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REVIEW

- 4252 Update on the association of hepatitis B with intrahepatic cholangiocarcinoma: Is there new evidence?
Fragkou N, Sideras L, Panas P, Emmanouilides C, Sinakos E
- 4276 Viral infections in inflammatory bowel disease: Tips and tricks for correct management
Craviotto V, Furfaro F, Loy L, Zilli A, Peyrin-Biroulet L, Fiorino G, Danese S, Allocca M
- 4298 Pancreatic cancer: A review of epidemiology, trend, and risk factors
Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, Gao F
- 4322 Minimally invasive image-guided therapy of primary and metastatic pancreatic cancer
Bibok A, Kim DW, Malafa M, Kis B
- 4342 Comprehensive review of diagnostic modalities for early chronic pancreatitis
Ge QC, Dietrich CF, Bhutani MS, Zhang BZ, Zhang Y, Wang YD, Zhang JJ, Wu YF, Sun SY, Guo JT

MINIREVIEWS

- 4358 Dysregulated liver function in SARS-CoV-2 infection: Current understanding and perspectives
Huang YK, Li YJ, Li B, Wang P, Wang QH
- 4371 Impact of surgery for chronic pancreatitis on the risk of pancreatic cancer: Untying the Gordian knot
Kalayarasan R, Narayanan S, Sahoo J, Mohan P
- 4383 Neoadjuvant therapy for pancreatic ductal adenocarcinoma: Opportunities for personalized cancer care
Hamad A, Brown ZJ, Ejaz AM, Dillhoff M, Cloyd JM
- 4395 Role of artificial intelligence in multidisciplinary imaging diagnosis of gastrointestinal diseases
Berbis MA, Aneiros-Fernández J, Mendoza Olivares FJ, Nava E, Luna A
- 4413 Hyperbaric oxygen therapy as a complementary treatment for radiation proctitis: Useless or useful? – A literature review
Alpuim Costa D, Amaro CE, Nunes A, Cardoso JS, Daniel PM, Rosa I, Branco JV

ORIGINAL ARTICLE**Retrospective Study**

- 4429 Multifocal autoimmune pancreatitis: A retrospective study in a single tertiary center of 26 patients with a 20-year literature review
Huang XM, Shi ZS, Ma CL

- 4441** Recent trends in the prevalence and distribution of colonic diverticula in Japan evaluated using computed tomography colonography

Isohata N, Nagata K, Utano K, Nozaki R, Nozu S, Kato T, Kijima S, Matsumoto H, Majima K, Ryu Y, Hirayama M, Endo S

Observational Study

- 4453** Prognostic role of plasma level of angiotensin-1, angiotensin-2, and vascular endothelial growth factor in hepatocellular carcinoma

Choi GH, Jang ES, Kim JW, Jeong SH

Prospective Study

- 4468** Determinants of disease-specific knowledge among children with inflammatory bowel disease and their parents: A multicentre study

Kowalska-Duplaga K, Gawlik-Scislo A, Krzesiek E, Jarocka-Cyrta E, Łazowska-Przeorek I, Duplaga M, Banaszkiewicz A

LETTER TO THE EDITOR

- 4481** Is there higher percentage of undetected osteopenia and osteoporosis among patients with ulcerative colitis in Saudi Arabia?

Olic Akrapovic I, Radic M, Tonkic A

ABOUT COVER

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Dysregulated liver function in SARS-CoV-2 infection: Current understanding and perspectives

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Abstract

Since it was first reported in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread rapidly around the world to cause the ongoing pandemic. Although the clinical manifestations of SARS-CoV-2 infection are predominantly in the respiratory system, liver enzyme abnormalities exist in around half of the cases, which indicate liver injury, and raise clinical concern. At present, there is no consensus whether the liver injury is directly caused by viral replication in the liver tissue or indirectly by the systemic inflammatory response. This review aims to summarize the clinical manifestations and to explore the underlying mechanisms of liver dysfunction in patients with SARS-CoV-2 infection.

Key Words: SARS-CoV-2; COVID-19; Dysregulated liver function; Cytokine storm

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is one of the most influential emerging infectious diseases worldwide. Accumulating evidence suggests

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that liver injury is common in COVID-19 patients, and many severe cases tend to be associated with dysregulated liver functions. In this review, we summarize the currently available data of liver enzyme abnormalities in patients confirmed to have COVID-19 and analyze multiple risk factors for liver injury. However, the mechanism of liver impairment seems to be multifactorial. The evidence of direct liver injury triggered by SARS-CoV-2 infection or indirect liver injury induced by overwhelmed cytokine storm will also be discussed.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has broken out worldwide and was declared as a global pandemic by the World Health Organization (WHO) on March 11, 2020 after it was first reported in December 2019. The virus was later isolated[1] and was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee for Taxonomy of Viruses. To date, this virus has spread to 220 countries, infecting 179601602 people with 3891974 deaths (as of June 24, 2021, source: Johns Hopkins University; <https://coronavirus.jhu.edu/map.html>), which constitutes a public health emergency of international concern.

The severity of symptoms in patients with COVID-19 ranges from mild self-limited respiratory disease to severe progressive pneumonia and respiratory failure, with an overall mortality rate of 2.3%[2]. The typical clinical manifestations of COVID-19 include elevated body temperature (> 37.3 °C), dry cough, dyspnea, leukocytosis, lung infiltration, and no significant improvement after antibiotic treatment for 3 d[3]. In addition to the respiratory system, various organs are reported to be involved in the process of SARS-CoV-2 infection, which caused complications that aggravate the infection[4]. Up to 50% of COVID-19 patients have been reported to have abnormal liver biochemical indicators, including elevated expression of aminotransferases, glutamyl transferase, and alkaline phosphatase (ALP)[3,5,6], and the proportion of infected patients with abnormal liver functions is greater in highly epidemic areas than other regions[7]. In addition, 58%-78% of patients with severe COVID-19 have apparent liver damage. Liver injury in turn increases the risk of other outcomes, such as cardiac arrest, requirement for intubation, acute respiratory distress syndrome, arrhythmia and shock[8]. Therefore, it is crucial to understand the mechanisms of the aberrant liver functions caused by this novel respiratory virus[9]. It is currently believed that three mechanisms may account for the liver damage in COVID-19 patients: (1) Hepatic bile duct endothelial cells and hepatocytes are directly infected by SARS-CoV-2 mediated by the cellular receptors; (2) A cytokine storm is induced by overactivated immune responses and causes inflammatory liver damage; and (3) Multiple risk factors such as underlying liver diseases may cause secondary liver damage following SARS-CoV-2 infection. In this review, we summarize the clinical manifestations and explore the potential underlying mechanisms of liver dysfunctions in patients with SARS-CoV-2 infection.

SARS-CoV-2: GENOME STRUCTURE AND TRANSMISSION

Coronaviruses (CoVs) are a group of enveloped positive single-stranded RNA viruses that belong to the Coronaviridae family of order Nidovirales[10]. CoVs are further grouped into α -, β -, γ -, and δ -coronaviruses. Among them, α - and β -CoVs can infect mammals and γ -coronaviruses infect birds and δ -coronaviruses infect both[11]. SARS-CoV-2, initially isolated from human airway epithelial cells, was identified as the seventh member of the CoVs capable of infecting humans. It genetically belongs to the β -CoV genus in the same clade with SARS-CoV and middle-east respiratory syndrome

coronavirus (MERS-CoV)[1,12].

Genome structure and variability

The SARS-CoV-2 genome shares around 76.5% amino acid sequence identity with SARS-CoV[13], which might be responsible for the shared transmission mode and pathogenesis of these two viruses. The SARS-CoV-2 genome contains 14 open reading frames, encoding 27 proteins (Figure 1A). Four major structural proteins are encoded by the 3'-terminus of the genome, including the spike surface glycoprotein (S), matrix protein (M), small envelope protein (E), and nucleocapsid protein (N)[11] (Figure 1B). The S protein initiates the infection by interacting with the cellular receptor through its receptor binding domain (RBD). SARS-CoV-2 infects the target cells by S protein on the surface of the virion binding to cellular angiotensin-converting enzyme 2 (ACE2) receptors followed by fusion of the cellular and viral membranes (Figure 1C). In this process, transmembrane protease serine 2 (TMPRSS2), together with the endosomal cysteine proteases cathepsin B and L (CatB/L), are used for S protein priming. The S protein of SARS-CoV-2 is efficiently cleaved at the junction of S1 and S2 proteins to produce an S2 subunit to facilitate SARS-CoV-2 entry[14]. Considering the major role played in the pathogenesis, S protein is considered to be a potential target for vaccine design and drug development[9]. E protein is involved in the assembly and release of virions. As the most abundant viral protein, M protein plays an important role in RNA packaging[15] and N protein mediates the transcription and replication of viral RNA [16].

The variability of the SARS-CoV-2 genome is lower when compared to other human CoVs. There were 149 mutations in 103 sequenced SARS-CoV-2 genomes in the early stage of the pandemic[17]. The virus was classified into two major variants (L and S) through population genetic analysis. The L type, derived from the S type of SARS-CoV-2, was reported to be evolutionarily more aggressive[17]. Recently, a more transmissible phylogenetic cluster (named lineage B.1.1.7), which has 23 specific genetic changes in S protein of SARS-CoV-2, was reported in the UK, and rapidly became the dominant strain in London. Mutation N501Y affects the structure of the RBD and P681H is adjacent to the furin-cleavage site, which increases the binding affinity of the virus to ACE2 receptors by 1000-fold. Moreover, the deletion 69-70del on the S protein facilitates viral evasion from immune surveillance. Collectively, these variations have raised concerns about potential antigenic drift of SARS-CoV-2 similar to that of influenza virus[18].

Transmission of SARS-CoV-2

SARS-CoV-2 is a zoonotic virus that spreads in humans through respiratory droplets [19]. Comparative sequence analysis of the SARS-CoV-2 genome has revealed a striking similarity with bat CoVs, indicating that bats may be the origin of this virus [20,21]. Although many COVID-19 cases initially reported in China were traced to have connection with Huanan Seafood Wholesale Market in Wuhan[6,22,23], several reports clearly indicate that the global spread of the SARS-CoV-2 might have preceded the discovery of the first case in Wuhan. The epidemic likely started between October 6 and December 11, 2019 in the USA, Italy and France[24,25]; however, debate still exists about the source of SARS-CoV-2. Since the transmission of SARS-CoV-2 needs intermediate hosts, pangolins have been suggested as a probable intermediate host [26]. In February 2020, evidence of human-to-human transmission of SARS-CoV-2 was first reported[27]. Thereafter, a case of SARS-CoV-2 provided proof that human-to-human transmission occurred during the incubation period[28]. With the appearance of the second-generation patients and many medical staff in the hospital being infected, the strong infectious ability of SARS-CoV-2 was confirmed[29]. With the detection of SARS-CoV-2 RNA in fecal sample from a COVID-19 patient in the USA, SARS-CoV-2 could also be transmitted through the fecal-oral route[30]. Since September 2020, the route of transmission from contaminated objects to people has been reported by tracing the origin of local confirmed cases in Qingdao, Tianjin, Dalian, Chengdu and other cities in China, further complicating epidemic prevention and control.

DYSREGULATED LIVER FUNCTION IN COVID-19 PATIENTS

The common clinical manifestations of patients with COVID-19 are cough, fever, shortness of breath, and other respiratory symptoms[31]. Gastrointestinal symptoms including nausea, vomiting, and diarrhea are also observed in some patients. The

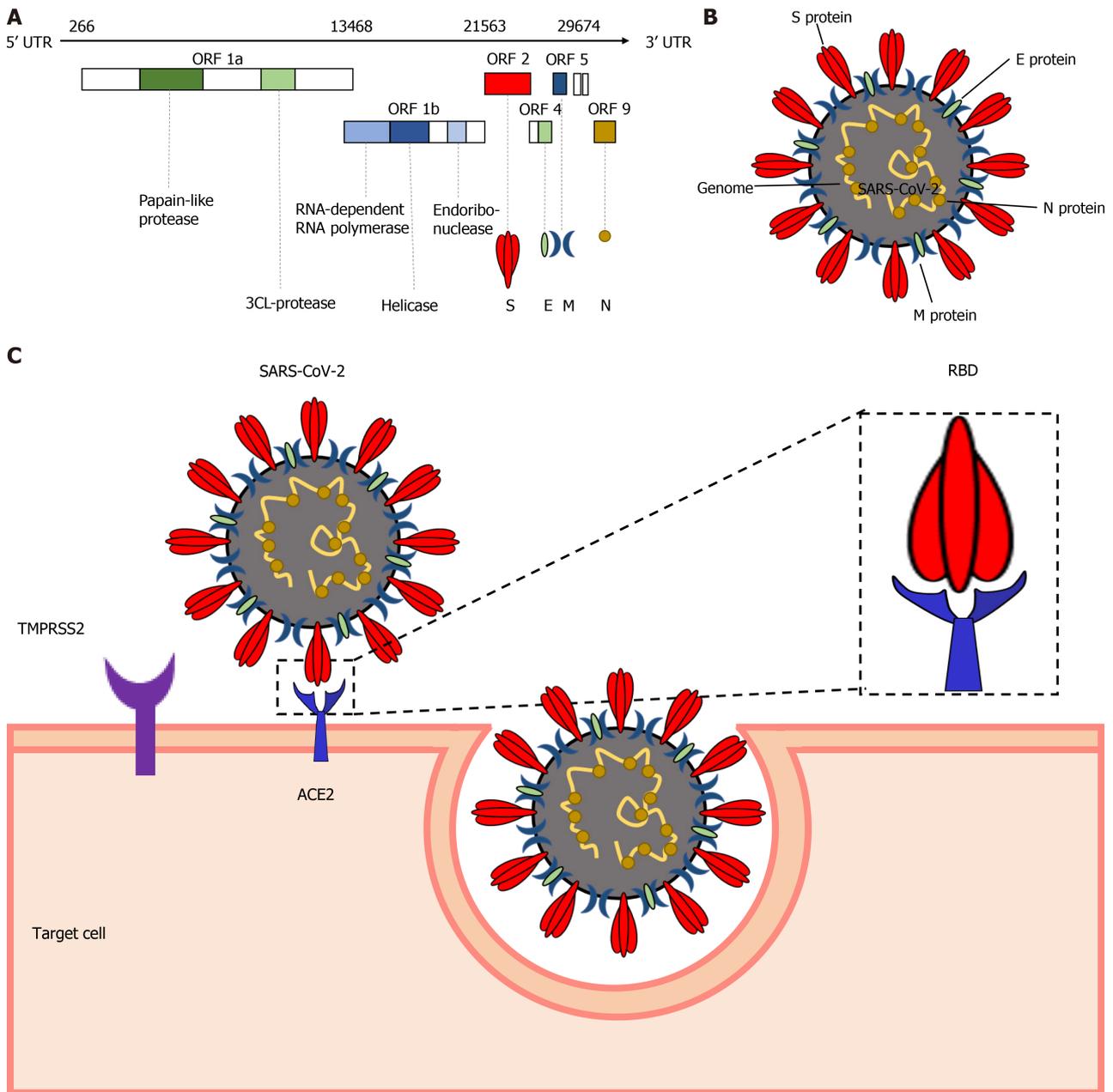


Figure 1 Severe acute respiratory syndrome coronavirus 2 genome and its pathogenesis. A: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome structure and its encoded proteins; B: Virion structure of SARS-CoV-2 illustrating viral structural proteins including spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N); C: SARS-CoV-2 entry to the target cells by binding the receptor-binding domain of S protein to cellular receptors, such as angiotensin-converting enzyme 2 and transmembrane protease serine 2. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RBD: Receptor-binding domain; TMPRSS2: Transmembrane protease serine 2; ACE2: Angiotensin-converting enzyme 2.

abnormal values of liver enzymes have frequently been noted in patients with COVID-19. Existing data suggest that, in most cases, liver enzyme elevations are mild to moderate and rarely severe. Limited pathophysiological studies have indicated that SARS-CoV-2 infection can cause liver injury, although SARS-CoV-2-induced liver injury is not the leading cause of death.

Altered biochemical markers

Liver injury in hospitalized patients is mainly manifested by changes in biochemical liver markers. Many studies have reported the presence of liver dysfunction in COVID-19 patients (Table 1). Respiratory failure is a common characteristic in severe cases, characterized by an imbalance of oxygen supply leading to an increase in transaminases[32]. As reported, 14%-53% of patients have elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), g-glutamyltransferase (GGT), hypoalbuminemia, and slightly elevated bilirubin[33]. The elevation of AST (39.4%) is more

Table 1 Altered biochemical markers of patients with coronavirus disease 2019

Region	No. of patients	Rate of abnormal liver test	Hepatocyte injury markers		Bile duct injury or cholestasis markers		Hepatic clearance markers	Infection-related biomarkers	Refs.
			ALT	AST	ALP	GGT	Total bilirubin	CRP	
Shenzhen, China	417	76.3%	23.4%	14.80%	N/A	24.4%	11.5%	N/A	[33]
Wuhan, China	115	N/A	9.57%	14.78%	5.21%	13.4%	6.96%	N/A	[34]
Wuhan, China	99	43%	28%	35%	N/A	N/A	18%	86%	[6]
Wuhan, China	1099	N/A	21.3%	22.20%	N/A	N/A	10.5%	60.7%	[31]
Shanghai, China	148	37.20%	18.2%	21.6%	4.10%	17.60%	6%	8.7-32.3%	[35]
Wuhan, China	69	N/A	33%	28%	N/A	N/A	N/A	67%	[41]
Fuyang, China	125	N/A	20.8%	21.60%	N/A	N/A	N/A	70.4%	[42]
Japan	22	68.20%	54.5%	N/A	N/A	54.50%	N/A	N/A	[36]
Turkey	554	N/A	27.6%		4%		N/A	N/A	[37]
Zaragoza, Spain	531	64.3%	28.6%	40.90%	N/A	47.30%	N/A	N/A	[38]
Wuhan, China	81	N/A	29.5%	17.90%	N/A	N/A	3.6%	41.8%	[43]
New York, United States	5700	N/A	39%	58.40%	N/A	N/A	N/A	6.4-26.9%	[44]

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: -glutamyltransferase; CRP: C-reactive protein; N/A: Not available.

significant than that of ALT (28.1%) in severe cases. Among these markers affected by viral infections, elevated AST is related to a higher risk of death, while elevated GGT [33-38], ALP[34-36], together with bilirubin levels[6,31,33-35], are associated with biliary tract damage. Some patients have hypoalbuminemia, an independent predictor of mortality, which may be related to inflammation and poor prognosis[39,40]. Some studies have also reported C-reactive protein (CRP) elevation in many severe COVID-19 cases[6,31,35,41-44], indicating that overactivation of the immune system might account for disease severity, which can be used to predict worse outcomes in COVID-19 patients. In the elderly population with underlying liver disease, liver enzymes, especially transaminases, are elevated due to lobular necrosis[45].

Pathophysiological characteristics of liver tissues in COVID-19 patients

Mild portal vein inflammation, moderate microvesicular steatosis, and necrotizing inflammation have been observed in liver autopsy tissue of COVID-19[10]. This is likely due to increase of monocyte chemoattractant protein 1 (MCP-1) in patients infected with SARS-CoV-2, which aggravates fatty hepatitis[46]. Autopsy results from COVID-19 patients in Wuhan have shown infiltration of monocytes and lymphocytes in the portal vein area, accompanied by hepatic sinus congestion and microthrombus formation[45]. Cytologically, hepatocyte degeneration with focal lobular necrosis and neutrophil infiltration are observed together with swollen mitochondria, endoplasmic reticulum expansion, and decreased glycogen particles in the hepatocytes. The histological manifestations are apoptosis and binuclear hepatocytes. In addition, immunohistochemical results have shown a lack of CD4+ cells and CD8+ T cells in liver tissue, suggesting that immunopathological insult may not be the main factor leading to liver injury.

POTENTIAL MECHANISMS OF LIVER INJURY IN COVID-19 PATIENTS

SARS-CoV-2 initiates membrane fusion and cytoplasmic invasion by entering respiratory endothelial cells expressing ACE2 and TMPRSS2, triggering an initial immune response characterized by inflammatory cytokine production. Afterwards,

the downstream proinflammatory immune responses of pathogenic Th1 cells and monocyte signaling pathways are activated[47]. Two hypotheses have been proposed to explain the mechanisms of liver dysfunctions in COVID-19 patients: direct injury by SARS-CoV-2[48] and indirect injury from a cytokine storm.

Direct effects of SARS-CoV-2 infection on liver injury

It has been reported that SARS-CoV-2 infection of various types of liver cells causes liver injury through direct cytopathic effects[48]. As a functional receptor for SARS-CoV-2 S protein binding, ACE2 is widely expressed on the surface of various human cells. Due to the low expression level of ACE2 in liver tissue (approximately 0.31%), SARS-CoV-2 was once considered unlikely to infect the liver. However, Li *et al*[49] systematically evaluated the expression of host receptor genes interacting with SARS-CoV-2 in liver tissue and their distribution patterns in different cell types using single-cell transcriptomics. ACE2 protein is expressed in various cell types in the liver, especially in bile duct cells[50], likely leading to direct injury to the liver (Figure 2). Boettler *et al*[51] proved that SARS-CoV-2 has a stronger affinity for bile duct cells than hepatocytes because of higher ACE2 receptor expression.

It has been proposed that SARS-CoV-2 infection of bile duct cells is the source of viral nucleic acid detection in feces[51]. Even in patients with negative throat swabs for viral RNA, 48% of feces were positive for SARS-CoV-2 RNA, which may be derived from portal vein viremia. Although SARS-CoV-2 can infect bile duct cells, the histological characteristics of bile duct injury have not been observed. Wang *et al*[48] observed many SARS-CoV-2 virions in the hepatocyte cytoplasm of two cases with COVID-19. Most of the viroosomes were found to have complete envelopes with crown protrusions, providing evidence that SARS-CoV-2 can enter and replicate in hepatocytes. However, the low expression level of ACE2 on hepatocytes cannot fully explain the hepatotropic nature of SARS-CoV-2. One possibility is that there are alternative receptors or co-receptors other than ACE2. This hypothesis has gradually been confirmed by the discovery of more co-receptors that facilitate SARS-CoV-2 entry. For example, tyrosine-protein kinase receptor UFO (AXL), heparan sulfate, scavenger receptor B type 1 (SR-B1), neuropilin-1 (NRP1) and CD147 have been identified as attachment factors for SARS-CoV-2 infection[52-57], although the abundance of these co-receptors in liver tissue remains to be determined. The other possibility is that the expression of ACE2 in hepatocytes is temporarily upregulated when the virus enters the cells, assisting infection. Again, more evidence is needed to support this hypothesis.

Indirect injury caused by cytokine storm

The variable symptoms in severe and asymptomatic patients with COVID-19 suggest that host immune responses contribute to the pathogenesis. SARS-CoV-2 infection leads to excessive production of a series of cytokines by macrophages and neutrophils known as a cytokine storm[47], which is one of the main features in COVID-19 patients and may be a key factor affecting disease severity and mortality. Cytokines are self-antigens that induce autoimmunity, and could account for the multisystem inflammatory syndrome often seen in COVID-19 patients. CD4⁺ and CD8⁺ T cells in the peripheral blood of COVID-19 patients are highly activated *via* Toll-like receptors. Elevated proinflammatory CD4⁺ T cells and cytotoxic granular CD8⁺ T cells suggests an antiviral immune response and excessive activation of T cells in the peripheral blood[10]. The host cells are attacked by activated T cells leading to necrosis and apoptosis, and many damage-related pattern molecules are involved to amplify the inflammatory signals. Lymphopenia is also observed in the disordered cytokine storm, but it is still unknown whether it is caused by destruction of lymphocytes or tissue infiltration. It has been demonstrated that the proinflammatory cytokines are elevated significantly in patients with severe COVID-19, leading to severe pneumonia. The inflammatory cytokines not only protect the host cells from injury but also cause blood clotting, thereby blocking the vessels and resulting in decrease of oxygen saturation and sepsis, which is considered to be one of the causes of insufficient lung ventilation. Therefore, hypoxic hepatitis is common in patients with severe COVID-19, especially elderly patients with right congestive heart failure who are prone to have hypoxic-ischemic liver injury[48].

More specifically, the cytokine storm induced by SARS-CoV-2 is characterized by high expression of interleukin (IL)-6 and tumor necrosis factor- α (TNF- α). Activated pathogenic Th1 cells produce proinflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6. GM-CSF in turn stimulates CD4⁺ T cells to secrete large quantities of cytokines, such as TNF- α , IL-10, IL-6 and type I interferons[58] (Figure 2). The inflammatory response is obvious in COVID-19

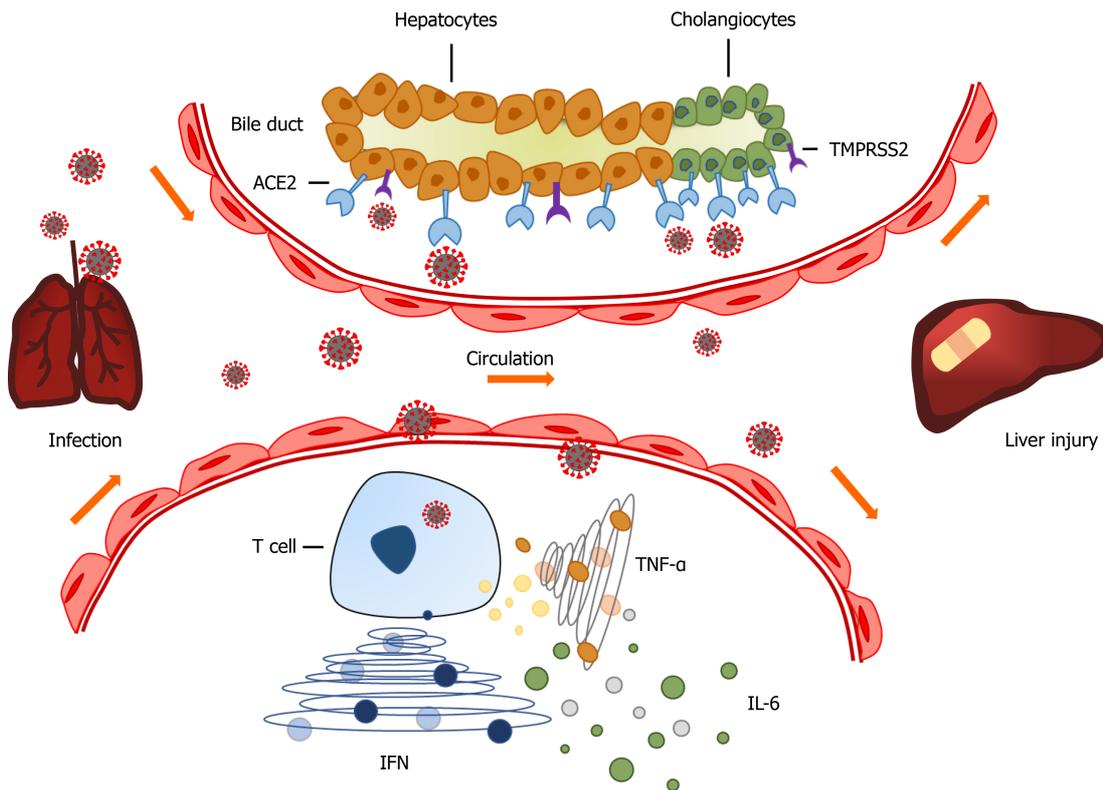


Figure 2 Schematic diagram of the two mechanisms of severe acute respiratory syndrome coronavirus 2-induced liver dysfunction. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes direct liver injury through binding to the angiotensin-converting enzyme 2 receptor and transmembrane protease serine 2 expressed on cholangiocytes and hepatocytes. Indirect injury by cytokine storm. T cells are stimulated to secrete large quantities of cytokines including type I interferons, interleukin-6, and tumor necrosis factor- α following SARS-CoV-2 infection, leading to systemic excessive inflammation syndrome. ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane protease serine 2; TNF- α : Tumor necrosis factor- α ; IL-6: Interleukin-6; IFN: Interferons.

patients as indicated by increased expression of inflammatory biomarkers such as lactate dehydrogenase (LDH), IL-6, IL-2, CRP, serum ferritin, and D-dimer[59-61]. It has been reported that 28% of patients who died of multiple organ damage, including liver failure, was due to an excessive inflammatory response. In the case of liver injury, ACE2 expression is upregulated due to the compensated proliferation of hepatic parenchymal cells derived from bile duct epithelial cells, which increases the opportunities of viral infection in liver tissue.

Neutralizing cytokine release syndrome (CRS) that blocks the signal transduction pathway of these cytokines contributes to the development of effective drugs for the treatment of patients with severe COVID-19, and targeting CRS has significant implications for reducing mortality. One such example is tocilizumab, an IL-6 inhibitor, which improves the condition of patients within 15 d and reduces mortality considerably[62]. Although the cytokine storm is involved in liver injury, these cytokines also function in viral suppression. Therefore, application of treatment regimens to block cytokine signal transduction must be careful. Clinically, the application of synthetic corticosteroid dexamethasone worsens outcomes in milder COVID-19 patients, but reduces mortality in severe cases[63]. Likewise, other studies have supported that immunosuppression has a beneficial effect if given at a late stage, whereas immunostimulation enhances antiviral activity in the early stage[64], indicating that the timing of treatment and the specific patient population need to be identified to personalize the therapeutic schemes.

Liver injury caused by other factors in COVID-19 patients

Current evidence is insufficient to conclude that liver injury in COVID-19 patients results entirely from SARS-CoV-2 infection. Considering the multisystem involvement in severe COVID-19 patients, liver injury may be caused by multiple factors, including drug toxicity, systemic inflammation, liver congestion, microvascular thrombosis, or damage induced by cytotoxic T cells and innate immune responses following SARS-CoV-2 infection.

Drug toxicity: Currently there is no specific treatment for COVID-19, although initial clinical guidelines recommended using antiviral drugs and monoclonal antibodies such as remdesivir, chloroquine, tocilizumab, lopinavir, ritonavir, and traditional Chinese medicine. However, it has been reported that both lopinavir and ritonavir have little clinical effect on COVID-19 patients[65]. According to WHO and National Health Commission of China guidelines, patients with moderate symptoms should receive timely treatment with *Coriolus versicolor*, abidor, chloroquine phosphate, and recombinant human interferon α -2b. For severe/critical patients, respiratory support, appropriate hormone therapy, and traditional Chinese medicine may be beneficial [66]. Chloroquine phosphate has been proved to cause significant liver damage[67]. A more recent study reported that ACE inhibitors and angiotensin II receptor blockers might contribute to liver impairment in COVID-19 patients, although more studies are needed to confirm these findings[33]. In addition, fever is one of the main symptoms for COVID-19 patients. Paracetamol, which is a commonly used antipyretic drug, has been proven to cause fulminant liver failure, so the possibility of excessive use of paracetamol leading to elevated ALT cannot be ruled out[59,68].

Liver congestion: Forty percent of patients are at high risk of venous thromboembolism (VTE) when admitted to hospital. High-risk VTE patients have elevated expression of ALT, AST and CRP[69]. It is well known that viral infection leads to a hypercoagulable state, increasing the risk of thromboembolism[70,71]. The incidence of VTE is 20% on day 7 and 42% on day 21, even among hospitalized patients taking anticoagulants[72]. Recent studies have found that in some younger patients, microvascular thrombosis causes end-stage organ damage and contributes to liver injury. Anticoagulant drugs can be used to prevent the development of VTE. A few studies have concluded that 80% of COVID-19 patients with cirrhosis and portal hypertension received anticoagulant therapy, such as low-molecular-weight heparin, and those patients do not have serious bleeding complications[73,74]. However, Wang *et al*[69] have reported that 11% of COVID-19 patients with high risk of VTE also have a high risk of bleeding. Therefore, evaluating the risk of thromboembolism and rational use of anticoagulants for the treatment of COVID-19 patients is critical.

Underlying liver diseases: Chronic liver diseases, including chronic viral hepatitis and nonalcoholic fatty liver disease (NAFLD), affect approximately 300 million people in China and constitute a major global burden of disease. Although chronic liver disease does not increase the infection risk of patients with SARS-CoV-2 in general, patients with liver cirrhosis or hepatocellular carcinoma tend to be more susceptible to SARS-CoV-2 infection due to systemic immunodeficiency. Furthermore, the underlying liver diseases may worsen disease progression in patients with COVID-19. A study consisting of > 17 million people in the United States found that although < 1% of the confirmed COVID-19 cases had chronic liver diseases, chronic liver disease was an independent risk factor for death from SARS-CoV-2 infection[75].

Hepatitis B virus (HBV) does not predispose COVID-19 patients to more severe outcomes, although HBV patients infected with SARS-CoV-2 normally present with aggravated liver damage together with more severe thrombocytopenia and monocytopenia, coagulation dysfunction, and more disturbed hepatic function in relation to albumin production and lipid metabolism[76], and these co-infected patients have a tendency to HBV reactivation[67]. Astrilizumab and baritinib, which are used clinically to antagonize adverse immune reactions, tend to induce HBV reactivation, leading to impaired liver function in HBV patients[77]. However, it is currently unclear whether viral infection aggravates cholestasis in patients with the cholestatic disease. Further in-depth research should focus on persistent liver damage and active viral replication in HBV patients after co-infection with SARS-CoV-2. Recent studies have demonstrated the possible impact of SARS-CoV-2 infection on NAFLD. It has been shown that SARS-CoV-2 infection increases the possibility of NAFLD progressing to nonalcoholic hepatitis. ACE inhibitors are commonly used in the anti-inflammatory and anti-obesity treatment of NAFLD. Although there have been no reports on the correlation between the use of ACE inhibitors and mortality, one study has shown that ACE inhibitors upregulate expression of ACE2 receptor, thereby increasing the viral entry in patients taking such drugs[78].

How the underlying liver diseases affect liver function in patients with COVID-19 remains elusive. Whatever mechanisms are involved in liver damage, we need to be more cautious in managing COVID-19 patients with underlying liver diseases. For example, the British Liver Foundation recommends that patients taking steroids or immunosuppressive drugs maintain strict social distance[79]. The European Association for Liver Research and the European Association for Clinical Microbiology

and Infectious Diseases recommend priority outpatient visits, prehospital assessment of risk factors, reduction of exposure through modification of waiting areas, reduction of waiting times, and use of online system to order medication.

CONCLUSION

Although liver dysfunction is common in patients with COVID-19, the detailed mechanisms remain incompletely understood. Available evidence suggests that the severity of liver damage is partly due to direct infection by SARS-CoV-2 to the liver and partly due to the cytokine storm produced by an overactive immune response. In addition, multiple risk factors, such as drug toxicity and liver congestion, need to be taken into account. For COVID-19 patients with underlying liver diseases, the causes of liver damage are more complex and more personalized management should be considered. Future directions should focus on deciphering the virus–host interactions to better understand the detailed molecular mechanisms of the liver impairment following SARS-CoV-2 infection. In the meantime, rapid development of effective preventive vaccines and specific antiviral drugs is critical to control this ongoing pandemic.

REFERENCES

- Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]
- Epidemiology Working Group for NCIP Epidemic Response**, Chinese Center for Disease Control and Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; **41**: 145-151 [PMID: 32064853 DOI: 10.3760/cma.j.issn.0254-6450.2020.02.003]
- Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
- Hamming I**, Timens W, Bultuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]
- Xu XW**, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, Li SB, Wang HY, Zhang S, Gao HN, Sheng JF, Cai HL, Qiu YQ, Li LJ. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020; **368**: m606 [PMID: 32075786 DOI: 10.1136/bmj.m606]
- Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]
- Feng G**, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, Poucke SV, Liu WY, Zheng MH. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. *J Clin Transl Hepatol* 2020; **8**: 18-24 [PMID: 32274342 DOI: 10.14218/JCTH.2020.00018]
- Desai J**, Patel U, Arjun S, Farraj K, Yeroushalmi K, Paz SG, Im J, Castillo A, Rammohan R, Mustacchia P. Impact of Liver Injury in COVID-19 Patients: Single-center Retrospective Cohort Analysis. *J Clin Transl Hepatol* 2020; **8**: 476-478 [PMID: 33447534 DOI: 10.14218/JCTH.2020.00075]
- Fehr AR**, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol* 2015; **1282**: 1-23 [PMID: 25720466 DOI: 10.1007/978-1-4939-2438-7_1]
- Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]
- Wu A**, Peng Y, Huang B, Ding X, Wang X, Niu P, Meng J, Zhu Z, Zhang Z, Wang J, Sheng J, Quan L, Xia Z, Tan W, Cheng G, Jiang T. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. *Cell Host Microbe* 2020; **27**: 325-328 [PMID: 32035028 DOI: 10.1016/j.chom.2020.02.001]
- Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and

- receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: [32007145](#) DOI: [10.1016/S0140-6736\(20\)30251-8](#)]
- 13 **Xu X**, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. 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; **63**: 457-460 [PMID: [32009228](#) DOI: [10.1007/s11427-020-1637-5](#)]
 - 14 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280. e8 [PMID: [32142651](#) DOI: [10.1016/j.cell.2020.02.052](#)]
 - 15 **Tang T**, Bidon M, Jaimes JA, Whittaker GR, Daniel S. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. *Antiviral Res* 2020; **178**: 104792 [PMID: [32272173](#) DOI: [10.1016/j.antiviral.2020.104792](#)]
 - 16 **Neuman BW**, Buchmeier MJ. Supramolecular Architecture of the Coronavirus Particle. *Adv Virus Res* 2016; **96**: 1-27 [PMID: [27712621](#) DOI: [10.1016/bs.aivir.2016.08.005](#)]
 - 17 **Tang XL**, Wu CC, Li X, Song YH, Yao XM, Wu XK, Duan YG, Zhang H, Wang YR, Qian ZH, Cui J, Lu J. On the origin and continuing evolution of SARS-CoV-2. *Guojia Kexue Pinglun* 2020; **6**: 1012-1023 [DOI: [10.1093/nsr/nwaa036](#)]
 - 18 **Rambaut A**, Loman N, Pybus O, Barclay W, Barrett J, Carabelli A, Connor T, Peacock T, Robertson DL, Volz E. on behalf of COVID-19 Genomics Consortium UK (CoG-UK) Preliminary genomic characterisation of an emergent SARS-CoV-2 Lineage in the UK defined by a novel set of spike mutations. *Genom Epidemiol.* 2020
 - 19 **Chu DK**, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ; COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet* 2020; **395**: 1973-1987 [PMID: [32497510](#) DOI: [10.1016/S0140-6736\(20\)31142-9](#)]
 - 20 **Zhang YZ**, Holmes EC. A Genomic Perspective on the Origin and Emergence of SARS-CoV-2. *Cell* 2020; **181**: 223-227 [PMID: [32220310](#) DOI: [10.1016/j.cell.2020.03.035](#)]
 - 21 **Wu F**, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. *Nature* 2020; **579**: 265-269 [PMID: [32015508](#) DOI: [10.1038/s41586-020-2008-3](#)]
 - 22 **Li X**, Zai J, Wang X, Li Y. Potential of large "first generation" human-to-human transmission of 2019-nCoV. *J Med Virol* 2020; **92**: 448-454 [PMID: [31997390](#) DOI: [10.1002/jmv.25693](#)]
 - 23 **Li Q**, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; **382**: 1199-1207 [PMID: [31995857](#) DOI: [10.1056/NEJMoa2001316](#)]
 - 24 **Deslandes A**, Berti V, Tandjaoui-Lambotte Y, Alloui C, Carbonnelle E, Zahar JR, Brichler S, Cohen Y. SARS-CoV-2 was already spreading in France in late December 2019. *Int J Antimicrob Agents* 2020; **55**: 106006 [PMID: [32371096](#) DOI: [10.1016/j.ijantimicag.2020.106006](#)]
 - 25 **Amendola A**, Bianchi S, Gori M, Colzani D, Canuti M, Borghi E, Raviglione MC, Zuccotti GV, Tanzi E. Evidence of SARS-CoV-2 RNA in an Oropharyngeal Swab Specimen, Milan, Italy, Early December 2019. *Emerg Infect Dis* 2021; **27**: 648-650 [PMID: [33292923](#) DOI: [10.3201/eid2702.204632](#)]
 - 26 **Zhang T**, Wu Q, Zhang Z. Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. *Curr Biol* 2020; **30**: 1578 [PMID: [32315626](#) DOI: [10.1016/j.cub.2020.03.063](#)]
 - 27 **Chan JF**, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514-523 [PMID: [31986261](#) DOI: [10.1016/S0140-6736\(20\)30154-9](#)]
 - 28 **Rothe C**, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, Zimmer T, Thiel V, Janke C, Guggemos W, Seilmaier M, Drosten C, Vollmar P, Zwirgmaier K, Zange S, Wölfel R, Hoelscher M. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med* 2020; **382**: 970-971 [PMID: [32003551](#) DOI: [10.1056/NEJMc2001468](#)]
 - 29 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: [32031570](#) DOI: [10.1001/jama.2020.1585](#)]
 - 30 **Holshue ML**, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK; Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* 2020; **382**: 929-936 [PMID: [32004427](#) DOI: [10.1056/NEJMoa2001191](#)]
 - 31 **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 Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
- 32 **Ebert EC.** Hypoxic liver injury. *Mayo Clin Proc* 2006; **81**: 1232-1236 [PMID: 16970220 DOI: 10.4065/81.9.1232]
- 33 **Cai Q,** Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574 [PMID: 32298767 DOI: 10.1016/j.jhep.2020.04.006]
- 34 **Zhang Y,** Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int* 2020; **40**: 2095-2103 [PMID: 32239796 DOI: 10.1111/liv.14455]
- 35 **Fan Z,** Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; **18**: 1561-1566 [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002]
- 36 **Abe K,** Yamamoto T, Matsumoto K, Kikuchi K, Miura R, Tachizawa N, Asaoka Y, Takezawa T, Matsunaga N, Obi S, Tanaka A. Clinical Features and Liver Injury in Patients with COVID-19 in the Japanese Population. *Intern Med* 2020; **59**: 2353-2358 [PMID: 32999264 DOI: 10.2169/internalmedicine.5777-20]
- 37 **Medetalibeyoglu A,** Catma Y, Senkal N, Ormeci A, Cavus B, Kose M, Bayramlar OF, Yildiz G, Akyuz F, Kaymakoglu S, Tukek T. The effect of liver test abnormalities on the prognosis of COVID-19. *Ann Hepatol* 2020; **19**: 614-621 [PMID: 32920162 DOI: 10.1016/j.aohep.2020.08.068]
- 38 **Bernal-Monterde V,** Casas-Deza D, Letona-Giménez L, de la Llama-Celis N, Calmarza P, Sierra-Gabarda O, Betoré-Glaria E, Martínez-de Lagos M, Martínez-Barredo L, Espinosa-Pérez M, M Arbones-Mainar J. SARS-CoV-2 Infection Induces a Dual Response in Liver Function Tests: Association with Mortality during Hospitalization. *Biomedicines* 2020; **8** [PMID: 32899640 DOI: 10.3390/biomedicines8090328]
- 39 **Aziz M,** Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. *Crit Care* 2020; **24**: 255 [PMID: 32456658 DOI: 10.1186/s13054-020-02995-3]
- 40 **Huang J,** Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, Lin S. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *J Med Virol* 2020; **92**: 2152-2158 [PMID: 32406952 DOI: 10.1002/jmv.26003]
- 41 **Wang Z,** Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. *Clin Infect Dis* 2020; **71**: 769-777 [PMID: 32176772 DOI: 10.1093/cid/ciaa272]
- 42 **Wang R,** Pan M, Zhang X, Han M, Fan X, Zhao F, Miao M, Xu J, Guan M, Deng X, Chen X, Shen L. Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China. *Int J Infect Dis* 2020; **95**: 421-428 [PMID: 32289565 DOI: 10.1016/j.ijid.2020.03.070]
- 43 **Shi H,** Han X, Jiang N, Cao Y, Alwalid O, Gu J, Fan Y, Zheng C. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020; **20**: 425-434 [PMID: 32105637 DOI: 10.1016/S1473-3099(20)30086-4]
- 44 **Richardson S,** Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]
- 45 **Li J,** Fan JG. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. *J Clin Transl Hepatol* 2020; **8**: 13-17 [PMID: 32274341 DOI: 10.14218/JCTH.2020.00019]
- 46 **Boeckmans J,** Rodrigues RM, Demuyser T, Piérard D, Vanhaecke T, Rogiers V. COVID-19 and drug-induced liver injury: a problem of plenty or a petty point? *Arch Toxicol* 2020; **94**: 1367-1369 [PMID: 32266419 DOI: 10.1007/s00204-020-02734-1]
- 47 **Hussman JP.** Cellular and Molecular Pathways of COVID-19 and Potential Points of Therapeutic Intervention. *Front Pharmacol* 2020; **11**: 1169 [PMID: 32848776 DOI: 10.3389/fphar.2020.01169]
- 48 **Wang Y,** Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; **73**: 807-816 [PMID: 32437830 DOI: 10.1016/j.jhep.2020.05.002]
- 49 **Li MY,** Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020; **9**: 45 [PMID: 32345362 DOI: 10.1186/s40249-020-00662-x]
- 50 **Chai XQ,** Hu LF, Zhang Y, Han WY, Lu Z, Ke AW, Zhou J, Shi GM, Fang N, Fan J, Cai JB, Lan F. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. 2020 Preprint. Available from: bioRxiv [DOI: 10.1101/2020.02.03.931766]
- 51 **Boettler T,** Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2**: 100113 [PMID: 32289115 DOI: 10.1016/j.jhepr.2020.100113]

- 52 **Chu H**, Hu B, Huang X, Chai Y, Zhou D, Wang Y, Shuai H, Yang D, Hou Y, Zhang X, Yuen TT, Cai JP, Zhang AJ, Zhou J, Yuan S, To KK, Chan IH, Sit KY, Foo DC, Wong IY, Ng AT, Cheung TT, Law SY, Au WK, Brindley MA, Chen Z, Kok KH, Chan JF, Yuen KY. Host and viral determinants for efficient SARS-CoV-2 infection of the human lung. *Nat Commun* 2021; **12**: 134 [PMID: 33420022 DOI: 10.1038/s41467-020-20457-w]
- 53 **Wang S**, Qiu Z, Hou Y, Deng X, Xu W, Zheng T, Wu P, Xie S, Bian W, Zhang C, Sun Z, Liu K, Shan C, Lin A, Jiang S, Xie Y, Zhou Q, Lu L, Huang J, Li X. AXL is a candidate receptor for SARS-CoV-2 that promotes infection of pulmonary and bronchial epithelial cells. *Cell Res* 2021; **31**: 126-140 [PMID: 33420426 DOI: 10.1038/s41422-020-00460-y]
- 54 **Cantuti-Castelvetri L**, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, van der Meer F, Kallio K, Kaya T, Anastasina M, Smura T, Levanov L, Szirovicza L, Tobí A, Kallio-Kokko H, Österlund P, Joensuu M, Meunier FA, Butcher SJ, Winkler MS, Mollenhauer B, Helenius A, Gokce O, Teesalu T, Hepojoki J, Vapalahti O, Stadelmann C, Balistreri G, Simons M. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* 2020; **370**: 856-860 [PMID: 33082293 DOI: 10.1126/science.abd2985]
- 55 **Daly JL**, Simonetti B, Klein K, Chen KE, Williamson MK, Antón-Plágaro C, Shoemark DK, Simón-Gracia L, Bauer M, Hollandi R, Greber UF, Horvath P, Sessions RB, Helenius A, Hiscox JA, Teesalu T, Matthews DA, Davidson AD, Collins BM, Cullen PJ, Yamauchi Y. Neuropilin-1 is a host factor for SARS-CoV-2 infection. *Science* 2020; **370**: 861-865 [PMID: 33082294 DOI: 10.1126/science.abd3072]
- 56 **Clausen TM**, Sandoval DR, Spliid CB, Pihl J, Perrett HR, Painter CD, Narayanan A, Majowicz SA, Kwong EM, McVicar RN, Thacker BE, Glass CA, Yang Z, Torres JL, Golden GJ, Bartels PL, Porell RN, Garretson AF, Laubach L, Feldman J, Yin X, Pu Y, Hauser BM, Caradonna TM, Kellman BP, Martino C, Gordts PLSM, Chanda SK, Schmidt AG, Godula K, Leibel SL, Jose J, Corbett KD, Ward AB, Carlin AF, Esko JD. SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. *Cell* 2020; **183**: 1043-1057. e15 [PMID: 32970989 DOI: 10.1016/j.cell.2020.09.033]
- 57 **Ulrich H**, Pillat MM. CD147 as a Target for COVID-19 Treatment: Suggested Effects of Azithromycin and Stem Cell Engagement. *Stem Cell Rev Rep* 2020; **16**: 434-440 [PMID: 32307653 DOI: 10.1007/s12015-020-09976-7]
- 58 **Zhou YG**, Fu BQ, Zheng XH, Wang DS, Zhao CC, Qi YJ, Sun R, Tian ZG, Xu XL, Wei HM. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. 2020 Preprint. Available from: bioRxiv [DOI: 10.1101/2020.02.12.945576]
- 59 **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. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]
- 60 **Chen G**, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130**: 2620-2629 [PMID: 32217835 DOI: 10.1172/JCI137244]
- 61 **Herold T**, Jurinovic V, Amreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, Klein M, Weinberger T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020; **146**: 128-136.e4 [PMID: 32425269 DOI: 10.1016/j.jaci.2020.05.008]
- 62 **Luo P**, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* 2020; **92**: 814-818 [PMID: 32253759 DOI: 10.1002/jmv.25801]
- 63 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Horby Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]
- 64 **Fajgenbaum DC**, June CH. Cytokine Storm. *N Engl J Med* 2020; **383**: 2255-2273 [PMID: 33264547 DOI: 10.1056/NEJMra2026131]
- 65 **Li YP**, Xie ZW, Lin WY, Cai WP, Wen CY, Guan YJ, Mo XN, Wang J, Wang YP, Peng P, Chen XD, Hong WX, Xiao GM, Liu JX, Zhang LG, Hu FY, Li F, Zhang FC, Deng XL, Li LH. An exploratory randomized controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). 2020 Preprint. Available from: medRxiv [DOI: 10.1101/2020.03.19.20038984]
- 66 **World Health Organization**. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected: interim guidance. [cited 25 January 2020]. Available from: <https://apps.who.int/iris/handle/10665/330674>
- 67 **Wu J**, Yu J, Shi X, Li W, Song S, Zhao L, Zhao X, Liu J, Wang D, Liu C, Huang B, Meng Y, Jiang B, Deng Y, Cao H, Li L. Epidemiological and clinical characteristics of 70 cases of coronavirus disease and concomitant hepatitis B virus infection: A multicentre descriptive study. *J Viral Hepat* 2021; **28**: 80-88 [PMID: 32929826 DOI: 10.1111/jvh.13404]
- 68 **de la Rica R**, Borges M, Aranda M, Del Castillo A, Socias A, Payeras A, Rialp G, Socias L, Masmiquel L, Gonzalez-Freire M. Low Albumin Levels Are Associated with Poorer Outcomes in a Case Series of COVID-19 Patients in Spain: A Retrospective Cohort Study. *Microorganisms* 2020; **8**

- [PMID: [32722020](#) DOI: [10.3390/microorganisms8081106](#)]
- 69 **Wang T**, Chen R, Liu C, Liang W, Guan W, Tang R, Tang C, Zhang N, Zhong N, Li S. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol* 2020; **7**: e362-e363 [PMID: [32278361](#) DOI: [10.1016/S2352-3026\(20\)30109-5](#)]
 - 70 **Ranucci M**, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, Falco M, Albano G, Menicanti L. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost* 2020; **18**: 1747-1751 [PMID: [32302448](#) DOI: [10.1111/jth.14854](#)]
 - 71 **Spiezia L**, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P, Simioni P. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thromb Haemost* 2020; **120**: 998-1000 [PMID: [32316063](#) DOI: [10.1055/s-0040-1710018](#)]
 - 72 **Middeldorp S**, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020; **18**: 1995-2002 [PMID: [32369666](#) DOI: [10.1111/jth.14888](#)]
 - 73 **Iavarone M**, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, Perricone G, Massironi S, Spinetti A, Buscarini E, Viganò M, Carriero C, Fagioli S, Aghemo A, Belli LS, Lucà M, Pedaci M, Rimondi A, Rumi MG, Invernizzi P, Bonfanti P, Lampertico P. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020; **73**: 1063-1071 [PMID: [32526252](#) DOI: [10.1016/j.jhep.2020.06.001](#)]
 - 74 **Loffredo L**, Pastori D, Farcomeni A, Violi F. Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis. *Gastroenterology* 2017; **153**: 480-487. e1 [PMID: [28479379](#) DOI: [10.1053/j.gastro.2017.04.042](#)]
 - 75 **Williamson EJ**, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584**: 430-436 [PMID: [32640463](#) DOI: [10.1038/s41586-020-2521-4](#)]
 - 76 **Liu R**, Zhao L, Cheng X, Han H, Li C, Li D, Liu A, Gao G, Zhou F, Liu F, Jiang Y, Zhu C, Xia Y. Clinical characteristics of COVID-19 patients with hepatitis B virus infection - a retrospective study. *Liver Int* 2021; **41**: 720-730 [PMID: [33351265](#) DOI: [10.1111/liv.14774](#)]
 - 77 **Varona Pérez J**, Rodriguez Chinesta JM. [Risk of hepatitis B reactivation associated with treatment against SARS-CoV-2 (COVID-19) with corticosteroids]. *Rev Clin Esp (Barc)* 2020; **220**: 534-536 [PMID: [32372768](#) DOI: [10.1016/j.rce.2020.04.012](#)]
 - 78 **Prins GH**, Olinga P. Potential implications of COVID-19 in non-alcoholic fatty liver disease. *Liver Int* 2020; **40**: 2568 [PMID: [32306495](#) DOI: [10.1111/liv.14484](#)]
 - 79 **Sivaraj V**, Pittrof R, Davies O, Kulasegaram R. Homelessness among an inpatient HIV-positive cohort at a tertiary care hospital in central London. *Int J STD AIDS* 2020; **31**: 705-707 [PMID: [32448076](#) DOI: [10.1177/0956462420918682](#)]



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