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No Durable Impact of COVID-19 on Intestinal Disease Activity in Subjects With IBD

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Although patients with inflammatory bowel disease (IBD) reported an increased frequency of gastrointestinal (GI) symptoms following infection,[1,2] the durable impact of COVID-19 on IBD activity and the microbiome is not well defined. Our study aims were to compare clinical, endoscopic, and laboratory markers of disease activity and the fecal microbiome in IBD participants 6 months pre- and post-COVID-19.

Methods

Using an established longitudinal cohort, we identified 118 IBD patients with COVID-19 infection (Supplementary Table 1). Clinical characteristics and disease activity were assessed up to 6 months before COVID-19, during COVID-19 (defined as 1–30 days postinfection), and up to 6 months after. Active disease was defined by a Harvey Bradshaw Index >4, Mayo Score ≥2, Simple Endoscopic Score-Crohn's Disease ≥2, or Mayo Endoscopic Score ≥1. 16S rRNA sequencing of V4 and V5 regions was analyzed using USEARCH and RDP database to generate OTU tables (Supplementary Methods).

Results

Although upper respiratory and new GI symptoms were common in patients with IBD (Supplementary Table 1), there were no significant changes in IBD clinical disease activity, endoscopic evaluation, or laboratory markers up to 7 months post-COVID-19 compared with the most recent evaluation up to 6 months before infection (Table 1). Active disease was present in 60% of the cohort before COVID-19 and 55% and 59% during and post-COVID-19, respectively.

Ten patients in our cohort reported a delay in medical therapy and 8 discontinued IBD medications during COVID-19; however, this subset and the 43 participants reporting GI symptoms during COVID-19 had no significant change in disease activity (Table 1). There were no differences in the need for corticosteroids, a change in medical therapy, or IBD-related surgery or hospitalization during or post-COVID-19 compared with the prior 6 months.

Preliminary studies in hospitalized patients with severe COVID-19 suggested the potential impact of infection on the microbiome.[3] From a subset of 12 patients for whom fecal samples were available before COVID-19, 16S rRNA sequence was performed to assess the impact of infection on microbiome composition. Paired and unpaired analysis between pre- and post-COVID-19 samples revealed no significant difference in alpha diversity (Shannon index, Supplementary Figure 1*A*) or beta diversity (Bray-Curtis distance metric, Supplementary Figure 1*B*). Similar to previous results suggesting that IBD activity correlates with changes in the microbiome,[4] principal coordinate analysis of Bray-Curtis distance metric revealed that the microbiome of mild disease (Harvey Bradshaw Index 5–7 or Mayo 3–5) was distinct from moderate disease (Harvey Bradshaw Index 8–16 or Mayo 6–10; Supplementary Figure 1*C*); however, there was no significant change comparing pre- and post-COVID-19 samples (Supplementary Figure 1*D*). In contrast, individual participants over time remained distinct (PERMANOVA, Subject × Time; $P = .04$; Supplementary Figure 1*E*). Similarly, principal coordinate analysis revealed no significant differences when stratified by those affected by COVID-19-associated diarrhea (Supplementary Figure 1*F*).

Discussion

With the increased frequency of new GI symptoms associated with COVID-19 in patients with IBD, there was initial concern that infection may lead to durable negative effects on IBD activity. This concern was further compounded by the need to delay or discontinue immunosuppressive therapy in IBD patients with active

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COVID-19.[5] Reassuringly, our data reveal no significant impact on disease activity during 6 months follow-up post-COVID-19. Although subjects profiled in this study were primarily managed as outpatients, most suffered from respiratory symptoms and about one-third with new-onset GI symptoms.[1,2] Given the limited number of subjects in this study with severe COVID-19, it is important to follow additional cases of severe COVID-19 in patients with IBD and to assess the impact of long-haul symptoms. Encouragingly, these results indicate no significant need for IBD-related surgery or hospitalization.

Initial reports suggesting distinct changes in the microbiome of patients with severe COVID-19 raised the possibility that patients with IBD may be at higher risk for microbiome alterations, which could subsequently impact disease activity.[3] Although our data show microbiome differences based on disease activity, we did not detect distinct changes in participants before and after COVID-19. Although validation in additional cohorts is required, our microbiome analysis reflects the first

What You Need to Know

Background

Although patients with inflammatory bowel disease reported an increased frequency of gastrointestinal symptoms following infection, the durable impact of COVID-19 on IBD activity and the microbiome is not well defined.

Findings

Longitudinal follow-up data over 6 months revealed no durable impact of COVID-19 on clinical IBD disease activity or microbiome composition.

Implication for patient care

While validation in additional cohorts is required, these data reassuringly suggest no long-term impact of COVID-19 on IBD disease activity and support guidelines for continued IBD maintenance care during the pandemic.

Table 1. Clinical, Endoscopic, and Laboratory Markers Pre-, During, and Post-COVID-19

Variables	Pre-COVID -180 to -1 d	COVID 0 to +30 d	Post-COVID +31 to +210 d	*P* value Pre vs Post
Clinical DAI, Avg (n)				.7397
HBI	4.7 (50)	4.7 (21)	4.9 (41)	.74
PMS	3.0 (25)	4.8 (6)	2.1 (19)	.24
Endoscopic DAI, Avg (n)				
SES-CD	7.2 (17)	7 (1)	8.9 (15)	.69
MES	1.5 (9)	2 (1)	1.7 (11)	.70
Biomarkers, Avg (n)				
C-reactive protein	1.2 (83)	2.5 (15)	1.3 (56)	.18
ESR	25 (63)	25 (14)	26 (44)	.95
Hemoglobin	12.8 (84)	12.6 (26)	13.2 (60)	.50
Fecal calprotectin	388 (44)	522 (12)	250 (40)	.20
Active disease, n (%)	49 (60)	16 (55)	38 (59)	.87
Delayed/discontinued	9 (69)	5 (83)	4 (40)	
COVID-19 GI symptoms	20 (61)	8 (39)	20 (71)	
Need for surgery, n (%)	3 (2.8)	0 (0)	2 (1.8)	.68
Need for IBD hospitalization, n (%)	6 (5.6)	2 (1.7)	7 (6.2)	> .99
Medication change, n (%)	53 (50)	33 (28)	45 (40)	.14
Newly started	42 (40)	14 (12)	36 (32)	
Steroid	17 (16)	4 (3.4)	15 (13)	
Delayed	2 (1.9)	10 (8.5)	5 (4.4)	
Discontinued	20 (19)	8 (6.8)	15 (13)	

NOTE. Unpaired Mann-Whitney and paired Wilcoxon revealed no significant differences between pre- and post-COVID-19 clinical, endoscopic, and laboratory values. Fisher exact test was used to compare differences in patient number with active disease, need for surgery, hospitalization, or medication change.
DAI, disease activity index; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; MES, Mayo Endoscopic Score; PMS, partial Mayo score; SES-CD, Simple Endoscopic Score-Crohn's Disease.

longitudinal analysis of the fecal microbiome before and after COVID-19. Moreover, these findings are consistent with more recent reports suggesting that microbiome changes seen in patients with severe COVID-19 may reflect antibiotic use as part of hospital care rather than COVID-19 severity.[6] Collectively, these data reveal no durable impact of COVID-19 on clinical IBD disease activity or microbiome composition and provide data supporting the current guidelines for continued IBD maintenance care during the pandemic.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.06.008.

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Reprint requests
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Conflicts of interest
The authors disclose the following: Dana J. Lukin has served as a consultant for AbbVie, Boehringer Ingelheim, Palatin, and Pfizer and received grant support from AbbVie, Janssen, Takeda, and the Kenneth Rainin Foundation. Randy S. Longman has served as a consultant for Pfizer and Bristol Myers Squibb. Ellen Scherl has served as a consultant and on the advisory board for AbbVie, Entera Health, Evidera, GI Health Foundation, Janssen, Protagonist Therapeutics, Seres Health, Takeda Pharmaceuticals, and Bristol Myers Squibb, received grant support from Abbott (AbbVie), AstraZeneca, Janssen Research and Development, Pfizer, UCB, the UCSF–CCFA Clinical Research Alliance, Genentech, Seres Therapeutics, and Celgene Corporation, is a shareholder of Gilead, and has received nonbranded Speakers Bureau honoraria from GIHealth Foundation and Janssen. The remaining authors disclose no conflicts.

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Supplementary Methods

IBD clinical disease activity (Harvey Bradshaw Index, partial Mayo score), endoscopic score, and laboratory markers (erythrocyte sedimentation rate, C-reactive protein, hemoglobin, fecal calprotectin) were assessed up to 6 months before COVID-19, during COVID-19 (defined as 1–30 days postinfection), and up to 6 months after. Values were compared using unpaired Mann-Whitney or paired Wilcoxon tests. The need for corticosteroids, a change in medical therapy, or IBD-related surgery/hospitalization during or post-COVID-19 was compared with the preceding 6 months. Values were compared using Fisher exact test. In a subset of 12 patients, 16S rRNA sequencing was performed as previous described and data were rarified at 10,000 reads per sample. Briefly, the 16S rRNA gene V4 and V5 regions were amplified as previously described (https://earthmicrobiome.org). Amplicons were then sequenced in an Illumina MiSeq platform using the 2 $\times$ 250 bp paired-end protocol. Read pairs were processed using USEARCH[1] and the RDP database[2] to generate a rarefied OTU table. Alpha and beta diversity analyses were then performed at the OTU-level. Microbiome analysis was performed in R studio (Boston, MA). Alpha and beta diversity was calculated using R package "phyloseq,"[3] whereas plots were constructed in "ggplot2." Beta divergence based on Bray-Curtis dissimilarity was calculated using microbiome package in R studio. Bray-Curtis distance metric was used to evaluate microbiome composition before and after COVID-19 and Monte Carlo permutation test (PERMANOVA) was used to assess differences between centroids shown in the principal coordinate plots.

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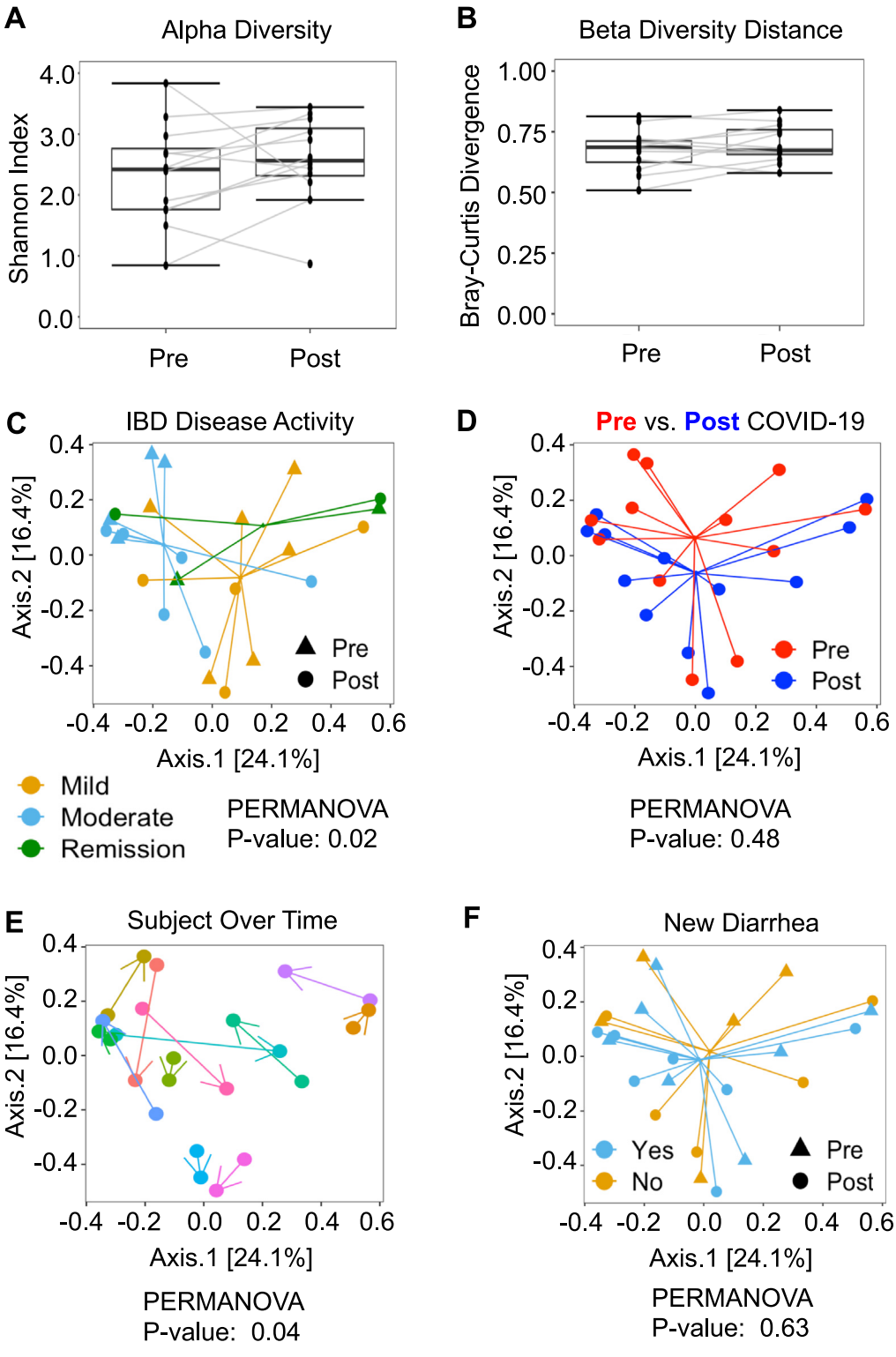

Supplementary Figure 1. IBD fecal microbiome before and after COVID-19. (*A, B*) Shannon index and Bray-Curtis divergence is shown for paired 16S rRNA microbiome samples from 12 participants pre- and post-COVID-19. (*C–F*) Principal coordinate analysis using Bray-Curtis distance metric showing the microbiome composition stratified by (*C*) IBD disease activity, (*D*) pre- or post-COVID-19, (*E*) individual participants (color coded), or (*F*) new diarrhea symptom. *P* value determined by PERMANOVA is shown.

Supplementary Table 1. Clinical Characteristics and Comorbidities of COVID-19 IBD Cohort

Variable	All IBD (n = 118)
Age, *y*, mean (SD)	42.1 (16)
Sex, n (%)	
Female	63 (54)
Male	54 (46)
IBD type	
Crohn's disease	73 (62)
Ulcerative colitis	40 (34)
Other colitis	5 (4.2)
Body mass index, kg/m^2 average (SD)	27 (6.8)
Comorbidities, n (%)	
Obesity	30 (25)
Former smoker	23 (20)
Current smoker	2 (1.7)
Diabetes	5 (4.3)
CAD	2 (1.7)
Heart failure	1 (0.9)
Hypertension	20 (17)
Asthma	8 (6.9)
COPD	0 (0)
Cirrhosis	1 (0.9)
Chronic kidney disease	1 (0.9
Current medications, n (%)	
Any biologic	65 (55)
Anti-TNF	23 (20)
Vedolizumab	22 (19)
Ustekinumab	20 (17)
JAK inhibitors	6 (5.1)
Immunomodulator	4 (3.4)
Steroids	19 (16)
Prednisone	8 (6.8)
Budesonide	11 (9.3)
Mesalamines	
Oral	40 (34)
Rectal	25 (21)
Hypertension medications	17 (15)
ACE-ARB medications	7 (6.0)
NSAIDS	4 (3.4)
COVID-19 symptoms, n (%)	
Upper respiratory	97 (87)
Gastrointestinal	43 (39)
COVID treatment, n (%)	
Steroids	6 (5.4)
Azithromycin	20 (18)
Hydroxychloroquine	12 (11)
Lopinavir/ritonavir	0 (0)
Tocilizumab	1 (0.9)
Remdesivir	1 (0.9)
Other antibiotics	2 (1.9)
COVID outcomes, n (%)	
ED visit	18 (15)
Hospitalization	8 (6.8)
Ventilation	1 (0.9)
ICU	1 (0.9)
Death	0 (0)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ED, emergency department; IBD, inflammatory bowel disease; ICU, intensive care unit; NSAIDS, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TNF, tumor necrosis factor.