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LETTER TO THE EDITORS

# Exploring trajectory recovery curves of post-COVID cognitive symptoms in previously hospitalized COVID-19 survivors: the LONG-COVID-EXP-CM multicenter study

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## Dear Sirs,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, responsible of causing coronavirus disease 2019 (COVID-19), primary affects the respiratory system; however, neurological symptoms (e.g., ageusia, anosmia, headache) and also other severe complication are commonly experienced at the acute phase [1, 2]. Neurological symptoms presented at the acute COVID-19 phase such as headache [3] or anosmia [4] are likely present at a post-COVID phase; however, other neurological symptoms, e.g., cognitive disorders, are "de novo" developed in up to 22% of COVID-19 survivors [5]. A recent meta-analysis reported prevalence rates of 32%, 27% and 22% for post-COVID brain fog, memory loss, and attention/concentration problems the six months after respectively [6]. However, the presence of post-COVID cognitive symptoms are questioned by others [7].

Interestingly, the recent definition of post-COVID includes cognitive dysfunction as one of the most common symptoms, after fatigue or dyspnoea [8]. The presence of post-COVID symptoms is overall associated with worse quality of life [9]. In fact, the presence of post-COVID cognitive symptoms represents a challenge for affected individuals since these symptoms affect daily life [10]. Although the presence of post-COVID cognitive symptoms is associated with nervous system changes [11], it seems that these symptoms generally improve over time [12]. However, most studies investigating these symptoms have used cross-sectional designs. Therefore, understanding the longitudinal pattern of post-COVID cognitive symptoms may have significant implications in diagnosis, triaging, and management of post-COVID individuals.

This letter to the editor presents the trajectory recovery curves of post-COVID cognitive symptoms using an exponentially fitted bar plot model of the longitudinal evolution of the symptoms in previously hospitalized COVID-19 survivors. We also illustrate the relationships of the cognitive symptoms by means of mosaic plots.

## Methods

The LONG-COVID-EXP-CM is a multicenter cohort study including COVID-19 survivors hospitalized during the first wave of the pandemic (from March 10 to May 31, 2020) in five urban hospitals of Madrid (Spain). All individuals were diagnosed of SARS-CoV-2 infection by oral/nasal RT-PCR technique and radiological findings at hospital admission. From all hospitalized patients during that period, a sample of 400 individuals from each hospital was randomly selected by Excel® software. The Ethics Committees of all hospitals approved the study design (HUFA 20/126, HCSC20/495E, HUIL/092-20, HSO25112020, HUF/EC1517). Informed consent was obtained from all the participants before collecting any data for the study.

Patients were scheduled for a telephone interview conducted by trained healthcare professionals at two follow-ups

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with a 5-month period in between. Participants were asked for self-reporting the presence of cognitive symptoms such as brain fog (defined as a self-perception of sluggish or fuzzy thinking), memory loss (defined as self-perception of unusual forgetfulness), and general concentration loss. Participants were specifically asked for those cognitive symptoms that they perceived starting after hospital discharge. Additionally, demographic data (i.e., age, gender, height, weight), pre-existing medical co-morbidities, and hospitalization data (e.g., symptoms at hospital admission, days at the hospital, intensive care unit [ICU] admission) were collected from medical records and adjusted in the analyses.

Python's library statsmodels 0.11.1 was used for producing the mosaic plots, while exponential bar plots were custom-made using Matplotlib 3.3.4. The exponential curves were fitted to the data according to the formula $y = Ke^{ct}$, where $y$ represents the modeled prevalence of any symptom (brain fog, memory loss, or concentration loss) at time $t$ (in months), and $K$ and $c$ are the parameters of the model. In addition, as a secondary aim, we compared demographic, clinical and hospitalization data between patients developing new-onset post-COVID cognitive symptoms at T1 and those individuals developing new-onset cognitive symptoms at T2 (delayed-onset post-COVID cognitive impairments) using chi-squared or one-way-ANOVA tests as needed.

## Results

From a total of 2,000 randomly selected patients from the five hospitals considered in the study, a total of 1,593 (mean age: 61.5, SD: 16 years, 46.5% women) were assessed at hospital admission (T0) and at T1 (mean: 8.4, range 6–10 months) and T2 (mean: 13.2, range 11–15 months) follow-up periods after hospital discharge (Table 1). The mosaic plots revealed that the prevalence of brain fog, memory loss or concentration loss decreased at T2 when compared with T1, from 9 to 5.3%, 16.1–12.5% and from 6.8 to 4.3%, respectively (Fig. 1). An important finding identified in the mosaic plots was that some patients self-reported the development of brain fog ($n = 43$, 2.7%), memory loss ($n = 101$, 6.3%), or concentration loss ($n = 39$, 2.453%) at T2 without experiencing these symptoms at T1 (Fig. 1). Table 2 reveals that no significant differences were seen

**Table 1** Demographic and hospitalization data of the sample ($n = 1593$)

| | |
|---|---|
| Age, mean (SD), years | 61.5 (16) |
| Gender, male/female (%) | 854 (53.5%) / 739 (46.5%) |
| Weight, mean (SD), kg | 74.5 (15) |
| Height, mean (SD), cm | 165 (17) |
| Pre-existing medical co-morbidities | |
| Hypertension | 415 (26.05%) |
| Diabetes | 204 (12.8%) |
| Chronic heart disease—cardiovascular disease | 188 (11.8%) |
| Asthma | 97 (6.1%) |
| Obesity | 65 (4.1%) |
| Chronic obstructive pulmonary disease | 63 (3.95%) |
| Rheumatological disease | 24 (1.5%) |
| Other (cancer, kidney disease) | 271 (17.0%) |
| Number of onset symptoms at hospital admission | 2.2 (0.8) |
| Main symptoms at hospital admission, *n* (%) | |
| Fever | 1193 (74.8%) |
| Dyspnoea | 484 (30.4%) |
| Myalgia | 483 (30.3%) |
| Cough | 443 (27.8%) |
| Headache | 266 (16.7%) |
| Vomiting | 172 (10.8%) |
| Anosmia | 130 (8.1%) |
| Ageusia | 114 (7.1%) |
| Dizziness | 55 (3.4%) |
| Stay at the hospital, mean (SD), days | 11 (10.5) |
| Intensive care unit (ICU) admission | |
| Yes/no, *n* (%) | 95 (5.9%)/1498 (94.1%) |
| Stay at ICU, mean (SD), days | 12 (11) |

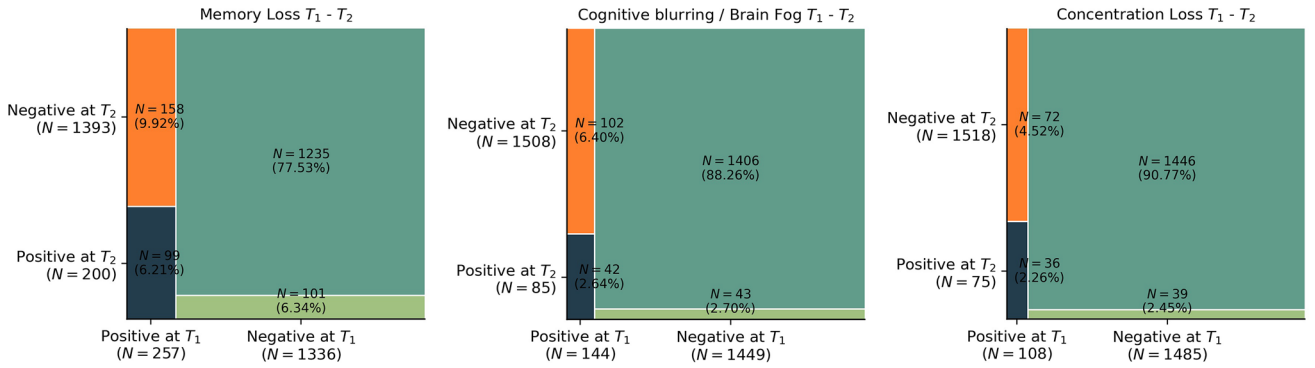


**Fig. 1** Mosaic plots of self-reported memory loss, brain fog, and concentration loss (from left to right): T1 (8.4 months after hospital discharge) vs T2 (13.2 months after hospital discharge)

**Table 2** Clinical and hospitalization data in patients developing post-COVID cognitive symptoms at T1 or T2 follow-up periods

| | Memory loss (T1, $N$ = 99) | Memory loss (T2, $n$ = 101) | Brain fog (T1, $n$ = 42) | Brain fog (T2, $n$ = 43) | Concentration loss (T1, $n$ = 36) | Concentration loss (T2, $n$ = 39) |
|---|---|---|---|---|---|---|
| Age (years), mean ± SD | 66.5 ± 14.0 | 62.5 ± 14.0 | 55.0 ± 16.0 | 62.5 ± 14.5 | 67.0 ± 16.0 | 63.0 ± 12.5 |
| Weight (kg), mean ± SD | 74.2 ± 13.7 | 73.6 ± 14.5 | 74.0 ± 11.5 | 73.6 ± 13.7 | 75.1 ± 16.9 | 80.0 ± 23.2 |
| Height (cm), mean ± SD | 165.0 ± 10.5 | 164.0 ± 9.5 | 162.0 ± 7.0 | 163.5 ± 9.7 | 166.0 ± 12.0 | 167.0 ± 12.0 |
| Female, *n* (%) | 52 (52.5%) | 55 (54.5%) | 26 (61.9%) | 23 (53.5%) | 21 (58.3%) | 22 (56.5%) |
| Medical co-morbidities | | | | | | |
| Hypertension, *n* (%) | 33 (33.3%) | 32 (31.7%) | 6 (14.3%) | 14 (32.5%) | 15 (41.7%) | 11 (28.2%) |
| Diabetes, *n* (%) | 21 (21.1%) | 11 (10.9%) | 5 (11.9%) | 7 (16.3%) | 10 (27.8%) | 5 (12.8%) |
| Cardiovascular disease | 21 (21.1%) | 11 (10.9%) | 2 (4.75%) | 4 (9.3%) | 8 (22.2%) | 6 (15.4%) |
| Asthma, *n* (%) | 11 (11.1%) | 6 (5.95%) | 5 (11.9%) | 3 (7%) | 4 (11.1%) | 4 (10.26%) |
| Obesity, *n* (%) | 3 (3.0%) | 6 (5.95%) | 6 (14.3%) | 0 (0%) | 3 (8.3%) | 6 (15.4%) |
| COPD, *n* (%) | 5 (5.05%) | 5 (4.95%) | 1 (2.4%) | 1 (2.3%) | 3 (8.3%) | 3 (7.7%) |
| Rheumatological disease | 2 (2%) | 2 (2%) | 1 (2.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Other, *n* (%) | 26 (26.25%) | 17 (16.85%) | 5 (11.9%) | 6 (13.95%) | 12 (33.3%) | 7 (17.95%) |
| Number of onset symptoms at hospital admission | 2.3 ± 0.75 | 2.35 ± 0.8 | 2.2 ± 0.8 | 2.5 ± 0.6 | 2.1 ± 1.0 | 2.4 ± 0.9 |
| Symptoms at hospitalization | | | | | | |
| Fever, *n* (%) | 71 (71.7%) | 75 (74.25%) | 30 (71.4%) | 32 (74.5%) | 24 (66.7%) | 25 (64.1%) |
| Dyspnoea, *n* (%) | 36 (36.35%) | 29 (28.7%) | 10 (23.8%) | 18 (41.9%) | 15 (41.7%) | 14 (35.9%) |
| Myalgia, *n* (%) | 30 (30.3%) | 30 (29.7%) | 12 (28.6%) | 17 (39.5%) | 14 (38.9%) | 13 (33.3%) |
| Cough, *n* (%) | 23 (23.25%) | 28 (27.7%) | 12 (28.6%) | 6 (14%) | 9 (25%) | 7 (17.95%) |
| Headache, *n* (%) | 21 (21.1%) | 23 (22.8%) | 4 (9.5%) | 11 (25.6%) | 4 (11.1%) | 8 (20.5%) |
| Vomiting, n (%) | 3 (3%) | 3 (3%) | 2 (4.8%) | 1 (2.3%) | 0 (0%) | 2 (5.1%) |
| Anosmia, *n* (%) | 11 (11.1%) | 10 (9.9%) | 4 (9.5%) | 6 (13.95%) | 3 (8.3%) | 9 (23.1%) |
| Ageusia, *n* (%) | 9 (9.1%) | 11 (10.9%) | 1 (2.4%) | 3 (7%) | 1 (2.8%) | 3 (7.7%) |
| Dizziness, *n* (%) | 7 (7.1%) | 5 (4.95%) | 3 (7.15%) | 2 (4.65%) | 1 (2.8%) | 4 (10.25%) |
| Days at hospital, mean ± SD | 9.8 ± 9.65 | 12.5 ± 11.2 | 8.0 ± 7.5 | 10.3 ± 12.95 | 10.5 ± 8.6 | 12.4 ± 10.9 |
| ICU admission, *n* (%) | 4 (4.05%) | 5 (4.95%) | 1 (2.4%) | 3 (7%) | 0 (0%) | 3 (7.7%) |

between patients developing new-onset post-COVID cognitive symptoms at T1 and those developing new-onset cognitive symptoms at T2 (delayed-onset post-COVID cognitive impairments).

Figure 2 plots the fitted exponential curve showing a trend of decreasing prevalence of post-COVID symptoms. In Fig. 2, vertical bars represent the percentage of patients that self-report memory loss (navy blue), brain fog (orange)

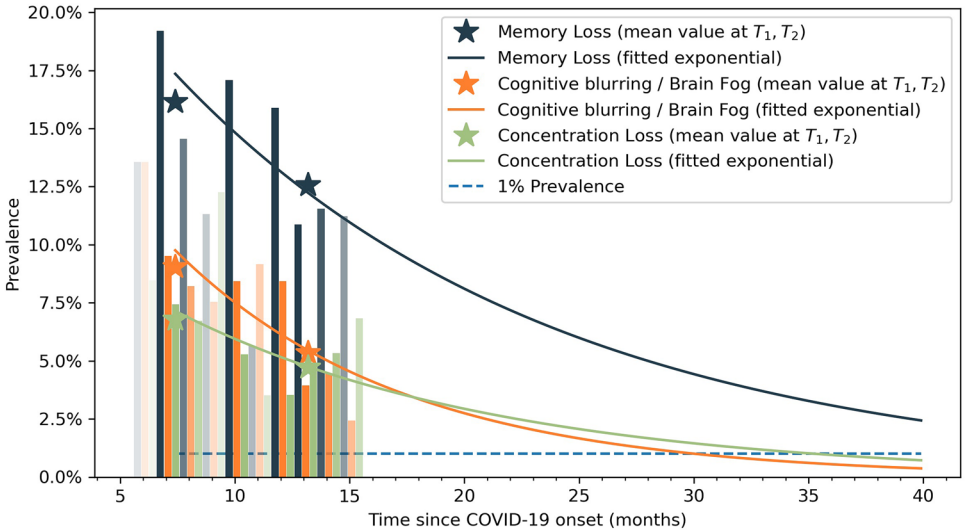


**Fig. 2** Recovery curve of self-reported memory loss (in navy blue), brain fog (in orange) or concentration loss (in light green) symptoms. Opacity indicates the sample size at that follow-up time. Asterisks represent the mean values employed at T1 and T2 follow-up periods

or concentration loss (light green) at any given time (opacity approximately indicates the sample size for that time). The mean values used for the development of the mosaic plots are marked with asterisks in the graphs.

## Discussion

To the best of the authors' knowledge, this is the first analysis of the trajectory curve of recovery of post-COVID cognitive symptoms in previously hospitalized COVID-19 survivors. The mosaic plots revealed that most patients developed "de novo" post-COVID cognitive symptoms. In fact, although the prevalence of post-COVID cognitive symptoms was considerable, a higher number of patients tended to recover than those that developed them "de novo", explaining the decreasing prevalence trend. Nevertheless, the trajectory curves were not as pronounced as expected, suggesting that cognitive symptoms will be long-lasting post-COVID symptoms. In fact, the trajectory curve of memory loss was slower than that of brain fog and concentration loss, suggesting that memory loss may be present for longer than three years after the infection thus requiring further attention and treatment.

An interesting result revealed by mosaic plots was that a proportion of COVID-19 survivors not experiencing cognitive symptoms at the first follow-up period presented them at a second and longer follow-up, supporting the hypothesis of a potential delayed-onset post-COVID cognitive symptom development [13]. This finding would support the hypothesis that COVID-19 might trigger a latent neurodegenerative process in this group of patients. We aimed to identify if these individuals developing delayed new-onset post-COVID cognitive symptoms presented difference acute-phase clinical findings than those developing new-onset post-COVID cognitive symptoms at an earlier follow-up, but not significant differences were identified. It is possible that other factors, e.g., differences in neurodegenerative or neuroinflammation biomarkers, could be related to a delayed-onset of post-COVID cognitive symptoms.

Prevalence rates of post-COVID cognitive symptoms observed in our study were lower than those previously reported [5, 6]; however, considering the longer-term follow-up period of the current study, this could be expected according to potential recovery [12]. Several theories including viral encephalitis, neuroinflammation, damage to blood–brain barrier integrity or altered excitability and neurotransmission in the primary motor cortex, could explain the development of post-COVID cognitive symptoms [14, 15]. Considering the long regeneration time of the nervous system neurons, the recovery of post-COVID cognitive symptoms could be longer than one could expect. Hence, identification of risk factors associated with the development of post-COVID cognitive symptoms may help to better understand the evolution and treatment of these symptoms. In fact, there is evidence suggesting that female gender, older age, and ICU admission are factors associated with post-COVID cognitive symptoms [5]. Additionally, this study focused on memory post-COVID cognitive symptoms, however, there is also evidence suggesting that executive function could be also affected in long haulers. We could hypothesize that subgroups of patients with different post-COVID cognitive impairments, i.e., memory vs. executive, could exist. Longitudinal studies investigating the evolution of executive impairments in people with long COVID are needed.

We acknowledge some potential weaknesses in this study. First, only hospitalized patients aged around 60-years old from the first wave were included. Second, we collected self-reported cognitive symptoms. Identification of specific cognitive deficits (memory, sensorineural, spatial) using

quantitative neurological tests should be conducted in future studies. In fact, we cannot rule out that some deficits were present before the infection, although participants were particularly asked for those symptoms starting after hospital discharge. Similarly, we just focused on post-COVID cognitive symptoms. An interaction between cognitive symptoms with other neurological symptoms, e.g., headache, or emotional disorders, e.g., anxiety or depression, might be present. Therefore, studies investigating the interactions between different post-COVID symptoms during the following years are needed.

## Conclusions

The current trend analysis revealed that self-reported post-COVID cognitive symptoms tend to spontaneously recover during the following three years after SARS-CoV-2 infection in previously hospitalized COVID-19 survivors. The trajectory curve of memory loss was slower than that of brain fog and concentration loss, suggesting that this symptom will be present longer than three years after the infection and will require further attention and treatment.

**Author contributions** All authors contributed to the study concept and design. CFdlP, JDMG, and OPV conducted literature review and did the statistical analysis. All authors recruited participants and collected data. OPV supervised the study. All authors contributed to interpretation of data. All authors contributed to drafting the paper. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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**Data availability statement** All data derived from this study are presented in the text.

## Declarations

**Conflicts of interest** No conflict of interest is declared by any of the authors.

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