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.

CORRESPONDENCE

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Gut Microbiome Metabolism Drives the Resolution of Patients With Coronavirus Disease 2019

Dear Editors:

After the outbreak of coronavirus disease 2019 (COVID-19), its long-term sequelae after recovery has become the wide-ranging concern. Sequelae symptoms and complications, including, but not limited to, chronic fatigue, lung fibrosis, anxiety, depression, cognitive impairment, and venous thromboembolism, have emerged in some patients after hospital stay.[1,2] However, little is currently known on the underlying mechanisms of these chronic health sequelae. Zhang et al[3] reported that severe or critical patients with COVID-19 are characterized by impaired capacity of gut microbiome for short-chain fatty acid (SCFA), L-isoleucine biosynthesis, and enhanced capacity for urea production for their gut microbiome.

To our knowledge, this is the first longitudinal cohort study of hospital survivors with COVID-19 so far to describe the dynamic gut microbiome functionality within 30 days after discharge. By metagenomic analysis, they found Bray-Curtis dissimilarity of microbial pathways in patients with COVID-19 with severe/critical illness was significantly higher than in individuals without COVID-19. In particular, SCFA biosynthesis of commensal bacteria served as the energy sources of host cells. Its impairment thus could contribute to the symptoms of fatigue and muscle weakness. Besides, they were also conscious of dietary factors of patients over the course of hospitalization, which were substantiated to be excluded. This study has comprehensively clarified how gut microbiome functionality modulates the outcome of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during hospitalization and beyond 1 month after discharge.

Even though Zhang et al[3] claimed the limitations of their dietary records before disease onset and mechanistic studies between SARS-CoV-2 infection and the gut immune system, this study is also lacking in plasma measurements to solidify its conclusion. All levels of plasma multiomics profiles were previously determined in 139 patients with COVID-19 from their serial blood draws collected during the first week of infection after diagnosis.[4] They identified the upregulation of chemokine (C-C motif) ligand 7 (CCL7), interleukin (IL) 10, and IL6 (that barely misses significance between moderate and severe disease with $P = .056$). Keratin-19 (KRT19) involved in the organization of muscle fibers is upregulated in all comparisons and may be a marker of tissue damage between moderate and severe COVID-19 cases. Several inflammation-associated proteins, including CCL7 and IL6, are anticorrelated with many plasma lipids. For healthy donors or mildly infected patients, these lipid levels drop precipitously.

Therefore, the mentioned plasma measurements were insufficient for the perspective of inflammatory reaction. More proinflammatory cytokines (eg, chemokine [C-X-C motif] ligand 6) and proteins associated with immune cell activation (eg, cluster of differentiation 244 and 40) as high contributing factors should be determined in patients with COVID-19 and their controls. In addition, relationships between plasma analytes, clinical measures, and disease severity also deserve to be explored. For example, blood urea nitrogen (in hospitalized patients) has many connections with amino acid metabolism, suggesting amino acid catabolism in advanced COVID-19.[4]

The discoveries reported by Zhang et al[3] highlight the effects that gut microbial metabolism can have on COVID-19 severity and demonstrate that microbiota functional capabilities are critical for the long-term recovery from SARS-CoV-2 infections. A highly diverse microbial community has an intrinsic capacity to act as a protective barrier against virus invasion and pathobiont expansion in the circulatory system. Gut metabolites or signaling molecules, such as SCFA, L-isoleucine, and urea production, play an important role in these inherent protective functions of the microbiota. The functional properties of native microbiota and its molecules mediating virus colonization should be the focus of further work, with the potential to harness them for new and improved therapies.

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Conflicts of interest
The authors disclose no conflicts.

Most current article

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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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