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.

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Correspondence

Fecal calprotectin levels in COVID-19: Lessons from a systematic review on its use in inflammatory bowel disease during the pandemic

Dear Editors

Fecal calprotectin measurement is often used for discriminating inflammatory bowel disease (IBD) from irritable bowel syndrome, distinguishing active IBD from remission and in management of Crohn's disease using a tight control approach. [1] Use of fecal calprotectin, especially home-based testing, has been suggested as a tool for remote monitoring during the COVID pandemic. Point of care calprotectin tests can help in evaluating disease activity in IBD patients. [2] Their use can help tide over the delays in diagnostic endoscopy which are frequent in the COVID era. [3] Recent reports, including one published in the journal, about elevations of fecal calprotectin in COVID-19 raise concerns about this strategy of home based monitoring using fecal calprotectin. [4–7] SARS-CoV2 RNA has been isolated in stool specimens. The interaction of SARS-CoV2 with the angiotensin converting enzyme-2 (ACE-2) receptors on gut epithelium could lead to myriad of gastrointestinal manifestations. [8] We therefore performed a systematic review to study the elevations of fecal calprotectin in COVID-19 and if these elevations were different in patients with or without gastrointestinal symptoms.

We searched the databases on PubMed and Embase on 27 September 2020 using the keywords "coronavirus, COVID-19, SARS-COV-2, nCOV, coronaviridae infection, coronavirus disease 2019" with 'AND' "Calprotectin or Calgranulin" **(Supplementary Table 1)**. After removing the duplicates, we screened for the original studies reporting about fecal calprotectin in COVID-19 patients. We excluded the studies which reported the use of serum calprotectin in COVID-19. Relevant data were extracted and used for analysis. We identified 52 titles, of which 12 duplicates were removed **(Supplementary Figure 1)**. Out of the remaining 40 articles, 8 articles were assessed for full text screening. Data from 4 articles were used in the systematic review and other 4 studies were excluded **(Supplementary Table 2).** These four studies reported about fecal calprotectin levels in 174 patients with COVID-19 (Table 1). The rates of elevated fecal calprotectin were variable amongst the studies but all studies had significant number of patients with elevated levels (29.3–75%). The elevations of fecal calprotectin were more frequent in those patients who had gastrointestinal symptoms in all the three studies which provided this information (Fig. 1).

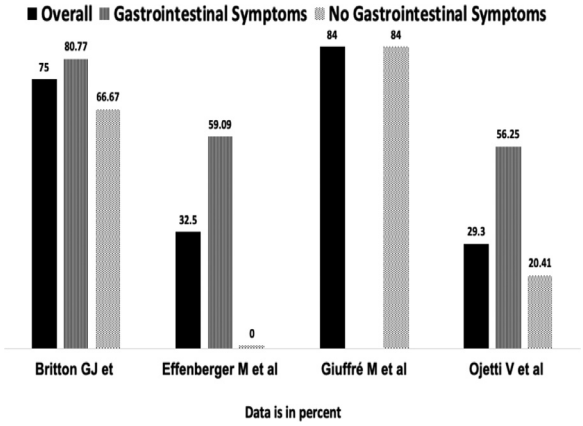

Fig. 1. Image showing the frequency of elevated fecal calprotectin in patients with COVID-19.

Our analysis showed that fecal calprotectin levels were elevated in a significant proportion of patients with COVID-19. The elevation of calprotectin could be related to gastrointestinal inflammation resulting from SARS-CoV-2 infection. This could be due to direct viral injury to the gastrointestinal epithelium. [8-9] Therefore, COVID-19 could cause elevated fecal calprotectin levels especially in the presence of GI symptoms. This could make the differentiation of COVID-19 infection difficult from disease flares in IBD. So the evaluation of IBD flares solely with fecal calprotectin may not be sufficient. Further, as patients of IBD with elevated fecal calprotectin levels could be immunocompromised, it would be better to exclude COVID-19 infection prior to increasing immunosuppression. Our study addresses an important area of ambiguity but comes with certain limitations. First, the included studies only analyzed the data of hospitalized COVID-19 patients. Also, there are no direct studies of fecal calprotectin in IBD patients infected with COVID-19. This limits the generalizability of our findings to patients having underlying IBD. Future prospective studies could throw more light on this issue.

To conclude, routine testing for COVID-19 should be done in all patients of IBD with elevated fecal calprotectin in COVID-19. Relying merely on fecal calprotectin for differentiating IBD flare from diarrhea due to COVID-19 is questionable.

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Table 1
Studies reporting on the use of Fecal calprotectin in COVID-19.

Study	Patient's characteristics	Comorbidities	Symptoms	Treatment received	Fecal calprotectin	Outcome	Comments
Britton GJ, 2020, USA	44 patients of symptomatic COVID-19 Mean age: 55.9 (15.1) years M:*F* = 21:23	HTN= 31 (70.5%) DM = 19 (43.2%) Obesity = 22 (50%) Lung disease = 15 (34.1%) Cardiac disease = 16 (36.4%) CKD = 13 (29.5%) CLD = 4 (9.1%) IBD = 1 (2.3%) Cancer = 8 (18.2%) Prior transplant = 3 (6.8%) Other autoimmune diseases and immunodeficiencies = 5 (11.4%)	GI Symptoms = 31 (70.5%) Diarrhea =26 (59.1%) Nausea = 15 (34.1%) Vomiting = 7 (15.9%)	Antibiotics = 28 (63.6%) Therapeutic anticoagulation =31 (70.5%) Convalescent plasma = 20 (45.5%) Hydroxychloroquine = 19 (43.2%) Steroids = 18 (40.9%) Remdesivir = 15 (33%)	Elevated in 33 /44(75%) overall Elevated in 21/26 (80.77%) of those with gastrointestinal symptoms Elevated in 12/18 (66.67%) of those without gastrointestinal symptoms	Mortality = 7 (15.9%) ICU admission = 13 (29.5%) Composite outcome (ICU admission or death) = 14 (31.8%)	
Effenberger M, 2020, Austria	40 patients of symptomatic COVID-19 M:*F* = 3:2	Comorbidities = 23 (57.5%) (smoking, allergies, arterialhypertension, type 2 diabetes, malignant diseases, chronic heart disease, chronic liver disease, chronic obstructive respiratory disease and immunosuppressive therapy)	Cough = 40 (100%) Fever = 34 (85%) Diarrhea = 22 (55%) Vomiting = 5(12.5%) Nausea = 5 (12.5%)	Antibiotics = 10 (25%) Antiviral therapy = 1 (2.5%)	Elevated in 13/40 (32.5%) overall Elevated in 13/22 (59.09%) of those with gastrointestinal symptoms Elevated in 0/18 (0%) of those without gastrointestinal symptoms		Excluded other causes of acute GI infection Compared three groups of COVID patient (without diarrhea, resolved diarrhea, acute diarrhea)
Giuffre M, 2020, Italy	25 patients of symptomatic COVID-19 without GI symptoms/IBD (all RT-PCR positive)	Heart disease = 10 (47.6%) Hypertension = 7 (33.3%)	GI symptoms = 0	Antibiotics = 5 (23.8%) Therapeutic anticoagulation =13 (61.9%)	Fecal calprotectin elevated in 21 (84%) patients	Intestinal perforation = 2	
Ojetti V, 2020, Italy	65 patients of symptomatic COVID-19 (RT-PCR positive) Median age: 38 years (IQR 34–55) M:*F* = 10:3	NA	GI symptoms = 16 (24.6%)	NA	Elevated in 19/65 (29.23%) overall Elevated in 9/16 (56.25%) of those with gastrointestinal symptoms Elevated in 10/49 (20.41%) of those without gastrointestinal symptoms		Excluded patients on/with Hydroxychloroquine, Terminal oncological diseases, Heart disease, Severe nephropathy Active IBD History of pulmonary fibrosis, Advanced interstitial disease, Severe COPD (GOLD 3–4; group C and D), Antibiotic therapy or received in last one month

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.10.021.

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