Liver manifestation associated with COVID-19 (Literature review)

Manifestación hepática asociada con COVID-19 (revisión de la literatura)

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Abstract

The World Health Organization (WHO) named the 2019-nCoV virus on January 12, 2020[1]. Subsequently, in a short period of time, Novel Coronavirus Infected Pneumonia (NCIP) spread around the world, and on January 30, 2020, the WHO declared NCIP an international public health emergency[2]. On February 11, 2020, it was renamed Coronavirus Disease 2019 (COVID-19)[3].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has been described as a form of the beta coronavirus cluster, is the cause of the pandemic and has 79.6% sequence identity with SARS-CoV[4]. COVID-19 is generally a self-limiting disease, but it can also be fatal: China's death rate is around 2.3 percent[5], from 5.8 percent in Wuhan to 0.7 percent in the rest of China[6]. The proportion of serious or fatal infections that can be attributed to specific infected populations may vary by country and region. A certain percentage of deaths occurred in elderly patients or comorbid conditions (obesity, hypertension, diabetes, cardiovascular disease, chronic lung disease and cancer)[5;7;8].

These results were also found in critically ill patients referred to the intensive care unit, indicating that adequate liver oxygen supply is provided by compensatory mechanisms, including in cases of severe respiratory failure during COVID-19 disease[9-17].

Keywords: COVID19, viral hepatitis, SARS-CoV-2, liver damage, cytopathic action

Resumen

La Organización Mundial de la Salud (OMS) nombró al virus 2019-nCoV el 12 de enero de 2020[1]. Posteriormente, en un corto período de tiempo, la neumonía infectada por el nuevo coronavirus (NCIP) se extendió por todo el mundo, y el 30 de enero de 2020, la OMS declaró a la NCIP una emergencia de salud pública internacional[2]. El 11 de febrero de 2020, pasó a llamarse Enfermedad por coronavirus 2019 (COVID-19)[3]. Síndrome respiratorio agudo severo El coronavirus 2 (SARS-CoV-2), que se ha descrito como una forma del grupo de coronavirus beta, es la causa de la pandemia y tiene una identidad de secuencia del 79,6% con el SARS-CoV[4]. COVID-19 es generalmente una enfermedad autolimitante, pero también puede ser fatal: la tasa de mortalidad en China es de alrededor del 2,3 por ciento[5], desde el 5,8 por ciento en Wuhan hasta el 0,7 por ciento en el resto de China[6]. La proporción de infecciones graves o mortales que pueden atribuirse a poblaciones infectadas específicas puede variar según el país y la región. Un cierto porcentaje de muertes ocurrieron en pacientes de edad avanzada o enfermedades concomitantes (obesidad, hipertensión, diabetes, enfermedades cardiovasculares, enfermedades pulmonares crónicas y cáncer)[5,7,8]. Estos resultados también se encontraron en pacientes
críticamente enfermos derivados a la unidad de cuidados intensivos, lo que indica que los mecanismos compensatorios proporcionan un suministro adecuado de oxígeno al hígado, incluso en casos de insuficiencia respiratoria grave durante la enfermedad por COVID-19[9-17].

Palabras clave: COVID19, hepatitis viral, SARS-CoV-2, daño hepático, acción citopática

Introduction

Patients with COVID-19 have liver dysfunctions of varying degrees of severity. Liver damage can be multifactorial and heterogeneous in its etiology. In the context of COVID-19, the clinician needs to determine if liver damage is related to an underlying liver disease, the drugs used to treat COVID-19, direct exposure to the virus, or a complicated course of the disease. Recent studies have proposed several theories about potential mechanisms of liver damage in these patients.

Changes in liver function tests within the framework of cytolytic and / or cholestatic syndrome are observed in almost half of patients with COVID-19 infection; these changes (elevation of ALT and AST in particular) correlate with the severity of COVID-19. The risk is increased if the patient has preexisting liver disease and advanced age.

Another factor is the use of hepatotoxic drugs and drug combinations that increase their total hepatotoxicity, including antiviral ones.

SARS-CoV-2 can directly bind to ACE2-positive cholangiocytes and cause liver damage with a pattern of acute viral (coronavirus) hepatitis. Often this damage is accompanied by the development of acute pancreatitis with an increase in amylase levels and impaired endocrine pancreatic function.

The activation of the immune system and the "cytokine storm" can contribute to the immune-mediated process of liver damage in COVID-19, especially if we understand that the synthesis of acute phase proteins under the influence of pro-inflammatory cytokines occurs precisely in hepatocytes (in addition to macrophages).

Objective of the study: To study the features of liver damage in COVID19 and its consequences.

Research objectives:

1. To study and give clinical and laboratory characteristics of liver damage in moderate-severe and severe COVID19
2. To study the clinical picture and substantiate the diagnostic criteria for acute viral hepatitis caused directly by SARS-CoV-2
3. Differentiate liver damage in patients after suffering COVID19, associated with the reactivation of hepatitis B and other hepatotropic viruses and study the features of the clinical course

Expected results:

1. Options for the involvement of the liver in the pathological process in COVID19 and their frequency will be determined: associated with the direct cytopathic effect of the virus; the development of a "cytokine storm" - damage mediated by the action of cytokines and acute phase proteins;
2. A characteristic of the clinical and laboratory picture of the involvement of the liver in the acute inflammatory process with the threat of ARDS in the acute period of COVID19 will be given.
3. Criteria and risk factors on the part of the patient for the development of acute coronavirus hepatitis are highlighted, clinical and laboratory characteristics of its course and outcomes are given
4. Variants of hepatitis B reactivation in patients after suffering COVID19 will be studied

Materials and methods

Background

A number of unexplained pneumonia cases have been recorded in Wuhan, Hubei Province, China, since December 2019. The Chinese Center for Disease Control and Prevention (CCDC) reported a novel coronavirus from a patient's throat swab on January 7, 2020[18], which was called the 2019-nCoV virus by the World Health Organization (WHO) on January 12, 2020[1]. Subsequently, in a short period of time, novel coronavirus-infected pneumonia (NCIP) spread to the world, and on January 30, 2020, WHO announced NCIP as an international public health emergency[2]. On 11 February 2020, it was renamed Coronavirus Disease 2019 (COVID-19)[3].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has been described as a form of beta coronavirus cluster, is responsible for the pandemic and shares a 79.6 percent sequence identity with SARS-CoV[4]. COVID-19 is a self-limiting disease in general, but it can also be lethal, with a fatality rate in China of around 2.3 percent[5], ranging from 5.8 percent in Wuhan to 0.7 percent in the rest of China[6]. The proportion of serious or fatal infections that may be associated with separate populations of infection may vary by country and region. Patients of elder age or underlying medical comorbidities (obesity, hypertension, diabetes, cardiovascular disease, chronic lung disease and cancer) had more fatal cases[5;7;8].

Suddenly, the COVID-19 pandemic posed an immense burden of treatment[19] and raised medical ethics concerns[20], since, to date, specific treatments and/or vaccinations have been lacking. COVID-19 can manifest itself in various ways. There may be several subjects that remain asymptomatic[21], but the exact number is still unknown. For example, in certified nursing facilities where more than half of residents with positive test results were asymptomatic at the time of testing and most likely contributed to transmission, particular settings may promote the spread of infection[22;23]. Stage I (early infection),

stage II (pulmonary phase), and stage III (hyperinflammation phase) are included in the proposed three-stage classification scheme of potential increasing severity for COVID-19 infection[24]. Although the most common and important clinical presentation is secondary to lung involvement (fever, cough), SARS-CoV-2 virus infection can lead to systemic and multi-organ disease[25], including nausea/vomiting or diarrhea of the gastrointestinal tract[25-27]. The second organ involved, after the lung[28- 30], tends to be the liver.

The spectrum of liver involvement in COVID-19

COVID-19 associated liver injury is characterized as any liver damage occurring in patients with or without pre-existing liver disease during the course of disease and treatment of COVID-19[9-11,31-34]. This includes a broad range of possible pathomechanisms, in- cluding direct cytotoxicity due to active viral replication of SARS-CoV-2 in the liver[35;36], immune-mediated liver damage due to extreme inflammatory response/systemic inflammatory response syndrome (SIRS) in COVID-19[37] hypoxic changes due to respiratory failure, coagulopathy- related vascular changes, endotheliitis, or coagulopathy- related hypoxic changes. The prevalence of elevated liver transaminases (ALT and AST) ranges from 2.5 to 76.3 percent in COVID-19 patients. Well[9;34;38;39]. The combined prevalence for AST and ALT outside the reference range was 20 percent-22.5% and 14.6 percent-20.1 per- cent respectively in a recent meta-analysis[9;40].

SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to achieve cellular entry into the human lower respiratory tract, which has also been shown to be highly expressed in gastrointestinal epithelial cells[41;42]. While patients usually present respiratory symptoms such as cough, dyspnea, and shortness of breath, gastrointestinal manifestations such as diarrhea, nausea, vomiting, and abdominal pain have been documented in multiple cases of diagnosed COVID-19 patients[43;44]. A study found that in 83.3% of patients with a mild infection, SARS-CoV-2 RNA can be detected in feces for up to a month, raising doubt of the gastrointestinal tract as a further site of viral replication[44]. In addition, another research showed that 53.4 percent of 73 COVID-19 patients were found to have viral RNA existing in their stool; 23.3 percent of those patients had positive stool samples even after the viral RNA was removed from their respiratory tract [45]. As such, these features have clinical consequences for the careful treatment of infected persons, the possible fecal-oral route of transmission and successful preventive control of infections. In up to 35% of cases, these anomalies may be followed by significantly elevated total levels of bilirubin[9;34;38;39]. While cholestatic liver enzyme elevations [alkaline phosphatase (ALP) and gamma glutamyl transferase (γGT)] were initially considered to be rather uncommon[7;31;46;47]. Latest systemic studies have highlighted ALP and γGT elevations in 6.1% and 21.1% of COVID-19 patients, respectively[9;40].

In addition, a biphasic pattern was identified with initial transaminase raising followed by cholestatic liver enzymes, which may represent hepatocellular/canalicular SIRS-induced cholestasis or more serious bile duct damage at the later stage of the disease[48].

While SARS-CoV-2 liver injury has been recorded to be mild, a considerable proportion of patients, particularly those with a more serious course of illness, may be affected. Hepatic dysfunction can affect the multi-system manifestations of COVID-19, such as ARDS, coagulopathy and multi-organ failure, given the central role of the liver in the synthesis of albumin, acute phase reactants and coagulation factors[31;49-54].

In addition, the liver is the human organism's key metabolic and detoxifying organ, and even a mild loss of liver function could alter the safety profile and therapeutic efficacy of liver-metabolized antiviral drugs. It is therefore important to consider in more detail the causes of SARS-CoV-2-associated liver injury. Systematic data on underlying histopathological modifications is scarce so far. Hepatic steatosis and activation of Kupffer cells tend to be frequently observed in liver of COVID-19 patients deceased, along with vascular changes including intrahepatic portal vein branch derangement, typically mild lobular and portal inflammation, ductular proliferation, and necrosis of liver cells[36;48;55-57].

Examination of liver biopsies of a cohort of 48 deceased patients with COVID-19 showed substantial portal and sinusoidal luminal thrombosis, along with portal fibrosis convoyed by major activation of pericytes[57].

Results and Discussion

Direct viral Infection of hepatocyte (SARS-CoV2 hepatitis)

Quantitative reverse transcription Polymerase chain reaction (QRT-PCR) has lately been shown to have SARS-CoV-2 viral RNA in the liver and several other organs outside the respiratory system[58]. While the exact cellular replication site remained unspecified because nucleic acids were separated by homogenization of the entire tissue. In situ hybridization study, however, revealed SARS-CoV-2 virions in vessel lumens and endothelial cells of COVID-19 liver specimen portal veins[57]. In addition, electron microscopic inspection of liver samples from two deceased of SARS-CoV-2 patients with elevated liver enzymes showed that intact viral particles were present in the hepatocyte cytoplasm[35].

Based on recent, but still restricted, findings[35;57;58] of hepatic tropism for SARS-CoV-2 and direct cytopathic effects, the possible mechanism of liver injury associated with COVID-19 should be considered, although a classic hepatic image has not been recorded[35;48;55-57]. For a particular tissue, the availability of viral receptors on the host cell surface is a significant determinant of viral tro-

pism[59]. Fundamentally, the entry of SARSCoV-2 in cells is regulated by the virus' S protein, which interacts directly with host ACE2 and TMPRSS2. Human Protein Atlas is used to analyze the expression pattern of human ACE2 and TMPRSS2 proteins to understand whether SARS-CoV-2 could be capable of infecting liver cells. Interestingly, in the intestine and gall bladder, the expression levels of the two proteins are highest, but they tend to be virtually absent in the liver. Such data may be incomplete or lack sensitivity, because the expression of ACE2 in the Human Protein Atlas often tends to be absent in the lungs, where infection is certainly known to occur.

In a recent review, Chai and colleagues applied single-cell RNAseq to healthy human liver samples and stablished that bile duct epithelium (cholangiocytes) levels of ACE2 expression are similar to those of alveolar cells in the lungs, while hepatocellular ACE2 expression is little but still detectable[60]. Important expression of ACE2 and TMPRSS2 in liver parenchymal cells is further confirmed by bioinformatics studies from the single-cell transcriptome database Single Cell Portal[61]. Remarkably, according with past findings, sinusoidal endothelial cells tend to be ACE2-negative[62]. This discovery may be significant given recent reports of large intrahepatic vessel endothe- liitis caused by COVID-19 disease[55;63] and excessive expression of ACE2 in other endothelia, including central and portal veins, which might also become infected with the virus[57].

Studies in both mice and humans showed increased hepatic ACE2 expression in hepatocytes under fibrotic/cirrhotic conditions in the liver[64;65]. As pre-existing liver damage might thus worsen SARS-CoV 2 hepatic tropism, this result could be of great relevance. In addition, hypoxia has been revealed to be a significant regulator of hepatocellular ACE2 expression, which is a common trait in extreme COVID-19 cases[64]. This could explain why extrapulmonary distribution of SARS-CoV-2 is found primarily in patients with ARDS and other hypoxic conditions. Importantly, ACE2 expression may also be upregulated by inflammatory conditions/diseases in the liver as seen for other organs[66;67]. While drug-induced liver injury (DILI) in COVID-19 patients may lead to liver damage[68], it may be of interest to investigate whether hepatic ACE2 overexpression is induced by DILI or specific drugs.

In vitro studies have also shown that the S protein of lineage B beta-coronaviruses substantially increases its receptor affinity when it is pre-incubated with trypsin, i.e., when it is activated proteolytically[69] because liver epithelial cells express trypsin[70] and a plethora of other serine proteases that constantly reshape the extracellular matrix[71], the expression of ACE2 necessary for SARS-CoV-2 target and liver recognition may be lower than in other tissues with decreased extracellular proteolytic activity[72]. According to these observations, it has recently been found, that the S protein of SARS-CoV-2 carries a furin-like proteolytic site never seen before in other coronaviruses of the same lineage[73]. Surprisingly, furin is mainly found in organs suggested to be permissive for SARS-CoV-2 infection, like salivary glands, kidneys, pancreas, and liver[61].

Lastly, other variables, such as ganglioside (GM1)[74], may affect the interaction of S protein-ACE2. Therefore, to gain new molecular and therapeutic perspectives, study should also investigate the S protein-ACE2 interactome more thoroughly. Ou and colleagues tested pseudovirions containing the SARS-CoV-2 S protein in a new study for their ability to infect various cell lines. It is important to note that HuH7 cells, a hepatocyte cell line, and Calu3 cells, a human lung carcinoma cell line, remained more effectively transfected than control pseudovirions by viral vectors carrying the SARS-CoV-2 S protein[75]. In addition, these researches have shown that viral entry can rely on the endocytotic pathway of PIKfyve-TCP2. A cross-check in the Human Protein Atlas discovered that both PIKfyve and TPC2 are expressed at a level similar to that of the lung in the liver and gall bladder, demonstrating the possible relevance of this pathway to hepatic tropism, which consequently extends from basic targeting and identification to intracellular viral replication support.

Letko and colleagues took benefit of HuH7 cells as a lenient model for SARS-CoV and SARS-CoV-2 binding and recognition[67], additional proving SARS-CoV-2 tropism for hepatocytes, in an attempt to develop a new and successful functional viromics screening method aimed at predicting the probability of zoonotic events of known lineage B betacoronaviruses. Notably, after pulmonary (Calu3) and intestinal (CaCo2) cell models[67], the latter representing organs with histopathologically established SARS-CoV-2 infection, HuH7 cells were classified as the third most permissive cell line in this research.

Nevertheless, the capacity to bind and internalize viral particles does not unavoidably mean that successful viral replication is also permissible for the cell type under study. In this context, both Chu and colleagues and Harcourt et al have shown that HuH7 cells support viral replication of SARS-CoV-2[76;77]. Hepatocyte cell lines are now such a proven type of permissive cell for infection with SARS-CoV and SARS-CoV-2 that HuH7 cells have also lately been used as a positive control for immunostaining SARS-CoV-2[78].

While hepatocytes are identified as putative hosts for SARS-CoV-2 in the above-mentioned observations, it is important to note that all data are derived from studies in which cancer cell lines have been used. The ACE2 protein expression in HuH7 cells should be contrasted with that of primary human hepatocytes in order to explain the translational potential of these observations. In addition, future studies are required to discover the molecular changes caused by SARS-CoV-2 infection in hepatocytes.

Recent research by Yang and colleagues, who established SARS-CoV-2 hepatocyte tropism using organoids derived from human pluripotent stem cell (hPSC) hepatocytes and

primary adult human hepatocytes, provides a valid source of knowledge[79]. Pseudovirions expressing SARS-Cov-2 S protein were capable of to infect human hepatocytes in these systems, while infection with SARS-CoV-2 led to vigorous viral replication[79]. Analyses of gene expression have also shown that primary hepatocytes infected with SARS-CoV-2 over-express pro-inflammatory cytokines whereas downregulating main metabolic processes, as mirrored by the inhibition of expression of CYP7A1, CYP2A6, CYP1A2 and CYP2D6[79].

In a recent study, Wang and colleagues have applied electron microscopy imaging to liver samples of two deceased patients with COVID-19 and found hepatocyte viral structures that are strikingly similar to SARS-CoV-2 virions[36]. This increases the possibility that the histopathological changes observed in these patients may be due to the direct cytopathic effects of SARS-CoV-2[37], although there seems to be a lack of a standard hepatitis pattern[37;47;55-57]. On the other hand, in order to validate these preliminary observations of hepatocellular SARS-CoV-2 involvement, further researches with larger biopsy/autopsy cohorts and combined imaging (including immune electron microscopy) may be required.

Cholangiocytes are involved in the synthesis and flow of bile and in the immune response[79]. Preservation of ACE2 and TMPRSS2 expression was shown by single-cell sequencing of human long-term liver ductal organoid cultures[80]. Cholangiocytes experienced syncytia formation after SARSCoV-2 infection, and the quantity of SARS-CoV-2 genomic RNA increased dramatically 24 hours after infection. Similar findings have been gained when SARS-CoV-22 infects adult human cholangiocyte organoids[79]. These findings indicate that in vitro human liver ductal organoids may be prone to SARS-CoV-2 infection and propose that in vivo bile duct epithelium viral replication may also happen.

On the other hand, even with considerably higher ACE2 expression compared with hepatocytes, no clear evidence of cholangiocellular SARS-CoV-2 infection in patients by COVID-19 has been stated to date. Since bile is predominantly formed by hepatocytes and cholangiocytes, the detection of SARS-CoV-2 viral RNA or proteins in bile may be indirect evidence of SARS-CoV-2 cholangiocellular infection due to the persistent and direct interaction among biliary fluids and the cholangiocellular apical membrane. These differences may be based on the fact that throughout the surgical resolution of bile duct obstruction, the positive-checked bile sample was found[81], while the negatively tested bile was gotten from 48h post-mortem autopsies[82;55].

Tight junctions enable cholangiocytes from noxious bile constituents to serve as a defensive barrier for parenchymal liver cells. SARS-CoV-2 viral infection reduced mRNA expression of cholangiocellular tight junction proteins for instance claudin 1 in vitro[80], suggesting decreased cholangiocyte barrier activity. This consequently, may cause liver damage by leakage into the periductal space and adjacent liver parenchyma of potentially noxious bile. Noteworthy, expression of SLC10A2/ASBT bile acid carriers and ABCC7/CFTR chloride channel was substantially decreased by SARS-CoV-2 infection[80]. Bile acid sensing/signaling through cholangiocytes and bicarbonate secretion can be affected by negative regulation of these hepatobiliary transporters, ultimately leading to biliary variations seen in SARS-CoV-2 infection[55]. In addition, SARS-CoV-2 virus-infected cholangiocytes upregulated inflammatory pathways, describing the activation of a reactive phenotype of cholangiocytes[79]. Future research will need to open whether and how SARS-CoV-2 can change pro-inflammatory and pro-fibrogenic cytokine secretion and play a role to the 'reactive cholangiocyte phenotype' that could spread inflammation and fibrosis[83].

Antecedent chronic liver diseases tend to be independent risk factors for pitiable SARS-CoV2 infection outcomes, and the degree of cirrhosis has been identified as a mortality indicator in COVID-19 patients[84]. The instigation of hepatic stellate cells is a major factor as the key cellular source of fibrosis in the developement of chronic liver disease[85] and is promoted by pro-inflammatory and profibrotic signals for instance angiotensin II, developed as part of the pro-fibrotic branch of the renin-angiotensin system by the catalytic action of ACE[86]. Noteworthy, by generating anti-inflammatory and anti-fibrotic angiotensin-(1-7) and thus reducing the angiotensin II/angiotensin-(1-7) ratio, ACE2 frustrates ACE action[86]. ACE2 expression, nevertheless, was not observed either in quiescent or fibrogenic/activated hepatic stellate cells[64;87-9]. These results indicate that SARS-CoV-2 could be a very non-permissive host for these cells. However, the pro-inflammatory environment produced by direct or indirect hepatocellular and cholangiocellular damage associated with SARS-CoV-2 infection can smooth the path of the activation and subsequent induction of fibrosis of hepatic stellate cells. In patients which have underlying CLD, for example NAFLD, the prospect may be even more important. While available evidence indicate that SARS-CoV-2-related liver damage is mild and temporary, enduring follow-up researches would be needed to rule out hepatic fibrosis, particularly in the attendance of pre-existing liver diseases, as a possible long-term results of SARS-CoV-2 infection disease.

Monocyte derived macrophages (MoM) and alveolar macrophages are accepted to express ACE2[91;92] and there is evidence of SARS-CoV[92] and SARS-CoV-2 alveolar macrophage infection with immunohistochemistry finding of viral protein[82;83]. A histopathological examina- tion of the distribution of ACE2 tissues, though, showed no staining in Kupffer cells and further hepatic immune cells[62], while proliferation of Kupffer cells is usually observed in COVID-19 patient livers[35;55]. More in-detail research upon ACE2 expression and de novo single-cell RNAseq analysis were further provoked by the recent SARS-CoV-2 pandemic[60], as was also shown in silico evaluations of RNAseq databases[93;94] that Kupffer

cells do not express ACE2. Nevertheless, it must be held in mind that all the evidence mentioned relates to normal human liver samples. thus, to gain conclusive insights into macrophage ACE2 expression patterns, quantification of ACE2 expression in samples attained from patients with underlying chronic liver disease or acute liver damage may be appropriate.

Noteworthy, MoM can attack the liver and effectively replenish the hepatic resident macrophage population after liver damage and/or Kupffer cell depletion[95-97] (and reviewed in depth in)[98]. Although in vitro studies have shown that MoM does not support successful SARS-CoV (and most likely SARS-CoV-2) replication, infected MoM can function as carriers of the pathogen, preferring ACE2-expressing cell infection in the attack organ[99]. In addition, activation and proliferation of Kupffer cells are commonly observed as a result of systemic inflammation, and activation of Kupffer cells has been documented in liver samples of deceased SARS-CoV-2 infected patients[35;55]. Therefore, even though Kupffer cells do not express ACE2, by propagating inflammatory stimuli, monocytic cells can play a key role in COVID-19-mediated liver injury.

Hepatic Steatosis by SARS-CoV-2 Infection

In liver autopsies of novel coronavirus infection, microvesicular and macrovesicular steatosis have been detected as the only risk factor for liver damage and SARS-CoV-2 hepatocellular infection has been confirmed in certain cases[35;55]. It is necessary to distinguish hepatic lipid accu- mulation due to SARS-CoV-2 infection from pre-existing NAFLD, which has been presented to increase the risk of poor result in patients with COVID-19[56]. Substantial contributors to the production of hepatic steatosis in COVID-19 could be deregulated in host lipid metabolism and mitochondrial function due to possible direct SARS- CoV-2 cytopathic effects and/or cytokine storm-induced immunopathology along with drug side effects (e.g., cor-ticosteroids).

Genetic or acquired mitochondrial β-oxidation defects usually cause microvesicular steatosis[100]. Preliminary findings indicate that mitochondrial function is impaired by SARSR-CoV-2[101]. In addition, a study also reported mitochondrial crista abnormalities in patients with COVID-19 liver specimens[35]. Excitingly, impaired mitochondrial function has also been involved in NAFLD/NASH pathogenesis[102]. Therefore, infection with SARS-CoV-2 could also exacerbate the metabolic condition and aggravate these processes with pre-existing NAFLD.

It is understood that endoplasmic reticulum (ER) stress induces de novo lipogenesis in hepatocytes[103]. In the induction of ER stress, some researches have included the infection of SARSCoV. For example, major up-regulation of glucose-regulated protein 78 (GRP78) and GRP94 ER stress indicators has been detected in several cell lines for SARS-CoV infection[104-106]. The protein of the coronavirus S tends to be a significant burden for the host ER and may play a critical role in inducing ER stress[104;105]. Readjustment of intracellular membranes throughout SARSCoV-2 infection by huge reduction of lipid constituents from the ER can also lead to ER stress[107]. In addition, in vitro SARS-CoV infection overactivates the ER stress-related PERK-eIF2-alpha pathway[108]. Lastly, elec- tron microscopy studies that have demonstrated hepatocellular SARS-CoV-2 infection have documented pathological ER dilatation in infected hepatocytes[35], most likely causing ER stress. Generally, such data could show that, like other coronaviruses, SARS-CoV-2 induces ER stress on infection, and that de novo lipogenesis induced by ER stress can also lead to the production of steatosis in patients with COVID-19.

The mammalian target of rapamycin (mTOR)[109], which is also the key regulator for autophagy, also induces de novo lipogenesis[110]. SARS-CoV has formerly been shown to hijack the autophagy pathway via processes extremely conserved in novel corona virus that depend on viral non-structural protein 6 (nsp6)[111-113]. In addition, mTOR hyperactivation and inhibition of the mTOR signaling pathway by rapamycin inhibiting viral replication have been saw in MERS-CoV-infected HuH7 cells[114]. Considering the recent findings that autophagy is limited by SARS-CoV-2 infection[115], it is tempting to thik that SARS-CoV-2, SARS-CoV and MERS-CoV share a common mechanism of infection based on mTOR. In addition, substantially increased mTOR activity was seen in IL-6 stimulation[116]. Therefore, SARS-CoV-2 infection could result in hyper-activation of hepatic mTOR signaling through direct hepatic cell infection or indirect systemic IL-6-dependent cytokine storm-related effects that could pay out for the steatotic phenotype in patients with COVID-19 liver injury.

Induction of host lipogenesis may be necessary for the SARS CoV-2 life cycle, but detrimental for the host. Certainly, improved de novo lipogenesis could provide adequate quantities of lipids for the virus to produce the vesicular systems necessary for viral replication and exocytosis. In addition, mTOR-mediated protein synthesis promotion[117;118] and autophagolysosome formation inhibition[119;120] can favor viral replication whereas preventing viral degradation and sufficient immune response ignition. Since insulin and glucose signaling positively control the function of mTOR in the liver[121;122], essential overactivation of mTOR in patients with obesity and diabetes mellitus[123;124] could at least partially explain their increased risk of worse COVID-19 outcomes.

Cytokines storm

A main contributing factor may be the cytokine storm feature of SARS-CoV-2-associated viral sepsis[125], as cytokines for instance TNF-alpha, IL-1 and IL-6 can cause hepatocellular cholestasis by down-regulating hepatobiliary uptake and excretory systems[126;127], which are close to the pathomechanisms observed in sepsis-induced cholestasis[126-130]. Additional research would have to investigate whether serum bile acids, alike to sepsis,

may be important prognostic parameters in SARS-CoV-2 infection as the most reliable markers of cholestasis[127- 131]. continued IL-6 systemic signaling triggered by infec- tion with SARS-CoV-2 provokes a suppression of albumin synthesis based on C/EBPβ [132]. Cholestasis in SIRS due to repressed hepatobiliary excretory activity, in addition to hypo-albuminemia, may be considered as part of the negative acute phase response in COVID-19.

Hepatic inflammation encompassing inherent immune cell activation and cytokine release is a well-established awakening of multiple causes of liver damage[133]. An association was found between lymphopenia and liver injury in some of the presented case series of SARS-CoV-2 infection, and CRP 20 mg/L and a lymphocyte count <1.1x10^9/L were independent risk factors for liver damage. In particular, lymphopenia in the SARS-CoV-2 infection research was stated to be more prone to fatal outcomes in 63 percent to 70.3 percent of patients and those with lesser lymphocyte counts[134].

Along with hepatocellular characteristics, bile duct modifications have been perceived in postmortem researches, for example ductular proliferation[55]. IL-6 is a dominant mitogenic cholangiocellular factor[135] and provokes a proliferative and pro-inflammatory phenotype[83;136]. Consequently, bile ducts of patients with SARS-CoV-2 infection may be subjected to a 'triple hit' from (I) respiratory failure hypoxia (potentially exacerbated by peribiliary arterial plexus obliteration by vascular/thrombotic changes); (ii) systemic SIRS lead to a reactive cholangiocyte phenotype or secretory phenotype linked with senescence, thereby actively spreading inflammation along with fibrosis and (iii) expected cholangiocyte viral infection itself. As a result, the hepatobiliary system can come to be a significant target for SARS-CoV-2 infection long-term liver complication. Critical Sclerosing Cholangitis (SSC-CIP) is an uncommon but clinically important complication in seriously ill patients with serious trauma, burn injury, severe respiratory failure or vasopressor therapy because of hemodynamic instability [137;138]. The key causes for the degradation of the biliary epithelium in SSC-CIP are malperfusion and hypoxia along with repeated inflammatory stimuli[127], both conditions existing in serious patients with COVID-19.

Longstanding hepatic follow-up for SARS-CoV-2 infected survivors who have undergone a serious course of illness, for instance ARDS with ECMO and elongated ICU admission, may also be considered. timely diagnosis is important for the best management of SSC-CIP symptoms and disease progress that might be counteracted with anti-cholestatic, cholangio-protective drugs like UDCA or newer norUDCA[139-141].

Pre-existence Hepatitis B re-activation

Reactivation of pre-existing hepatitis B is one of the major complications of SARS-CoV-2 infection in the liver. A recent research showed that patients co-infected with novel corona virus and HBV with liver damage are more likely to have a worse outcome and a poor prognosis[142].

Hepatitis B reactivation was characterized as sudden re-emergence of HBV-DNA viremia in patients with HBV infection that was before inactive or resolved, or abrupt and quick increase of HBV-DNA levels by at least 2 log10 in patients with HBV-DNA previously measurable.

As discussed earlier, SARS-CoV-2 induces cytokine storms in the body. consequently, special procedures are used to inhibit the immune system from hyperactivating. One of these therapies is the use of corticosteroids, which, owing to the lack of favorable clinical and analytical success of other approaches, has become a preferred weapon.

Corticosteroids, like all immunosuppressant drugs, are not risk-free and can contribute to certain complications. Reactivating pre-existing infections, especially hepatitis B viruses, is one of the hazards of taking corticosteroids.

In a case study, Aldhaleei et al, identified the reactivation of the hepatitis B virus (HBV) caused by SARS-CoV-2 in a young adult with impaired mental status and serious transaminitis. The patient's aspartate aminotransferase (AST; 4,933 U/L), alanine aminotransferase (AL T; 4,758 U/L) and total bilirubin (183.9 mmol/L) levels were very high[143].

A further retrospective review of 347 patients with COVID-19, including 20 patients with chronic HBV infection and 327 without chronic HBV infection, revealed 3 reactivations of pre-existing inactive hepatitis B infection.

On the other hand, a research conducted by Yu et al showed that the effects of SARS-CoV-2 on the dynamics of chronic HBV infection did not seem clear. In these people, SARS-CoV-2 infection will not be the cause of HBV reactivation[144].

As can be seen, research into the effect of the SARS-CoV-2 on reactivation of the hepatitis B virus is limited. Existing researches also are contradictory, with some emphasizing that the SARS-CoV-2 activates inactivated hepatitis B, but some explain that COVID-19 has no effect on chronic hepatitis B virus reactivation. Therefore, it is needed more research in this area.

Hypoxic Hepatitis due to SARS-CoV2

Multifactorial causes of hypoxic hepatitis are present. Generally, more than 90% of all cases are due to heart failure, sepsis, and respiratory failure[145-148]. Furthermore, due to increased central venous pressure, right-sided heart failure has been shown to worsen liver damage due to liver congestion[145-151]. Hypoxia cause in hepatic cell death in cases of long-lasting hemodynamic and/or respiratory failure, which is histopathologically characterized as centrilobular necrosis[152].

ARDS is the most common complication of COVID-19 disease which needing critical care management, envolving invasive ventilation, elevated positive end-expiratory pressure (PEEP) and vasoconstrictor therapy in the case of hemodynamic instability[153-156]. These causes can be

followed by right ventricular dysfunction due to high vascular pulmonary resistance due to hypoxaemia and ARDS hypercapnia[157;158].

In addition, COVID-19 lead to a hyper-coagulate condition with a substantial incidence of pulmonary thrombotic complications that worsen acute right-sided heart failure and thus liver congestion[159]. In most cases, nevertheless, SARS-CoV-2-related liver injury was usually mild and did not reach >5 times the upper limit of reference, so it did not meet the diagnostic requirements for hypoxic hepatitis[9].

These results have also been found in critically ill patients referred to the ICU, indicating that sufficient oxygen supply to the liver is guaranteed by compensatory mechanisms, including in cases of serious respiratory failure during COVID-19 disease [9-17].

Drug-Induced Liver Injury

At the onset of SARS-CoV-2 outbreak, Evidence-based treatment was not existing. Several studies have been conducted over time, enabling us to provide scientifically based guidelines for the treatment of COVID-19 disease. Different antiviral (remdesivir, lopinavir/ritonavir), antibiotic (macrolide), antimalarial/antirheumatic (hydroxychloroquine), immunomodulating (corticosteroids, tocilizumab) and antipyretic (acetaminophen) medications have been used in clinical or off-label trials in the meantime.

Hepatotoxic potential has previously been established in in vitro/in vivo trails and their respective registration researches for several of these drugs (e.g. ritonavir, remdesivir). In addition, corticosteroid treatment, which is now suggested by the WHO in patients with serious infection with SARS-CoV-2 [160], is specifically linked with steatosis or glycogenosis[161].

The first event of tocilizumab-associated DILI in a SARS-CoV-2 infected patient has lately been identified[70] Tocilizumab has limited hepatic metabolism, and interaction with the IL-6 pathway, which plays a vital role in the healing of the liver, is the most possible etiology of its hepatotoxic impact[162].

Conclusions

Longstanding hepatic follow-up for SARS-CoV-2 infected survivors who have undergone a serious course of illness, for instance ARDS with ECMO and elongated ICU admission, may also be considered. timely diagnosis is important for the best management of SSC-CIP symptoms and disease progress that might be counteracted with anti-cholestatic, cholangioprotective drugs like UDCA or newer norUDCA[139-141].

These results were also found in critically ill patients referred to the intensive care unit, indicating that adequate liver oxygen supply is provided by compensatory mechanisms, including in cases of severe respiratory failure during COVID-19 disease [9-17].

As can be seen, research into the effect of the SARS-CoV-2 on reactivation of the hepatitis B virus is limited. Existing researches also are contradictory, with some emphasizing that the SARS-CoV-2 activates inactivated hepatitis B, but some explain that COVID-19 has no effect on chronic hepatitis B virus reactivation. Therefore, it is needed more research in this area.

CONFLICT OF INTEREST

None.

References

1. WHO.Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected:interim guidance. Available: HYPERLINK "https://www.who.int/internalpublicationsdetail/clinicalmanagementofsevereacuteresp" https://www.who.int/internalpublicationsdetail/clinicalmanagementofsevereacuteresp iratoryinfectionwhennovelcoronavirus(ncov)infectionissuspected

2. WHO.Statement on the second meeting of the International Health Regulations. 2005. Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV) Available: https://www.who.int/newsroom/detail/30-01-2020-statement-on-thesecond-meeting-of-the-international-healthregulations-(2005)-emergency-committee regarding-the-outbreak-of-nov- el-coronavirus-(2019-ncov)

3. WHO.WHO Director-General's remarks at the media briefing on 2019-nCoV on 11February 2020. Available: HYPERLINK "https://www.who.int/dg/speeches/detail/w%20ho-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on- 11-february-2020" https://www.who.int/dg/speeches/detail/w ho-director-general-s-remarks-at-the-media-briefing-on- 2019-ncov-on-11-february-2020

4. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579:270-273 [PMID: 32015507DOI: 10.1038/s41586-020-2012-7]1

5. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72â ¯314 Cases from the Chinese Center for Disease Control and Prevention. JAMA2020; 323:1239-1242 [PMID: 32091533DOI: 10.1001/jama.2020.2648] 2.

6. WHO. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-2019). February 16-24, 2020

7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment

Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med2020; 382:1708-1720 [PMID: 32109013DOI: 10.1056/NEJMoa2002032]4

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet2020; 395:1054-1062 [PMID: 32171076 DOI: 10.1016/s0140-6736(20)30566-3]

9. Kulkarni AV, Kumar P, Tevethia HV, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. Aliment Pharmacol Ther. 2020;52.

10. Bertolini A, van de Peppel IP, Bodewes FA, et al. Abnormal liver function tests in COVID-19 patients: relevance and potential pathogenesis. Hepatology. 2020. https://doi.org/10.1002/hep.31480

11. Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and Liver. J. Hepatol. 2020. HYPERLINK "https://doi.org/10.1016/j" https://doi.org/10.1016/j. jhep.2020.06.006

12. Bloom PP, Meyerowitz EA, Reinus Z, et al. Liver Biochemistries in Hospitalized Patients with COVID-19. Hepatology. hep.31326 (2020): https://doi.org/10.1002/hep.31326

13. Hao SR, Zhang SY, Lian JS, et al. liver enzyme elevation in coronavirus disease 2019: a multicenter, retrospective, Cross-Sectional Study. Am J Gastroenterol. 2020; 115:1075-1083.

14. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1827 Patients in a Major U.S. Hospital Network. Hepatology. 2020. https://doi.org/10.1002/hep.31487

15. Yip TCF, Lui GCY, Wong VWS, et al. Liver injury is independently associated with adverse clinical outcomes in patients with COVID-19. Gut. 2020. HYPERLINK "https://doi.org/10.1136/gutjn%20l-2020" https://doi.org/10.1136/gutjn l-2020 321726

16. Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol. 2020. https://doi.org/10.1016/j.jhep.2020.06.001

17. Jiang S, Wang R, Li L, et al. Liver Injury in Critically Ill and Non-critically Ill COVID-19 Patients: A Multicenter, Retrospective, Observational Study. Front Med. 2020;7.

18. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. (2020-01-11) [2020-03-05]. HYPERLINK "http://nc.yuntsg.com/one1.do" http://nc.yuntsg.com/one1.do.

19. Verelst F, Kuylen E, Beutels P. Indications for healthcare surge capacity in European countries facing an exponential increase in coronavirus disease (COVID-19) cases, March 2020. Euro Surveill 2020:25.

20. Mannelli C. Whose life to save? Scarce resources allocation in the COVID-19 outbreak. J Med Ethics 2020.

21. Albano D, Bertagna F, Bertolia M, Bosio G, Lucchini S, Motta F, et al. Incidental Findings Suggestive of Covid-19 in Asymptomatic Patients Undergoing Nuclear Medicine Procedures in a High Prevalence Region. J Nucl Med 2020.

22. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19. N Engl J Med 2020.

23. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med 2020.

24. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. The Journal of Heart and Lung Transplantation 2020.

25. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020.

26. Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. Gastroenterology 2020.

27. Gao QY, Chen YX, Fang JY. Novel coronavirus infection and gastrointestinal tract. J Dig Dis 2019; 21:125–6. 2020.

28. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020.

29. Li J, Fan JG. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. J Clin Transl Hepatol 2020; 8:13–7.

30. Rismanbaf A, Zarei S. Liver and Kidney Injuries in COVID-19 and Their Effects on Drug Therapy; a Letter to Editor. Arch Acad Emerg Med 2020;8: e17.

31. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40: liv.14435.

32. Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease - what we know on 1st May 2020. Aliment Pharmacol Ther. 2020. https://doi.org/10.1111/apt.15813

33. Wu J, Song S, Cao HC, Li LJ. Liver diseases in COVID-19: Etiology, treatment and prognosis. World J Gastroenterol. 2020; 26:2286-2293.

34. Yadav DK, Singh A, Zhang Q, et al. Involvement of liver in COVID-19: systematic review and meta-analysis. Gut. 2020. https://doi.org/10.1136/gutjn l-2020-322072

35. 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.

36. Wang Y, Lu F, Zhao J. Reply to: Correspondence relating to "SARSCoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19". J Hepatol. 2020. HYPERLINK "https://doi" https://doi.org/10.1016/j.jhep.2020.06.028

37. Kucharski AJ, Russell TW, Diamond C, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis. 2020; 20:553558.

38. Kumar-MP, Mishra S, Jha DK, et al. Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. Hepatol Int. 2020. https://doi.org/10.1007/s12072-020-10071 -9

39. Paliogiannis P, Zinellu A. Bilirubin levels in patients with mild and severe Covid-19: A pooled analysis. Liver International. 2020; 40:1787-1788.

40. Parasa S, Desai M, Chandrasekar VT, et al. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients with Coronavirus Disease 2019. JAMA Netw Open. 2020;3: e2011335.

41. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS,

Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status, Mil. Med. Res. 7 (1) (2020) 11, HYPERLINK "https://doi.org/10.1186/s40779-020-00240-0" https://doi.org/10.1186/s40779-020-00240-0.

42. Buruk K, Ozlu T. New Coronavirus: SARS-COV-2, Mucosa, 2020, pp. 1–4 doi:10.33204/mucosa.706906.

43. Jin X, Lian J, Hu J. et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms, Gut (2020), HYPERLINK "https://doi.org/10.1136/gutjnl-2020-320926Published" https://doi.org/10.1136/gutjnl-2020-320926Published Online First: 24 March.

44. Jiehao Cai, Jing Xu, Daojiong Lin, zhi Yang, Lei Xu, Zhenghai Qu, et al., A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features, Clinical Infectious Diseases, ciaa198, HYPERLINK "https://doi.org/10.1093/cid/" https://doi.org/10.1093/cid/ ciaa198.

45. Chen J. et al., Clinical Features of Stool SARS-CoV-2 RNA Positive in 137 COVID-19 Patients in Taizhou, China, (2020),https://doi.org/10.2139/ssrn.3551383 Available at SSRN: or HYPERLINK "https://ssrn.com/abstract=3551383" https://ssrn.com/abstract=3551383.

46. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497-506.

47. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. J Hepatol. 2020. https://doi.org/10.1016/j.jhep.2020.04.006

48. Bernal-Monterde V, Casas-Deza D, Letona-Giménez L, et al. SARSCoV-2 Infection Induces a Dual Response in Liver Function Tests: Association with Mortality during Hospitalization. Biomedicines. 2020; 8:328

49. Xie M, Chen Q. Insight into 2019 novel coronavirus — An updated interim review and lessons from SARS-CoV and MERS-CoV. Int J Infect Dis. 2020; 94:119-124.

50. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. The Lancet Gastroenterol Hepatol. 2020; 5:428-430.

51. Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver Int. 2020. https://doi.org/10.1111/liv.14470

52. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA - J Am Med Assoc. 2020; 324:782-793.

53. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020; 395:1517-1520.

54. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet. 2020; 395:1417-1418.

55. Lax SF, Skok K, Zechner P, et al. Pulmonary arterial thrombosis in covid-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020; M20–2566: https://doi.org/10.7326/M20-2566

56. Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. J Hepatol. 2020. https://doi.org/10.1016/j.jhep.2020.03.044

57. Sonzogni A, Previtali G, Seghezzi M, et al. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. Liver Int. 2020;40: 2110-2116.

58. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and Renal Tropism of SARS-CoV-2. N Engl J Med. 2020. https://doi.org/10.1056/NEJMc 2011400

59. Chappell JD, Dermody TS. Biology of Viruses and Viral Diseases. In Bennet JE, Dolin R, Blase MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (vol. 2, 1681-1693. e4). Elsevier Inc.; 2014.

60. Chai X, Hu L, Zhang Y, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv. 2020. HYPERLINK "https://doi" https://doi.org/10.1101/2020.02.03.931766

61. Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: Putative mechanisms of liver involvement in COVID-19. Liver Int. 2020; 40:2038-2040.

62. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; 203:631-637.

63. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMo a2015432

64. Paizis G, Tikellis C, Cooper ME, et al. Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. Gut. 2005; 54:1790 1796.

65. Huang Q, Xie Q, Shi CC, et al. Expression of angiotensin-converting enzyme 2 in CCL4-induced rat liver fibrosis. Int J Mol Med. 2009; 23:717-723.

66. Suárez-Fariñas M, Tokuyama M, Wei G, et al. Intestinal inflammation modulates the expression of ACE2 and TMPRSS2 and potentially overlaps with the pathogenesis of SARS-CoV-2 related disease. Gastroenterology. 2020.

67. Gkogkou E, Barnasas G, Vougas K, Trougakos IP. Expression profiling meta-analysis of ACE2 and TMPRSS2, the putative anti-inflammatory receptor and priming protease of SARS-CoV-2 in human cells, and identification of putative modulators. Redox Biol. 2020; 36:101615.

68. Muhovi D, Bojovi J, Bulatovi A, et al. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. Liver Int. 2020; 40:1901-1905.

69. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol.2020;5:562-569.

70. Koshikawa N, Hasegawa S, Nagashima Y, et al. Expression of trypsin by epithelial cells of various tissues, leukocytes, and neurons in human and mouse. Am J Pathol. 1998; 153:937-944.

71. Mohammed FF, Khokha R. Thinking outside the cell: Proteases regulate hepatocyte division. Trends Cell Biol. 2005; 15:555-563.

72. Shulla A, Heald-Sargent T, Subramanya G, et al. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. J Virol. 2011; 85:873-882.

73. Coutard B, Valle C, de Lamballerie X, et al. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like

cleavage site absent in CoV of the same clade. Antiviral Res. 2020; 176:104742.

74. Fantini J, Di Scala C, Chahinian H, Yahi N. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents. 2020. HYPERLINK "https://doi.org/10.1016/j.ijant" https://doi.org/10.1016/j.ijant imicag.2020.105960

75. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020; 11:1620.

76. Chu H, Chan JFW, Yuen TTT, et al. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARSCoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. The Lancet Microbe. 2020;1: e14-e23.

77. Harcourt J, Tamin A, Lu X, et al. Severe acute respiratory syndrome coronavirus 2 from patient with coronavirus disease, United States. Emerg Infect Dis. 2020; 26:1266-1273.

78. Zhang H, Zhou P, Wei Y, et al. Histopathologic Changes and SARSCoV-2 Immunostaining in the Lung of a Patient with COVID-19. Ann Intern Med. 2020;172.

79. Yang L, Han Y, Nilsson-Payant BE, et al. A Human Pluripotent Stem Cell-based Platform to Study SARS-CoV-2 Tropism and Model Virus Infection in Human Cells and Organoids. Cell Stem Cell. 2020; 27:125-136.e7.

80. Zhao B, Ni C, Gao R, et al. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. Protein and Cell. 2020;1. https://doi.org/10.1007/s13238-020-00718 -6

81. Han D, Fang Q, Wang X. SARS-CoV-2 was found in the bile juice from a patient with severe COVID-19. J Med Virol. 2020. HYPERLINK "https://doi.org/10.1002/jmv.26169" https://doi.org/10.1002/jmv.26169.

82. Skok K, Stelzl E, Trauner M, Kessler HH, Lax SF. Post-mortem viral dynamics and tropism in COVID-19 patients in correlation with organ damage. Virchows Arch. 2020. https://doi.org/10.1007/s0042 8-020-02903 -8.

83. Banales JM, Huebert RC, Karlsen T, et al. Cholangiocyte pathobiology. Nat Rev Gastroenterol Hepatol. 2019; 16:269-281.

84. Moon AM, Webb GJ, Aloman C, et al. High Mortality Rates for SARS-CoV-2 Infection in Patients with Pre-existing Chronic Liver Disease and Cirrhosis: Preliminary Results from an International Registry. J Hepatol. 2020. HYPERLINK "https://doi.org/10.1016/j" https://doi.org/10.1016/j. jhep.2020.05.013

85. Mederacke I, Hsu CC, Troeger JS, et al. Fate tracing reveals hepatic stellate cells as dominant contributors to liver fibrosis independent of its aetiology. Nat Commun. 2013;4.

86. Shim KY, Eom YW, Kim MY, Kang SH, Baik SK. Role of the renin-angiotensin system in hepatic fibrosis and portal hypertension. Korean J Intern Med. 2018; 33:453-461.

87. Lubel JS, Herath CB, Tchongue J, et al. Angiotensin-(1–7), an alternative metabolite of the renin-angiotensin system, is upregulated in human liver disease and has antifibrotic activity in the bile-ductligated rat. Clin Sci. 2009; 117:375-386.

88. De Minicis S, Seki E, Uchinami H, et al. Gene Expression Profiles During Hepatic Stellate Cell Activation in Culture and In Vivo. Gastroenterology. 2007; 132:1937-1946.

89. Marcher AB, Bendixen SM, Terkelsen MK, et al. Transcriptional regulation of Hepatic Stellate Cell activation in NASH. Sci Rep. 2019; 9:1-13.

90. Akil A, Endsley M, Shanmugam S, et al. Fibrogenic Gene Expression in Hepatic Stellate Cells Induced by HCV and HIV Replication in a Three Cell Co-Culture Model System. Sci Rep. 2019; 9:1-12.

91. Keidar S, Gamliel-Lazarovich A, Kaplan M, et al. Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients. Circ Res. 2005; 97:946-953.

92. Shieh WJ, Hsiao CH, Paddock CD, et al. Immunohistochemical, in situ hybridization, and ultrastructural localization of SARSassociated coronavirus in lung of a fatal case of severe acute respiratory syndrome in Taiwan. Hum Pathol. 2005; 36:303-309.

93. Zhu Y, Jiang M, Gao L, Huang X. Single Cell Analysis of ACE2 Expression Reveals the Potential Targets for 2019-nCoV. Preprints.org. 2020;1-14. https://doi.org/10.20944/ prepr ints2 02002. 0221.v1

94. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun. 2020; 526:135-140.

95. Scott CL, Zheng F, De Baetselier P, et al. Bone marrow-derived monocytes give rise to self-renewing and fully differentiated Kupffer cells. Nat Commun. 2016;7.

96. Blériot C, Dupuis T, Jouvion G, et al. Liver-Resident Macrophage Necroptosis Orchestrates Type 1 Microbicidal Inflammation and Type-2-Mediated Tissue Repair during Bacterial Infection. Immunity. 2015; 42:145-158.

97. David BA, Rezende RM, Antunes MM, et al. Combination of mass cytometry and imaging analysis reveals origin, location, and functional repopulation of liver myeloid cells in mice. Gastroenterology. 2016; 151:1176-1191.

98. Guillot A, Tacke F. Liver Macrophages: Old Dogmas and New Insights. Hepatol Commun. 2019; 3:730-743.

99. Abassi Z, Knaney Y, Karram T, Heyman SN. The Lung Macrophage in SARS-CoV-2 Infection: A Friend or a Foe? Front Immunol. 2020; 11:1312.

100. Tandra S, Yeh MM, Brunt EM, et al. Presence and significance of microvesicular steatosis in nonalcoholic fatty liver disease. J Hepatol. 2011; 55:654-659.

101. Miller B, Silverstein A, Flores M, et al. SARS-CoV-2 induces a unique mitochondrial transcriptome signature. Prepr. 2020. https://doi.org/10.21203/ RS.3.RS-36568/ V1. https://www.researchsquare.com/article/rs-36568/v1

102. Koliaki C, Szendroedi J, Kaul K, et al. Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. Cell Metab. 2015; 21:739-746.

103. Rutkowski DT, Wu J, Back SH, et al. UPR Pathways Combine to Prevent Hepatic Steatosis Caused by ER Stress-Mediated Suppression of Transcriptional Master Regulators. Dev Cell. 2008; 15:829-840.

104. Chan C-P, Siu KL, Chin KT, et al. Modulation of the unfolded protein response by the severe acute respiratory syndrome coronavirus spike protein. J Virol. 2006; 80:9279-9287.

105. Versteeg GA, van de Nes PS, Bredenbeek PJ, Spaan WJM. The Coronavirus Spike Protein Induces Endoplasmic Reticulum Stress

and Upregulation of Intracellular Chemokine mRNA Concentrations. J Virol. 2007; 81:10981-10990.

106. Minakshi R, Padhan K, Rani M, et al. The SARS Coronavirus 3a Protein Causes Endoplasmic Reticulum Stress and Induces LigandIndependent Downregulation of the Type 1 Interferon Receptor. PLoS One. 2009;4: e8342

107. Knoops K, Kikkert M, Van Den Worm SH, et al. SARS-Coronavirus Replication Is Supported by a Reticulovesicular Network of Modified Endoplasmic Reticulum. PLoS Biol. 2008;6.

108. Krähling V, Stein DA, Spiegel M, Weber F, Mühlberger E. Severe Acute Respiratory Syndrome Coronavirus Triggers Apoptosis via Protein Kinase R but Is Resistant to Its Antiviral Activity. J Virol. 2009; 83:2298-2309.

109. Peterson T, Sengupta S, Harris T, et al. MTOR complex 1 regulates lipin 1 localization to control the srebp pathway. Cell. 2011; 146:408-420

110. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. Nat Rev Mol Cell Biol. 2020; 21:183-203.

111. Prentice E, Jerome WG, Yoshimori T, Mizushima N, Denison MR. Coronavirus Replication Complex Formation Utilizes Components of Cellular Autophagy. J Biol Chem. 2004; 279:10136-10141.

112. Cottam EM, Maier HJ, Manifava M, et al. Coronavirus nsp6 proteins generate autophagosomes from the endoplasmic reticulum via an omegasome intermediate. Autophagy. 2011; 7:1335-1347.

113. Cottam EM, Whelband MC, Wileman T. Coronavirus NSP6 restricts autophagosome expansion. Autophagy. 2014; 10:1426-1441.

114. Kindrachuk J, Ork B, Hart BJ, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. Antimicrob Agents Chemother. 2015; 59:1088-1099.

115. Gassen NC, Papies J, Bajaj T, et al. Analysis of SARS-CoV-2-controlled autophagy reveals spermidine, MK-2206, and niclosamide as putative antiviral therapeutics. bioRxiv. 2020.04.15.997254 (2020). HYPERLINK "https://doi.org/10.1101/2020.04.15.997254" https://doi.org/10.1101/2020.04.15.997254.

116. He M, Shi X, Yang M, et al. Mesenchymal stem cells-derived IL-6 activates AMPK/mTOR signaling to inhibit the proliferation of reactive astrocytes induced by hypoxic-ischemic brain damage. Exp Neurol. 2019; 311:15-32.

117. Brunn GJ, Hudson CC, Sekuli A, et al. Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin. Science (80-.). 1997; 277:99-101.

118. Hannan KM, Brandenburger Y, Jenkins A, et al. mTOR-Dependent Regulation of Ribosomal Gene Transcription Requires S6K1 and Is Mediated by Phosphorylation of the Carboxy-Terminal Activation Domain of the Nucleolar Transcription Factor UBF†. Mol Cell Biol. 2003; 23:8862-8877.

119. Hosokawa N, Hara T, Kaizuka T, et al. Nutrient-dependent mTORCl association with the ULK1-Atg13-FIP200 complex required for autophagy. Mol Biol Cell. 2009; 20:1981-1991.

120. Kim YM, Jung CH, Seo M, et al. MTORC1 phosphorylates UVRAG to negatively regulate autophagosome and endosome maturation. Mol Cell. 2015; 57:207-218.

121. Gwinn DM, Shackelford DB, Egan DF, et al. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol Cell. 2008; 30:214-226.

122. Inoki K, Zhu T, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. Cell. 2003; 115:577-590

123. Harrington LS, Findlay GM, Gray A, et al. The TSC1-2 tumor suppress controls insulin-PI3K signaling via regulation of IRS proteins. J Cell Biol. 2004; 166:213-223.

124. Hsu PP, Kang SA, Rameseder J, et al. The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. Science (80-.). 2011; 332:1317-1322.

125. Dhainaut JF, Marin N, Mignon A, Vinsonneau C, Sprung C. Hepatic response to sepsis: Interaction between coagulation and inflammatory processes. Crit Care Med. 2001;29: (Lippincott Williams and Wilkins).

126. Geier A, Fickert P, Trauner M. Mechanisms of disease: Mechanisms and clinical implications of cholestasis in sepsis. Nat Clin Pract Gastroenterol Hepatol. 2006; 3:574-585.

127. Horvatits T, Drolz A, Trauner M, Fuhrmann V. Liver Injury and Failure in Critical Illness. Hepatology. 2019; 70:2204-2215.

128. Trauner M, Fickert P, Stauber RE. Inflammation-induced cholestasis. Gastroenterol Hepatol (Australia). 1999; 14:946-959.

129. Moseley RH. Sepsis-associated cholestasis. Gastroenterology. 1997; 112:302-306.

130. Bauer M, Press AT, Trauner M. The liver in sepsis: Patterns of response and injury. Curr Opin Crit Care. 2013; 19:123-127.

131. Recknagel P, Gonnert FA, Westermann M, et al. Liver dysfunction and phosphatidylinositol-3-kinase signalling in early sepsis: experimental studies in rodent models of peritonitis. PLoS Med. 2012;9: e1001338.

132. Xu Z, Karlsson J, Huang Z. Modeling the Dynamics of Acute Phase Protein Expression in Human Hepatoma Cells Stimulated by IL-6. Processes. 2015; 3:50-70.

133. McDonald B and Kubes P. Innate immune cell trafficking and function during sterile inflammation of the liver. Gastroenterology2016; 151: 1087–1095.

134. Li L, Li S, Xu M, et al. Risk factors related to hepatic injury in patients with corona virus disease 2019. medRxiv Preprint 10 March 2020: doi: HYPERLINK "https://doi.org/10.1101/2020.02.28.20028514" https://doi.org/10.1101/2020.02.28.20028514

135. Yokomuro S, Tsuji H, Lunz JG, et al. Growth control of human biliary epithelial cells by interleukin 6, hepatocyte growth factor, transforming growth factor β1, and activin A: Comparison of a cholangiocarcinoma cell line with primary cultures of non- neoplastic biliary epithelial cells. Hepatology. 2000; 32:26-35.

136. O'Hara SP, Tabibian JH, Splinter PL, Larusso NF. The dynamic biliary epithelia: Molecules, pathways, and disease. J Hepatol. 2013; 58:575-582.

137. Gelbmann CM, Rümmele P, Wimmer M, et al. Ischemic-like cholangiopathy with secondary sclerosing cholangitis in critically ill patients. Am J Gastroenterol. 2007; 102:1221-1229.

138. Zilkens C, Friese J, Koeller M, Muhr G, Schinkel C. Hepatic Failure After Injury - A Common Pathogenesis with Sclerosing Cholangitis? Eur J Med Res. 2008; 13:309-313.

139. Fiorotto R, Spirlì C, Fabris L, et al. Ursodeoxycholic Acid Stimulates Cholangiocyte Fluid Secretion in Mice via CFTR-Dependent ATP Secretion. Gastroenterology. 2007; 133:1603-1613.

140. Beuers U, Trauner M, Jansen P, Poupon R. New paradigms in the treatment of hepatic cholestasis: From UDCA to FXR, PXR and beyond. J Hepatol. 2015;62: S25-S37.

141. Fickert P, Hirschfield GM, Denk G, et al. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. J Hepatol. 2017; 67:549-558.

142. Zou X, Fang M, Li S, et al. Characteristics of liver function in patients with SARS-CoV-2 and chronic HBV co-infection.Clin Gastroenterol Hepatol. 2020; S1542-3565(20):30821.

143. Aldhaleei W A, Alnuaimi A, Bhagavathula A S (June 15, 2020). COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case from the United Arab Emirates. Cureus 12(6): e8645. DOI 10.7759/cureus.8645

144. Yu R, Tan S, Dan Y, Lu Y, Zhang J, Tan Z, He X, Xiang X, Zhou Y, Guo Y, Deng G, Chen Y and Tan W. Effect of SARS-CoV-2 coinfection was not apparent on the dynamics of chronic hepatitis B infection. Virology 553 (2021) 131–134

145. Horvatits T, Trauner M, Fuhrmann V. Hypoxic liver injury and cholestasis in critically ill patients. Curr Opin Crit Care. 2013; 19:128-132.

146. Waseem N, Chen P-H. Hypoxic Hepatitis: A Review and Clinical Update. J Clin Transl Hepatol. 2016; 4:263-268.

147. Henrion J, Descamps O, Luwaert R, et al. Hypoxic hepatitis in patients with cardiac failure: incidence in a coronary care unit and measurement of hepatic blood flow. J Hepatol. 1994; 21:696-703.

148. Henrion J. Hypoxic hepatitis. Liver International. 2012; 32:1039-1052.

149. Horvatits T, Drolz A, Trauner M, Fuhrmann V. Liver Injury and Failure in Critical Illness. Hepatology. 2019; 70:2204-2215.

150. Birrer R, Takuda Y, Takara T. Hypoxic hepatopathy: Pathophysiology and prognosis. Intern Med. 2007; 46:1063-1070.

151. Seeto RK, Fenn B, Rockey DC. Ischemic hepatitis: Clinical presentation and pathogenesis. Am J Med. 2000; 109:109-113.

152. Mallory FB. Necroses of the Liver. J Med Res. 1901; 6:264-280.7.

153. 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; 8:475-481.

154. Qiu H, Tong Z, Ma P, et al. Intensive care during the coronavirus epidemic. Intensive Care Med. 2020; 46:576-578.

155. Arabi YM, Fowler R, Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med. 2020; 46:315-328.

156. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020; 46:854-887.

157. Vieillard-Baron A, Naeije R, Haddad F, et al. Diagnostic workup, etiologies and management of acute right ventricle failure: A stateof-the-art paper. Intensive Care Med. 2018; 44:774-790.

158. Fayssoil A, Mustafic H, Mansencal N. The Right Ventricle in COVID-19 Patients. J Clean Prod. 2020;130.

159. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected with Pulmonary CT Angiography. Radiology. 2020;296: E186-E188.

160. Corticosteroids for COVID-19. Available at https://www.who.int/publi cations/i/item/WHO-2019-nCoV-Corti coste roids -2020.1

161. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury (National Institute of Diabetes and Digestive and Kidney Diseases, 2012).

162. Tocilizumab. LiverTox: Clinical and Research Information on DrugInduced Liver Injury (National Institute of Diabetes and Digestive and Kidney Diseases, 2012).