Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Conflicts of interest
The authors disclose no conflicts.

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Reply. We would like to thank Zhang et al[1] for their interest in our article and for highlighting the importance of mechanistic studies to shed light on functional properties of native microbiota and its molecules mediating virus colonization.

We found that impaired short-chain fatty acids (SCFAs) and L-isoleucine biosynthesis in the gut microbiome correlated with coronavirus disease 2019 (COVID-19) severity as well as increased plasma concentrations of C-X-C motif chemokine ligand 10 (CXCL-10), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and C-reactive protein (CRP).[2] Among other cytokines assessed, including interleukin (IL) 10, IL12, IL1b, IL6, and tumor necrosis factor (TNF)-α and chemokines such as CXCL-8 and C-C motif chemokine ligand 2 (CCL-2), we found that only increased plasma levels of IL10 significantly associated with more severe symptoms in patients with COVID-19.

It is likely that elevated endogenous systemic IL10 stimulates inflammatory cytokine production and directly activates and promotes effector cluster of differentiation 8-positive T-cell proliferation, which may play a pathologic role in COVID-19 severity.[3] Intriguingly, fecal butyrate level in patients with COVID-19 showed a significantly negative correlation with plasma IL10, suggesting that microbiota-derived butyrate may be involved in preventing overexpression of IL10 in COVID-19.

To this end, emerging studies have provided new insights into the relationship between the gut microbiome, host immunity, and disease severity in COVID-19. In a separate cohort of 100 hospitalized patient with COVID-19, we found that disrupted gut microbiota were associated with higher levels of TNF-α, IL10, and CXCL10.[4] Others have reported that *Enterococcus faecalis* was negatively correlated with cluster of differentiation 8-positive T cells and IL4, and *Eubacterium ramulus* was negatively correlated with IL6 in patients with COVID-19.[5] These cytokines and chemokines are involved in interferon-driven T helper type 1 (Th1) response,[6] implying that the gut microbiota may regulate Th1 response in severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection, while more cytokines and proteins associated with immune cell activation should be determined to support this notion.

We agree with the authors that relationships between plasma markers, clinical measures, and disease severity deserve in-depth exploration. In our study, we detected clinical measurements, including blood counts (platelet count, white cell count, neutrophil count) and the plasma concentrations of lactate dehydrogenase (LDH), CRP, albumin, hemoglobin, alkaline phosphatase, and aspartate aminotransferase, alanine aminotransferase (ALT), total bilirubin, and creatinine, and elucidate their relationship with disease severity and microbial functions. We found increased levels of LDH, CRP, and ALT and decreased levels of platelet count, albumin, and hemoglobin (MaAsLin2 [R Foundation for Statistical Computing, Vienna, Austria] false discovery rate corrected $P < .05$) significantly associated with more severe symptoms in patients with COVID-19.

LDH, ALT, and albumin are well-known markers of liver or kidney dysfunction,[7] highlighting host tissue damage in patients with severe COVID-19. Importantly, the fecal level of butyric acid positively correlated with the plasma level of albumin, indicating microbiota-derived butyrate may have the potential to prevent tissue damage caused by SARS-COVID-2 infection. We also evaluated blood urea nitrogen level mentioned by Zhang et al in their letter[1] in patients with COVID-19 and found patients with severe symptoms showed a significantly higher blood urea nitrogen level than those patients with mild symptoms. This may be associated with higher serum concentrations of urea and disruption of urea cycle functions during COVID-19 infection,[2,8] highlighting kidney dysfunction and abnormal amino acid catabolism in patients infected with SARS-COVID-2.

In summary, current evidence supports the notion that the gut microbiota may contribute to disease severity in COVID-19 via regulation of Th1 response, and proof-of-concept studies dissecting how microbiota-derived molecules mediate host immune response in patients with COVID-19 and disease severity are desperately needed to provide more mechanistic insights, and this will be of benefit to exploiting microbial-based therapy.

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Conflicts of interest
SCN is the scientific co-founder of GenieBiome Ltd, and the Chinese University of Hong Kong holds a provisional patent for A Synbiotic Composition for Immunity. FZ discloses no conflicts.

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Should We Continue or Discontinue Inflammatory Bowel Disease Medication in Patients With Coronavirus Disease 2019?

Dear Editors:

We read with great interest the study by Ungaro et al,[1] "Impact of Medications on COVID-19 Outcomes in Inflammatory Bowel Disease: Analysis of More Than 6000 Patients From an International Registry." The authors compared the association between inflammatory bowed disease (IBD) medications during coronavirus disease 2019 (COVID-19) diagnosis and COVID-19 adverse events in the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE)-IBD database and showed that the prognosis of patients receiving steroids for IBD at the time of COVID-19 diagnosis was poor. In addition, the authors suggested that use of IBD medications, specifically tumor necrosis factor (TNF) antagonists, interleukin (IL) 12/23 antagonists, and integrin antagonists, may be a favorable prognostic factor for COVID-19.

However, the authors noted that measurement bias may occur if patients voluntarily discontinued their medication. SECURE-IBD has not accumulated real data on the withdrawal or postponement of IBD medication during the COVID-19 pandemic. The International Organization for the study of Inflammatory Bowel Disease (IOIBD),[2] European Crohn's and Colitis Organisation (ECCO)-COVID Taskforce,[3] and JAPAN IBD COVID-19 Taskforce[4] have provided guidelines on the continuation or withdrawal of IBD medications in patients with COVID-19 based on transitional evidence. However, the correct method of continuation/withdrawal of medications remains unclear. This is because only a few reports have been published on the clinical outcomes of IBD patients with COVID-19 who have stopped their IBD medications.

A retrospective multicenter registry study of Japanese patients with inflammatory bowel disease with COVID-19 (Japan COVID-19 surveillance in inflammatory bowel disease [J-COSMOS], UMIN000040656) has collected data regarding IBD disease activity, medications at COVID-19 diagnosis, withdrawal during COVID-19, and outcome of COVID-19.[5] We performed an interim analysis of the risk of postponing/discontinuing IBD medications during concomitant COVID-19 in 187 patients enrolled in J-COSMOS from June 2020 to October 2021. Of the 187 patients, the diagnosis of patients was ulcerative colitis in 104, Crohn's disease in 74, IBD unclassified in 3, and intestinal Behçet's disease in 6. First, we found that the percentage of Japanese patients with IBD and severe COVID-19 based on the World Health Organization classification was 7%. No deaths were recorded.

In this survey, among 144 patients receiving mesalamine at the time of COVID-19 diagnosis, 7.9% (11 of 140) of patients who continued it and 25% (1 of 4) of those who discontinued it had severe COVID-19. Of 57 patients receiving thiopurines, 3.6% (1 of 28) of patients who continued them and 3.4% (1 of 29) of those who discontinued them had severe COVID-19. In addition, none of the 48 patients who continued TNF inhibitors had severe COVID-19, and 3.8% (1 of 26) of the patients who discontinued them had severe COVID-19. The Fisher exact test showed no significant difference between the continuation and discontinuation of IBD drugs and COVID-19 severity (Supplementary Table 1). No patient receiving budesonide, ustekinumab, vedolizumab, or tofacitinib for IBD at the time of COVID-19 diagnosis had severe COVID-19. Furthermore, we examined whether continuation and discontinuation of IBD medications could contribute to worsening IBD clinical activity based on the partial Mayo score or the Harvey-Bradshaw Index. We found that neither continuation nor discontinuation of any medication during COVID-19 affected the exacerbation of IBD activity (Supplementary Figure 1). Meanwhile, 6.1% (10 of 163) of patients with IBD who continued medication had mild exacerbation of disease activity. Our current registry indicates that the continuation or discontinuation of IBD medications does not contribute to COVID-19 disease outcomes.

Despite the significance of our data, the limitation are (1) the number of IBD patients with COVID-19 in Japan was small, (2) we did not collect any data regarding when IBD medications were stopped or restarted and how long the patients with IBD had COVID-19, and (3) the number of patients with severe COVID-19 was too small to analyze the confounding factors of the relationship between continuation or discontinuation of IBD medications and COVID-19 severity.

In summary, our interim data suggest that neither continuation nor discontinuation of IBD medications affects COVID-19 severity. In addition, discontinuation of IBD medications did not contribute to flares of IBD during COVID-19. The SECURE-IBD and J-COSMOS data show 3 factors are implicated in the continuation or discontinuation of IBD medications in IBD patients with COVID-19: severity of COVID-19, IBD refractoriness, and type of IBD medications. Therefore, further accumulation of real-world data is required to manage IBD during the COVID-19 pandemic.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2022.03.008.