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Short Communication

# Exploring the trajectory recovery curve of the number of post-COVID Symptoms: The LONG-COVID-EXP-CM Multicenter Study

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ABSTRACT

*Objectives:* This multicenter study investigated the recovery curve of the number of post-COVID-19 symptoms in previously hospitalized patients using an exponential decay model and mosaic plots.
*Methods:* Patients hospitalized during the first wave of the pandemic (from March 10, 2010–May 31, 2020) due to COVID-19 from 5 hospitals in Madrid, Spain were scheduled for 2 telephone interviews at 2 follow-ups with a 5-month period in between and were asked about the presence of post-COVID-19 symptoms. The total number of post-COVID-19 symptoms was monitored. Clinical features, symptoms at hospital admission, and hospitalization data were collected from medical records.
*Results:* A total of 1593 patients who had COVID-19 were assessed 8.4 (T1) and 13.2 (T2) months after hospitalization. The mean number of post-COVID-19 symptoms was 2.6 (SD 2.0) at T1 and 1.5 (SD 1.4) at T2. The trajectory curve showed a decrease in prevalence trend. The analysis also revealed that 985 (61.8%) subjects reported more (T1>T2), 549 (34.5%) equal (T1 = T2), and 59 (3.7%) fewer (T1<T2) post-COVID-19 symptoms in the first tertile (T1: 8.4 months) compared with the second tertile (T2: 13.2 months) assessment.
*Conclusions:* Current trajectory analysis revealed an overall decrease in the tendency in the number of post-COVID-19 symptoms throughout the 2 years after the infection.


## Introduction

Evidence supports that between 35% to 60% of COVID-19 survivors will experience post-COVID-19 symptoms (Fernández-de-las-Peñas et al., 2021). The presence of post-COVID-19 symptoms is associated with worse quality of life (Malik et al., 2022). Almost 90% of studies investigating post-COVID-19 symptoms are cross-sectional (Fernández-de-las-Peñas et al., 2021; Malik et al., 2022). Longitudinal studies assessing symptoms at different follow-up up periods have provided heterogeneous results. Huang et al. (2021) reported a decrease of most post-COVID-19 symptoms, whereas Seeßle et al. (2021 Jul 5) reported a decrease in some post-COVID-19 symptoms but an increase in others. Understanding the longitudinal evolution of post-COVID-19 symptoms could optimize patient care and public health outcomes.

This multicenter study presents 2 approaches analyzing the trajectory recovery curve of the number of post-COVID-19 symptoms: (1) an exponential bar plot model to assess the trajectory curve of post-COVID-19 symptoms; (2) mosaic plots to investigate the patient-to-patient changes in post-COVID-19 symptoms during the first year after hospitalization.

## Methods

The LONG-COVID-EXP-CM is a multicenter cohort study including individuals hospitalized during the first wave of the pandemic (from March 10, 2020–May 31, 2020) in 5 hospitals of Madrid, Spain due to SARS-CoV-2 infection (ICD-10 code) diagnosed using RT-PCR technique and radiological findings. From all patients hospitalized during the first wave, a sample of 400 individuals from each hospital was randomly selected by a computer software. The ethics committees of all involved hospitals approved the study (HCSC20/495E, HSO25112020, HUFA 20/126, HUIL/092-20, HUF/EC1517). Informed consent was obtained from all participants.

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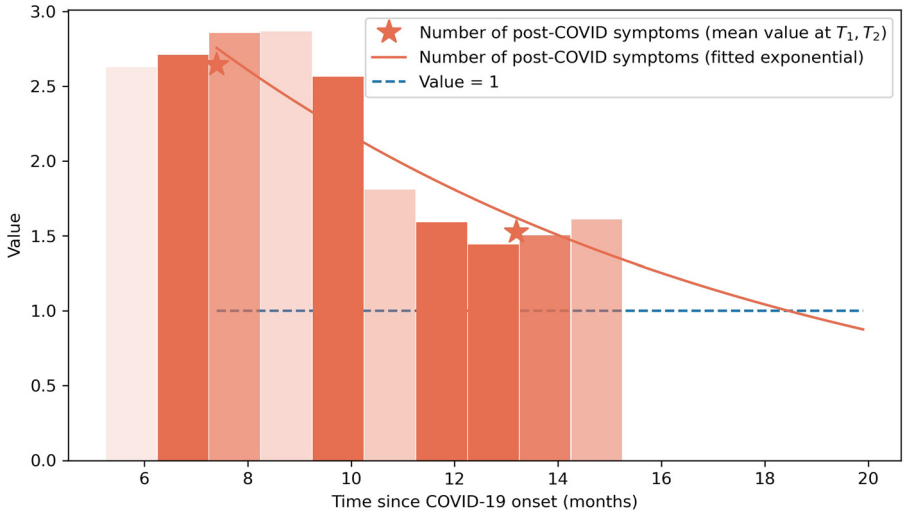


**Figure 1.** Recovery curve of the number of post-COVID-19 symptoms. Opacity indicates the sample size at that follow-up time. Asterisks represent then mean values taken at T1 and T2 follow-up periods.

Patients were scheduled for 2 telephone interviews at 2 follow-up periods with a 5-month period in between. Patients were systematically asked about a list of post-COVID-19 symptoms but were free to report any additional symptom that they experienced. We pooled the total number of post-COVID-19 symptoms. Demographic (age, gender, height, weight), clinical (medical comorbidities), and hospitalization (onset symptoms at hospital admission, days at the hospital, and intensive care unit admission) data were collected from medical records. These variables were adjusted in the analyses.

The exponential curves were fitted to the data according to the formula $y = Ke^{ct}$; where $y$ represents the number of post-COVID-19 symptoms at a time $t$ (in months), and $K$ and $c$ are the parameters of the model. The mosaic plots were created categorizing the number of post-COVID-19 symptoms in individuals with ≥3 post-COVID-19 symptoms.

## Results

From 2000 patients randomly selected to participate, data from 1593 (46.4% women, age: 61 ± 16 years) were collected at hospital admission, at T1 (mean: 8.4, range 6 to 10), and T2 (mean: 13.2, range 11 to 15) months after hospital discharge.

The mean number of post-COVID-19 symptoms was 2.6 ± 2.0 at T1 and 1.5 ± 1.4 at T2 Figure 1. graphs the fitted exponential curve showing a decrease in prevalence trend in the number of post-COVID-19 symptoms. The analysis also revealed that 985 (61.8%) subjects reported more (T1>T2), 549 (34.5%) equal (T1 = T2), and 59 (3.7%) fewer (T1<T2) post-COVID-19 symptoms at T1 compared with T2 assessment.

Figure 2 shows the mosaic plots according to the prevalence of individuals with ≥3 post-COVID-19 symptoms. As it can be seen, 47.8% (763/1,593) patients exhibited ≥3 post-COVID-19 symptoms at T1, whereas just 25.3% (403/1,593) at T2. Only 1 of 5 patients (n = 302, 18.9%) were free of any post-COVID-19 symptom at T1, whereas 32.1% (n = 511) were free of any post-COVID-19 symptom at T2.

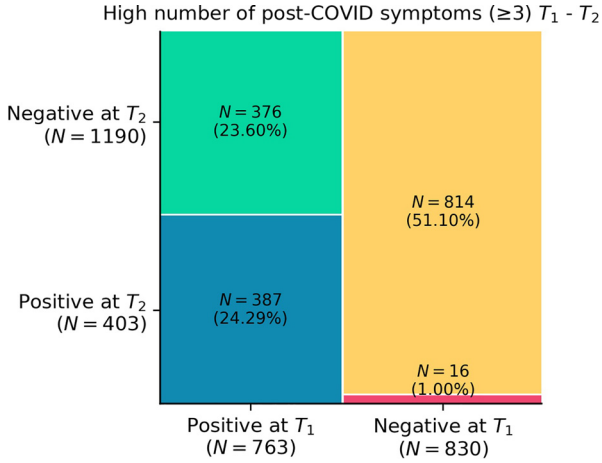


**Figure 2.** Mosaic plot of the number of post-COVID-19 symptoms categorized (≥3 post-COVID-19 symptoms) at T1 (8.4 months after hospital discharge) versus T2 (13.2 months after hospital discharge).

## Discussion

To the best of our knowledge, this is the first study to analyze the trajectory recovery curve of the number of post-COVID-19 symptoms in previously hospitalized COVID-19 survivors. The overall tendency was a decrease in the number of post-COVID-19 symptoms throughout the following 2 years after the infection. The mosaic plots revealed that almost 50% of patients developed ≥3 post-COVID-19 symptoms the months after infection (T1), with a decrease of 50% at 1 year (T2).

There is evidence that long-lasting proinflammatory cytokine and interleukin storms associated with the SARS-CoV-2 virus could lead to an exaggerated immune response by inducing hyperactivation of T cells, macrophages, and natural killer cells (Coomes and Haghbayan, 2020; Mulchandani et al., 2021). This immune response could promote atypical response of the mast cells (Afrin et al., 2020) and an overexpression of the angiotensin-converting enzyme II (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptor at different levels (Shiers et al., 2020), explaining the plethora of post-COVID-19 symptoms. The trajectory curve identified suggests that post-COVID-19 symptoms could be present up to 2 years after infection. Therefore, identifying the risk factors associated with post-COVID-19 symptomatology may help in their management (Fernández-de-las-Peñas et al., 2022 Jan 8).

These results should be considered according to weaknesses of the study. First, only hospitalized patients aged 60 years were included. Second, we pooled the number of post-COVID-19 symp-

toms. The trajectory curve of any particular post-COVID-19 symptom or those grouped by system could be different.

## Consent to participate

Participants provided informed consent before collecting data.

## Consent for publication

No personal info of any patient is provided in the text.

## Role of the Funding Source

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## Author Contributions

Dr Fernández-de-las-Peñas and Dr. Pellicer-Valero had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Dr. Martín-Guerrero. Supervision: Dr. Pellicer-Valero.

## Conflict of Interest

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

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