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Large-scale genetic correlation studies explore the causal relationship and potential mechanism between gut microbiota and COVID-19-associated risks

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Abstract

Recent observational studies suggest that gut microorganisms are involved in the onset and development of coronavirus disease 2019 (COVID-19), but the potential causal relationship behind them remains unclear. Exposure data were derived from the MiBioGen consortium, encompassing 211 gut microbiota ($n = 18,340$). The outcome data were sourced from the COVID-19 host genetics initiative (round 7), including COVID-19 severity ($n = 1,086,211$), hospitalization ($n = 2,095,324$), and susceptibility ($n = 2,597,856$). First, a two-sample Mendelian randomization (TSMR) was performed to investigate the causal effect between gut microbiota and COVID-19 outcomes. Second, a two-step MR was used to explore the potential mediators and underlying mechanisms. Third, several sensitivity analyses were performed to verify the robustness of the results. Five gut microbes were found to have a potential causality with COVID-19 severity, namely *Betaproteobacteria* (beta = 0.096, $p = 0.034$), *Christensenellaceae* (beta = -0.092, $p = 0.023$), *Adlercreutzia* (beta = 0.072, $p = 0.048$), *Coprococcus 1* (beta = 0.089, $p = 0.032$), *Eisenbergiella* (beta = 0.064, $p = 0.024$). Seven gut microbes were found to have a potential causality with COVID-19 hospitalization, namely *Victivallaceae* (beta = 0.037, $p = 0.028$), *Actinomyces* (beta = 0.047, $p = 0.046$), *Coprococcus 2* (beta = -0.061, $p = 0.031$), *Dorea* (beta = 0.067, $p = 0.016$), *Peptococcus* (beta = -0.035, $p = 0.049$), *Rikenellaceae RC9 gut group* (beta = 0.034, $p = 0.018$), and *Proteobacteria* (beta = -0.069, $p = 0.035$). Two gut microbes were found to have a potential causality with COVID-19 susceptibility, namely *Holdemanella* (beta = -0.024, $p = 0.023$) and *Lachnospiraceae FCS020 group* (beta = 0.026, $p = 0.027$). Multi-omics mediation analyses indicate that numerous plasma proteins, metabolites, and immune factors are critical mediators linking gut microbiota with COVID-19 outcomes. Sensitivity analysis suggested no significant heterogeneity or pleiotropy. These findings revealed the causal correlation and potential mechanism between gut microbiota and COVID-19 outcomes, which may improve our understanding of the gut-lung axis in the etiology and pathology of COVID-19 in the future.

Keywords COVID-19, Gut microbiota, Mendelian randomization, Mediation analysis

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Introduction

The 2019 coronavirus disease pandemic (COVID-19), which began in late 2019 and rapidly developed into a global pandemic caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, remains a global emergency requiring close attention. Until April 4, 2023, COVID-19 has caused more than 761 million cases and 6.89 million deaths (WHO, 2023) [1]. Numerous studies have shown that the virus remains in the human body for more than six months after COVID-19 is cured and causes ongoing damage to many tissues and organs, also known as a long COVID [2, 3]. Long-term COVID is a general term for the persistence of physical and mental symptoms after acute SARS-CoV-2 infection, including fatigue, depression, chronic pain, and cognitive decline [4]. Evidence suggests that the incidence of long COVID is 10–12% in COVID-19 vaccinated cases, 10–30% in ambulatory patients, and 50–70% in hospitalized patients [5, 6]. In an observational study, Douaud et al. found changes in several specific areas of brain structure and more significant cognitive decline in COVID-19 patients compared to controls [7]. Xie et al. found that COVID-19 patients had a persistently increased risk of cardiovascular disease, including cerebrovascular stroke, arrhythmias, and myocardial injury, after infection, which persisted from 1 month to 1-year post-infection [8]. Zollner et al. found that the persistence of SARS-CoV-2 RNA was detected in intestinal mucosal epithelial cells of patients after mild COVID-19 infection for up to 7 months [3]. Interestingly, recent evidence from many epidemiological investigation studies suggests a close relationship between gut microbiota composition and COVID-19 risks.

The human gut microbiota is a community of bacteria, archaea, fungi, and viruses in the intestinal tract that plays an important role in host food digestion, genetic evolution, drug metabolism, immune regulation, and neuroendocrine feedback [9]. Specifically, bacteria within this community are categorized into hierarchical taxonomic levels, including phylum, order, family, genus, and class [10]. Studies from cross-sections suggest that gut microbiota-mediated amino acid and neurotransmitter metabolites are involved in the dynamics of multiple immune factors in COVID-19, such as interferons, interleukins, and the CXCLs family [11]. Significant changes in gut microbiome composition can influence the expression of inflammatory markers, potentially leading to immune dysregulation [12]. This dysregulation may have a significant impact on the prognosis of those affected by COVID-19. Gut microbiota affects the onset and progression of COVID-19 by regulating the receptor angiotensin-converting enzyme 2 (ACE2) and intestinal immunity in the form of the gut-lung axis. The SARS-CoV-2 virus enters human alveolar cells and produces large amounts of circulating cytokines, causing an imbalance in the intestinal flora, which disrupts the mucosal barrier of the digestive tract and causes bacterial metabolites and toxins to enter the circulatory system, ultimately exacerbating the inflammatory response of the respiratory system [13, 14]. Limited preliminary clinical studies have revealed a potential modulatory effect of certain bacteria, such as *Bifidobacterium* and *Lactobacillus*, on the pathological processes of SARS-CoV-2 infection [15]. However, these results come from cross-sectional, case–control, and cohort studies and lack direct and valid evidence for a causal relationship between gut microbiota and COVID-19. In addition, the exact potential mechanisms between gut microbiota and COVID-19 outcomes remain unknown. Therefore, it is essential to comprehensively explore the crucial role of gut microbiota in the pathogenesis and pathological progression of COVID-19. To address these limitations, this study investigates the causal role and underlying mechanisms of gut microbiota in COVID-19 severity, hospitalization, and susceptibility based on the latest large-scale human genome-wide association study (GWAS) using a two-sample MR and two-step MR approach.

MR is an effective clinical research method that uses genetic variations to explore the causal relationship between potential exposure risk and disease outcome in observational studies based on specific hypotheses [16, 17]. Like randomized controlled trials, the study population was randomized into control and experimental groups due to instrumental variables (IVs) of different exposures, starting at birth and continuing throughout their whole life. In contrast to traditional observational studies, MR based on single nucleotide polymorphisms (SNPs) and Mendelian inheritance can infer causal effects in the presence of unknown confounders and avoid reversal of causality [18]. Three principled assumptions ensure the robustness of the causal inference inferred by MR: (i) SNPs are strongly associated with exposure; (ii) SNPs should exclude any confounding factors that may affect the exposure-outcome association; (iii) The association of SNPs to outcomes is mediated only through exposure and without any other pathway. Two-sample MR analysis was performed using two GWAS analyses of exposure-related and outcome-related SNPs from different populations of the same race and combining them into one causal inference [19].

Consequently, this paper is dedicated to exploring the association between gut microbes and COVID-19 and discovering specific causal bacteria taxa using MR analysis. We selected large-scale GWAS summary statistics of gut microbiota from the MiBioGen consortium for the exposure and large-scale GWAS summary statistics of

COVID-19 outcomes (COVID-19 severity, hospitalization, and susceptibility) from the Covid-19 Host Genetics Initiative for the outcome.

Materials and methods

Collection and organization of summary statistics for GWAS

All data used in this paper are listed in Supplementary Table 1 and are publicly available. For exposure, the GWAS summary statistics of gut microbiota were downloaded from the MiBioGen consortium (https://mibiogen.gcc.rug.nl/) [20]. The gut microbiota in this study was divided into five classes (phylum, class, order, family, and genus), totaling 211 taxa. A total of 18,340 individuals were enrolled in the study. For outcome, the GWAS summary statistics of COVID-19 outcomes were downloaded from the Covid-19 Host Genetics Initiative released on April 8, 2022 (COVID-19-hg GWAS meta-analyses round 7) (https://www.covid19hg.org/results/r7/). Briefly, for COVID-19 susceptibility, 2,597,856 individuals were enrolled in the study; for COVID-19 hospitalization, 2,095,324 individuals were enrolled in the study; for COVID-19 severity, 1,086,211 individuals were enrolled in the study. For the mediator, the GWAS summary statistics of 731 immune cell traits came from 3,757 individuals [21]; the GWAS summary statistics of 1,400 plasma metabolites came from 8,299 individuals [22]; the GWAS summary statistics of 4,907 plasma proteins came from 35,559 individuals [23].

The instrumental variables (IVs) for each gut microbial taxa were selected as in the previous study [20, 24, 25] using three principles: (i) SNPs are strongly correlated with exposure ($p < 1 \times 10^{-5}$); (ii) SNPs clumped following the PLINK algorithm (LD < 0.001 and < 1 MB from the index variant); (iii) elimination of SNPs with pleiotropic effects.

TSMR and sensitivity analyses

We conducted a two-sample MR analysis to calculate the causal correlation between gut microbiota and COVID-19 outcomes. Three MR methods were used to determine causality: random effects inverse variance weighting (IVW) [26], the Weighted median method [27], and MR-Egger regression [28]. The IVW method is more powerful than other methods under certain conditions and is therefore chosen as the primary analytical method, while several other methods complement it [29]. In addition, MR PRESSO [30], MR Egger intercept test [31], Cochran's Q test [32], and leave-one-out analysis were used to perform sensitivity analysis to determine whether IVs are heterogeneous and pleiotropic. Details were shown in the Supplementary methods.

Multi-omics mediation analysis

We conducted a two-step MR to calculate the role of potential mediators (plasma metabolites [22], plasma proteins [23], and immune cells [21]) between gut microbiota and COVID-19 outcomes as previously described [33, 34].

Statistical analysis

The results of the Mendelian analysis were presented using three values: beta, 95% confidence interval (95% CI), and *p*. The significance threshold for each taxon level was $p = 0.05$. The R (version 4.0.5) software packages (Two-Sample MR [35], clusterProfiler [36], enrich plot [37], and DOSE [38]) were applied for statistical analysis.

Results

Overview

The design scheme of the whole study is shown in Fig. 1. With the IVW approach, we found substantial evidence suggesting a causal relationship between gut microbiota and COVID-19 risk. In summary, the statistical significance of 14 gut microbiota taxa was less than 0.05, including one class, two families, ten genera, and one phylum. The results of IVW, MR Egger, and weighted median analyses between these gut microbiota taxa and COVID-19 severity, hospitalization, and susceptibility were presented in Fig. 2. The IVs for these gut microbiota taxa were displayed in Supplementary Tables 2–15. The results of MR analyses are presented in Supplementary Table 16.

The causal effect of gut microbiota on COVID-19 risk

First, for COVID-19 severity, the IVW method identified four microbial taxa, namely, *Beta-proteobacteria* (beta = 0.096, $p = 0.034$), *Adlercreutzia* (beta = 0.072, $p = 0.048$), *Coprococcus 1* (beta = 0.089, $p = 0.032$), *Eisenbergiella* (beta = 0.064, $p = 0.024$), was related to an increased risk of COVID-19 severity; one microbial taxa, namely, *Christensenellaceae* (beta = -0.092, $p = 0.023$), was related to a reduced risk of COVID-19 severity (Fig. 3). The SNPs of these microbial taxa used for MR analysis were listed in Supplementary Tables 2–6, respectively. Second, for COVID-19 hospitalization, the IVW method identified four microbial taxa, namely, *Victivallaceae* (beta = 0.037, $p = 0.028$), *Actinomyces* (beta = 0.047, $p = 0.046$), *Dorea* (beta = 0.067, $p = 0.016$), and *Rikenellaceae RC9 gut group* (beta = 0.034, $p = 0.018$), was related to an increased risk of COVID-19 hospitalization; three microbial taxa, namely, *Coprococcus 2* (beta = -0.061, $p = 0.031$), *Peptococcus* (beta = -0.035, $p = 0.049$), and *Proteobacteria* (beta = -0.069, $p = 0.035$), was related to a reduced risk of COVID-19 hospitalization

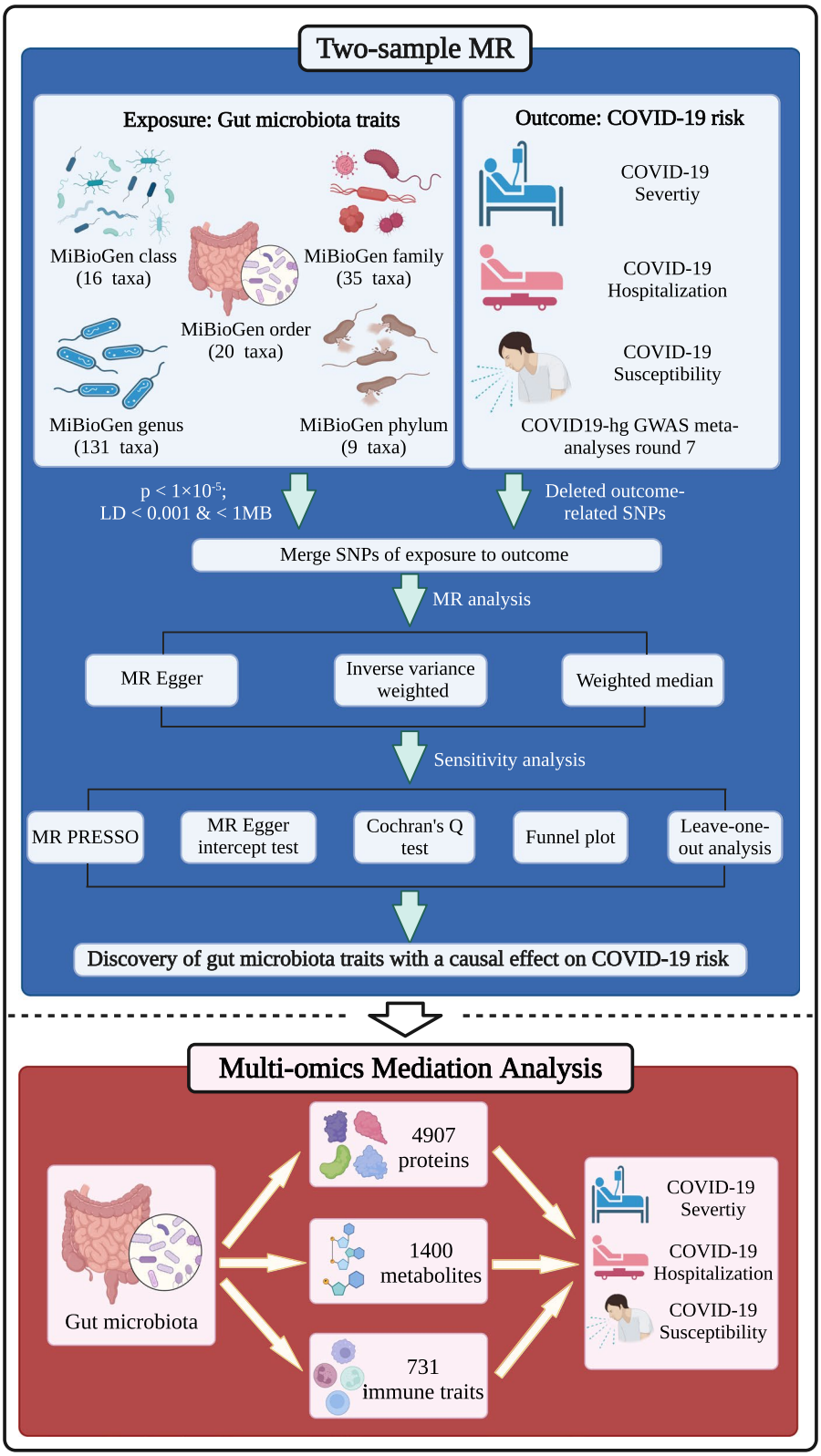

Fig. 1 The design diagram of the whole study identifies the correlation between gut microbiota and COVID-19 risk. The figure was created by the Biorender

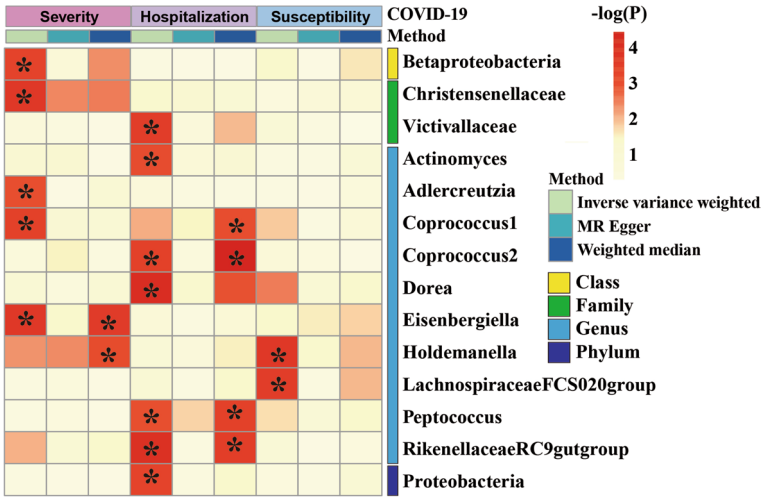

Fig. 2 IVW, MR Egger, and weighted median results of the causal relationship between gut microbiota and COVID-19 risk. *, $p < 0.05$

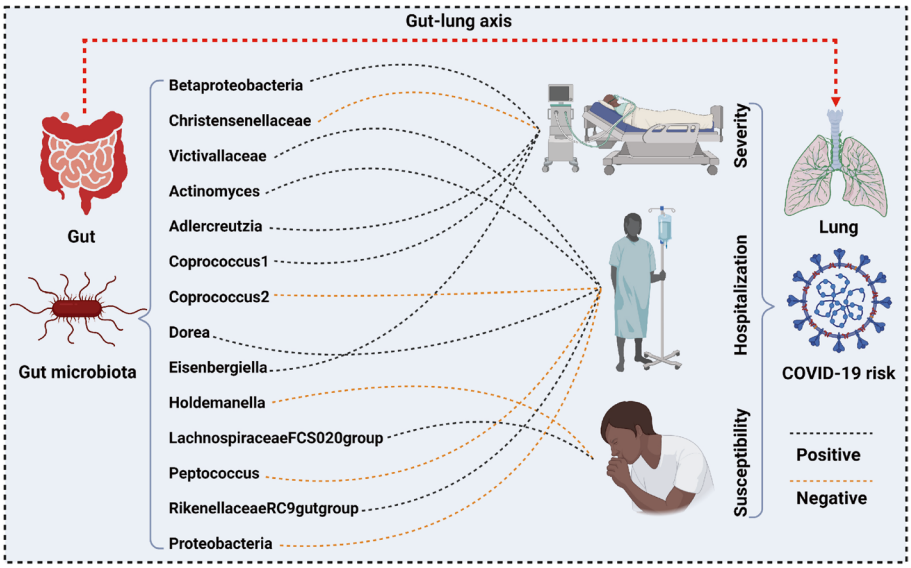

Fig. 3 The gut-lung axis suggests an important role for gut microbiota in the infection and exacerbation of COVID-19. The figure was created by the Biorender

(Fig. 3). The SNPs of these microbial taxa used for MR analysis were listed in Supplementary Tables 7–13, respectively. Third, for COVID-19 susceptibility, the IVW method identified one microbial taxa, namely, *Lachnospiraceae FCS020 group* (beta = 0.026, $p = 0.027$), was related to an increased risk of COVID-19 susceptibility; one microbial taxa, namely, *Holdemanella* (beta = -0.024, $p = 0.023$), was related to a reduced risk of COVID-19 susceptibility (Fig. 3). The SNPs of these microbial taxa used for MR analysis were listed in Supplementary Tables 14–15, respectively.

There were no pleiotropy and heterogeneity effects among the selected SNPs using the MR-Egger intercept test, MR-PROSSO global test, and Cochran's Q test (Supplementary Tables 17–19). Scatter plots, funnel plots, and leave-blank plots are shown in Supplementary Figs. 1–9.

The potential mediators and underlying mechanisms between gut microbiota and COVID-19 outcomes

Finally, we employed multi-omics mediator analyses to elucidate the role of three types of mediators in the association between gut microbiota and COVID-19

outcomes, aiming to uncover potential pathological mechanisms within the gut-lung axis. MR analyses utilizing plasma proteins as mediators revealed that numerous proteins mediated the causal link between these microbial taxa and COVID-19 outcomes, such as EFNA3, PCNP, TIGIT, BDNF, and MAP3K3 (Fig. 4). MR analyses utilizing plasma metabolites as mediators revealed that numerous plasma metabolites mediated the causal link between these microbial taxa and COVID-19 outcomes, such as picolinate levels, ceramide

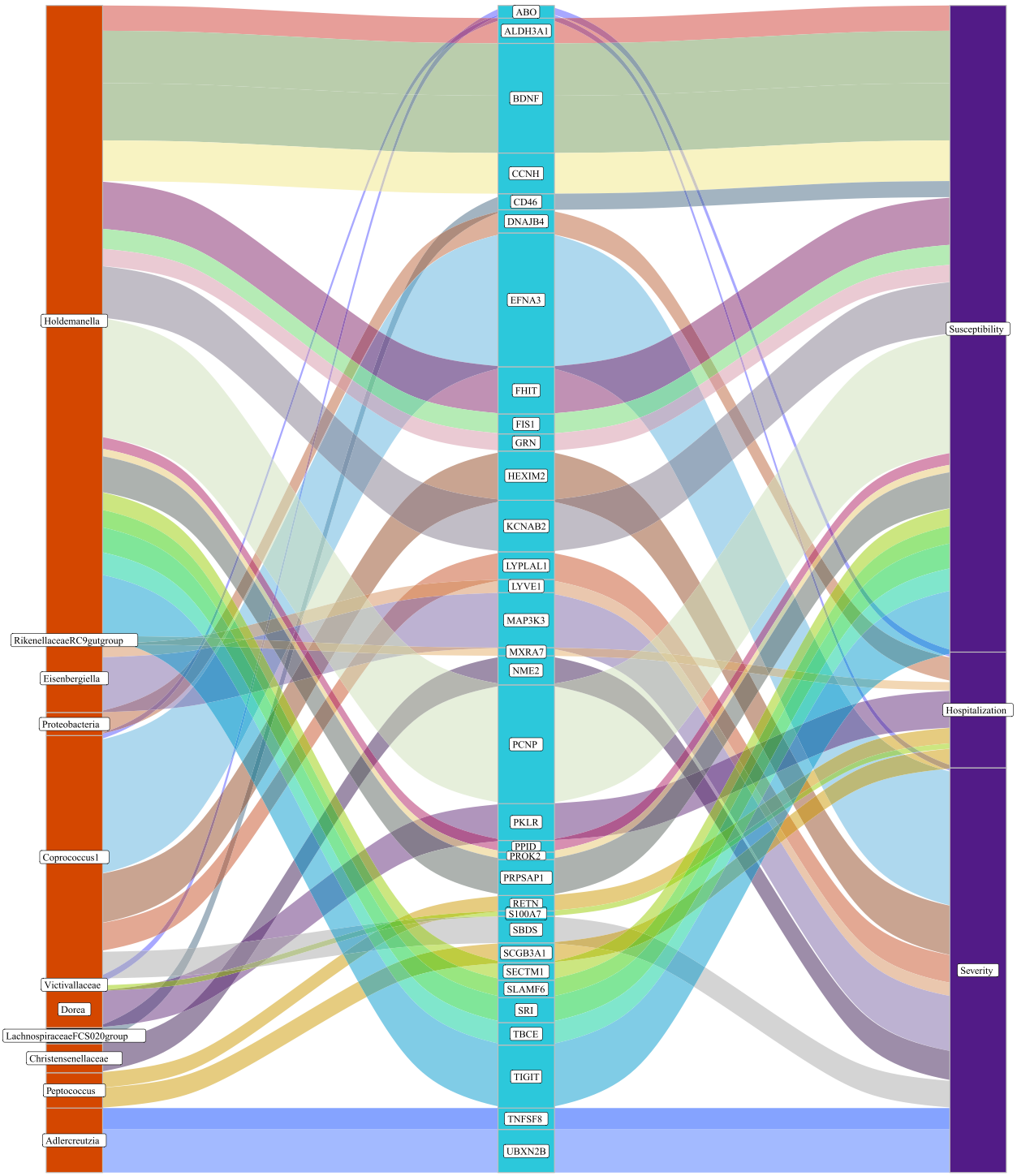

Fig. 4 The mediating role of plasma proteins between gut microbiota and COVID-19 outcomes

(d18:1/16:0) levels, aspartate to mannose ratio, 5alpha-pregnant-3beta,20beta-diol mono sulfate levels, and pimeloylcarnitine/3-methyladipoylcarnitine (C7-DC) levels (Fig. 5). MR analyses utilizing immune traits as mediators revealed that numerous immune cells mediated the causal link between these microbial taxa and COVID-19 outcomes, such as TCRgd T cell absolute count, CD14 on monocytic myeloid-derived suppressor cells, CD11c on CD62L + myeloid dendritic cell, CD27 on IgD- CD38- B cell, and CD8 on CD28 + CD45RA- CD8 + T cell (Fig. 6). Details are shown in the Supplementary Table 20.

Discussion

To the best of our knowledge, this is the first time to systematically clarify the causal effect and underlying mediators of gut microbiota on COVID-19 outcomes using large-scale public databases. This paper performed a two-sample ME approach for 211 gut microbiota taxa based on 24 cohorts (18,340 cases) to investigate the potential role of intestinal flora in the severity, hospitalization, and susceptibility leading to COVID-19. In total, findings of our results revealed four gut microbial taxa (i.e., *Beta-proteobacteria*, *Adlercreutzia*, *Coprococcus 1*, and *Eisenbergiella*) that directly contribute to the development of COVID-19 severity, four gut microbial taxa (i.e., *Victivallaceae*, *Actinomyces*, *Dorea*, and *Rikenellaceae RC9 gut group*) that directly contribute to the development of COVID-19 hospitalization, one gut microbial taxa (i.e., *Lachnospiraceae FCS020 group*) that directly contribute to the development of COVID-19 susceptibility. Moreover, findings of our results revealed one gut microbial taxa (i.e., *Christensenellaceae*) that directly contributes to the reduction of COVID-19 severity, three gut microbial taxa (i.e., *Coprococcus 2*, *Peptococcus*, and *Proteobacteria*) that directly contribute to the reduction of COVID-19 hospitalization, one gut microbial taxa (i.e., *Holdemanella*) that directly contribute to the reduction of COVID-19 susceptibility. Furthermore, it was found that a lot of mediators play an important role in the relationship between these gut microbial taxa and COVID-19 outcomes.

Emerging evidence highlights the critical role played by intestinal flora involved in the infection and exacerbation of COVID-19 through the regulation of host immunity. Clinical studies have shown that the type of gut microbiota in people infected with COVID-19 is significantly altered, characterized by an enrichment of opportunistic pathogens, a decrease in beneficial bacteria, and an increase in compound synthesis and metabolism [39]. *Proteobacteria* belong to one of the most abundant phyla, mainly divided into alpha-, beta-, gamma-, and epsilon-*Proteobacteria*, most of which are Gram-negative

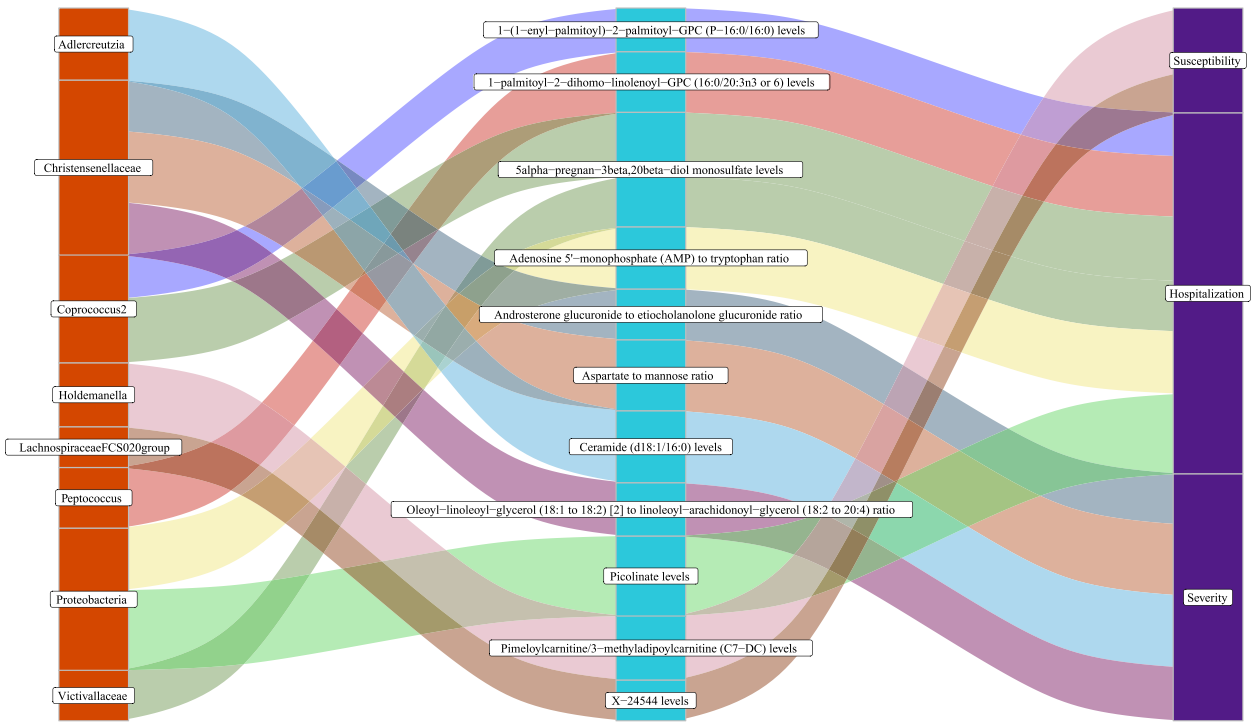

Fig. 5 The mediating role of plasma metabolites between gut microbiota and COVID-19 outcomes

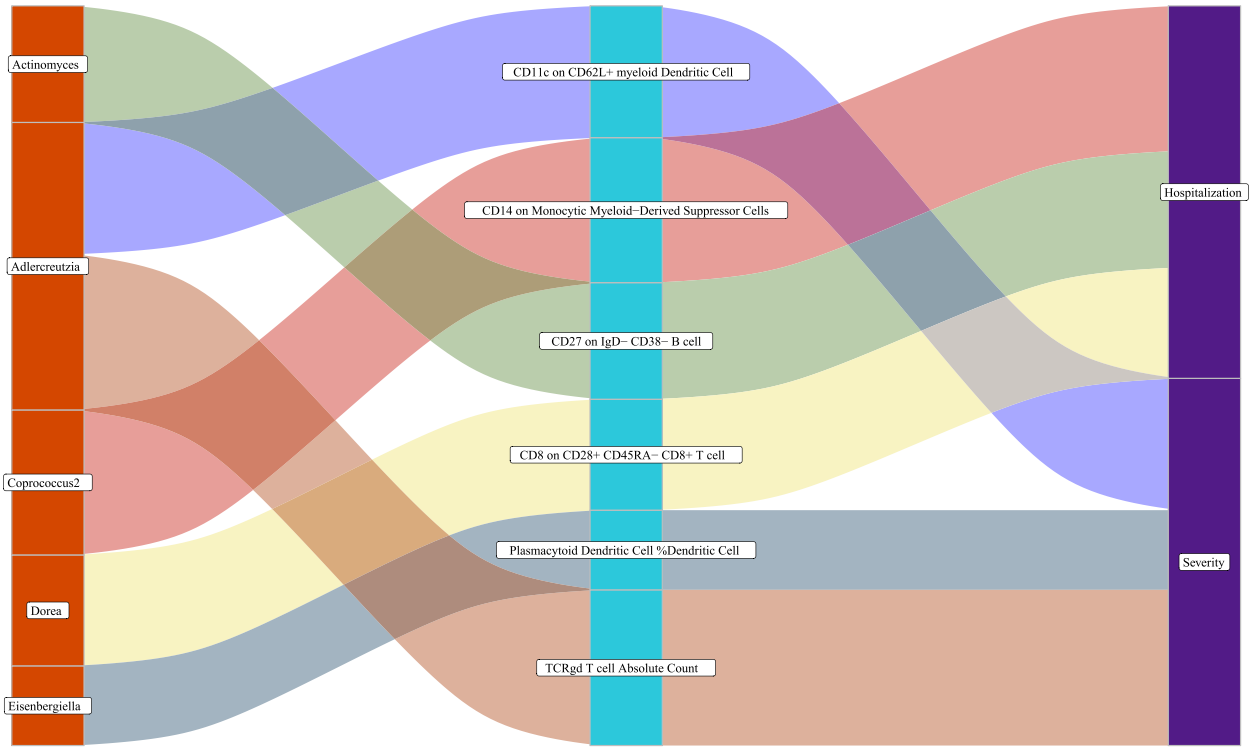

Fig. 6 The mediating role of immune traits between gut microbiota and COVID-19 outcomes

bacteria with outer membranes composed mainly of lipopolysaccharides [40]. Gao et al. found *Proteobacteria*, *phyla Firmicutes*, *Bacteroidota*, and *Fusobacteriota* to be the most predominant intestinal flora in patients with COVID-19. They also found that the expression levels of *Proteobacteria*, *Bacteroidota*, and *Patescibacteria* were decreased, and the expression levels of *phyla Firmicutes* were increased in patients with COVID-19 compared to the healthy population, suggesting that these bacteria may play an important role in COVID-19 immunity [41]. Similarly, another study showed that the degree of abundance of *Proteobacteria* and *Bacteroidetes* was significantly increased in patients with severe COVID-19 [42]. In contrast, in another study of nasopharyngeal microbiome detection by nasal test strips, Gupta et al. found that *Proteobacteria* mRNA expression was significantly higher in COVID-19-infected patients than in uninfected patients, with an average of ~28% (sample size = 89) [43]. Bernard-Raichon et al. found that mice infected with COVID-19 had elevated *c* expression and dysbiosis, which disrupted the intestinal barrier with increased permeability, leading to bacterial and endotoxin entry into the circulation and ultimately exacerbating systemic inflammation [44].

Adlercreutzia is a specialized anaerobic coccus belonging to the phylum *Actinomycetes*, which does not form spores and is not involved in sugar metabolism [45]. Mańkowska-Wierzbicka et al. found that Actinobacteria and Proteobacteria were highly enriched in COVID-19 patients following a 3-month recovery [46]. Depletion of *Adlercreutzia* was more pronounced in the digestive system of COVID-19 patients than in non-COVID-19 subjects after treatment with antibiotics [12]. It was also found that many species, including *Adlercreutzia*, *Dorea*, *Coprococcus*, and *Ruminococcus,* were diminished in patients vaccinated with BNT-162b and CoronaVac [47]. Although the pathological mechanisms and clinical significance of the altered diversity of the intestinal flora caused by the COVID-19 vaccine are unknown, it is theoretically expected to lead to changes in certain lifestyle habits. *Coprococcus* is a genus of anaerobic cocci, including Gram-positive anaerobic cocci involved in carbohydrate metabolism and acid production, which are closely related structurally to *Ruminococcus* and behaviorally to the genus *Lachnospira* [48]. SARS-CoV-2 infection resulted in higher levels of *Lactobacillus* and *Bifidobacterium* and lower levels of *Bacteroidetes*, *Coprococcus*, and *Parabacteroides* compared to conventional influenza virus infection [49]. Meanwhile, COVID-19 patients who tested positive for SARS-CoV-2 RNA had higher fecal IL-18 expression than those who tested negative for SARS-CoV-2 RNA. Xu et al. found that the

abundance of 16 specific gut microbes, including *Coprococcus*, was altered following SARS-CoV-2 infection, leading to impaired polyamine biosynthesis II and sulfur oxidation metabolism and exacerbating COVID-19 severity. Further cellular transcriptome analysis revealed several critical viral transcriptional and apoptotic pathways were upregulated in *Coprococcus* low-level samples [50]. Genus Clostridium such as *Coprococcus*, *Roseburia*, *Lachnospira*, *Dorea*, and *Ruminococcus* can regulate immune and inflammatory responses following SARS-CoV-2 infection by mediating the release of inflammatory cytokines through the modulation of Treg-inducing activity [51]. *Eisenbergiella*, a genus of bacteria from the *Lachnospiraceae* family, was enriched in elderly hospitalized patients infected with SARS-CoV-2 and maintained a high level several weeks after initial diagnosis [52]. Another study found that *Eisenbergiella tayi* and *Actinomyces oris* may contribute to the severity of COVID-19 by regulating energy metabolism, genetic information processing, and biofilm formation [53].

The family *Victivallaceae*, a member of the order *Vibrionaceae*, is a Gram-negative anaerobic bacterium without cilia [54]. So far, the expression of *Victivallaceae* in patients with COVID-19 and the relationship with susceptibility and severity of COVID-19 are still unknown. The results of this paper suggest that *Victivallaceae* contribute to the development of COVID-19 hospitalization and that there is a causal relationship. *Actinomyces*, Gram-positive parthenogenic anaerobic bacteria from the genus *Actinomyces*, are normal inhabitants of the upper respiratory tract [55]. Although the relationship between *Actinomyces* and COVID-19 susceptibility is unknown, *Actinobacteria* rich in BUN and urea were found to have high expression associated with mild COVID-19 and low expression associated with lethal COVID-19 [56]. Evidence suggests that reduced numbers of oropharyngeal *Actinomyces* and *Aspergillus* in COVID-19 patients are associated with improved WHO scores during hospitalization [42]. On the contrary, another two observational studies found that *Actinomyces* expression was upregulated in patients with SARS-CoV-2 infection and correlated with the severity and mortality of COVID-19 [57, 58]. *Actinomyces* may mediate inflammation and immunity in the infection of SARS-CoV-2 by mediating the function of immune cells (e.g., granulocytes and macrophages) in the inflammatory area. *Dorea* is a genus of Gram-positive bacteria commonly found in the intestinal tract, belonging to the family *Lachnospiraceae* and without spores. Treatment with antibiotics in COVID-19 hospitalized patients resulted in a significant decrease in *Dorea formicigenerans*, *Lachnospiraceae bacterium*, *Eubacterium rectale*, and *Ruminococcus obeum* [14]. The *Rikenellaceae RC9 gut group* belongs to a new type of *Rikenellaceae* family that exerts anaerobic metabolism in the digestive tract of some animals. Our results indicated that the *Rikenellaceae RC9 gut group* increases the risk of COVID-19 hospitalization, and there is a causal relationship. Limited studies suggest that the *Lachnospiraceae FCS020 group* is upregulated in the high responder population after injection of SARS-CoV-2 vaccines in healthy people [59]. The *Christensenella* family is a genus of anaerobic and non-sporulating bacteria from *Christensenellaceae* and is positively correlated with the degree of inflammatory response in the lungs. A study by Troseid et al. found that *Christensenellaceae* expression was decreased in COVID-19 patients hospitalized in the ICU [60]. Certain species of bacterial families were significantly reduced after treatment with the SARS-CoV-2 antibody in combination with remdesivir, for example, *Christensenellaceae*, *Barnesiellaceae*, and *Lachnospiraceae* [61]. *Hodmanella* is a Gram-staining positive bacterium common to the human intestine that exerts anti-tumor and anti-inflammatory effects by releasing long-chain- and short-chain fatty acids. Our data suggest that the *Holdemanella* genus has a causal role in reducing COVID-19 sensitivity. Given that SARS-CoV-2 can enter the intestinal epithelium via receptors including ACE-2 and membrane-bound serine protease, the gut-lung axis has become a hot topic for researchers. In particular, a large number of observational studies show a close and non-negligible relationship between gut microbiota and COVID-19 pathological process. Generally, SARS-CoV-2 virus infection causes dysbiosis of the intestinal microbiome, leading to an imbalance of host autoimmunity, ultimately dominating the development of COVID-19.

Both prior research and our own findings suggest a potential role for gut flora in influencing the risk of COVID-19. However, the exact mechanism of gut microbiota participation in the COVID-19 pathological changes remains unclear. Interestingly, we identified several mediators closely associated with immunopathology, which may partially elucidate the specific mechanisms through which gut flora influences the outcomes of COVID-19. DnaJ homolog subfamily B member 4 (DNAJB4), which belongs to the heat shock protein family, serves as a molecular chaperone [62]. It operates by attaching to the cell adhesion protein E-calmodulin and directing it towards the plasma membrane. Research has demonstrated that the knockdown of DNAJB4 results in myofibrillar dysfunction, potentially precipitating early-onset respiratory failure [63]. This paper found that DNAJB4 partially mediated the causality between *Proteobacteria* and COVID-19 hospitalization. TIGIT, also known as a T cell immunoreceptor, is an immune receptor expressed on certain T cells and natural killer (NK) cells. Studies have demonstrated a strong correlation

between the level of TIGIT expression in T cells and the severity of symptoms in COVID-19 patients [64]. This paper detected the mediating role of TIGIT between *Holdemanella* and COVID-19 susceptibility. As a pivotal "bridge" between innate and adaptive immunity, dendritic cells (DCs) serve multiple critical roles in the infection process of SARS-CoV-2. In this study, we discovered that *Eisenbergiella* modulates the severity of COVID-19 by altering the ratio of DCs.

Conclusion

In conclusion, this two-sample MR study is the first to comprehensively explore the causal impact and potential mechanisms of gut microbiota on COVID-19 outcomes. Our findings provide new insights into preventing, developing, and treating SARS-CoV-2 infection by targeting specific bacterial taxa. In this study, we identified potential mechanisms through which gut bacteria may affect COVID-19 progression via various mediators. Nonetheless, more studies are needed to explore the specific pathological mechanisms of these mediating factors. Our findings indicated that timely and effective intervention targeting these gut microbes could mitigate the adverse outcomes of COVID-19. Further exploration of these potential mediators will offer some theoretical basis to elucidate the connection between enterobacteria and COVID-19 prognosis in future studies. However, several limitations of our paper should also be recognized. First, all data analyzed is based on publicly available online data and lacks data from other sources or our own data for validation. Second, considering the relatively limited number of SNPs in the gut microbiota datasets, we could only include SNPs that met the gene-wide locus significance level ($p < 1 \times 10^{-5}$) in this study. Third, the data for the outcome are all from European populations. The exposed data are primarily from European populations and a small proportion from other races, which may lead to partial bias in the results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12866-024-03423-0.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

JW-Z and PL conceived, designed, and funded the research. JW-Z and JW wrote the first draft of the manuscript. HL, JW-Z, JW, XB-Z, ZY-D, HZ, NZ, RY-L, PL, and MR-L contributed to data acquisition, analysis, and interpretation. HL, JW-Z, JW,XB-Z, ZY-D, HZ, NZ, RY-L, PL, and MR-L contributed to the revision of the paper. All authors contributed to the article and approved the final manuscript.

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Availability of data and materials

All data used in this study were available in the original research. Data generated in this study were included in the main text and supplementary files.

Declarations

Ethics approval and consent to participate

All data used by this study were publicly available from participant studies with the approvement of the ethical standards committee related to human experimentation. No additional ethical approval was required in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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