

Exploring the recovery curve for gastrointestinal symptoms from the acute COVID-19 phase to long-term post-COVID: The LONG-COVID-EXP-CM Multicenter Study

To the editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly affects the respiratory system; however, extrapulmonary (e.g., gastrointestinal or musculoskeletal) symptoms are also experienced during the acute phase.¹ The presence of gastrointestinal symptoms, particularly diarrhea, at onset is associated with hospitalization² and represents an overall risk factor for poor hospitalization outcomes and increased severity.³

These symptoms are also present after the acute phase. Previous studies reported a prevalence of gastrointestinal post-COVID symptoms ranging from 10% to 25%.^{4,5} Most studies investigating post-COVID gastrointestinal symptoms used cross-sectional designs. Since the presence of long-term post-COVID symptoms is associated with lower quality of life,⁶ understanding the longitudinal pattern of gastrointestinal symptoms could have significant implications for diagnosis, triaging, and management of these patients. This Letter to the Editor analyzes the recovery curve of gastrointestinal symptoms using mosaic plots and an exponential bar plot model, showing the evolution of these symptoms from hospital admission to the first year after hospital discharge.

The LONG-COVID-EXP-CM is a multicenter cohort study, including patients with a diagnosis of SARS-CoV-2 by the reverse transcription polymerase chain reaction technique and radiological findings hospitalized during the first wave of the pandemic (from March 10 to May 31, 2020) in five hospitals of Madrid (Spain). A sample of 400 patients from each hospital was randomly selected. The Ethics Committees of all hospitals approved the study (HUFA20/126, HUIL/092-20, HCSC20/495E, HSO25112020, HUF/EC1517). Informed consent was obtained from all participants. Patients were scheduled for a telephone interview conducted by trained healthcare professionals at two follow-up periods with a 5-month period in between. They were systematically asked about gastrointestinal post-COVID symptoms, particularly diarrhea. Clinical (age, gender, height, weight, comorbidities) and hospitalization (onset symptoms at hospital admission, days at hospital, intensive care unit admission) data were collected from hospital records. The exponential curves were fitted to the data according to the formula $y = Ke^{ct}$, where y represents the modeled prevalence of a symptom (diarrhea or gastrointestinal) at time t (in months), and K and c are the parameters of the model.

From 2000 individuals randomly selected and invited to participate, a total of 1593 (age: 61.5, SD: 16 years, 46.5% women) were included at hospital admission (T0), and at 8.4 (range 6–10, T1) and 13.2 (range 11–15, T2) months after discharge. The prevalence of diarrhea decreased from 10.8% ($n = 172$) at hospital admission (T0) to 2.25% ($n = 36$) at T1, to 1% ($n = 16$) at T2 (Figure 1). As shown in Figure 1, 94% of patients ($n = 162/172$) presenting diarrhea at hospital admission (T0) had recovered at T1. Further, 71% ($n = 26/36$) of those with diarrhea at T1, developed it “de novo” (did not experience diarrhea at T0). The prevalence of gastrointestinal symptoms was 6.7% ($n = 107$) at T1 and 4.5% ($n = 72$) at T2. Figure 2 graphs the fitted exponential curves visualizing a decreased prevalence trend over time.

This is the first time analyzing the curve of recovery of post-COVID gastrointestinal symptoms in previously hospitalized COVID-19 survivors. Our prevalence rates of post-COVID gastrointestinal symptom agree with previous data.^{4,5} Nevertheless, most studies included smaller samples, data from single centers, and shorter follow-up periods.^{4,5} At hospital admission, the presence of diarrhea was noted but not the gastrointestinal symptoms since most patients specified only diarrhea. It is possible that overall gastrointestinal symptoms can be underreported at the acute phase of infection if not specifically investigated since they are not as bothersome as other COVID-19-related symptoms, such as fever, dyspnea, or chest pain.

Since gastrointestinal cells exhibit high expression levels of the angiotensin-converting enzyme II receptor (ACE2) and transmembrane serine protease 2 (TMPRSS3), they can be invaded by SARS-CoV-2, resulting in gastrointestinal inflammation.^{7,8} Accordingly, gastrointestinal symptoms may be responsible for enhanced exposure and significant viral load for a prolonged time period. In fact, our exponential recovery curve suggests that gastrointestinal symptoms can be present until three or more years after hospitalization. Identifying the risk factors associated with the development of gastrointestinal symptoms could help to better management of long-haulers.

Limitations are as follows. First, only hospitalized patients were included. Second, we focused on gastrointestinal symptoms. Interactions between different post-COVID symptoms are common. For instance, Blackett et al. observed that mental health was associated with gastrointestinal symptoms at the post-COVID phase, suggesting that gastrointestinal symptoms may be partially due to heightened stress and anxiety levels.⁸ Future studies should investigate interactions between different post-COVID symptoms.

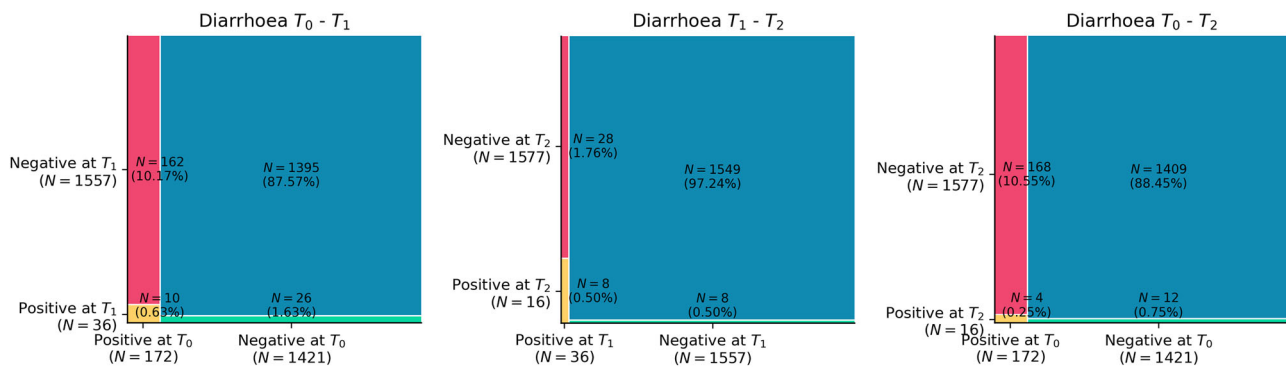


FIGURE 1 Mosaic plots of diarrhea at (from left to right): T0 (hospital admission) vs. T1 (8.4 months after hospital discharge), T1 vs. T2 (13.2 months after hospital discharge), and T0 vs. T2.

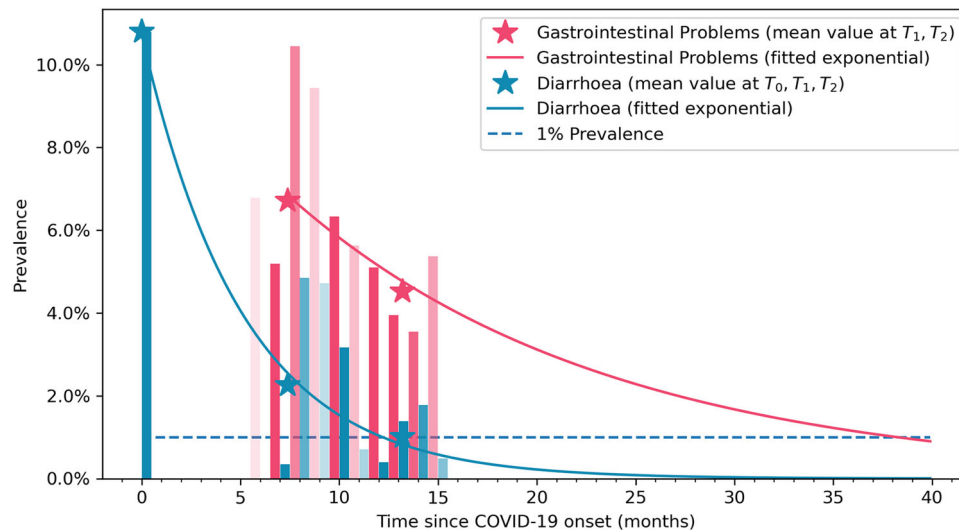


FIGURE 2 Recovery curve of self-reported diarrhea (in light blue) or gastrointestinal (in light red) symptoms. Vertical bars represent the percentage of patients who have diarrhea (in light blue) or gastrointestinal symptoms (light red) at any given time (opacity indicates the sample size at that follow-up). The mean values used for the development of the mosaic plots have been marked with asterisks in the graphs.

In conclusion, exponential recovery curves reveal that gastrointestinal symptoms tend to recover the following 2 or 3 years after SARS-CoV-2 infection in previously hospitalized COVID-19 survivors.

AUTHOR CONTRIBUTIONS

All authors contributed to the study concept and design. César Fernández-de-las-Peñas, José D. Martín-Guerrero, and Oscar J. Pellicer-Valero conducted literature review and did the statistical analysis. All authors recruited participants and collected data. Juan Torres-Macho and Carlos Guijarro supervised the study. All authors contributed to the interpretation of data and 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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CONFLICTS OF INTEREST



The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT


Data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Participants provided informed consent before collecting data.

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