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Journal of Clinical Virology 128 (2020) 104386

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19

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ARTICLE INFO

Keywords:
COVID 19
SARS-CoV-2
Gastrointestinal
Hepatobiliary
Pandemic

ABSTRACT

There is an increasing number of confirmed cases and deaths caused by the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) contributing to the Coronavirus disease 2019 (COVID-19) pandemic. At this point, the need for further disease characterization is critical. COVID-19 is well established as a respiratory tract pathogen; however, recent studies have shown an increasing number of patients reporting gastrointestinal manifestations such as diarrhea, nausea, vomiting, and abdominal pain. The time from onset of gastrointestinal symptoms to hospital presentation is often delayed compared to that of respiratory symptoms. 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. In this article, SARS-CoV-2 and its disease COVID-19 will be reviewed with consideration of the latest literature about gastrointestinal symptomatology, the mechanisms by which the virus may inflict damage, and the possibility of viral replication contributing to a fecal-oral route of transmission.

1. Introduction

SARS-CoV-2 is an enveloped, non-segmented, positive-sense RNA virus responsible for the 2019 coronavirus disease (COVID-19) pandemic [1,2]. To date, on April 17, 2020, there have been 2,074,529 confirmed cases and 139,378 deaths globally [3]. COVID-19 is rapidly transmissible, posing a considerable threat to global public health [4]. SARS-CoV-2 uses the receptor angiotensin-converting enzyme 2 (ACE2) to gain cellular entry into the lower respiratory tract of humans, which has also been noted to be highly expressed in gastrointestinal epithelial cells [1,5]. Though patients typically endorse respiratory symptoms such as cough, dyspnea, and shortness of breath, there have been numerous reported cases of diagnosed COVID-19 patients exhibiting gastrointestinal manifestations such as diarrhea, nausea, vomiting, and abdominal pain [6,7]. A study has shown that SARS-CoV-2 RNA can be detected in feces for up to a month in 83.3 % of patients with a mild infection, raising suspicion for the gastrointestinal tract as an additional site of viral replication [8]. Additionally, another study demonstrated that out of 73 COVID-19 patients, 53.4 % were found to have viral RNA present in their stool – 23.3 % of those patients had positive stool samples even after the viral RNA cleared from their respiratory tract [9]. As such, these characteristics have clinical implications regarding the proper management of infected individuals, a potential fecal-oral route of transmission, and effective preventative infection control.

2. Gastrointestinal symptomology

The most characterized symptoms of COVID-19 include fever, cough, fatigue, dyspnea, sore throat, headache, and myalgias or arthralgias [6]. Approximately 80 % of patients demonstrate mild symptoms; 20 % have severe disease; about 5 % of patients exhibit critical disease symptoms such as respiratory arrest, septic shock, or multiple organ failure [6]. The median incubation period for COVID-19 is five days [10]. As SARS-CoV-2 has widely been studied as a respiratory tract pathogen, its extent of involvement in the gastrointestinal system is currently under investigation. A multicenter and cross-sectional study demonstrated that approximately 50 % of patients experienced symptoms such as diarrhea, nausea, vomiting, abdominal pain. Similar studies in China supported the presence of these symptoms among COVID-19 patients (Table 1) [7,11,16,17]. Furthermore, the time from onset of gastrointestinal symptoms to hospital presentation is delayed compared to respiratory symptoms (9.0 vs. 7.3 days)

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https://doi.org/10.1016/j.jcv.2020.104386
Received 18 April 2020; Accepted 25 April 2020

Table 1
Percentage of 2019 coronavirus disease COVID-19 patients exhibiting gastrointestinal manifestations in various studies completed from China.

Incidence of Gastrointestinal (GI) Manifestations exhibited in COVID-19 Patients			
Study	Number of Patients, N	GI symptoms, N (%)	No GI symptoms N, (%)
Pan L, et al. [11]	203	103 (50.7 %)	100 (49.3 %)
Jin X., et al. [7]	651	74 (11.3 %)	577 (88 %)
Fang D, et al. [16]	201	159 (79.1 %)	42 (20.8 %)
Zhang JJ, et al [17]	139	55 (39.6 %)	84 (60.4 %)

COVID-19-coronavirus disease 2019, N- Number.

[11].

Additional studies have characterized similar results among COVID-19 patients. One study examining 651 patients in the Zhejiang Province of China showed that 11.4 % presented with at least one gastrointestinal symptom consisting of nausea, vomiting, or diarrhea; the average age of these patients was 46.1 years, with 10.8 % having pre-existing liver disease [7]. Of COVID-19 patients with gastrointestinal symptoms, a subset also experienced significantly higher rates of fever, fatigue, shortness of breath, and headache [7].

The first COVID-19 patient in the United States presented with nausea, vomiting, cough, with additional gastrointestinal symptoms of loose bowel movements and abdominal pain during his hospitalization. He eventually tested positive for SARS-CoV-2 RNA in his stool and respiratory specimens upon rRT-PCR testing [12,13]. Additionally, the first case of hematochezia as a possible initial presenting symptom of COVID-19 was reported. Although the patient's stool specimens were not tested for viral RNA, this case highlights a rare gastrointestinal manifestation of the COVID-19 [14].

A recent paper by Tian et al. reviewing studies to date on gastrointestinal manifestations and COVID-19 infection investigated the incidence of specific symptoms in both children and adults. Diarrhea was the most common symptom in both children and adults, lasting approximately four days. There was a higher proportion of children who exhibited vomiting compared to adults. Furthermore, other symptoms noted were anorexia (39.9 %–50.2 %), vomiting (3.6 %–66.7 %), nausea (1 %–29.4 %), abdominal pain (2.2 %–6.0 %), and gastrointestinal bleeding (4 %–13.7 %) [12]. Additional studies have characterized similar results amongst COVID-19 patients (see Table 2) [7,11,16–24]. It is crucial to note that adult and children patients with COVID-19 may present with digestive symptoms in the absence of respiratory symptomatology.

The gastrointestinal manifestations secondary to SARS-CoV-2 infection can occur through different mechanisms. Firstly, ACE2 receptors, by which the virus uses to gain cellular entry, is expressed in both the respiratory tract and gastrointestinal tract epithelium, creating the potential for viral replication in the gastrointestinal tract. Secondly, there could be a direct injury of the gastrointestinal system due to an inflammatory response [11]. Absorptive enterocytes may be infected and destroyed by SARS-CoV-2, potentially leading to malabsorption, unbalanced intestinal secretion, and an activated enteric nervous system resulting in symptoms like diarrhea [15].

3. Hepatobiliary system

An increasing number of COVID-19 patients have been noted to experience hepatic injury, ranging on a spectrum of mild to severe damage [25]. Hepatic injury has been evident in specific laboratory abnormalities in these patients – the pathophysiology behind SARS-CoV-2 infection may suggest the injury is due to the disease process.

According to the American College of Gastroenterology (ACG), abnormal liver enzymes are observed in 20–30 % of persons with confirmed COVID-19 infection [26]. In a study examining 148 confirmed SARS-CoV-2 infected patients in China, 50.7 % of patients were found to have abnormal liver functions at admission [25]. Additional studies have demonstrated similar results with abnormalities in liver enzymes and total bilirubin (Table 3) [11,16,18,20–23], [30,31]. Patients with elevated liver function tests were more likely to have a moderate-high degree fever, and these elevations were significantly more prevalent in male patients (68.67 % vs. 38.36 %). Additionally, in these patients, the CD4+ and CD8 + T cells were substantially lower as compared to those with normal liver function tests [25]. Per the ACG, drops in leukocyte counts are observed in COVID-19 infection, and an elevated white blood cell count is considered a poor prognostic sign [26]. Studies have found that most liver injuries are mild and transient, but severe liver damage can also occur [27]. A higher magnitude of liver injury was noted in individuals with severe COVID-19, in which cases hepatoprotective drugs can be administered [5,27].

The definitive mechanism by which liver injury occurs in COVID-19 patients is unclear. There are multiple theories of the pathophysiology of the viral infection that could explain this phenomenon:

(1) ACE2-mediated direct viral infection of hepatocytes,

Table 2
Incidence of specific gastrointestinal symptoms exhibited by COVID-19 patients in studies completed from China.

Incidence of Type of Gastrointestinal Symptoms exhibited in COVID-19 Patients						
Study	Number of Patients, N	Anorexia, N (%)	Nausea, N (%)	Vomiting, N (%)	Diarrhea, N (%)	Abdominal Pain, N (%)
Pan L, et al. [11]	103	81 (78.6 %)	NA	4 (3.9 %)	35 (34 %)	2 (2 %)
Jin X., et al. [7]	74	NA	13 (17.5 %)	14 (18.6 %)	56 (75 %)	NA
Fang D, et al. [16]	201	NA	59 (29.4 %)	32 (16 %)	44 (22 %)	12 (6 %)
Guan W, et al. [18]	1095	NA	55 (5 %)	55 (5 %)	42 (3.8 %)	NA
Zhang JJ, et al. [17]	139	17 (12.2 %)	24 (17.3 %)	7 (5 %)	18 (13 %)	8 (13 %)
Wang D, et al. [19]	138	55 (40 %)	14 (10 %)	5 (3.6 %)	14 (10 %)	3 (2.2 %)
Shi H, et al. [20]	81	1 (1%)	NA	4 (5 %)	3 (4 %)	NA
Zhou F, et al. [21]	191	NA	7 (4%)	7 (4 %)	9 (5 %)	NA
Mo P, et al. [22]	155	NA	3 (3.7 %)	3 (4 %)	7 (4.5 %)	3 (2 %)
Chen N, et al. [23]	99	NA	1 (1 %)	1 (1 %)	2 (2 %)	NA
Yang X. et al. [24]	52	NA	NA	2 (4 %)	NA	NA

COVID-19-coronavirus disease 2019, NA- not applicable.

Table 3
Percentage of COVID-19 patients exhibiting hepatobiliary laboratory abnormalities including AST, ALT, and total bilirubin in studies completed from China.

Hepatobiliary Laboratory Abnormalities seen in COVID-19 Patients				
Study	Number of Patients, N	AST, N (%)	ALT, N (%)	Total Bilirubin, N (%)
Pan L, et al. [11]	204	22 (11 %)	27 (13 %)	NA
Fang D, et al. [16]	304	24 (8 %)	19 (6 %)	6 (2 %)
Guan W, et al. [18]	741	168 (22 %)	158 (21 %)	76 (10 %)
Chen N, et al. [23]	99	35 (35 %)	28 (28 %)	18 (18 %)
Xu X, et al. [30]	62	10 (16 %)	26 (20 – 32)$^{+}$	NA
Huang C et al. [31]	41	15 (37 %)	32 (21 – 50)$^{+}$	11.7 (9.5 – 13.9)$^{++}$
Zhou F, et al. [21]	189	NA	59 (31 %)	NA
Mo P, et al. [22]	155	32 (24 – 48)$^{++}$	23 (16 – 38)	NA
Shi H, et al. [20]	81	43 (53 %)	NA	NA

COVID-19-coronavirus disease 2019, AST-Aspartate aminotransferase, ALT- Alanine aminotransferase, ++ median in mmol/L, + median in U/L, N- number.

(2) Critically-ill status and immune-mediated injury, or
(3) Drug hepatotoxicity [5].

As it has been established that the receptor ACE2 by which SARS-CoV-2 uses to gain cellular entry is highly expressed in gastrointestinal epithelial cells, the virus could have the ability to infect cholangiocytes via this receptor to dysregulate liver function [1,5]. Liver injury may also occur as ACE2 expression in liver tissue is upregulated as a compensatory proliferation of hepatocytes derived from bile duct epithelial cells [11]. While SARS-CoV-2 may cause dysregulation of hepatic function by binding directly to ACE2-receptor cholangiocytes, histological examination of a liver biopsy obtained from a deceased COVID-19 patient showed no viral inclusions, but rather microvesicular steatosis and mild lobular activity [27,5]. Furthermore, in critically-ill COVID-19 patients, hepatocellular injury or even liver failure may be secondary to hypotension and immune-mediated inflammation, such as cytokine storm or pneumonia-associated hypoxia [27]. Lastly, drug-induced hepatotoxicity may play a role in the elevation of liver enzymes, including medications such as remdesivir (an RNA polymerase inhibitor) and hydroxychloroquine 5,28].

Patients with pre-existing liver disease are an important group of individuals that require additional attention. In a study of 1099 COVID-19 patients, 23 patients had hepatitis B infection – severe cases of COVID-19 were more likely to have hepatitis B infection than non-severe cases (2.4 % vs. 0.6 %) [29]. Furthermore, in patients with COVID-19 with autoimmune hepatitis, the role of glucocorticoids in disease management is currently unclear [27]. In the setting of primary biliary cholangitis (PBC), COVID-19 may aggravate cholestasis. Therefore, alkaline phosphatase and gamma-glutamyl transfersase (GGT) levels should carefully be monitored. Given their immunocompromised state, patients with hepatic cirrhosis or cancer may be more susceptible to COVID-19 [27].

4. Pancreas

In a recent study by Wang et al. examining 52 patients with COVID-19 pneumonia, 17 % of patients experienced pancreatic injury defined by any abnormality in amylase or lipase [32]. They did not exhibit clinical symptoms of severe pancreatitis, however. The ACE2 receptor is also highly expressed in pancreatic islet cells, therefore SARS-CoV-2 infection can theoretically cause islet damage resulting in acute diabetes. Of the nine patients with pancreatic injury, six had abnormal blood glucose levels. Mechanisms by which pancreatic injury could occur include the direct cytopathic effects of SARS-CoV-2, or indirect systemic inflammatory and immune-mediated cellular responses, resulting in organ damage or secondary enzyme abnormalities [32,33]. Antipyretics, which most of the patients in this study took prior to admission, could also cause drug-related pancreatic injury [32]. Further research is necessary to definitively determine the effect of SARS-CoV-2 on pancreatic function and regulation.

5. Routes of Transmission

SARS-CoV-2 can be found in the respiratory secretions of patients 1–2 days before onset of clinical symptoms and for up to two weeks after symptoms subside. The virus has previously been found in whole blood, serum, urine, and fecal samples [6]. A study by Cai et al. demonstrated that some pediatric patients were noted to have a high frequency of SARS-CoV-2 RNA detection in feces. It also confirmed prolonged viral RNA shedding in feces for at least two weeks and upwards of more than a month, raising suspicion that the gastrointestinal tract acts as another site of viral replication [8]. A study conducted by Xiao et al. demonstrated results favoring gastrointestinal viral replication with potential fecal-oral route of transmission [34]. Amongst 73 hospitalized COVID-19 patients in China, ranging from 10 months to 78 years old, 53.42 % tested positive for SARS-CoV-2 RNA in the stool. Positive stool results ranged from 1 to 12 days, and 23.29 % continued to have positive stool results after having negative respiratory samples [34]. Upon endoscopy and biopsy, the study also found that SARS-CoV-2 RNA was detected with positive staining of the viral nucleocapsid protein in gastric, duodenal, and rectal epithelium. These findings further support the evidence of replication of infectious virions occurring within the gastrointestinal tract [34].

Accordingly, fecal-oral transmission must be taken into consideration. Of great significance is the fact that viral RNA in feces can remain even after viral RNA in the respiratory tract clears - therefore providing a potential source of spread. Considerations for testing of viral RNA in feces by rRT-PCR can be taken to monitor for adequate source and infection control [34].

6. Diagnostic testing & laboratory abnormalities

Currently, nasopharyngeal samples are used for the testing of suspected COVID-19; however, with the occurrence of gastrointestinal manifestations, the use of fecal testing may be beneficial as well. Additionally, recognizing that gastrointestinal symptoms could be the initial presentation of COVID-19, prompt and timely diagnostic testing is necessary for early detection.

The use of fecal nucleic acid tests to diagnose COVID-19 have recently increased. A study by Zhang et al. demonstrated that fecal specimens were as accurate as pharyngeal specimens [35]. It was also found that a positive stool test did not correlate to the severity of the lung infection. Advantages of stool testing include the possibility that it may reduce infections in medical staff compared to oropharyngeal swab specimens [35]. The definitive role of endoscopy and colonoscopy in the diagnosis of COVID-19 remains largely unclear at this point. According to the Spanish Society of Digestive Pathology and the Spanish Association of Gastroenterology, upper endoscopies, ERCP, and placement of peg tube procedures have a high risk of infection transmission; colonoscopies and lower echoendoscopies are intermediate risk [36]. The American Society of Gastrointestinal Endoscopy currently has

similar recommendations as of March 13, 2020: endoscopy is a high-risk procedure because of the potential transmission of the virus via a fecal-oral route and the risk of transmitting COVID-19 during its incubation period in asymptomatic patients [37]. Aggressive Personal Protective Equipment (PPE) should be utilized during these procedures for adequate infection control.

Apart from diagnostic tests, certain laboratory abnormalities have been noted in patients with COVID-19. In a study of 1099 confirmed COVID-19 cases from mainland China, patients exhibited lymphocytopenia (83.2 %), thrombocytopenia (36.2 %), and leukopenia (33.7 %) on admission [18]. Based on a study involving 140 COVID-19 patients, those with severe disease were noted to have an elevated D dimer (2.0-fold), C-reactive protein (1.7-fold), procalcitonin (2.0-fold), lactate dehydrogenase (2.1-fold), decreased lymphocyte count, and leukopenia as compared to individuals with milder disease [10].

Recognizing that the earliest presenting symptoms of COVID-19 could be gastrointestinal rather than respiratory may improve early detection with various available diagnostic tests. Extending beyond the usage of nasopharyngeal sample testing alone to include routine fecal RNA testing can be beneficial. Furthermore, identifying common laboratory abnormalities that these patients exhibit can also help in assessing the severity of the infection.

7. Treatment and management

To date, there is no specific antiviral treatment recommended for the treatment of COVID-19 nor is there a vaccine currently available, however clinical trials are in effect with medications such as lopinavir/ritonavir, chloroquine, hydroxychloroquine, aerosolized alpha-interferon, tocilizumab and remdesivir (an RNA polymerase inhibitor) [28]. Current treatment options remain primarily supportive including oxygen therapy, antipyretics, etc. Depending on the severity of disease, critically-ill individuals may require mechanical ventilation or hemodynamic support in cases of septic shock. In general, aggressive fluid management should be avoided in patients at risk of severe illness and with severe acute respiratory infection [28]. Systemic corticosteroids are not recommended for the treatment of COVID-19 pneumonia or acute respiratory distress syndrome (ARDS).

Gastrointestinal symptoms such as nausea and vomiting are conservatively managed with antiemetic medications. Prior to initiating supportive care, it is recommended to perform an additional work up to rule out other infectious etiologies such as *Clostridium difficile* toxin assay and a gastrointestinal pathogen panel. The use of antibiotics remains controversial but recommended only if coinfection is noted.

Given that patients can have positive stool results after having tested negative by nasopharyngeal samples, management should include effective infection control. Patients and their families should be notified that viral shedding may take place in the active phase of COVID-19 infection. As such, close contacts are at a heightened risk of becoming infected. Patients should be advised to practice proper hand hygiene and maintain social distancing. The reinfection rate of COVID-19 is currently unknown; therefore, patients should be warned that there is a possibility that it may occur and to screen for symptoms accordingly.

8. Conclusion

While SARS-CoV-2 has been established as a respiratory tract pathogen, its pathogenesis may also be responsible for the gastrointestinal manifestations that accompany COVID-19. Some patients have experienced symptoms such as diarrhea, nausea, vomiting, and abdominal pain. Additionally, laboratory abnormalities, hepatic injury, and pancreatic injury have been evident in a subset of patients, ranging on a spectrum with the severity of disease. As the viral receptor ACE2 is present in the gastrointestinal tract, it may play a role in the virus's ability to dysregulate the digestive system, hepatobiliary function, and pancreatic function, thereby resulting in gastrointestinal symptoms. Of note, a majority of the information presented in this narrative review was derived from reports originating from various regions in China. Consequently, application of these findings on a global scale is limited during an evolving pandemic. Likewise, the data displayed in our tables highlight variance among similar studies. As it has been shown that SARS-CoV-2 RNA can remain in stool longer than respiratory specimens, it may serve as evidence for gastrointestinal viral replication and subsequent shedding. Currently, while fecal-oral transmission has not been definitively proven, there is evidence to support its possibility, warranting the need for additional precautions.

Funding

We did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

The authors contributed to and reviewed all aspects of the article.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgements

None.

References

[1] Y.R. Guo, Q.D. Cao, Z.S. Hong, Y.Y. Tan, S.D. Chen, H.J. Jin, K.S. Tan, D.Y. Wang, Y. Yan, The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status, Mil. Med. Res. 7 (1) (2020) 11, https://doi.org/10.1186/s40779-020-00240-0.

[2] World Health Organization, Naming the Coronavirus Disease (COVID-19) and the Virus That Causes It, World Health Organization, 2020, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.

[3] World Health Organization, Coronavirus Disease 2019 (Covid-19) Situation Report – 88, (2020).

[4] S. Singh, et al., Coronavirus: a threat to global public health, Indian J Comm Health. 32 (1) (2020) 21–27.

[5] S.H. Wong, R.N. Lui, J.J. Sung, Covid-19 and the digestive system, J. Gastroenterol. Hepatol. (2020), https://doi.org/10.1111/jgh.15047.

[6] K. Buruk, T. Ozlu, New Coronavirus: SARS-COV-2, Mucosa, 2020, pp. 1–4 doi: 10.33204/mucosa.706906.

[7] X. Jin, J. Lian, J. Hu, et al., Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms, Gut (2020), https://doi.org/10.1136/gutjnl-2020-320926 Published Online First: 24 March.

[8] Jiehao Cai, Jing Xu, Daojiong Lin, zhi Yang, Lei Xu, Zhenghai Qu, et al., A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features, Clinical Infectious Diseases, ciaa198, https://doi.org/10.1093/cid/ciaa198.

[9] J. Chen, et al., Clinical Features of Stool SARS-CoV-2 RNA Positive in 137 COVID-19 Patients in Taizhou, China, (2020), https://doi.org/10.2139/ssrn.3551383 Available at SSRN: or https://ssrn.com/abstract=3551383.

[10] S.A. Lauer, K.H. Grantz, Q. Bi, et al., The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application, Ann. Intern. Med. (2020), https://doi.org/10.7326/M20-0504 [Epub ahead of print 10 March 2020].

[11] L. Pan, et al., Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: a Descriptive, Cross-sectional, Multicenter Study, Preprint at (2020) https://journals.lww.com/ajg/Documents/COVID_Digestive_Symptoms_AJG_Preproof.pdf.

[12] Y. Tian, L. Rong, W. Nian, Y. He, Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission, Aliment. Pharmacol. Ther. (2020), https://doi.org/10.1111/apt.15731.

[13] M.L. Holshue, C. Debolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, et al., First case of 2019 novel coronavirus in the United States, N. Engl. J. Med. 382 (10) (2020) 929–936, https://doi.org/10.1056/nejmoa2001191.

[14] L. Guotao, Z. Xingpeng, D. Zhihui, W. Huirui, SARS-CoV-2 infection presenting with hematochezia, Mã©decine Mal. Infect. (2020), https://doi.org/10.1016/j.medmal.2020.03.005.

[15] H. Zhang, et al., The Digestive System Is a Potential Route of 2019-nCov Infection: a

Bioinformatics Analysis Based on Single-cell Transcriptomes, Preprint at (2020) https://www.biorxiv.org/content/10.1101/2020.01.30.927806v1.
[16] D. Fang, J.D. Ma, J.L. Guan, et al., Digestive manifestations in hospitalized patients with COVID-19: a single-center descriptive study, Chin. J. Dig. Dis. 40 (3) (2020), https://doi.org/10.3760/cma J.D.issn.0254-1432.2020.0005.
[17] J.-J. Zhang, X. Dong, Y.-Y. Cao, Y.-D. Yuan, Y.-B. Yang, Y.-Q. Yan, et al., Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy (2020), https://doi.org/10.1111/all.14238.
[18] W.-J. Guan, Z.-Y. Ni, Y. Hu, W.-H. Liang, C.-Q. Ou, J.-X. He, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. (2020), https://doi.org/10.1056/nejmoa2002032.
[19] D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–Infected pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069, https://doi.org/10.1001/jama.2020.1585.
[20] H. Shi, X. Han, N. Jiang, Y. Cao, O. Alwalid, J. Gu, et al., Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study, Lancet Infect. Dis. 20 (4) (2020) 425–434, https://doi.org/10.1016/s1473-3099(20)30086-4.
[21] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062, https://doi.org/10.1016/s0140-6736(20)30566-3.
[22] P. Mo, Y. Xing, Y. Xiao, L. Deng, Q. Zhao, H. Wang, et al., Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa270.
[23] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513, https://doi.org/10.1016/s0140-6736(20)30211-7.
[24] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, et al., Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir. Med. (2020), https://doi.org/10.1016/s2213-2600(20)30079-5.
[25] Z. Fan, et al., Clinical Features of COVID-19 Related Liver Damage, Preprint at (2020) https://www.medrxiv.org/content/10.1101/2020.02.26.20026971v2.
[26] ACG News Team, Joint GI Society Message on COVID-19, American College of Gastroenterology, 2020, https://gi.org/2020/03/15/joint-gi-society-message-on-covid-19/.
[27] C. Zhang, L. Shi, F.-S. Wang, Liver injury in COVID-19: management and challenges, Lancet Gastroenterol. Hepatol. 5 (5) (2020) 428–430, https://doi.org/10.1016/s2468-1253(20)30057-1.
[28] M. Cascella, M. Rajnik, A. Cuomo, et al., Features, evaluation and treatment coronavirus (COVID-19), StatPearls [Internet], StatPearls Publishing, Treasure Island (FL), 2020https://www.ncbi.nlm.nih.gov/books/NBK554776/.
[29] R. Mao, J. Liang, J. Shen, S. Ghosh, L.-R. Zhu, H. Yang, et al., Implications of COVID-19 for patients with pre-existing digestive diseases, Lancet Gastroenterol. Hepatol. 5 (5) (2020) 426–428, https://doi.org/10.1016/s2468-1253(20)30076-5.
[30] Xu, X.-W., Wu, X.-X., Jiang, X.-G., Xu, K.-J., Ying, L.-J., Ma, C.-L., et al. (2020). Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. Bmj, m606. doi: 10.1136/bmj.m606.
[31] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/s0140-6736(20)30183-5.
[32] F. Wang, H. Wang, J. Fan, Y. Zhang, H. Wang, Q. Zhao, Pancreatic injury patterns in patients with COVID-19 pneumonia, Gastroenterology (2020), https://doi.org/10.1053/j.gastro.2020.03.055.
[33] F. Liu, et al., Highly ACE2 Expression in Pancreas May Cause Pancreas Damage After SARS-CoV-2 Infection, Preprint at (2020) https://www.medrxiv.org/content/10.1101/2020.02.28.20029181v1.full.pdf.
[34] F. Xiao, M. Tang, X. Zheng, Y. Liu, X. Li, H. Shan, Evidence for gastrointestinal infection of SARS-CoV-2, Gastroenterology (2020), https://doi.org/10.1053/j.gastro.2020.02.055.
[35] J. Zhang, S. Wang, Y. Xue, Fecal specimen diagnosis 2019 novel coronavirus–infected pneumonia, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25742.
[36] E.P.-C. Martínez, Recommendations by the SEPD and AEG, both in general and on the operation of gastrointestinal endoscopy and gastroenterology units, concerning the current SARS-CoV-2 pandemic (March, 18), Revista Española De Enfermedades Digestivas (2020), https://doi.org/10.17235/reed.2020.7052/2020.
[37] American Society for Gastrointestinal Endoscopy, ASGE Releases Recommendations for Endoscopy Units in the Era of COVID-19, American Society for Gastrointestinal Endoscopy, 2020, https://www.asge.org/docs/default-source/default-document-library/press-release_impact-of-covid-19-on-endoscopy.pdf.