Post-acute COVID-19 syndrome and gut dysbiosis linger beyond 1 year after SARS-CoV-2 clearance

We recently published in Gut to show that gut dysbiosis persisted for at least 6 months in patients with post-acute COVID-19 syndrome (PACS). Murine and human studies have also reported microbial alterations associated with different PACS symptoms. With the pandemic entering its third year, PACS could potentially affect recovered individuals for over 1 year. It remains unknown whether PACS-associated gut dysbiosis would also linger for such a long time.

Here, we conducted a prospective study to determine long-term alterations in the gut microbiome of patients with COVID-19 using shotgun metagenomic sequencing (online supplemental materials). A total of 155 patients with COVID-19 in Hong Kong were followed up for an average of 14 months after SARS-CoV-2 viral clearance, and 155 age-, sex-, and body mass index-matched subjects without COVID-19 were recruited as controls. Patients with COVID-19 were infected with the original or earlier variants of SARS-CoV-2 from January 2020 to February 2021. Consistent with previous finding that 76.4% of patients had PACS 6 months after recovery from acute COVID-19, we found that the prevalence of PACS was 78.7% at an average of 14-month (IQR 11–18 months) follow-up. The three most common symptoms were fatigue (50.9%), memory problems (44.5%), and difficulty in sleeping (35.5%, figure 1A). Gut dysbiosis in these patients did not fully recover. Both bacteria diversity (p=0.0036, figure 1B) and richness (p=0.00032, figure 1C) of patients with COVID-19 were still significantly lower than that of controls. Principal coordinates analysis of beta diversity also showed distinct separation of patients with COVID-19 from controls (F=8.3822, p<0.001, figure 1D). These observations suggest persistent gut dysbiosis beyond 1 year in patients with PACS.

Specifically, the gut microbiome of recovered patients with COVID-19 was characterised by enrichment of potentially pathogenic bacteria, Erysipelotrichia ramosum and Ruminococcus gnavus, as well as depletion of beneficial bacteria such as Bifidobacterium.

Figure 1  Post-acute COVID-19 syndrome (PACS) and gut dysbiosis 1 year after SARS-CoV-2 clearance. (A) Prevalence of PACS symptoms at an average of 14-month follow-up after viral clearance. The alpha diversity (B) and richness (C) in patients with post-acute COVID-19 compared with subjects without COVID-19. (D) Principal coordinates analysis (PCoA) of gut microbiota composition of patients with post-acute COVID-19 compared with subjects without COVID-19. (E) Volcano plot for the general associations between PACS and microbes at species level calculated by MaAsLin2. False discovery rate (FDR) below 0.05 was considered as significant. (F) Heatmap of microbial species associated with different PACS symptoms. Associations were coloured by direction of effect (red, positive; blue, negative), with associations significant at FDR <0.05 marked with a plus (positive correlations (PC)) or minus (negative correlations (NC)), respectively.
adolescentis and B. pseudocatenulatum (figure 1E and online supplemental table 1). The latter two beneficial bacteria could potentially improve inflammation and neurological symptoms.1,8 Interestingly, PACS affecting different bodily systems showed a similar pattern of microbial alterations (figure 1F). Almost all PACS symptoms were significantly associated with depletion of beneficial bacteria such as Gemmiger formicilis8 and B. adolescentis,7 suggesting the possibility to develop universal microbiome-based therapies or interventions targeting various symptoms. It is worth noting that some beneficial bacteria were not associated with specific PACS symptoms. For example, B. pseudocatenulatum were not found to be associated with any of the respiratory symptoms suggesting that possible functions of different beneficial bacteria should be carefully considered when conducting clinical studies. Consistent with the key microbial species identified thus far,1,8,9 the enrichment of potentially pathogenic bacteria including R. gnavus, Clostridium bolteae, Flavonifractor plautii and E. ramosum was associated with the majority of the PACS symptoms. Thus, effective elimination or inhibition of these bacteria via dietary intervention, microbiota modulation or drugs may also have significant implications for alleviating PACS. To move forward, more extensive validation on the above associations is needed to address the potential confounders that could possibly alter the microbiome, such as host milieu, diet or medication history.

Taken together, our findings showed that post-COVID-19 gut dysbiosis could linger beyond 1 year and is closely associated with PACS. Although the exact mechanism underlying the pathogenesis of PACS is largely unknown, these data further support the emerging role of gut microbiota alterations in PACS. Current management of PACS relies heavily on symptomatic treatment of individual symptoms. Gut microbiota modulation could potentially be developed as a novel holistic approach that targets multiple systems and symptoms. In the future, more clinical trials are needed to shed light on the efficacy and safety of microbiome-based interventions for PACS.

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References