




BRIEF REPORT

# Clinical features of Japanese patients with gastrointestinal long-COVID symptoms

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## Key words

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## Introduction

Although the development of new therapeutic approaches and vaccines has decreased coronavirus disease 2019 (COVID-19)-associated mortality, prolonged systemic symptoms after COVID-19, termed long-COVID, have been a major concern, considering their potential impact on health-related quality of life (QOL).<sup>1,2</sup> Gastrointestinal (GI) symptoms, including diarrhea and abdominal pain, have been reported in patients with long-COVID even months after the initial COVID-19 symptoms have resolved.<sup>3</sup> Although emerging evidence suggests that GI symptoms in long-COVID are affected by the dysregulation of the immune system or ongoing inflammation and damage to the GI tract caused by the initial COVID-19 infection,<sup>4</sup> the clinical features of patients with GI long-COVID symptoms remain elusive. Our study aimed to clarify these features.

## Materials and methods

**Study design and patient enrolment.** A prospective nationwide cohort study was conducted on patients aged 18 years or older, as previously reported.<sup>2,5</sup> The patients analyzed included those admitted and discharged with a confirmed diagnosis of COVID-19 by positive polymerase chain reaction or antigen testing for COVID-19, from January 2020 to February 2021, at 26 participating medical institutions in Japan. The Keio University Hospital, the principal institution, had sent study descriptions and consent forms to potential research candidates in December 2020, and study invitations were subsequently mailed from 25 participating institutions that obtained ethical review committee approval and permission to conduct the study (Approval number: #20200243). Invitations for this study were mailed to all in-patients at each hospital, and those who provided consent were asked to complete a questionnaire on paper (paper patient-reported outcome [PRO]) or a smartphone application (electronic PRO) at 3, 6, and 12 months after diagnosis.

Final consent was obtained from 1200 participants in the 26 participating hospitals. This study analyzed 1066 cases with both medical information on the electronic data capture (EDC)

system and a 3-month post-diagnosis PRO; 943 cases with both medical information and PROs regarding GI long-COVID symptoms, including diarrhea and abdominal pain (Fig. S1, Supporting information), were eventually included. Patients with GI long-COVID symptoms were defined as those having diarrhea or abdominal pain at least once at 3, 6, and 12 months after diagnosis.

**Questionnaire and data collection.** Patients were asked for the presence of 22 representative long-COVID symptoms (e.g. dyspnea, fatigue, muscle weakness, memory impairment) in addition to GI long-COVID symptoms at the time of hospitalization and at 3, 6, and 12 months after diagnosis.<sup>2,5</sup> Patients were also asked to fill out the Short Form-8 (SF-8) and Euro Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) QOL questionnaires. SF-8 was used as a measure of health-related QOL status; it provides a continuous health-related QOL status among sick and healthy people using eight questions (physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health). The physical component summary (PCS) and mental component summary (MCS) scores were also computed from these eight items.<sup>6</sup> Each item was assessed on a 5- or 6-point Likert scale and converted according to the scoring system, with 50 points representing the Japanese national standard value for good health and functioning. Higher responses on the 0–100 scale indicated better health. The EQ-5D-5L is a scale for assessing health-related QOL status; it is a five-dimensional questionnaire that comprises the following items: “mobility,” “self-care,” “usual activities,” “pain/discomfort,” and “anxiety/depression.” The Japanese value set for the EQ-5D-5L, which has been developed based on the societal preferences of the general population, was used to calculate the index values from five responses in each patient. The visual analog scale, which reflects the overall health status of the respondents (0 [the worst imaginable health] to 100 [the best imaginable health]), was assessed, as well as the EQ-5D-5L index value.<sup>7</sup>

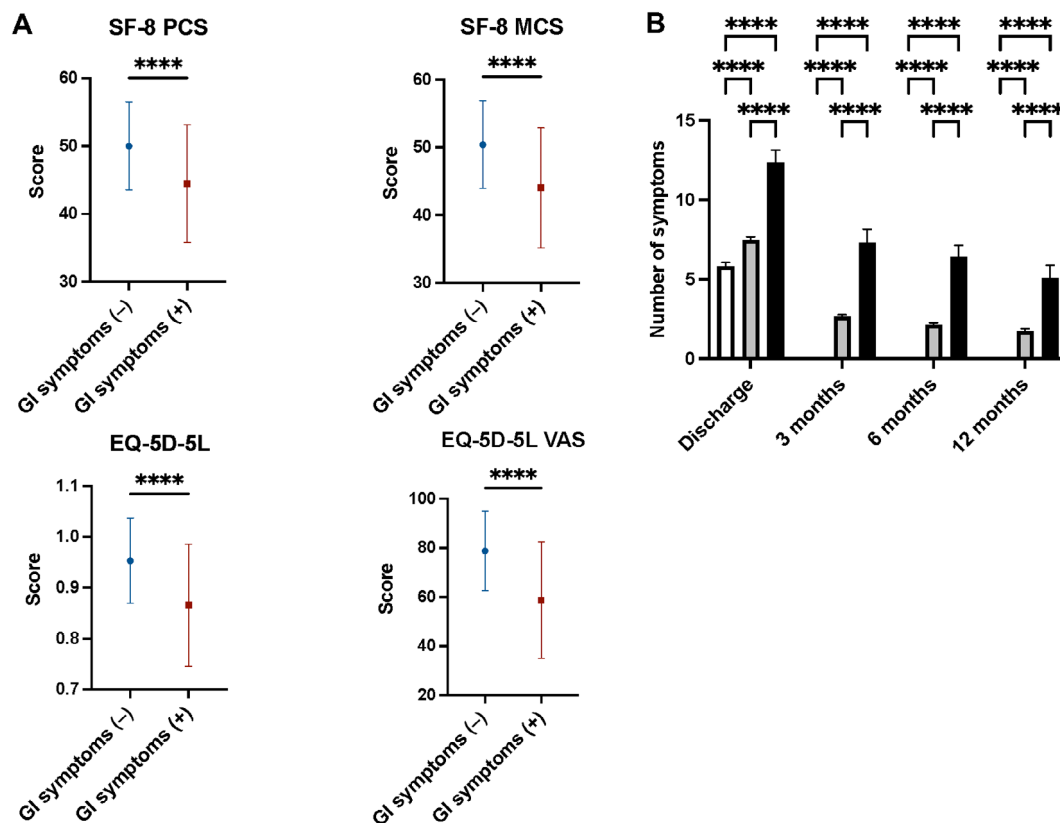
Clinical information including age, sex, body mass index (BMI), comorbidities, cigarette smoking, COVID-19 severity, and COVID-19-related complications during medical treatment was collected using the EDC system. Poor clinical outcomes were defined as the need for oxygen supplementation via high-flow oxygen therapy, mechanical ventilation, or extracorporeal membrane oxygenation.<sup>8</sup>

**Statistical analysis.** Continuous variables are presented as median and interquartile range (IQR), and categorical variables are presented as frequency and proportion. Comparisons between the two groups (patients with or without GI long-COVID symptoms) were performed with Fisher's exact test or Student's *t*-test. The three groups (patients with GI long-COVID symptoms, with long-COVID symptoms other than GI symptoms, or without long-COVID symptoms) were compared using the analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Least-squares regression analysis was performed to evaluate health-related QOL parameters according to sex and age as well as with or without GI long-COVID symptoms. Univariate logistic regression analysis was performed to calculate the odds ratio

(OR) to assess the association between clinical characteristics and GI long-COVID symptoms. The results of the univariate analysis are presented as ORs with 95% confidence intervals. All *P*-values were two-tailed, and *P* < 0.05 was considered statistically significant. All statistical analyses were performed using JMP version 16.0 (SAS Institute, Cary, NC, USA).

## Results

**Baseline clinical characteristics.** The clinical characteristics of the 943 COVID-19 patients included in this study are summarized in Table S1. Fifty-eight patients (6.2%) had GI long-COVID symptoms. Their median (IQR) age was 57 (47–66) years, and 37 (63.8%) patients were male; these proportions were comparable to those among patients without GI long-COVID symptoms. The median BMI of patients with GI long-COVID symptoms (22.8 [20.9–26.6] kg/m<sup>2</sup>) tended to be lower than that of patients without GI long-COVID symptoms (23.8 [21.4–26.4] kg/m<sup>2</sup>). The frequency of patients with GI symptoms at the time of infection was also comparable. Among the 58 patients with GI long-COVID symptoms, 3 (5.2%) had



**Figure 1** (a) Health-related quality of life parameters in patients with and without gastrointestinal long-COVID symptoms at 12 months after diagnosis. The parameters are presented as least squares means according to the presence/absence of GI long-COVID symptoms after adjustment for age and sex. EQ-5D-5L, Euro Quality of Life 5 Dimensions 5 Level; GI, gastrointestinal; MCS, mental component summary scores; PCS, physical component summary scores; SF-8, the Short Form-8; VAS, visual analog scale. Statistical analysis was performed by Student's *t*-test. Data are shown as mean  $\pm$  SD. \*\*\*\**P* < 0.0001. (b) Number of other long-COVID symptoms in patients with and without GI long-COVID symptoms at each timepoint. GI, gastrointestinal. Statistical analysis was performed by analysis of variance (ANOVA), followed by Tukey's multiple comparison test. \*\*\*\**P* < 0.0001.  no symptom;  GI symptoms (-), other symptoms (+);  GI symptoms (+).

poor clinical outcomes during hospitalization; this frequency was comparable to that among patients without GI long-COVID symptoms (49 [5.7%] patients).

**Association between health-related QOL parameters and GI long-COVID symptoms.** The health-related QOL parameters (SF-8 and EQ-5D-5L) in patients with and without GI long-COVID symptoms at 12 months after diagnosis are shown in Figure 1a. Both the PCS and MCS of the SF-8 in patients with GI long-COVID symptoms were significantly lower than in those without GI long-COVID symptoms ( $P < 0.0001$ ). Patients with GI long-COVID symptoms also showed significantly decreased EQ-5D-5L index and visual analog scale values compared to patients without GI long-COVID symptoms ( $P < 0.0001$ ).

**Number of other long-COVID symptoms with or without GI long-COVID symptoms.** The number of other long-COVID symptoms (e.g. dyspnea, fatigue, muscle weakness, memory impairment) in patients with GI long-COVID symptoms was significantly higher than that in patients without GI long-COVID symptoms who had at least one long-COVID symptom at each time point after COVID-19 diagnosis (Fig. 1b). Moreover, patients with GI long-COVID symptoms had a higher proportion of the 22 representative long-COVID symptoms, especially fatigue and dyspnea, than those without GI long-COVID symptoms who had at least one long-COVID symptom at each timepoint (Fig. S2).

**Association between clinical characteristics and GI long-COVID symptoms.** Univariate logistic analysis evaluated the association between clinical characteristics, including sex, age, BMI, comorbidities, and poor clinical outcomes during hospitalization, and GI long-COVID symptoms. There were no significant clinical characteristics related to GI long-COVID symptoms (Table S2).

## Discussion

The present study is a large-scale prospective cohort study focusing on clinical characteristics of patients with GI long-COVID symptoms. Patients with GI long-COVID symptoms showed lower health-related QOL parameters and had more varied long-COVID symptoms compared to patients without GI long-COVID symptoms. Of note, there were no significant clinical characteristics associated with GI long-COVID symptoms.

Health-related QOL parameters, including SF-8 and EQ-5D-5L, were significantly worse in patients with GI long-COVID symptoms than in patients without GI long-COVID. GI long-COVID symptoms not only lowered the overall health-related status, as shown by the EQ-5D-5L, but also lowered both the physical and the mental status of health-related QOL, as shown by the SF-8 PCS and MCS. Although previous studies have reported that long-COVID, including GI symptoms, affects QOL,<sup>1,2</sup> no study reported that GI long-COVID symptoms result in lower health-related QOL. We also found that the number of long-COVID symptoms other than GI symptoms was significantly higher in patients with GI long-COVID symptoms who had at least one long-COVID symptom. Several studies have

shown that the number of symptoms could be an important parameter for explaining long-COVID status.<sup>9,10</sup> In agreement with this, our results indicate that patients with GI long-COVID symptoms have multiple long-COVID symptoms alongside the GI symptoms and show lower health-related QOL.

We also found that there were no significant background clinical characteristics related to GI long-COVID symptoms, although a previous study reported severity of infection and presence of GI symptoms at the time of infection as predictive factors for GI long-COVID symptoms.<sup>11</sup> Although the pathophysiological mechanisms of GI long-COVID are not clearly understood, emerging evidence shows that persistent and aberrant inflammation and microbial dysbiosis in the gut microbiome could affect GI long-COVID.<sup>4</sup> Our results also suggest that unmeasured factors in this study, including immune cell populations and fecal microbiome composition, could be associated with GI long-COVID symptoms. Further research is needed to elucidate the pathogenesis of GI long-COVID symptoms.

This study has several limitations. First, there were no data regarding GI symptoms before COVID-19 infection for the included patients. Additionally, we did not systematically record whether patients in this study were diagnosed with GI diseases after COVID-19 or whether they received treatment to mitigate GI symptoms. Despite these limitations, this study provided valuable data on GI long-COVID in Japan, which can stimulate further GI long-COVID-related research.

## Conclusion

Patients with GI long-COVID symptoms showed lower health-related QOL parameters and had more diverse long-COVID symptoms compared to patients without GI long-COVID symptoms. Further research is needed to clarify the predictive factors associated with GI long-COVID symptoms.

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## Ethics statement

This study was approved by the Ethics Committee of Keio University School of Medicine (Approval number: #2020243). Additionally, approval and permission to conduct the study was obtained from each participating institutional ethical review committee.

**Data availability statement.** The datasets generated and/or analyzed during this study are not publicly available due to ethical restrictions, but could be made available from the corresponding author upon reasonable request.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

**Figure S1.** Patient selection flow diagram.

**Figure S2.** Proportion of symptoms in patients with and without gastrointestinal symptoms. (a) At 3 months after diagnosis, and (b) at 12 months after diagnosis.

**Table S1.** Patient clinical characteristics.

**Table S2.** Relationship between clinical characteristics and gastrointestinal long-COVID symptoms.