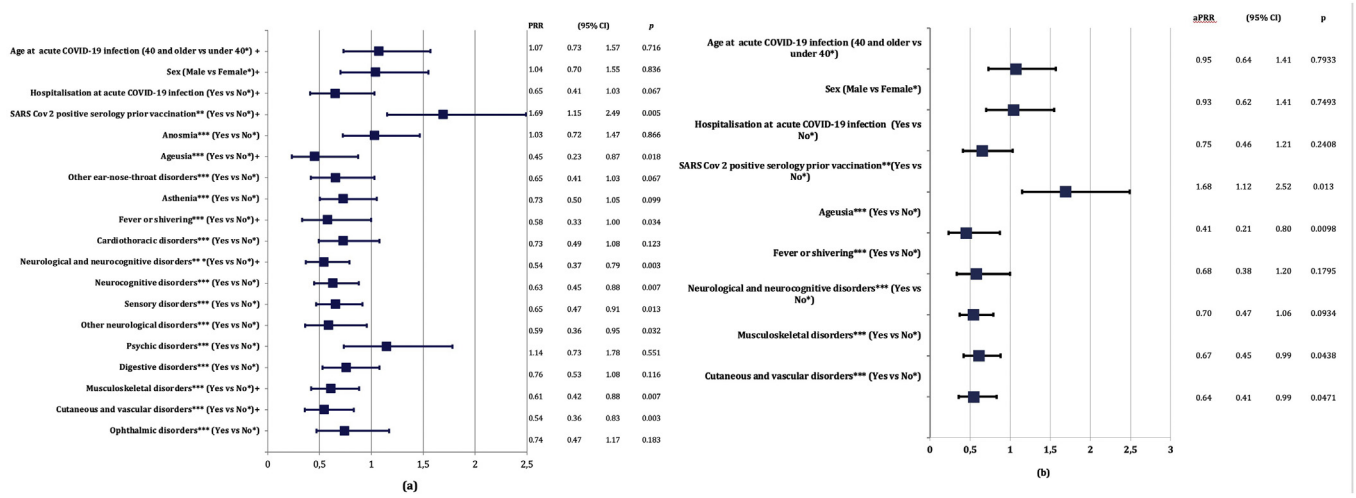


Figure 2. Factors associated with significant improvement of symptoms or complete remission
PRR = prevalence rate ratio obtained using Poisson regression, aPRR = adjusted prevalence rate ratio (adjusted on age, sex, and hospitalization at initial COVID-19 infection and all covariates with P<0.05 included on model), CI =confidence interval
A "significant improvement of symptoms or complete remission" was defined as giving an overall post-COVID self-assessment score between 8 and 10, at 12 months, +: variables included in multivariable analysis
The comparison groups are "significant improvement or complete remission at 12-month" vs "no significant improvement and no remission at 12-month" for each variable. The result gives the prevalence rate ratio to have a significant improvement or a complete remission at 1 year of a category compared to the reference group.
*Reference group
**SARS-CoV 2 positive serology at least once before vaccination
***__Disorders at first consultation of long covid clinic__ (results are based on self-report)
Other ear-nose-throat disorders: *tinnitus, vestibular involvement, odynophagia, rhinorrhea, dysphagia or other otorhinolaryngologic symptoms.* **Cardiothoracic disorders:** *dyspnea, cough, thoracic pain, tightness, tachycardia, bradycardia, or desaturation.* **Neurological and neurocognitive disorders**: *neurocognitive, sensory symptoms, other neurological.* **Neurocognitive disorders**: *concentration and attention disorders (bradypsychia), immediate memory disorders.* **Sensory disorders**: *tingling, burning, neurogenic pain or balance disorders or paresthesia.* ***Other neurological disorders***: *difficulty swallowing, difficulty articulating, bladder retention thermoregulation disorders, deafness, dysphonia, insomnia/hypersomnia.* **Psychic disorders**: *anxiety, emotionality, thymic disorders, mood disorders.* **Digestive disorders**: *diarrhea, abdominal pains, constipation, gastroparesis, or vomiting/nausea.* **Musculoskeletal disorders**: *myalgias, muscle weakness, arthralgias, or tenosynovitis.* **Cutaneous and vascular disorders:** *urticaria, eczema, subcutaneous hematoma or vascular inflammation.* **Ophthalmic disorders**: *dry eyes, cloudy vision conjunctivitis, orbital pain, or visual blurring.*

or less pronounced effects. Third, we do not have controls who did not have long COVID for comparison. It was not possible to do so as we only receive patients with long COVID in our clinic. The response rate was correct, and comparatively with responders, non-responders showed no significant differences in demographics or clinical characteristics at acute infection and at onset of long COVID.

One strength of this paper is that it was a longitudinal study in which the symptoms were collected over time. Additionally, the study's focus is on assessing the return to work and daily activities at the one-year mark. This information sheds light on the long-term impact of these aspects, which are still relatively underexplored in the literature. A second strength was the high response rate from patients to the one-year questionnaire. This provides a robust sample size for studying factors associated with prognosis and adds credibility to the findings. And finally, we developed a scale for assessing the patient report of improvement and remission at 12 months that will have to be replicated in other cohorts.

In conclusion, while the study has limitations, it offers important insights into the one-year prognosis of patients with long COVID, emphasizing the challenges they face in returning to their daily activities. The observation that SARS-CoV-2 antibody development prior any vaccination may have a positive influence on the course of the disease opens the door to potential immunotherapeutic interventions for those without such antibodies. Further research and larger-scale studies are needed to validate and expand upon these findings.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Author contributions

Dominique Salmon: Study Design, Patient follow-up, Data Collection, Article Writing, Result Validation. **Dorsaf Slama:** Patient follow-up, Data Collection, Critical Review. **Françoise Linard:** Patiente follow-up Critical Review. **Nicolas Dumesges:** Critical Review. **Valérie Lebaut:** Data Collection. **Florence Hakim:** Data Collection. **Pauline Oustric:** Critical Review. **Emilie Seyrat:** Critical Review. **Patricia Thoreux:** Article Writing, Critical Review. **Esaie Marshall:** Study Design, Statistical Analysis, Article Writing, Result Validation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.11.038.

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