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CE-RESEARCH LETTER TO THE EDITOR

Gastrointestinal symptoms at the acute COVID-19 phase are risk factors for developing gastrointestinal post-COVID symptoms: a multicenter study

César Fernández-de-las-Peñas[1] · José Martín-Guerrero[2] · Esperanza Navarro-Pardo[3] · Juan Torres-Macho[4,5] · Mª Gabriela Canto-Diez[4,6] · Oscar Pellicer-Valero[2]

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Dear editor

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly affects the respiratory system; however, other systems can also be affected [1]. Diarrhea, nausea, and vomiting are the gastrointestinal symptoms most commonly experienced during the acute phase of the infection with prevalence rates of 9.8%, 10.4%, and 7.7%, respectively [2]. The presence of gastrointestinal symptoms in the acute phase represents an overall risk for developing severe COVID-19, but this associated risk seems to be symptom-specific [3]. For instance, diarrhea, but not nausea and vomiting, is a risk factor for severe COVID-19 [4]. On the contrary, others reported that gastrointestinal symptoms are associated with lower mortality [5] and a more favorable course [6] of the disease if not associated with the presence of other symptoms such as dyspnea.

Gastrointestinal symptoms are also often present after the acute phase. Two meta-analyses have reported prevalence rates of gastrointestinal post-COVID symptoms ranging from 2% to 8.5% [7, 8]. No study has previously investigated those risk factors associated with gastrointestinal post-COVID symptoms at long-term. This multicenter study describes the potential risk factors for developing gastrointestinal post-COVID symptoms at long-term in a sample of subjects hospitalized by COVID-19.

Methods

This multicenter study included patients hospitalized with a positive diagnosis of SARS-CoV-2 by RT-PCR technique and radiological findings during the first wave of the pandemic (March 10th to May 31st, 2020) in five public hospitals in Madrid (Spain). From all patients hospitalized during that period, a sample of 400 individuals from each hospital was randomly selected. The Local Ethics Committees of all hospitals approved the study (HCSC20/495E, HSO25112020, HUFA 20/126, HUIL/092-20, HUF/EC1517). Informed consent was obtained from all participants before collecting data.

Patients were scheduled for a telephone interview which was conducted by trained healthcare professionals and were systematically asked for the following list of post-COVID symptoms: fatigue, dyspnea, chest pain, cough, palpitations, anosmia, ageusia, voice problem, hair loss, skin rashes, brain fog, memory loss or gastrointestinal problems. Particular attention was paid to gastrointestinal post-COVID symptoms. More than one symptom could be reported by each participant. Clinical features (i.e., age, gender, height, weight, medical comorbidities), symptoms at hospital admission, and hospitalization data [e.g., days at the hospital, intensive care unit (ICU) admission] were collected from hospital medical records.

Descriptive data are presented as mean (standard deviation, SD) or percentages as appropriate. Missing values

✉ César Fernández-de-las-Peñas
cesar.fernandez@urjc.es

1 Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Madrid, Spain

2 Intelligent Data Analysis Laboratory, Department of Electronic Engineering, ETSE (Engineering School), Universitat de València (UV), Valencia, Spain

3 Department of Developmental and Educational Psychology, Universitat de València (UV), Valencia, Spain

4 Department of Medicine, Universidad Complutense de Madrid (UCM), Madrid, Spain

5 Department of Internal Medicine, Hospital Universitario Infanta Leonor-Virgen de la Torre, Madrid, Spain

6 Department of Allergology, Hospital Universitario Infanta Leonor-Virgen de la Torre, Madrid, Spain

(< 2% weight and height, and < 0.2% in the remaining) were imputed using median imputation. Multivariate logistic regressions were used to analyze the influence of clinical/hospitalization data on gastrointestinal post-COVID symptoms at long-term (dependent variable) using Python's library statsmodels 0.11.1 [9]. Adjusted odds ratio (OR) with their 95%confidence intervals (95% CI) were calculated.

Results

From 2000 patients randomly selected and invited to participate, 6 refused participation, 11 were not contacted, and 14 had deceased after hospital discharge. A total of 1969 patients (46.5% women, mean age 61, SD 16 years) were included. The most prevalent symptoms at hospital admission included fever (74.6%), dyspnea (31.5%), and myalgia (30.7%). Diarrhea and vomiting at hospital admission were present in 10.7% and 2.8% of patients, respectively. Almost 57.5% of participants ($n = 1133$) reported at least one medical comorbidity (Table 1).

Participants were assessed at a mean of 8.4 months (SD 1.5) after hospital discharge. Thirty-seven percent ($n = 737$, 37.4%) were completely free of any post-COVID symptom, 444 (22.6%) had one symptom, 505 (25.6%) had two symptoms and 283 (14.4%) had ≥ 3 post-COVID symptoms. The most frequent post-COVID symptoms were fatigue (61.3%) and dyspnea (23.3%). Overall gastrointestinal symptoms were reported by 133 (7%) of the patients, with diarrhea being experienced by 49 (2.5%).

The regression model revealed that gastrointestinal post-COVID symptoms were associated with presenting vomiting (OR 4.298, 95% CI 2.156–8.567, $P < 0.001$), diarrhea (OR 2.087, 95% CI 1.266–3.439, $P = 0.004$), or headache (OR 1.797, 95% CI 1.147–2.815, $P = 0.01$) as symptoms at hospital admission. Similarly, the presence of diarrhea as a long-term post-COVID symptom was also associated with the presence of diarrhea as an acute symptom at hospital admission (OR 2.872, 95% CI 1.400–5.892, $P = 0.004$).

Table 1 Demographic and clinical data of the sample ($n = 1969$)

Age, mean (SD), years	61 (16)
Gender, male/female (%)	1054 (53.5%)/915 (46.5%)
Weight, mean (SD), kg	75 (15)
Height, mean (SD), cm	165 (16.5)
Main symptoms at hospital admission, *n* (%)	
Fever	1469 (74.6%)
Dyspnea	620 (31.5%)
Myalgia	604 (30.7%)
Cough	549 (27.9%)
Headache	332 (16.9%)
Diarrhea	210 (10.7%)
Anosmia	167 (8.5%)
Throat pain	102 (5.2%)
Ageusia	66 (33.5%)
Vomiting	55 (2.8%)
Medical comorbidities	
Hypertension	514 (26.1%)
Diabetes	236 (12.0%)
Cardiovascular disease	234 (11.9%)
Asthma	126 (6.4%)
Obesity	88 (4.5%)
Chronic obstructive pulmonary disease	77 (3.9%)
Stroke	38 (2.0%)
Rheumatological disease	31 (1.6%)
Other (cancer, kidney disease)	332 (16.9%)
Stay at the hospital, mean (SD), days	11.3 (11.4)
Intensive care unit (ICU) admission	
Yes/No, *n* (%)	130 (6.6%)/1839 (93.4%)
Persistent post-COVID symptoms, *n* (%)	
Fatigue	1206 (61.3%)
Dyspnea	459 (23.3%)
Loss memory	341 (17.3%)
Skin rashes	236 (12.0%)
Brain fog	189 (9.5%)
Attention disorders	140 (7.1%)
Palpitations	140 (7.1%)
Gastrointestinal disorders	133 (6.7%)
Ocular/vision disorders	116 (5.9%)
Anosmia	80 (4%)
Ageusia	53 (2.7%)
Diarrhea	49 (2.5%)

Discussion

This multicenter study found that the presence of gastrointestinal symptoms such as diarrhea and vomiting in the acute phase of COVID-19 infection was a risk factor for the development of gastrointestinal post-COVID symptomatology at long-term follow-up. Further, the presence of headache as an onset symptom at hospital admission was also associated with gastrointestinal post-COVID symptoms.

The presence of gastrointestinal symptoms 8 months after hospital discharge (7%) was similar to the presence of these symptoms at hospital admission (10%). The prevalence of gastrointestinal symptoms at the acute and post-COVID phases observed in our study is similar to published data [2, 7, 8]. Nevertheless, most studies included in previous meta-analyses included smaller samples, data from single centers, and post-COVID follow-up periods shorter than 3 months [7, 8]. Our study increases the strength of the evidence with a large, multicenter design evaluating post-COVID gastrointestinal symptoms at a longer follow-up period.

Identification of risk factors is needed for close monitoring and early intervention of patients at a higher risk of developing post-COVID symptoms. A recent meta-analysis found very limited data on predictors of post-COVID symptoms without studies assessing gastrointestinal post-COVID symptoms associated risk factors [10]. In our study, the presence of gastrointestinal symptoms at the acute phase of the infection was associated with the presence of gastrointestinal post-COVID symptoms eight months after infection. Our results are similar to a previous study showing that the presence of gastrointestinal symptoms in the acute phase of the infection was a risk factor for developing symptoms after hospital discharge; however, this study included a small sample, and this association did not reach statistical significance [11]. Since gastrointestinal cells exhibit high expression levels of the angiotensin-converting enzyme II receptor (ACE2), they can be invaded by SARS-CoV-2 virus, resulting in gastrointestinal inflammation, and, therefore, the presence of gastrointestinal symptoms during the acute phase of the infection [12]. It is possible that, in predisposing individuals, the cytokine storm initiated during the acute phase of COVID-19 would facilitate the persistence of the virus several months after the infection, thereby, promoting the persistence of these symptoms. In this scenario, the presence of gastrointestinal symptoms during the acute phase of the infection and at long-term follow-up supports that this subgroup of individuals may exhibit persistent post-COVID symptomatology since symptoms are present from the beginning of the disease process [13].

Additionally, experiencing headache as an onset symptom was also a risk factor for presenting gastrointestinal post-COVID symptoms at long-term period. The presence of headache could also promote the persistence of gastrointestinal post-COVID symptoms since an association between headache and gastrointestinal diseases has been described in the literature, although the underlying mechanisms behind this association are not fully understood [14].

Finally, we acknowledge some weaknesses. First, only hospitalized patients were included. Second, we did not collect objective measures of COVID-19 disease, such as inflammatory biomarkers, or blood oxygen saturation. Third, the cross-sectional design does not permit to determine cause-and-effects association between the reported findings. Longitudinal studies investigating the time course of gastrointestinal symptoms from the onset of the infection and the following years after the acute infection are needed.

In conclusion, the presence of gastrointestinal symptoms during the acute phase of the infection is associated with a higher risk of suffering from gastrointestinal post-COVID symptoms at long-term.

Author contributions All authors contributed to the study conception and design. Material preparation was performed by CFP, data collection by EN-P, JT-M, and MªGC-D, and analysis by JM-G and OP-V. The first draft of the manuscript was written by all authors. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed in relation to this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of all involved hospitals (HCSC20/495E, HSO25112020, HUFA 20/126, HUIL/092-20, HUF/EC1517).

Statement of human and animal rights This study included human participants but not animals. All participants provided their informed consent before collecting any data.

Consent to participate All participants signed the informed consent before participating in the study.

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

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