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LETTER TO THE EDITORS

Long-term neurological symptoms after acute COVID-19 illness requiring hospitalization in adult patients: insights from the ISARIC-COVID-19 follow-up study

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Dear Editor,

Coronavirus disease-2019 (COVID-19) has devastated healthcare systems and public health globally [1]. Many patients develop a wide spectrum of persisting or new symptoms 3 months after the acute COVID-19 illness (long-COVID-19), and these symptoms can persist for at least 2 months [2, 3]. There is significant variability in the definitions with the lack of standardization and hence the reported frequency of long-COVID-19 also varies.

Furthermore, there is sparser data with a significant heterogeneity on neurological long-COVID-19 symptoms [4].

Neurological manifestations represent a possible presentation of long-COVID-19 [5–7]. Data on the type of symptoms and prevalence of neurological long-COVID-19 are still in evolution [1, 5]. Hence, a clear understanding of neurological long-COVID-19 would aid healthcare systems in implementing health resources to measure and manage this global healthcare burden.

Herein, in this study we aimed to characterize the type and prevalence of neurological symptoms related to neurological long-COVID-19 from a large international multicenter cohort of adults after discharge from hospital for acute COVID-19.

This is an international, multicenter, prospective, observational cohort using the ISARIC WHO COVID-19 Clinical Characterization Protocol, approved by the WHO Ethics Committee (RPC571 and RPC572).

Local Ethics approval was obtained from participating centers according to local regulatory rules as appropriate.

Inclusion criteria were*:* patients ≥ 18 years-old; patients previously admitted to hospital with COVID-19; follow-up data available at least 1-month post- discharge from hospital or health center; person (or family member/next of kin for patients who lack capacity) consent to participate.

The case report form (CRF) was completed as a patient self-assessment through an online link, telephone

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interview, or in-clinic. Data were collected as first presentation of symptoms and persistent presentation. First presentation described participants who did not have neurological symptoms at hospitalization. Persistent presentation is persistence of symptoms among those who had neurological symptoms evaluated at initial hospitalization. Survey follow-up was defined as three monthly intervals from post-discharge follow-up, up to 12 months. Six main neurological symptoms were collected during hospitalization and follow-up. Additional neurological symptoms were collected at follow-up only. Specifics of survey schematic overview of the follow-up data time frame are reported in *Supplementary Material (SM) Item S1*. Follow-up asking for new or persistent neurological symptoms has been performed by phone call or in-person interview at each time point: 1–3 months, 4–6 months, 7–9 months, and 10–12 months.

Main neurological symptoms included confusion, anosmia, ageusia, fatigue/malaise, muscle aches/joint pain, and seizures. Additional neurological symptoms included dizziness, erectile dysfunction, fainting/ blackouts, headache, loss of sensation, muscle weakness, paresthesia, problems seeing, problems speaking or communicating, problems swallowing or chewing, problems with balance, tinnitus, and tremors.

Observed prevalence of neurological symptoms were estimated based on survey follow-up time, age at disease onset and sex. Unadjusted symptom prevalence by survey follow-up period was summarized as percentages with 95% confidence intervals (CIs), assuming a Gamma distribution. Symptom prevalence estimates were stratified by initial versus repeat follow-up assessment. Period prevalence by follow-up was also calculated. Symptom prevalence by age and sex was examined by logistic regression. Regression models with neurological symptoms as an outcome included fixed effects for sex and age, and their interaction, nested within the survey follow-up period. Age was modelled by polynomial terms up to order of 3. Analyses were completed in R using the lmerTest package.

Overall, 11,357 adults (median age = 56 (IQR = 45 to 67) years; 42% female) with acute COVID-19 hospitalization from January 2020 to December 2022 were analyzed (*SM Item S2*). Frequencies are stratified by the availability of neurological signs and symptoms evaluated at disease onset/hospital admission as shown in *SM Item S3*. Baseline characteristics are presented in *SM Item S4*.

Fatigue/malaise was the most frequent neurological manifestation reported at acute hospitalization with 54.9% (95%CI 53.6–56.2%), followed by muscle aches/joint pain 35.8% (95%CI 34.5–37.0%), ageusia 20.7% (95%CI 19.6–21.8%), anosmia 18.3% (95%CI 17.2–19.3%), confusion 7.9% (95%CI 7.1–8.7%), and seizures 0.9% (95%CI 0.5–1.2%).

More than half (55.3%) of participants had one or more neurological symptoms during their hospitalization. At follow-up, first presentation of symptoms was found in 40.6% (95%CI = 38.0–43.4%) at 1–3 months, 39.1% (95%CI = 36.5–41.9%) at 4–6 months, 23.1% (95%CI = 19.0–27.8%) at 7–9 months, and 4.4% (95%CI = 2.4–7.4%) at 10–12 months had 1 or more neurological symptoms. Persistent presentation of symptoms was found in 53.3% (95%CI = 50.6–56.1%) at 1–3 months, 58.4% (95%CI = 56.0–60.9%) at 4–6 months, 55.4% (95%CI = 52.1–58.8%) at 7–9 months, and 40.4% (95%CI = 37.3–42.8%) at 10–12 months had 1 or more neurological symptoms.

At 1–3 months, estimates of first presentation of symptoms were: fatigue/malaise 51.8% (95%CI = 48.0–55.9%), muscle aches/joint pain 18.6% (95%CI = 16.9–20.4%), ageusia 5.2% (95%CI = 4.1–6.4%), anosmia 4.1% (95%CI = 3.1–5.2%), and confusion 10.9% (95%CI = 9.6–12.4%). Estimates of persistent presentation of symptoms were: fatigue/malaise 41.9% (95%CI = 39.4–44.5%), muscle aches/joint pain 27.6% (95%CI = 25.6–29.7%), ageusia 7.9% (95%CI = 6.8–9.2%), anosmia 7.7% (95%CI = 6.6–8.9%), and confusion 19.4% (95%CI = 17.2–21.7%).

At 4–6 months, estimates for first presentation of symptoms were: fatigue/malaise 50.8% (95%CI = 46.9–54.9%), muscle aches/joint pain 19.4% (95%CI = 17.6–21.3%), ageusia 3.5% (95%CI = 2.6–4.7%), anosmia 4.4% (95%CI = 3.3–5.6%), and confusion 11.5% (95%CI = 10.1–13.1%). Estimates of persistent presentation of symptoms were: fatigue/malaise 44.3% (95%CI = 42.2–46.5%), muscle aches/ joint pain 34.2% (95%CI = 32.3–36.1%), ageusia 6.7% (95%CI = 5.9–7.6%), anosmia 6.9% (95%CI = 6.1–7.8%), and confusion 29.4% (95%CI = 27.3–31.6%).

At 7–9 months, estimates of first presentation of symptoms were: fatigue/malaise 26.1% (95%CI = 20.5–32.8%), muscle aches/joint pain 20.5% (95%CI = 16.9–24.7%), ageusia 3.9% (95%CI = 2.1–6.6%), anosmia 4.1% (95%CI = 2.3–6.9%), and confusion 9.4% (95%CI = 7.0–12.5%). Estimates of persistent presentation of symptoms were: fatigue/malaise 43.6% (95%CI = 40.6–46.7%), muscle aches/joint pain 30.1% (95%CI = 27.6–32.7%), ageusia 6.2% (95%CI = 5.1–7.5%), anosmia 7.1% (95%CI = 5.9–8.4%), and confusion 26.6% (95%CI = 23.9–29.5%).

At 10–12 months, estimates of the first presentation of symptoms were: fatigue/malaise 3.1% (95%CI = 1.4–5.8%), muscle aches/joint pain 2.5% (95%CI = 1.1–4.9%), ageusia and anosmia 0.0%, and confusion in 2.2% (95%CI = 0.9–4.5%). Estimates of persistent presentation of symptoms were: fatigue/malaise 29.9% (95%CI = 27.6–32.4%), muscle aches/joint pain 23.1% (95%CI = 21.0–25.2%), ageusia 3.3% (95%CI = 2.6–4.2%),

anosmia 3.9% (95%CI = 3.1–4.9%), and confusion 16.9% (95%CI = 15.2–18.8%).

Table 1 shows estimates of first and persistent presentation of symptoms. *SM Item S5* shows period prevalence of neurological symptoms post-hospital discharge. Additional symptoms assessed by survey only, not evaluated at acute hospitalization, are shown in *SM Item S6*. Missing data points were excluded from the analysis of each symptom. Trajectories of prevalence of neurological symptoms post-hospital discharge between males and females are shown in Fig. 1. *SM Item S7* shows trajectories of prevalence of neurological symptoms post-acute onset of COVID-19 between males and females.

The main findings of this international, multicenter, observational follow-up study are that (1) all symptoms declined over follow-up time, except confusion and insomnia; (2) among symptoms not evaluated during acute hospitalization, estimates of muscle weakness, headache, problems with balance, paresthesia, problems speaking/communicating, dizziness, problems seeing, tremor, tinnitus, fainting, and problems swallowing/chewing gradually declined from 1–3 months to 10–12 months follow-up, whereas estimates of loss of sensation, erectile dysfunction, and problems sleeping gradually increased over time.

To the best of our knowledge, this is one of the largest cohorts (11,357 subjects) reporting post-COVID-19 neurological symptoms investigating.

It is noteworthy that the median age of our cohort was 56 years (IQR = 45 to 67), suggesting that most of them were actively working before acute COVID-19. This has been previously highlighted in another cohort, with many patients having difficulty returning to work and previous activities, with significant socio-economic consequences as documented previously how long-COVID-19 impacted employment and working full-time [6].

Long-term and cognitive symptoms have been previously reported in COVID-19 subjects [5]. Previous large investigations reported that around 10% of subjects diagnosed with acute COVID-19 still had symptoms after 1-year of follow-up [7]. In our cohort, fatigue/malaise, followed by muscle aches/joint pain were the most frequent neurological symptoms reported at the time of acute illness, with a trend toward decreasing frequency at each follow-up, suggesting gradual recovery of functional activities and progressive rehabilitation [8].

Interestingly, we noted a different recovery between symptoms of the central and peripheral nervous systems. Anosmia and ageusia (peripheral) disappeared completely, whereas confusion and insomnia (central) persisted. The occurrence of anosmia and ageusia is supposed to be caused by a local inflammatory response to SARS-CoV-2 infection targeting peripheral neurons. On the other hand, several systemic factors have been identified as possible responsible for central nervous system symptoms, some of them difficult to recover, including hypoxia, cerebrovascular illness, immune response, medical resources and treatments, social isolation, psychological repercussions of the pandemic, and the worry of spreading the sickness [9].

Many COVID-19 survivors were bed bound with persistent disconnection from their environment during their acute illness/hospital admission. Contributors of this status included prolonged use of sedatives and delirium during hospitalization. This may explain why we observed a trend toward increased estimates of erectile dysfunction, loss of sensation, and problems sleeping. Other common explanations for persistent neurological symptoms include residual tissue damage, viral persistence, and chronic inflammation [10], but also increasing age in patients with an underlying disease [11].

The major strength of this study is the description of the prognosis of the disease with inclusion of many subjects across 16 countries, highly representative of the general population, up to 12 months following hospital discharge [6]. Nevertheless, it is worth noting that only 22 patients were from the Americas, thus consideration of our findings in this population should be careful. Inconsistent data capture (sampling bias) and lack of rigorous definitions are a limitation. Indeed, a protocol for 12-months follow-up was not systematically implemented in all participating centers, and the data captured is rather driven by current clinical practice in each site. However, we use a large cohort with pragmatic data capturing across multiple countries that represents real-world reported observations. Lack of comparison group is a further limitation of this study. Moreover, a cluster analysis early on in our study was deemed infeasible based on the complex patterns of missing data observed (e.g., non-response to selected symptoms at initial hospitalization and/or survey follow-up; loss to follow-up). Finally, our results are based on the analysis of individual symptom prevalence. A more in-depth approach to analysis would be to instead consider patterns in co-occurring symptoms over time, for example, by cluster analysis. Given complexities in the data arising from differences in individual follow-up time and loss to follow-up, this option could not be explored. The application of clustering algorithms should be considered by future studies pending data availability.

Long-COVID-19 symptoms are common and persist over time. Registry activities and rehabilitation protocols should be implemented to define the burden of long-COVID-19 globally with standardized definitions and data capture instruments and ensure adequacy of resource distribution.

Table 1 Observed prevalence and persistence of neurological symptoms over survey follow-up post hospital discharge

Symptom*	Hospitalization	1 – 3 months		4 – 6 months		7 – 9 months		10 – 12 months	
	First presentation of symptom	First presentation of symptom	Repeat presentation of symptom	First presentation of symptom	Repeat presentation of symptom	First presentation of symptom	Repeat presentation of symptom	First presentation of symptom	Repeat presentation of symptom
Confusion	7.9% (7.1% to 8.7%) 331/4190	10.9% (9.6% to 12.4%) 242/2217	19.4% (17.2% to 21.7%) 289/1493	11.5% (10.1% to 13.1%) 242/2103	29.4% (27.3% to 31.6%) 761/2589	9.4% (7.0% to 12.5%) 49/520	26.6% (23.9% to 29.5%) 351/1319	2.2% (0.9% to 4.5%) 7/323	16.9% (15.2% to 18.8%) 342/2022
Fatigue/malaise	54.9% (53.6% to 56.2%) 3172/5781	51.8% (48.0% to 55.9%) 687/1325	41.9% (39.4% to 44.5%) 1040/2483	50.8% (46.9% to 54.9%) 629/1239	44.3% (42.2% to 46.5%) 1641/3702	26.1% (20.5% to 32.8%) 74/283	43.6% (40.6% to 46.7%) 794/1822	3.1% (1.4% to 5.8%) 9/295	29.9% (27.6% to 32.4%) 618/2067
Anosmia	18.3% (17.2% to 19.3%) 964/5280	4.1% (3.1% to 5.2%) 64/1574	7.7% (6.6% to 8.9%) 173/2252	4.4% (3.3% to 5.6%) 61/1397	6.9% (6.1% to 7.8%) 245/3544	4.1% (2.3% to 6.9%) 14/339	7.1% (5.9% to 8.4%) 124/1756	0.0% (–) 0/305	3.9% (3.1% to 4.9%) 81/2058
Ageusia	20.7% (19.6% to 21.8%) 1092/5271	5.2% (4.1% to 6.4%) 81/1568	7.9% (6.8% to 9.2%) 178/2252	3.5% (2.6% to 4.7%) 50/1409	6.7% (5.9% to 7.6%) 237/3531	3.9% (2.1% to 6.6%) 13/336	6.2% (5.1% to 7.5%) 109/1756	0.0% (–) 0/305	3.3% (2.6% to 4.2%) 68/2053
Muscle aches/ joint pain	35.8% (34.5% to 37.0%) 2060/5761	18.6% (16.9% to 20.4%) 439/2366	27.6% (25.6% to 29.7%) 697/2525	19.4% (17.6% to 21.3%) 426/2197	34.2% (32.3% to 36.1%) 1272/3720	20.5% (16.9% to 24.7%) 110/536	30.1% (27.6% to 32.7%) 544/1809	2.5% (1.1% to 4.9%) 8/322	23.1% (21.0% to 25.2%) 476/2063
1 or more neurological symptoms	67.5% (66.4% to 68.7%) 4231/6264	40.6% (38.0% to 43.4%) 897/2207	53.3% (50.6% to 56.1%) 1483/2783	39.1% (36.5% to 41.9%) 809/2067	58.4% (56.0% to 60.9%) 2284/3910	23.1% (19.0% to 27.8%) 112/485	55.4% (52.1% to 58.8%) 1045/1887	4.4% (2.4% to 7.4%) 14/318	40.0% (37.3% to 42.8%) 830/2075

Follow-up defined in months post hospital discharge. Data are reported as observed prevalence and 95% confidence intervals, assuming a Gamma distribution. (–): confidence interval not defined due to no cases reported. First assessment of symptoms was defined as the first time a patient completed a follow-up survey. Follow-up assessment of symptoms was defined as a patient who already completed their first survey and are being surveyed again. Estimates are stratified by first versus repeat symptom assessment to examine symptom persistence following hospital discharge. Observed prevalence at acute hospitalization is also presented

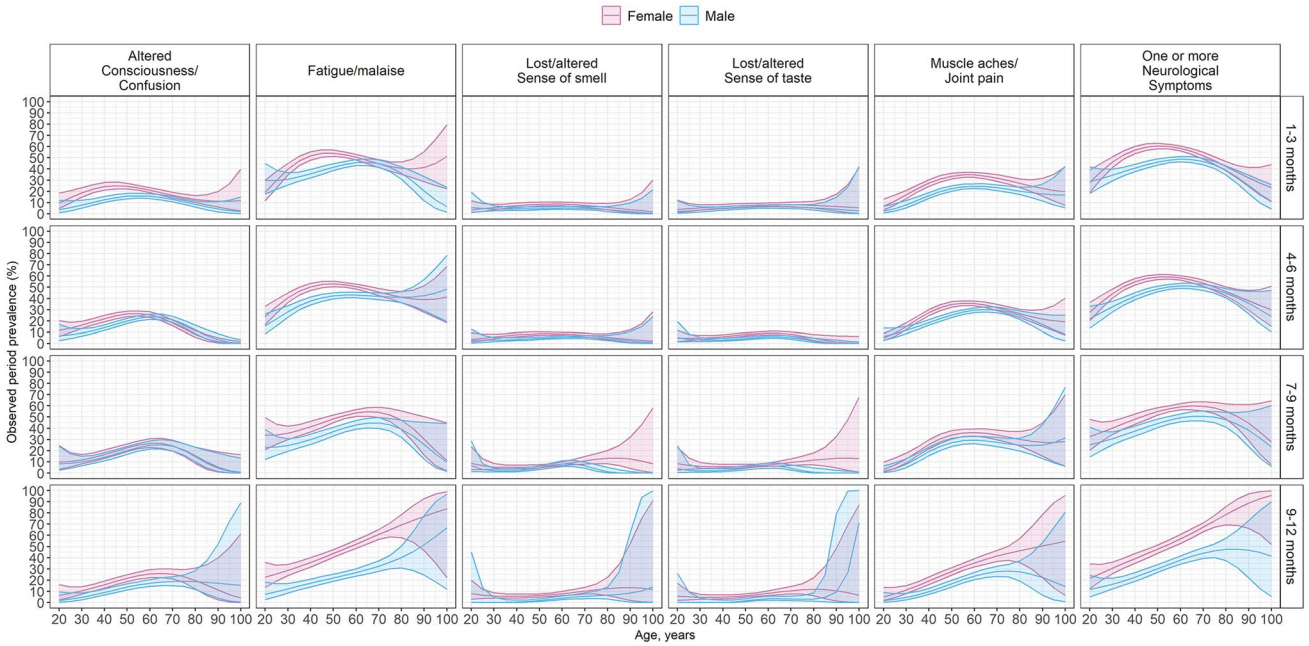

Fig. 1 Observed prevalence by age and sex, months following hospital discharge. Observed prevalence of common neurological symptoms by age at hospitalization*, sex, and survey follow-up time. Follow-up time is defined in months since hospital discharge. Seizures excluded due to insufficient cases reported. Estimates presented are from a logistic regression model fitted to each symptom as the dependent variable, with fixed effects for sex (categorical), age (continuous) and their interaction. Age was modelled using polynomial terms up to order 3

Availability of data and material:

The data that underpin this analysis are highly detailed clinical data on individuals hospitalized with COVID-19. Due to the sensitive nature of these data and the associated privacy concerns, they are available via a governed data access mechanism following review of a data access committee. Data can be requested via the IDDO COVID-19 Data Sharing Platform (http://www.iddo.org/covid-19). The Data Access Application, Terms of Access and details of the Data Access Committee are available on the website. Briefly, the requirements for access are a request from a qualified researcher working with a legal entity who have a health and/or research remit; a scientifically valid reason for data access which adheres to appropriate ethical principles. The full terms are at https://www.iddo.org/document/covid-19-data-access-guidelines. A small subset of sites who contributed data to this analysis have not agreed to pooled data sharing as above. In the case of requiring access to these data, please contact the corresponding author in the first instance who will look to facilitate access.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-12133-y.

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Declarations

Conflicts of interest None.

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