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Review Article

Gastrointestinal and Liver Involvement in COVID-19: A Roadmap from Early Identification to Treatment

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1. Abstract

December 2019 has brought another historical pandemic which has posed a serious threat to global health. As of 24th August 2020, 23 311719 confirmed cases and of 806410 deaths have been reported due to this most challenging disease of the 21st century so far, named as coronavirus disease 2019 (COVID-19). It was started in Wuhan, China and eventually entered different countries very rapidly and declared as the sixth public health emergency of international concern by the World Health Organization. The spectrum of symptomatic COVID-19 ranges from mild respiratory tract infection to severe pneumonia that may progress to acute respiratory distress syndrome or multi-organ dysfunction. However, COVID-19 infection can present with gastrointestinal and hepatic manifestation even in the absence of respiratory involvement. In light of the varying clinical manifestations and possibility of multisystem involvement, it is imperative for healthcare professionals worldwide to adapt their practices according to the rapidly evolving situation.

In this review, the trait and possible peculiarities of hepatic and gastrointestinal involvement caused by SARS-CoV-2 infection are summarized. Moreover, this review aims to consolidate the current evidence regarding the gastrointestinal manifestations of COVID-19, investigation, and subsequent management strategies regarding these patients.

2. Keywords: COVID 19; SARS- COV-2; Gastrointestinal and Liver involvement

3. Introduction

As of 24th August 2020, 23 311 719 confirmed cases and of 806 410 deaths have been reported due to the most challenging disease of the 20th century so far, named as corona virus disease 2019 (COVID-19) [1]. It was December 2019 when the clusters of unfamiliar cases of pneumonia with severe acute respiratory syndrome (ARDS) have been reported in Wuhan, China. Subsequently a novel corona virus i.e. "severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)" has been identified as the causative pathogen leading to COVID-19 [2, 3]. Being highly contagious the novel SARS-CoV-2 had not only lead to a rapid outbreak in China but also had spread exponentially across almost every country and all continents within few weeks hence declared as global pandemic [4-6].

Corona virus (CoVs) is a virus of the coronavirus family, which has the largest genome of all known RNA viruses and is widely found in humans, mice, pigs, cats, dogs, and other animals. Seven corona virus species are known to cause human disease, of which four species (HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1) cause respiratory infections in immuno compromised individuals, infants, and the elderly [7]. The other three are highly pathogenic human corona viruses, including the severe acute respiratory syndrome corona virus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV), and the 2019 new corona virus (SARS-CoV-2) summarized in (Table 1). These three viruses can cause respiratory,

intestinal, hepatic, and neuronal diseases, and may lead to acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death in severe cases [3, 8, 9]. However, a study from China found that up to 50% of COVID-19 patients may have digestive symptoms [10]. In light of the varying clinical manifestations and possibility of multisystem involvement, it is imperative for healthcare professionals worldwide to adapt their practices according to the rapidly evolving situation. Therefore, this review aims to consolidate the current evidence regarding the gastrointestinal manifestations of COVID-19, investigation, and subsequent management strategies regarding these patients.

Table 1: Summary of studies regarding GI and Liver involvement of COVID-19

Reference	Cases	Preexisting liver disease (%)	GI symptoms			Liver Function Tests
			Diarrhea n(%)	Nausea/ vomiting (%)	Abdominal pain n(%)	
Wan et al [14]	232	-	49 (21)	-	-	ALT, AST and bilirubin within normal limits
Guan et al [20]	1099	23 (2.1)	42 (3.8)	55 (5.0)	-	Raised ALT= 158/741 (21.3%) Raised AST= 168/757 (22.2%) Raised Total bili= 76/722 (10.5%)
Fan et al (55)	148	-	6 (4.1)	3 (2.0)	-	Deranged LFTs= 75 (50.7%)
Wang et al (56)	138	4 (2.9)	14 (10.1)	5 (3.6)	3 (2.2)	Median ALT and AST within normal limits
Chen et al (57)	99	-	2 (2)	1 (1)	-	Raised ALT= 28 (28%) Raised AST= 35 (35%) Raised Total bilirubin= 18 (18%)
Shi et al (58)	81	7 (9)	3 (4)	4 (5)	-	Raised AST= 43 (53%)
Klopfenstein et al (59)	114	-	55 (48)	Nausea= 25 (45.5%), Vomiting= 19 (34.5%)	19 (34.5)	-
Xu et al (60)	62	7 (11)	3 (8)	-	-	Raised AST= 10 (16.1%)
Yang et al (61)	52	-	-	2 (4)	-	Liver dysfunction= 15 (29%)
Huang et al (62)	41	1 (2)	1/38 (3)	-	-	Raised AST= 15 (37%)
Zhang et al (63)	82	2 (2.4)	10 (12.2)	2 (2.3)		Raised ALT= 22/72 (30.6%) Raised AST= 44/72 (61.1%) Raised Total bilirubin= 22/72 (30.6)
Jin et al (25)	74	8 (10.8)	53 (71.6)	11 (14.8)	-	-
XY Li et al (64)	64	4 (6.3)	-	-	-	-

3.1. What are the Common Manifestations of COVID-19?

The common clinical manifestations of COVID-19 are fever, myalgia or fatigue, and nonproductive cough. Fever is usually detected but the patient may not always be febrile on presentation [11, 12]. Headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting are some of the less common symptoms [13]. The intensive care unit (ICU) care is required for aged patients or patients likely to have comorbidities including hypertension, diabetes, cardiovascular diseases, and cerebro vascular disorders. Subsequent problems during hospitalization are mostly acute respiratory syndrome (ARDS), arrhythmia, and shock. However, whether these underlying conditions could increase the risk of COVID 19 and their impact on prognosis still needs to be defined. Lymphopenia is a common feature in patients with COVID-19 and might be a critical factor associated with disease severity and mortality [14]. According to scientific observations, as the status of the patient gets worse, urea and creatinine blood levels gradually rise [15]. The spectrum of symptomatic COVID-19 ranges from mild respiratory tract infection to severe pneumonia that may progress to acute respiratory distress syndrome or multi-organ dysfunction [16].

3.2. When to Suspect COVID-19 Infection with GI Symptoms?

Gastrointestinal involvement is now well known in coronavirus infections of animals and humans [17]. SARS-CoV-2 RNA was first detected in a stool specimen of the first reported COVID-19 patient; hence much attention has been paid to gastrointestinal tract symptoms of SARS-CoV-2 [18].

The most common GI manifestation of COVID-19 is diarrhea, with an incidence rate of 2% to 50% seen in various clinical studies [19]. Diarrhea may occur preceding or following respiratory symptoms and physicians should bear in mind that in some cases, diarrhea may be the only presenting feature of COVID-19 [10]. A study by Tian et. al found that the mean duration of diarrhea in COVID-19 was 4.1 ± 2.5 days [20]. The COVID-19 patients with diarrhea tend to be older, have more co-morbidity, more severe disease, and a higher rate of hospitalization compared to COVID-19 patients who do not have diarrhea [21]. Although the exact mechanism of diarrhea in COVID-19 is unclear, molecular studies have shown that the virus binds through Angiotensin-Converting Enzyme 2 (ACE2) receptor expressed in the lungs, esophagus, and enterocytes [22]. This is postulated to alter enterocyte permeability, resulting in a state of malabsorption and diarrhea [19, 23].

Other signs and symptoms include anorexia, nausea, vomiting, and abdominal pain. Vomiting is more commonly seen in children and rarely, GI bleed in adults may occur as well [20]. In patients with new-onset GI symptoms of nausea, vomiting, diarrhea, or abdominal pain, monitoring for respiratory symptoms is advised and COVID-19 testing should be advised in settings where there is already a high prevalence of COVID-19 [24]. However, respiratory symptoms may not always be present, as a recent study by Jinet. al found that out of 74 patients presenting with GI manifestations of COVID-19, only 8 (10.8%) had shortness of breath [25].

GI manifestations have also been investigated with the previous corona viruses as well. A retrospective study evaluated the 10 gastrointestinal symptoms of the first cohort of patients with SARS in Hong Kong in 2003, where watery diarrhea, without blood or mucus, was a frequent symptom, occurring in 28/138 patients (20.3%) at disease presentation. In 8 patients (5.8%) diarrhea was combined with fever, while 25 additional patients experienced diarrhea in the following 3 weeks, accounting for a total of 53 patients (38.4%). Mean duration

of diarrhea was 3.7 days and evacuations ranged from few stools to 30 per day, and those patients had a higher need for ventilator support (26.4% vs. 8.2%; $p = 0.004$) and intensive care (49.0% vs. 11.8%; $p < 0.001$), suggesting a greater disease severity, although no correlation with the mortality rate was found [17].

3.3. When to Suspect COVID with Liver Involvement?

Liver injury is not usually among the initial manifestations of COVID-19. It has been seen in hospitalized patients with increased severity of disease [26]. In a recent study of 417 patients hospitalized due to COVID-19, abnormal liver function tests (LFTs) were seen in up to 76% and liver injury in 21.5% of the patients. Derangement of LFTs occurred within 2 weeks of hospital admission and was associated with the use of antiviral drugs lopinavir/ritonavir [27]. The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are seen to rise more than three times the normal upper limit, whereas alkaline phosphatase usually remains normal [28].

In a cohort study of 1099 patients with COVID-19, abnormal liver function tests including elevated AST, ALT and total bilirubin (TBIL) were found in 168 (168/757, 22.2%), 158 (158/741, 21.3%) and 76 (76/722, 10.5%) of patients [29]. The mechanism of liver injury in COVID-19 is attributed to interplay between virus entry mediated through ACE2 on hepatocytes and the role of inflammatory cytokines released as part of the Systemic Inflammatory Response Syndrome in severely ill patients [30, 31]. However, the drug-induced liver injury (DILI) is also a cause for concern as some of the antiviral drugs and hydroxychloroquine used for the treatment of COVID-19 are metabolized by the liver and can have hepatotoxic side effects [32].

The previous corona viruses SARS-CoV and MERS-CoV have also resulted in derangement of liver function which was associated with the severity of underlying coronavirus infection [33]. In patients with SARS, Duan et al reported that serum IL-1, IL-6 and IL-10 levels in patients with abnormal liver function were higher than those in patients with normal liver function, suggesting a possible correlation between liver damage and the inflammatory responses induced by SARS-CoV infection [34]. Several retrospective studies have shown that patients with MERS had elevated liver enzymes and bilirubin levels, as well as decreased albumin levels [35, 36].

3.4. How to Investigate Suspected COVID Patients with GI Signs and Symptoms?

A stepwise approach should be followed in the investigation of all suspected COVID-19 patients. Most guidelines initially recommend the use of a standardized checklist to assess relevant signs and symptoms for the risk stratification of suspected cases [37, 38]. In those whom further testing is required, there are several modalities available. In patients with both respiratory and digestive symptoms, High-Resolution Computed Tomography (HRCT) scan is a highly sensitive modality for the diagnosis of COVID-19, however, this facility is expensive, lacks specificity, is not widely available in resource-limited settings and there are issues related to decontamination in between suspected patients [39, 40].

The reverse transcription-Polymerase Chain Reaction (PCR) detection of viral nucleic acids from the stool, oral, and nasal swab specimens is widely being used for the diagnosis of COVID-19. Tian et al found that fecal PCR testing was as accurate as PCR of respiratory specimens to detect COVID-19 [13]. In convalescent patients, Virus nucleic acid can still be detectable in the stool for up to ten days following negative PCR of respiratory specimens [41]. Once a patient has tested positive, contact tracing and testing of suspected "contacts are also advisable" to prevent further disease propagation.

It is not necessary to check LFTs in all patients with COVID-19. Stable patients who are managed on an out-patient basis do not need LFT testing whereas those managed on an in-patient basis, having a pre-existing liver disease or GI symptoms should get LFTs checked [42].

In hospitalized patients with known or suspected COVID-19, the American Gastroenterological Association (AGA) recommends that baseline LFTs should be checked on admission and then monitored throughout the hospital stay; especially in the context of hepatotoxic effects of the drug treatment they receive [17].

3.5. How to Manage COVID Patients with GI Involvement?

Management of COVID-19 is still a dilemma, with several therapies under investigation including the use of antivirals (remdesivir, lopinavir/ritonavir), hydroxychloroquine, steroids, azithromycin, convalescent plasma and many other drugs [43, 44]. As there is no definitive cure or vaccine yet, prevention is key, with emphasis on maintaining good hygiene practices [45].

Concern has been raised regarding the fecal shedding of COVID-19 and its implications in terms of disease propagation, patient isolation protocols, and safety of performing colonoscopy procedures during the pandemic. To minimize risks of disease transmission, many international societies including the European Society for Gastrointestinal Endoscopy and the American Gastroenterological Association have recently issued guidelines suggesting that elective colonoscopies should be postponed [46]. They also recommend specific Personal Protective Equipment usage protocols when performing urgent colonoscopies [17]. Where possible, procedures of COVID-19 positive patients should be performed in negative pressure rooms [24].

The IL-6 inhibitor Tocilizumab is among the potential therapies being investigated for the management of COVID-19. However, there is a risk of Hepatitis B reactivation with this drug which can lead to fulminant hepatic failure in such patients [47]. More recently, dexamethasone is emerging as one of the possible therapies for COVID-19; this drug is relatively safe and potentially beneficial to use in patients with pre-existing liver disease [48].

4. Future Directions

Current management strategies as highlighted in the former section are still being explored with no definitive treatment available to date. As the virus gains entry to the GIT by binding to ACE2 receptors on enterocytes, bile duct epithelial cells, and hepatocytes, an interesting area that could be explored in future studies is the role of ACE2 in management of such patients [22, 49].

The impact of COVID-19 on patients with pre-existing liver disease including Hepatitis B, Hepatitis C, alcoholic liver disease and non-alcoholic fatty liver diseases needs to be studied, as well as the hepatotoxic effect of potential drug regimens being used in clinical trials [24, 50].

Postmortem examination of COVID-19 patients, including histopathological examination of the liver and intestines, could provide valuable information regarding disease mechanism and manifestations [51]. In one study, core liver biopsies from patients who had expired due to COVID-19 showed mild sinusoidal dilatation with lymphocytes accumulated in the portal tracts, however, this could also be a consequence of underlying co-morbidities and larger sample size would be needed to verify these findings and their implications [52].

A few recent studies have proposed that the anti-HCV drug sofosbuvir could be a potential therapeutic option for the management of COVID-19 [53]. In terms of hepatotoxicity and use in patients with pre-existing liver disease, this drug is relatively safe and well-tolerated among the potential drugs under investigation however clinical trials would be needed to establish its efficacy [54].

5. Conclusion

The COVID-19 proves to be a rapidly evolving challenge for healthcare professionals worldwide. Physicians should be mindful of the GI manifestations of COVID-19, as this may be the initial disease presentation without any respiratory symptoms. Early identification of such cases will not only help in early delivery of care but also in preventing further spread in close contacts.

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