ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 June 14; 27(22): 2921-3141

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents Weekly Volume 27 Number 22 June 14, 2021

FRONTIER

REVIEW

MINIREVIEWS

World Journal of Gastroenterology

Weekly Volume 27 Number 22 June 14, 2021

Contents

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
June 14, 2021

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https://www.wjgnet.com/bpg/gerinfo/242

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World J Gastroenterol 2021 June 14; 27(22): 3130-3137

DOI: 10.3748/wjg.v27.i22.3130

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Prospective Study

High fecal calprotectin levels are associated with SARS-CoV-2 intestinal shedding in COVID-19 patients: A proof-of-concept study

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Author contributions: Zerbato V and Di Bella S conceived/organized the study and wrote the manuscript; Giuffrè M performed the statistics; Zerbato V, Jaracz AW, Gobbo Y, Luppino D and Valentini M collected samples and provided help with conduction of the study; Segat L, Koncan R and D'Agaro P performed the virologic analysis; Macor P, Crocé LS, Ruscio M and Luzzati R reviewed the manuscript.

Institutional review board statement: This study was conducted according to the declaration of Helsinki and

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Abstract

BACKGROUND

One third of coronavirus disease 2019 (COVID-19) patients have gastrointestinal symptoms. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA has been detected in stool samples of approximately 50% of COVID-19 individuals. Fecal calprotectin is a marker of gastrointestinal inflammation in the general population.

AIM

To investigate if fecal calprotectin correlates with SARS-CoV-2 intestinal shedding in COVID-19 patients with pneumonia.

METHODS

Patients with SARS-CoV-2 pneumonia admitted to the Infectious Disease Unit (University Hospital of Trieste, Italy) from September to November 2020 were

approved by the Ethics Committee (Unique Regional Ethical Committee, Friuli Venezia-Giulia 16 April 2020), No. CEUR 2020-OS-072.

Clinical trial registration statement: This study did not involve clinical trials.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: All study participants provided written consent prior to study enrollment.

CONSORT 2010 statement: CONSORT not applicable.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 2, 2021
Peer-review started: February 7,

consecutively enrolled in the study. Fecal samples were collected and analyzed for quantification of fecal calprotectin (normal value < 50 mg/kg) and SARS-CoV-2 RNA presence by polymerase chain reaction (PCR). Inter-group differences were determined between patients with and without diarrhea and patients with and without detection of fecal SARS-CoV-2.

RESULTS

We enrolled 51 adults (40 males) with SARS-CoV-2 pneumonia. Ten patients (20%) presented with diarrhea. Real-time-PCR of SARS-CoV-2 in stools was positive in 39 patients (76%), in all patients with diarrhea (100%) and in more than two thirds (29/41, 71%) of patients without diarrhea. Obesity was one of the most common comorbidities (13 patients, 25%); all obese patients (100%) (P = 0.021) tested positive for fecal SARS-CoV-2. Median fecal calprotectin levels were 60 mg/kg [interquartile range (IQR) 21; 108]; higher fecal calprotectin levels were found in the group with SARS-CoV-2 in stools (74 mg/kg, IQR 29; 132.5) compared to the group without SARS-CoV-2 (39 mg/kg, IQR 14; 71) (P < 0.001).

CONCLUSION

High fecal calprotectin levels among COVID-19 patients correlate with SARS-CoV-2 detection in stools supporting the hypothesis that this virus can lead to bowel inflammation and potentially to the 'leaky gut' syndrome.

Key Words: COVID-19; SARS-CoV-2; Obesity; Fecal calprotectin; Gut; Viral shedding

Core Tip: In this prospective study of 51 hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia, whether fecal calprotectin correlated with SARS-CoV-2 intestinal shedding was investigated. We found that high fecal calprotectin level is a common finding among hospitalized coronavirus disease 2019 (COVID-19) patients, especially those with SARS-CoV-2 fecal shedding. Obese COVID-19 patients showed high fecal viral shedding.

Citation: Zerbato V, Di Bella S, Giuffrè M, Jaracz AW, Gobbo Y, Luppino D, Macor P, Segat L, Koncan R, D'Agaro P, Valentini M, Crocé LS, Ruscio M, Luzzati R. High fecal calprotectin levels are associated with SARS-CoV-2 intestinal shedding in COVID-19 patients: A proof-of-concept study. *World J Gastroenterol* 2021; 27(22): 3130-3137
URL: https://www.wjgnet.com/1007-9327/full/v27/i22/3130.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i22.3130

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) expresses a high affinity to human angiotensin-converting enzyme 2 (ACE2) receptors. High ACE2 expression was identified within the oral cavity, type II pulmonary alveolar cells, ileal and colonic enterocytes, myocardial cells, vascular endothelium, proximal tubule, and bladder urothelial cells[1].

One-third of coronavirus disease 2019 (COVID-19) patients have gastrointestinal symptoms, with diarrhea being the most common symptom[2]. Moreover, critically ill COVID-19 patients often develop intestinal complications. Ileus, gastrointestinal bleeding, and bowel ischemia are the most common[3,4]. Spontaneous intestinal perforations among COVID-19 patients are also increasingly seen in clinical practice [4].

SARS-CoV-2 RNA has been detected in stool samples of approximately 50% COVID-19 individuals[5]. Often, viral detection in stools persists after viral clearance from respiratory samples[6], with a mean duration of fecal viral shedding of 17 d[7].

It is likely that SARS-CoV-2 can also be transmitted *via* the fecal–oral route and that the potential of this mode of transmission has been widely underestimated[8].

The pathogenesis of gastrointestinal symptoms caused by SARS-CoV-2 is likely

2021
First decision: February 27, 2021
Revised: March 12, 2021
Accepted: April 21, 2021
Article in press: April 21, 2021
Published online: June 14, 2021

P-Reviewer: Apostolou K
S-Editor: Fan JR
L-Editor: Webster JR
P-Editor: Liu JH

multifactorial, including disruption of the intestinal mechanical barrier integrity, alteration of the gut microbiome, increased translocation of bacteria and their metabolites, and systemic inflammatory response to the virus, which in critically ill patients could be disproportionate, with uncontrolled production and release of cytokines[1].

Calprotectin is a protein derived principally from neutrophils. Upon neutrophil activation or death, calprotectin is released extracellularly, where it has a role within the innate immune response with direct antimicrobial effects. It is present in many body fluids, in proportion to the degree of inflammation. The concentration of calprotectin in feces is about six times that in plasma, and its measurement is used as a surrogate marker of gastrointestinal inflammation[1,9].

Fecal calprotectin in COVID-19 patients was found to be a marker of intestinal inflammation, both in patients with and without gastrointestinal symptoms[10,11]. Ojetti *et al*[12] also found a significant correlation between the development of pneumonia among COVID-19 patients and a high level of fecal calprotectin[11,12].

Serum calprotectin has been proposed as a severe COVID-19 progression marker, supporting innate immunity as a potential perpetrator of inflammation in COVID-19. It should be kept in mind that neutropenia seen in the peripheral blood of COVID-19 patients should in part reflect neutrophil migration to the tissues[12-14] and complement activation in different organs of COVID-19 patients[15] contributes to tissue damage and to the recruitment of neutrophils.

Given these premises, we aimed to investigate if fecal calprotectin correlates with SARS-CoV-2 intestinal shedding in hospitalized patients with COVID-19 pneumonia.

MATERIALS AND METHODS

We performed a prospective monocentric study enrolling consecutive adults (aged >18 years) with SARS-CoV-2 pneumonia admitted to the Infectious Diseases Unit of Trieste University Hospital, Italy, from September to November 2020. Patients with inflammatory bowel diseases, gastrointestinal malignancy, and other known gastrointestinal disorders were categorically excluded.

SARS-CoV-2 detection in stool samples was determined by real-time polymerase chain reaction (RT-PCR) (LightMix® Modular SARS and Wuhan CoV E-gene and RdRp kit-TIB Molbiol, Berlin, Germany, with LightCycler Multiplex RNA Virus Master-Roche, Basel, Switzerland). According to the manufacturer's specifications, fecal calprotectin levels were tested with the LIAISON®-Calprotectin (Diasorin, Vercelli, Italy) (normal value < 50 mg/kg). These tests were performed on hospital admission, regardless of gastrointestinal signs or symptoms.

The following data were collected on admission: Age, gender, comorbidities, gastrointestinal signs/symptoms, blood cell count, biochemical parameters, and clinical outcomes. In addition, administered drugs prior to and during hospitalization were collected. Diarrhea and obesity were defined as loose stools ≥ three times/day and a body mass index ≥ 30, respectively.

According to the size of our sample, the Shapiro-Wilk test was performed to verify the normal distribution of variables. Inter-group differences (patients with diarrhea *vs* patients without diarrhea and patients with fecal SARS-CoV-2 *vs* patients without fecal SARS-CoV-2) were determined with the Mann-Whitney U test for continuous variables and the Pearson's Chi Square Test for discrete variables. For all analyses, two-sided statistical significance was defined as a $P < 0.05$. Data were analyzed using SPSS (Statistical Package for Social Science) version 25.0 (IBM SPSS Statistics for MAC OS. Armonk NY: IBM Corp.).

This study was conducted according to the declaration of Helsinki and approved by the Ethics Committee (Unique Regional Ethical Committee, Friuli Venezia-Giulia 16 April 2020), No. CEUR 2020-OS-072.

RESULTS

We enrolled 51 consecutive adults with SARS-CoV-2 pneumonia. Patient age ranged from 28 to 87 years [median 64 years, interquartile range (IQR) 57; 71] and 40 (78%) were males. The most common comorbidities were: Hypertension (34 patients, 67%), diabetes mellitus (5, 25%), obesity (5, 25%), heart disease (5, 25%), chronic kidney disease (5, 10%) and chronic obstructive pulmonary disease (5, 10%). Two (4%) patients were active smokers. Ten (20%) patients had diarrhea.

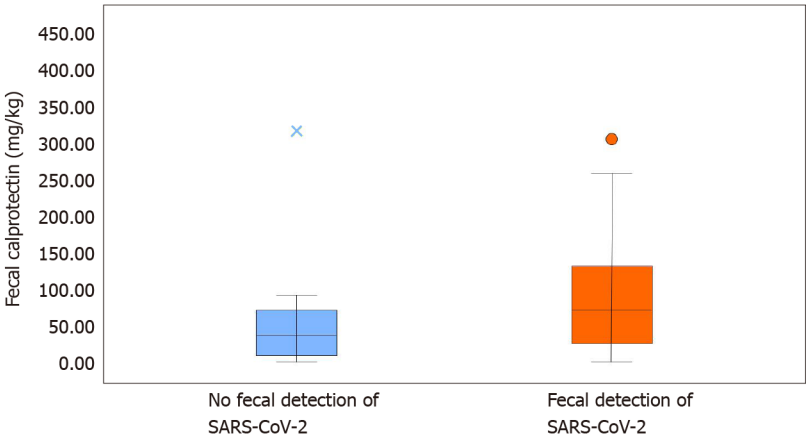

Figure 1 Fecal calprotectin content detected in stool with or without severe acute respiratory syndrome coronavirus 2 virus. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Median fecal calprotectin levels were 60 mg/kg (IQR 21; 108). RT-PCR of SARS-CoV-2 in stools was positive in 39 patients (76%) (Figure 1). The clinical features and biochemical parameters of enrolled patients are reported in Table 1.

No statistically significant differences in the compared variables between the two groups (patients with diarrhea *vs* patients without diarrhea) were found (Table 1). Both groups showed increased fecal calprotectin levels: 58 mg/kg (IQR 31; 75) in the diarrhea group and 64 mg/kg (IQR 18; 108) in those without diarrhea. Fecal SARS-CoV-2 was detected in all patients with diarrhea and in more than two thirds (29/41, 71%) of patients without diarrhea.

Comparing patients with and without fecal SARS-CoV-2 shedding (Table 2), we found higher fecal calprotectin levels in the former (74 mg/kg, IQR 29; 132.5) compared to the latter group (39 mg/kg, IQR 14; 71) ($P < 0.001$) (Figure 2). None of the patients without SARS-CoV-2 shedding had diarrhea. Neutrophil count was higher in patients with fecal SARS-CoV-2 shedding ($P = 0.035$), as well as D-dimer levels ($P = 0.011$) and white blood cell count ($P = 0.038$). C-reactive protein was higher in patients without fecal SARS-CoV-2 shedding ($P = 0.029$). Fecal SARS-CoV-2 was found in all obese patients ($P = 0.021$).

DISCUSSION

SARS-CoV-2 fecal shedding is a common finding among COVID-19 patients irrespective of gastrointestinal symptoms[16,17]. Our results confirmed that fecal SARS-CoV-2 was present in approximately three quarters of our patients with COVID-19 pneumonia.

Fecal calprotectin was found to be a marker of intestinal inflammation, both in COVID-19 patients and in the general population[10,11]. Our work demonstrates that hospitalized COVID-19 patients with pneumonia have high fecal calprotectin levels, regardless of gastrointestinal symptoms.

To our knowledge this is the first study to investigate whether fecal calprotectin correlates with SARS-CoV-2 intestinal shedding in COVID-19 patients. In our study, calprotectin levels were significantly higher in those with SARS-CoV-2 fecal shedding. This finding supports the hypothesis that bowel inflammation can lead to the "leaky gut" syndrome with potential distribution of the virus to other organs[18].

While the detection of SARS-CoV-2 in feces does not necessarily lead to more gastrointestinal symptoms, the presence of SARS-CoV-2 in gastrointestinal tissue generally correlates with more severe symptoms[19].

High fecal calprotectin in COVID-19 patients is likely secondary to increased neutrophil activation in the intestinal tract. In fact, SARS-CoV-2 can activate neutrophil extracellular traps and increase levels of intracellular reactive oxygen species[20].

In our cohort, all obese patients had SARS-CoV-2 RNA detected in stools. Obesity is one of the main risk factors for severe COVID-19 and poor clinical outcomes[20,21], and is associated with a strong inflammatory response both in the general population and in COVID-19 patients[22]. This could justify a more prolonged viral shedding in

Table 1 Clinical and biochemical characteristics of coronavirus disease 2019 patients with and without diarrhea, *n* (%)

	Overall, *n* = 51	Patients with diarrhea, *n* = 10	Patients without diarrhea, *n* = 41	Significance
Gender, male	40 (78.4)	8 (80)	32 (78)	NS
Age	64 (57; 71)	63 (56; 70)	65 (57; 71)	NS
Hypertension	34 (66.6)	6 (60)	28 (68.3)	NS
Heart disease	13 (25.5)	4 (40)	9 (21.9)	NS
Diabetes	13 (25.5)	2 (20)	11 (26.8)	NS
COPD	5 (9.8)	1 (10)	4 (9.75)	NS
CKD	5 (9.8)	1 (10)	4 (9.75)	NS
Active smokers	2 (3.9)	1 (10)	1 (2.4)	NS
Obesity	13 (25.5)	2 (20)	11 (26.8)	NS
WBC (cell count/μL)	6730 (5256; 9110)	6595 (4672; 7420)	6730 (5420; 9480)	NS
Neutrophils (cell count/μL)	5455 (3700; 7760)	5310 (3112; 6527)	5310 (3112; 6725)	NS
CRP (mg/L)	74 (27; 131)	73 (25; 161)	74 (29; 127)	NS
D-dimer (ng/mL FEU)	720 (545; 1061)	710 (560; 1511)	720 (540; 1060)	NS
Fecal calprotectin(mg/kg)	60 (21.5; 108)	58 (31; 75)	64 (18; 108)	NS
Fecal-RNA detection (*n* = positive)	39 (76.5)	10 (100)	29 (70.8)	NS
Deceased	3 (5.9)	1 (10)	2 (4.8)	NS
Hospital stay	5 (2.5; 8)	5 (2.75; 6.75)	5 (3; 9.25)	NS

COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CRP: C-reactive protein; NS: Not significant; WBC: White blood cells.

this subgroup of patients.

Our work has two main limitations. First, this was a monocentric study with a small sample of patients. Second, SARS-CoV-2 was detected in stools by PCR. This technique does not discriminate between live virus and non-infectious viral particles. Only a few studies have reported live SARS-CoV-2 in the stools of COVID-19 patients[23-26]. There is also limited evidence on the duration of fecal viral shedding[7].

Our study demonstrates that higher fecal calprotectin levels correlate with SARS-CoV-2 fecal shedding in hospitalized COVID-19 patients with pneumonia. Our results support the role of neutrophils in SARS-CoV-2 pathogenesis.

CONCLUSION

In conclusion, our study provides two main results: (1) Fecal SARS-CoV-2 is present in approximately three quarters of hospitalized patients with COVID-19 pneumonia and in all patients with diarrhea; interestingly, all obese COVID-19 patients show fecal viral shedding; and (2) High fecal calprotectin levels are a common finding among hospitalized COVID-19 patients, especially those with SARS-CoV-2 fecal shedding. We believe that our results could strengthen the hypothesis that SARS-CoV-2-induced intestinal damage mediated by innate immunity (complement activation and consequent activated neutrophil migration) could contribute to COVID-19 pathogenesis.

Table 2 Clinical and biochemical characteristics of coronavirus disease 2019 patients with and without severe acute respiratory syndrome coronavirus 2 fecal detection, *n* (%)

	Overall, *n* = 51	Patients without fecal SARS-CoV-2, *n* = 12	Patients with fecal SARS-CoV-2, *n* = 39	Significance
Gender, male	40 (78.4)	12 (100)	28 (71.8)	NS
Age	64 (57; 71)	62 (57; 68)	65 (56; 72)	NS
Hypertension	34 (66.6)	6 (50)	28 (71.8)	NS
Heart disease	13 (25.5)	1 (8.3)	12 (30.8)	NS
Diabetes	13 (25.5)	2 (16.6)	11 (28.2)	NS
COPD	5 (9.8)	0 (0)	5 (12.8)	NS
CKD	5 (9.8)	1 (8.3)	4 (10.25)	NS
Active smokers	2 (3.9)	1 (8.3)	1 (2.6)	NS
Obesity	13 (25.5)	0 (0)	13 (33.3)	$P = 0.021$
WBC (cell count/μL)	6730 (5256; 9110)	6105 (4870; 8400)	7110 (5525; 9115)	$P = 0.038$
Neutrophils (cell count/μL)	5455 (3700; 7760)	4390 (3485; 7417)	5550 (3965; 8110)	$P = 0.035$
CRP (mg/L)	74 (27; 131)	113 (88; 150)	58 (24.5; 125)	$P = 0.029$
D-dimer (ng/Ml FEU)	720 (545; 1061)	580 (402; 791)	723 (562; 1157)	$P = 0.011$
Fecal calprotectin (mg/kg)	60 (21.5; 108)	39 (14; 71)	74 (29; 132.5)	$P < 0.001$
Diarrhea	41 (80.4)	0 (0)	29 (74.35)	$P < 0.001$
Deceased	3 (5.9)	0 (0)	3 (7.7)	NS
Hospital stay	5 (2.5; 8)	3 (2; 5)	5 (3; 9.75)	NS

COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CRP: C-reactive protein; NS: Not significant; WBC: White blood cells; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

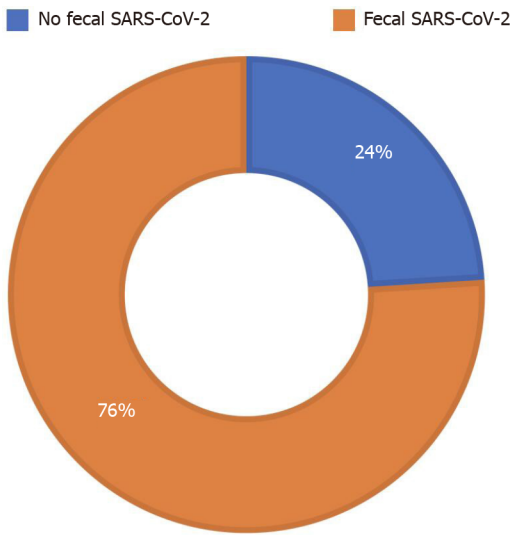

Figure 2 Comparison of patients with and without fecal severe acute respiratory syndrome coronavirus 2 shedding. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

ARTICLE HIGHLIGHTS

Research background

One third of coronavirus disease 2019 (COVID-19) patients have gastrointestinal symptoms. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA has been detected in stool samples of approximately 50% of COVID-19 individuals. Fecal calprotectin is a marker of gastrointestinal inflammation.

Research motivation

The pathogenesis of gastrointestinal symptoms caused by SARS-CoV-2 is multifactorial and little evidence is available on this topic.

Research objectives

To investigate whether fecal calprotectin correlates with SARS-CoV-2 intestinal shedding in COVID-19 patients with pneumonia.

Research methods

Fecal samples from patients with SARS-CoV-2 pneumonia were collected and analyzed for quantification of fecal calprotectin and SARS-CoV-2 RNA presence using polymerase chain reaction (PCR).

Research results

Real-time-PCR of SARS-CoV-2 in the stools of 51 patients with pneumonia was positive in 39 patients (76%), in all patients with diarrhea (100%) and in more than two thirds (29/41, 71%) of those without diarrhea. Higher fecal calprotectin levels were found in the group with SARS-CoV-2 in stools [74 mg/kg, interquartile range (IQR) 29; 132.5] compared to the group without SARS-CoV-2 (39 mg/kg, IQR 14; 71) ($P < 0.001$).

Research conclusions

High fecal calprotectin levels in COVID-19 patients correlates with SARS-CoV-2 detection in stools.

Research perspectives

Our results support the hypothesis that SARS-CoV-2-induced intestinal damage mediated by innate immunity could contribute to COVID-19 pathogenesis.

ACKNOWLEDGEMENTS

We thank Dr. Lisa Fusaro for her kind help.

REFERENCES

1 **Syed A**, Khan A, Gosai F, Asif A, Dhillon S. Gastrointestinal pathophysiology of SARS-CoV2 - a literature review. *J Community Hosp Intern Med Perspect* 2020; **10**: 523-528 [PMID: 33194122 DOI: 10.1080/20009666.2020.1811556]

2 **Ye L**, Yang Z, Liu J, Liao L, Wang F. Digestive system manifestations and clinical significance of coronavirus disease 2019: A systematic literature review. *J Gastroenterol Hepatol* 2020 [PMID: 33150978 DOI: 10.1111/jgh.15323]

3 **Kaafarani HMA**, El Moheb M, Hwabejire JO, Naar L, Christensen MA, Breen K, Gaitanidis A, Alser O, Mashbari H, Bankhead-Kendall B, Mokhtari A, Maurer L, Kapoen C, Langeveld K, El Hechi MW, Lee J, Mendoza AE, Saillant NN, Parks J, Fawley J, King DR, Fagenholz PJ, Velmahos GC. Gastrointestinal Complications in Critically Ill Patients With COVID-19. *Ann Surg* 2020; **272**: e61-e62 [PMID: 32675498 DOI: 10.1097/SLA.0000000000004004]

4 **Giuffrè M**, Bozzato AM, Di Bella S, Occhipinti AA, Martingano P, Cavallaro MFM, Luzzati R, Monica F, Cova MA, Crocè LS. Spontaneous Rectal Perforation in a Patient with SARS-CoV-2 Infection. *J Pers Med* 2020; **10** [PMID: 33049924 DOI: 10.3390/jpm10040157]

5 **Gupta S**, Parker J, Smits S, Underwood J, Dolwani S. Persistent viral shedding of SARS-CoV-2 in faeces - a rapid review. *Colorectal Dis* 2020; **22**: 611-620 [PMID: 32418307 DOI: 10.1111/codi.15138]

6 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load

in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]

7 **Cevik M**, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2021; **2**: e13-e22 [PMID: 33521734 DOI: 10.1016/S2666-5247(20)30172-5]

8 **Xiao F**, Sun J, Xu Y, Li F, Huang X, Li H, Zhao J, Huang J. Infectious SARS-CoV-2 in Feces of Patient with Severe COVID-19. *Emerg Infect Dis* 2020; **26**: 1920-1922 [PMID: 32421494 DOI: 10.3201/eid2608.200681]

9 **Ayling RM**, Kok K. Fecal Calprotectin. *Adv Clin Chem* 2018; **87**: 161-190 [PMID: 30342711 DOI: 10.1016/bs.acc.2018.07.005]

10 **Effenberger M**, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, Hilbe R, Seiwald S, Scholl-Buergi S, Fritsche G, Bellmann-Weiler R, Weiss G, Müller T, Adolph TE, Tilg H. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut* 2020; **69**: 1543-1544 [PMID: 32312790 DOI: 10.1136/gutjnl-2020-321388]

11 **Giuffrè M**, Di Bella S, Sambataro G, Zerbato V, Cavallaro M, Occhipinti AA, Palermo A, Crescenti A, Monica F, Luzzati R, Crocè LS. COVID-19-Induced Thrombosis in Patients without Gastrointestinal Symptoms and Elevated Fecal Calprotectin: Hypothesis Regarding Mechanism of Intestinal Damage Associated with COVID-19. *Trop Med Infect Dis* 2020; **5** [PMID: 32947803 DOI: 10.3390/tropicalmed5030147]

12 **Ojetti V**, Saviano A, Covino M, Acampora N, Troiani E, Franceschi F; GEMELLI AGAINST COVID-19 group. COVID-19 and intestinal inflammation: Role of fecal calprotectin. *Dig Liver Dis* 2020; **52**: 1231-1233 [PMID: 33060042 DOI: 10.1016/j.dld.2020.09.015]

13 **Shi H**, Zuo Y, Yalavarthi S, Gockman K, Zuo M, Madison JA, Blair C, Woodward W, Lezak SP, Lugogo NL, Woods RJ, Lood C, Knight JS, Kanthi Y. Neutrophil calprotectin identifies severe pulmonary disease in COVID-19. *J Leukoc Biol* 2021; **109**: 67-72 [PMID: 32869342 DOI: 10.1002/JLB.3COVCRA0720-359R]

14 **Bauer W**, Diehl-Wiesenecker E, Ulke J, Galtung N, Havelka A, Hegel JK, Tauber R, Somasundaram R, Kappert K. Outcome prediction by serum calprotectin in patients with COVID-19 in the emergency department. *J Infect* 2020 [PMID: 33217473 DOI: 10.1016/j.jinf.2020.11.016]

15 **Li Q**, Chen Z. An update: the emerging evidence of complement involvement in COVID-19. *Med Microbiol Immunol* 2021; 1-9 [PMID: 33811541 DOI: 10.1007/s00430-021-00704-7]

16 **van Doorn AS**, Meijer B, Frampton CMA, Barclay ML, de Boer NKH. Systematic review with meta-analysis: SARS-CoV-2 stool testing and the potential for faecal-oral transmission. *Aliment Pharmacol Ther* 2020; **52**: 1276-1288 [PMID: 32852082 DOI: 10.1111/apt.16036]

17 **Patel KP**, Patel PA, Vunnam RR, Hewlett AT, Jain R, Jing R, Vunnam SR. Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. *J Clin Virol* 2020; **128**: 104386 [PMID: 32388469 DOI: 10.1016/j.jcv.2020.104386]

18 **Synowiec A**, Szczepański A, Barreto-Duran E, Lie LK, Pyrc K. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. *Clin Microbiol Rev* 2021; **34** [PMID: 33441314 DOI: 10.1128/CMR.00133-20]

19 **Lin L**, Jiang X, Zhang Z, Huang S, Fang Z, Gu Z, Gao L, Shi H, Mai L, Liu Y, Lin X, Lai R, Yan Z, Li X, Shan H. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020; **69**: 997-1001 [PMID: 32241899 DOI: 10.1136/gutjnl-2020-321013]

20 **Jayawardena R**, Jeyakumar DT, Misra A, Hills AP, Ranasinghe P. Obesity: A potential risk factor for infection and mortality in the current COVID-19 epidemic. *Diabetes Metab Syndr* 2020; **14**: 2199-2203 [PMID: 33395781 DOI: 10.1016/j.dsx.2020.11.001]

21 **Hoong CWS**, Hussain I, Aravamudan VM, Phyu EE, Lin JHX, Koh H. Obesity is Associated with Poor Covid-19 Outcomes: A Systematic Review and Meta-Analysis. *Horm Metab Res* 2021; **53**: 85-93 [PMID: 33395706 DOI: 10.1055/a-1326-2125]

22 **McNeill JN**, Lau ES, Paniagua SM, Liu EE, Wang JK, Bassett IV, Selvaggi CA, Lubitz SA, Foulkes AS, Ho JE. The role of obesity in inflammatory markers in COVID-19 patients. *Obes Res Clin Pract* 2021; **15**: 96-99 [PMID: 33390322 DOI: 10.1016/j.orcp.2020.12.004]

23 **Lui RN**. Safety in endoscopy for patients and healthcare workers during the COVID-19 pandemic. *Tech Innov Gastrointest Endosc* 2020 [PMID: 33103130 DOI: 10.1016/j.tige.2020.10.004]

24 **Wang W**, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020; **323**: 1843-1844 [PMID: 32159775 DOI: 10.1001/jama.2020.3786]

25 **Zhang Y**, Cao C, Shuangli Z. Isolation of SARs-CoV-2 from stool specimen of a confirmed case of COVID-19. [cited 16 January 2021]. Available from: https://www.cebm.net/study/isolation-of-sars-cov-2-from-a-stool-specimen-of-confirmed-case-of-covid-19/

26 **Li L**, Tan C, Zeng J, Luo C, Hu S, Peng Y, Li W, Xie Z, Ling Y, Zhang X, Deng E, Xu H, Wang J, Xie Y, Zhou Y, Zhang W, Guo Y, Liu Z. Analysis of viral load in different specimen types and serum antibody levels of COVID-19 patients. *J Transl Med* 2021; **19**: 30 [PMID: 33413461 DOI: 10.1186/s12967-020-02693-2]

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