Received: 7 March 2024 | Accepted: 21 September 2024

DOI: 10.1111/ene.16510

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Neurological long COVID in the outpatient clinic: Is it so long?

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Funding information
Ministero della Salute, Grant/Award Number: NET-2018-12366666; NEXTGENERATIONEU (NGEU), Grant/Award Number: PE0000006 and ECS00000035

Abstract

Background and purpose: Neurological involvement in long COVID (coronavirus disease 2019) is well known. In a previous study we identified two subtypes of neurological long COVID, one characterized by memory disturbances, psychological impairment, headache, anosmia and ageusia, and the other characterized by peripheral nervous system involvement, each of which present a different risk factor profile. In this study, we aimed to clarify the persistence of neurological long COVID symptoms with a significantly longer term follow-up.

Methods: We prospectively collected data from patients with prior COVID-19 infection who showed symptoms of neurological long COVID. We conducted a descriptive analysis to investigate the progression of neurological symptoms over time at 3-, 6-, 12-, and 18-month follow-ups. We performed a k-means clustering analysis on the temporal evolution of the symptoms at 6, 12, and 18 months. Finally, we assessed the difference between the recovery course of vaccinated and non-vaccinated patients by computing the cumulative recovery rate of symptoms in the two groups.

Results: The study confirmed the presence of two subtypes of neurological long COVID. Further, 50% of patients presented a complete resolution of symptoms at 18 months of follow-up, regardless of which subtype of neurological long COVID they had. Vaccination against SARS-Cov-2 appeared to imply a higher overall recovery rate for all neurological symptoms, although the statistical reliability of this finding is hampered by the limited sample size of the unvaccinated patients included in this study.

Conclusions: Neurological long COVID can undergo complete resolution after 18 months of follow-up in 50% of patients and vaccination can accelerate the recovery.

KEYWORDS
clustering, COVID-19, neurological long COVID, recovery rate, vaccination

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INTRODUCTION

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, neurological involvement following infection has been noted, both in the acute phase and in so-called long COVID. In a previous study, we demonstrated how neurological long COVID symptoms are heterogeneous and we identified two subtypes of neurological long COVID, related differently to disease severity in its acute phase [1]. In the present study, we continued the follow-up of the previously analyzed patients to clarify the persistence of neurological symptoms over time and to define whether it is possible to assume recovery from neurological long COVID, also analyzing the influence of vaccination on the trajectory of long COVID symptoms.

METHODS

Population overview

As reported in our previous study [1], in November 2020, we established the Neurological Long COVID Outpatient Clinic at the Neurological Clinic of San Martino Hospital in Genoa to assess patients with post-COVID neurological symptoms. Patients were referred from the long COVID outpatient clinic of the Department of Pneumology, including patients with a previous admission to the Department of Pneumology, the intensive care unit (ICU) or the Department of Infectious Diseases, as well as patients who did not require admission during the acute phase of the infection.

Data collection

Patient data were collected prospectively from November 2020 to December 2022. The diagnosis of COVID-19 was confirmed in all patients by polymerase chain reaction on naso-pharyngeal swab even in asymptomatic cases at onset. Of the 553 patients evaluated at the long COVID outpatient clinic of the Department of Pneumology, where they were recruited for respiratory function assessment after the acute phase of COVID-19, 152 patients complained of neurological symptoms and were referred to the neurological post-COVID outpatient clinic between 1 November 2020 and 31 December 2022. The main neurological symptoms reported by patients were as follows: anosmia and ageusia, headache, dizziness, memory disorder, psychological disorder, fatigue, peripheral nervous system (PNS) involvement, sleep disorder, and other symptoms not classifiable in the above groups. Other data collected included: (a) pre-infection comorbidities, smoking habits and body mass index (BMI); (b) information about symptoms of acute COVID-19 infection (i.e., upper respiratory tract symptoms, gastroenteritis, and pneumonia); (c) number of symptoms at onset of the acute infection (i.e., anosmia, ageusia, cough, rhinitis, fever, myalgia, gastrointestinal symptoms); (d) information about therapy for the acute infection (e.g., corticosteroid, heparin, antibiotics, remdesivir, tocilizumab); (e) type of administration devices for oxygen therapy and duration of ventilation; (f) number and subtype of extra-neurological complications experienced during the acute phase of infection; (g) duration of hospitalization; and (h) information about vaccination (i.e., timing of vaccination and type of administered vaccine). Exclusion criteria were: (a) missing follow-up assessment and (b) presence of neurological symptoms not related to SARS-CoV-2 infection. Of the 152 patients, 13 missed the follow-up evaluation, therefore, the statistical analyses were performed on the remaining 139 patients. Patients were assessed at four time points (3, 6, 12, and 18 months) after SARS-CoV-2 infection.

Statistical analysis

We conducted a descriptive analysis to investigate the progression of neurological symptoms over time at 3-, 6-, 12-, and 18-month follow-ups. The evolution of each symptom over time was described using the cumulative recovery rate:

$$\text{RecoveryRate}_{\text{symptom}} = \frac{n_t}{n_0},$$

where n_t is the number of patients initially affected by a specific symptom and recovered at time t, and n_0 is the total number of patients.

Then, we performed a k-means clustering analysis [2] on the temporal evolution of five major symptoms (i.e., symptoms of PNS involvement, memory disturbances, psychological impairment, headache, anosmia, and/or ageusia) to investigate whether the neurological long COVID subtypes at 3-month follow-up identified in our previous work were stable at 6, 12 and 18 months. As a first step, we randomly generated a set of 70% of patients and clustered them by means of the unsupervised algorithm whereby, as inspired by our previous results, we set *a priori* the number of clusters at $k=2$. The remaining 30% of patients were used as a test set for the clustering result. Testing of potential risk factors (i.e., sex, BMI, age, smoking habit, number of comorbidities at onset, number of COVID-19 symptoms at onset, number of non-neurological complications during the acute phase of the infection, severity of COVID-19 at onset, dyspnea at onset, smell loss at onset, time of onset of the neurological complications) was carried out to assess the separability of those clusters. Moreover, we performed a symptoms survival analysis based on the non-parametric Kaplan–Meier test in the two different groups *for all the time-points (3,6,12) in the 18-month window* to analyze the survival rate of the five main symptoms: PNS involvement disorder, memory disorder, anosmia/ageusia, headache, and psychological disturbances.

Subsequently, a logistic regression was performed to analyze the impact of sex, age, BMI, and comorbidities on symptom persistence at 18 months in patients with no symptom improvement.

Finally, we assessed whether there was any indication of a noteworthy difference between the recovery course of vaccinated and non-vaccinated patients, by computing the cumulative recovery rate of symptoms over the two groups.

RESULTS

Demographic characteristics and clinical data

Table 1 summarizes the demographic characteristics and aspects of the course of acute infection for the total cohort of 139 patients. Figure 1 shows the distribution of neurological symptoms over time and highlights that PNS involvement, memory disturbances and anosmia/ageusia remained the most frequent neurological symptoms over the course of 18 months.

Figure 1 and Table 2 show that, after 18 months, more than 50% patients experienced a complete regression of neurological symptoms. Figure 2 shows the cumulative recovery rate of symptoms for each time period. Sleep disorder was the neurological symptom with the highest recovery rate in the first 3 months and was the only symptom that disappeared completely after 18 months; further, it was the only symptom with a recovery rate of more than 25% between 3 and 6 months. By contrast, in the period 6–12 months, the recovery rate of headache, fatigue and other symptoms, rose to over 50% (Table 3).

Clustering analysis

Longitudinal clustering analysis of the five major symptoms (anosmia/ageusia; headache; memory disturbances; psychological disturbances; symptoms of PNS involvement) performed in the training set of 98 patients (70% of 139 subjects) yielded two well separated groups, denoted here as long COVID type 1 (Figure 3, red cluster), containing 55 patients, and long COVID type 2 (Figure 3, blue cluster), comprising 43 patients. This is coherent with our previous artificial intelligence (AI)-based analysis performed in a subset of the current cohort of patients at Month 3, where we highlighted the existence of the same two distinct subtypes of long COVID [1]. Upon examining the centroid profiles of the two clusters (Figure 3, bottom panel), we observed that the long COVID type 2 cluster encompassed all individuals who reported symptoms associated with PNS involvement. Conversely, the long COVID type 1 cluster primarily consisted of individuals who reported symptoms of memory disturbance, psychological impairment, headache, anosmia, and ageusia, in line with the findings of the previous analysis [1] (Figure 3, magnified panel). Indeed, the inclusion of the new longitudinal variables did not result in significant shifts in the centroids of the two clusters compared to our previous findings, and PNS involvement emerged once again as the primary symptom distinguishing the two clusters across different time periods.

A posteriori risk factor analysis of demographics, clinical presentation, severity of COVID-19, and hospitalization course showed that, consistent with our previous analysis performed at Month 3, the number of comorbidities at onset ($p=0.04$, Bonferroni-corrected), BMI ($p=5\times10^{-4}$, Bonferroni-corrected), the number of COVID symptoms ($p=4\times10^{-3}$, Bonferroni-corrected), the number of non-neurological complications ($p=1.05\times10^{-6}$), and a more severe course of acute infection ($p=1.79\times10^{-6}$) were all, on average, higher in the long COVID type 2 subgroup.

TABLE 1 Demographic characteristics and clinical data.

Characteristic	*n* (%)
Number of patients	139
Sex	
Female	72 (51.8)
Male	67 (48.2)
Smoking habit	
Non-smoker	81 (58.3)
Smoker	12 (8.6)
Ex-smoker	46 (33.1)
BMI category	
Underweight	5 (4.2)
Healthy weight	55 (45.8)
Overweight	60 (50)
Manifestation of acute COVID-19	
Pneumonia	111 (79.9)
Upper respiratory tract symptoms	27 (19.4)
Gastrointestinal symptoms	1 (0.7)
Number of acute symptoms	
No symptoms	3 (2.2)
1 symptom	5 (3.6)
2 symptoms	38 (27.5)
3 symptoms	35 (25.4)
4 symptoms	19 (13.8)
5 symptoms	23 (16.7)
6 symptoms	10 (7.2)
7 symptoms	3 (2.2)
8 symptoms	1 (0.7)
9 symptoms	1 (0.7)
Oxygen therapy	
No oxygen therapy	43 (30.9)
Nasal cannula/mask	28 (20.15)
Non-invasive ventilation	28 (20.15)
Intubation/tracheostomy	40 (28.8)
Prone ventilation	21 (15.2)
Days of admission stay	
No admission	28 (20.1)
<30 days	55 (39.6)
>30 days	56 (40.3)
Severity of acute phase	
Low	71 (51.5)
Moderate	26 (18.8)
Severe	41 (29.7)
Vaccination after infection	
Vaccinated	15 (7)
Unvaccinated	124 (93)

Validation in the test set of unseen patients (41 out of 139) confirmed that 85% of "severe" patients (i.e., patients in the validation set who had three out of five risk factors higher than the average

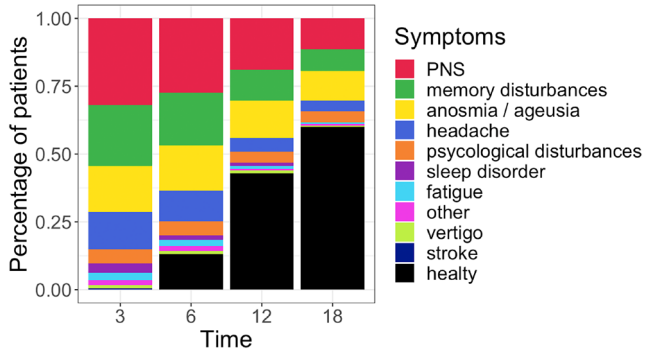

FIGURE 1 Evolution of symptoms over time in 139 patients; note the progressive increase in the percentage of healthy patients over time.

TABLE 2 Evolution of symptoms over the different periods, as displayed in Figure 1.

Symptom	3 months	6 months	12 months	18 months
	n(%)	*n*(%)	*n*(%)	*n*(%)
Peripheral nervous system	56 (32)	48 (27.4)	33 (18.9)	20 (11.4)
Memory disturbances	39 (22.3)	34 (19.4)	20 (11.4)	14 (8)
Anosmia / ageusia	30 (17.1)	29 (16.6)	24 (13.7)	19 (10.9)
Headache	24 (13.7)	20 (11.4)	9 (5.1)	7 (4)
Psychological disturbances	9 (5.1)	9 (5.1)	7 (4)	7 (4)
Sleep disorder	6 (3.4)	3 (1.7)	2 (1.1)	0 (0)
Fatigue	5 (2.9)	4 (2.3)	2 (1.1)	1 (0.6)
Other	3 (1.7)	3 (1.7)	1 (0.6)	1 (0.6)
Vertigo	2 (1.1)	2 (1.1)	2 (1.1)	1 (0.6)
Stroke	1 (0.6)	0 (0)	0 (0)	0 (0)
Healthy	0 (0)	23 (13.1)	75 (42.9)	105 (60)

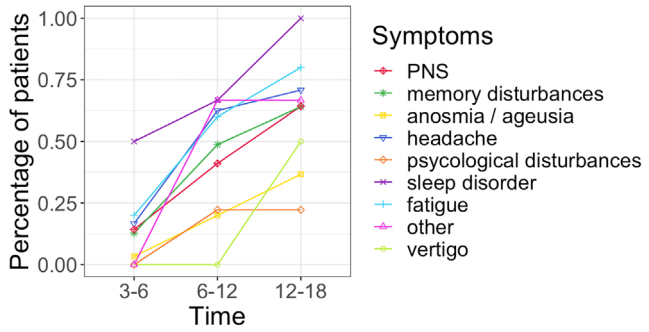

FIGURE 2 Cumulative recovery rate of symptoms in 139 patients (for a given symptom, the rate is the number of patients recovered at time *t* over the number of patients initially ill) at individual time points. PNS, peripheral nervous system.

value as computed in the training set) were predicted to be in the long COVID type 2 cluster, and 56% of "mild" patients (i.e., the not "severe" patients) were predicted to be in the long COVID type 1 cluster. These results indicate an overall accuracy of 0.74 (with a sensitivity of 0.76 and a specificity of 0.7).

TABLE 3 Cumulative recovery rate of symptoms over the different periods as displayed in Figure 2.

Symptoms	3–6 months, %	6–12 months, %	12–18 months, %
PNS	14.3	41.1	64.3
Memory disturbances	12.8	48.7	64.1
Anosmia/ageusia	3.3	20	36.7
Headache	16.7	62.5	70.8
Psychological disturbances	0	22.2	22.2
Sleep disorder	50	66.7	100
Fatigue	20	60	80
Other	0	66.7	66.7
Vertigo	0	0	50

Abbreviation: PNS, peripheral nervous system.

Further, the symptom survival analysis at 3, 6, 12 and 18 months showed that there was no significant difference in symptom persistence between the two clusters, as confirmed by the high *p* values obtained in the Kaplan–Meier test ($p = 0.32$ for PNS involvement, $p = 0.33$ for memory disorder, $p = 0.6$ for anosmia and ageusia, $p = 0.12$ for headache, $p = 0.87$ for psychological disturbances).

Finally, we examined the overall cumulative recovery rate of patients within the two clusters, both in the training and in the test set. The trends were virtually identical between the two clusters, indicating no significant differences in the recovery time expectancy within each group (Table 4). A more significant difference in the rate of recovered patients at Month 12 was found only in the test set (34% in the long COVID type 1 cluster and 5% in the other cluster).

Risk factors related to poor recovery

Table 5 summarizes the logistic regression results for the correlations between sex, age, BMI, comorbidities, and symptom persistence at 18 months. No significant results were found, although a slight correlation was noted between male sex and ongoing anosmia and ageusia.

Vaccinated versus unvaccinated patients

Table 1 shows that, out of the 139 patients included in the longitudinal analysis, only 15 (10.8% of the total patient cohort) did not receive a COVID-19 vaccination following their infection. It is worth highlighting that, among the unvaccinated patients, symptoms were limited to neuropathy, memory issues, anosmia and ageusia, headaches, and fatigue; therefore, only these symptoms were considered for comparison between the two groups. Figure 4 shows the cumulative recovery rate of the symptoms and

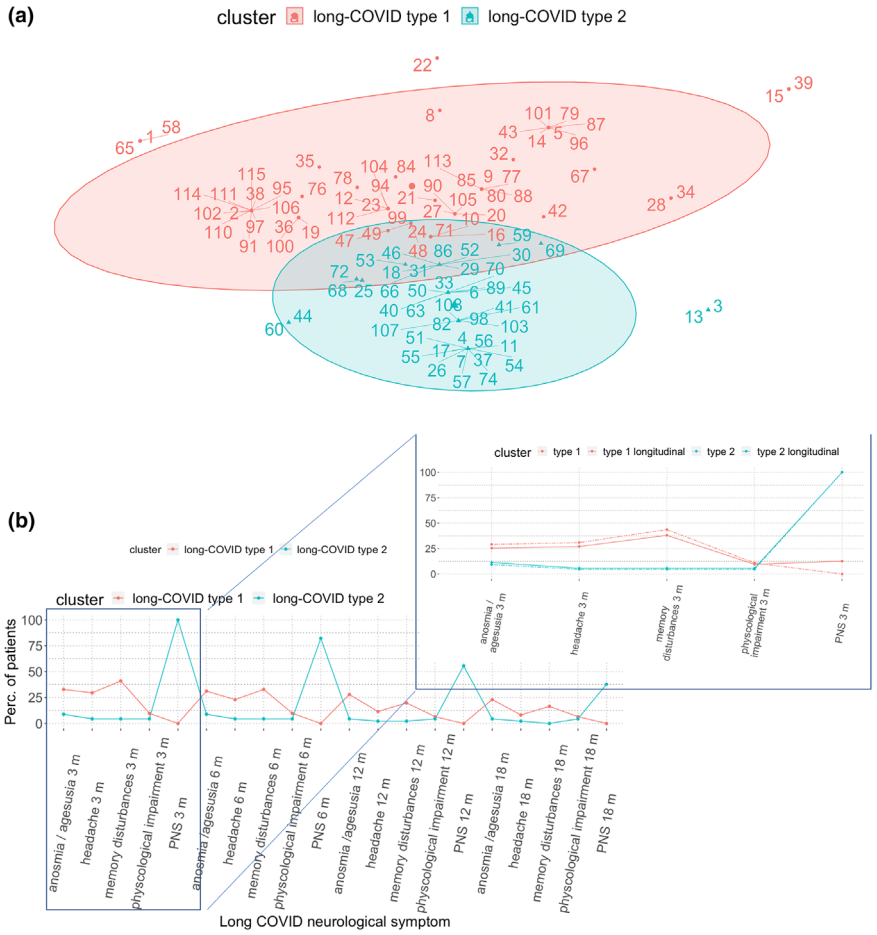

FIGURE 3 Longitudinal clustering results for 98 patients (training set). (a) The two clusters that emerged from the analysis of the set of five neurological symptoms, visualized along the two principal components. (b) Profile of the centroids. Magnified panel: Comparison between the centroid profiles of the clusters retrieved with the longitudinal analysis (continuous lines) and the ones retrieved using only symptoms at 3 months (dashed lines).

TABLE 4 Overall cumulative recovery rate for patients within the two clusters, in the training set and test set.

	6 months	12 months	18 months
	n(%)	*n*(%)	*n*(%)
Training set (98 patients)			
Long COVID type 1	10 (18)	22 (40)	33 (60)
Long COVID type 2	7 (16)	21 (49)	24 (56)
Test set (41 patients)			
Long COVID type 1	0 (0)	14 (34)	15 (37)
Long COVID type 2	1 (3)	2 (5)	12 (29)

highlights that, apart from symptoms related to PNS involvement, vaccinated patients exhibited a higher overall cumulative recovery rate compared to their unvaccinated counterparts across all symptoms. For instance, 69.7% of vaccinated patients (n = 23) completely recovered from memory disturbances within 18 months, while only 33.3% of unvaccinated patients (n = 2) recovered from the same symptom in the same time frame. Regarding instead PNS disturbances, all unvaccinated patients recovered within 18 months since the onset of the infection, while only 60% recovered among the vaccinated ones.

Finally, by performing the Kaplan–Meier test we noted that, although there was no significant difference in the survival rate of symptoms between the vaccinated and non-vaccinated groups ($p=1$ for anosmia/ageusia; $p=0.43$ for headache; $p=0.14$ for memory disturbances; $p=0.08$ for PNS), symptoms related to headache and memory disturbances had a greater survival rate in unvaccinated patients compared to vaccinated patients, while for the symptoms related to PNS involvement the opposite was true (Figure 4 and Table 6).

DISCUSSION

This study was a continuation of a previous work [1], focused on the clinical characteristics of neurological long COVID in a heterogeneous patient population. Over 3 years, as we cared for our patients over time in our Neuro-COVID Outpatient Clinic, our main question was "Does neurological long COVID represent a persistent or circumscribed syndrome over time?". Another point of interest was to clarify whether, just as the clinical aspects of COVID-19 infection have changed over the years [3, 4], the neurological consequences could accordingly demonstrate differences in terms of clinical presentation and its persistence over time.

Analysis of the data collected showed that neurological long COVID symptoms were most represented by PNS involvement symptoms, memory disorders, and anosmia/ageusia. Overall, the high prevalence of these neurological symptoms is in line with the

TABLE 5 Correlation between demographic and clinical characteristics and poor recovery.

	Anosmia and ageusia	Memory disturbances	PNS symptoms	Headache	Psychological symptoms
Sex (male)					
Effect size	1.3	0.99	−0.47	0.32	−0.77
p value	**0.06**	0.18	0.39	0.69	0.40
Age					
Effect size	−0.02	0.06	0.04	0.013	0.07
p value	0.33	0.08	0.11	0.69	0.17
BMI					
Effect size	−0.004	−0.09	−0.11	0.035	−0.07
p value	0.93	0.33	0.13	0.64	0.63
Number of comorbidities					
Effect size	0.4	−0.34	−0.07	0.15	−1.75
p value	0.3	0.46	0.86	0.77	0.07

Note: Positive coefficients indicate that higher values of the predictor increase the likelihood of the response being 1 (i.e. persistence of the symptom), while negative coefficients indicate the opposite. Bold indicate observation of trend between being male and having a poor recovery in terms of anosmia/ageusia ($p = 0.06$).

Abbreviations: BMI, body mass index; PNS, peripheral nervous system.

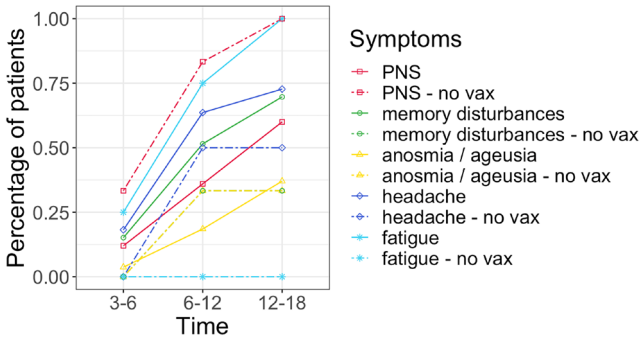

FIGURE 4 Cumulative recovery rate of symptoms of vaccinated (124) and unvaccinated (15) patients. In the figure, the curves related to memory disturbances and anosmia and ageusia of unvaccinated patients coincide and therefore only one is visible. PNS, peripheral nervous system.

TABLE 6 Cumulative recovery rate of symptoms of vaccinated and unvaccinated patients (124 and 15 patients respectively).

Symptoms	3–6 months *n*(%)	6–12 months *n*(%)	12–18 months *n*(%)
PNS involvement			
Vaccinated	6 (12)	18 (36)	30 (60)
Unvaccinated	2 (33.3)	5 (83.3)	6 (100)
Memory disturbances			
Vaccinated	5 (15.2)	17 (51.5)	23 (69.7)
Unvaccinated	0 (0)	2 (33.3)	2 (33.3)
Anosmia and ageusia			
Vaccinated	1 (3.7)	5 (18.5)	10 (37)
Unvaccinated	0 (0)	1 (33.3)	1 (33.3)
Headache			
Vaccinated	4 (18.2)	14 (63.6)	16 (72.7)
Unvaccinated	0 (0)	1 (50)	1 (50)
Fatigue			
Vaccinated	1 (25)	3 (75)	4 (100)
Unvaccinated	0 (0)	0 (0)	0 (0)

Abbreviation: PNS, peripheral nervous system.

most recent evidence reported in the literature [5, 6]. The prevalence of certain symptoms appears to be higher in nonhospitalized than hospitalized patients, proving that what determines the development of a neurological disorder is the presence of the virus per se, rather than the severity of the infection [5, 7, 8]. SARS-CoV-2 nucleic acids and proteins can be found in 50% of asymptomatic patients 4 months after infection; this viral persistence and the related significant levels of vascular-related proinflammatory biomarkers may contribute to immune activation and unresolved inflammation [9].

Data in the literature regarding the duration of neurological long COVID symptoms are heterogeneous. Most studies report a follow-up duration of less than 6 months and a higher prevalence of long COVID symptoms in the earlier months after discharge [9]. One prospective study observed up to half of patients with at least one persistent symptom beyond 6 months after COVID-19 infection [10]. In a long COVID cohort, the likelihood of symptoms lasting beyond 8 months was greater than 90%, while more than 85% of patients reported relapsing

symptoms [9]. Another study showed that at least one neurological disease not diagnosed prior to COVID-19 was found in 12% of patients at 1-year follow-up [6]. In our case series, at Month 18, 50% of patients reported the disappearance of the neurological symptoms that had required evaluation at the time of referral to our outpatient clinic. We observed the best recovery rate for the sleep disorder: at the 3-month follow-up, half of the patients with this symptom no longer reported the disturbance, while after 18 months this disorder had disappeared in all patients. To our knowledge there are no similar data in the literature showing a complete regression of sleep disturbance during follow-up. A recovery rate of approximately 50% at 2 years after acute infection is frequently observed, covering both neurological and non-neurological symptoms of long COVID [11–13]. Moreover, clinical improvement seems to follow a continuous trend, being present as early as 6 months after the onset of symptomatology and then increasing in the subsequent months [12]. However, an important proportion of patients still have disabling symptoms after 18 months, and need support in terms of medical care, drug therapy, and rehabilitation treatment. Only long-term follow-up will clarify whether continued clinical improvement can be observed over the months or whether the recovery rate will reach a plateau, with a proportion of patients presenting long COVID neurological symptoms for life.

In our previous work, we described the presence of two different clusters of neurological long-COVID: long-COVID type 1, characterized by the presence of memory disturbance, anosmia and ageusia, headache and psychological disturbance, and long-COVID type 2, characterized by the presence of PNS involvement [1]. We showed that certain demographic or hospitalization-related characteristics, such as a more severe acute phase of infection, correlated with the development of long COVID type 2 [1]. To maintain continuity with our previous work, we performed another cluster analysis, again observing a separation of patients into two clusters. However, we emphasize that this is not a validation of the previous study, as that has already been validated [1]. In addition, the new analysis showed no statistically significant differences in the recovery rate between patients in the two clusters. Studies focused on risk factors for the development of long COVID demonstrated the relevance of the severity of the disease in its acute phase [14, 15] and the demographic characteristics of patients, such as older age or gender [16], although some studies suggest that some long COVID symptoms are more prevalent in patients who have not been hospitalized or who are younger [5, 17]. Our previous study established that neurological long COVID symptoms can be observed regardless of the severity of the disease; the difference between the two subgroups lies in the different probability of developing one neurological symptom compared to another [1]. To build on the ideas and results of our first study, we investigated the longitudinal behavior of two clusters of neurological long COVID patients. The results showed a uniform regression of neurological symptoms over time, leading to the loss of cluster differentiation at follow-up. Even with regard to recovery rate, data on its correlation with the severity of disease are heterogeneous. Some evidence suggests that, even in patients who have shown severe symptoms, a satisfactory recovery rate is observed, with 50% of patients not requiring clinical intervention [13]. Our results confirm no difference in recovery trends in neurological symptoms. Regardless of the acute phase or symptoms, approximately 50% of patients in the Neuro-COVID Outpatient Clinic were in good health at 18 months.

To understand why some patients continued to experience neurological symptoms at 18 months, we performed a logistic regression on demographic and clinical factors (sex, age, BMI, comorbidities). No significant results were found, except for a slight correlation between male sex and persistent anosmia and ageusia. However, the small sample size limited the power of this analysis. The literature on the persistence of long COVID includes heterogenous data. Some studies correlate persistent symptoms to biological factors, such as baseline antibody levels [18] or virus persistence [19], while others suggest that severe disease, ICU stay and having four or more symptoms all correlate with poorer recovery [20, 21]. The impact of age has shown mixed results: some studies suggest that age over 50 years predicts persistence [21], while others found that patients aged over 70 years recover faster [20]. More data in larger populations are needed to clarify these risk factors.

Finally, we compared the trends in improvement of neurological long COVID symptoms in unvaccinated versus vaccinated patients. Despite limitations from differing group sizes, we observed a trend of faster improvement in vaccinated patients. However, this finding did not achieve statistical significance due to the sample size differences. The analysis performed showed that, apart from PNS symptoms, vaccinated patients exhibited a higher overall cumulative recovery rate compared to their non-vaccinated counterparts across all symptoms. Regarding the effect of SARS-CoV-2 vaccination on the nervous system, some vaccination-related neurological complications were found during the vaccination campaign (i.e., cerebral venous sinus thrombosis, Bell's palsy, acute transverse myelitis, acute disseminated encephalomyelitis, and acute demyelinating polyneuropathy) [22], but other studies highlighted the positive effect of vaccination, demonstrating that at least one vaccine dose was associated with a protective effect against long COVID [23]. The effect of vaccination on the trajectory of long COVID symptoms seems heterogeneous, as some patients reported an improvement in symptoms following vaccination, while some patients showed a worsening; in most cases, vaccination did not affect the symptom trajectory of pre-existing long COVID [23, 24]. In a study involving adults aged between 18 and 69 years infected with SARS-CoV-2 before vaccination against COVID-19, the authors found that a first vaccine dose was associated with an initial 13% decrease in the odds of experiencing long COVID [25]. Our study showed that vaccinated patients had a higher overall cumulative recovery rate compared to their non-vaccinated counterparts across all symptoms, suggesting that vaccination can boost the resolution of neurological long COVID symptoms, which, as demonstrated in this work, occurs independently in most patients, albeit at different times. However, the statistical reliability of this finding is hampered by the small sample size of non-vaccinated patients included in this study, and therefore no firm conclusions can be drawn. The mechanisms by which vaccination can accelerate symptom recovery are not yet known and have only been hypothesized [20, 25, 26]. If it is true that some of the

long COVID symptoms may be associated with the persistence of a virus reservoir in the body, then it is possible that such viral residues may be eliminated following vaccination [25], and that vaccine administration may also interfere with the molecular mimicry mechanisms underlying long COVID manifestations with autoimmune genesis [26].

In conclusion, in this study, we again observed the presence of the two subtypes of neurological long COVID described in our previous work [1]. This categorization remained stable even when assessing symptom presence at fixed individual time points (only at 6, 12, or 18 months). Longitudinal follow-up of our patients demonstrated that neurological long COVID symptoms tended to improve after a certain interval of time, while only one symptom, that of sleep disturbance, disappeared during follow-up. In addition, vaccination appeared to change the trajectory of neurological long COVID symptoms, accelerating the resolution of some of these. These observations taken together allow us to hypothesize that most patients may go on to have complete resolution of symptoms and that neurological long COVID is not so long. The principal limitation of this work relates to the small sample size, especially regarding the vaccinated versus unvaccinated comparison, which allowed us to identify a trend of symptom improvement in vaccinated patients but this did not reach statistical significance.

AUTHOR CONTRIBUTIONS

Stefano Giuseppe Grisanti: Conceptualization; writing – original draft; writing – review and editing; investigation. **Sara Garbarino:** Conceptualization; data curation; methodology; writing – original draft; writing – review and editing; funding acquisition; formal analysis. **Margherita Bellucci:** Investigation; data curation; funding acquisition. **Cristina Schenone:** Investigation; funding acquisition; data curation. **Valentina Candiani:** Data curation; formal analysis; funding acquisition. **Simmaco Di Lillo:** Data curation; formal analysis. **Cristina Campi:** Data curation; formal analysis; funding acquisition. **Emanuela Barisione:** Investigation. **Teresita Aloe:** Investigation. **Elena Tagliabue:** Investigation. **Alberto Serventi:** Investigation. **Giampaola Pesce:** Investigation. **Sara Massucco:** Investigation. **Corrado Cabona:** Investigation. **Anastasia Lechiara:** Investigation. **Antonio Uccelli:** Investigation. **Angelo Schenone:** Investigation; funding acquisition. **Michele Piana:** Conceptualization; methodology; writing – review and editing; supervision; funding acquisition. **Luana Benedetti:** Conceptualization; methodology; writing – review and editing; project administration; supervision; funding acquisition.

FUNDING INFORMATION

This work was supported by: NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)—A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022) for the activities related to data collection, and the formulation of the study's rationale (Luana Benedetti, Cristina Schenone, Margherita Bellucci, Angelo Schenone, and Michele Piana). NGEU and funded by the MUR, NRRP, project RAISE (ECS00000035)—Robotics and AI for Socio-economic Empowerment (DN. 1053 del 23.06.2022)—for the activity related to data analysis (Valentina Candiani and Cristina Campi). The Italian Ministry of Health, grant number NET-2018-12,366,666 (NeuroArtP3) for the activity related to the interpretation of data analysis results (Sara Garbarino).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the ethics committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients involved in this study gave their informed consent prior to their inclusion in the study.

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How to cite this article: Grisanti SG, Garbarino S, Bellucci M, et al. Neurological long COVID in the outpatient clinic: Is it so long? *Eur J Neurol*. 2025;32:e16510. doi:10.1111/ene.16510