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Effect of Covid-19 on liver enzymes

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Abstract

So far, scientific data has confirmed that the at-risk group with increased likelihood and severe course of infection with the Coronavirus includes elderly patients and patients with chronic cardiovascular diseases such as high blood pressure, coronary heart disease and diabetes. Little is known about the effects of other chronic diseases, particularly liver disease. However, it is already clear that patients with severe cirrhosis and cirrhosis, and patients after liver transplantation are also a group at increased risk of infection and a severe course of COVID-19. Therefore, they are strictly described as self-isolation and reduced social contacts. We analyzed the available data on the effect of SARS-CoV-2 infection on the course of chronic liver disease and made preliminary conclusions Published in Guidelines for Physicians Treating Patients with Liver Disease, it contains basic principles for medical tactics during a pandemic. We bring to your attention these recommendations in a summary.

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Key words

SARS-CoV-2, ACE-2, ALT ,Patients , hepatitis B , COVID-19, liver

1.Intrudction

Coronaviruses are widespread in nature and are the causes of various colds (up to 25%). Most of them cause a viral infection that does not cause serious harm to health, but some, such as SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome) coronavirus - coronavirus of the Middle East respiratory syndrome) lead to the development of severe respiratory syndrome with high mortality [1, 2.] In nature, many species of bats are the natural host for coronaviruses. Evolving due to mutations, pre-adaptation processes they periodically cause epidemics in human populations. So, the outbreak of unknown pneumonia that began at the end of December 2019 in China, caused the development of an emergency in the field of public health, which subsequently led to a pandemic caused by new coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus - severe coronavirus acute respiratory syndrome) [2, 3]. The World Health Organization (WHO) officially named SARS-CoV-2 infections, - COVID-19 ("Coronavirus Disease 2019 "- a disease caused by the new coronavirus 2019). The mortality from this infection is 0.5-3% [4].

Liver dysfunction in COVID-19 patients may be due to the direct effect of the virus or the secondary effect of factors such as systemic inflammatory response, hypoxia (associated with lung damage), multiple organ failure, the use of hepatotoxic drugs [5]. From the first days of observation of patients with coronavirus infection, doctors of clinical specialties pay attention to an increase in biochemical indicators characterizing liver damage, and specialists in radiation diagnostics (mainly CT) note in a number of patients a decrease in the density of liver tissue, which is always at the level of chest scanning. When analyzing autopsy material of 2000 patients from Moscow clinics, the proportion of

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concomitant diseases that directly the effect on the liver was quite large: obesity (n = 385), chronic hepatitis / cirrhosis liver (n = 24) [6]. However, fails to explain changes in the liver only by these premorbid conditions. In studies in dynamics, attention is drawn to an increase in liver density, which may indicate a transient nature of the changes. Morphological changes It has been established that SARS-CoV-2 uses the angiotensin-converting enzyme receptor 2 (ACE-2) to enter the target cell.[7] Surface expression of ACE-2 is most common in alveolar epithelial cells lungs, enterocytes of the small intestine, vascular endothelium, also in many other cells, including in cholangiocytes [8]. It is assumed that the interaction of the virus with cholangiocytes can lead to their dysfunction and induce systemic an inflammatory reaction leading to liver damage [9]. But at the same time, pathological changes predominate directly in the hepatocytes, and not in the liver ducts.Liver biopsies of COVID-19 patients show mild microvesicular steatosis and moderate lobular and portal activity (inflammation with areas of focal necrosis).[10]

Another histopathological study reports moderate sinusoidal dilatation and minimal lymphocytic infiltration [11].

However, these changes are nonspecific and may be caused by both SARS-CoV-2 infection and hypoxemia, which is characteristic to varying degrees

for patients with lung disease with COVID-19 or drug damage to the liver. Important note that none of these samples contained found intranuclear or intracytoplasmic viral inclusions, which are described, for example, in alveolocytes.[12]

Fig 1 shown Normal ranges for selected liver tests

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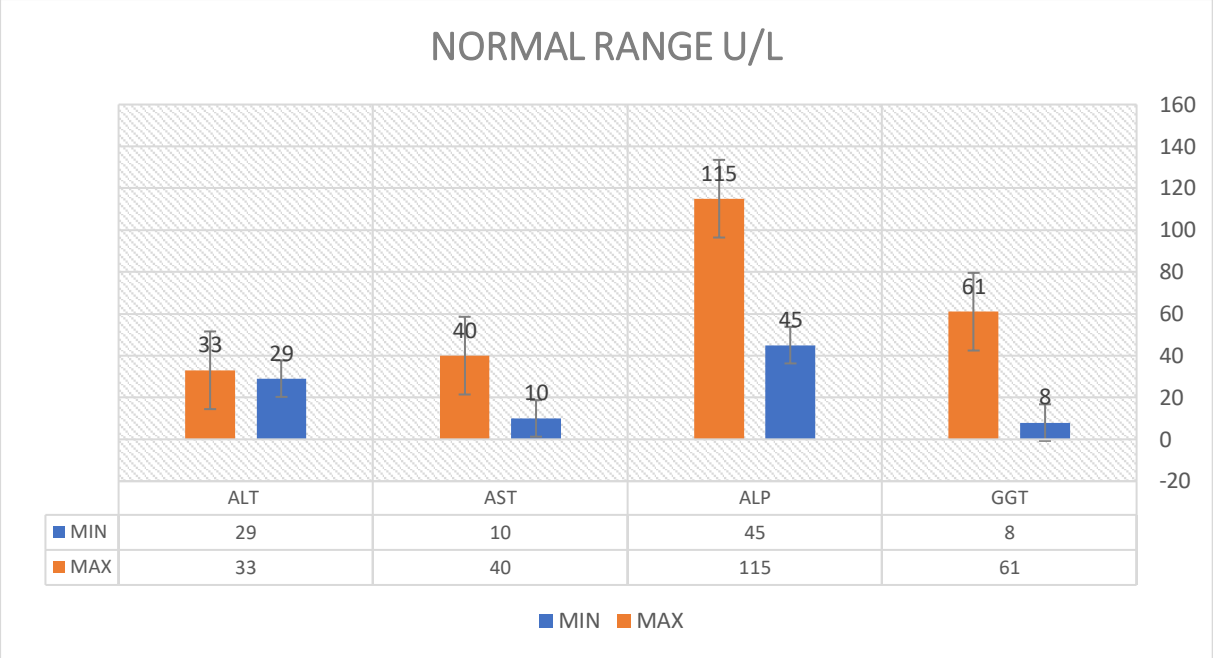

1.1 Summary of recommendations: How does Covid-19 disease affect the liver

Published studies did not list chronic liver disease as risk factors for complications, but in cases where the patient had high Alanine Aminotransferase levels, and low albumin and platelet counts, the risk of dying from coronavirus infection was higher.

It remains unclear whether this change in laboratory parameters is associated with a more severe course of infection or only with the presence of chronic liver disease. This laboratory picture may reflect liver damage caused by the virus itself, or an overactive inflammatory response of the body to the virus, followed by disturbances in the blood clotting system. All these facts still need clarification.

It is known that systemic viral infections, including COVID19, in which the virus enters the body and spreads through the bloodstream, can cause a short-term increase in ALT levels without much damage to liver function. This change in biochemical parameters can reflect the general activation of immunity and inflammation caused by inflammatory proteins (cytokines - protein substances that immune cells secrete in response to the penetration of the virus into the body).

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According to Chinese Physician, critically ill patients with COVID-19 often show signs of liver impairment Therefore, patients with cirrhosis and COVID-19 are at a higher risk of not decompensating and developing liver failure [13].

EASL COVID19 recommendations Additionally, scientists have found that SARS-CoV-2 can directly infect liver cells and the cells lining the bile ducts inside and outside the liver (bile cells), because they contain, albeit in a low concentration, a special enzyme (angiotensin converting). That the SARS-CoV-2 virus uses to enter the cell. This may explain the detection of the virus in stool. The same enzyme is found in the cell membranes of the intestine, kidneys, and lungs, which may play a major role in the risk of developing acute respiratory distress [14].

So far, experts have no information confirming that SARS-CoV-2 infection can cause liver damage in healthy people, but for people with chronic liver disease, it is an additional harmful factor.

The effect of viral COVID 19 infection on the course of chronic liver disease Patients with chronic liver disease need increased attention of doctors during an outbreak, because against the background of the worsening of their disease, the risk of infection with the COVID 19 virus increases not only, but also its more severe course.

In patients with severe cirrhosis and cirrhosis, a higher risk of infection is due to the immune deficiency condition. The same applies to liver transplant patients and patients with autoimmune liver disease who receive immunosuppressive therapy.

On the other hand, there is an assumption, not yet proven through scientific research, that taking medications to suppress immunity might provide some protection against the over-activation of immune system cells and the release of more cytokines than necessary. This actually causes the hyperinflammatory syndrome, which leads to profound disturbances in the functioning of the body.

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Scientific data linking chronic liver disease to the pathway of SARS-CoV-2 infection remains insufficient for a general summary and there are still problems that are not fully understood, but there is also data confirmed by research and scientific publications [15].

1.2 Information that has already been confirmed by scientific evidence

1. There is no convincing evidence that people living with hepatitis B or hepatitis C are at the highest risk of contracting COVID-19, but their infection is much more severe and contributes to the progression of liver disease
2. Patients with non-alcoholic fatty liver disease (NAFLD), especially steatohepatitis (NASH) who suffer from comorbid metabolic diseases such as diabetes, hypertension and obesity, are at increased risk of more severe COVID-19.
3. It is not recommended to reduce immunosuppressive therapy in patients with autoimmune liver diseases. Its reduction should be considered only with the development of special conditions and always after consultation with a doctor (for example, in the case of a severe course of COVID-19; a decrease in the number of lymphocytes in the blood or the development of bacterial or fungal superinfection due to drug treatment).
4. In patients with compensated cirrhosis, consideration should be given to delaying hepatocellular carcinoma monitoring and screening for esophageal varices. It is recommended to conduct a risk assessment for the presence of varicose veins using non-invasive methods - using laboratory tests to control platelet count and performing shear wave ultrasound elastography of the liver.
5. Patients with hepatocellular failure and after liver transplantation are at very high risk and are at significant risk of contracting and more severe COVID-19 infection.

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In addition, the COVID-19 epidemic increases the pressure on healthcare systems around the world, which could negatively affect the treatment of patients with chronic liver disease who require ongoing medical attention [16,17].

1.3 Morphological changes

It has been established that SARS-CoV-2 uses the angiotensin-converting enzyme receptor 2 (ACE-2) to enter the target cell.[4 ,3] Surface expression of ACE-2 is most common in alveolar epithelial cells lungs, enterocytes of the small intestine, vascular endothelium, also in many other cells, including in cholangiocytes [18]. It is assumed that the interaction of the virus with cholangiocytes can lead to their dysfunction and induce systemic an inflammatory reaction leading to liver damage [19]. But at the same time, pathological changes predominate directly in the hepatocytes, and not in the liver ducts. Liver biopsies of COVID-19 patients show mild microvesicular steatosis and moderate lobular and portal activity (inflammation with areas of focal necrosis) [20]. Another histopathological study reports moderate sinusoidal dilatation and minimal lymphocytic infiltration However, these changes are nonspecific and may be caused by both SARS-CoV-2 infection and hypoxemia, which is characteristic to varying degrees for patients with lung disease with COVID-19 or drug damage to the liver. Important note that none of these samples contained found intranuclear or intracytoplasmic viral inclusions, which are described, for example, in alveolocytes [21]. According to pathologists, in the liver, fatty degeneration of different severity, petechial hemorrhages, in some cases - lymphoid infiltration of the portal tracts and extensive necrosis, which are most likely associated with angiopathies [22].

1.4 Laboratory changes

In the vast majority of cases, with an increase in laboratory liver signs and changes on computed tomography, patients do not notice any clinical manifestations, such as symptoms of dyspepsia or jaundice [23]. Some discomfort in the right hypochondrium is possible with an increase in the size of

the organ, but this is not always associated with the presence of steatosis. Liver damage in COVID-19 is manifested in a moderate increase in the levels of serum aminotransferase (AST) and alanine aminotransferase (ALT), accompanied by a moderate increase in the level of total bilirubin [24]. As a rule, an increase in amine transporters is observed 1-3 times from the upper bound of the base. In a study by Q. Cai et al. A normal level of ALT was observed in 49.79%, and AST in 63.09% of patients. In addition, the authors found an increase in gamma-glutamyl transferase (GGT) in 39.06% of cases [25]. Being a sign of cholestasis, GGT may indirectly indicate possible damage to the cells of the bile ducts. In this regard, it is desirable to consider other signs, the most accessible of which is alkaline phosphatase The authors declare no conflicts of interest. Vinokurov A.S., Nikiforova M.V., Oganesyan AA, Vinokurova O.O., Yudin A.L., Yumatova E.A. Covid-19. Liver damage - features of perception and possible causes. Medical visualization. 2020; 24 (3): 26--36. https://doi.org/10.24835/1607-0763-2020-3-26-36 Received: 12.06.2020 Accepted for publication: 09/03/2020. Published Online: 09/30/2019 28 Medical Visualization 2020, Vol. 24, Issue 3, Original Research |

The parent substance there is also an increase in the level of lactate dehydrogenase (LDH) up to 399-447 units / liter in patients with an acute course of the disease [11, 12]. LDH is a cytoplasmic glucose-soluble enzyme present in nearly all tissues [13], mostly in the liver, kidneys, lungs, heart muscle, and skeletal muscles [14]. In case of liver damage, attention should be paid to an increase in the level of LDH-4 and LDH-5 enzymes [15, 16]. LDH is also known to be an independent mortality factor for patients with severe acute respiratory syndrome [13]. However, in the absence of separation of the different parts of LDH in practice, the 'contribution' of liver damage to the development of this condition remains unclear. No significant increase in the level of bilirubin, either bound or free, was observed in the publications under consideration.

1.5 Possible causes of swollen liver in COVID-19

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ACE2 receptors are found in organs throughout the body, including the heart, kidneys, liver, and central nervous system and The barbed protein SARS-CoV-2, which stands out from the virus, binds to ACE2, which acts as a "door" to provide access to the inside of human cells. Once inside the cell, the virus hijacks the cellular machinery of reproduction, kills the host cell [26].

ACE2 is found abundantly on the surface of lung cells, making the lungs a primary target for SARS-CoV-2. However, epithelial cells of the bile duct and liver also express ACE2, providing an easy access point for SARS-CoV-2 to bind directly to ACE2-positive bile cells and disrupt liver function. Elevated levels of AST and ALT have been observed in patients with COVID-19, indicating some degree of liver impairment caused by the virus [27].

a neighing virus with a corona-like S-glycoprotein. The genome-wide sequence of the SARSCoV-2 virus has shown that it is 96% similar to the SARS-like coronavirus in bats. Also given the virus is 79.5% identical to SARS-CoV [28], and some encoded proteins, such as the main proteinase of the coronavirus, papain-like proteinase and RNA-dependent RNA polymerase [29], have 96% similar to SARS-CoV. In view of their close relationship, it is believed that the pathogenetic mechanisms of infection in SARS-CoV and SARS-CoV-2 act on the same principle.To enter the host cell and ensure fusion of the virus membrane with the host cell membrane during infection with SARS-CoV-2 uses a surface spike glycoprotein (S). S-glycoprotein is a trimeric protein. It plays a key role in ensuring the survival of coronaviruses as not only acts as an important functional part of the virion, but and fully assures mergers and acquisitions with the membranes of the host cell. In addition, S-protein, which is the largest surface [30].

1.6 Hepatotoxic drugs

A few medications have been utilized with an end goal to treat COVID-19 or its manifestations, like antipyretics, anti-toxins, antiviral medications and steroids. A portion of these medications showed promising outcomes, while others were

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less effective. Medicine instigated liver injury has been seen to be the reason for a portion of the liver irregularities saw with COVID-19 [31]. Histology uncovers gentle microvascular steatosis and gentle hepatitis that may reflect drug harm to the liver from infection treatment or side effects Despite the long history of acetaminophen as the most well-known reason for intense and poisonous liver disappointment, it has been the medication of decision for treating the fever and muscle torment related with COVID-19. However, acetaminophen has been associated to be the reason with the medication initiated liver injury in COVID-19 patients. Non-steroidal mitigating drugs (NSAIDs), another medication regularly utilized for fever and muscle torment, have not been utilized as much as acetaminophen in treating manifestations of COVID-19, as they were at first idea to worsen the infection [32].

1.7 Systemic inflammatory response

A new study has linked certain symptoms of the Coronavirus with the immunity that patients may develop after surviving the deadly virus, according to the researchers, suffering from specific symptoms during the course of the disease can be a sign that a person is more likely to develop a longer, "lasting" immunity against the Corona virus [33]

Research conducted suggested that hospitalized Corona patients have higher levels of antibodies against the new Corona virus compared to non-hospital patients [34]. The results of the study were published as a preprint and have not yet been subjected to peer review [36].

Having a fever is one of the most common symptoms of corona. In some cases, people infected with Coronavirus develop more severe symptoms such as a high temperature, severe cough and shortness of breath. According to the new research, a high fever could be a sign that your immune response is generating high levels of antibodies and The more inflammatory cytokines are released, the greater the volume of tissue and organ injury and death. Therefore, a cytokine storm is seen as a progression of the disease that can affect the lungs, intestines,

and liver (as indicated by elevated liver enzymes) and lead to death [37] Currently, COVID-19 is considered to be a systemic disease with impaired immune system function, and mainly affects the lungs, as well as the heart, kidneys and intestines. Acute forms of the disease are associated with hyperimmune inflammation, impairment of the renin-angiotensin-aldosterone system, the development of endothelial dysfunction and special forms of vasculopathy (thrombotic microangiopathy and intravascular coagulopathy). This condition, according to a number of experts, should be called a thrombophilic inflammatory process, or coagulopathy associated with COVID-19.

Three forms of symptom manifestation and the SARS-CoV-2 cycle have been reported:Mild (no pneumonia or mild pneumonia)

- 81% of cases; Severe (eg, shortness of breath, hypoxia, or> 50% lung damage during imaging within 24-48 hours)
- 14%; Very severe (with the development of acute respiratory syndrome, respiratory failure or multiple organ dysfunction)
- 5%. The overall case fatality rate was 2.3%; In non-critical cases, deaths were not recorded

1.8 Severe hypoxia

Respiratory failure is a hallmark of COVID-19. Therefore, hepatitis caused by hypoxia is common in severe cases. Severe hypoxia, hypoxia and hypovolemia are the main cause of ischemic liver damage / hypoxia in cases of COVID-19 with acute lung failure and / or shock. This liver injury is associated with metabolic acidosis, excess calcium, and changes in mitochondrial membrane permeability and is usually manifested by elevated cytolysis.[32]

In addition, SARS-CoV-2 non-structural proteins are hypothesized to modulate hemoglobin structure in erythrocytes, resulting in impaired oxygen transport, iron disintegration, porphyrin formation, and increased ferritin levels. This effect can lead to an increase in inflammatory processes in the lungs, the development of

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oxidative stress, hypoxemia, hypoxia, symptoms of acute respiratory distress syndrome and hypoxia in multiple organs [38].

1.9 Medical damage to the liver

The most common cause of liver damage in COVID-19 is associated with drug-induced liver damage, which results from the use of cause-directed therapy for SARS-CoV-2 infection and pathogen therapy for COVID-19.[20 ,19]

During an epidemic, initial clinical guidelines recommended drugs to treat SARS-Cov-2 infections, some of which, including lopinavir / ritonavir, hydroxychloroquine, azithromycin, umifenovir, famipiravir, and recombinant interferon beta-1b, have potential hepatotoxicity

The hepatotoxicity of hydroxychloroquine has been described in isolated clinical observations in the treatment of patients with systemic lupus erythematosus, late cutaneous porphyria, rheumatoid arthritis, and malaria. According to the Liver Tox Registry, Hydroxychloroquine belongs to Class C and is likely to cause liver-specific damage.[34]

Lopinavir / ritonavir is an antiretroviral drug that has a well-known and well-studied drug-drug interaction with immunosuppressant drugs. It should not be administered concomitantly with mTOR inhibitors When used simultaneously with calcineurin inhibitors (cyclosporine, tacrolimus), the concentration of lopinavir / ritonavir should be carefully monitored. There is evidence for the use of the drug in patients with cirrhosis. The risk of hepatotoxicity is low in patients with chronic liver disease. It is not recommended for use in patients with decompensated cirrhosis. According to the LiverTox Registry, lopinavir is Class D, and ritonavir is Class C.[34 ,26]

Perhaps, in addition to the direct hepatotoxicity of drugs, the possibility of developing idiopathic (immune-mediated) liver damage must be determined separately, the most common cause being antibiotics.[35]

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Be aware of drug interactions with patients with comorbidities and frequently use the Liverpool database of drugs that can be used in the treatment of Covid-19 .[36]

Accordingly, all patients receiving cause-and-disease treatment for COVID-19 need to monitor hepatic parameters to prevent severe hepatitis chemotherapy in patient's treatment phase.

2. CONCLUSION

COVID-19 is a systemic disease that dysfunctions in the immune system, and mainly affects the lungs, as well as the heart, kidneys, intestines, liver and spleen. The mechanisms of liver damage that occur during SARS-CoV-2 infection are still poorly understood.

Among the main pathogenic effects on the liver, the following should be highlighted:

Activation of immunity and inflammation induced by circulating cytokines with the onset of a cell storm and the failure of many organs;

Direct cytotoxicity due to the active reproduction of the virus in hepatocytes with the participation of ACE2 as a receptor for its introduction into the cell;

Acute hypoxia, which leads to an increase in inflammatory processes, oxidative stress, hypoxemia, hypoxia, the development of symptoms of acute respiratory distress syndrome and hypoxia in multiple organs;

Drug damage to the liver as part of direct drug hepatotoxicity and individual (immune) harm; Reactivation of pre-existing liver disease (hepatitis B, C, and E), development of NAFLD, progression of cirrhosis and decompensation.

Timely anti-inflammatory treatment for COVID-19, careful clinical monitoring is critical and should be individualized based on comorbidity and immune status in order to achieve best results.

The liver enzyme changes in COVID-19 are usually temporary. There were no fatal outcomes directly related to hepatic failure in non-chronic patients.

All patients who undergo COVID-19 need further monitoring to assess the long-term consequences.

References

1. Noris, M., Benigni, A. and Remuzzi, G., 2020. The case of complement activation in COVID-19 multiorgan impact. Kidney international

2. Zaim, S., Chong, J.H., Sankaranarayanan, V. and Harky, A., 2020. COVID-19 and multi-organ response. Current problems in cardiology, p.100618.

3. Rod, J.E., Oviedo-Trespalacios, O. and Cortes-Ramirez, J., 2020. A brief-review of the risk factors for covid-19 severity. Revista de saude publica, 54, p.60.

4. Kreivenaite, E., Gedgaudas, R., Valantiene, I., Mickiene, A. and Kupcinskas, J., 2020. COVID-19 in a Patient with Liver Cirrhosis. Journal of gastrointestinal and liver diseases: JGLD, 29(2), pp.263-266.

5. Agren, D., 2020. Understanding Mexican health worker COVID-19 deaths. The Lancet, 396(10254), p.807.

6. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X. and Guan, L., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet, 395(10229), pp.1054-1062.

7. Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D.S. and Du, B., 2020. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine, 382(18), pp.1708-1720.

8. Yang, F., Shi, S., Zhu, J., Shi, J., Dai, K. and Chen, X., 2020. Analysis of 92 deceased patients with COVID-19. Journal of medical virology, 92(11), pp.2511-2515.

9. Mao, R., Qiu, Y., He, J.S., Tan, J.Y., Li, X.H., Liang, J., Shen, J., Zhu, L.R., Chen, Y., Iacucci, M. and Ng, S.C., 2020. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic

review and meta-analysis. The lancet Gastroenterology & hepatology, 5(7), pp.667-678.

10. Sultan, Shahnaz, Osama Altayar, Shazia M. Siddique, Perica Davitkov, Joseph D. Feuerstein, Joseph K. Lim, Yngve Falck-Ytter, and Hashem B. El-Serag. "AGA Institute rapid review of the GI and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the consultative management of patients with COVID-19." Gastroenterology (2020).

11. Jothimani, D., Venugopal, R., Abedin, M.F., Kaliamoorthy, I. and Rela, M., 2020. COVID-19 and Liver. Journal of hepatology.

12. Schaefer, E.A., Arvind, A., Bloom, P.P. and Chung, R.T., 2020. Interrelationship between coronavirus infection and liver disease. Clinical Liver Disease, 15(5), p.175.

13. Mantovani, A., Beatrice, G. and Dalbeni, A., 2020. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. Liver International, 40(6), pp.1316-1320.

14. Wang, Y., Liu, S., Liu, H., Li, W., Lin, F., Jiang, L., Li, X., Xu, P., Zhang, L., Zhao, L. and Cao, Y., 2020. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. Journal of hepatology, 73(4), pp.807-816.

15. T.N. Chau, K.C. Lee, H. Yao, T.Y. Tsang, T.C. Chow, Y.C. Yeung, *et al*. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology, 39 (2004), pp. 302-310

16. Elmunzer, B.J., Spitzer, R.L., Foster, L.D., Merchant, A.A., Howard, E.F., Patel, V.A., West, M.K., Qayad, E., Nustas, R., Zakaria, A. and Piper, M.S., 2020. Digestive manifestations in patients hospitalized with COVID-19. MedRxiv.

17. Poissy, J., Goutay, J., Caplan, M., Parmentier, E., Duburcq, T., Lassalle, F., Jeanpierre, E., Rauch, A., Labreuche, J. and Susen, S., 2020. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation, 142(2), pp.184-186.

18. Muhovic, D. et al. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. Liver Int. 40, 1901–1905 (2020).

19. Mahamid, M., Mader, R. & Safadi, R. Hepatotoxicity of tocilizumab and anakinra in rheumatoid arthritis: management decisions. Clin. Pharmacol. 3, 39–43 (2011).

20. Beigel, J. H. et al. Remdesivir for the treatment of Covid-19 - final report. N. Engl. J. Med. 383, 1813–1826 (2020).

21. Montastruc, F., Thuriot, S. & Durrieu, G. Hepatic disorders with the use of remdesivir for coronavirus 2019. Clin. Gastroenterol. Hepatol. 18, 2835–2836 (2020).

22. WHO Solidarity Trial Consortium. et al. Repurposed antiviral drugs for Covid-19 - Interim WHO Solidarity Trial Results. N. Engl. J. Med. 384, 497–511 (2021).

23. Ponziani, F. R. et al. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2 positive patients. Aliment. Pharmacol. Ther. 52, 1060–1068 (2020).

24. Yip, T. C. F. et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut https://doi.org/10.1136/gutjnl-2020-321726 (2020).

25. Weber, S. et al. Liver function test abnormalities at hospital admission are associated with severe course of SARS-CoV-2 infection: a prospective cohort study.

26. Ding, Z. Y. et al. Association of liver abnormalities with in-hospital mortality in patients with COVID-19. J. Hepatol.

27. Zhang, Y. et al. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int.* **40**, 2095–2103 (2020)

28. Yadav, D. K. et al. Involvement of liver in COVID-19: systematic review and meta-analysis. Gut https://doi.org/10.1136/gutjnl-2020-322072 (2020).

29. Lei, F. et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatology 72, 389–398 (2020). Multicentre retrospective cohort study of 5,771 patients hospitalized with COVID-19 in China describing longitudinal patterns in liver biochemistry.

30. Wang Y, Liu S, Liu H, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol*. 2020 doi: 10.1016/j.jhep.2020.05.002.

31. Bangash, M. N. et al. SARS-CoV-2: is the liver merely a bystander to severe disease? J. Hepatol. 73, 995–996 (2020).

32. Noor, M. T. & Manoria, P. Immune dysfunction in cirrhosis. J. Clin. Transl. Hepatol. 5, 50–58 (2017).

33. Pose, E. et al. PD-L1 is overexpressed in liver macrophages in chronic liver diseases and its blockade improves the antibacterial activity against infections. Hepatology https://doi.org/10.1002/hep.31644 (2020).

34. American Liver Foundation. [Internet]. New York: American Liver Foundation; c2017. Liver Function Tests; [updated 2016 Jan 25; cited 2017 Mar 18]; [about 3 screens]. Available from: http://www.liverfoundation.org/abouttheliver/info/liverfunctiontests/

35. Hinkle J, Cheever K. Brunner & Suddarth's Handbook of Laboratory and Diagnostic Tests. 2nd Ed, Kindle. Philadelphia: Wolters Kluwer Health, Lippincott Williams & Wilkins; c2014. Alanine Aminotransferase (ALT); p. 31.

36. Friedman LS. Approach to the patient with abnormal liver and biochemical function tests. https://www.uptodate.com/contents/search. Accessed Jan. 17, 2020.

37. Kwo PY, et al. ACG clinical guideline: Elevation of abnormal liver chemistries. American Journal of Gastroenterology. 2017; doi:10.1038/ajg.2016.517.

38. G. Feng, K.I. Zheng, Q.Q. Yan, R.S. Rios, G. Targher, C.D. Byrne, *et al*. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol, 8 (2020), pp. 18-24

39. Y. Ding, L. He, Q. Zhang, Z. Huang, X. Che, J. Hou, *et al*. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol, 203 (2004), pp. 622-630