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Liver Injury in Covid-19: Etiology, Treatment, Prognosis and Challenges

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Abstract: *Since its outbreak in December-2019, in Wuhan-China, the corona virus disease (COVID-19) caused by severe acute respiratory syndrome corona virus-2 (SARS- CoV-2) has become a global threat to human health with confirmed cases exceeding 24 Million and nearly 8,22,000 deaths reported worldwide as of August 27, 2020. During previous SARS epidemic, as per studies around 60% patients suffered with various degrees of liver damage. Most of the studies on COVID-19 focused on the lung injury of COVID-19, however recent studies are unfolding the fact that liver injury is also a major effect of COVID-19 in patients. This review summarizes the available data on liver abnormalities related to COVID-19 and critically evaluates the possible causes of livery injury and provide recommendations and references for clinical treatment and management.*

Keywords: *COVID-19, SARS-CoV2, Liver Injury, Cholangiocytes, Ace-2.*

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I. Introduction

Corona viruses are single stranded enveloped RNA viruses, of family Coronaviridae and subfamily Orthocoronavirinae. Two corona viruses severe acute respiratory syndrome corona virus (SARS-CoV) and middle eastern respiratory syndrome corona virus (MERS-CoV), caused epidemics in the years 2003 and 2012 respectively.The recent pandemic Covid-19 is caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV2) which was labelled by International Taxonomy Group.

It is known that these viruses tend to target the upper respiratory tract causing mild to severe symptoms and also death in numerous cases. However recently there has been some insight into the impact of SARS-CoV2 on the other organs as number of studies and reports have indicated that more than half of the patients suffering from COVID-19 showed different stages of liver injury. Chau TN et al reported that more than 60% of patients suffering from COVID-19 are showing abnormal liver functions.

A recent study stated that SARS-CoV2 virus may bind to the angiotensin converting enzyme 2 (ACE2) on the cholangiocytes,leading to cholangiocyte dysfunction thus resulting in systematic inflammatory response leading to liver injury. One more factor that may result in liver injury is hepatotoxicity of drugs used for treatment. In some studies elevated levels of Alanine aminotransferase(ALT) and Aspartate aminotransferase(AST) in the patients were also reported ranging from 14% - 53%. [4,5,6] Concentrations of pro inflammatory cytokines in the serum, along with C reactive proteins TNF- α, IL-6 were seen in elevated levels in most of the severe cases which indicates that disease severity may be associated with cytokine storm syndrome. [7,8]

Hence the purpose of this review is to clarify the available data on liver abnormalities associated with COVID-19 and evaluate the possible causes and association between current medication and liver damage and provide a reference for management.

COVID-19 AND HEPATIC DYSFUNCTION:

It is fascinating to know about the prognosis and pattern of liver injury in COVID-19. Involvement of liver in COVID-19 may be related to direct cytopathic effect of the virus or maybe drug induced injury or an immune reaction. As there is an high expression of Ace2 in cholangiocytes, the liver is thus a major target for SARS-CoV2. Other than this COVID-19 is also causing worsening of underlying liver diseases in patients, leading to liver failure with increased death rate. In severely ill patients, hepatic dysfunction was significantly higher and resulted in increased mortality.

Various studies were carried out reporting Hepatic manifestations in COVID-19. Some of those studies are:

AUTHORS	COUNTRY	AUTHOR COMMENTS
WU et al.[9]	CHINA	7 Patients had underlying CLD. Bilurubin was much higher In patients with ARDS related death.
ZHANG et al.[10]	CHINA	Mortality rate was 1.7%
CAO W et al.[11]	CHINA	Higher levels of ALT & AST in severe COVID-19 patients
FAN et al. [12]	CHINA	Patients with abnormal LFT had longer hospital stay
ARENTZ et al.[13]	USA	3 patients (14.7%) developed acute liver injury
WANG et al.[14]	CHINA	3.9% patients had underlying Chronic liver disease.
CHEN et al.[15]	CHINA	High ALT & AST in deceased patients. High mortality in patients with acute liver injury (76.9%)
GRASELLI et al.[16]	ITALY	15- 30% mortality in patients between 50 to 70 years of age.

TAB 1. RESULTS OF HEPATIC MANIFESTATIONS IN COVID-19.

COVID-19 LIVER HISTOLOGY:

Covid-19 is primarily characterized by symptoms of viral pneumonia. The patients have experienced many changes in liver. The studies on covid 19 until recently shown the levels of aminotransferases and bilirubin are twice compared to others. These abnormalities though directly doesn't prove the liver dysfunction but can be presented as clinical challenges. The common symptom experienced by early covid patients is anoxia. Due to absence of oxygen there is a rise in serum aminotransferases which results in Ischemic hepatitis. Usually patients with serious covid-19 have increased liver dysfunction rates. The count of CD4 and CD8 cells in peripheral blood examination is reduced, but they are hyper reactive in a pro-inflammatory state. Also there is an increase in CCR6+ TH17 in CD4 T cells and cytotoxic granules are in high concentrations in CD8 T cells. The SARS-Cov infection had shown hepatic dysfunction in patients where there was an increase in the size of hepatocytes. It is likely that the pathogenesis of COVID-19 is similar. [17, 18, 19, 20]

LIVER ABNORMALITY IN SARS:

SARS is a respiratory disease that results in acute pulmonary inflammation and epithelial damage. Liver enzyme defects are common in patients with SARS although hepatic dysfunction has not been reported to be a prominent feature of this disease. Disregulation of the coagulative and fibrinolytic pathways has been documented In patients with SARS-CoV-2 infection, possibly due to overactivation of the innate immune response with unregulated release of cytokines with subsequent hyperinflammation. The development of liver disease in SARS patients might be related to any of these pathogenic processes. (i) Direct attack of virus against the liver (ii) Systemic inflammation correlated with " Cytokines storm " (iii) Acute hepatic decompensation in patients with longstanding pre-existing liver disease. (iv)Hypoxic liver damage due to imbalance between availability of oxygen to the organs and demand. (v) drug induced liver injury associated with hepatotoxic therapies.[21, 22]

LIVER ABNORMALITY IN MERS:

As in SARS cases, the pathological symptoms of hepatic damage in MERS cases are moderate portal tract and lymphocytic inflammation, as well as mild cellular hydropic degradation in hepatic parenchyma. Substantial pro-inflammatory cytokine responses were identified in patients during the acute phase of MERS-CoV infection and serum concentrations IFN-y, TNF-α, IL-15 and IL-17 risen exponentially. However there is also a shortage of correlation between pro-inflammatory cytokine reactions and liver damage. It needs to be studied whether the liver injury reported during MERS-CoV infection is the product of direct virus infection, inflammation mediated pathogenesis or the administration of liver damaging drugs in the treatment process. [23]

HEPATOCELLULAR CARCINOMA AND COVID-19:

Reportedly the likelihood of infection is increased in patients suffering with chronic liver disease (CLD), liver transplant and cancer due to impaired immune function. Among the cases identified SARS-CoV-2 infection may induce an increased risk of hepatic decompensation in patients with a cirrhotic liver. As a consequence patients diagnosed with hepatocellular carcinoma could be at greater risk for extreme signs of

Covid-19, and therefore more likely to be admitted in intensive care. Patients with HCC encountered treatment delays in COVID-19. Treatment availability relies on the liver function and general condition of the patient and HCC patients with Covid-19 induced severe liver damage can no longer qualify for any care. Early stage HCC patients undergo surgery transplantation or ablation which is found curative. Covid-19 has also hindered the clinical research of novel pharmaceutical drugs in several therapeutic fields. Although the size of covid-19 effect on HCC is not completely understood the COVID-19 CHIEF study is undertaken to measure this effects, with the centre hospitalier universitaire attempting to estimate the prevelance of COVID-19 in both hospital and outpatient HCC population.[24]

DIRECT EFFECT OF SARS-COV-2 ON LIVER:

Studies on the mechanisms of SARS-CoV-2 related liver injury are limited. SARS-CoV-2 has also been shown to use ACE-2 as its entry receptor, as SARS-CoV does. There are trials which include unbiased assessment of cell type differential expression of ACE-2 in healthy liver tissue using single cell RNA seq results from two separate cohorts and unique expression in cholangiocytes identified. The findings suggested that virus could bind positive cholangiocytes directly to ACE-2 but not specifically to hepatocytes indicating SARS and COVID-19 liver disorders couldn't be due to hepatocyte disruption but cholangiocyte dysfunction and other factors such as drug mediated and systemic inflammatory response induced liver injury. This suggests that liver injury occurred in COVID-19 patients may be due to disruption of bile duct cells but not liver cells by the infection of virus.[25, 26, 27]

DRUG INDUCED LIVER INJURY (DILI) DURING TREATMENT OF COVID-19:

Pandemic coronavirus infection (COVID-19) spreading from china causes a massive flow. The frequent association of COVID-19 infection with liver abnormalities is of information and one emerging point. Various infectious agents and anti-cancer medicines with advance authorization to market are either suggested to prevent covid-19 replication or to minimize the health and respiratory effects. This involves multiple drugs alone or in combination including hydroxychloroquine associated with or not with azithromycin, lopinavir/ritonavir associated with or not associated with interferon beta. Remdesivir, barcitinib, darunavir, imatinib and umifenovir and their instant availability has contributed to their distribution as humanitarian use outside of many countries research trials. Patients with type-1 or type 2 diabetes are developing hypertension frequently acquire blood pressure lowering ACE inhibitors and angiotensin-2 type-1 receptor blockers, which can lead to over expression of ACE-2. While there is no evidence of clinical data it must be taken into consideration that ACE-2 upregulation could be at the root of a higher susceptibility to COVID-19. In addition, metabolic syndrome which is a major risk factor of non-alcoholic fatty liver disease (NAFLD) often affects this patients. NAFLD can sensitize the liver to hepatotoxicants such as acetamoniphen which is the approved and commonly used anti-pyretic symptomatic treatment. While it not actiually known whether there is a correlation between COVID-19 and liver steatosis it is concerning thet in the recent postmortem histopathological analysis of a liver biopsy of COVID-19 patient microvesicular liver steatosis has been observed. Although this results needs to be validated in larger trials it has also been shown that the patients with COVID-19 have elevated serum levels of monocyte chemoattractant protein-1 (MCP-1), a chemokine believed to trigger steatohepatitis. Correspondingly, predisposing factors for the development of steatohepatitis such as consumption of steatosis inducing medications like sodium valproate, amiodarone, tamoxifen and methotrexate may play a role in the combination of COVID-19 and drug induced liver injury. Knowing that liver failure and NAFLD are more frequent in the elderly, who are also more likely to experience serious COVID-19, it is generally best to carefully monitor COVID-19 patients for the drug therapy which might lead to DILI. [28, 29, 30, 31, 32, 33]

POST LIVER TRANSPLANT PATIENTS AND COVID-19 :

COVID-19 is not ready to leave anyone. There are many cases to show that patients with liver transplant are also being affected with COVID-19. There have been recent case reports from Wuhan, one of a 37 year old man who was suffering from hepatitis B and HCC. But the patient soon developed fever post transarterial chemoembolisation. After 7 days of treatment with antibiotics a liver transplantation was done. As fever didn't subside even after 9 days, a CT scan of chest was done and abnormalities were detected in both the lungs of the patient. In the third week a repeat CT scan showed a bilateral ground glass appearance, after a nasal swab test COVID-19 results came positive. Dose of his tacrolimus was decreased and maintained at 10ng/ml.His liver enzymes elevated by the fourth week but gradually decreased. PCR was also positive for two months but slowly decreased and stabilized.[34]

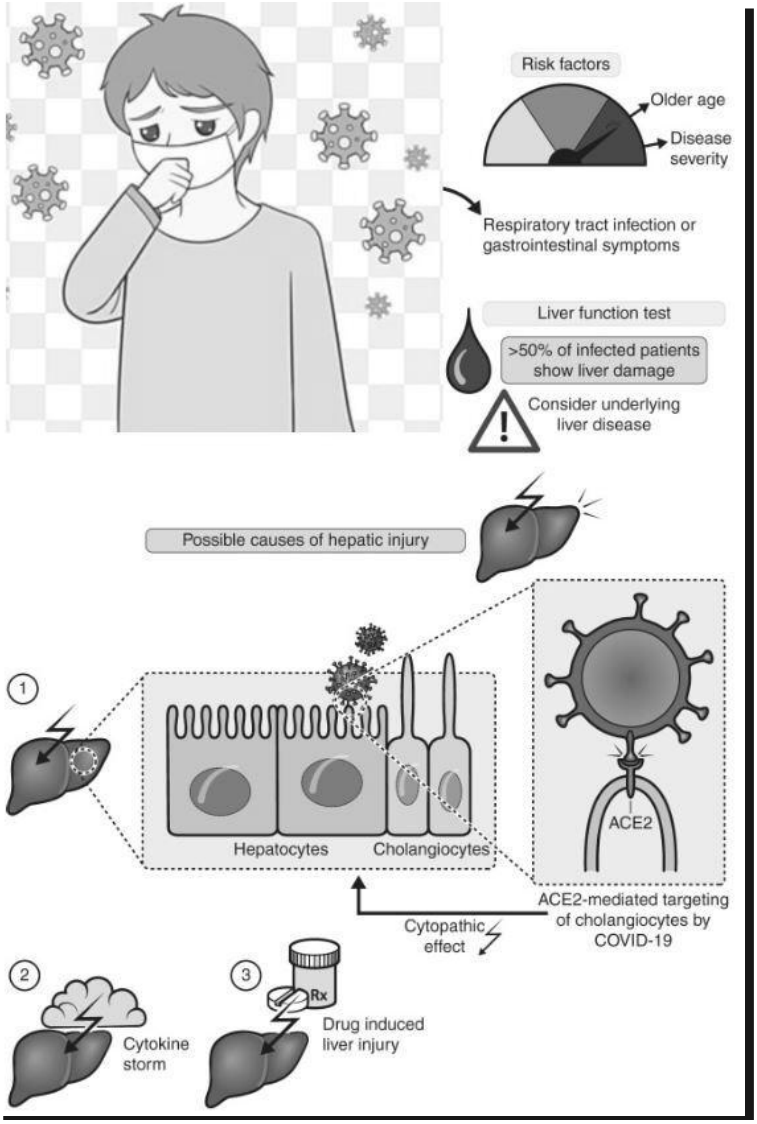
Another patient underwent a cadaveric liver transplantation in July,2017. He recently developed fever and was tested positive with severe COVID-19. For 1 month he received corticosteroids and tacrolimus was discontinued. His allograft function was however normal.[35]

Studies of SARS-CoV and MERS-CoV showed that post liver transplant patients who were on immunosuppressants were at low risk of mortality, similar studies on SARS-CoV2 are however limited. Some

immunosuppressive drugs have anti viral properties as a part of their mechanism of action. Studies showed that SARS CoV was inhibited by cyclosporines at high doses, also mycophenolic acid showed antiviral properties against MERS CoV.[36]Also everolimus (mTOR inhibitor) showed anti viral properties against MERS CoV and SARS CoV.[37]

Immunosupressants in liver transplant patients who are positive for COVID-19 and high dose of steroids needs to be maintained at 10mg/day. Also patients may be more infectious when on immunosuppressants as they have higher concentration of virus.[38]

PATHOPHYSIOLOGY OF LIVER INJURY IN PATIENTS WITH COVID-19:



(ACE-2 – Angiotensin Converting Enzyme)

FIG 1. ***PATHOPHYSIOLOGY AND CLINICAL CHARECTERISTICS OF LIVER INJURY IN COVID-19 PATIENTS[39,40,41]***

DIRECT EFFECT OF THE VIRUS ON LIVER:

Liver plays a vital role in the host defense mechanism against microbes as it receives both portal and systemic circulation. Some viruses has direct effect on cholangiocytes and liver cells, but it may be multifactorial. Study by Yang et al. showed that SARS-CoV2 ha direct cytopathic effect on the liver rather than other factors as seen in sepsis.[42] SARS CoV2 was detected in 41% of liver tissue in autopsy studies done in patients and a viral load of 1.6 * 10.6 copies/g of tissue were seen.[43] Hepatocellular necrosis, fatty denegeration and cellular infiltration were observed in the liver biopsy of SARS patients. In some cases of COVID-19 inflammation in the portal and lobular are were observed.[44]

ROLE OF CHOLANGIOCYTES IN COVID-19:

Many studies done have proved that SARS-CoV2 uses ACE2 receptor protein (Angiotensin 2 converting enzyme) to attack the host system. [45]ACE2, the cell entry receptor is widely exhibited in the human body. It is present in the lungs, GIT, hepatobiliary system (hepatocytes and cholangiocytes), renal system, cardiovascular system and also pancreas. Some of the recent studies have also shown that cholangiocytes has high expression of ACE2 than other hepatocytes.[46] It is shown that SARS CoV2 may directly bind to the cholangiocytes which has ACE2 expression to exert a cytopathic effect. The disordering of cholangiocyte function may cause hepatobiliary damage. The cholestatic markers including gamma glutamyl transferase(GGT) found in some serious cases of COVID-19 , supports this.[47] Dysregulation of genes involved in the transportation of bile acid and tight junction formation of cholangiocytes is seen due to the viral infection.[48]

DRUG DRUG INTERACTIONS OF IMMUNOSUPPRESSIVE THERAPY AND EXPERIMENTAL COVID-19 DRUGS:

	IMMUNOSUPRESSANTS	COVID-19 THERAPY
1.	*Cyclosporin Or Tacrolimus*	Tocilizumab
2.	*Sirolimus*	Chloroquine., Hydrochloroquine, Atazanavir, Lopinavir, Ritonavir
3.	*Baciliximab*	Tocilizumab
4.	*Azathioprine*	Ribavarin, Tocilizumab, Interferon-B
5.	*Mycophenolate*	Lopinavir, Ritonavir
6.	*Calcineurin Inhibitor*	Chloroquine, Hydrochloroquine, Lopinavir,Ritonavir, Atazanavir

TAB2. MODIFIED FROM LIVERPOOL DRUG INTERACTIONS GROUP (https://www.hep-druginteractions.org/)

PROGNOSIS OF PATIENTS WITH LIVER INJURY IN COVID-19:

Recent studies have shown that the weak prognosis in COVID-19 patients is associated to gender, age, underlying conditions such as hypertension, diabetes, cardio-vascular disorders, secondary ARDS and other contributing factors. A spike in the count of neutrophil and neutrophil to lymphocyte ratio typically suggests a greater degree of seriousness of the condition and a poor clinical prognosis. There were shown to be no significant associations between ALT, AST, total bilirubin, alkaline phosphatase, albumin and other markers of liver activity and extreme covid-19 suggesting that the liver has not been the primary target organ. However ALT, AST, total bilirubin and other indicators of liver function in patients with severe covid-19 were substantially increased compared in patients with mild covid-19 and the markers of liver function eventually returned to normal during recovery period. Many patients with serious liver injury were generally prescribed hepatoprotective medications. In addition liver dysfunction was associated with activation of the clotting and fibrinolytic mechanisms in covid-19 patients, a relatively lower platelet production, elevated granulocyte count, neutrophil to lymphocyte ratio and elevated ferritin levels. Though these parameters were considered to be non-specific inflammation markers they also corresponds to a failure of innate immune regulation. It is important to note that this transition in the immune balance has occurred with age; thus the situation for geriatric patients can be worse. It is not known what effect glucocorticoid administration has on prognosis of covid-19 patients with auto-immune hepatitis. [49, 50, 51]

MANAGEMENT AND CHALLENGES:

Although the data is not conclusive- antiviral medications, antibiotics, intravenous fluids and corticosteroids are currently being used for the treatment. While remdisivir was initially promising a recent randomized control trial found no clinical benefit in covid-19 except for the non-significant faster recovery. In addition hepatic damage was observed in 10-13% of the population treated with remdisivir.[52]Being a RNA virus one would expect wide spectrum ribavirin to work, sadly it was associated with serious toxicity including severe hemolysis during the SARS epidemic. Regulated for HIV infection, lopinavir/ritonavir showed in-vitro efficacy against SARS-Cov and was active in MERS-CoV.[53] These drugs are being studied in Covid-19. Protease inhibitor lopinavir has shown to be effective in regulating SARS-CoV. Ritonavir has been applied to improve lopinavir trough levels by the induction of CYP450 enzymes in the liver. For the reduction of secondary infection antibiotics such as fluoroquinolones and third generation cephalosporins were used. Corticosteroids like methylprednisolone have been used to reduce inflammation in covid-19 patients and dexamethasone recently been shown to decrease mortality.[54] Its use can lead to chronic hepatitis-B reactivation. Therefore, antiviral treatment should be offered to HBsAg-positive patients and it is suggested to check the status of hepatitis-B core antibody and treating patients with anti-virals for the duration of steroid therapy, if appropriate.

Further studies should concentrate on the causes of covid-19 liver injury and the effect of current liver related co-morbid conditions on covid-19 treatment and outcome.[55]

II. Conclusion And Recommendations:

Abnormal liver function parameters are constant in patients with severe COVID-19. Various study findings over the span of last 8 months support that liver injury may be associated with severe outcomes of COVID-19. The liver injury may be direct or multifactorial and more studies are required to exactly chart the casualty between COVID-19 and liver injury. Hence patients with underlying liver diseases and liver transplantation patients are at high risk of COVID-19 and its progression to severe state. Therefore it is important to identify and care for patients with chronic liver disease. Drugs that inhibit inflammatory response and protect liver functions are advised to be given to patients with liver injury and adverse effects of certain drugs on liver in hospitalized COVID-19 patients should also be evaluated. Further research is warranted in this area for detailed evaluation of effect of COVID-19 on underlying chronic liver diseases.

References:

[1]. de Groot, R. J., Baker, S. C., Baric, R., Enjuanes, L., Gorbalenya, A. E., Holmes, K. V., ... & Woo, P. C. Y. (2012). Family coronaviridae. Virus taxonomy, 806-28.

[2]. Chau, T. N., Lee, K. C., Yao, H., Tsang, T. Y., Chow, T. C., Yeung, Y. C., ... & Lai, C. L. (2004). SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology, 39(2), 302-310.

[3]. Chai, X., Hu, L., Zhang, Y., Han, W., Lu, Z., Ke, A., ... & Cai, J. (2020). Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. biorxiv.

[4]. Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., ... & Yu, T. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet, 395(10223), 507-513.

[5]. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cheng, Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, 395(10223), 497-506.

[6]. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Zhao, Y. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama, 323(11), 1061-1069.

[7]. Ali, N. (2020). Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. Journal of Medical Virology.

[8]. Liu, J., Li, S., Liu, J., Liang, B., Wang, X., Wang, H., ... & Xiong, L. (2020). Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 55: 102763.

[9]. Wu, C., Chen, X., Cai, Y., Zhou, X., Xu, S., Huang, H., ... & Song, J. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine.

[10]. Zhang, C., Shi, L., & Wang, F. S. (2020). Liver injury in COVID-19: management and challenges. The lancet Gastroenterology & hepatology, 5(5), 428-430.

[11]. Cao, W. (2020). Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. medRxiv.

[12]. Fan, Z., Chen, L., Li, J., Cheng, X., Yang, J., Tian, C., ... & Cheng, J. (2020). Clinical features of COVID-19-related liver damage. Clinical Gastroenterology and Hepatology.

[13]. Arentz, M., Yim, E., Klaff, L., Lokhandwala, S., Riedo, F. X., Chong, M., & Lee, M. (2020). Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. Jama, 323(16), 1612-1614.

[14]. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Zhao, Y. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama, 323(11), 1061-1069.

[15]. Chen, T., Wu, D., Chen, H., Yan, W., Yang, D., Chen, G., ... & Wang, T. (2020). Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. Bmj, 368.

[16]. Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., ... & Iotti, G. (2020). Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. Jama, 323(16), 1574-1581.

[17]. Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., ... & Tai, Y. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine, 8(4), 420-422.

[18]. Sun, J., Aghemo, A., Forner, A., & Valenti, L. (2020). COVID-19 and liver disease. Liver International.

[19]. Zhang, C., Shi, L., & Wang, F. S. (2020). Liver injury in COVID-19: management and challenges. The lancet Gastroenterology & hepatology, 5(5), 428-430.

[20]. Bangash, M. N., Patel, J., & Parekh, D. (2020). COVID-19 and the liver: little cause for concern. The Lancet. Gastroenterology & Hepatology, 5(6), 529.

[21]. https://www.globaldata.com/hepatocellular-carcinoma-treatments-negatively-impacted-covid-19-says-globaldata/

[22]. Chai, X., Hu, L., Zhang, Y., Han, W., Lu, Z., Ke, A., ... & Cai, J. (2020). Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. biorxiv.

[23]. Banales, J. M., Huebert, R. C., Karlsen, T., Strazzabosco, M., LaRusso, N. F., & Gores, G. J. (2019). Cholangiocyte pathobiology. Nature Reviews Gastroenterology & Hepatology, 16(5), 269-281.

[24]. Xu, L., Liu, J., Lu, M., Yang, D., & Zheng, X. (2020). Liver injury during highly pathogenic human coronavirus infections. Liver International, 40(5), 998-1004.

[25]. Olry, A., Meunier, L., Délire, B., Larrey, D., Horsmans, Y., & Le Louët, H. (2020). Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. Drug Safety,

[26]. Fang, L., Karakiulakis, G., & Roth, M. (2020). Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. The Lancet. Respiratory Medicine, 8(4), e21.

[27]. Massart, J., Begriche, K., Moreau, C., & Fromenty, B. (2017). Role of nonalcoholic fatty liver disease as risk factor for drug-induced hepatotoxicity. Journal of clinical and translational research, 3(1), 212.

[28]. Zhang, K., Liu, Y., Yang, X., Sun, H., Shu, X., Zhang, Y., ... & Xu, Q. (2020). HBV promotes the recruitment of IL-17 secreting T cells via chemokines CCL22 and CCL17. Liver International, 40(6), 1327-1338.

[29]. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cheng, Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, 395(10223), 497-506.

[30]. Boeckmans, J., Rodrigues, R. M., Demuyser, T., Piérard, D., Vanhaecke, T., & Rogiers, V. (2020). COVID-19 and drug-induced liver injury: a problem of plenty or a petty point?. Archives of Toxicology, 1-3.

[31]. Qin, J., Wang, H., Qin, X., Zhang, P., Zhu, L., Cai, J., ... & Li, H. (2020). Perioperative presentation of COVID-19 disease in a liver transplant recipient. Hepatology.

[32]. Liu, B., Wang, Y., Zhao, Y., Shi, H., Zeng, F., & Chen, Z. (2020). Successful treatment of severe COVID-19 pneumonia in a liver transplant recipient. American Journal of Transplantation.

[33]. Tanaka, Y., Sato, Y., & Sasaki, T. (2013). Suppression of coronavirus replication by cyclophilin inhibitors. Viruses, 5(5), 1250-1260.

[34]. Chan, J. F., Chan, K. H., Kao, R. Y., To, K. K., Zheng, B. J., Li, C. P., ... & Hayden, F. G. (2013). Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. Journal of Infection, 67(6), 606-616.

[35]. American Society of Transplantation 2019-nCoV (Coronavirus): FAQs for organ donation and transplantation.www.myast.org

[36]. Fix, O. K., Hameed, B., Fontana, R. J., Kwok, R. M., McGuire, B. M., Mulligan, D. C., ... & Loomba, R. (2020). Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology.

[37]. Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... & Du, B. (2020). Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine, 382(18), 1708-1720.

[38]. Zhao, B., Ni, C., Gao, R., Wang, Y., Yang, L., Wei, J., ... & Xie, Y. (2020). Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. Protein & Cell, 1-5.

[39]. Yang, Z., Xu, M., Yi, J. Q., & Jia, W. D. (2005). Clinical characteristics and mechanism of liver damage in patients with severe acute respiratory syndrome. Hepatobiliary & pancreatic diseases international: HBPD INT, 4(1), 60-63.

[40]. Farcas, G. A., Poutanen, S. M., Mazzulli, T., Willey, B. M., Butany, J., Asa, S. L., ... & Kain, K. C. (2005). Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus. Journal of Infectious Diseases, 191(2), 193-197.

[41]. Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., ... & Tai, Y. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine, 8(4), 420-422.

[42]. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., ... & Müller, M. A. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell.

[43]. Fan, Z., Chen, L., Li, J., Cheng, X., Yang, J., Tian, C., ... & Cheng, J. (2020). Clinical features of COVID-19-related liver damage. Clinical Gastroenterology and Hepatology.

[44]. Xu, L., Liu, J., Lu, M., Yang, D., & Zheng, X. (2020). Liver injury during highly pathogenic human coronavirus infections. Liver International, 40(5), 998-1004.

[45]. Zhao, B., Ni, C., Gao, R., Wang, Y., Yang, L., Wei, J., ... & Xie, Y. (2020). Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. Protein & Cell, 1-5.

[46]. Du, Y., Tu, L., Zhu, P., Mu, M., Wang, R., Yang, P., ... & Li, T. (2020). Clinical features of 85 fatal cases of COVID-19 from Wuhan. A retrospective observational study. American journal of respiratory and critical care medicine, 201(11), 1372-1379.

[47]. Zhang, Y., Zheng, L., Liu, L., Zhao, M., Xiao, J., & Zhao, Q. (2020). Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver International.

[48]. Wu, J., Song, S., Cao, H. C., & Li, L. J. (2020). Liver diseases in COVID-19: Etiology, treatment and prognosis. World Journal of Gastroenterology, 26(19), 2286.

[49]. Tian, D., & Ye, Q. (2020). Hepatic complications of COVID-19 and its treatment. Journal of Medical Virology.

[50]. Chu, C. M., Cheng, V. C. C., Hung, I. F. N., Wong, M. M. L., Chan, K. H., Chan, K. S., ... & Peiris, J. S. M. (2004). Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax, 59(3), 252-256.

[51]. Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., ... & Zhao, Y. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama, 323(11), 1061-1069.

[52]. Jothimani, D., Venugopal, R., Abedin, M. F., Kaliamoorthy, I., & Rela, M. (2020). COVID-19 and Liver. Journal of hepatology.

[53]. Zhao, B., Ni, C., Gao, R., Wang, Y., Yang, L., Wei, J., ... & Xie, Y. (2020). Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. Protein & Cell, 1-5.

[54]. Yang, Z., Xu, M., Yi, J. Q., & Jia, W. D. (2005). Clinical characteristics and mechanism of liver damage in patients with severe acute respiratory syndrome. Hepatobiliary & pancreatic diseases international: HBPD INT, 4(1), 60-63.

[55]. Farcas, G. A., Poutanen, S. M., Mazzulli, T., Willey, B. M., Butany, J., Asa, S. L., ... & Kain, K. C. (2005). Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus. Journal of Infectious Diseases, 191(2), 193-197.

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