SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Gastroenterology

Gastrointestinal Manifestations in COVID 19: A Moroccan Bicentric Study

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DOI: 10.36347/sasjm.2023.v09i02.004 | **Received:** 05.10.2022 | **Accepted:** 12.11.2022 | **Published:** 09.02.2023

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Abstract **Original Research Article**

Since its declaration in December 2019, SARS-CoV-2 has been rapidly responsible for a major global pandemic. The disease is mainly characterized by respiratory symptoms; nevertheless digestive manifestations have been frequently reported. The objective of our study is to describe the epidemiological, clinical, evolutionary profile of diagnosed cases of COVID-19 with digestive manifestations. This is a retrospective bicentric descriptive study carried out in patients with COVID-19 at the Hassan II Hospital in Agadir and at the Mohammed VI University Hospital in Marrakech, from April 2020 to May 2021. Digestive manifestations are frequent and varied in patients infected with SARS-CoV-2. They may present as the main complaint or the only manifestation of the disease, leading to delayed diagnosis and increased risk of transmission. It has been noted that SARS-CoV-2 RNA can be detected in fecal matter for an extended period of time, even after respiratory samples have tested negative and patients are asymptomatic. Treatment of these symptoms is mandatory to prevent transmission of the disease and progression to complications that can worsen the prognosis.

Keywords: Gastrointestinal, hepatobiliary, pancreatic, ACE, covid 19, fecal matter.

INTRODUCTION

Coronavirus 2 is responsible for SARS-CoV-2 (Severe Acute Respiratory Syndrom) which has been evolving into a rapidly progressive pandemic since the end of 2019 with a mortality rate of 0.5-3% [1, 2]. Without really effective treatment known to date but with many vaccines. Although respiratory symptoms are the most common and condition the prognosis of the disease, extra-pulmonary manifestations, in particular digestive ones, have been frequently reported in infected patients, raising the potential tropism of SARS-CoV2 for the digestive tract [3]. The gastrointestinal and hepatobiliary symptoms are diverse and most often intertwined, being distributed variably between the series. They can precede the respiratory symptoms and confuse the diagnosis, with an impact both on the prognosis and on the chain of transmission of the virus [4, 5].

AIM OF THE STUDY

To describe the epidemiological, diagnostic and evolutionary profile of diagnosed cases of COVID-19 with digestive manifestations.

METHODS

This is a bicentric, descriptive retrospective study, extended over a period of one year from April 2020 to May 2021, carried out in patients who were hospitalized during this period for infection confirmed by SARS-CoV-2, at the Hassan II regional medical center (RMC) in Agadir and at the Mohammed VI university hospital center (UHC) in Marrakech.

RESULTS

During the period of the study, 682 files were collected, including 400 patients at the RMC in Agadir and 200 patients at the UHC in Marrakech, with a general prevalence of digestive manifestations of 48.2% (329) (figure1). The median age was 60 years. Male sex was more predominant (54.70%) and sex ratio was 1.21. Comorbidity was noted in the majority of patients: diabetes (29%), high blood pression (15%), heart disease (5.1%) and renal failure (6%), only two patients were followed for chronic hepatitis B.

Digestive manifestations revealed the disease in 25% of cases and isolated without respiratory signs in 3.65% of cases. The clinical signs were often

intertwined with association in the same patient of several warning signs, the most frequent symptom was diarrhea (34.65%) followed by anorexia (25.83%), vomiting (20. 67%), diffuse abdominal pain (16.41%) and epigastric pain (14.6%) (figure 2). Gastrointestinal bleeding was present in 14 patients as hematemesis (0.60%), melena (1.82%) and rectal bleeding (1.82%). Clinical examination was normal in 70% of patients; abdominal tenderness was observed in 54 patients (16.4%). The main hepatic abnormalities were: hepatic cytolysis (21.28%), cholestasis (6.66%), hypo albuminemia (21.87%), lipasemia was high in one patient. The PCR tests carried out on the stools in 14 patients (4.25%) were all positive. The ultrasound anomalies found were: vesicular lithiasis in four patients (1.21%), aerocolia (0.91%), parietal hematoma (0.91%). Abdominal CT was performed in 29 cases (8.81%), finding intestinal pseudo-obstruction in 1.82% of cases, one case of acute pancreatitis stage B (0.30%) and one case of peritonitis with mesenteric ischemia (0.30%). Fibroscopy was performed in 2 patients (0.61%). The treatment of digestive manifestations was symptomatic in all patients. The evolution was good in 172 patients (52.3%), digestive complications were reported in 5.15% of cases, dominated by digestive bleeding in 3.65%, and a fatal outcome in 25.3%. 147 patients (44.68%) presented side effects under treatment, gastrointestinal and hepatic side effects were reported in 14.23% of patients.

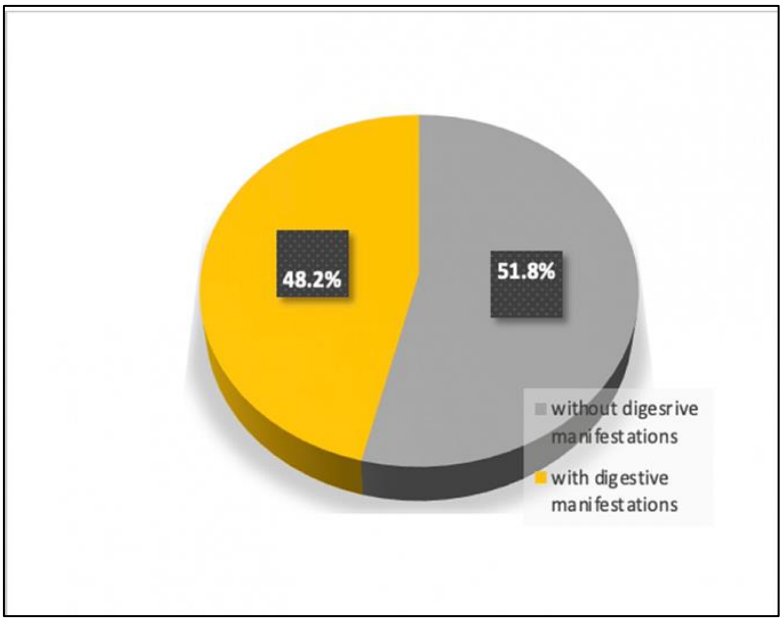

Figure 1: **Prevalence of digestive manifestations of Covid 19 in our study**

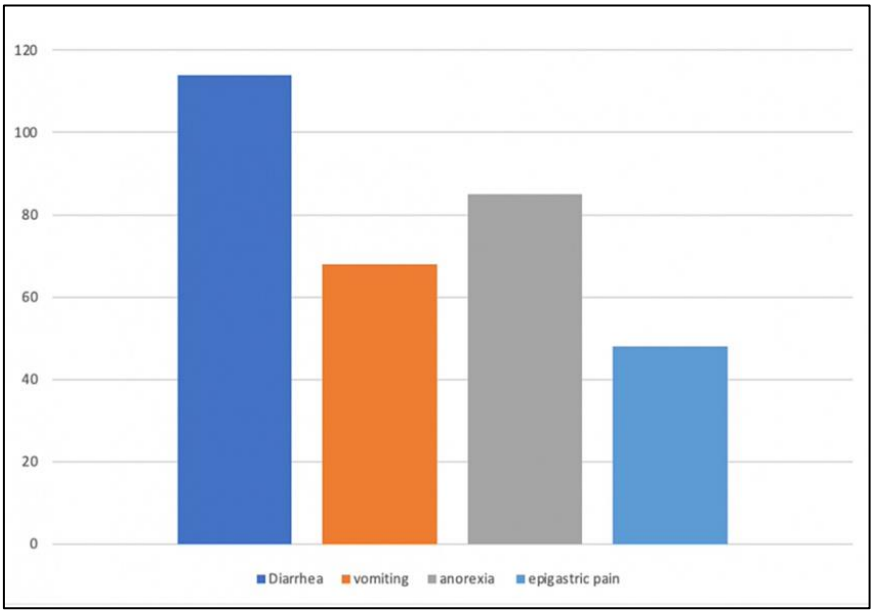

Figure 2: Distribution of the population studied according to digestive manifestations

DISCUSSION

1. Epidemiology

The prevalence of gastrointestinal symptoms during Covid-19 varies between 3% to 57% depending on the studies [6-9]. In 15 papers on 2800 patients with COVID-19, including 13 studies from China, one study from Singapore, and one paper by the World Health Organization; the prevalence of gastrointestinal symptoms varied widely from 3% to 39.6% [5] (Table 1).

The age of patients infected with SARS-CoV-2 varies between 30 and 79 years with a median age of 47 years [2]. The frequency of the disease and of the digestive manifestations, more particularly in these age groups, can be explained by a decrease in the concentration of circulating ACE 2. Indeed, this soluble form plays a protective role against cell penetration of the virus. It is strongly expressed in children and the youngest subjects and women. This explains, for some authors, the relative protection of children compared to adults and of women compared to men [10]. Studies in Wuhan have shown that the majority of Covid-19 patients are adult men. For digestive manifestations, concerned mainly men [9].

Table 1: prevalence of digestive manifestations by series

Authors	Total number patients	Prevalence of digestive manifestations
Yang *et al.*, [6]	52	3,84%
Luo S *et al.*, [7]	1141	16,03%
Han C *et al.*, [8]	206	56,80%
Hajifathalian K *et al.*, [9]	1059	33,05%
Notre série	329	48,24%

2. Mechanism of Digestive Damage

A digestive tropism has been evoked in the presence of digestive symptoms in infected patients. The enterocyte has been identified as the target cell of SARS-CoV-2 in the digestive tract. Indeed, the enterocyte strongly co-expresses the two key proteins of SARS-CoV-2 cell entry at namely angiotensin converting enzyme 2 and transmembrane serine protease. Furthermore, recent in vitro studies have confirmed that SARS-CoV-2 actively infects human enterocytes with the production and release of viable and infectious viral particles [3]. The ACE2 receptor is also expressed in the esophagus, gastric, salivary and cholangiocytes.

Faecal-oral transmission was reported early in the outbreak due to the high concentration of ACE2 receptors in the small intestine [11]. Xiao *et al.*, demonstrated detection of SARS-CoV-2 RNA in stomach, duodenal and rectal epithelium. In their study, they noted that in more than 20% of patients with SARS-CoV-2, the stool test for viral RNA was positive [12]. It has been suggested that SARS-CoV-2 may persist longer in the digestive tract than in the respiratory tract. This viral excretion can persist even after viral clearance in the respiratory tract with an average of 11.2 days after the negative tests in the respiratory tract [13]. Wu *et al.*, reported that stool specimens remain positive even after 33 days of negative respiratory swabs [14].

3. Gastro-Intestinal Manifestations

Gastrointestinal symptoms may be the only clinical manifestation of COVID-19 or might precede other symptoms. In a study by Luo *et al.*, in 1141 cases, 16% had gastrointestinal symptoms as the main mode of revealing the disease [15]. In a cohort study carried out in 799 patients in China, the time between the onset of symptoms and admission to hospital was 10 days with variations between 7 and 13 days [16].

The most common gastrointestinal manifestations are: (table 2) diarrhea, anorexia, nausea and vomiting, abdominal pain and more rarely gastrointestinal bleeding. Several studies report contradictory results regarding the relationship between digestive symptoms and the severity of the clinical presentation. In our study, the prevalence of digestive manifestations was higher in patients with severe forms. This can be explained, on the one hand, by the viral load which is higher in these patients leading to greater digestive lesions, and on the other hand by a greater cytokine inflammatory reaction.

Table 2: comparison of the prevalence of digestive manifestations according to the studies

Series	Number of cases	Diarrhea	Nausea/Vomiting	Anorexia	Abdominal pain
Luo *et al.*, [17]	1141	5,96%	18,93%	15,77%	3,94%
Wang *et al.*, [18]	138	10,14%	10,14%	39,85%	2,17%
Yang *et al.*, [15]	305	49,50%	15,90%	50,20%	6%
Notre série	329	34,65%	20,67%	25,83%	16,41%

The prevalence of diarrhea varies between 3 and 49% according to the different studies [15]. Diarrhea is explained by several mechanisms. On the one hand, the infection of the enterocyte by SARS-CoV-2 induces a secondary inflammatory reaction with structural and functional alterations of the enterocytes inducing malabsorption, abnormalities of intestinal secretion and activation of the enteric nervous system [19]. On the other hand, the treatments used can also cause diarrhea either by action on the digestive mucosa or on the intestinal flora. Vomiting is more frequent in children [15] with a prevalence varying between 3.6% and 15.9% in adults and between 6.5% and 66.7% in children [15]. Gastrointestinal bleeding in patients with COVID-19 is as common as other gastrointestinal symptoms. A review of the literature in 2,023 cases of COVID-19 estimated a prevalence of gastrointestinal bleeding between 4% and 13.7% [19].

The predisposing factors for gastrointestinal bleeding in patients with COVID-19 are: history of gastrointestinal bleeding, taking certain treatments such as: anticoagulants and non-steroidal anti-inflammatory drugs [20]. Endoscopic examinations are reserved for emergency situations because of the high risk of contagiousness. Of the limited data available in endoscopy, the most frequent endoscopic lesions are peptic ulcer, erosive gastritis and acute colitis [21] (figure 3-6). Indeed, it has been shown that age and male sex are contributing factors, by increasing the intestinal expression of SARS-CoV-2 receptors [22]. Some treatments increase the risk of digestive damage or the risk of worsening the damage, such as corticosteroids used in patients with inflammatory bowel disease [23]. Some studies have also demonstrated a higher incidence of digestive manifestations in patients with irritable bowel syndrome [21].

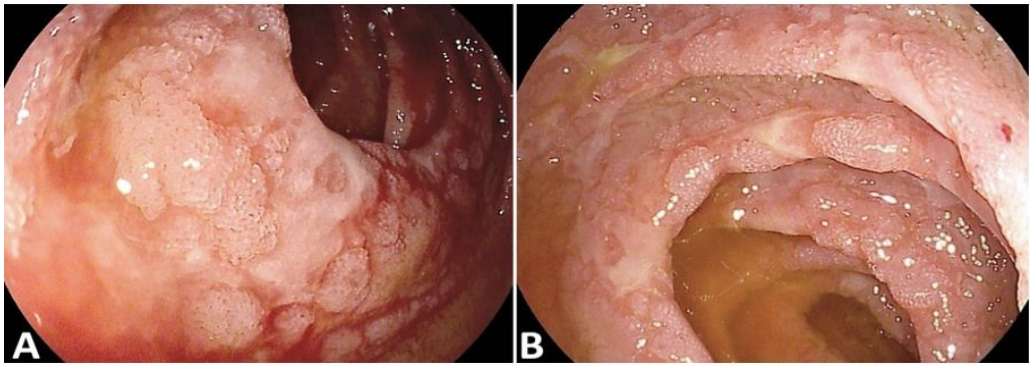

Figure 3: Intestinal erosions and ulcers in a patient with COVID-19, with persistent abdominal pain

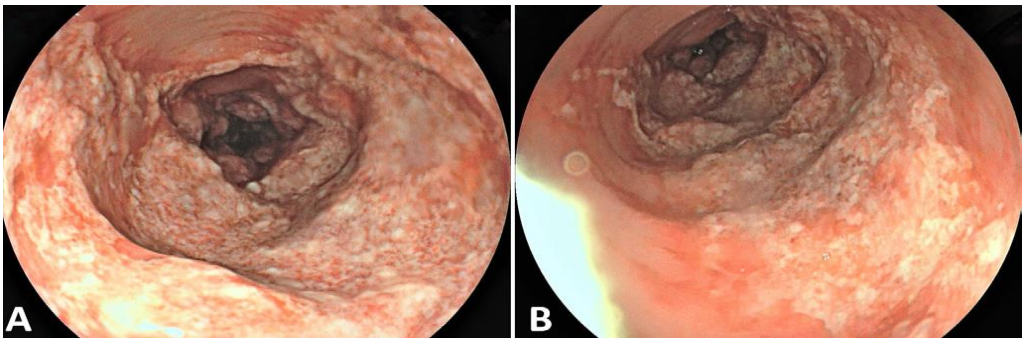

Figure 4: Unilateral ulcerations of the sigmoid colon in a patient with COVID-19 and presenting with lower gastrointestinal bleeding

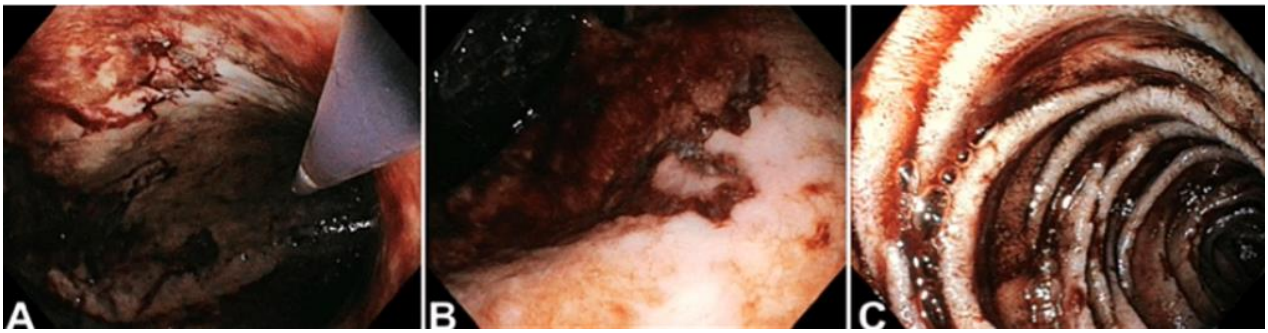

Figure 5: (A, B, C) Ulcer of the lesser curvature and the 2nd duodenal portion in a patient with COVID-19 and admitted for upper gastrointestinal bleeding

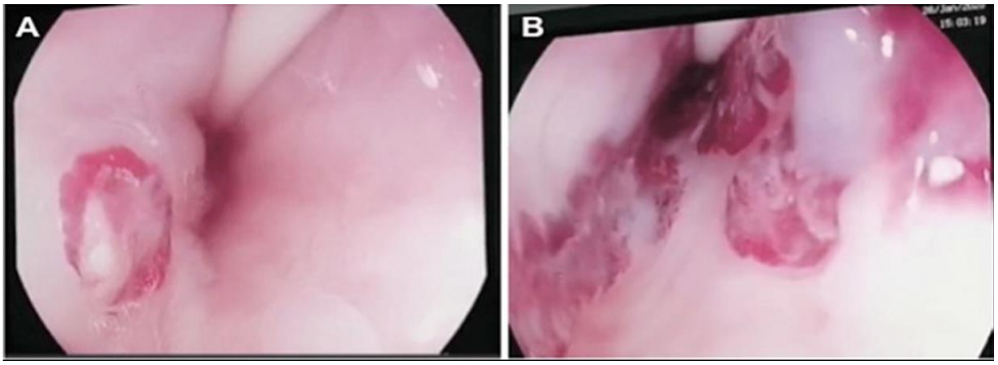

Figure 6: A round ulcer covered with whitish deposits in the esophagus

4. Hepatobiliary Manifestations

Hepatic damage is due to several factors, from one side, direct hepatic invasion by the virus, and on the other side the cytokine storm by, excessive reaction secondary to inflammatory factors (IL6, IL10, IL12, IFN), inducing multi-visceral failure. In addition, drug origin can also be incriminated in liver damage such as Lopinavir/Ritonavir [24-26].

Liver dysfunction was reported in 14–53% of cases during the pandemic [25]. The hepatic complications described during SARS-CoV2 infection are: hepatic cytolysis, cholestasis and decompensated hepatopathy. It has been shown that liver test abnormalities are more frequent in patients with severe forms. Huang *et al.,* described a higher prevalence in intensive care unit patients (61.5% versus 25.0%) [27].

The prevalence of COVID-19 infection in patients with acute cholecystitis during the pandemic was 16.3% [24]. In a prospective and retrospective study, carried out in Spain, in 257 patients admitted for acute cholecystitis, 42 patients (16.3%) tested positive for SARS-CoV-2 [28].

5. Pancreatic Manifestations

The ACE2 receptor is also highly expressed in pancreatic islet, explaining the possibility of pancreatic damage in patients with COVID-19.

Mechanisms by which pancreatic injury could occur include direct cytopathic effects of SARS-CoV-2, or indirect due to systemic inflammatory and immune or secondary cellular responses to molecules used in treatment [19].

The incidence of pancreatic damage is 17% according to Wang *et al.,* in a case series of 59 patients with COVID-19. Liu *et al.,* also reported a 17% incidence of pancreatic lesions in 67 patients with COVID-19 [29].

According to Chiarello *et al.,* the association of pancreatitis and COVID-19 has a poor prognosis due to the worsening of lung damage by the release of cytokines induced by pancreatitis [30].

6. Evolution

The evolution of digestive manifestations during COVID-19 is often favorable. Symptoms resolve within an average of 5 days. However, despite the rapid recovery from symptoms, viral excretion in the stool takes more time, it can persist for 30 days [23].

The occurrence of gastrointestinal and hepatic complications is conditioned by several factors, namely: advanced age, comorbidities, severity of the disease. 74-86% of critically ill patients with COVID-19 have gastrointestinal or liver complications. The main complications that have been reported in patients are: gastrointestinal bleeding (2-13%), intestinal perforation and intestinal ischemia (0.22-10.5%), pancreatitis (17%), cholecystitis (16.3%), hepatitis (5.88%) and Ogilvie syndrome (1.9%) [31].

CONCLUSION

Given the frequency of digestive manifestations, the enterocyte tropism of SARS-CoV-2 is well established. Hepatic tropism is also plausible. These manifestations can be indicative of a COVID-19 infection but can also be the cause of diagnostic errors and delays in the absence of respiratory manifestations. The treatment of these symptoms is mandatory in order to prevent the transmission of the disease and the evolution towards complications which can worsen the prognosis.

During this work, we were able to explain the mechanisms of occurrence of the digestive attack in order to establish an appropriate therapeutic strategy.

The management is individualized; it is determined by the patient's background, the severity of the disease, the causal factor and the means available according to each hospital center.

REFERENCES

1. Statista, COVID-19: Faits et chiffres, https://fr. statista.com /themes/6050/ le-coronavirus-covid-19.
2. Wang, Y., Wang, Y., Chen, Y., & Qin, Q. (2020). Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia

(COVID-19) implicate special control measures. *Journal of medical virology*, *92*(6), 568-576.
3. Ghanem, M., Bouchabou, B., Bouali, R., & Elloumi, H. (2020). Digestive manifestations in COVID-19: Prevalence and prognostic impact. *La Tunisie Medicale*, *98*(8-9), 643-650.
4. Hu, B., Guo, H., Zhou, P., & Shi, Z. L. (2021). Characteristics of SARS-CoV-2 and COVID-19. *Nature Reviews Microbiology*, *19*(3), 141-154. DOI: 10.1038/s41579-020-00459-7.
5. Schmulson, M., Dávalos, M. F., & Berumen, J. (2020). Alerta: los síntomas gastrointestinales podrían ser una manifestación de la COVID-19. *Revista de Gastroenterología de México*, *85*(3), 282-287. Doi: 10.1016/j.rgmx.2020.04.001.
6. Yang, X., Yu, Y., Xu, J., Shu, H., Liu, H., Wu, Y., ... & Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*, *8*(5), 475-481. DOI: 10.1016/S2213-2 600(20)30079-5.
7. Luo, S., Zhang, X., & Xu, H. (2020). Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). *Clinical Gastroenterology and Hepatology*, *18*(7), 1636-1637. https://doi.org/10.1016/j.cgh.2020.03.043.
8. Han, C., Duan, C., Zhang, S., Spiegel, B., Shi, H., Wang, W., ... & Hou, X. (2020). Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. *The American journal of gastroenterology*. 115(6), 916-923. Doi: 10.14309/ajg.0000 000 000 000 664.
9. Hajifathalian, K., Krisko, T., Mehta, A., Kumar, S., Schwartz, R., Fortune, B., ... & Cohen, D. (2020). Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: clinical implications. *Gastroenterology*, *159*(3), 1137-1140. Doi: 10.1053/j. gastro. 2020.05.010. S0016
10. Liu, D. X., Fung, T. S., Chong, K. K. L., Shukla, A., & Hilgenfeld, R. (2014). Accessory proteins of SARS-CoV and other coronaviruses. *Antiviral research*, *109*, 97-109.
11. Meyerowitz, E. A., Richterman, A., Gandhi, R. T., & Sax, P. E. (2021). Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. *Annals of internal medicine*, *174*(1), 69-79.
12. Chauhan, S. (2020). Comprehensive review of coronavirus disease 2019 (COVID-19). *Biomedical journal*, *43*(4), 334-340.
13. Lotfi, M., Hamblin, M. R., & Rezaei, N. (2020). COVID-19: Transmission, prevention, and potential therapeutic opportunities. *Clinica chimica acta*, *508*, 254-266.
14. Arslan, M., Xu, B., & El-Din, M. G. (2020). Transmission of SARS-CoV-2 via fecal-oral and aerosols–borne routes: Environmental dynamics and implications for wastewater management in underprivileged societies. *Science of the Total Environment*, *743*, 140709.
15. Yuan, T., Long, R., Weidong, N., & Yan, H. (2020). Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther*, 51(9), 843-851. doi: 10.1111/apt.15731.
16. Song, S., Jun, S., Liangru, Z., Yun, Q., Jin-Shen, H., Jin-Yu, T., Marietta, I., Siew, C, Ng., Subrata, G., Ren, M., & Jie, L. (2020). Involvement of digestive system in COVID-19: manifestations, pathology, management and challenges. *Therapeutic Advances in Gastroenterology*, 13, 1-12, DOI: 10.1177/1756284820934626
17. Zhang, J., Garrett, S., & Sun, J. (2021). Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19. *Genes & diseases*, *8*(4), 385-400. https://doi.org/10.1 016/j. gendis.2020
18. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*, *323*(11), 1061-1069.
19. Patel, K. P., Patel, P. A., Vunnam, R. R., Hewlett, A. T., Jain, R., Jing, R., & Vunnam, S. R. (2020). Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. *Journal of Clinical Virology*, *128*, 104386.
20. Martin, T. A., Wan, D. W., Hajifathalian, K., Tewani, S., Shah, S. L., Mehta, A., ... & Sharaiha, R. Z. (2020). Gastrointestinal bleeding in patients with coronavirus disease 2019: a matched case-control study. *The American Journal of Gastroenterology*, 115(10), 1609-1616. doi: 10.14309/ajg.0000000000000805.
21. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*, *395*(10223), 497-506.
22. Vanella, G., Capurso, G., Burti, C., Fanti, L., Ricciardiello, L., Lino, A. S., ... & Arcidiacono, P. G. (2021). Gastrointestinal mucosal damage in patients with COVID-19 undergoing endoscopy: an international multicentre study. *BMJ open gastroenterology*, *8*(1), e000578. Doi: 10.1136/ bmjgast-2020-000578.
23. Hunt, R. H., East, J. E., Lanas, A., Malfertheiner, P., Satsangi, J., Scarpignato, C., & Webb, G. J. (2021). COVID-19 and gastrointestinal disease: implications for the gastroenterologist. *Digestive Diseases*, *39*(2), 119-139. DOI: 10.1159 /00 0512152.
24. Zhong, P., Xu, J., Yang, D., Shen, Y., Wang, L., Feng, Y., ... & Sun, Y. (2020). COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. *Signal transduction and targeted therapy*, *5*(1), 1-8. DOI: doi.org /10.103 8/s41392-020-00373-7.

25. Jothimani, D., Venugopal, R., Abedin, M. F., Kaliamoorthy, I., & Rela, M. (2020). COVID-19 and the liver. *Journal of hepatology*, *73*(5), 1231-1240. doi: 10.1016/j.jhep.2020.06.006. Epub 2020 Jun 15. PMID: 32553666; PMCID: PMC7295524.
26. Huang, H., Li, H., Chen, S., Zhou, X., Dai, X., Wu, J., ... & Ge, M. (2021). Prevalence and characteristics of hypoxic hepatitis in COVID-19 patients in the intensive care unit: A first retrospective study. *Frontiers in Medicine*, *7*, 607206. Doi: 10.3389 /fmed .2020.60 7206.
27. Balaja III, W. R., Jacob, S., Hamidpour, S., & Masoud, A. (2021). COVID-19 Presenting as Acute Icteric Hepatitis. *Cureus*, *13*(7). e16359. DOI: 10.7759/cureus.16359.
28. Garrido, I., Liberal, R., & Macedo, G. (2020). COVID-19 and liver disease—what we know on 1st May 2020. *Alimentary pharmacology & therapeutics*, *52*(2), 267-275. doi: 10.1111/apt.15813.
29. Martínez Caballero, J., González González, L., Rodríguez Cuéllar, E., Ferrero Herrero, E., Pérez Algar, C., Vaello Jodra, V., ... & Martínez Fernández, R. (2021). Multicentre cohort study of acute cholecystitis management during the COVID-19 pandemic. *European Journal of Trauma and Emergency Surgery*, *47*(3), 683-692. doi: 10.1007/s000 68-021-01631 -1.
30. Kandasamy, S. (2020). An unusual presentation of COVID-19: acute pancreatitis. *Annals of Hepato-biliary-pancreatic Surgery*, *24*(4), 539-541. doi: 10.14701/ ahbps.2020.24 .4.539.
31. Beata, J., Marek, O., & Sławomir, M. (2021). Association between acute pancreatitis and COVID-19 infection: What do we know? *World J Gastrointest Surg*, 13(6), 548-562. DOI: 10.4240/wjgs.v13.i6.548.
32. Dandan, T., & Qing, Y. (2020). Hepatic complications of COVID-19 and its treatment. *J Med Virol*, 92(10), 1818-1824, doi: 10.1002 /jmv .26036.