DOI:10.34084/bshr.989891 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Review / Derleme

http://dergipark.org.tr/tr/pub/bshr

SARS-CoV-2 Infection and Liver Involvement

SARS-CoV-2 Enfeksiyonu ve Karaciğer Tutulumu

Mehmet Çoban[1], Dilşat Gündoğdu Çoban[1], Öner Özdemir[2]

[1] Specialist in Pediatrics, Department of Pediatrics, Sakarya University Research and Education Hospital, Sakarya, Türkiye

[2] Full Professor, Department of Pediatrics, Division of Allergy and Immunology, Sakarya University Research and Education Hospital, Sakarya, Türkiye

ORCID ID: Mehmet Çoban https://orcid.org/0000-0003-3611-3501, Dilşat Gündoğdu Çoban https://orcid.org/0000-0002-6845-7432 Öner Özdemir: https://orcid.org/0000-0002-5338-9561

***Sorumlu Yazar / Corresponding Author:** Öner Özdemir, **e-posta / e-mail:** ozdemir_oner@hotmail.com

Geliş Tarihi / Received : 01-09-2021 **Kabul Tarihi / Accepted:** 06-01-2022 **Yayın Tarihi / Online Published:** 30-04-2022

Çoban M., Çoban D.G., Özdemir Ö. SARS-CoV-2 Infection and Liver Involvement, J Biotechnol and Strategic Health Res. 2022; 6(1):1-7

Öz

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus that can also be transmitted from person to person via the droplet (secretions shed when speaking, sneezing, or coughing) route, suspended droplet nuclei, and the mucous membranes of the eyes, nose, and mouth after touching a contaminated surface. It enters the cells through the angiotensin converting enzyme 2 (ACE- 2) receptor. Although non-specific respiratory symptoms such as fever, loss of smell/taste, runny nose, and cough are most common, SARS-CoV-2 can lead to a systemic and multiorgan involvement, including the gastrointestinal tract. The liver is the second most frequently involved organ after the lung. Gastrointestinal symptoms such as diarrhea, anorexia, nausea, vomiting, loss of appetite and abdominal pain are also common. Abnormal liver function enzyme levels may also be observed. The liver is affected by direct infection of hepatocytes, medical therapy of the management, or by indirect means if there is an underlying co-morbid disease. However, there are significant differences between studies in the reporting of gastrointestinal and liver symptoms. The most frequently reported gastrointestinal symptom in COVID-19 disease is diarrhea, reported in 1-36% of patients. In this review, it is aimed to review the current data on the effects of COVID-19 on the liver.

Anahtar Kelimeler COVID-19, hepatitis, AST, ALT, childhood.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) insandan insana damlacık yolu (konuşurken, hapşırırken veya öksürürken saçılan sekresyonlar vb.), asılı damlacık çekirdekleri ve kontamine yüzeylere dokunma sonrası gözler, burun ve ağız mukozası ile temas sonrası bulaşabilen zarflı, tek zincirli bir RNA virüsüdür. Hücrelere anjiotensin converting enzim 2 (ACE- 2) reseptör aracılığı ile girmektedir. En sık ateş, koku/tat kaybı, burun akıntısı ve öksürük gibi non-spesifik solunum yolu semptomları görülse de SARS-CoV-2 enfeksiyonu gastrointestinal sistemi de içeren sistemik ve çoklu organ tutulumu ile giden bir tabloya yol açabilir. Karaciğer, akciğerden sonra ikinci sık tutulan organdır. İshal, anoreksi, mide bulantısı, kusma, iştah kaybı ve karın ağrısı gibi gastrointestinal semptomlar da sık görülmektedir. Anormal karaciğer fonksiyon enzim düzeyleri de gözlenebilir. Karaciğer hepatositlerin direk enfekte olmasıyla, tedavide kullanılan ilaçlar üzerinden ya da altta yatan bir ko-morbid hastalık varsa indirekt yollar ile etkilenir. Bununla beraber, gastrointestinal ve karaciğer semptomlarının bildirilmesinde, çalışmalar arasında ciddi farklılıklar söz konusudur. COVID-19 hastalığında da en sık bildirilen gastrointestinal semptom ishal olup, hastaların %1-36'sında bildirilmiştir. Bu derlemede COVID-19 hastalığının karaciğer üzerindeki etkilerine ilişkin güncel verilerin gözden geçirilmesi amaçlanmıştır.

Keywords *COVID-19, hepatit, AST, ALT, çocukluk çağı*

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen of 2019 novel coronavirus disease (COVID-19), has posed a serious threat to public health all over the world. The World Health Organization (WHO) has declared the outbreak of SARS-CoV-2 infection an international public health emergency. Respiratory system has been considered as the major damage caused by SARS-CoV-2 infection. However, gastrointestinal system has also been reported to occur during the course of the disease in severe cases.[1] It is not clear if the reason lay with the virus or the medications used in treatment of it. Also unclear is if COVID-19 makes existing liver disease worse.

SARS-CoV-2, the causative agent of the new coronavirus disease (COVID-19), which started in Wuhan, China in December 2019, has so far infected approximately 239.5 million people and caused a pandemic that resulted in the death of 4.89 million people.[1] SARS-CoV-2 infection is an RNA virus transmitted by droplet route. It enters cells via angiotensin converting enzyme 2 (ACE-2) receptor.[2,3]

The symptoms and severity of COVID-19 varies widely, but the majority of patients present with flu-like symptoms such as fever, cough, malaise, dyspnea, anosmia, and loss of taste.[4,5] Although mild symptoms are seen in most of the cases, it causes the development of acute respiratory distress syndrome (ARDS) in some patients. The course of the disease varies according to the patient's age, immune status and co-morbid diseases (hypertension, diabetes, chronic obstructive pulmonary disease, etc.). The incidence of severe disease has increased, especially in patients with co-morbidities. The incubation period is 2-11 days for other SARS viruses, while it is 4-5 days for SARS-CoV-2 disease. Symptoms may appear within 1-14 days of contact with the virus, but they're most common on the 4th and 5th days.[4-6] There are studies showing that asymptomatic patients are also contagious.[7]

Nucleic acid amplification methods (real-time reverse-transcriptase polymerase chain reaction, rRT-PCR), serological tests and computed tomography (CT) findings of SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swab samples are the most commonly used methods in the diagnosis of COVID-19.[8,9] In the identification and confirmation of COVID-19 cases; the rRT-PCR test is accepted as the gold standard test and is frequently used method in line with the protocol prepared by the World Health Organization (WHO).[10]

Since antibody tests cannot be used at an early stage in acute infection, their use in clinical diagnosis is limited. Tests which show antibody responses can be used for retrospective diagnosis by detecting the elevation of antibody levels in blood samples that are taken from patients in acute and convalescent periods in patients with negative SARS-CoV-2 RT-PCR results but with strong suspicion of COVID-19 disease.[7-11]

Other Coronaviruses, SARS-CoV-2 and Gastrointestinal System

In previous studies about SARS and Middle East Respiratory Syndrome (MERS) patients; it was determined that corona viruses invaded the gastrointestinal tract. In a study conducted in 2004, it was shown that SARS-CoV RNA was also detected in stool samples.[8] SARS- COV-2 shares the same genome structure 82% with SARS-CoV and 50% with Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[12]

A study in 2003, electron microscopic examination of autopsy and biopsy materials of the SARS virus showed that the virus was actively replicating in the small and large intestines.[13] Similarly, in a study conducted in 2017, MERS-CoV virus was shown to cause enteric infection and show high affinity to intestinal epithelium.[14] It has been shown that SARS-CoV-2 can colonize the gastrointestinal tract like other coronaviruses as a result of the detection of the first coronavirus case in the United States (USA) from sto-

ol and respiratory tract materials by rRT-PCR in 2020.[15]

In a meta-analysis, higher Ferritin values were found in patients with severe disease and deceased patients when patients with severe disease and mild disease were compared. It has been observed that there is a relationship between severe acute liver injury and high Ferritin value.[16] Similar to cytokine release, immune activation and inflammation caused by some systemic viral infections, high laboratory values (pro-inflammatory values and cytokine values) of COVID-19 patients have been detected.[17,18] Albumin is a negative acute phase reactant which is synthesized by the liver, has a down-regulation effect on ACE-2 receptors. It suggests that hypoalbuminemia may be associated with increased mortality. The reason for the increase in AST, ALT, bilirubin, GGT and ALP is not known exactly, but it should be kept in mind that liver damage due to the use of multiple drugs such as anti-virals, antibiotics, antipyretics and analgesics used in the treatment with cytokine storm may also have a possible effect on the deterioration in laboratory tests.[19]

It has been shown in many studies that COVID-19 disease affects different systems such as the cardiovascular system, nervous system and gastrointestinal system. It has been determined that SARS-CoV-2 has a very high affinity for the ACE-2 receptor.[7, 11-14, 20-23] SARS-CoV-2 also enters the cells of the gastrointestinal tract via ACE receptors. The abundance of ACE-2 receptors in the gastrointestinal tract (hepatocytes and cholangiocytes) makes it a potential target for SARS-CoV-2 disease. Kuppfer cells, on the other hand, do not have ACE-2 receptors. Biopsy results of patients infected with SARS-CoV-2 and undergoing liver biopsy showed an increase in the number of mitosis and ballooning degeneration in hepatocytes. This suggests that COVID-19 disease may induce apoptosis of hepatocytes. On the other hand, Kuppfer cells do not have ACE-2 receptors. Biopsy results of patients infected with SARS-CoV-2 and undergoing liver biopsy showed an increase in the number of mitosis and ballooning degeneration in hepatocytes. This suggests that COVID-19 disease may induce apoptosis of hepatocytes.

In a study conducted with children infected with SARS-CoV-2, liver transaminases were found to be higher in children less than 3 years of age than in children over 3 years of age.[24] This suggests that it may be related to the immature immune system. Data are limited because SARS-CoV-2 infection in children is mostly asymptomatic. The effect of cytokine storm (IL-6 and IL-10) is great in liver damage seen in adults. IL-6 and IL-10 values of children infected with SARS-CoV-2 were found to be similar in those with normal and high transaminase values.[24] While fatigue, fever and joint pain were detected in addition to respiratory system complaints in COVID-19 patients, gastrointestinal system symptoms such as anorexia, diarrhea, vomiting and abdominal pain were reported in many patients (figure 1). According to the data obtained from the analysis of published case series and studies related to the COVID-19 pandemic, 3% -79% of patients have gastrointestinal symptoms.[25] While the most common gastrointestinal symptom in adults was anorexia, diarrhea was the most common gastrointestinal symptom in both adults and children.

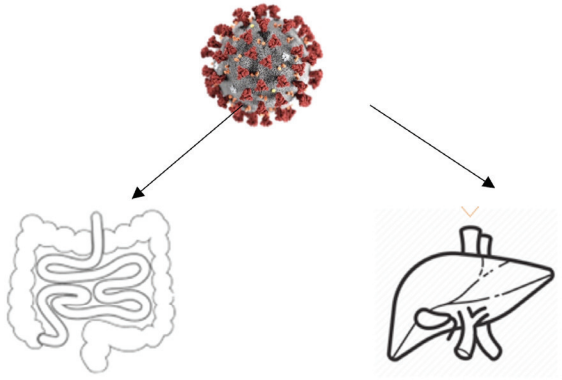

Figure 1: *Gastrointestinal system involvement and findings*

COVID-19 and Reflection of Liver Involvement in the Clinical Practice

Development of liver damage in COVID-19 patients is reflected in the laboratory as an increase in liver function enzymes (AST, ALT, bilirubin, etc.) and a decrease in serum albumin value. This has brought to mind the question of whether markers can be used to determine the severity and prognosis of COVID-19 disease, and many retrospective studies have been conducted on this subject. Various studies have reported that 14% -53% of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values may increase during the course of the disease, accompanied by a mild increase in bilirubin.[14]

The Mechanism of Liver Injury

The mechanism of liver damage hasn't clearly known, it is thought that it may cause direct invasion of hepatocytes by viruses, immune-mediated damage, toxicity of drugs used in the treatment, hypoxia, ischemia, systemic inflammatory syndrome (SIRS), sepsis, or exacerbation of underlying liver disease.[26] It has been determined that ACE-2 receptors, which are the target receptors for SARS-CoV-2, are highly expressed in epithelial cells of the gastrointestinal tract (gastric, duodenal and rectal).[4,5] ACE-2 receptors can be expressed in hepatic cholangiocytes and hepatocytes.[6] These receptors make gastrointestinal tract as a target for SARS-CoV-2 infection, which can actively infect and replicate. The intense affinity of the SARS-CoV-2 virus, especially to cholangiocytes, it's high binding rate to the ACE-2 receptor and it suggest that it's associated with impaired liver function.[12] In a meta-analysis of 3.772 patients obtained from 326 studies examining, SARS-CoV-2 and liver damage, it was concluded that there is a relationship between liver dysfunction and mortality.[27]

Medications such as hydroxychloroquine, immune modulators (tocilizumab, steroids, anakinra), anti-retroviral medications (remdesivir, favipravir, lopinavir), antibiotics (azithromycin, ceftriaxone) and antipyretics (paracetamol, ibuprofen), which are used in the treatment of COVID-19 disease, also have hepatotoxic effects. Patients are recommended to have close follow-up who have treatment with single and/or combined use of these potential hepatotoxic medications for possible liver damage.[26,28]

Histo-Pathology of Liver Injury

Moderate microvascular hepatosteatosis, mild portal and lobular activity were detected in liver biopsy material taken from a patient who died as a result of COVID-19 infection.[29] In another study, autopsy of four patients who died due to COVID-19 revealed mild sinusoidal dilatation in the middle zone of the liver, patchy hepatic necrosis and a slight increase in sinusoidal lymphocytes in the liver biopsy taken from the other two cases, direct SARS-CoV-2 RNA was detected.[30]

Clinical and Laboratory Findings of Liver Damage (Hepatitis) Due to COVID-19

In a study by Tian SF et al. with 148 COVID-19 patients; elevated liver function enzymes were found in 4 patients (37.2%).[12] Another study by Zhang et al. with 56 COVID-19 patients; showed an increase gamma-glutamyl transferase (GGT) value in 54% of the cases.[26] Liver function enzymes were elevated in 45 of 93 patients whose liver function enzymes were normal at the time of admission. The rate of use of lopinavir / ritonavir was higher and the length of hospital stay was longer in patients with elevated liver function enzymes.

In a study involving patients with COVID-19 in China, elevation in liver tests (AST, ALT, total bilirubin, GGT, etc.) was found in 76.3% of the patients, and this elevation was found in 21.5% of the patients while they were hospitalized. It has been reported to occur in the first two weeks. In another study, it was found that patients with biochemical findings suggestive of hepatocellular or mixed-type liver injury upon admission to hospital had a higher risk of progression to serious disease during their hospitalization.[31] In another study, liver function enzymes were found

to be elevated in 29% of deaths related to COVID-19.[32]

In a multicenter study of 1.099 patients, high AST levels were found in 112 (18%) patients without severe disease and 56 patients (39.4%) with severe disease. In addition, the rate of high ALT (28%) in patients with severe disease was found to be higher than those with mild disease (20%).[33] In another study, approximately half of the patients were found to have elevated GGT levels.[34]

Especially in studies from China, nearly half of the patients had gastrointestinal symptoms such as diarrhea, nausea, vomiting and abdominal pain, 20%-50% of COVID-19 patients had positive PCR testing in their stools, and SARS-CoV-2 was detected in some of the cases. It has been reported that it can be detected in feces for a long time (up to 30 days). This indicates that the coronavirus is excreted in the feces. Updated data have determined that SARS-CoV-2 RNA can be isolated from anal/rectal swabs and stool.[35,36]

Follow-up of Liver Damage (Hepatitis) due to SARS-CoV-2 in the Clinic

In most of the studies, it has been reported that liver dysfunction is mild, self-limiting, spontaneously regressed with supportive treatment, and has no effect on the course of COVID-19 disease.[37] Elevated levels of serum transaminase enzymes have also been explained by hepatotoxicity of drugs used in the treatment, cytokine storm and/or hypoxia associated with pneumonia.[37,38] The rate of liver dysfunction is not known exactly because there is not enough study with pediatric patients yet. It is known that children infected with SARS-CoV-2 infection have a milder disease and have a better prognosis than adults.

In a study conducted with 10 children born to mothers with COVID-19 pneumonia, elevated liver enzymes were found in only two children.[39] Rarely, mild increases in ALT and AST levels have been found in children infected with COVID-19. Because they are found to be normal in the vast majority of cases, the American Association for Liver Diseases Research recommends that all children with elevated liver enzymes must be evaluated for underlying liver diseases.[40] In addition; COVID-19 infection is more risky in chronic liver disease because of the immunosuppression in these patients. The effect of SARS-CoV-2 infection on the liver was more common in patients with non-alcoholic fatty liver disease and those with chronic liver disease.

Liver dysfunction has also been found in pediatric patients with COVID-19 infection.[37] In a study conducted with asymptomatic COVID-19 positive pediatric patients, isolated liver function enzymes were found to be elevated, and no other pathology was detected during their follow-up. The liver function test values of these patients regressed with supportive treatment, and they did not need further treatment.[1-5]

In COVID-19 disease patient who progresses with mild hepatic transaminase elevation; should be treated and liver enzymes must be closely monitored.

CONCLUSION

It has been determined that SARS-CoV-2 infection may be associated with different degrees of abnormal liver function tests, especially with transient and mildly elevated serum transaminase levels. It should be kept in mind that SARS-CoV-2 infection can also be seen in children as non-icteric hepatitis accompanying by mild upper respiratory tract infection. However, there are many studies that suggest that patients with chronic hepatitis, autoimmune liver diseases, or liver transplants patients more likely to progress severe COVID-19 disease. Therefore, close follow-up of liver function tests is recommended after the diagnosis of COVID-19 disease, especially in patients infected with SARS-CoV-2, who are in the risk group. Patients who do not have a known disease before, the causes of another underlying disease that may cause abnormal liver function enzymes should be considered, and further examination should be performed for differential diagnosis.

Declaration of Conflicting Interests

The authors declare that they have no conflict of interest.

Financial Disclosure

No financial support was received.

Author Contributions

MÇ and DÇ designed, wrote the article and reviewed the literature. ÖÖ contributed to writing and supervised/revised the article.

Kaynaklar

1. WHO Coronavirus (COVID-19) Dashboard, Situation by Region, Country, Territory & Area https://covid19.who.int/table
2. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-280.e8. doi:10.1016/j.cell.2020.02.052
3. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020; 12(1):8. doi: 10.1038/s41368-020-0074-x.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 382(18):1708-1720. doi: 10.1056/NEJMoa2002032.
5. Centers for Disease Control and Prevention (2020). People who are at higher risk for severe illness https://www.cdc.gov/coronavirus/2019-ncov/need-extraprecautions/people-at-higherrisk.html (Accessed on April 01, 2020).
6. Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020; 20(6):689-696. doi: 10.1016/S1473-3099(20)30198-5.
7. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med. 2020;382(10);970-1. https://doi.org/10.1056/nejmc2001468.
8. Li D, Wang D, Dong J, et al. False-negative results of real-time reverse-transcriptase polymerase chain reaction for severe acute respiratory syndrome coronavirus 2: Role of deep-learning-based ct diagnosis and insights from two cases. Korean J Radiol. 2020;21(4):505-8. doi: 10.3348/kjr.2020.0146.
9. Tahamtan A, Ardebili A. Real-time RT-PCR in COVID-19 detection: issues affecting the results. Expert Rev Mol Diagn. 2020; 20(5):453-4. https://doi.org/10.1080/14737159.2020.1757437
10. WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. Interim guidance 1-7, World Health Organization. [https://apps.who.int/iris/handle/10665/331501] (Accessed on 19/01/2021).
11. Hung IF, Cheng VC, Wu AK, et al. Viral loads in clinical specimens and SARS manifestations. Emerg. Infect. Dis. 2004; 10(9):1550-7. doi: 10.3201/eid1009.040058.
12. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol. Hepatol. 20205(5):428-430. doi: 10.1016/S2468-1253(20)30057-1.
13. Leung WK, To KF, Chan PK, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology 2003; 125(4):1011-7. doi: 10.1016/s0016-5085(03)01215-0.
14. Zhou J, Li C, Zhao G, et al. Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. Sci. Adv. 2017; 3(11):eaao4966. doi: 10.1126/sciadv.aao4966.
15. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-936. doi: 10.1056/NEJMoa2001191.
16. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 28; 395(10229): 1054–1062. doi: 10.1016/S0140-6736(20)30566-3.
17. García de Guadiana-Romualdo L, Morell-García D, Morales-Indiano C, et al. Characteristics and laboratory findings on admission to the emergency department among 2873 hospitalized patients with COVID-19: the impact of adjusted laboratory tests in multicenter studies. A multicenter study in Spain (BIOCOVID-Spain study). Scand J Clin Lab Invest. 2021; 81(3):187-193. doi: 10.1080/00365513.2021.1881997.
18. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, et al. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta. 2020;510:475–82. doi: 10.1016/j.cca.2020.08.019.
19. Doğan Ö, Devrim E. Tanı ve İzlemde Laboratuvar Testleri. COVID-19 içinde Ed: Memikoğlu O, Genç V. E-Kitap Ankara Üniversitesi Basımevi, 2020; 35-40
20. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. New Engl J Med. 2020;382(8):727-733. doi: 10.1056/NEJMoa2001017.
21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052.
22. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395(10224):565-574. doi: 10.1016/S0140-6736(20)30251-8.
23. Walls AC, Park YJ, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020; 181(2):281-292.e6. doi: 10.1016/j.cell.2020.02.058
24. Zhou YH, Zheng KI, Targher G, et al. Abnormal liver enzymes in children and infants with COVID-19: A narrative review of case-series studies. Pediatr Obes. 2020; 15(12): e12723. doi: 10.1111/ijpo.12723.
25. Tian Y, Rong L, Nian W, et al. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020; 51(9): 843-851. doi: 10.1111/apt.15731.
26. Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998-1004. doi: 10.1111/liv.14435.
27. Zeng-hong W. Dong liang Y. A meta-analysis of the impact of COVID-19 on liver dysfunction. Eur J Med Res. 2020;25(1):54. doi: 10.1186/s40001-020-00454-x.
28. Olry A, Meunier L, Délire B, et al. Drug Induced Liver Injury and COVID 19 Infection: The Rules Remain the Same. Drug Saf. 2020; 43(7):615-617. doi: 10.1007/s40264-020-00954-z.
29. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respir Med. 2020;8(4)420-422. doi: 10.1016/S2213-2600(20)30076-X.
30. Tian SF, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through post-mortem core biopsies. Modern Pathology. 2020; 33(6):1007-1014. doi: 10.1038/s41379-020-0536-x.
31. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507-513. doi: 10.1016/S0140-6736(20)30211-7.
32. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 2020. 382(18):1708-1720. doi: 10.1056/NEJMoa2002032 .
33. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir. Med. 2020; 8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5.
34. Schaefer EAK, Arvind A, Chung RT, et al. Interrelationship Between Coronavirus Infection and Liver Disease. Clinical Liver Disease 2020; 15(5):175-180. doi: 10.1002/cld.967.
35. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg. Microbes. Infect. 2020; 9: 386- 389. doi: 10.1080/22221751.2020.1729071.
36. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat. Med. 2020. 26(4):502-505. doi: 10.1038/s41591-020-0817-4.
37. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020; 5: 529-530. doi: 10.1016/S2468-1253(20)30084-4.
38. Wu J, Song S, Cao HC, Li LJ. Liver diseases in COVID-19: Etiology, treatment and prognosis. World J Gastroenterol 2020; 26: 2286-2293. doi: 10.3748/wjg.v26.i19.2286.
39. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9:51-60. doi: 10.21037/tp.2020.02.06.
40. American Association for the Study of Liver Diseases . Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic. https://www.aasld.org/about-aasld/covid19-resources. Accessed April 14, 2020.