ABSTRACT

Background: The first case of coronavirus was found in December 2019 in Wuhan a city in China since then it has severe impact all over the world. The typical signs and symptoms of coronavirus patients consist of cough, fever, lethargy, and shortness of breath (SOB).

Objectives: The current review contains summarized and complete information on the effect of coronavirus on GIT, Liver and its manifestations, prognosis, mechanisms, treatment, and challenges.

Methodology: The data was collected via an electronic search of numerous scientific sources including Google scholar, PubMed, and Science Direct.

Results: The main complaints in COVID-19 positive patients are linked to the respiratory system but many patients also complained of gastrointestinal problems like vomiting, abdominal pain, diarrhoea, and in some cases, anorexia, increased acidity, and bloating. The mechanisms of GI damage in corona-virus patients are direct virus-mediated cytotoxic damage in the intestinal epithelium, dysregulation of the RAAS in the intestinal epithelium, malabsorption of tryptophan in the intestinal epithelium. Various scientific studies also report that COVID-19 patients had abnormal levels of ALT and AST suggesting a possible liver injury. The possible mechanisms of liver damage in corona-virus patients are direct hepatic infection by corona-virus, cytokine storm, and drug-induced damage. The prognosis is poor in both GI and liver abnormalities in corona-virus patients. According to some studies, patients with considerable liver injury should be treated with anti-inflammatory, hepatoprotective, and jaundice-decreasing agents. Natural plants and herbs can be used in coronavirus patients with GI and liver abnormalities. However, further research is necessary in this area for a complete assessment of the effect of coronavirus infection on GI and liver abnormalities and appropriate testing of therapeutic agents used against these abnormalities.

Conclusion: In a nutshell, our results conclude that both gastrointestinal symptoms and liver damage are not unusual in patients with coronavirus infection. Severe coronavirus patients had a greater risk of developing gastrointestinal symptoms and liver damage.

Keywords: COVID-19, Liver, GIT, Corona-virus
INTRODUCTION
Corona-virus infection rapidly occurred since its first case was found in Wuhan a city in China in December 2019 and has severe impact all over the world. On 11 March 2020, WHO declared coronavirus as a pandemic (1, 2). Since the 1960s coronaviruses have been known to the world. Many strains of coronaviruses were transmissible to humans causing clinical symptoms generally related to the common cold (3, 4). WHO named this disease as COVID-19 officially (5, 6). Coronavirus belongs to the Coronaviridae family. It is composed of four species out of which alpha and beta forms can infect mammals comprising of humans (7). COVID-19 incubation time is 1 to 14 days, commonly 3 to 7 days (8). Some studies also reported that the incubation period is about 5 days (5, 9). SARS-CoV-2 infection can be diagnosed by chest radiography or with the help of laboratory testing (PCR) (10, 11).

Sign and symptoms
The signs and symptoms of coronavirus-ill patients comprises of cough, fever, fatigue, shortness of breath (SOB), muscular and chest pain, nasal and throat congestion, anorexia, heart irregularities, and dizziness (9, 12). Some patients also report symptoms related to the gastrointestinal tract that includes diarrhoea, nausea, abdominal pain, vomiting, and an increase in liver enzymes. These symptoms were possibly due to the spread of coronavirus infection to the digestive system including the GIT tract and liver (13, 14).

COVID-19 mechanism of causing injury
The coronavirus virus would possibly disturb the ACE2 enzyme activity (15, 16). Some studies support that the pathway of transmission of coronavirus is the fecal-oral route (17, 18). As discussed before the mechanism of SARS-CoV-2 causing damage to the digestive system is possible due to its interaction with ACE2 receptor through which it gets entry into the target cells (19, 20). ACE2 receptors are generally spread among different body organs like kidney, liver, small intestine, nasal and oral mucosa etc. As compared to the respiratory tract ACE2 receptors are higher in concentration in the GI tract so the effects of the coronavirus on the digestive system are not surprising (3). In some patients digestive symptoms are also observed as the first appearance of coronavirus infection in addition with increase in liver enzymes alanine transaminase (ALT) and aspartate aminotransferase (AST). These cases recommended that the coronavirus can damage the digestive system and may elucidate the series of digestive symptoms that occur in coronavirus infection (21, 22).

Case studies
In a descriptive study, containing 204 confirmed COVID-19 patients. The results have shown that 41.6 % of patients showed nausea or vomiting and 17.2% of patients suffered from diarrhea (14). The intestinal injury produced by coronavirus infection has been confirmed by autopsy and biopsy (23). The pH value of normal gastric acid is normally between 1.5 and 3.5 as the previous SARS-CoV-1 virus is deactivated at a pH less than 3.0 and greater than 12.0 supposing these inactivation values are similar for SARS-CoV-2, so it means gastric acid will not stop the entry of all viruses in the stomach as some viruses will be hidden in food particles (24, 25). COVID-19 patients also report an increase in levels of ALT, AST, and hypoalbuminemia. Bilirubin level was also found to be enhanced in certain patients. Coronavirus patients may exhibit liver abnormalities due to viral hepatitis or due to the toxicity of any drug. The SARS-CoV-2 mechanism of damaging the liver cells is the same as it damages the GIT tract through interruption with the ACE2 receptor (26, 27). A cohort study of 56 coronavirus patients shows that GGT was found raised in 54% of the patients. The ratio of liver injury was also greater in severe coronavirus patients. Another study conducted in Wuhan shows that out of 99 total corona-virus patients 43 patients had high value AST or ALT (26, 28).

Treatment strategy for corona virus infection
The medicines that are used for COVID-19 infection treatment strategy are lopinavir/ritonavir, chloroquine or hydroxychloroquine and remdesivir also shown some good results. It is crucial to avoid inappropriate use of antibiotics, particularly combinations of broad spectrum antibiotics. Use of corticosteroids is also very debatable. Methyl
prednisolone can be used as a suitable drug for COVID-19 patients. In case of high temperature (fever) ibuprofen can be used. Proton pump inhibitors such as omeprazole, esomeprazole or H2 receptor blockers like ranitidine can be used in corona-virus patients with risk factors for stress ulcers, and GIT bleeding (12, 29, 30).

Now recently, traditional Chinese medicines (TCM) were extensively used for treating SARS-CoV infection. Many COVID-19 infected Patients were treated with Chinese herbal medicine shown improvements in their symptoms, improved lung infiltrate, less side effects, and shorter hospital admission periods. In the history, herbal medicines have played an vital role in treating infections (31, 32). A lot of studies have shown promising results in the favor of herbal medicines against corona infection (33, 34). In 2003, a lot of traditional Chinese medicines were used to stop and treat SARS infection but during the treatment of corona-virus patients in China, it was established that the interference of TCM can decrease the severe symptoms of corona virus patients. Herbal agents could be beneficial as treatment to fight against corona-virus patients (35). Liver protective drugs were generally given to patients suffering from liver impairment in COVID-19 (36, 37). The benefits of TCM in the treatment of corona-virus contain active relief of symptoms, delaying the growth of disease from mild and moderate to severe, decreasing death rates and elevation of rehabilitation (38).

**METHODOLOGY**

The current review offers summarized and complete information on the effects of coronavirus on GIT and liver and its manifestations, prognosis, mechanisms, treatment and challenges. All the present information was collected via an electronic search of multiple scientific sources comprising of Google Scholar, PubMed, and Science Direct. The study record comprises of different research articles, review articles, and numerous scientific reports. The authors selected the following keywords to find relevant readings such as “Liver injury in corona-virus” “GI manifestations and mechanisms in COVID-19” “Liver injury mechanism in COVID-19” and “Treatment of GIT and liver abnormalities in COVID-19”. These terms or sentences were used either alone or in different combinations. Various studies reporting the effect of coronavirus on GIT and liver abnormalities are included in this review. Mostly latest scientific data were collected and compiled in this review article.

**RESULTS AND DISCUSSION**

**GIT manifestations in COVID-19**

The main complaints in coronavirus-positive patients are related to the respiratory system, but a lot of patients also complaints of gastrointestinal problems like vomiting, diarrhoea, abdominal pain, and in some cases anorexia, increased acidity, and bloating. The drug normally used for digestive problems seems not to be effective in coronavirus patients with GI problems (39).

**GIT symptoms**

The reported GI symptoms of corona patients are; nausea, vomiting, diarrhoea, abdominal pain, satiety, GERD, melena, bloated stomach, loss of taste, and gastrointestinal bleeding in rare cases as shown in Figure no 1. The disease may also destroy bowel tissues and reduce intestinal movement (40). Several studies have reported different GI symptoms in coronavirus patients as shown in Table no 1 (41).

**Table 1. GIT symptoms associated with COVID-19**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guan et al.</td>
<td>1,099</td>
<td>55 (5.0%)</td>
<td>55 (5.0%)</td>
<td>42 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Wang et al.</td>
<td>138</td>
<td>14 (10.1%)</td>
<td>5 (3.6%)</td>
<td>14 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>Xiao et al.</td>
<td>73</td>
<td>-</td>
<td>-</td>
<td>26 (35.6%)</td>
<td></td>
</tr>
<tr>
<td>Pan et al.</td>
<td>204</td>
<td>-</td>
<td>8 (3.9%)</td>
<td>29 (14.2%)</td>
<td>83 (40.6%)</td>
</tr>
<tr>
<td>Lu et al.</td>
<td>171</td>
<td>11 (6.4%)</td>
<td>-</td>
<td>15 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Liu et al.</td>
<td>137</td>
<td>-</td>
<td>-</td>
<td>11 (8%)</td>
<td></td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>141</td>
<td>7 (3.7%)</td>
<td>7 (3.7%)</td>
<td>9 (4.7%)</td>
<td></td>
</tr>
</tbody>
</table>
After COVID-19, the patient’s digestive tract doesn’t function the same as before this is called “post-infectious dysmotility.” Viruses cause irregularity in the functioning of the digestive tract. COVID-19 might have the same effect (42). Studies have shown that COVID-19 can also mimic gastrointestinal cancer. A case study of a 35-year-old male coronavirus patient in the US shows a history of nausea and vomiting for 2 days followed by abdominal discomfort and diarrhoea (43). In a study of 1099 patients of COVID-19 from 552 different hospitals in China, nausea or vomiting was observed in 55 patients and diarrhoea in 42 patients (44).

**GIT prognosis in COVID-19**

A study shows a prognostic classification which was based on the illness, duration and presence of gastrointestinal manifestations specifically diarrhea. COVID-19 symptoms predict a worse patient prognosis (45). When people with digestive symptoms are compared with people without GI symptoms, they indicate a worse prognosis. A comparison of coronavirus patients without GIT symptoms reveals that those with GI symptoms are more prone to lethargy, cough, and headache. A higher viral load is seen when GIT is involved in this disease (46).

**Mechanisms of GIT injury in COVID-19**

ACE2 is seen to be involved in GI manifestation by SARS-CoV-2. ACE2 is not only present in lung cells but also in gastric, duodenal and rectal epithelial cells (19, 23, 47). Furin and Cathapsein L are involved in coronavirus entry (48, 49). TMPRSS2 and TMPRSS4 also encourage the entry of coronavirus in small intestinal enterocytes. Both ACE2 and TMPRSS2 were co-expressed in the ileum and colon demonstrating that coronavirus can enter enterocytes of the gastrointestinal tract. In COVID-19 patients, the accumulation of ANG II levels is increased and may contribute to the severity of the disease. However, the role of ANG II in this disease needs further investigation (50). SARS-CoV-2 uses ACE2 for entry and causes the release of pro-inflammatory cytokines. After entry through ACE2, it causes malabsorption and unbalanced intestinal secretion which leads to diarrhea (51). COVID-19 induces inflammatory reactions in GIT by disturbing its function when enters through ACE2, chemokines, and cytokines are released with the infiltration of neutrophils, macrophages, and T cells to the infected area. The binding of ACE2 with B0AT1 contributes to the absorption of tryptophan, which is essential for intestinal haemostasis. When corona-virus binds to ACE2, the ACE2 and B0AT1 interaction is disturbed, which leads to tryptophan malabsorption (52). In a study, identification of intestinal flora outcomes, changes in the gut microbiota reveals disorders of the intestinal flora as shown in Figure no 2. Changes occur in gastrointestinal flora which could affect the lungs, whereas changes in lungs flora also occur which could affect GIT through immune regulation, which is called gut-lung-axis (53). Before the appearance of any respiratory symptoms, Coronavirus patients could experience some GI disturbances (22). Corona-virus is also found in stool samples of patients by PCR. There are suggestions that in the gastrointestinal tract, the virus stays longer than in the respiratory system. The virus has been found in fecal samples even after the patient doesn’t experience symptoms anymore, and even after removal of the virus from the respiratory tract. It gives the idea of a new route of transmission in addition to the respiratory route (16, 54). It is necessary to evaluate the risk of fecal transmission to reduce the spread of
disease (23, 55, 56). So, pathogenic mechanisms of GI injury are; direct virus-mediated cytotoxic damage in the intestinal epithelium, dysregulation of the RAAS in the intestinal epithelium, malabsorption of tryptophan in the intestinal epithelium, endothelial damage, and thrombo-inflammation in blood vessels, dysregulation of the immune system and gut dysbiosis as shown in Figure no 3.

**Liver manifestations in COVID-19**

A Study in China shows that 2-11% of patients with coronavirus had liver abnormalities and 14–53% of patients showed abnormal values of ALT and AST during disease development. In people with coronavirus, the prevalence of liver injury was found to be as 39.6% to 43.4%, mainly due to the elevated levels of ALT, AST, and elevated levels of hypoalbuminemia and a slight rise in total bilirubin levels (26, 59, 60). In a study, Wang et al. propose that patients with coronavirus shows increase levels of both ALT and AST. Only some patients had higher levels of total bilirubin, direct bilirubin and indirect bilirubin. GGT levels are accompanied by more or less increased prothrombin time (61-64).

Abnormalities of liver in corona-virus patients occur may be due to liver cell dysfunction that may be due to other co-morbid conditions like viral hepatitis (65). In coronavirus patients there is the possibility that the drugs used in the treatment of COVID infection are linked with liver injury, the use of several drugs i.e. antibiotics, antivirals, anti-pyretic, pain killers and herbal or Chinese medicines may cause liver irregularities in corona-virus patients. Antiviral drugs may enhance the risk of drug-induced liver damage (66). Patients with severe coronavirus infection seem to have higher chances of liver function irregularities. Therefore, liver damage is more widespread in severe cases of coronavirus infection than in mild ones (67, 68). Around 300 million people in China are affected by liver disorders like viral hepatitis and fatty liver diseases. Additionally, patients of corona-virus with liver cirrhosis might be more vulnerable to corona infection because of their systemic immune-compromised position.

**Liver function tests parameters and abnormalities**

In liver function tests abnormalities there is an increase in the following liver enzymes: ALT, AST, GGT, ALP and total bilirubin. As Coronavirus is a new communicable disease. So, we classified these irregularities as hepatocellular, cholestatic or mixed injury as shown in Table 2. Persons who had increased ALT/AST values were defined as hepatocyte type; people who had increased both ALP and
GGT values were defined as cholangiocyte type; and people who had increased ALT/AST/GGT levels were defined as a mixed type. According to the national guidelines of China these are classified as mild or severe cases based on chest X-ray and clinical findings (70).

**Table 2. Classification of liver abnormalities (69)**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver damage</td>
<td>ALT/AST Levels increased</td>
</tr>
<tr>
<td>Hepatocellular injury</td>
<td>ALT/AST Levels increased</td>
</tr>
<tr>
<td>Cholestatic injury</td>
<td>ALT/GGT Levels increased</td>
</tr>
<tr>
<td>Mixed Anomaly</td>
<td>ALT/AST/GGT Levels increased</td>
</tr>
<tr>
<td>Cytokine Storm</td>
<td>CRP/ Serum ferritin/LDH/ IL-2/IL-6 Levels increased</td>
</tr>
<tr>
<td>Mild cases of corona-virus</td>
<td>Dry cough, fever, lethargy, headache, all these symptoms are present</td>
</tr>
<tr>
<td>Severe cases of corona-virus</td>
<td>1) Respiration value ≥ 30 breaths per minute 2) SpO2 levels ≤ 95% 3) PaO2/FiO2 levels ≤ 300 mmHg</td>
</tr>
</tbody>
</table>

**Prognosis of liver injury in corona-virus infection**

Current study reports have revealed that the weak prognosis in corona-virus patients is linked to gender, age, co-morbid diseases like high blood pressure, diabetes mellitus and cardiovascular complications. A rise in the number of neutrophils to lymphocyte ratio normally proposes a larger degree of importance to the illness. There were no significant links among ALT, AST, alkaline phosphatase, total bilirubin, and other biomarkers of liver injury and serious corona-virus patients indicating that the liver has not been the primary or major target organ. Still, in severe corona-virus patients the ALT/AST, total bilirubin, and other parameters of liver function tests were notably enhanced as compared to the patients with mild corona-virus disease. However, these biomarkers returned to normal once the patient recovers from coronavirus infection. It has been seen that many people with severe liver injury were usually given hepatoprotective agents (71) (72).

**Mechanisms of liver injury in Corona-virus infection**

Possible mechanisms of liver injury (Figure 4) in coronavirus patients are direct hepatic infection by coronavirus. In SARS-CoV-2 ACE2 is the host cell receptor and cellular entry involves TMPRSS2 (47). In a sub population of cholangiocytes, messenger RNA (mRNA) is involved but no or negligible expression is present in hepatocytes, and no expression is found in other liver cell types (73-75). ACE2 protein has not been spotted in hepatocytes (76). Around 2–10% of people with coronavirus presents with diarrhoea and coronavirus RNA has been found in their stool and blood samples. In some patients with COVID-19, the liver could be affected by the hypoxia and cytokine storm that follows a coronavirus infection, which is linked with multi-organ failure (77, 78). AST levels propose a virus-specific mediated mechanism of liver damage. AST is produced in the muscle, and patients with coronavirus have signs of muscle injury. The elevations of AST levels are also linked with ALD, ischemia and cirrhosis, enlightening the influence of corona-virus on the liver. The corona-virus RNA has been found in feces may propose possible spread from the bowel to the liver, through the portal circulation. Both Hepatocytes and cholangiocytes could be possible targets during viral corona infection. In People with cirrhosis, there is dysfunction of the macrophages, reticuloendothelial system, and the adaptive immune response, in the development of a more lethal form of liver disorders due to the coronavirus (79, 80).
Management of GIT and liver-related abnormalities in Corona-virus patients

At present, there is no exact treatment for the coronavirus patients. So, the basis of COVID-19 patient's management with any type of GIT or liver abnormalities is symptomatic therapy, isolation, supportive medical care, and attention that include pulmonary ventilation and inhibition of any underlying inflammatory “storm” (81). Currently different drugs such as Tocilizumab, Favipiravir, and Remdesivir are being used in coronavirus patients but all with unconfirmed efficacy. The use of some anti-viral drugs such as Lopinavir/Ritonavir can cause Git adverse reactions such as diarrhoea, abdominal pain, nausea, vomiting, and increased serum aminotransferase (liver enzymes) levels in the body (82). According to the CPA corona-virus patients with substantial liver injury should be cured with anti-inflammatory, hepatoprotective, and jaundice-decreasing agents which are vitamin E (Tocopherol), bicycloil, and glycyrrhizic acid. The treatment of serious patients should be selected according to the liver damage and to avoid drug interactions, a minimal number of drugs should be used. In corona-virus patients with liver damage, the crucial step of treatment is to target the virus by using anti-viral drugs, balanced oxygen therapy, anti-infective drugs, and symptomatic treatment (72). Some studies have shown that some antibiotics, antiviral agents, steroids, and Lopinavir/ritonavir that are used to treat coronavirus patients may cause liver injury by increasing serum aminotransferase levels so such drugs should use with caution in corona-virus patients with liver injury (72, 83). People infected with hepatitis B and C if affected by COVID-19 should follow a healthy lifestyle (84).

**Herbal/Phytochemicals treatment**

*Adiantum capillus-veneri* is a medicinal herb. This plant extract shows potential efficacy as the earliest physicians used it for treating multiple disorders. The leaves of this herb showed an antidiarrheal effect that was confirmed through castor oil-induced diarrhoea in mice models. This plant also shows antispasmodic activity (85). The leaves of *Hedera helix* L. - Araliaceae and fruit of *Pimpinella anisum* L.Apiaceous also showed anti-spasmodic activity. So these phytochemicals can be used for diarrhoea and abdominal pain associated with coronavirus (86). Ginger is a very popular spice and it has very good digestive properties. Vitamin C also has an immune-boosting effect (87). *Emblica officinalis* Gaertn usually known by the name Amla is an important medicinal plant that belongs to the family Euphorbiaceae. Its fruit is very useful as a liver tonic. *Andrographis paniculata* belongs to the family Acanthaceae commonly famous as Kalmegh is also very useful in liver disorders (88). Onion (botanical name) *Allium cepa* with its bioactive compounds apigenin, quercetin, selenium and cinnamon (*C. zeylanicum*) along with its main compounds, cinnamaldehyde, linalool and eugenol also exert some hepatoprotective effect (83). Glycyrrhizin is also the favored anti-inflammatory agent to protect against liver disorders (72). All these natural plants and herbs can be used in COVID-19 patients with liver abnormalities. Some Phytochemicals that are used as hepatoprotective agents are shown in Figure no 5.
Figure 5. Phytochemicals that are used as hepatoprotective agents (86,87)

Challenges in managing GIT and liver-related abnormalities in COVID-19
It is recommended that future research must be the focus on long-term effects of coronavirus on the gut microbiome (89). Presently, there is no specific drug for the treatment of coronavirus patients and there are no adequate studies on the treatment of COVID-linked GI symptoms. Certain drugs are in their different phases to treat coronavirus infection but need more extensive testing (90). Different herbal components and phytochemicals are also in use against COVID-19 and its co-morbid diseases linked with coronavirus-like digestive symptoms but need more in-vivo/in-vitro studies in the future for their conformational use. Likewise, there is no direct proof of liver failure in SARS-COV-2 patients without previous liver disease. Different actions should be suggested for the patients with corona-virus during their hospital stay. Additionally some scientific studies are necessary to explain the causes of liver injury in corona-virus patients (91). Another important challenge is the condition of the coronavirus patients with liver injury. Considering their immuno-compromised position, more serious observation or aggressive therapeutic tactics are needed for severe coronavirus patients along-with pre-existing conditions like advanced chronic liver disease, especially in older patients. Further advanced research studies should focus on the reasons for liver injury in corona-virus patients and the effect of this liver injury on the treatment and outcome of corona-virus patients (28).

LIMITATIONS AND FUTURE RECOMMENDATIONS
At present there is no exact treatment for the GI symptoms and liver damage produced by coronavirus infection. Some allopathic and herbal drugs are in use for these complications. However, further research is necessary in this area for a complete evaluation of the effect of coronavirus infection on GIT and liver abnormalities and proper testing of therapeutic agents used against these abnormalities.

CONCLUSION
In this review, we summarized the latest reports of GIT symptoms and liver damage produced by coronavirus infection. In a nutshell, our results recommend that both GI symptoms and liver damage are not unusual in patients with coronavirus disease. Severe coronavirus patients had a greater risk of developing gastrointestinal symptoms and liver damage. Liver test abnormalities are more common in severe coronavirus patients. GI symptoms have a tendency to develop into more severe or dangerous diseases and have a poor disease outcome. Increased consideration should be given to the care of this unique crew of patients.

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Authors’ Contributions
SH contributed to study concept, study design and data collection. AAU and SS contributed in data analysis and interpretation. AG and FA did the literature review and critically reviewed the manuscript. All the authors read and approved the final manuscript.

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Not applicable

Conflict of Interest
The authors declared no conflict of interest among them.

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REFERENCES


Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation.


