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Original Research Article

Prevalence of Liver Dysfunction in COVID-19 Infections and Its Correlation with Severity and Mortality

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Abstract

Aim: To evaluate the prevalence of liver dysfunction and its correlation with severity and mortality in patients with Covid-19 infection. **Materials and methods:** Total 120 patients fulfilled the inclusion criteria were enrolled for the study after giving informed consent and were divided into two groups (moderate and severe Covid-19 infection). Patients were treated as per national guideline for Covid-19 infection as mentioned in flow chart above. Hemogram and Liver function test and inflammatory markers (C-reactive protein, Lactate dehydrogenase, D-dimer and ferritin) were performed on every alternate day of hospitalization. Patients were followed during whole hospitalization course and weekly for 1 month after discharge with these tests. Approval for the study was sought from Institutional Ethical committee. **Results:** The median levels of ALT, AST, ALP, GGT, LDH, TBIL, DBIL, and albumin were 20 U/L (IQR, 14–31), 20 U/L (IQR, 17–26), 75 U/L (IQR, 55–193), 21 U/L (IQR, 14–36), 198 U/L (IQR, 172–232), 8.4 umol/L (IQR, 6.5–11.3), 3.4 umol/L (IQR, 2.3–4.6), and 45 g/L (IQR, 41–47), respectively. Severe patients had significantly higher levels of ALT (26 vs 20 U/L, p=0.017), AST (31 vs 20 U/L, p < 0.001), GGT (30 vs 21 U/L, p < 0.001), LDH (334 vs 197 U/L, p < 0.001), TBIL (10.2 vs 8.3 umol/L, p=0.029), DBIL (4.9 vs 3.3 umol/L, p < 0.001), but significantly lower albumin (37 vs 45 g/L, p < 0.001) than non-severe patients. Abnormal AST (40% vs 7%, p < 0.001), LDH (90% vs 35%, p < 0.001), DBIL (20% vs 7%, p < 0.001), and albumin (50% vs 8%, p < 0.001) were commonly observed in severe patients, compared with non-severe patients. On multivariate analysis, age >60 years, male gender, BMI > 30 kg/m2, comorbidity, abnormal LDH and albumin on hospital admission, and abnormal peak hospitalization LDH and albumin were associated with progression to severe COVID-19 (OR > 1; p < 0.05). **Conclusion:** This large sample retrospective cohort study, we described the longitudinal changes of liver function parameters in patients with COVID-19. In addition, we con- firmed patients with abnormal liver function parameters were at increased risk of severe COVID-19 and death.

Keywords: Covid-19, LFT, Mortality

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Introduction

In December 2019, an infectious severe acute respiratory syndrome was reported in China, found to be caused by a coronavirus [1]. Initially named as 2019 novel coronavirus (2019-nCoV), the virus was later termed as SARS-C0V2 [2]. This virus has been reported to have some features of SARS-CoV reported in 2003 and MERS-CoV reported in 2012. On 11 March 2020, the WHO declared COVID-19 (Coronavirus disease 2019) as a pandemic, which has resulted in more than 170 million infections with 3,565,027 deaths worldwide and in India 28 million are infected with 3,31,909 deaths until 31 May 2021 [3,4]. Currently, the primary diagnostic tool to detect cases of SARS-CoV-2 infections is real-time reverse transcriptase polymerase reaction (RT-PCR) from nasopharyngeal swabs and bronchoalveolar lavage fluids. Rapid antigen testing and measurements of antibody titer are also conducted for surveillance testing. Additionally, some hematology and biochemistry parameters complement the diagnosis [5].

The primary organ targeted in SARS is the lung, hence designated as 'severe acute respiratory syndrome' and 'SARS atypical pneumonia' [6] However, other organ dysfunctions, including gastrointestinal symptoms [7], abnormal liver functions [8], lymphadenopathy [9] and splenic atrophy, have also been observed in patients. These occurrences reflect widespread immunopathology or extra pulmonary dissemination and replication of SARS-coronavirus (CoV) [10]. Partial autopsies also indicate multiple organ infection by the virus [11]. The pathological changes can be attributed either to the direct cytotoxic effect by local replication of the virus or indirectly due to immune response induced by the viral infection. There are certain reports on the impact of COVID-19 on other organs, including varying levels of liver disease in patients [12]. A recent study found the binding of SARS-CoV-2 virus to ACE 2 (ACE2) on cholangiocytes leading to its dysfunction, which may result in liver injury through inducing a systemic inflammatory response [13]. Several hospital-based studies have reported liver damage in patients with COVID-19 in terms of elevated levels of liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with 14% to 53% rise in comparison to their normal levels [14-17]. Further, moderate micro vesicular steatosis, mild lobular and portal activity found in the liver biopsy specimens of a dead COVID-19 patient indicated the involvement of SARS-CoV-2 in liver damage [18].

Severity of COVID-19

As per the national guidelines for community-acquired pneumonia and the diagnosis and treatment plan for the new coronavirus in India, all patients are classified into non-severe or severe cases based on observations from symptoms and clinical examination [18]. Patients with no clinical signs and symptoms (asymptomatic) and patients with mild symptoms (such as fever, cough, sore throat, headache, nasal congestion) and uncomplicated upper respiratory tract infection are classified as non-severe type.

Mild COVID-19 is defined as symptomatic patients with uncomplicated upper respiratory tract infection, mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, and headache, but without evidence of viral pneumonia or hypoxia.

Moderate COVID-19 is defined as patients (adult and child) with pneumonia with no signs of severe disease and with presence of clinical features of dyspnea and or hypoxia, fever, cough, including oxygen saturation <94% (range 90–94%) on room air, respiratory rate ≥24 breaths/m.

Severe COVID-19 is defined as patients either with significant respiration rate ≥30

times/m, oxygen saturation ≤93%, partial pressure of oxygen/fraction of inspired oxygen ≤300 mmHg, or multiple organ or respiratory failure that requires intensive care unit (ICU) monitoring and treatment are classified as severe type. The assessment of disease severity was performed at the same time on the day of inpatient admission before treatment. Patient were treated as per national guideline of treatment for covid-19 [19-21].

Material and methods

The present observational study was carried out at Dept. of gastroenterology, IGIMS, Patna among 120 patients diagnosed with moderate to severe Covid-19 infection based on clinical criteria of national guidelines and confirmed RT-PCR from nasopharyngeal swab and fulfilled the inclusion and exclusion criteria.

Inclusion criteria:

Patients of any gender and age 18 years or above.
Diagnosed and admitted patients with moderate and severe Covid-19 infection as per national guidelines of Covid-19.

Patients giving informed consent.

Exclusion criteria:

Any underlying liver diseases currently or in past.
Alcoholism (Defined as >1drink/day for women and >2drink/day for men)
Viral hepatitis (HIV, HBV, HCV, HAV and HEV)
Pregnant women.
Patient below 18 years.
Any malignancy.
Patient on drugs causing liver dysfunction.

Methodology

All patients fulfilling the inclusion criteria were enrolled for the study after giving informed consent and were divided into two groups (moderate and severe Covid - 19 infection). Patients were treated as per national guideline for Covid-19 infection. Hemogram and Liver function test and inflammatory markers (C-reactive protein, Lactate dehydrogenase, D-dimer and ferritin) will be performed on every alternate day of hospitalisation. Patients were followed during whole hospitalization course and weekly for 1 month after discharge with these tests. Approval for the study was sought from Institutional Ethical committee. Patients who want to take part in the program voluntarily and sign the informed consent were enrolled in this study.

Results

Of 120 patients with COVID-19, the median age was 37 years (IQR, 25–50), 80 patients (66.67%) were male, 40 patients (33.33%) had obesity, and 22 patients (18.33%) had comorbidity, mainly including hypertension (10%) and diabetes mellitus (5%). In this study, twenty-three patients had chronic liver diseases, including chronic hepatitis B (n=7), alcoholic or nonalcoholic fatty liver disease (n=5), and auto- immune liver disease (n=1). 1 patient had both chronic hepatitis B and fatty liver disease. 6 patients had chronic heart diseases, including coronary artery disease (n=2), chronic cardiac dysfunction (n=1), and cardiomyopathy (n=3). 1 patient had both coronary artery disease and chronic cardiac dysfunction. 3 patients had chronic pulmonary diseases, including asthma (n=1), chronic obstructive pulmonary disease (n=1). The median levels of white blood count (WBC), lymphocyte, platelet, procalcitonin (PCT), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were 5.7×109/L (IQR, 4.4–7.2), 1.5×109/L (IQR, 1.1–2.2), 217×109/L (IQR, 172–252), 0.05 ng/mL (IQR, 0.02–0.12), 0.5 mg/L (IQR, 0.5–6.2), and 27 mm/h (IQR, 10–55), respectively. Severe patients with COVID-19 had higher age (median, 62 vs 33 years, $p < 0.001$) and BMI (mean, 28.9 vs 27.2 kg/ m2, $p < 0.001$), more common male

gender (80% vs 60%, p=0.012), obesity (50% vs 30%, p = 0.002), and comorbidity (70% vs 15%, p<0.001) than non-severe patients. Compared with non-severe patients with COVID- 19, severe patients had significantly higher PCT (0.10 vs 0.05 ng/mL, p < 0.001), CRP (40 vs 0.5 mg/L, p < 0.001), ESR (12 vs 3 mm/h, p < 0.001), but significantly lower lymphocyte count (0.7 vs 1.5×109/L, p < 0.001) and platelet count (171 vs 221 × 109/L, p < 0.001).

Table 1: Liver Function Tests of study population with COVID-19 on Hospital Admission

Characteristic	Non-Severe=100	Severe=20	p-value
Number	100	20	-
ALT (U/L)	20 (14–31)	26 (16–36)	0.017
ALT, abnormal (> 44 U/L)	12 (12%)	4 (20%)	0.24
AST (U/L)	20 (17–26)	31 (24–51)	< 0.001
AST, abnormal (> 38 U/L)	7 (7%)	8 (40%)	< 0.001
ALP (U/L)	75 (55–196)	69 (49–177)	0.45
ALP, abnormal (> 338 U/L)	2 (2%)	0	0.87
GGT (U/L)	21 (14–35)	30 (21–60)	< 0.001
GGT, abnormal (> 73 U/L)	7 (7%)	3 (15%)	0.13
LDH (U/L)	197 (171–229)	334 (264–452)	< 0.001
LDH, abnormal (> 211 U/L)	35(35%)	18 (90%)	< 0.001
TBIL (umol/L)	8.3 (6.5–11.2)	10.2 (7.9–14.9)	0.029
TBIL, abnormal (> 21 umol/L)	4 (4%)	1 (5%)	0.91
DBIL (umol/L)	3.3 (2.3–4.5)	4.9 (3.7–7.0)	< 0.001
DBIL, abnormal (> 7 umol/L)	7 (7%)	4 (20%)	< 0.001
Albumin (g/L)	45 (42–47)	37 (33–40)	< 0.001
Albumin, abnormal (< 38 g/L)	8 (8%)	10 (50%)	< 0.001

Liver function parameters of 120 patients on hospital admission are summarized in Table 1. The median levels of ALT, AST, ALP, GGT, LDH, TBIL, DBIL, and albumin were 20 U/L (IQR, 14–31), 20 U/L (IQR, 17–26), 75 U/L (IQR, 55–193), 21 U/L (IQR, 14–36), 198 U/L (IQR, 172–232), 8.4 umol/L (IQR, 6.5–11.3), 3.4 umol/L (IQR, 2.3–4.6), and 45 g/L (IQR, 41–47), respectively. Severe patients had significantly higher levels of ALT (26 vs 20 U/L, p=0.017), AST (31 vs 20 U/L, p < 0.001), GGT (30 vs 21 U/L, p < 0.001), LDH (334 vs 197 U/L, p < 0.001), TBIL (10.2 vs 8.3 umol/L, p=0.029), DBIL (4.9 vs 3.3 umol/L, p < 0.001), but significantly lower albumin (37 vs 45 g/L, p < 0.001) than non-severe patients. Abnormal AST (40% vs 7%, p < 0.001), LDH (90% vs 35%, p < 0.001), DBIL (20% vs 7%, p < 0.001), and albumin (50% vs 8%, p < 0.001) were commonly observed in severe patients, compared with non-severe patients.

Table 2: Association between Admission and Peak Hospitalization Liver Tests and Clinical Outcomes

	Severe COVID-19 (Multivariate Model)		Death (Multivariate Model)	
	OR (90% CI)	p-value	OR (90% CI)	p-value
Age > 60 years	4.02 (1.58–10.20)	0.003	6.54 (2.34–14.77)	0.005
Male gender	2.71 (1.27–8.79)	0.019	1.46 (0.28–6.35)	0.37
BMI > 30 kg/m2	3.46 (1.32–9.43)	0.012	1.88 (1.23–4.35)	0.021
Comorbidity	6.08 (2.45–15.10)	<0.001	6.84 (2.93–21.85)	<0.001
Hospital Admission				
Abnormal ALT	0.37 (0.07–1.90)	0.234	0.99 (0.04–26.30)	0.88
Abnormal AST	3.01 (0.70–13.03)	0.141	1.50 (0.16–14.47)	0.73
Abnormal ALP	0.22 (0.01–5.86)	0.218	0.85 (0.12–18.95)	0.81
Abnormal GGT	0.67 (0.12–1.19)	0.951	0.58 (0.07–4.55)	0.62
Abnormal LDH	3.36 (1.41–8.78)	0.002	2.11 (0.29–15.48)	0.47
Abnormal TBIL	0.49 (0.01–17.06)	0.696	1.02 (0.07–14.73)	0.99
Abnormal DBIL	1.85 (0.14–6.31)	0.325	4.62 (0.45–47.39)	0.19
Abnormal Albumin	2.45 (1.16–7.51)	0.026	4.74 (0.70–31.95)	0.11
Peak Hospitalization				
Abnormal ALT	2.28 (0.96–6.46)	0.139	3.47 (1.25–8.16)	0.006
Abnormal AST	3.92 (0.56–11.25)	0.141	4.92 (1.28–16.16)	<0.001
Abnormal ALP	0.29 (0.01–7.21)	0.453	1.45 (0.07–30.66)	0.78
Abnormal GGT	2.15 (0.98–7.86)	0.088	3.79 (0.60–57.87)	0.12
Abnormal LDH	3.84 (1.67–9.88)	<0.001	0.89 (0.01–47.85)	0.58
Abnormal TBIL	0.21 (0.03–1.66)	0.139	5.75 (1.87–18.20)	<0.001
Abnormal DBIL	0.49 (0.01–17.06)	0.696	1.39 (0.05–35.27)	0.87
Abnormal Albumin	3.94 (1.36–11.43)	0.002	2.16 (0.87–5.59)	0.76

The association between liver function parameters and clinical outcomes is shown in Table 2. On multivariate analysis, age >60 years, male gender, BMI > 30 kg/m2, comorbidity, abnormal LDH and albumin on hospital admission, and abnormal peak hospitalization LDH and albumin were associated with progression to severe COVID-19 (OR > 1; $p < 0.05$). The dynamic profile of liver function parameters in patients by severity of COVID-19. Severe COVID-19 patients had markedly higher levels of ALT, AST, GGT, LDH, TBIL, DBIL, but significantly lower levels of albumin than non-severe patients from baseline to 30 days after admission ($p < 0.05$). The peak of ALT, LDH, TBIL, DBIL value, and the trough of albumin was observed on 6–10 day of hospitalization. The peak of ALP and GGT value was observed on 11–15 day of hospitalization. On multivariate analysis, age >60 years (OR=6.54; 95% CI 2.34–14.77; $p < 0.005$), BMI > 30 kg/m2 (OR=1.88; 95% CI 1.23–4.35; p=0.021), comorbidity (OR=6.84; 95% CI 2.93–21.85; $p < 0.001$), and abnormal peak hospitalization ALT (OR=3.47; 95% CI 1.25–8.16; p=0.007), AST (OR=4.92; 95% CI 1.28–16.16; $p < 0.001$), and TBIL (OR=5.75; 95% CI 1.87–18.20; $p < 0.001$) were associated with death.

Discussion

Although COVID-19 is well known for causing respiratory symptoms, it can also cause extra pulmonary manifestations, including hepatocellular injury [22]. In this study of 120 patients with COVID-19, ALT and AST abnormalities were observed in 15% and 8% of patients at admission, respectively, and in 30% and 15% of patients at peak hospitalization, respectively. Based on a meta-analysis, the pooled prevalence estimates of elevated liver function abnormalities in China were

as follows: ALT 15.0% and AST 15.0% [23]. However, some studies from America showed higher prevalence ranging between 40–50.6% in cohorts ranging from 116 to 2780 patients [24-26]. Obviously, abnormal liver function parameters are less common in Chinese patients than that reported in the U.S [25, 26]. The differences in baseline factors (chronic liver diseases, obesity, alcohol consumption) and hospital management (antiviral medication use) may potentially account for some of this disparity. Moreover, the different laboratory references of liver function parameters in different health-care systems might lead to the different definitions of liver injury, which may be one of the reasons for the disparity in the prevalence of liver injury between Chinese patients and the US patients. For example, the ULN of ALT ranges from 40 U/L to 50 U/L in the studies from China [27-29], but ranges from 33 U/L to 50 U/L in the studies from the US [30].

This study showed that the pattern of abnormal liver function tests is predominantly hepatocellular (at admission: ALT 15%, AST 10%; at peak hospitalization: ALT 30%, AST 15%) rather than cholestatic, although less common elevations in ALP (2% at admission, and 3% at peak hospitalization), GGT (5% at admission, and 15% at peak hospitalization), and TBIL (5% at admis- sion, and 10% at peak hospitalization) can be observed. Given that angiotensin converting enzyme-2 (ACE2), the entry receptor for SARS-CoV-2, is much more heavily expressed in cholangiocytes than in hepatocytes [31], therefore our findings suggest that the direct cytopathic effect of the SARS-CoV-2 may not be the main mechanism of COVID-19-related liver damage. Hepatic dysfunction in COVID-19 could be related to an uncontrolled immune reaction, sepsis or drug-induced liver injury, besides the direct cytopathic effect of the virus [32].

This study shows an association between antiviral medications use (Hydroxychloroquine, Lopinavir/ Ritonavir, and TCM) and peak hospitalization ALT > 5 ULN in patients with COVID-19. Previous studies also showed that the use of certain drugs showed an association with the progression of liver damage in patients with COVID-19.33,34,35 An American study reported that Hydroxychloroquine and Lopinavir/Ritonavir use was the predictor of peak hospitalization liver parameters >5 ULN [33]. A Chinese study reported that a significantly higher proportion of patients with abnormal liver function (57.8%) had received Lopinavir/Ritonavir after admission compared to patients with normal liver function (31.3%) [34]. Another Chinese study reported that the use of Lopinavir/ Ritonavir ± Ribavirin + interferon beta (OR 1.94, p=0.006) was independently associated with ALT/AST elevation [35]. Based on previous studies and our results, we suggested Hydroxychloroquine, Lopinavir/Ritonavir, and TCM should be used with caution in patients with abnormal ALT and LDH at hospital admission.

In a Chinese cohort of 675 patients with COVID-19, compared to patients with normal AST levels, mortality and risk of mechanical ventilation significantly increased 19.27-fold and 116.72-fold, respectively, in patients with AST above 3-fold ULN [36]. In another Chinese cohort, Cai et al found that the presence of abnormal liver tests and liver injury were associated with the progression to severe COVID-19 [6]. In a large Hong Kong cohort of 1040 COVID-19 patients, Yip et al found ALT/AST elevation and acute liver injury are independently associated with adverse clinical outcomes including admission to intensive care unit, use of invasive mechanical ventilation and/or death in COVID-19 patients [35]. Saini et al retrospectively analysed liver function tests of 170 patients with con- firmed

COVID-19, and also found number of patients with raised levels of any of the liver enzymes were 89 (58.5%), out of which 43 (48.31%) had liver injury, which manifested as increased severity in terms of ICU requirement (p=0.0005) [37]. In this study, abnormal liver parameters during hospitalization are associated with illness severity and mortality of COVID-19, with the strongest associations observed between peak liver tests and severe COVID-19, as well as peak liver tests and death. Based on previous studies and our results, we suggested monitoring levels of liver function parameters, which could assist in the optimum management of patients with COVID-19.

Many TCM were used in patients with COVID-19 in our cohort; therefore, the effect of TCM on liver functions should not be neglected in COVID-19 patients [38]. In fact, the TCM-related liver injury is not uncommon in patients with COVID-19 [39]. A meta-analysis showed that the TCM as a complementary therapy for treating COVID-19 may not be beneficial for improving liver function based on the current evidence [38]. In this study, we found that the TCM use is one of the predictors of peak hospitalization ALT > 5 ULN. Based on previous studies and our results, we suggested that prevention and management of TCM- induced liver injury should be concerned in COVID-19 patients who received TCM therapy.

Besides liver injury, other gastrointestinal manifestations were also concerned in COVID-19 patients. At the age of COVID-19 crisis, gastrointestinal physicians may face rare gastrointestinal symptoms such as dysentery, pure hyperbilirubinemia, and so on. For example, Hormati et al have reported the clinical data in detail as well as the result of chest CT of a COVID-19 patient with dysentery [40]. In a case series, Hormati et al also have reported pure hyperbilirubinemia may be considered as rare gastrointestinal symptom of COVID-19 [41]. Therefore, it is necessary that all gastrointestinal physicians should be aware of the possible occurrence of these gastrointestinal symptoms (hepatic involvement, pure hyperbilirubinemia, dysentery) as an important prognosis of COVID-19 pneumonia and it should be exactly addressed in new referred patients to gastrointestinal clinic. In addition, Hormati et al address preventive strategies that may significantly reduce close contact between patients and gastrointestinal physicians for successful control of COVID-19 infection [42]. Preventive strategies should be performed to prevent transmission of COVID-19 infection from infected patients to uninfected gastrointestinal physicians and staff members during the performance of high-risk procedures [42].

This study has several limitations:

Firstly, the retrospective observational cohort study design with inclusion restricted to patients who were hospitalized within a single hospital, and limited access to laboratory, and medication variables, which may influence clinical outcomes.

Second, this study did not elucidate the etiology of liver function test elevations in hospitalized patients with COVID-19. However, based on previous studies, we have reasons to believe that the drug's effects, possible viral inclusion in liver cells, systemic inflammation, and hypoxia are potential causes of liver injury in patients with COVID-19 [43].

Third, in our hospital, the qualitative analysis (positive or negative) of SARS-CoV-2 RNA is used to guide the diagnosis and treatment of COVID- 19 patients. Although CT (cycle-threshold)-value for viral load can support in the better interpretation of clinical decisions, in this retrospective study, the quantification of SARS-CoV-2 viral load is not available.

Conclusion

In conclusion, in this large sample retrospective cohort study, we described

the longitudinal changes of liver function parameters in patients with COVID-19. In addition, we con- firmed patients with abnormal liver function parameters were at increased risk of severe COVID-19 and death. The COVID- 19-related liver injury is related to antiviral medication use.

References

1. Zhu NA, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727–33.
2. Gorbalenya AE, Baker SC, Baric RS, et al. severe acute respiratory syndrome-related coronavirus: the species and its viruses–a statement of the coronavirus study group. Bio Rxivorg 2020.
3. WHO director-general's opening remarks at the media briefing on COVID-19.
4. WHO Coronavirus Disease. (COVID-19) dashboard.
5. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019nCoV) infected pneumonia (standard version). Milit Med Res 2020; 7:4.
6. World Health Organization. Communicable disease surveillance & response (CSR). Severe Acute Respiratory Syndrome (SARS).
7. To KF, Tong JH, Chan PK, et al. Tissue and cellular tropism of the coronavirus associated with severe acute respiratory syndrome: an in-situ hybridization study of fatal cases. J Pathol 2004; 202:157–63.
8. Peiris JS, Lai ST, Poon LL , et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003; 361:1319–25.
9. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol 2003; 200:282–9.
10. Holmes KV. SARS coronavirus: a new challenge for prevention and therapy. J Clin Invest 2003; 111:1605–9.
11. Farcas GA, Poutanen SM, Mazzulli T, et al. Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus. J Infect Dis 2005; 191:193–7.
12. Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 2004; 39:302–10.
13. Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Bio Rxiv 2020.
14. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497–506.
15. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382:1708–20.
16. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8:420–2.
17. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. J Hepatol 2020.
18. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020; 5:428–30.
19. World Health Organization. Antigen-detection in the diagnosis of SARS-CoV2 infection using rapid immunoassays. Interim guidance.
20. Antigen_Detection-2020.
21. Centers for Disease Control and Prevention. COVID-19 (coronavirus disease): people with certain medical conditions. 2020.
22. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifesta- tions of COVID-19. Nat Med. 2020;26:1017–1032.

23. Sultan S, Altayar O, Siddique SM, et al. AGA Institute rapid review of the gastrointestinal and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the con- sultative management of patients with COVID-19. Gastroenterology. 2020;159:320–334.e27.
24. Cholankeril G, Podboy A, Aivaliotis VI, et al. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome Coronavirus 2: early experience from California. Gastroenterology. 2020;159(2):775–777.
25. Hajifathalian K, Krisko T, Mehta A, et al. Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: clinical implications. Gastroenterology. 2020;159:1137–1140.e2.
26. Singh S, Khan A. Clinical characteristics and outcomes of corona- virus disease 2019 among patients with preexisting liver disease in the United States: a Multicenter Research Network Study. Gastroenterology. 2020;159:768–771.e3.
27. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. J Hepatol. 2020;73:566–574.
28. Zhang Y, Zheng L, Liu L, et al. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int. 2020;40:2095–2103.
29. Lei F, Liu YM, Zhou F, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatology. 2020;72:389–398.
30. Phipps MM, Barraza LH, LaSota ED, et al. Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large US cohort. Hepatology. 2020;72(3):807–817.
31. Pirola CJ, Sookoian S. COVID-19 and ACE2 in the liver and gastro-intestinal tract: putative biological explanations of sexual dimorphism. Gastroenterology. 2020;159:1620–1621.
32. Jothimani D, Venugopal R, Abedin MF, et al. COVID-19 and the liver. J Hepatol. 2020;73:1231–1240.
33. Hundt MA, Deng Y, Ciarleglio MM, et al. Abnormal liver tests in COVID-19: a retrospective observational cohort study of 1827 patients in a major U.S. hospital network. Hepatology. 2020;72 (4):1169–1176.
34. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol. 2020;18:1561–1566.
35. Yip TC, Lui GC, Wong VW, et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut. 2020;70 (4):733–742.
36. Huang H, Chen S, Li H, et al. The association between markers of liver injury and clinical outcomes in patients with COVID-19 in Wuhan. Aliment Pharmacol Ther. 2020.
37. Saini RK, Saini N, Ram S, et al. COVID-19 associated variations in liver function parameters: a retrospective study. Postgrad Med J. 2020.
38. Shi S, Wang F, Li J, et al. The effect of Chinese herbal medicine on digestive system and liver functions should not be neglected in COVID-19: an updated systematic review and meta-analysis. IUBMB Life. 2021.
39. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:667–678.
40. Hormati A, Ghadir MR, Saeidi M, et al. Dysentery as a rare GI symptom

found in COVID-19 patients. Gastroenterol Hepatol. 2021;44:31–34.
41. Hormati A, Ghadir MR, Saeidi M, et al. Hepatic involvement as hyperbilirubinemia in patients with COVID-19: case series from Iran. Infect Disord Drug Targets. 2021;21:
42. Hormati A, Ghadir MR, Zamani F, et al. Preventive strategies used by GI physicians during the COVID-19 pandemic. New Microbes New Infect. 2020;35:100676.
43. Ali N, Hossain K. Liver injury in severe COVID-19 infection: current insights and challenges. Expert Rev Gastroenterol Hepatol. 2020;14:879–884.