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Life Sciences 260 (2020) 118312

Contents lists available at ScienceDirect

Life Sciences

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

Review article

Attaching clinical significance to COVID-19-associated diarrhea

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ARTICLE INFO

Keywords:
Coronavirus disease 2019 (COVID-19)
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Diarrhea
Diagnosis
Treatment
Intestinal flora
Prognosis

ABSTRACT

The Corona Virus Disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), erupted in 2020 and created severe public health and socioeconomic challenges worldwide. A subset of patients, in addition to presenting with typical features such as fever, cough and dyspnea, was also afflicted with diarrhea. However, the clinical features and prognoses related to COVID-19-associated diarrhea have not attracted sufficient attention. This review of the medical literature examines the incidence, pathogenesis, clinical characteristics, fecal virus changes, prognoses and influencing factors of COVID-19-associated diarrhea. The reported incidence of diarrhea in patients with COVID-19 ranged from 2% to 49.5%. The main cause of diarrhea was found to be invasive by SARS-CoV-2 of ACE-2-expressing epithelial cells of the small intestine, causing local intestinal damage. This cellular invasion may be the key factor for the much longer duration of SARS-CoV-2 positivity observed for feces compared to pharyngeal swabs. The associated diarrhea in these patients upsets the balance of intestinal flora, resulting in more-severe disease intensity and worse prognosis. Clinicians should be vigilant to this kind of COVID-19-associated diarrhea, and design more effective prevention and treatment options for patients with positive fecal nucleic acid tests and intestinal microflora disorders.

1. Introduction

Corona Virus Disease 2019 (COVID-19) is a new type of viral infectious disease which is highly contagious and spreads quickly, mainly via respiratory droplets and direct contact [1,2]. The global outbreak was declared a pandemic in the second week of March 2020, and the number of confirmed cases rose to 4 million within a few months, including more than 282,000 deaths. The COVID-19 pandemic not only threatened human health, but also severely disrupted the global economy and people's daily lives worldwide [3,4]. COVID-19 patients typically present with fever, cough, sputum production, dyspnea, headache and fatigue. Patients with severe COVID-19 often require mechanical ventilation and can die from acute respiratory distress syndrome (ARDS) [5,6]. Some patients with COVID-19 were afflicted with diarrhea, and a small number showed only gastrointestinal symptoms such as diarrhea, anorexia, nausea and vomiting [7]. Diarrhea might be the earliest sign of COVID-19 infection, but because of its non-specificity, diagnosis can be delayed and nosocomial infections acquired during the delay. The first COVID-19 patient in the United States presented with fever and cough and developed diarrhea within two days of hospital admission [8]. In a patient in China, after respiratory samples turned negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), fecal samples were still positive for the virus for 30 days; thus, there may be a risk of fecal-oral transmission of the virus [9]. To improve awareness and vigilance of COVID-19-associated diarrhea, we reviewed the current medical literature (up to May 2020) for data concerning the incidence, pathogenesis, clinical characteristics, fecal virus changes and prognostic factors of COVID-19 cases with diarrhea. We searched the following databases: PubMed, Web of Science and EMBASE. The search terms used were '2019-nCoV', 'SARS-CoV-2', 'COVID-19', 'diarrhea', 'gastrointestinal symptom', 'stool' and 'feces'.

2. Incidence of COVID-19-associated diarrhea.

The World Health Organization defines diarrhea as three or more

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https://doi.org/10.1016/j.lfs.2020.118312
Received 29 July 2020; Received in revised form 14 August 2020; Accepted 19 August 2020
Available online 23 August 2020
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Table 1
Data on diarrhea in patients with COVID-19.

First author	Study country	Hospital	N of patients	Diarrhea *n* (%)	Diarrhea duration	Evacuations per day	State of patients	Nucleic acid tests in feces	Prognoses
Guan [11]	China	552 hospitals	1099	42(3.8%)	NA	NA	5.0% were admitted to the ICU, 2.3% underwent invasive mechanical ventilation.	NA	1.4% died.
Chen [12]	China	Jing yintan hospital	99	2(2%)	NA	NA	NA	NA	11 (11%) patients died of multiple organ failure
Huang [13]	China	Jing yintan hospital	41	1(2.4%)	NA	NA	Dyspnoea in 22 (55%) of 40 patients	NA	Six (15%) died
Fang [14]	China	Wuhan tongji hospital	305	146(49.5%)	(4.1 ± 2.5) d, 3.3d (mean)	(3.3 ± 1.6) per day,up to 9.	Severe group:46(15.1%), non severe group: 259 (84.9%)	positive rate in severe group vs in non severe group (94.6%vs 82.5%)	NA
Xiao [15]	China	Fifth affiliated hospital of Zhuhai	73	26(35.6%)	NA	NA	NA	NA	NA
Young [16]	Singapore	Singapore 4 hospitals in Singapore	18	3 (16.6%)	NA	NA	2 required intensive care	Virus was detectable in the stool (4/8 [50%]) and blood (1/12 [8%]) by PCR	There were no deaths
Wan [17]	China	18 hospitals	232	49(21%)	NA	NA	NA	NA	Diarrhea symptoms were significantly correlated with severe infection of new crown, ventilator use and admission to ICU
Wei [18]	China	Wuhan Union Hospital	84	26(31%)	3.7 days	na	The duration of fever and dyspnea in diarrhea group vs in non diarrhea group(10.5 ± 4.7 vs 7.6 ± 3.4d,8.1 ± 3.2 vs4.7 ± 2.3d).	Stool samples from a higher proportion of patients with diarrhea tested positive for virus RNA (69%) than from patients without diarrhea (17%)	The hospitalization time of diarrhea patients vs non diarrhea ones(16.5 ± 5.2 vs 11.8 ± 5.6d).
Luo [19]	China	Zhongnan Hospital of Wuhan University	183	68(37.1%)	NA	NA	NA	NA	NA
Liu [20]	China	Affiliated Hospital of Jianghan University	30	9(30%)	NA	NA	NA	NA	NA
Pan [21]	China	Wuhan Hanan Hospital; Wuhan Union Hospital; Huanggang Central Hospital	204	35(17.2%)	NA	3 per day (mean)	NA	NA	Difficult to cure and discharge (34.3% vs 60%)
Li [22]	China		1995	96(4.8%)	NA	NA	NA	NA	Fatality rate 5%
Lu [23]	China	Wuhan Children's Hospital	171	15(8.8%)	NA	NA	NA	NA	Two patients death
D'Amico [24]	China Singap French Japan United States		3042	292(10,1%)	NA	NA	NA	NA	NA

NA = no analysis.

loose or liquid stools per day [10]. We found 14 articles reporting COVID-19-associated diarrhea, and the incidence varied widely, ranging from 2% to 49.5% (Table 1).

In the early stages of the COVID-19 pandemic, reports of COVID-19-associated diarrhea were relatively rare. Before January 31, 2020, the proportion of patients with diarrhea was relatively small, ranging from 2% to 10%. Dr. Zhong's team evaluated the data of 1099 Chinese people as of January 31, 2020 and reported that the incidence of diarrhea in patients who had been diagnosed with COVID-19 was 3.8% [11]. Chen et al. [12] reported the incidence of COVID-19-associated diarrhea to be only 2%. Similarly, Huang et al. [13] reported that only one of 41 patients had diarrhea as the initial sign, an incidence of 2.4%.

In later stages of the COVID-19 pandemic the proportion of patients with diarrhea increased significantly, and the increase seen in the city of Wuhan, Hubei Province, China was very obvious. In a single-center, descriptive study of digestive system manifestations of COVID-19 in hospitalized patients in Wuhan, the incidence of diarrhea in COVID-19 patients was as high as 49.5% (146/295) [14]. In Guangdong Province, China, the incidence of COVID-19-associated diarrhea was 35.6% [15]. In a study in Singapore, 3 of 18 patients with COVID-19 had diarrhea (16.6%) [16]. Another study found that 21% of 232 COVID-19 patients experienced diarrhea during hospitalization. At the same time, many COVID-19 patients also had bloody stools and positive results for fecal viral nucleic acid [17]. In a study of 84 cases, the incidence of diarrhea was 31% and the percentage of diarrheic fecal samples positive for viral RNA was 69% [18]. These results not only indicated that diarrhea in COVID-19 patients was a common condition, but also supported the possibility of COVID-19 transmission by the digestive tract. Therefore, a number of researchers expressed the opinion that the incidence of diarrhea in SARS-CoV-2-infected persons had been underestimated or underreported [10,19,20].

From a cross-sectional perspective as of early March 2020, a multicenter study of Chinese COVID-19 patients reported the incidence of diarrhea to be 17.2% [21]. More recently, a systematic review and meta-analysis evaluated 1995 cases of COVID-19 and found a diarrhea rate of 4.8% [22]. So far, there have been few studies on diarrhea in COVID-19-infected children. An analysis of COVID-19 in children (median age 6.7 years) reported an incidence of diarrhea of 8.8% [23]. A pooled analysis of available studies (to March 2020) by D'Amico et al. found an overall diarrhea rate of 10.4% in patients with COVID-19 [24].

Most patients with COVID-19 were administered broad-spectrum antibiotics and antiviral drugs, which could cause drug-related diarrhea during hospitalization. In cases of diarrhea after admission, drug-related diarrhea should be excluded to determine the true incidence of COVID-19-associated diarrhea. On the other hand, the different reported incidences of diarrhea in January to April 2020 might also be related to individual differences in the number of angiotensin converting Enzyme 2 (ACE2) receptors in the intestinal tract or to differences in the number of infecting viral particles [25]. Coronaviruses like SARS-CoV-2 gain entry into epithelial cells by interacting with ACE2 receptors on the host cell-surface to induce fusion of viral and host cell-membranes. Oral Chinese herbs were often used in the treatment of COVID-19 in China but rarely in Western countries; therefore, laxative effects of herbal treatments could also increase the incidence of COVID-19-associated diarrhea.

3. Pathogenesis of diarrhea in patients with COVID-19

Although the specific mechanism of diarrhea in COVID-19 is not fully understood, viral infection may cause changes in intestinal permeability, resulting in poor fluid absorption by fragile intestinal epithelial cells and altered intestinal secretion, leading to diarrhea. Mouse models show that changes in ACE2, the binding receptor for the SARS-CoV-2 spike protein, are related to colitis, indicating that viral activity may cause changes to epithelial enzymes and increase susceptibility to intestinal inflammation and diarrhea [26,27]. ACE2 is expressed not only in alveolar epithelial cells, but also in the upper and stratified epithelial cells of the esophagus and the intestinal epithelial cells of the ileum and colon [28,29]. SARS-CoV-2 virus may infect the saliva, or virus particles in the alveoli may reach the throat, and enter the gastrointestinal tract when swallowed. ACE2 can control intestinal inflammation and diarrhea, and SARS-CoV-2 acts on ACE2 to cause diarrhea [30]. Specifically, SARS-CoV-2 invades small-intestinal epithelial cells expressing ACE2, especially in the proximal and distal intestine where ACE2 is highly expressed; so the small intestine is more likely than the colon to be attacked by SARS-CoV-2, causing local damage leading to diarrhea [30]. Endoscopic sampling of the digestive tract showed that in a patient's stomach, duodenum and rectum, epithelial cells expressed ACE2, and viral nucleocapsid protein was detected in the cytoplasm [15]. Moreover, large amounts of infiltrating plasma cells and lymphocytes and interstitial edema were visible in the lamina propria without obvious damage.

SARS-CoV-2 damages the digestive system directly or indirectly by the inflammatory response. A chain reaction of inflammatory factors and viremia may also damage the digestive system. An “inflammatory storm” is an excessive immune response caused by an infection [31]. Over-activated cytokines, immune dysregulation, and inflammatory storms may also cause inflammatory damage to the intestine, leading to diarrhea [31]. It is noteworthy that as much as 53.4% of patients had detectable viral nucleic acids in their stool samples, suggesting that SARS-CoV-2 might directly damage the intestinal mucosa, causing digestive disturbances, including diarrhea [32].

Therapeutic drugs such as cephalosporins and macrolide antibiotics may also contribute to diarrhea in COVID-19 patients. Antiviral agents such as the broad-spectrum compound umifenovir can also cause diarrhea. Antibiotic and antiviral drugs have been commonly used in the treatment of COVID-19, but there are few studies on drug-induced diarrhea, and prospective studies are needed. Hypoglycemic drugs, non-steroid anti-inflammatory drugs (NSAIDs), proton pump inhibitors and other drugs can also cause diarrhea as a side effect, but this has not been evaluated in patients with COVID-19.

Diarrhea can occur in long-term hospitalized patients with severe COVID-19. Such patients often experience respiratory failure or multiple organ failure with gastrointestinal involvement, including nausea, vomiting and diarrhea. Severe COVID-19 hospitalized patients receiving long-term broad-spectrum antibiotics may also be prone to fungal infections of the digestive tract due to killing of commensal bacteria, resulting in diarrhea. Unfortunately, this area of fungal pathogenesis in COVID-19 is under-researched so far.

At present, we still lack dynamic observations via live imaging of SARS-CoV-2 invasion of the intestinal structure, and further research in this area is still needed. However, in recovered patients the damage to the intestinal structure caused by SARS-CoV-2 was limited, and the diarrhea was often self-limiting [9], so the intestinal lesions related to SARS-CoV-2 may also be mild and heal in the short term.

4. Clinical characteristics of COVID-19-associated diarrhea

At present, there are many reports of gastrointestinal signs and symptoms in patients with COVID-19, but relatively few reports of diarrhea alone. Both the incidence of diarrhea and the associated gastrointestinal symptoms vary greatly in COVID-19 patients. Fang et al. [14]described the results of a single-center, descriptive study of 305 hospitalized patients with severe and critical COVID-19 in the Wuhan area. Half (49.5%) of the patients developed diarrhea, which occurred 1–8 days after COVID-19 clinical onset, and the average duration of diarrhea was 4.1 $\pm$ 2.5 days. The number of diarrhea episodes could be up to 9 a day, with a mean of 3.3 $\pm$ 1.6, of which 34.3% were dilute watery feces [14]. Excluding drug-related diarrhea, it was estimated that 22.2% of patients still have diarrhea, which was also accompanied by gastrointestinal signs and symptoms such as decreased appetite in

50.2% (101/201) of patients, nausea in 29.4%, vomiting in 15.9% and abdominal pain in 6.0% [14].

A study of non-severe COVID-19 suggested that diarrhea was usually not serious, typically showing as loose stools without dehydration, usually three times a day. Moreover, as the COVID-19 worsened, the effects on the digestive system became more and more obvious. Notably, patients without digestive system signs and symptoms were more likely to be cured and discharged (60% vs. 34.3%) than those with digestive system involvement [21].

Anorexia was the most common gastrointestinal disorder in adults (39.9–50.2%), diarrhea was the most common digestive disorder in adults and children (2–49.5%), and vomiting was more common in children, 6.5–66.7% [33]. Wei et al. [34] reported that among 84 cases, signs and symptoms of COVID-19 were more frequent in patients with diarrhea than in those without diarrhea. These included headache (58% vs 22%), myalgia or fatigue (65% vs 34%), cough (85% vs 45%), expectoration (54% vs 21%), nausea (38% vs 10%) and vomiting (19% vs 2%). Fever and dyspnea lasted longer in patients with diarrhea compared to those without diarrhea (fever: 10.5 ± 4.7 vs 7.6 ± 3.4 days; dyspnea: 8.1 ± 3.2 vs 4.7 ± 2.3 days). Patients with diarrhea had longer hospital stays than patients without (16.5 ± 5.2 vs 11.8 ± 5.6 days). Although the clinical signs and symptoms of these COVID-19 diarrhea patients were severe, there were no differences in laboratory tests such as routine blood and lung imaging between the diarrhea and non-diarrhea groups [34]. Abdominal imaging results are lacking, but needed.

Interestingly, some patients experienced only diarrhea and vomiting, without fever and cough. Ping and colleagues [35] reported 9 cases of diarrhea and vomiting in COVID-19 adults, without fever and cough, before admission. Most of these patients were sent to the gastroenterology department instead of the fever clinic and respiratory department because they did not have cough, sputum production and fever or other respiratory signs and symptoms. As a result, the diagnoses and treatments were improper and caused adverse effects.

5. Detection of fecal viral nucleic acid in patients with COVID-19-associated diarrhea

Diarrhea may be an indicator of SARS-CoV-2 infection. Thus, clinicians should pay more attention to patients with diarrhea during outbreaks of pneumonia, and perform fecal nucleic acid examination on patients with diarrhea so as to avoid delaying COVID-19 diagnosis. SARS-CoV-2 was detected in a throat swab and fecal samples from the first reported COVID-19 patient in the United States [8]. Wei et al. [18] reported that positive SARS-CoV-2 test results of stool samples at admission were higher in patients with diarrhea than in those without diarrhea (69% vs 17%), while negative test results of swabs were lower in patients with diarrhea than in those without (77% vs 97%). SARS-CoV-2 throat swab tests turned negative for longer periods in patients with diarrhea compared to patients without diarrhea (12.5 ± 4.0 vs 9.2 ± 3.9 days). Furthermore, there were more patients with diarrhea (45% vs 20%) among patients whose SARS-CoV-2 throat swab test turned negative compared with non-diarrhea patients.

A large study in China found that stool samples remained positive for an average of 27.9 days, which was 11.2 days longer than the positivity in respiratory samples. Even after the SARS-CoV-2 test of the respiratory tract sample turned negative, the stool sample could still be positive for nearly 5 more weeks [36]. Yang et al. [37] also found that fecal specimens were still positive after SARS-CoV-2 was negative in pharyngeal swabs, and the positive rate of patients with SARS-CoV-2 detected in fecal samples was between 36% and 53%. Some patients had diarrhea without respiratory symptoms, which might cause doctors to overlook early diagnosis and treatment of COVID-19. Certain limitations and difficulties in nucleic acid examination could also lead to delayed or undiagnosed COVID-19. Evidence of SARS-CoV-2 in stool, gastrointestinal histology and the prolonged presence of viral nucleic acid in stool strongly suggest that oral-fecal transmission is possible, and is also the rationale for a fecal PCR test. Recently, SARS-CoV-2 virus particles were isolated from feces from COVID-19 patients, providing direct evidence that SARS-CoV-2 could potentially be transmitted by feces [9].

6. Prognoses and factors influencing COVID-19-associated diarrhea

Most COVID-19 cases were flu-like and cured by active treatment. Individuals with asymptomatic infections were cured naturally by an immune response without the person being aware. Most critically ill COVID-19 patients were elderly people with underlying diseases such as diabetes and hypertension, so COVID-19 may progress gradually and eventually result in respiratory failure, ARDS, shock, viremia, and multiple organ failure [38]. However, patients with COVID-19-associated diarrhea were prone to severe illness and admitted to the intensive care unit (ICU), suggesting a link between the presence of diarrhea and the severity of COVID-19. Patients with COVID-19 diarrhea were more prone to need mechanical ventilation, and the prevalence of ARDS was higher than in patients without gastrointestinal involvement (6.76% vs 2.08%) [38].

One study found that the diarrhea is significantly associated with SARS-CoV-2 infection severity, the use of ventilators, and ICU admission, excluding confounding factors [17]. The gastrointestinal signs and symptoms of COVID-19 could be used to predict whether patients would develop severe respiratory disorders, which helped to design more beneficial treatment plans for patients [17].

The intestinal bacterial profile in patients with COVID-19 is related to the severity of SARS-CoV-2 infection [39]. Some elderly people have less intestinal flora and a high incidence of severe COVID-19. Patients with COVID-19-associated diarrhea are prone to dysbiosis of the intestinal flora, resulting in severe illness. The high-risk score of critically ill COVID-19 patients was positively correlated with pro-inflammatory factors which are closely related to the human intestinal flora [39].

Diarrhea can be beneficial in that it can eliminate pathogenic bacteria after gastrointestinal infection, and it could similarly aid in the removal of SARS-CoV-2 in diarrhea patients, despite the patient discomfort and the disruption caused to the resident intestinal flora. One study found that human α-defensin 5 (HD5), which is similar to lectin, binds to ACE2 with a high affinity of 39.3 nM and weakens subsequent recruitment of SARS-CoV-2 S1 protein [40]. Experiments in vitro further proved that HD5 has a significant dose-dependent preventive effect on SARS-CoV-2 S1 protein binding to intestinal epithelial cells [40]. This discovery revealed the innate defense function of lectin-like intestinal defensins against SARS-CoV-2, which may provide new insights into the prevention and treatment of SARS-CoV-2 infection.

The core gut microbiome and its related metabolites may be used as potential targets for the prevention of intestinal illness in susceptible people and for the development of new therapeutic drugs for COVID-19. Probiotics regulate the intestinal microflora in patients with diarrhea caused by COVID-19, especially the dysbacteriosis caused by antibiotics [41]. Treatment with probiotics may be beneficial, and further study is needed.

7. Conclusion

In conclusion, diarrhea in COVID-19 cases disrupts the intestinal flora balance, affects the inflammatory response, increases the severity of COVID-19, and upsets prognoses. Using probiotics, such as HD5, to regulate flora for intervention strategies may help reduce or prevent the grave consequences of COVID-19.

Funding

This work was supported by Shandong Province Higher Educational

Science and Technology Program for Youth Innovation (2020KJL004).

CRediT authorship contribution statement

X. Sun designed the study, participated in the revision of the manuscript. F. Wang, S. Zheng and C. Zheng participated in the data collection, data analysis and writing of the draft manuscript.

Declaration of competing interest

No conflict of interest.

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