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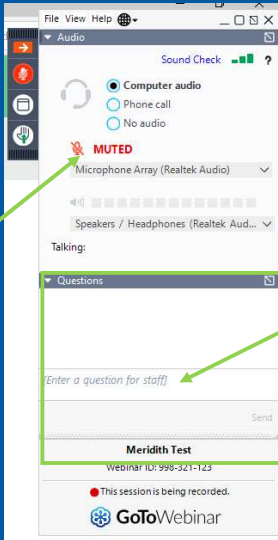
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## Participating in the Webinar



All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

Meridith Test  
Webinar ID: 998-221-123  
This session is being recorded.  
GoToWebinar

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## How to Receive CME and MOC Points

**LIVE VIRTUAL GRAND ROUNDS WEBINAR**

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

**ABIM Board Certified physicians need to complete their MOC activities by December 31, 2023 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2024 for this activity.**

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## MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.  
THESE ANSWERS WILL BE REVIEWED.

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3rd Space Endoscopy  
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Moderator: Vivek Kaul, MD, FACG  
At Noon and 8pm Eastern



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Moderators: Vivek Kaul, MD, FACG and Vladimir M. Kushnir MD  
Faculty: Amer AlSamman, MD; Adam Buckholz, MD; Daniel Castaneda, MD; Sarah M. Enslin, PA-C; and Daniela Guerrero Vinsard, MD  
Panelists: Prabhleen Chahal, MD, FACG; Jean Chalhoub, MD; Ryan B. Perumpail, MD; Aparna Repaka, MD; Brandon A. Wuerth, MD

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## Disclosures



**Max J. Schmulson, MD**

Alfasigma Mexico: Advisory Board, Grant Support, Speakers Bureau;  
Carnot: Speakers Bureau;  
Ferrer Central America: Grant Support, Speakers Bureau;  
Gemelli Biotech: Advisory Board, Consultant;  
Laboratorios Tecnofarma SA Bolivia: Speakers Bureau;  
Medicamenta Ecuatoriana S.A.: Speakers Bureau;  
Medix: Speakers Bureau;  
Megalabs Ecuador: Speakers Bureau;  
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**Sarah K. McGill, MD, MSc, FACG**

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Finch Pharmaceuticals: Research Grant;  
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Guardant Health: Research Grant;  
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Seattle Genetics: Stockholder

*\*All of the relevant financial relationships listed for these individuals have been mitigated*

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## Post-COVID-19 Disorders of Gut-Brain Interaction (DGBI)/Functional Gastrointestinal Disorders (FGID)

**Dr. Max Schmulson W.**



Professor of Medicine

Laboratory of Liver, Pancreas and Motility (HIPAM)-Unit of Research in Experimental Medicine, Faculty of Medicine-Universidad Nacional Autónoma de México (UNAM).

Gastroenterology and Endoscopy, American British Cowdray (ABC) Medical Center.

Gastroenterology and Gastrointestinal Motility, Clínica Lomas Altas.

Mexico City

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### Síntomas GI en COVID-19

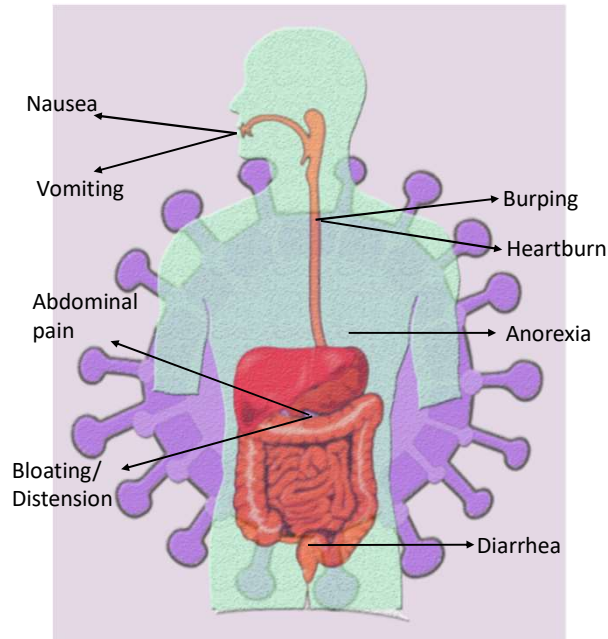
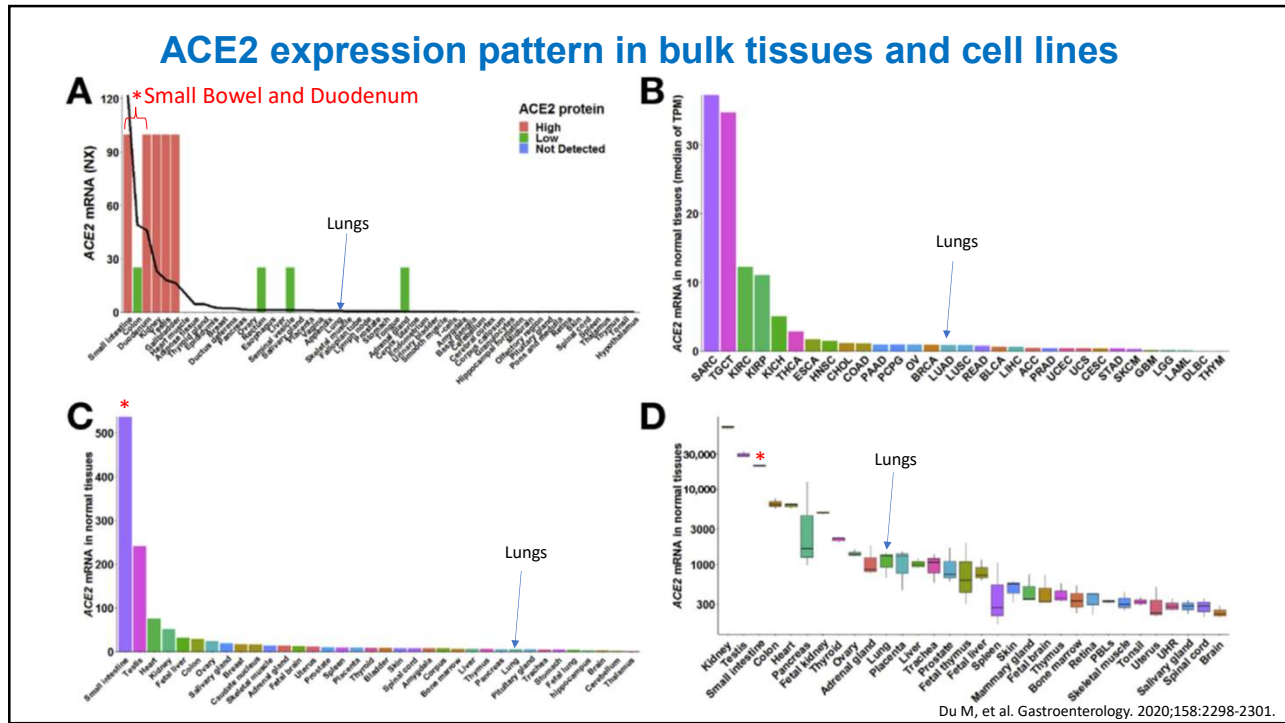


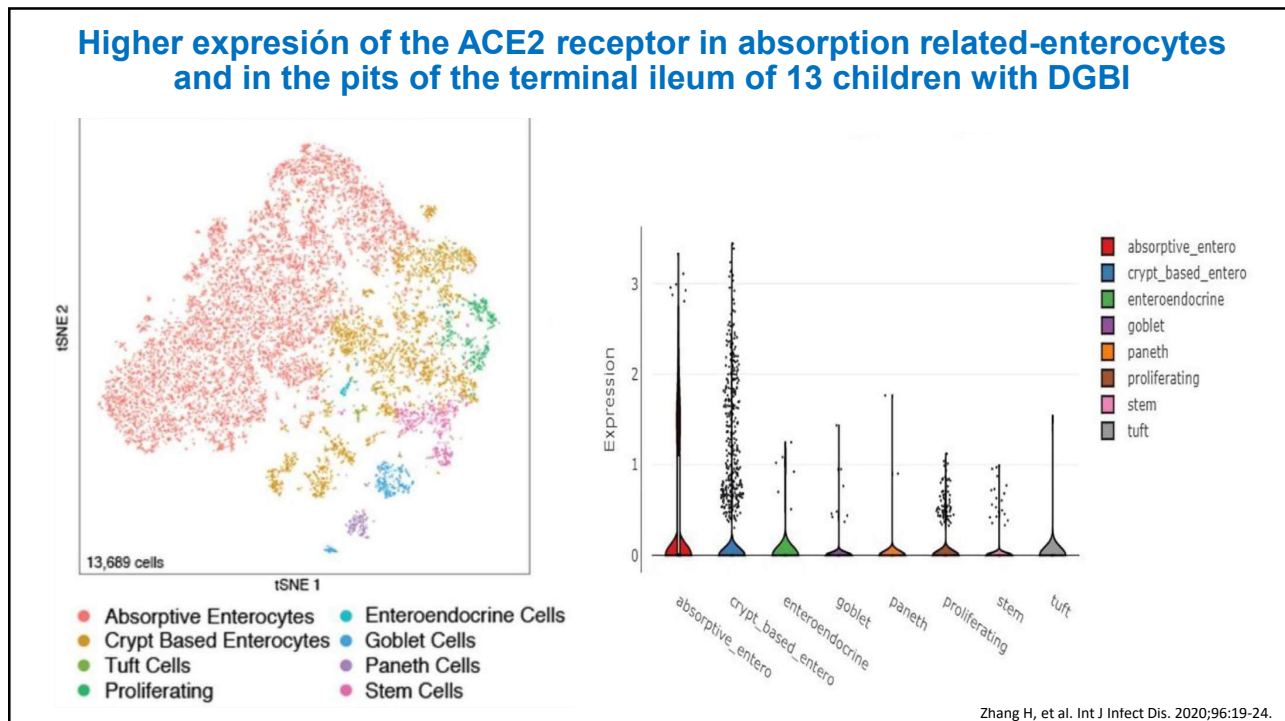
Figure by Marco Gudiño-Zayas and Max Schmulson  
Unit of Experimental Medicine, Faculty of Medicine-UNAM. 2020.

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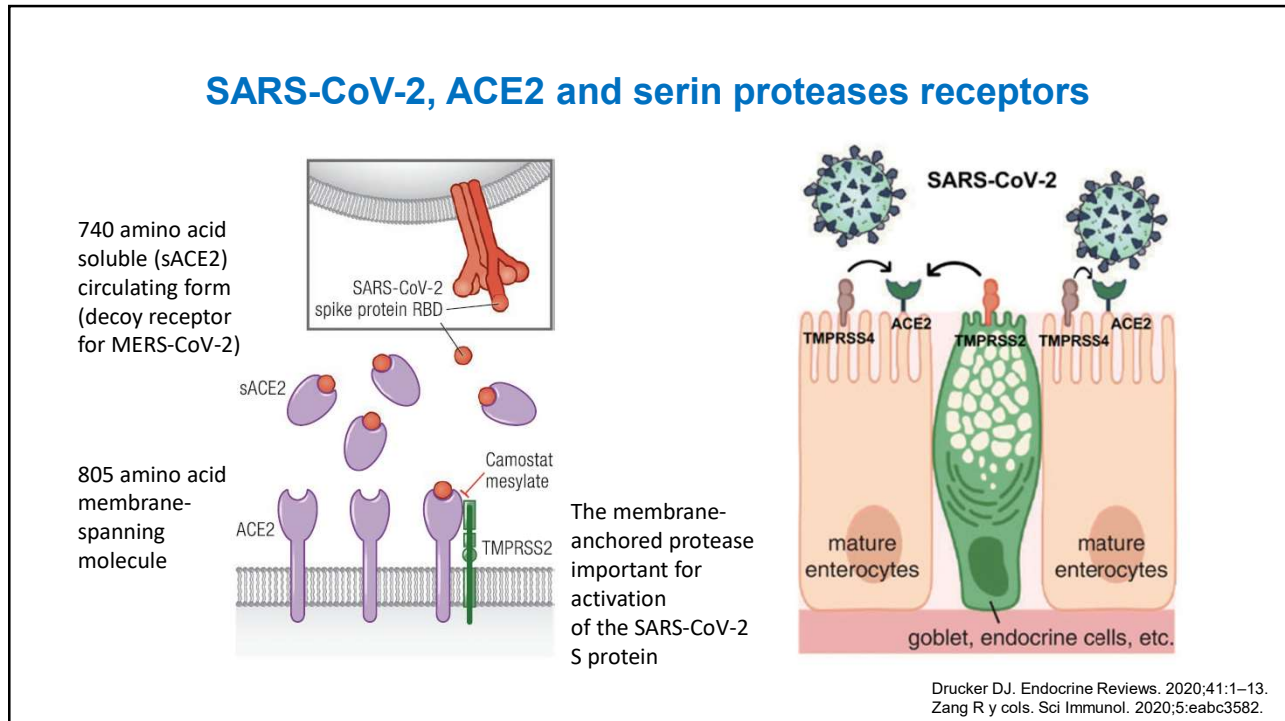


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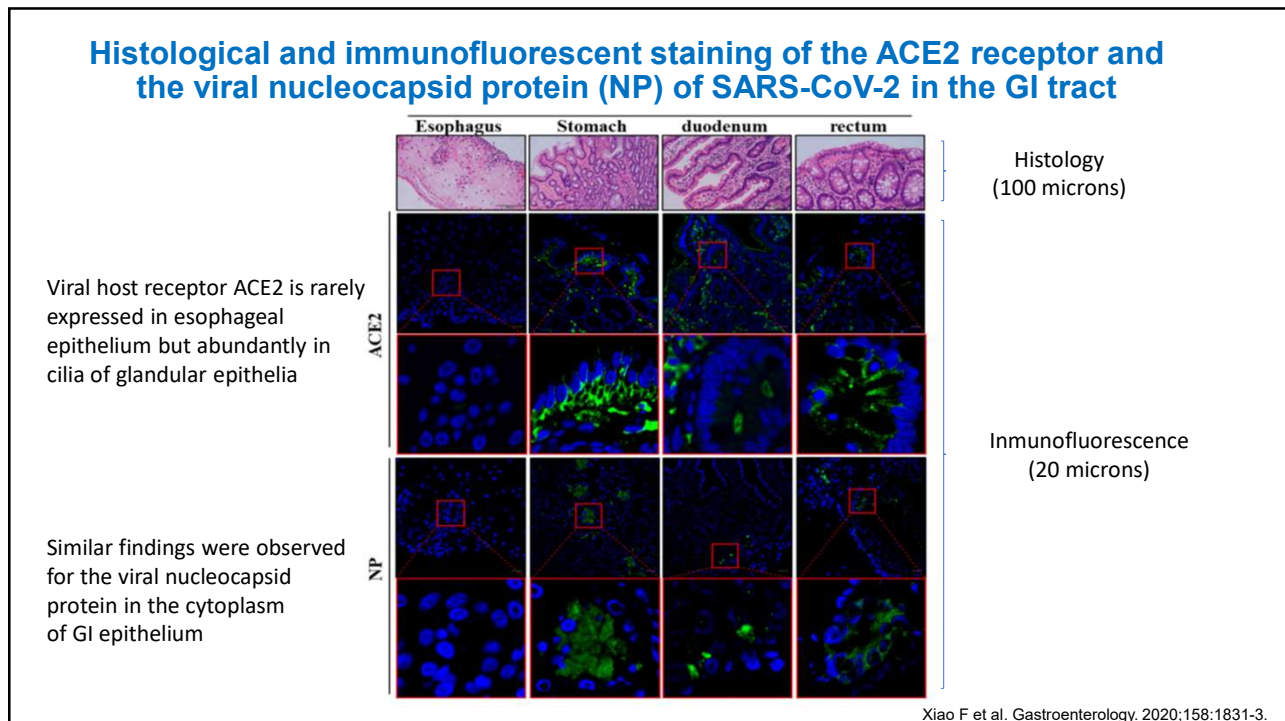


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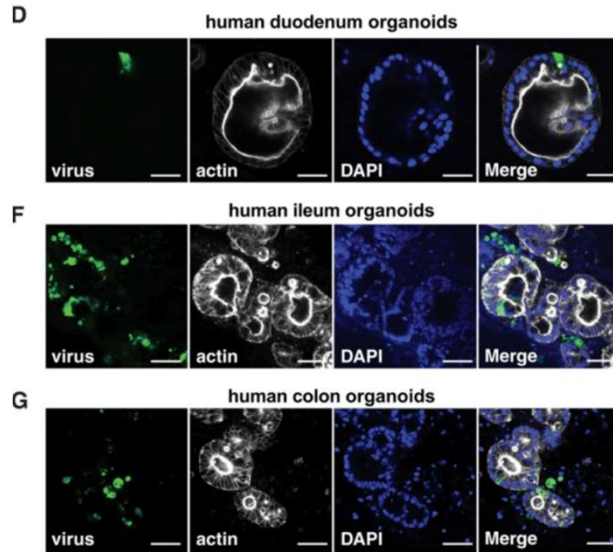
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## Infection of SARS-CoV-2 in ACE2+ mature enterocytes in human small intestinal and colonic organoids

Using a chimeric vesicular stomatitis virus (VSV) in which the native glycoprotein (G) was genetically replaced with SARS-CoV-2 S protein

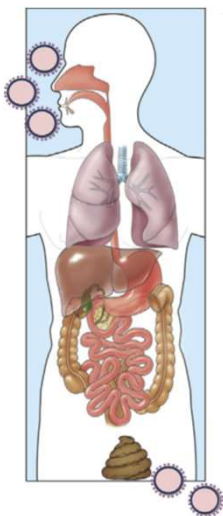


Enteroids were stained for:  
 -Virus (green)  
 -Actin (phalloidin, white)  
 -Nucleus (DAPI: 4',6-Diamidino-2-phenylindole, blue)

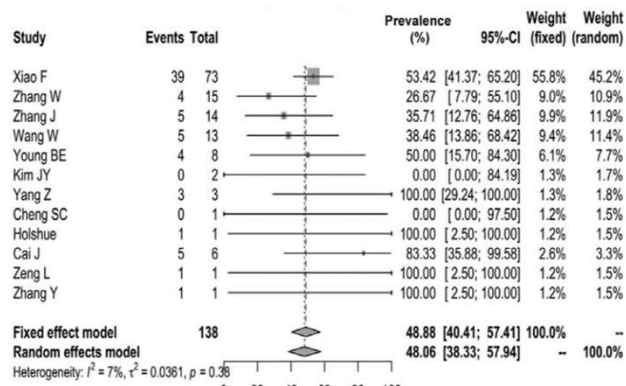
Zang R et al. Sci Immunol. 2020;5:eabc3582.

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## Stool viral RNA positivity rate

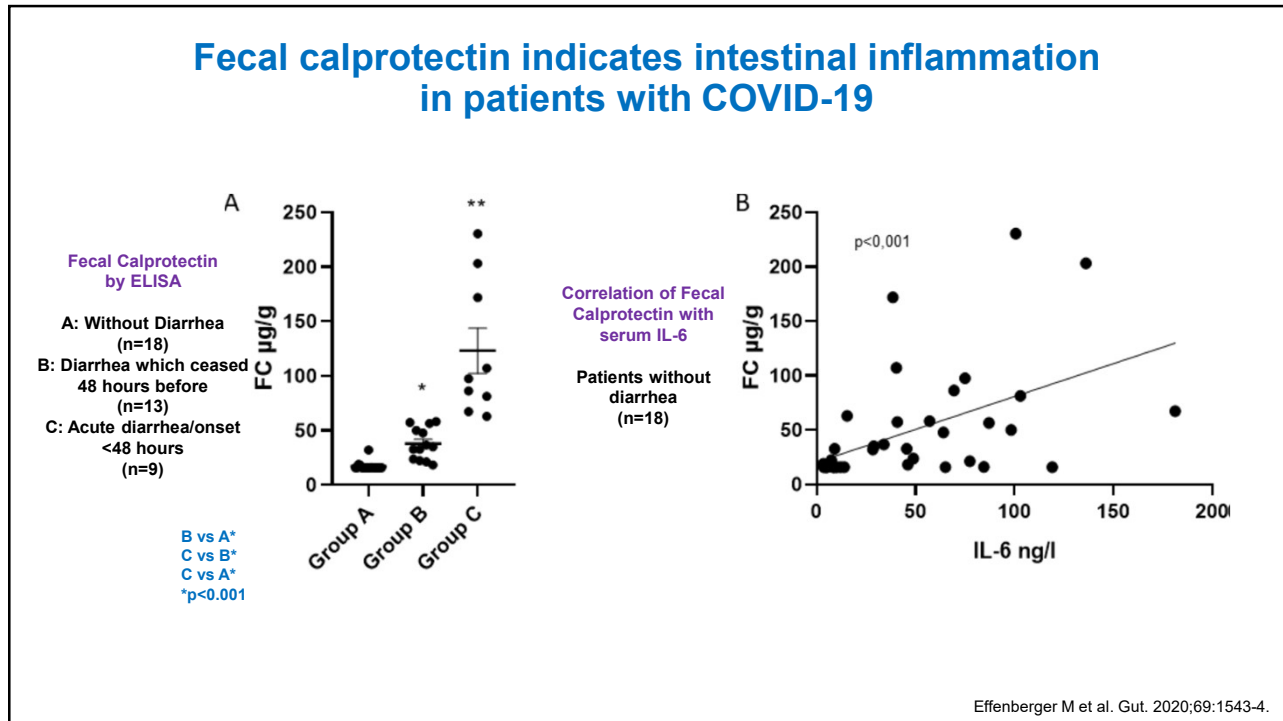


### Stool viral RNA positivity rate

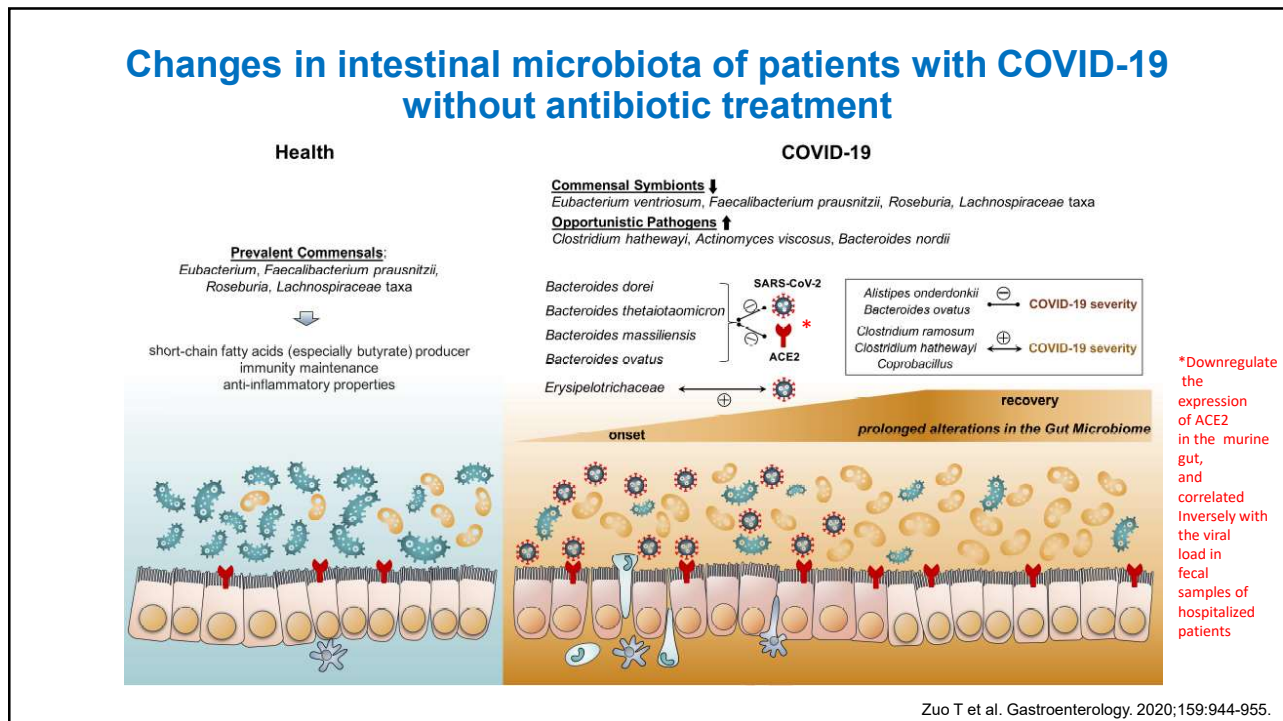


Cheung KS et al. Gastroenterology 2020;159:81-95.

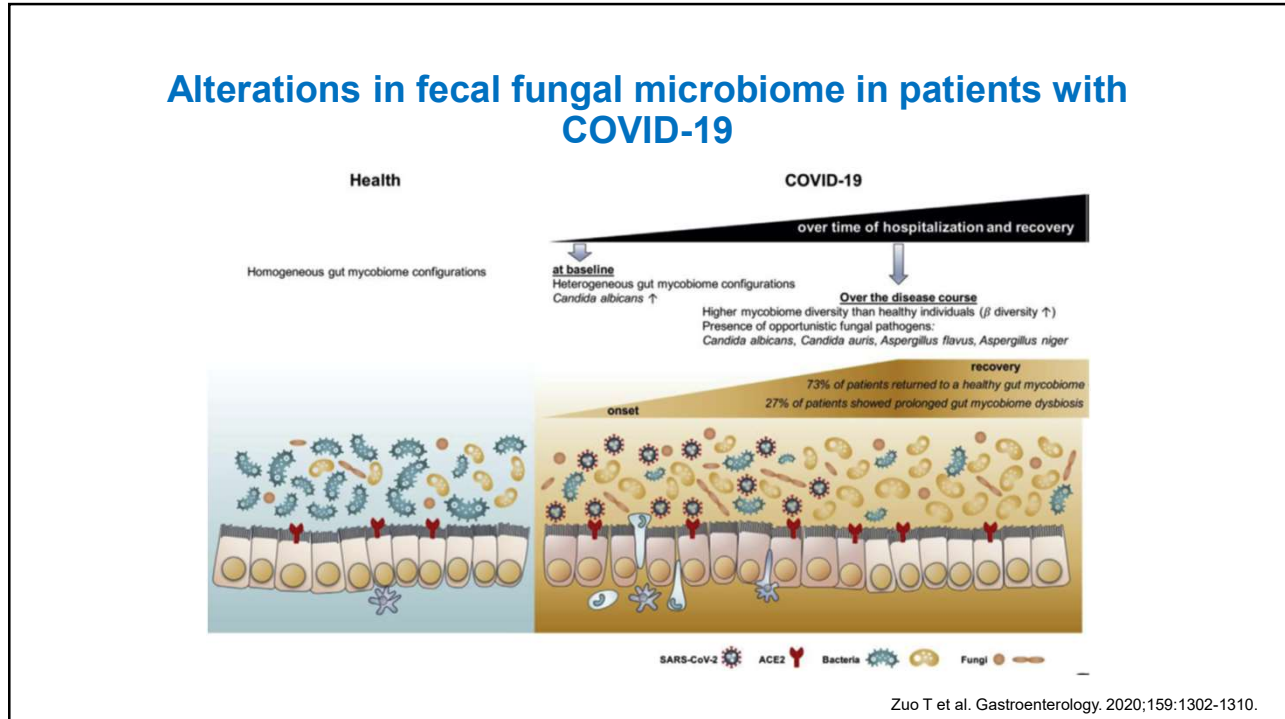
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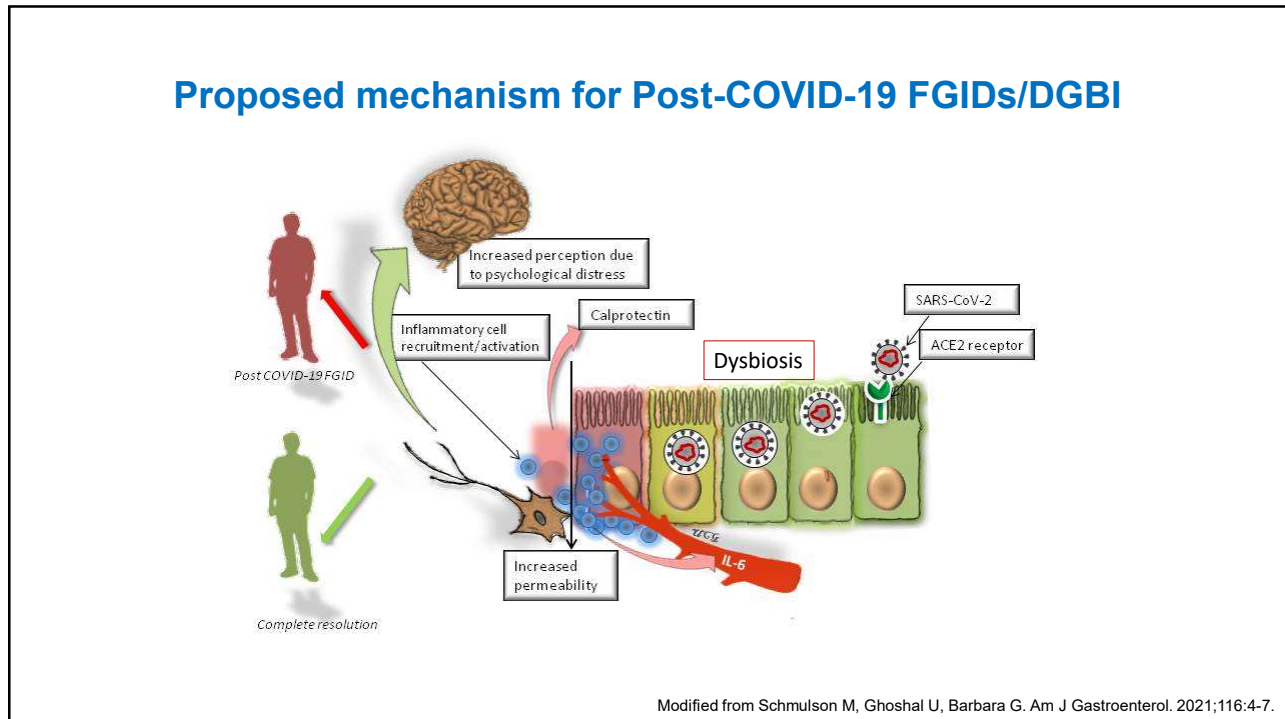
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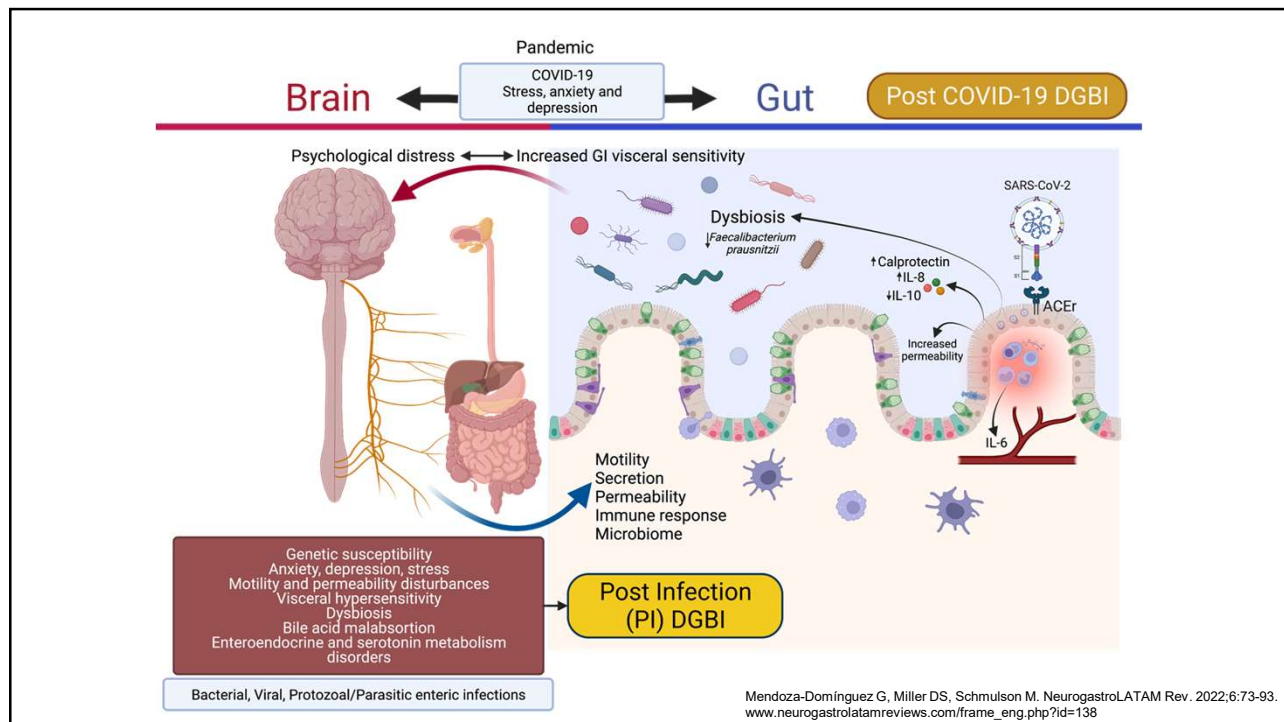
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## Proposed diagnostic criteria for Post-COVID-19 FGIDs/DGBI

### 1. Fulfilling Rome IV criteria for any FGID in the last 3 months, with symptom onset at least 6 months before diagnosis associated with:

- Previous COVID-19 infection confirmed by SARS-CoV-2 Real Time-PCR performed at Regional Reference Laboratories
- Symptom development immediately after resolution of acute COVID-19 infection

### 2. Should not meet criteria for FGIDs before onset of acute illness

FGIDs: Functional gastrointestinal disorders; DGBI: Disorders of Gut-Brain Interaction; COVID-19: Coronavirus Disease 2019, SARS-CoV-2, Severe acute respiratory syndrome - Coronavirus - 2; PCR, Polymerase chain reaction

Schmulson M, Ghoshal U, Barbara G. Am J Gastroenterol. 2020;116:4-7.

26

### Effects of home confinement and social distancing in the general population: Syst. Rev. 26 studies

**Anxiety**

- Prevalence: 8.3% a 45.1%

**Depression**

- Prevalence: 14.6% a 46.4%

**Most vulnerable ones:**  
**Females, Younger age, Unemployed, Previous mental health or psychiatric illnesses**

### Mental disorders following COVID 19 and other epidemics: Syst. Rev and Metaanalysis 247 on COVID 19

**Probable Anxiety**

- Prevalence: 20.7% (IC 95% 12.9-29.7)

**Probable Depression**

- Prevalence: 18.1% (IC 95% 13.0–23.9)

**Psychological Distress**

- Prevalence: 13.0% (IC 95% 0–34.1)

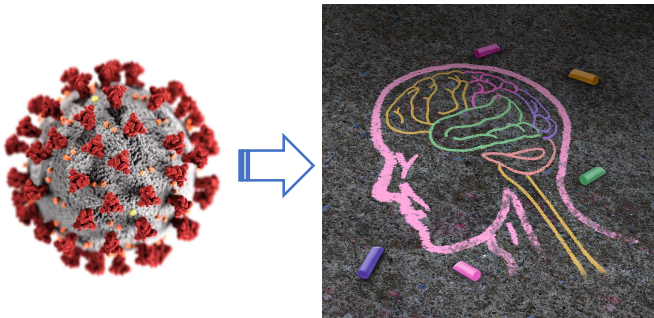
**Most vulnerable ones:**  
**Female sex, Lower income, Pre-existing medical conditions, Perceived risk of infection, Exhibiting COVID-19-like symptoms, Use of social media, Financial stress, Loneliness**

Rodríguez-Fernández P et al. Int. J. Environ. Res. Public Health 2021;18:6528.  
 Leung CMC et al. Transl Psychiatry. 2022;12:205.

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## The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis

31 Studies (5153 patients)



**Depression: 45% (95% CI: 37–54%, I<sup>2</sup> = 96%)**

**Anxiety: 47% (95% CI: 37–57%, I<sup>2</sup> = 97%)**

**Sleep disturbances: 34% (95% CI: 19-50%, I<sup>2</sup> = 98%)**

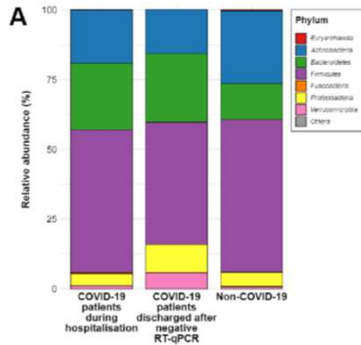
**Lack of contact with families and loved ones during quarantine or hospitalization**  
**Fear relating to the disease due to poor knowledge or misinformation regarding to COVID-19**  
**Feeling of self-blame and social stigma**

Deng J et al. Ann NY Acad Sci. 2021;1486:90-111.

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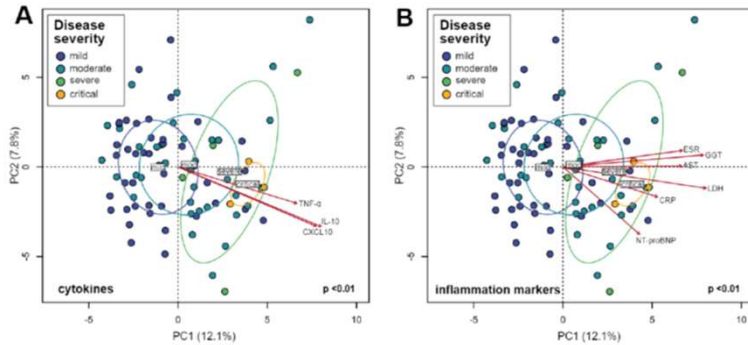
## Gut microbiota composition reflects disease severity and dysfunctional immune responses patients with COVID 19

**Relative abundance of the phyla in stools**



Decrease representation of immunomodulator commensals: *Faecalibacterium prausnitzii*, *Eubacterium Rectale*, y *Bifidobacterias*

**Association between gut microbiota and cytokine plasma concentrations and inflammatory markers**



CXCL10: C-X-C Motif Chemokine Ligand 10 or Interferon gamma-induced protein 10  
 NT-pro BNP: N-terminal prohormone of Brain Natriuretic Peptide

Yeoh YK et al. Gut. 2021;70:698-706.

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CLINICAL REVIEW

**Bacterial and Fungal Gut Dysbiosis and *Clostridium difficile* in COVID-19**

A Review

Laura Linares-García, BSc,\* María E. Cárdenas-Barragán, MS\*  
 Winston Hernández-Ceballos, MS\*\*/ Carlos S. Pérez-Solano, MS\*\*†  
 Allison S. Morales-Guzmán, BSc,\* Danielle S. Miller, MS‡  
 and Max Schmalz MD, FRP\*

J Clin Gastroenterol. 2022;56:285-298.

**Bacterial abnormalities**

Phylum: † Bacteroidetes, † Proteobacteria, † Actinobacteria, † Firmicutes, † Fusobacteria

Class: † Spirochetes, † Streptococcus

Order: † Veillonella

Family: † Actinomycetes

Genus: † Coprobacillus

Species: † *C. ramosum*, † *C. hathewayi*, † *F. prausnitzii*, † *B. dorei*, † *B. thetaiotaomicron*, † *B. massiliensis*, † *B. ovatus*, † *C. leptum*, † *Eubacterium rectale*

**Fungal abnormalities**

Phylum: † Ascomycota, † Mucoromycota

Species: † *A. flavus*, † *A. niger*, † *C. albicans*, † *C. auris*

**Metabolism Abnormalities**

Non-absorbed metabolites: † Saccharose, † 2-nalmitolglycerol

Harmful components: † 1,5-anhydroglucitol, † D-ximital, † Oxalate

Microbial compounds: † 2,4-di-tert-butylphenol

**Treatment**

**Probiotics**

Multi-strain oral probiotics (Lactobacilli, Bifidobacteria, Streptococcus)

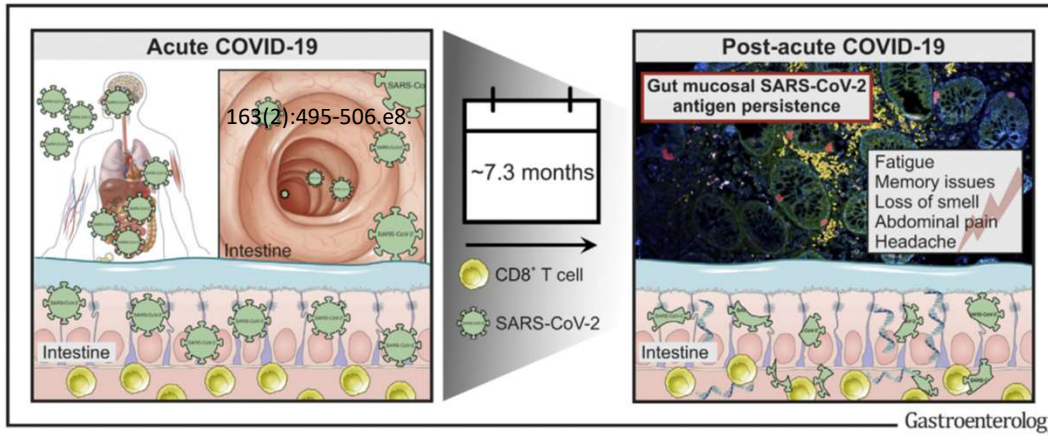
**Fecal transplant**

Oral capsules:  
-With fresh samples  
-With frozen samples

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## Postacute COVID-19 is Characterized by Gut Viral Antigen Persistence in Inflammatory Bowel Diseases

46 IBD patients with PCR-confirmed SARS-CoV-2 were scoped (upper and lower) 94–257 days (average, 7.3 months) after infection



Zollner A et al. Gastroenterology. 2022;163:495-506.e8.

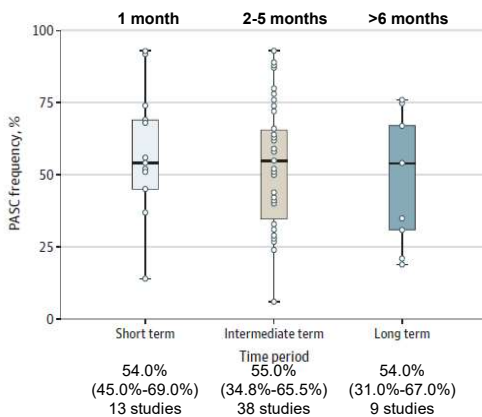
31

JAMA Network | Open.

Original Investigation | Infectious Diseases

### Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review

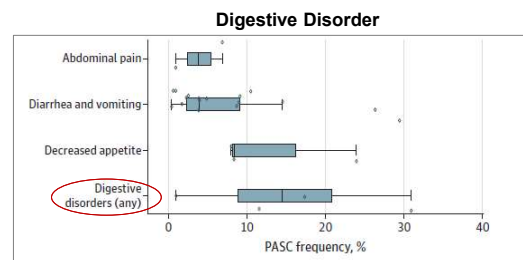
Destin Groff, BA; Ashley Sun, BA; Anna E. Ssentongo, DrPH, MPH; Djibril M. Ba, PhD, MPH; Nicholas Parsons, MPH; Govinda R. Poudel, PhD; Alain Lékoukou, MD, MSc; John S. Oh, MD; Jessica E. Ericson, MD, MPH; Paddy Ssentongo, MD, PhD, MPH; Vernon M. Chinchilli, PhD



Groff D et al. JAMA Network Open. 2021;4:e2128568.

- 2100 Studies were identified / 57 were selected including 250351 survivors of COVID-19 (79% hospitalized)
- 45 Studies were from countries with high socioeconomic level
- Age: 54.4±8.9 years, Men: 140196 (56%)

Chest abnormalities-Imaging, median [IQR]: 62.2% [45.8-76.5%]  
 Functional Impairment: 44.0% [23.4-62.6%]  
 Fatigue/Muscular Weakness: 37.5% [25.4-54.5%]  
 Concentration problems: 23.8% [20.4-25.9%]  
 Anxiety disorders: 29.6% [14.0-44.0%]

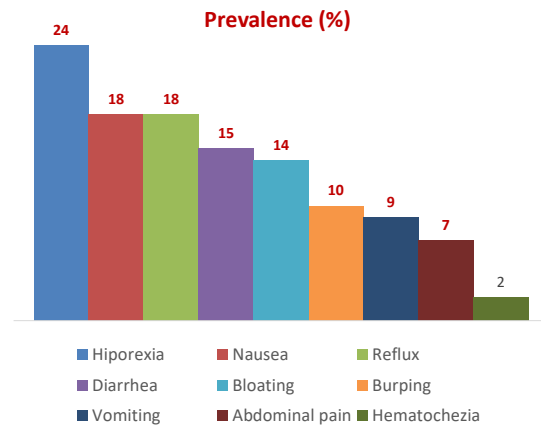


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## Gastrointestinal sequelae 90 days after discharge for COVID-19 in patients in China

- Study in 12 hospitals from Hubei and Guandong (between 16-01 and 7-03, 2020)
- 117 patients
- 45% older than 60
- 52 (44%) reported GI sequelae at discharged (only 1 reported resolution at 90 days)



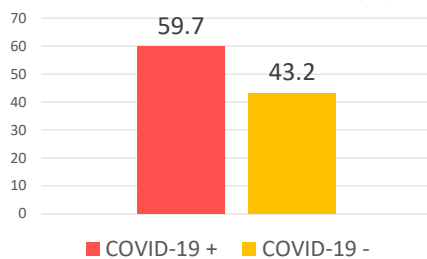
Weng J et al. Lancet Gastroenterol Hepatol. 2021 Mar 9:S2468-1253(21)00076-5.

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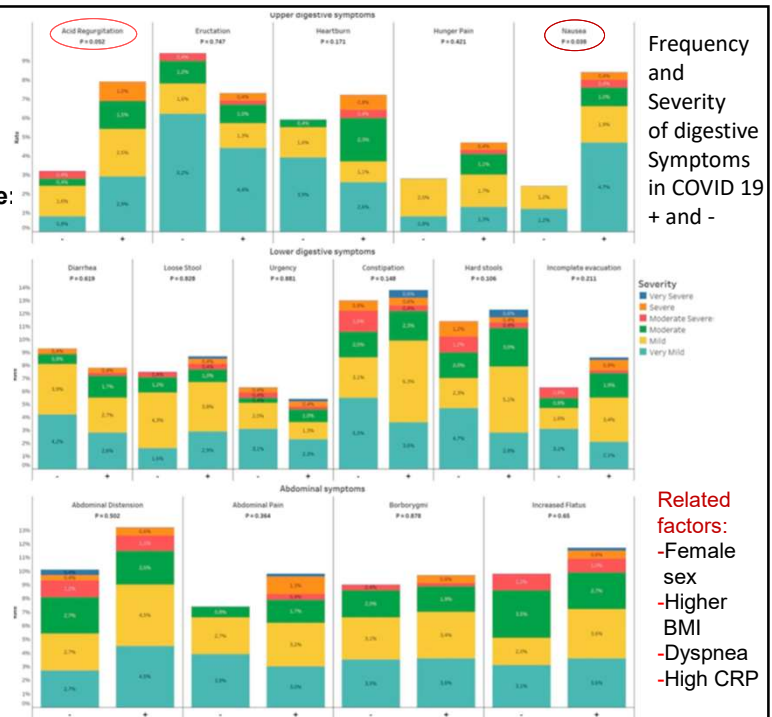
## GI symptoms one month post-COVID-19

871 of 2036 hospitalized patients in Europe: 575 COVID-19 + 296 COVID-19 -

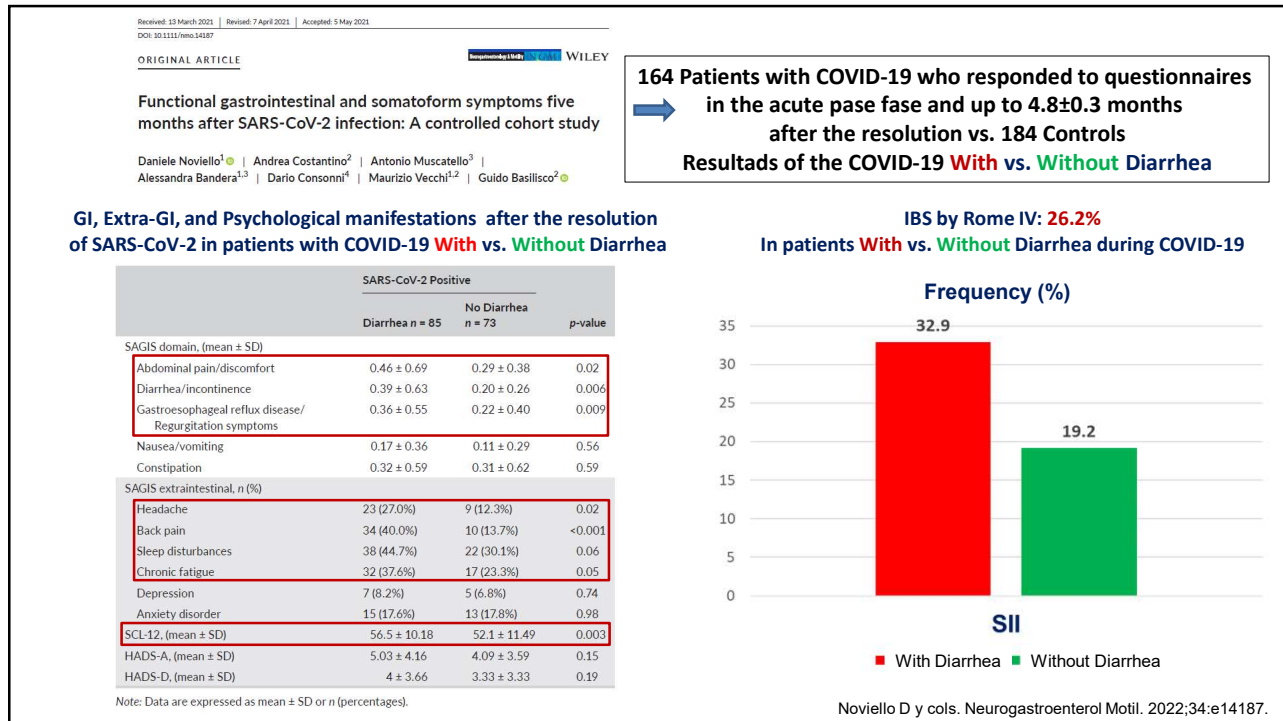
### Frequency of GI symptoms in COVID-19 vs. Controls (%)



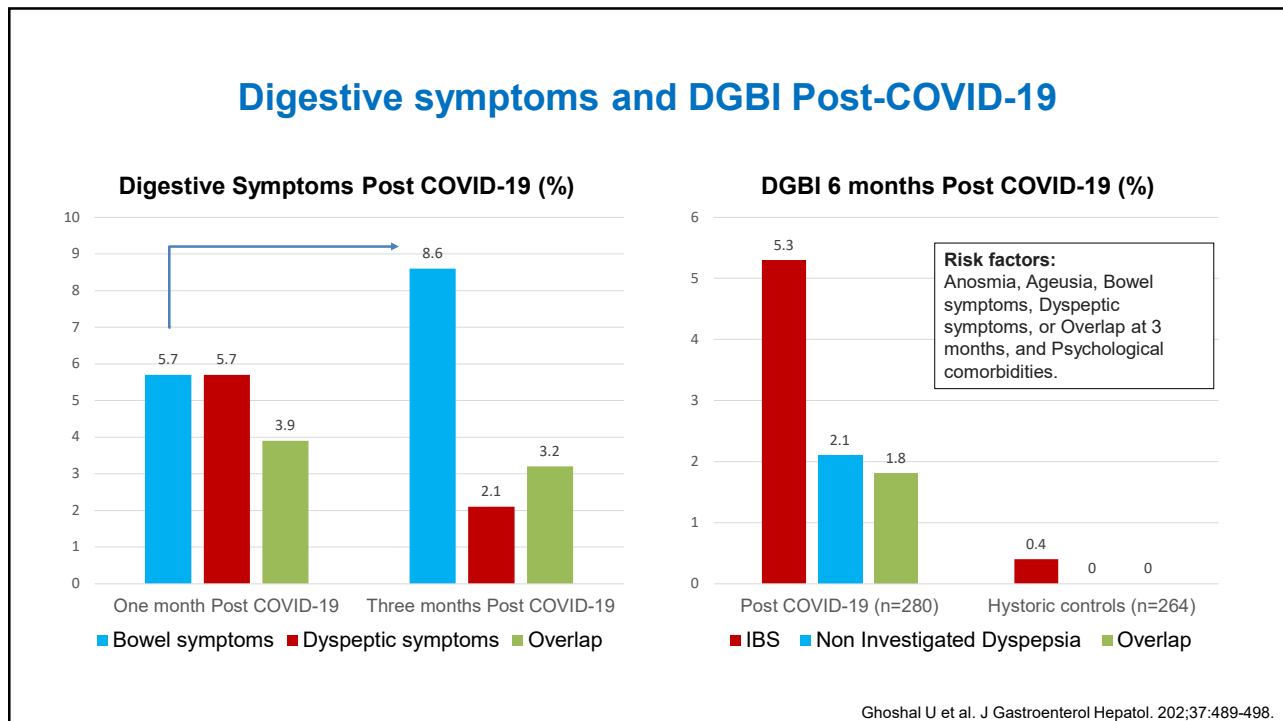
Marasco G et al. Am J Gastroenterol. 2022;117:147-157.



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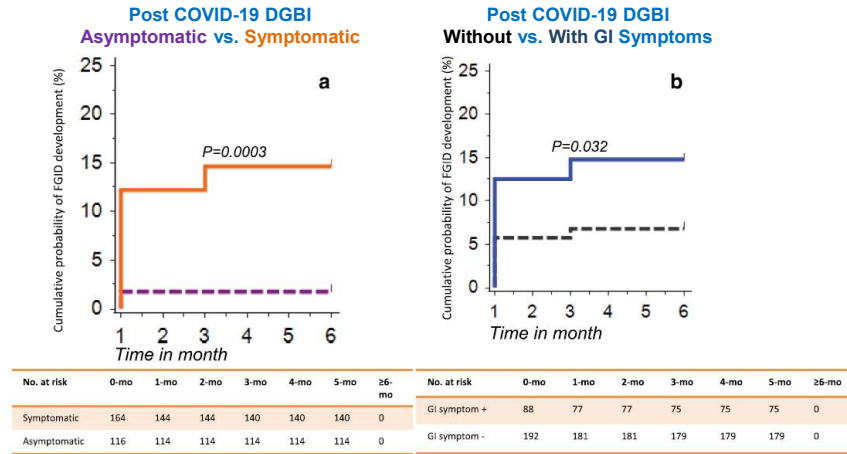


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## Development of DGBI in patients with Asymptomatic vs. Symptomatic COVID-19, and in those With vs. Without GI Symptoms



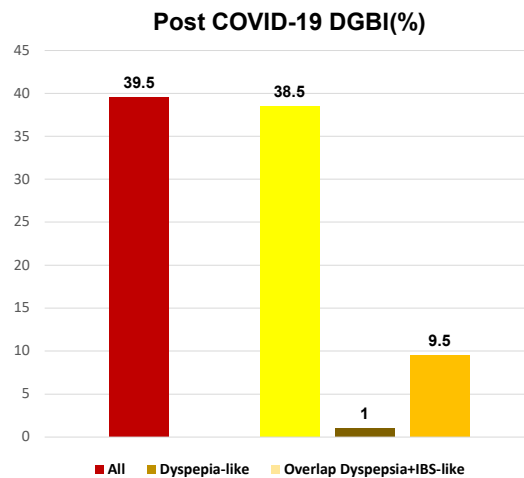
**Figure 3** Kaplan–Meier curves showing the development of functional gastrointestinal disorders (e.g. irritable bowel syndrome [IBS], uninvestigated dyspepsia [UD], and their overlap) at 6 month follow-up (a) among symptomatic as compared to the asymptomatic patients with coronavirus disease-19 (COVID-19), and (b) among those with and without gastrointestinal (GI) symptoms. (a) — — — Asymptomatic; — — — Symptomatic. (b) — — — No GI symptoms; — — — GI symptoms +.

Ghoshal U et al. J Gastroenterol Hepatol. 202;37:489-498.

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## Post COVID-19 DGBI and associated factors in a hospital from a USA metropolitan area (Suffolk county)

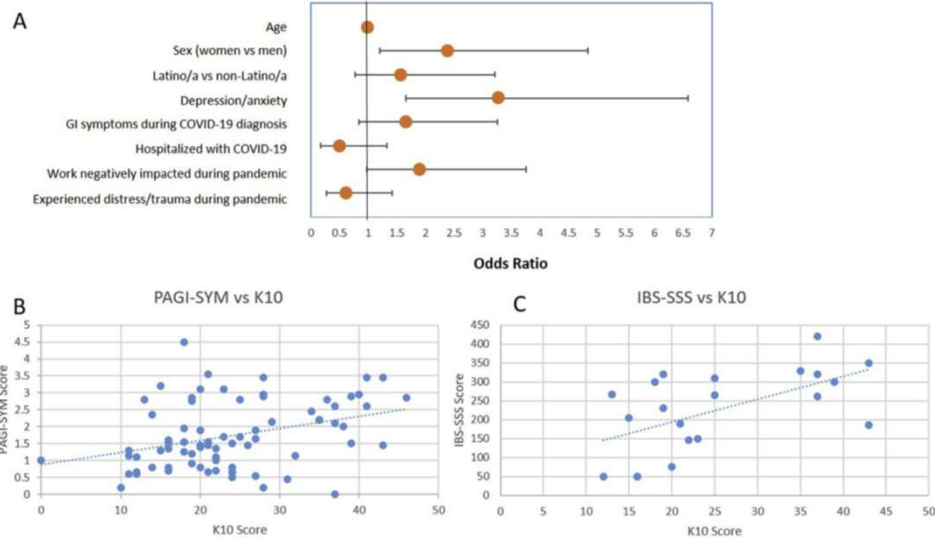
- Retrospective study 6 months post COVID-19 that occurred between April and September 2020
- Patients were contacted by phone (those with previous dyspeptic or IBS symptoms, or with organicity that could explain the symptoms)
- English or Spanish speaking patients
- Determine the presence of Dyspepsia-like or IBS-like, by Rome-IV
- 891 patients identified
  - Met inclusion criterio (n): 459
  - Fulfilled screening (n): 272 (72 were excluded because of previous symptoms)
  - Analyzed (n): 200



Vélez C et al. Clin Gastroenterol Hepatol. 2022;20:e1488-e1492.

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## Post COVID-19 DGBI and associated factors in a hospital from a USA metropolitan area (Suffolk county)



K10: Kessler Psychological Distress Scale  
 PAGI-SYM: Patient Assessment of Gastrointestinal Disorders–Symptom Severity

Vélez C et al. Clin Gastroenterol Hepatol. 2022;20:e1488-e1492.

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ORIGINAL ARTICLE

Neurogastroenterology & Motility WILEY

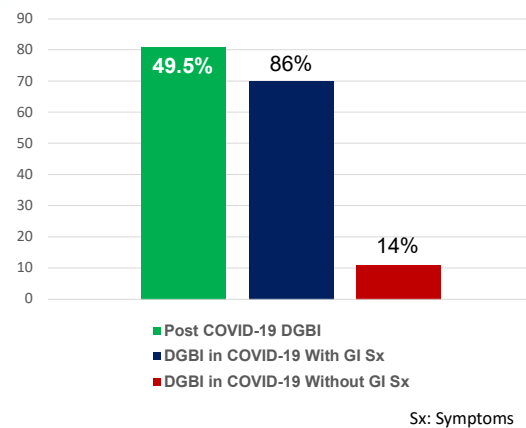
### Gastrointestinal symptoms and the severity of COVID-19: Disorders of gut–brain interaction are an outcome

Ramin Ebrahim Nakhli<sup>1</sup> | Aaron Shanker<sup>2</sup> | Irene Sarosiek<sup>2</sup> | Jeffrey Boschman<sup>1</sup> | Karina Espino<sup>2</sup> | Solmaz Sigaroodi<sup>2</sup> | Ihsan Al Bayati<sup>2</sup> | Sherif Elhanafi<sup>2</sup> | Amin Sadeghi<sup>3</sup> | Jerzy Sarosiek<sup>2</sup> | Marc J. Zuckerman<sup>2</sup> | Ali Rezaie<sup>4</sup> | Richard W. McCallum<sup>2</sup> | Max J. Schmulson<sup>5</sup> | Ali Bashashati<sup>1,6</sup> | Mohammad Bashashati<sup>2</sup>

#### Internet study of 2 Phases

- **Phase 1:** Patients with COVID-19 (n=1114)  
 -Demographics, comorbidities, symptoms, complications, hospitalization
- **Phase 2.** Determine the presence of Post COVID-19 DGBI by Rome IV (n=164), Association with Anxiety (GAD-7) and Depression (PHQ-9)
- Uni and Multivariate analyses identified 5 Groups of patients based on: GI Symptoms, Anosmia and Chest Pain
- The presence of GI symptoms were independent predictors of COVID-19, but not always correlated with known factors of severity such as Age>65, Diabetes Mellitus, Deficiency of Vit D

#### Frequency (%) of Post COVID-19 DGBI



Nakhli RE et al. Neurogastroenterol Motil. 2022;00:e14368.

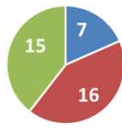
40

### Gastrointestinal symptoms and the severity of COVID-19: Disorders of gut-brain interaction are an outcome

Ramin Ebrahim Nakhli<sup>1</sup> | Aaron Shanker<sup>2</sup> | Irene Sarosiek<sup>2</sup> | Jeffrey Boschman<sup>1</sup> | Karina Espino<sup>2</sup> | Solmaz Sigaroodi<sup>2</sup> | Ihsan Al Bayati<sup>2</sup> | Sherif Elhanafi<sup>2</sup> | Amin Sadeghi<sup>3</sup> | Jerzy Sarosiek<sup>2</sup> | Marc J. Zuckerman<sup>2</sup> | Ali Rezaie<sup>4</sup> | Richard W. McCallum<sup>2</sup> | Max J. Schmulson<sup>5</sup> | Ali Bashashati<sup>1,6</sup> | Mohammad Bashashati<sup>2</sup>

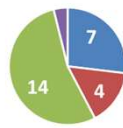
**Depression (65%),** but not Anxiety (48%), was more common in those with DGBI Post-COVID-19

**Functional Dyspepsia Subtypes (n)**



- Postprandial Distress S.
- Epigastric Pain S.
- Mixed

**IBS Subtypes (n)**



- IBS-D
- IBS-C
- IBS-M
- IBS-U

### DGBI Pre and Post COVID-19

	DGBI*	
	Post-COVID-19	Pre-COVID-19
Functional chest pain	17	2
Functional heartburn	11	8
Reflux hypersensitivity	9	6
Globus	3	0
Functional dysphagia	16	1
Functional dyspepsia	38	1
Belching disorders	8	0
Cyclic vomiting syndrome	5	1
Rumination syndrome	9	0
Irritable bowel syndrome	26	17
Functional constipation	9	7
Functional diarrhea	12	1
Functional abdominal bloating/distention	12	5
Opioid-induced constipation	0	2
Centrally mediated abdominal pain	1	3
Fecal incontinence	6	1
Functional anorectal pain	0	1
Functional defecation disorders	0	1

\*Some patients may have multiple DGBI.

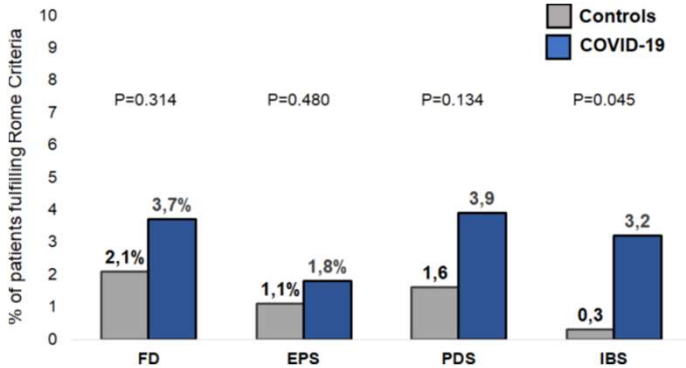
Nakhli RE et al. Neurogastroenterol Motil. 2022;00:e14368.

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## IBS Post COVID-19 in a Multicenter-Multinational Study of 2183 hospitalized patients

The main analysis included 883 patients, 614 with COVID-19 and 269 controls (1300 were excluded because of previous GI symptoms or surgeries)

### IBS and Functional Dyspepsia 12 months Post COVID-19



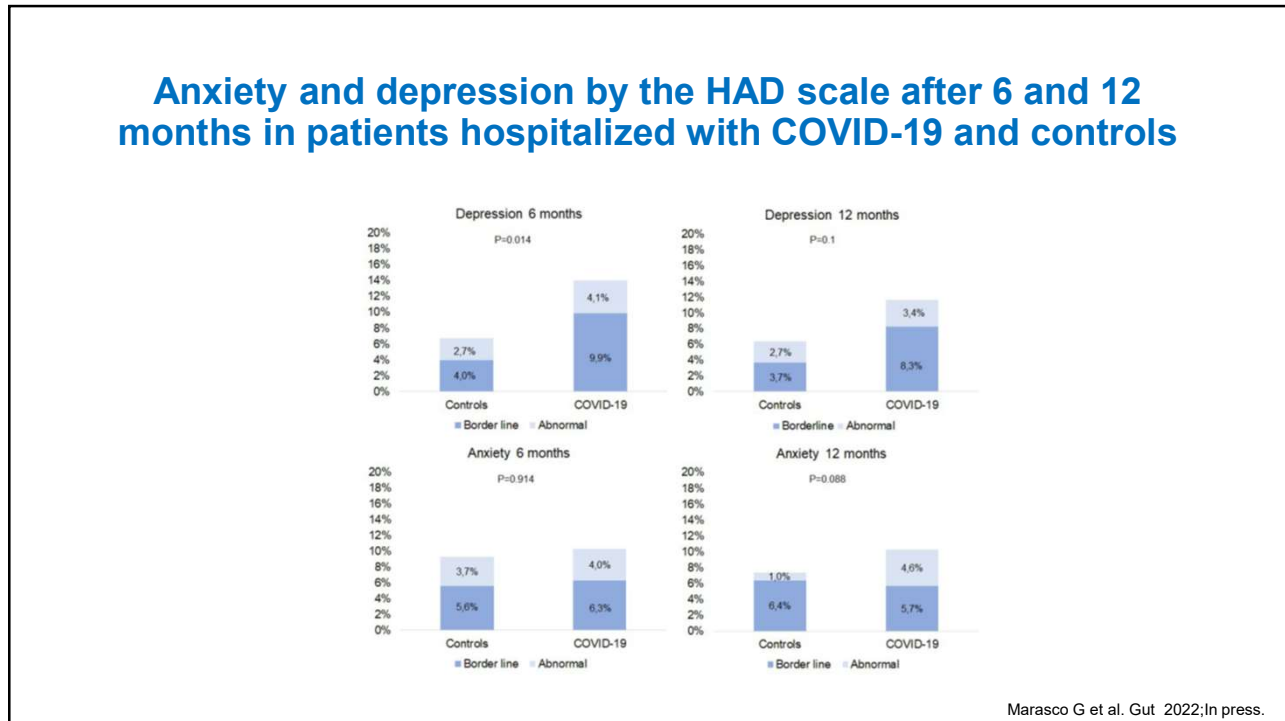
### Risk factors for IBS 12 months Post COVID-19

Factor	RM (IC 95%) p
Alergies	10.024 (1.766, 56.891) 0.009
PPIs	4.816 (1.447, 16.025) 0.010
Dyspnea	4.157 (1.336, 12.934) 0.014

Other factors that were studied: Chronic liver diseases, Antibiotics, Cough, Anxiety by the HAD 6 months before

Marasco G et al. Gut. 2022;In press.

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## Diarrhea because of *C. difficile*: A differential diagnosis from diarrhea Post COVID-19

CLINICAL REVIEW

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### Bacterial and Fungal Gut Dysbiosis and *Clostridium difficile* in COVID-19

A Review

*Laura Linares-García, BSc,\* María E. Cárdenas-Barragán, MS\**  
*Winston Hernández-Ceballos, MS\*† Carlos S. Pérez-Solano, MS\*†*  
*Alizon S. Morales-Guzmán, BSc,\* Danielle S. Miller, MS,‡*  
*and Max Schulson MD, FRF\**

Linares-García L et al. J Clin Gastroenterol. 2022; 56:285-298.

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## ORIGINAL ARTICLE

## The Impact of COVID-19 Pandemic on Neurogastroenterologists in Latin America

### Results of an Online Survey

Max Schmulson, MD, RFF,\* Marco Gudiño-Zayas, DST,† Albis Hani, MD,‡  
and The Sociedad Latinoamericana de Neurogastroenterología (SLNG)

- All reported a negative impact in their practice, **88.6% a reduction of 61%-100% mainly** in consultations and endoscopies
- **Reasons for a negative impact in their GI practice:** Patients fear, mandatory lockdown, physicians own decision, to prevent infection spreading
- **Decrease in emergency endoscopies** in 33.3%, in Manometries/pH only 4%
- **Telemedicine:** Implemented by 83%, but only 64.7% were reimbursed
- **Mobilization of Gastroenterologists to COVID-19 wards:** 11.5%
- **Anxiety and Depression** because of the pandemic: 78.7%
- **Increase in consultations for FGIDs/DGBI: 36.1%**
- **Differences by countries:** Colombia, mandatory lockdown ( $p=0.001$ ); **México, higher frequency of treating patients with COVID-19 ( $p=0.053$ ); México/Colombia, mobilization to COVID-19 wards ( $p=0.012$ ); Brazil, lower prohibition for elective procedures ( $p=0.012$ ) and reimbursement for Telemedicine ( $p=0.034$ )**

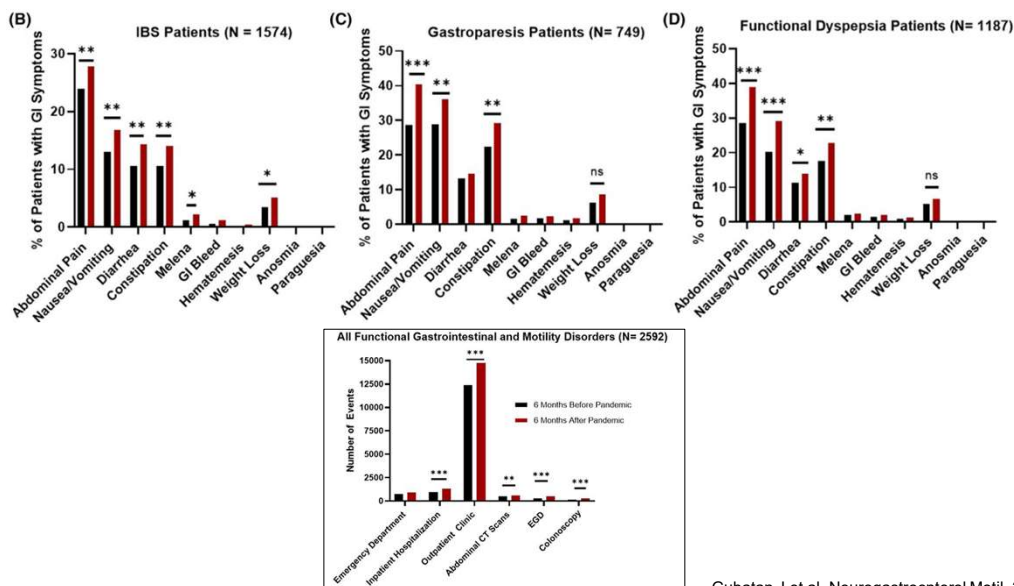
Reported and increase  
in consultations for  
FGIDs/DGBI

36.1%

Schmulson M et al. J Clin Gastroenterol. 2021;55:684-690.

45

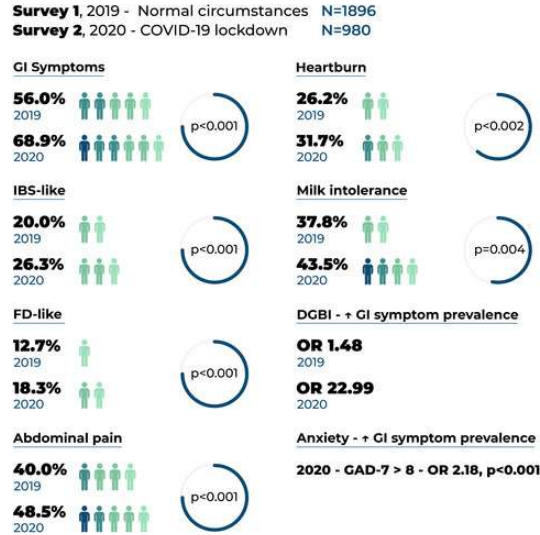
## Increase in gastrointestinal symptoms and use of healthcare resources in patients with DGBI and gastroparesis during the COVID-19 pandemic



Gubatan J et al. Neurogastroenterol Motil. 2022;34:e14243.

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## Increased prevalence of GI symptoms and DGBI during the COVID-19 pandemic: An internet-based survey in Bulgaria



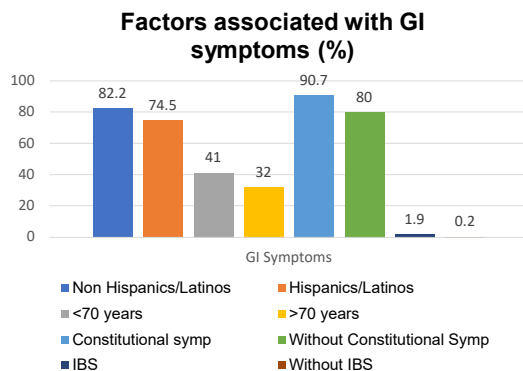
Nakov R et al. *Neruogastro Motil.* 2022;34:e14197.

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## IBS as a risk factor for GI symptoms and diarrhea in patients with COVID-19 in the USA

Registry of 1992 patients hospitalized for COVID-19, 1406 were eligible

**GI Symptoms: 540 (38%), Diarrhea: 346 (25%)**



**Multivariate analysis**

**GI Symptoms:**

- Lower risk in >80 vs. 18-79 years: OR 0.41, p<0.01
- Higher risk in patients **With IBS vs. Without IBS: OR 7.7, p=0.02**
- Higher risk in Midwest vs. Other regions of the USA: OR 1.66, p=0.06

**Diarrhea:**

- Lower risk in >80 vs. 18-79 years: OR 0.43, p<0.01
- Higher risk in **IBS vs. Without IBS: OR 6.72, p<0.01**
- Higher risk With vs. Without Constitutional Symptoms: OR 2.15, p=0.001
- Higher risk With vs. Without Immunosuppressors: OR 1.56, p=0.02
- Lower risk With vs. Without Diabetes: OR 0.69, p=0.01

Aroniadis OC et al. *Dig Dis Sci.* 2022;67:3860-3871.

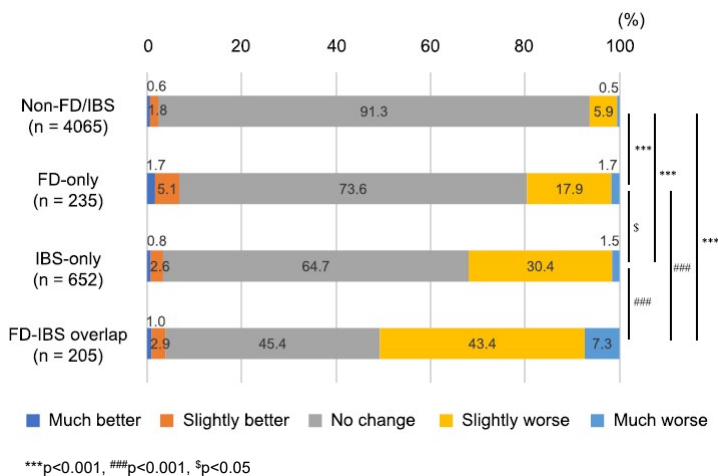
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## Impact of COVID-19 on gastrointestinal symptoms in patients with Functional Dyspepsia and IBS vs. Controls

Internet survey in 5157 subjects in Japan in May 2020, 8.5% with Functional Dyspepsia (FD), 16.6% with Irritable Bowel Syndrome (IBS) and 4% with FD-IBS overlap

- During the pandemic, 11.9% reported **deterioration** of GI symptoms and 2.8% **improvement**
- Factors associated with **deterioration**: FD-IBS overlap (the most important one), psychological comorbidities, stress at work/school
- Factors associated with **improvement**: Younger age, commuting by public transportation as usual, work/study from home



Oshima T et al. J Gastroenterol Hepatol. 36:1820-1827.

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## Impact of the COVID-19 pandemic and lockdown stress on psychological aspects and quality of life in subjects With vs. Without IBS in France

Survey among members (n=794) of the French Association of Patients that Suffer of IBS (*Association des patients souffrant du syndrome de l'intestin irritable [APSSII]*), and family and friends

Consequences	IBS (n=232)	Without IBS (n=72)	p
Anxiety (HAD)	10.6±3.9	6.9±3.6	<0.001
Depression (HAD)	7.3±3.85	4.8±3.7	<0.001
HAD Global	17.8±6.5	11.8±6.5	<0.001
Fatigue (0-7)	4.9±1.5	3.6±1.6	<0.001
Sleep disturbances (%)	61.5	53	0.216
New sleep disturbances	12	9.1	0.216
Increase in the sleep disturbances	27.7	13.6	0.038
IBS-QOL (0-100)	47.6±19.9	---	
QOL in general	77.8±16.8	52.2±27.2	<0.001


Sabate JM et al. Med Public Health. 2021 Sep;18:100660.

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## Conclusiones

- GI symptoms are very frequent in COVID-19. The main reason for that is the presence of the ACE2 receptor that is required for the attachment of the SARS-CoV-2 spike (S) glycoprotein to the human cells and further released their viral components, and their highest expression within the human body is in the intestinal epithelial cells.
- The inflammation in the gut, increased permeability, dysbiosis, and psychological stress triggered by COVID-19, and the remaining of unviable viral particles, are all potential mechanisms for the development of Post-COVID-19-DGBI.
- The GI sequels of COVID-19 and the development of Post COVID-19 DGBI, have already been reported globally. The variability in their prevalence is due to the differences in the design and methodology of the studies. Therefore, physicians and gastroenterologists need to be aware of these possibilities.
- *C. difficile* infection needs to be ruled out in patients with newly developed Post COVID-19, especially if they were hospitalized or received antibiotics.
- Also, the history of DGBI predisposes to a higher frequency of GI symptoms during COVID-19, higher psychological distress, lower quality of life, and as a consequence, a higher use of healthcare resources by these patients.


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## Questions?



Max J. Schmulson, MD



Sarah K. McGill, MD, MSc, FACP

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