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Trajectories of the evolution of post-COVID-19 condition, up to two years after symptoms onset

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ABSTRACT

Objectives: We aimed to identify trajectories of the evolution of post-COVID-19 condition, up to 2 years after symptom onset.

Methods: The ComPaRe long COVID e-cohort is a prospective cohort of patients with symptoms lasting at least 2 months after SARS-CoV2 infection. We used trajectory modeling to identify different trajectories in the evolution of post-COVID-19 condition, based on symptoms collected every 60 days using the long COVID Symptom Tool.

Results: A total of 2197 patients were enrolled in the cohort between December 2020 and July 2022 when the Omicron variant was not dominant. Three trajectories of the evolution of post-COVID-19 condition were identified: “high persistent symptoms” (4%), “rapidly decreasing symptoms” (5%), and “slowly decreasing symptoms” (91%). Participants with highly persistent symptoms were older and more likely to report a history of systemic diseases. They often reported tachycardia, bradycardia, palpitations, and arrhythmia. Participants with rapidly decreasing symptoms were younger and more likely to report a confirmed infection. They often reported diarrhea and back pain. Participants with slowly decreasing symptoms were more likely to have a history of functional diseases.

Conclusion: Most patients with post-COVID-19 condition improve slowly over time, while 5% have rapid improvement in the 2 years after symptom onset and 4% have a persistent condition.

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Introduction

As of April 2023, 760 million people worldwide were infected with SARS-CoV-2 [1]. Most patients fully recover from the infection, but according to studies 6–30% experience relapsing and re-mitting symptoms beyond 4 to 12 weeks after infection [2–5]. The presence of persistent symptoms is referred to as post-COVID-19 condition, “long COVID,” or “postacute sequelae of SARS-CoV-2” (PASC). Post-COVID-19 condition is defined, according to the World Health Organization (WHO), as an illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within 3 months from the onset of COVID-19, with symptoms and effects that last for at least 2 months and cannot be explained by an alternative diagnosis [6]. Over 100 symptoms

of post-COVID-19 condition have been reported, with the most frequent being fatigue, dyspnea, chest pain, altered smell and taste, and cognitive disturbances [7–10].

According to the US Department of Health and Human Services, understanding the clinical spectrum and the natural history of the post-COVID-19 condition is a public health priority [11]. Despite the general consensus that post-COVID-19 is a complex syndrome resulting from different intertwined clinical entities (e.g., organ injury from the acute disease or its treatment [12–14]; post-viral fatigue syndrome [15]; prolonged viral shedding or presence of a viral reservoir [16,17]; autoimmune mechanisms [18,19], or mental factors [20]) most longitudinal studies have focused on describing the prevalence of patients with one or more symptoms at specific time points after acute infection, without investigating the existence of a distinct subgroup of patients [7,8,21]. Studies assessing the heterogeneity of post-COVID-19 condition are scarce and most have looked for the existence of symptom clusters at specific time points after acute infection (e.g., 6 months or 1 year) [21–24]. In

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these studies, clustering therefore related to the similarities in the clinical presentation and symptoms of patients rather than their evolution over time. We found no study investigating whether the careful study of the evolution of patients with post-COVID-19 condition over time could lead to the identification of distinct phenotypes of the disease and whether the evolution of a given patient could be predicted in the early stage of post-COVID-19 condition.

We conducted a study to identify whether distinct trajectories of the evolution of post-COVID-19 condition, up to 2 years after symptom onset, could be identified. We then determined how patients' clinical characteristics and symptom presentation differed between these trajectories. To accomplish our objectives, we used data from a large nationwide prospective longitudinal cohort of patients with post-COVID-19 condition, in France.

Methods

Design

We used trajectory modeling to identify distinct trajectories of the evolution of post-COVID-19 condition. This method allowed us to simultaneously estimate the probabilities for multiple trajectories rather than single population means, as is the case for traditional regression models. The reporting of this study followed the Guidelines for reporting on latent trajectory studies (GROLTS-Checklist) [25].

Data sources

Data were obtained from ComPaRe (Communauté de Patients pour la Recherche, www.compare.aphp.fr), an e-cohort of more than 50,000 patients with chronic conditions in France, who are regularly followed up using patient-reported outcome measurements (PROMs) and patient-reported experience measurements (PREMs) [26]. Within the ComPaRe platform, a cohort specific to post-COVID-19 condition, the ComPaRe long COVID cohort, was launched in December 2020, and recruitment is ongoing. Participants were recruited through a social media and media campaign, by partner patient associations, and by a specific call for participation on the "TousAntiCOVID" app, the official French contact tracing app used by 12 million people.

The Institutional Review Board of Hôtel-Dieu Hospital, Paris (IRB 0008367) approved the ComPaRe cohort. All patients provided informed consent electronically before participating in the e-cohort, which was considered equivalent to the written informed consent by the ethics and regulatory bodies which authorized the study in France.

Study population

In our analyses, we included all adult participants (≥ 18 years old) with post-COVID-19 condition who reported either a suspected or laboratory-confirmed SARS-CoV-2 infection (confirmed by polymerase chain reaction (PCR) swab or serological assay and self-reported by participants); and at least one symptom among a list of 53, within 3 months from the onset of COVID-19 and persisting for at least 2 months. We included participants with a suspected COVID-19 disease according to the definition of post-COVID-19 condition by the WHO, because a high number of patients infected with the SARS-CoV2 virus were not tested during the first wave in France, and because retrospective laboratory confirmation of SARS-CoV-2 infection by reverse transcription-quantitative PCR or serological assays may be unreliable [6,27,28]. We excluded participants for whom no date of symptom onset was entered, or who reported a date of symptom onset before January 24, 2020.

Follow-up

In the ComPaRe long COVID cohort, participants received self-reported questionnaires every 60 days, on a computer or smartphone. The questionnaires asked about their symptoms and the impact of the disease on them. The participants received automatic email reminders every 20 days. Participants who had not completed their questionnaires at least 45 days after receipt received a telephone reminder from an investigator (CS). However, no questionnaire was administered by telephone.

Symptoms onset

The date of symptom onset (i.e., the beginning of acute COVID-19) was retrospectively self-reported by all participants. Participants who reported reinfection with SARS-CoV2 (confirmed or not) were censored on the date of their reinfection. In the ComPaRe long COVID cohort, participants who repeatedly reported that they no longer had symptoms in three consecutive questionnaires were considered in remission (i.e., remission was confirmed after 180 days without any symptom), and their follow-up was censored on this date.

Outcomes

Our main outcome was the long COVID Symptom Tool (ST) score [29]. The long COVID ST is a validated patient-reported instrument assessing 53 symptoms of post-COVID-19 condition classified as general (n = 11 symptoms), thoracic (n = 6), digestive (n = 3), ear/nose/throat (n = 5), eyes (n = 3), genitourinary (n = 2), hair and skin (n = 4), musculoskeletal (n = 4), neurological (n = 11), and blood and lymph circulation (n = 4) symptoms. The ST score is the total number of symptoms reported within 30 days of the completion date. It ranges from zero (no symptoms) to 53 (all symptoms were identified). The long COVID ST score showed excellent reliability (intraclass correlation coefficient of 0.83, 95% CI: 0.80–0.86) [29].

Covariates

We used the following covariates, collected at baseline, in the models: age (as a continuous variable), sex, smoking status (current smokers vs others), educational level (≥ 2 years post-secondary education vs others), confirmed SARS-CoV2 infection, hospitalization during the acute infection, hospitalization in an intensive care unit during the acute infection, body mass index (as continuous variable), history of diabetes, cardiovascular diseases (i.e., history of hypertension, congestive cardiac failure, valvular heart disease, and atrial fibrillation, myocardial infarction, stroke, angina, transient ischemic attack, or peripheral vascular disease), cancers (solid and blood cancers), chronic respiratory diseases (asthma, chronic obstructive pulmonary disease or interstitial lung disease), chronic kidney diseases, systemic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis or other inflammatory arthropathy, scleroderma, myositis or vasculitis), psychiatric diseases (anxiety, depression, chronic psychosis), and functional diseases (fibromyalgia, chronic fatigue syndrome, tension headache, and irritable bowel disease) [9,20,30].

Statistical analysis

Identification of post-COVID-19 condition trajectories

We used latent class mixed modeling (LCMM) to identify distinct trajectories in the evolution of the long COVID ST score over

time. This approach characterizes trajectories in repeated measurements, with the assumption that several underlying subpopulations (i.e., latent trajectories) exist. The LCMM does not require the same number of measurements per participant or measurement time points. In our models, the time metric was the time in days from symptom onset. Model building involved five steps. First, we normalized the outcome variables using the method described by Proust Lima et al [31]. Second, we tested different link functions (splines and beta cumulative distribution functions) to identify the best-fitting model. Third, we assessed the associations between covariates and the growth component of the model using the Wald test in a model with a single latent trajectory. We retained significant associations at $P < 0.05$ level in the final model. Fourth, we determined the optimal number of latent trajectories in the model by adding trajectories one at a time, appraising the Bayesian information criterion, Akaike information criterion, and entropy of the model. Finally, we tested whether class-specific fixed effects improved the fit of the final model. We chose not to include covariates that predicted latent class membership. The LCMM assumes the situation of missingness at random, and we considered that this assumption was plausible because (i) our study exhibited few missing data, and (ii) we had several measurements for all participants included in the study, and missingness was assumed to be random given an individual's score on these observed measurements. The output of the final model provided the posterior likelihood of belonging to each latent trajectory for each participant. More details on the development of the model are provided in the Supplementary Methods, Table S1, and Figure S1.

To describe the symptoms experienced by patients belonging to each trajectory, we calculated the proportion of patients reporting each symptom, in the subgroup of participants who had at least one measurement in the first year of their disease. We used a similar approach to describe the frequency of disease relapse and calculated the proportion of patients reporting less than weekly, weekly, and more frequent relapses in the subgroups of participants who had at least one measurement in the 6, 12, 18, and >18 months of their disease, in each of these time windows.

We performed a sensitivity analysis restricted to participants with a confirmed SARS-CoV2 infection (by PCR swab or serological assay).

A numerical resampling method (bootstrap) with 100 replications was used to evaluate model robustness. In each bootstrap sample, we assigned each participant the latent trajectory to which they had the highest likelihood of belonging. We compared the discordances in the assigned trajectories with those assigned by the original model using Cohen's kappa.

Estimation of the number of patients belonging to each post-COVID-19 condition trajectory

To correct for the selection bias in our cohort, we estimated the proportion of participants following each trajectory using a weighted dataset obtained by calibration on margins with weights for age (<24, 25–34, 35–49, 50–69, and ≥ 70 years), sex, and hospitalization during the acute phase of the disease derived from the data from the Office of National Statistics in the United Kingdom [3,32].

Determinants of each of the post-COVID-19 condition trajectories

We assessed the association between the probability of belonging to each latent trajectory as a function of participants' clinical and demographic characteristics at baseline using linear regressions. Associations were considered statistically significant if the P -value was 0.05.

Analyses were performed using R version 4.05 (<http://www.R-project.org>), the R Foundation for Statistical Computing, Vienna, Austria), version 4.0.5 and the *lcmm* package [33].

Results

Population

A total of 2197 participants were included in the study (among the 2236 participants included in the ComPaRe long COVID cohort between December 2020 and July 2022, 39 were excluded from the analyses because they had no date of symptom onset [$n = 15$] or a date of symptom onset before January 24, 2020 [$n = 24$]). The median age was 46 years (interquartile range [IQR], 38–54 years), and 1738 (79%) were women. A total of 1526 participants (69%) were confirmed to have SARS-CoV-2 infection by PCR swabs and/or serological assays. The majority of participants (90%) were included in the cohort before June 07, 2021, when the Alpha variant was predominant in France [34]. Demographic and clinical characteristics of the participants are presented in Table 1.

Follow-up

Overall, our data covered 19,729 person-months, with a median follow-up period of 291 days (IQR, 60–469 days) and 10,799 long COVID ST score measurements were collected, with a median of 4 and IQR of 2 to 8 measurements per participant. In total, 77 participants reported reinfection with COVID-19, and 141 participants repeatedly reported no symptoms in three consecutive questionnaires and were considered in remission at this time. The follow-ups were censored at the date of reinfection or remission. In total, 13% of participants had missing data 18 months after enrollment in the cohort (Table S2).

Trajectories of post-COVID-19 condition symptoms

We identified three trajectories of the evolution of post-COVID-19 condition (Figure 1). The first trajectory “high persistent symptoms” referred to participants with a high COVID ST score (i.e., they reported multiple symptoms) at symptom onset with little or no variation over time ($n = 94$, 4.3%). Compared to participants with different trajectories, these participants often reported tachycardia, bradycardia, palpitations, arrhythmia (93%), paresthesia (78%), hot flushes (76%), sweats (69%), heat/cold intolerance (65%) and photophobia and/or phonophobia (59%) in the first year after symptom onset (Table 1, Table S3). Approximately half of the participants with highly persistent symptoms reported daily relapses with little change between symptom onset (54%) and ≥ 18 months after onset (53%). A minority of these participants reported “less than weekly” relapses, ranging from 4% at symptom onset to 10% at 18 months after onset (Table S4).

The second trajectory “rapidly decreasing symptoms” referred to participants with a moderate long COVID ST score at symptom onset (average score = 28) and for whom the number of symptoms gradually decreased over time (average score < 1 after 600 days) ($n = 107$, 4.9%). Participants with rapidly decreasing symptoms were more likely to report neck, back, and/or lower back pain (65%) and diarrhea (52%) in the first year after symptom onset (Table 1, Table S3). Among participants with rapidly decreasing symptoms, the proportion of participants reporting “less than weekly” relapses increased from 26% to 75% between symptom onset and ≥ 18 months after onset (Table S4).

Finally, the third trajectory “slowly decreasing symptoms” referred to participants with a low long COVID ST score at symptom onset (average score = 16) who improved very slowly over time (average score = 12 after 2 years) ($n = 1996$, 90.8%) (Table 1 and Table S3). Among participants with slowly decreasing symptoms, the proportion of participants reporting “less than weekly” relapses increased from 11% to 30% between symptom onset and ≥ 18 months after onset (Table S4).

Table 1
Participants' demographic and clinical characteristics (n = 2197).

Characteristic	Total N = 2197	Trajectory 1 «High persistent symptoms» N = 94	Trajectory 2 «Rapidly decreasing symptoms» N = 107	Trajectory 3 «Slowly decreasing symptoms» N = 1996
Age, n (%), years, median (Q1-Q3)	46 (38-54)	44 (37-51)	43 (35-51)	46 (39-54)
Female sex, n (%)	1738 (79)	79 (84)	90 (84)	1569 (79)
Body mass index, n (%)				
<25	1342 (61)	61 (65)	66 (62)	1215 (61)
25-30	537 (24)	15 (16)	26 (24)	496 (25)
>30	315 (14)	18 (19)	15 (14)	282 (14)
Education level, n (%)				
Middle or high school	523 (24)	28 (30)	23 (21)	472 (24)
≥ 2 years post-secondary education	1674 (76)	66 (70)	84 (79)	1524 (76)
Cigarette smoking, n (%)				
Never	1013 (46)	34 (36)	48 (45)	931 (47)
Former	871 (40)	44 (47)	39 (36)	788 (39)
Occasionally	115 (5)	3 (3)	3 (3)	109 (5)
Daily	196 (9)	13 (14)	17 (16)	166 (8)
Comorbidities, n (%)				
At least one comorbidity	553 (25)	26 (28)	64 (60)	463 (23)
Cardiovascular disease	157 (7)	3 (3)	11 (10)	143 (7)
Chronic respiratory disease	185 (8)	13 (14)	16 (15)	156 (8)
Chronic kidney disease	14 (1)	1 (1)	1 (1)	12 (1)
Cancer	34 (2)	0	4 (4)	30 (2)
Diabetes	40 (2)	2 (2)	2 (2)	36 (2)
Psychiatric disease	109 (5)	6 (6)	12 (11)	91 (5)
Functional disease	129 (6)	5 (5)	12 (11)	112 (6)
Systemic disease	44 (2)	3 (3)	1 (1)	40 (2)
Hospitalization during the acute COVID-19, n (%)	365 (17)	19 (20)	11 (10)	335 (17)
Hospitalization in an intensive care unit, n (%)	90 (4)	3 (3)	1 (1)	86 (4)
Confirmed SARS-CoV-2 infection, n (%) (n = 2196)	1526 (69)	56 (60)	74 (69)	1396 (70)
Time since symptom onset, days, median (Q1-Q3)	852 (652-897)	906 (639-921)	874 (701-920)	863 (671-919)
Period ^a				
Wild type or Alpha	1989 (90)	82 (87)	107 (100)	1800 (90)
Delta	87 (4)	12 (13)	0	75 (4)
Omicron	121 (6)	0	0	121 (6)
Symptoms in the first year of their post-COVID-19 condition, n (%) (n = 1681) ^b	n = 1681	n = 68	n = 99	n = 1514
Hot flushes	480 (29)	52 (76)	34 (34)	394 (26)
Sweats	425 (25)	47 (69)	30 (30)	348 (23)
Diarrhea	504 (30)	44 (65)	51 (52)	409 (27)
Neck, back, and low back pain	790 (47)	60 (88)	64 (65)	666 (44)
Heat/Cold intolerance	327 (19)	44 (65)	26 (26)	257 (17)
Photophobia/Phonophobia	286 (17)	40 (59)	19 (19)	227 (15)
Paresthesia	634 (38)	53 (78)	36 (36)	545 (36)
Tachycardia/Bradycardia/palpitations/Arrhythmia	779 (46)	63 (93)	50 (50)	666 (44)
Frequency of relapses in the first 6 months of their post-COVID-19 condition, n (%) (n = 690) ^c	n = 690	n = 26	n = 43	n = 621
Less than weekly relapses	78 (11)	1 (4)	11 (26)	66 (11)
Weekly relapses	178 (26)	4 (15)	10 (23)	164 (26)
Daily relapses	251 (36)	14 (54)	14 (33)	223 (26)
Permanent symptoms	183 (27)	7 (27)	8 (19)	168 (27)

^a Alpha period represents patients whose symptom onset was before June 07, 2021, when >75% of patients had an infection with the Alpha variant (Santé Publique France). Omicron period represents patients whose symptom onset was after December 27, 2021, when >75% of patients had an infection with the Omicron variant.

^b Analysis was limited to participants who had at least one observation point in their first year after symptom onset (i.e., exclusion of participants who enrolled in the cohort more than one year after onset).

^c Analysis was limited to participants who had at least one observation point in their first 6 months after symptom onset (i.e., exclusion of participants who enrolled in the cohort more than 6 months after onset).

The results from the trajectory modeling were similar in the subgroup of participants with confirmed SARS-CoV2 infection (Figure 2). Among the 1526 participants with laboratory-confirmed SARS-CoV2 infection, 3%, 4%, and 93% of patients had “high persistent symptoms”, “rapidly decreasing symptoms” and “slowly decreasing symptoms”, respectively.

Our latent class model showed excellent discrimination of 0.89, meaning that it adequately assigned participants to specific trajectories (Supplementary Methods). It also showed high robustness: among the 100 bootstrap samples, three latent trajectories

were identified in 99, whereas two latent trajectory solutions were found in the remaining one. The median agreement between trajectory assignment in bootstrap samples and the original classification was high (kappa = 0.81) (Figures S2 and S3).

Estimation of the number of patients belonging to each post-COVID-19 condition trajectory

To correct for the selection bias in our cohort, we assessed the proportion of patients belonging to each trajectory identified

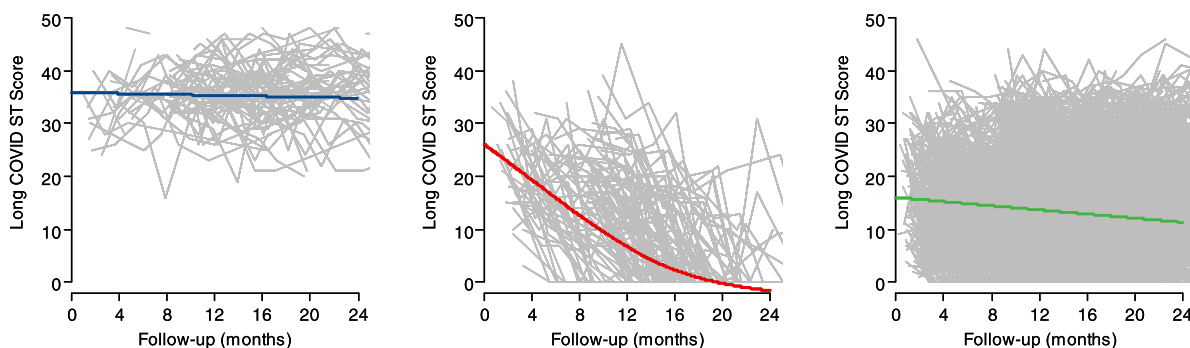


Figure 1. The three trajectories of post-COVID-19 symptoms ($n = 2197$) The panels represent each of the three trajectories of post-COVID-19 condition identified using latent class mixed models. Trajectory 1 (panel A, blue line) represents participants with highly persistent symptoms. Trajectory 2 (panel B, red line) represents participants with rapidly decreasing symptoms. Trajectory 3 (panel C, green line) represents participants with slowly decreasing symptoms. Individual trajectories of symptoms for each participant can be visualized by thin gray lines. Participants were grouped according to the trajectory for which they had the highest probability of membership.

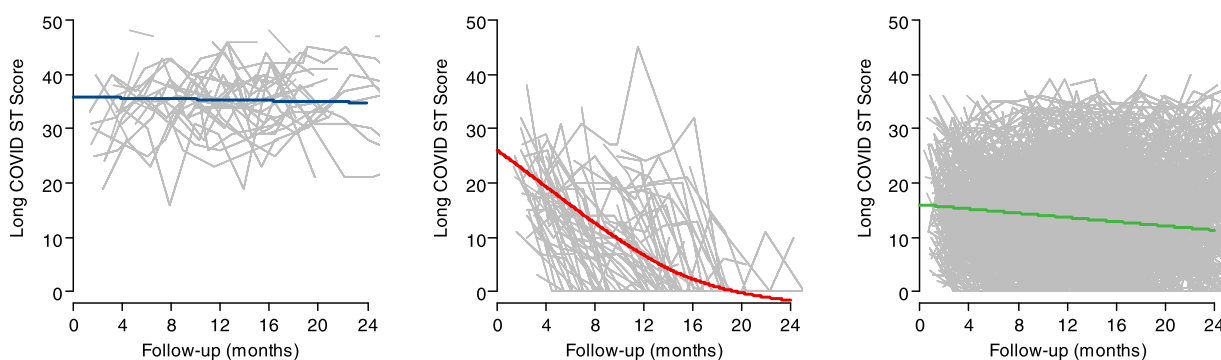


Figure 2. The three trajectories of post-COVID-19 symptoms among patients with laboratory-confirmed COVID-19 ($n = 1526$) The panels represent each of the three trajectories of post-COVID-19 condition identified using latent class mixed models among patients with laboratory-confirmed COVID-19. Trajectory 1 (panel A, blue line) represents participants with highly persistent symptoms. Trajectory 2 (panel B, red line) represents participants with rapidly decreasing symptoms. Trajectory 3 (panel C, green line) represents participants with slowly decreasing symptoms. Individual trajectories of symptoms for each participant can be visualized by thin gray lines. Participants were grouped according to the trajectory for which they had the highest probability of membership.

earlier in a weighted sample representative of patients reporting post-COVID-19 in the survey from the Office of National Statistics in the United- Kingdom. We found that 3%, 6%, and 91% of patients had “high persistent symptoms”, “rapidly decreasing symptoms,” and “slowly decreasing symptoms”, respectively.

Determinants of the post-COVID-19 condition trajectories

Participants with an increased likelihood of having “high persistent symptoms” (as compared to having “slowly decreasing symptoms”), were older (odds ratio [OR] 1.04, 95% CI: 1.03–1.06 per year, that is OR 1.48, 95% CI: 1.34–1.79 per 10 years), current smokers (OR 1.49, 95% CI 1.03 to 2.15), had a history of a systemic disease (OR 2.55, 95% CI: 1.03–6.32), and no history of functional diseases (OR > 10) (Table 2).

Participants with an increased likelihood of having “rapidly decreasing symptoms” (as compared to having “slowly decreasing symptoms”) had a confirmed SARS-CoV-2 infection (OR 2.59, 95% CI: 1.90–3.52), were current smokers (OR 1.91, 95% CI: 1.27–2.89), and had no history of functional diseases (OR 2.96, 95% CI: 1.60–5.47). Older participants and those with systemic diseases had a reduced likelihood of having rapidly decreasing symptoms (OR 0.96, 95% CI: 0.95–0.98 per year, and OR 0.25, 95% CI: 0.09–0.70, respectively) (Table 2).

We found no evidence of an association among body mass index, education level, and hospitalization during acute infection with trajectories. (Table 2 and Table S5).

Discussion

In this nationwide study of 2197 participants (19,729 participants-months), we identified three distinct trajectories of the evolution of post-COVID-19 condition over time. Overall, 91% of patients improved slowly over time. Older patients and those with a history of a systemic disease were more likely to have high persistent symptoms (4% of the participants). Younger patients and those with a confirmed infection were more likely to have rapidly decreasing symptoms over time (5% of the participants).

To our knowledge, this is the first study aimed at exploring the heterogeneity of the longitudinal evolution of patients with post-COVID-19 condition. This answers one of the core research questions from the National Research Action Plan on Long COVID by the US Department of Health and Human Services [11]. Three recent large-scale studies have investigated symptom clusters at a given time point. Sudre *et al.* assessed participants with symptoms over 28 days and identified two main patterns of symptomatology: individuals reporting exclusively fatigue, headache, and upper respiratory complaints, and those with additional multisystem complaints [35]. Subramanian *et al.* assessed participants with symptoms over 12 weeks and identified three clusters: 80% of participants had a broad spectrum of symptoms dominated by pain, fatigue, and rash; 6% of participants had mainly respiratory complaints; and 14% of participants expressed mainly depression and anxiety [22]. Finally, the Post-hospitalization COVID-19 study (PHOSP) identified four clusters with different severities of mental and physical pain [23].

Table 2

Associations between participants' baseline demographic and clinical characteristics and their probability of post-COVID-19 symptoms trajectory membership.

Characteristics	OR (95% CI) for belonging to trajectory 1 "High persistent symptoms" (n = 94)	OR (95% CI) for belonging to trajectory 2 "Rapidly decreasing symptoms" (n =107)
Age ^a	1.04 (1.03-1.06)	0.96 (0.95-0.98)
Female sex	1.01 (0.73-1.39)	1.39 (0.97-1.99)
Body mass index ^a	0.98 (0.96-1.01)	1.02 (0.99-1.04)
Education level	0.96 (0.71-1.29)	0.96 (0.69-1.35)
Smoking status	1.49 (1.03-2.15)	1.91 (1.27-2.89)
Confirmed covid	0.96 (0.73-1.26)	2.59 (1.90-3.52)
No Hospitalization	1	1
Hospitalization	1.40 (0.96-2.05)	0.91 (0.59-1.39)
Intensive care	1.52 (0.77-2.99)	1.71 (0.80-3.65)
Comorbidities		
Cardiovascular disease	1.03 (0.62-1.74)	0.68 (0.38-1.22)
Chronic respiratory disease	1.11 (0.70-1.76)	0.63 (0.38-1.06)
Chronic kidney disease	1.54 (0.31-7.62)	0.80 (0.13-4.81)
Cancer	0.73 (0.26-2.04)	2.35 (0.74-7.50)
Diabetes	0.46 (0.17-1.21)	2.20 (0.74-6.56)
Psychiatric disease	0.96 (0.53-1.72)	1.08 (0.56-2.09)
No functional disease	128658.69 (74369.27-222579.29)^b	2.96 (1.60-5.47)
Systemic disease	2.55 (1.03-6.32)	0.25 (0.09-0.70)

BMI, body mass index; CI, confidence interval; OR, odds ratio.

OR were obtained by modeling the logit of the probability of belonging to each trajectory obtained in the latent class modeling, as compared to the reference trajectory "slowly decreasing symptoms".

^a OR is per unit of age or BMI;^b ORs are included but are extremely large when there is a separation in the probability of belonging to trajectory 1 and 3, between participants with and without a history of functional diseases.

Differences in the findings of these studies and ours may originate from differences in (i) the periods investigated (e.g., Sudre *et al.* investigated participants in 2020), (ii) contexts (UK, USA, and France), and (iii) approach. Indeed, our study was the only one to identify distinct trajectories of the evolution of post-COVID-19 condition over time, rather than clustering symptoms at a given time point.

In our study, we found a strong association between a history of systemic diseases and "high persistent symptoms". The PHOSP study also found that the more severe the patients, the higher the inflammatory markers were [23]. Similarly, a recent preprint found that the longitudinal evolution of the C-reactive protein serum concentration in patients after COVID-19 followed three types of distinct profiles very similar to our findings (i.e., high persistent, decreasing, and low persistent trajectories) [36].

SARS-CoV-2 is not unique in its ability to cause postacute symptoms. Several infections, such as Q fever, Dengue, or H1N1/09 influenza A virus, also exhibit unexplained chronic disability after the acute infection. In a recent review, Choutka *et al.* described the similarity in the symptom profiles of postacute infectious syndromes, as well as the overlap of clinical features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which suggests a potential common etiopathogenesis [37]. Our results could therefore also inform the evolution of these syndromes. As we included some patients without a laboratory-confirmed infection, it is also possible that some participants were misdiagnosed as having post-COVID-19 condition while having other similar conditions. The strengths of this study include the prospective follow-up of a large population of participants and their regular assessment using validated participant-reported outcome measures developed from the participants' lived experiences. In addition, our study had only a few missing data points. Second, we assessed the robustness of latent trajectory modeling using bootstrapping methods and found excellent replicability of the results.

This study had several limitations. First, recruitment of participants in the ComPaRe long COVID cohort included a social media and general media campaign that may have selected younger, female, well-educated, and more severe participants. Yet, one strength of our study is that our recruitment relied on the use of

the French National Contact tracing application which covered the general population, in France. In addition, even if our "raw" population was not representative of patients with post-COVID-19 condition, this should not have impacted the identification of trajectories because our population was diverse. Furthermore, to correct for a potential selection bias, we performed a weighted analysis using data from the Office of National Statistics in the United Kingdom. The weighted and raw analyses provided very similar results. Second, 30% of participants did not report laboratory-confirmed SARS-CoV2 infection, and we could not ascertain whether an alternative diagnosis might explain their symptoms. Nevertheless, we chose to include these participants because they followed the WHO definition of post-COVID-19 condition, and a high number of participants were infected with the SARS-CoV2 virus; however, individuals were not tested during the first wave in France [6]. It is to be noted that our results were unchanged in a sensitivity analysis restricted to patients with a confirmed infection. Third, our study involved mainly participants included before 7 June 2021 when the wild type and Alpha variant were predominant, and the results should be generalized with caution to other variants. Despite small numbers, none of participants who were infected during the Omicron period had "high persistent symptoms". These results agree with recent findings showing that the individual burden of post-COVID-19 condition was more important after wild-type infection than, Alpha/Delta and Omicron infections [38]. Fourth, our data exhibited little information about the participants' acute diseases. Indeed, as participants could enroll in the ComPaRe cohort at any time point after their initial infection (with an interval between symptom onset and enrollment exceeding 365 days for 23% of participants), we made the methodological choice to minimize memory bias by not retrospectively asking for symptoms experienced during the acute phase of the infection. This limited our ability to include the presentation of participants during the acute phase as determinants of post-COVID-19 trajectories. Finally, our study did not correct for individual symptoms present before SARS-CoV-2 infection that could have modified the dynamics of the disease [8].

To conclude, we present the first study to describe the natural history of post-COVID-19 condition, accounting for the hetero-

generality of this complex multifaceted infection. We identified three different trajectories of evolution that may be associated with the participants' comorbidities and clinical presentations. Our research is important for disentangling the underlying mechanisms of post-COVID-19 assuming that different mechanisms (e.g. persistent inflammatory state, viral reservoir, autoimmunity, or psychological manifestations) could be associated with different evolutions. Further research is required to link the trajectories identified with clinical and biological markers, which could help predict the membership of a given patient to a given trajectory.

Second, from a clinical perspective, our results showed that most patients had persistent symptoms and improved slowly over time. These results will help frame healthcare needs and the required response by the care system, as well as provide patients with evidence-based information on their prognosis.

Conclusion

The natural history of post-COVID-19 condition reveals that most patients will have persistent symptoms with only little improvement over time, whereas approximately 5% of patients will have rapidly decreasing symptoms within 2 years after symptom onset.

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Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

Generated the idea: VTT. Conceived and designed the experiments: CS, RP, and VTT. Collected data: CS, IP, and VTT. Analyzed data: CS, RP, PR, and VTT. Wrote the first draft of the manuscript: CS. Contributed to the writing of the manuscript: CS, RP, IP, PR, and VTT. The ICMJE criteria for authorship were read and met: CS, RP, IP, PR, and VTT. Agree with the manuscript results and conclusions: CS, RP, IP, PR, and VTT. VTT and RP are guarantors. They had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

All data generated and used in the study are from the ComPaRe e-cohort platform. All data presented in this study are available to public research teams for health-related research in the public interest. Researchers who wish to access the data must comply with the conditions detailed on <https://compare.aphp.fr>. Contact for access requests is contact.compare@aphp.fr. All requests for data are examined by the ComPaRe scientific committee and responded to within 3 months from submission.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2023.05.007](https://doi.org/10.1016/j.ijid.2023.05.007).

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