Coronavirus Disease 2019 (COVID-19) and Its Gastrointestinal and Hepatic Manifestations

Paul Wasuwanich, M.D.*,, Supharerk Thawillarp, M.D.***, Thammasin Ingviya, M.D.****,*****, Wikrom Karnsakul, M.D.***

Division of Pediatric Gastroenterology, Nutrition, and Hepatology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, USA; ***Department of Disease Control, Ministry of Public Health, Thailand; ****Medical Data Center for Research and Innovation, Prince of Songkla University, Songkhla, Thailand; *****Department of Family and Preventive Medicine, Prince of Songkla University, Songkhla, Thailand.*

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a severe respiratory disease caused by the virus SARS-CoV-2 that became classified as a pandemic on March 11, 2020. COVID-19 is known to produce similar clinical manifestations to SARS of the last decade. Fever, dry cough, fatigue, myalgia, dyspnea, and sore throat are some of the most common symptoms and the median incubation period is around 4 days. While the respiratory symptoms often bring the patients to medical attention, clinical manifestations on the gastrointestinal tract and hepatobiliary system have also been cautiously observed. It has been reported that approximately 1-5% of cases developed diarrhea and nausea or vomiting, sometimes preceding the respiratory symptoms. As hemorrhagic colitis was reported in one case with SARS-CoV-2, detected in stool, there is a possibility of fecal-oral transmission of the virus is possible in humans. Thus, it is widely recommended that non-urgent and low prior endoscopic procedures be postponed. For patients requiring urgent endoscopic procedures, SARS-CoV-2 nucleic acid testing from the throat swabs is used as a screening test within 48 hours prior. Minimal personnel, infection control training, and usage of negative pressure rooms are recommended. Abnormal liver function tests have been commonly reported. Patients infected with SARS-CoV-2 can have a true liver injury, which is however mild. The abnormal liver function test values may be caused, at least partially, by muscle injury or hemolysis. Nevertheless drugs with hepatotoxicity should be used with increased caution.

Keywords: Epidemiology; Hepatology; SARS-CoV-2; Transplantation; Endoscopy (Siriraj Med J 2020; 72: 272-282)

Virology and Epidemiology

The coronavirus disease 2019 (COVID-19) is caused by the novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which originated from Wuhan, China in 2019.[1] SARS-CoV-2 is a positive-sense, RNA virus in the genus Betacoronavirus, genetically distinct from other severe coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) with only 50% and 79% similarity, respectively.[2]

The SARS-CoV-2 outbreak was officially declared a pandemic by the World Health Organization on March 11, 2020.[3] As of April 1, 2020, there have been more than 850,000 cases of COVID-19 globally affecting almost every country in the world (180 of the 195 countries) including the United States.[4,5] The reported COVID-19

Corresponding author: Wikrom Karnsakul
E-mail: wkarnsa1@jhmi.edu
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ORCID ID: http://orcid.org/0000-0001-7288-5459
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cases from the United States have surpassed 200,000 cases putting the United States' patient count as the highest globally with an epicenter in the state of New York. A similar trend was observed in deaths with reports of approximately 5,000 deaths and rising. The scale of the pandemic has overwhelmed New York's healthcare capacity and stressing several medical supply chains including ventilators, drug supplies, and personal protective equipment causing hospital administrators all over the United States and abroad to prepare for the worst-case scenarios.[6]

Clinical Manifestations

COVID-19 clinical presentation was similar to SARS from the last decade. Fever, dry cough, fatigue, myalgia, dyspnea, and sore throat are some of the most common symptoms.[7-9] The median incubation period was 4 days in an interquartile range (IQR) of 2 to 7 days.[10] The incubation period range of 2 to 14 days is commonly used in public health such as the United States Centers for Disease Control and Prevention (CDC) though that information has been based on the known incubation period of MERS-CoV viruses. However, Lauer et al. recently modeled that with a 14-day quarantine less than 1% of infected cases could develop symptoms after 14 days.[11] According to current evidence, SARS-CoV-2 can be transmitted through close contact or droplets, similar to influenza, via coughing or sneezing with a transmission radius of pathogen-bearing droplets of all sizes of 23 to 27 feet (~7-8 meters). Social distancing for a radius of 6 feet (~2 meters) is typically recommended by public health institutions though this should be seen as a minimum.[12–17] Currently, there have been no reports of airborne transmission of SARS-CoV-2, and the basic reproduction number (R_0) of SARS-CoV-2 is known to be approximately 2.2, lower than airborne diseases such as measles and rubella.[12,18] A study by van Doremalen et al. found that SARS-CoV-2 is viable and has a half-life of 1.1 hours in aerosol, similar to SARS-CoV.[19] This suggests that airborne transmission is possible, but it should be noted that SARS-CoV, which has similar survivability to SARS-CoV-2 in aerosol, is not known to be transmitted via aerosol. SARS-CoV-2 was found to be most stable on stainless steel and plastic surfaces with half-lives of 6-7 hours, and least stable on copper and cardboard surfaces with half-lives of 1-3 hours.[19] Transmission of SARS-CoV-2 by asymptomatic cases have been reported.[20] Although asymptomatic spread can occur during the prodromal phase particularly during the first week after infection, respiratory viral shedding is greatest when symptoms appear.[21]

Older patients and patients with significant chronic medical conditions including cardiopulmonary diseases, diabetes, chronic kidney disease, decompensated cirrhosis, HIV with low CD4 cell count, immunosuppression, and solid organ transplant recipients are at higher risk of acquiring and developing more serious presentation and outcomes such as acute respiratory distress syndrome and multi-organ failure.[10,22–27] Pregnant women with COVID-19 do not appear to have additional complications compared to the non-pregnant population with COVID-19 and vertical transmission of SARS-CoV-2 does not appear to occur.[28] The case-fatality rate is around 5%.[5] The pediatric population appear to have milder symptoms and may harbor the virus while appearing asymptomatic.[29] No data are currently available in children with immunocompromised conditions or chronic lung diseases. In addition to respiratory clinical manifestation, during the early report of COVID-19 in China in December 2019, several gastrointestinal symptoms were reported along with elevated liver enzyme values.[30] Hepatic manifestations have been suspected in multiple studies, but the evidence is not completely clear.

In this study, we reviewed the currently available published data on SARS-CoV-2 or COVID-19 and given gastrointestinal and hepatic manifestations, clinical outcomes, and management. Herein, we discuss recommendations and guidelines to ensure safety to healthcare providers and patients.

Review Methodology

We conducted a systematic search on PubMed and Google Scholars for research articles with the main keywords "COVID-19," "coronavirus disease 2019," "2019 novel coronavirus," or "2019-nCoV." These keywords were supplemented with "liver," "hepatic," "characteristics," "gastrointestinal," and "endoscopy." Non-English research articles, if translatable, were also reviewed. All relevant research articles found in the search were reviewed. Unpublished articles that have not been peer-reviewed were generally avoided. We reviewed research articles published between June 1, 2019 to March 30, 2020.

Gastrointestinal Manifestations and Considerations

In numerous studies of COVID-19, diarrhea was reported as a complication of the disease, ranging from 1-5% of cases.[1,10,22,23,31,32] Nausea or vomiting was reported in 1-5% of cases.[10,22,23,31] The frequency of gastrointestinal symptoms including nausea and/or diarrhea have typically been reported to be below 5% but a small study by Zhang et al. of 28 patients reported diarrhea in 50% of cases.[33] We believe the report by Zhang et al. would likely be an outlier and the cohort of patients studied may have been

exposed to co-infections or local environmental factors independent of SARS-CoV-2 that result in diarrhea. There have been some reports of just diarrhea as a first presentation preceding cough and fever which are the most common presentations with cough at 67.8%, fever at 43.8%, fatigue at 38.1%, sputum production at 33.7%, and shortness of breath at 18.7% of cases.[10] In a case report by Carvalho et al., a woman who was diagnosed with COVID-19 presented initially with bloody diarrhea, approximately 9 days before developing respiratory symptoms. The woman was also found to have hemorrhagic colitis which the authors have ruled out all other etiologies except for SARS-CoV-2.[34]

Reports from China have confirmed that SARS-CoV-2 can be detected in the feces of COVID-19 patients.[35] A study by Zhang et al. on 14 patients with COVID-19 reported that fecal specimens had similar accuracy to pharyngeal swab specimens in the diagnosis of COVID-19.[36] Due to this evidence, the possibility of fecal-oral transmission of SARS-CoV-2 is of great concern. A study on the viral structure of SARS-CoV-2 predicted that the virus would have intermediate levels of fecal-oral transmission and the authors also found that SARS-CoV-2 had the hardest outer shell of the coronavirus family, harder than those of SAR-CoV and MERS-CoV, suggesting that SARS-CoV-2 would be more resilient in body fluids and the environment.[37] However, there are currently no reports of human to human transmission via the fecal-oral route.

Recent evidence suggests the potential for SARS-CoV-2 transmission via fecal shedding.[38,39] Since the virus may be present in gastrointestinal secretions and viral RNA is detectable in stool, potential fecal-oral transmission from gastrointestinal contamination must be considered. As the outbreak of COVID-19 has quickly spread from China to other countries, governments and the medical institutions are taking action to prevent transmission, from common-sense recommendations to more extreme quarantine measures.[40] This is quite an unprecedented phenomenon.

Transplant Donor Considerations

Due to the potential of SARS-CoV-2 transmission through the transplantation of human cells, tissues, or cellular/tissue-based products, several public health institutions have added recommendations on increased precautions and screening of donors. On February 14, 2020, the United States Food and Drug Administration has suggested considering the donor for the following within the past 28 days of tissue recovery: travel to areas with COVID-19 outbreaks, cohabitation with infected individuals, or diagnosis/suspicion of COVID-19.[41] Similar guidelines were published by the European Society for Blood and Marrow Transplantation.[42] In Italy, an epicenter of COVID-19 pandemic in Europe, stronger measures were taken by the Italian National Transplant Center which has recommended testing for COVID-19 in all potential tissue and stem-cell living donors, as well as deceased donors.[43]

One of the transplantations of concern is fecal microbiota transplantation, a novel treatment that has been used in the management of recurrent *Clostridium difficile* infection which is becoming increasingly more widespread and standardized.[44] We believe that more cautious measures are needed in addition to existing guidelines for fecal microbiota transplantation such as those by Cammarota et al. as the risk of transmitting SARS-CoV-2 by fecal microbiota transplantation might be higher than that in other tissue transplants as evidence has shown that the SARS-CoV-2 can be found in feces and stool samples can remain positive for SARS-CoV-2 even after it is undetectable in respiratory tract.[39,45]

To prevent potential SARS-CoV-2 transmission, Ianiro et al. have recommended the following additions to current guidelines for fecal microbiota transplantation. Physicians should screen donors for the following within the previous 30 days: common COVID-19 symptoms such as fever, fatigue, dry cough, myalgia, dyspnea, and headache within the previous, donor's history of travel to regions known to be affected by COVID-19, or close contact with individuals known or suspected of having COVID-19. If any of the above is positive, the potential donor should either be tested for SARS-CoV-2 or simply be rejected. In countries where COVID-19 is widespread such as the United States and Italy, the SARS-CoV-2 testing should be considered in all donors, even those who appear asymptomatic or lack a history of high-risk travel or contact. An alternative method if SARS-CoV-2 testing is limited is that donor stools could be stored and quarantined for 30 days before use and released only if the donor does not develop symptoms. For stool already stored in stool banks, physicians should retrospectively check the health status of the donor before using frozen feces if the donation was made after community spread of COVID-19 had occurred in the country to avoid further potential spreading of SARS-CoV-2.[40]

Fecal-Oral Transmission Route Poses a Threat to Inflammatory Bowel Disease Patients

Due to the potential risk of fecal-oral transmission of SARS-CoV-2 and its presence in the gastrointestinal tract, patients with inflammatory bowel disease (IBD) are suspected of being a vulnerable group. Because

reports on the characteristics of COVID-19 on patients with IBD were lacking, SECURE-IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion – Inflammatory Bowel Disease) was created. SECURE-IBD is an international collaboration to create a global pediatric and adult registry to monitor and report on outcomes of COVID-19 occurring in IBD patients. The database contains only de-identified data and the summary data is displayed on the website at https://covidibd.org/. As of April 1, 2020, 239 cases have been reports on the SECURE-IBD database globally with preliminary data showing greater morbidity and mortality in patients with ulcerative colitis compared to those with Crohn's disease or unspecified IBD.[46]

Considerations in Patients Requiring Endoscopic Procedures

Gastrointestinal contamination with SARS-CoV-2 poses potential risks during endoscopy and colonoscopy to other patients, endoscopy personnel, as well as populations without clean drinking water. Recommendations for gastrointestinal endoscopy include rescheduling elective non-urgent endoscopic procedures. Some non-urgent procedures are high priority and may need to be performed such as cancer evaluations, prosthetic removals, or evaluation of significant symptoms. Classification of procedures into non-urgent/postpone and non-urgent/perform may be useful.[47] Of note, the United States Surgeon General on March 14, 2020 advised hospitals to postpone all elective surgeries.[48]

Pre-screening of all patients is mandatory for those with a high risk of exposure or symptoms of fever or respiratory symptoms, family members or close contacts with symptoms of COVID-19, any contact with a confirmed case of COVID-19, and recent travel to high-risk regions or countries.[49] Before undergoing endoscopy, the patient should also be checked for body temperature and symptoms upon arrival at endoscopy unit.[50] An alternative strategy that has been used in Thailand is to quarantine non-urgert patients in a hotel for 7-14 days or use mobile apps to ensure that the patient has been quarantined at home before arriving for the procedure.

In countries experiencing shortages of personal protective equipment (PPE), conservation of PPE is critical. Only essential medical personnel should be present for the endoscopy procedures. As for the endoscopy team, appropriate PPE should be reviewed and prepared for the availability on the day of procedures including gloves, masks, eyeshield/goggles, face shields, and gown per the guideline from the United States CDC.[51] All members of the endoscopy team should be trained in proper usage of PPE and any additional requirements given by public health institutions due to COVID-19.[50]

For patients confirmed to have COVID-19 or patients under investigations awaiting test results, isolation precautions should be taken with procedures performed in negative pressure rooms. Aerosolizing procedures should also be done in negative pressure rooms.[50,52] After the procedure, we recommend a follow-up by phone call within 7-14 days to inquire about a potential COVID-19 diagnosis or development of COVID-19 symptoms. Telemedicine should be utilized whenever possible for pre-procedure and post-procedure care.[53,54] Recently published recommendations from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) provide similar guidelines for pediatric patients.[55]

The use of an "aerosol box," basically a transparent box designed to cover the head or upper body of a patient, has been suggested as a method to reduce droplet contamination during endoscopic procedures. Canelli et al. found that the use of an "aerosol box" during endotracheal intubation can effectively contain droplet contamination within the box.[56] Ljubicic et al. demonstrated the successful use of an "aerosol box" during lower endoscopy, specifically endoscopic retrograde cholangiopancreatography (ERCP).[57] While the use of an "aerosol box" during upper endoscopy has not been reported in the published literature, commercial "aerosol boxes" designed to be used during upper endoscopy such as EndoSim's AerosolBarrier (TM). Although the "aerosol box" can reduce droplet spread, it is not recommended as a replacement of standard PPE, but rather a tool to be used with standard PPE. Since the box is not designed to be disposable, safe and effective methods for handling and sterilizing the box after procedures have to be in place.

Hepatic Manifestations and Considerations

During the past outbreaks of SARS and MERS, cases of liver injury have been reported in multiple studies with prevalence, based on elevated ALT, ranging from 53-87% in SARS and 11-56% in MERS.[58–64] This suggested that SARS-CoV-2 may have similar hepatic complications.

Abnormal liver enzymes have been observed in approximately 20-30% of patients with COVID-19. Multiple studies have reported liver injury in patients with COVID-19 indirectly with serum biomarkers such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT); however, there have been no direct confirmations via liver biopsies.[1,10,65] ALT was found to be elevated in 21-31% of cases and AST was

found to be elevated in 16-53% of cases.[1,10,22,23,31,66,67] Additionally, elevated total bilirubin was reported in 11-18% of cases, elevated lactate dehydrogenase was reported in 41-76% of cases, and low albumin was reported in 38-98% of cases.[1,10,22,23,66] In a large study of 1,099 patients with COVID-19 in China, Guan et al. found that 2.1% had a preexisting hepatitis B infection.[10] Acute liver injury has also been reported in an infant whose liver enzymes returned to normal after the virus was cleared.[68] Patients admitted to the ICU were reported to have higher frequencies of acute liver injury, 66.7% versus 26.2% according to a study of 102 patients with COVID-19 in China.[69] Additionally, patients admitted to the ICU were found to have significantly higher ALT, higher AST, higher lactate dehydrogenase, higher total bilirubin, and lower albumin levels compared to those not admitted to the ICU.[1,13]

A study by Guan et al. explored the mechanism of liver injury in COVID-19 patients through mouse models. They found that angiotensin-converting enzyme 2 (ACE2), the entry point into cells for SARS-CoV-2, is expressed in cholangiocytes, but scarcely expressed in hepatocytes. However, when there is inflammation in the liver, there is an up-regulation of ACE2 expression in the liver due to compensatory proliferation of hepatocytes derived from cholangiocytes which express ACE2 potentially allowing these hepatocytes to be infected by SARS-CoV-2.[70] In an unpublished study by Tian et al., autopsies of four patients who died from COVID-19, one of whom had abnormal liver enzyme values including elevated gamma-glutamyltransferase (GGT), revealed that the liver exhibited mild lobular infiltration by small lymphocytes, centrilobular sinusoidal dilation, and patchy necrosis. SARS-CoV-2 was also detected in liver tissue in one case.[71] Cytokine storm syndrome and drug-induced liver injury are common theories for mechanisms of liver injury in COVID-19 patients, however, histological evidence is lacking for these theories.

As there has been no direct confirmation of liver injury in COVID-19 patients, the abnormal biomarker values typically associated with the liver may have been caused extrahepatically. Elevated AST, ALT, and lactate dehydrogenase can be caused by muscle inflammation and hemolysis can account for elevated total bilirubin and lactate dehydrogenase.[72,73] Evidence exists for this alternative mechanism in COVID-19 patients; however, the evidence is not strong. Creatine kinase elevation likely indicates muscle inflammation, however, studies on COVID-19 patients have found varying results. A large study by Guan et al. found that creatine kinase was elevated in 19.0% of severe cases and 12.5% of non-severe cases, but statistical testing was not done to confirm the difference.[10] In a smaller study by Huang et al, creatine kinase was reported to have a median of 132.0 U/L (IQR: 82.0-493.0) in severe cases and 133.0 U/L (IQR: 61.0-189.0) in non-severe cases (p=0.31).[1] In another study, creatine kinase was found to be elevated 13% of cases, but also low in 23% of cases.[22] In a review, Zhang et al. reported that 54% of their cohort of 56 COVID-19 cases had elevated GGT levels, however, this result was unpublished.[26] In a detailed study of 3 patients with COVID-19 by Cao et al., one patient without a history of any liver disease had elevated GGT, AST, ALT, lactate dehydrogenase, low albumin, and normal total bilirubin. However, he also had a greatly elevated creatine kinase of 1081 U/L. This suggests that while this patient has evidence of mild liver injury, the muscle injury appears to contribute to the elevated ALT, AST, and lactate dehydrogenase.[74]

Additionally, a study by Zhou et al. found that 19% of cases had coagulopathy, a sign on potential liver injury.[23] And in other studies, low platelet count was reported in 36.2% of cases.[10]

This evidence suggests that true liver injury due to COVID-19 is likely occurring but the level of injury appears to be mild because while there are reports of abnormal liver function tests and coagulopathy, there were no reports of liver failure or signs of jaundice, ascites, hyperammonemia, or portal hypertension. While there have been reports of multiple organ failure, likely due to sepsis or acute respiratory distress syndrome, there have so far been no reports of severe liver injury such as acute-on-chronic liver failure or fulminant hepatitis caused directly by SARS-CoV-2.[22] As the liver and kidneys can be damaged in patients with COVID-19, considerations should be made on the dosage of drugs, especially those with known hepatotoxicity or renal toxicity risks. And liver and kidney functions should be monitored until the patient has cleared the virus.[75] For patients with pre-existing cirrhosis, especially those with decompensated cirrhosis, the hepatotoxicity of drug treatment options for COVID-19 must be highly considered as these patients have a high risk of developing a drug-induced liver injury. Remdesivir, a repurposed drug originally developed to treat Ebola, is currently one of the most promising drug treatments available for COVID-19.[76,77] Remdesivir has not been tested in patients with cirrhosis and due to its novelty, it is unknown whether this drug can cause hepatotoxicity.[78] Adeoye et al. predicted that remdesivir would be hepatotoxic, but this remains to be proven.[79] Liver function should be closely monitored in cirrhosis patients if remdesivir is administered. Chloroquine and hydroxychloroquine have been in use for decades and

have rarely been associated with liver injury according to the LiverTox database.[78] Baricitinib, another candidate drug for the treatment of COVID-19, may cause ALT elevations, but there have been no reports of hepatotoxicity associated with its use, thus, it is considered unlikely to be a cause of liver injury.[78]

Individuals without COVID-19 who are on immunosuppressive drugs for liver transplants or autoimmune-related conditions such as autoimmune hepatitis should continue taking their medications as the risk of organ rejection or autoimmune disease flares outweighs the chance acquiring SARS-CoV-2.[80] A case report by Qin et al. described an adult patient with COVID-19 who had liver transplantation within days of the viral infection. The patient managed to clear SARS-CoV-2 after 34 days of hospitalization while continuing to take immunosuppressive medication.[81] These patients and their caretakers should follow guidelines of the United States CDC for at-risk groups and they should avoid crowds, practice social distancing, and limiting travel.[82]

CONCLUSION

As COVID-19 becomes increasingly more widespread globally and within countries, increased precaution is a general trend across medical departments. Non-urgent and low priority surgeries and operations including endoscopy should be postponed. There is a risk of fecal-oral transmission of SARS-CoV-2 as the live virus has been found in the stool sample so endoscopies should be done with increased precaution and safety measures.

The current evidence suggests that there are indeed cases of true liver injury caused by COVID-19, however, the injury appears to be mild as severe injuries such as liver failure, independent of multiple organ failure, have not been reported. Histological evidence of liver injury has been reported. A plausible mechanism of liver injury is via the infection of hepatocytes derived from cholangiocytes which express ACE2 potentially allowing these hepatocytes to be infected by SARS-CoV-2. COVID-19 related liver injury was based on abnormal liver function tests or enzymes, which can have extrahepatic contributors such as muscle injury or hemolysis.

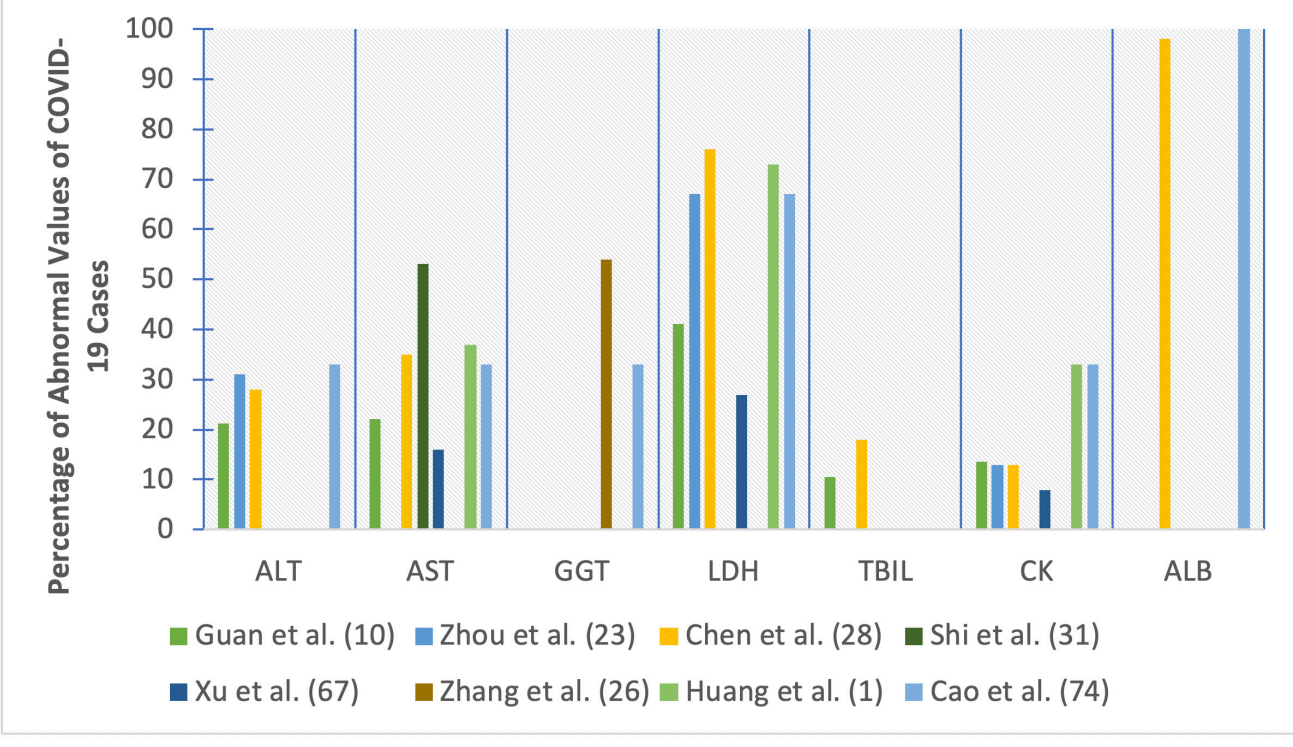

Fig 1. Frequency of hepatic panel and laboratory abnormalities in COVID-19 cases across multiple studies arranged from largest to smallest study.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; TBIL = total bilirubin; CK = creatine kinase; ALB = albumin.

1. Abnormal biomarker values were defined as having biomarkers values above the upper limit (or below the lower limit for albumin) of reference values specified by that particular study.
2. Some studies reported low creatine kinase levels, however, for the purposes of this figure, only elevated creatine kinase levels were concerned abnormal.

TABLE 1. Hepatic panel and laboratory values in overall COVID-19 cases.

Reference	Cohort Size, N	ALT (U/L) Overall	AST (U/L) Overall	GGT (U/L) Overall	LDH (U/L) Overall	TBIL (μmol/L) Overall	CK (U/L) Overall	ALB (g/L) Overall	Notes
Zhou et al.[23]	191	30.0 (17.0-46.0)	-	-	300.0 (234.0-407.0)	-	21.5 (13.0-72.4)	32.3 (29.1-35.8)	
Wang et al.[13]	138	24 (16-40)	31 (24-51)	-	261 (182-403)	9.8 (8.4-14.1)	14 (10-18)	-	
Chen et al.[22]	99	39.0 (22.0-53.0)	34.0 (26.0-48.0)	-	366.0 (260.0-447.0)	15.1 (7.3)*	85.0 (51.0-184.0)	31.6 (4.0)*	
Shi et al.[31]	81	46.2 (29.5)*	40.8 (17.9)*	-	-11.9 (3.6)*	-	32.9 (8.1)*		
Cai et al.[32]	80	22.5 (15.0-26.3)	25.1 (18.0-28.0)	25.5 (14-31.1)	-	-	-	-	Values were before intervention
Xu et al.[67]	62	22 (14-34)	26 (20-32)	-	205.0 (184.0-260.5)	-	69.0 (40.5-101.0)	-	
Huang et al.[1]	41	32.0 (21.0-50.0)	34.0 (26.0-48.0)	-	286.0 (242.0-408.0)	11.7 (9.5-13.9)	132.5 (62.0-219.0)	31.4 (28.9-36.0)	
Chen et al.[66]	21	26.0 (16.0-42.0)	27.0 (21.0-47.0)	-	336.0 (221.0-537.0)	8.8 (6.8-10.3)	73.0 (63.0-287.0)	33.7 (29.6-37.4)	
Cao et al.[74]	3	20 (15-52)	36 (25-54)	17 (15-87)	308 (163-651)	15.0 (8.4-15.5)	267 (46-1081)	33.4 (32.4-39.3)	Values were before immunoglobin intervention
Cui et al. J.[68]	1	84	100	-	-	33.7	46	-	Infant; DBIL=25.2 μmol/L

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; TBIL = total bilirubin; CK = creatine kinase; ALB = albumin.

1. Values are generally reported as medians with an interquartile range within parenthesis, however, some studies

TABLE 2. Hepatic panel and laboratory values in severe and non-severe subgroups of COVID-19.

Reference	Cohort Size, N	ALT (U/L)		AST (U/L)		LDH (U/L)		TBIL (μmol/L)		CK (U/L)		ALB (g/L)		Notes
		Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	
Zhou et al.[23]	191	40.0 (24.0-51.0)	27 (15.0-40.0)	-	-	521.0 (363.0-669.0)	253.5 (219.0-318.0)	-	-	39.0 (19.5-151.0)	18.0 (12.5-52.1)	29.1 (26.5-31.3)	33.6 (30.6-36.4)	Severe cases were deceased cases
Wang et al.[13]	138	35 (19-57)	23 (15-36)	52 (30-70)	29 (21-38)	435 (302-596)	212 (171-291)	11.5 (9.6-18.6)	9.3 (8.2-12.8)	18 (12-35)	13 (10-14)	-	-	
Yang et al.[65]	52	-	-	-	-	-	-	19.5 (4.3)*	13.1 (11.6)*	-	-	-	-	Severe cases were deceased cases
Huang et al.[1]	41	49.0 (29.0-115.0)	27.0 (19.5-40.0)	44.0 (30.0-70.0)	34.0 (24.0-40.5)	400.0 (323.0-578.0)	281.0 (233.0-357.0)	14.0 (11.9-32.9)	10.8 (9.4-12.3)	132.0 (82.0-493.0)	133.0 (61.0-189.0)	27.9 (26.3-30.9)	34.7 (30.2-36.5)	
Chen et al.[66]	21	42.0 (32.5-50.0)	16.0 (13.3-21.8)	47.0 (28.0-74.5)	24.0 (21.5-26.5)	537.0 (433.5-707.5)	224.0 (200.3-251.8)	8.8 (7.9-10.5)	7.8 (6.4-9.5)	214.0 (90.0-329.0)	64.0 (57.5-83.5)	29.6 (28.6-33.0)	37.2 (35.8-38.8)	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; TBIL = total bilirubin; CK = creatine kinase; ALB = albumin.

1. Values are generally reported as medians with an interquartile range within parenthesis, however, some studies or biomarkers have been reported as means with a standard deviation within parenthesis which we have indicated by * in the table cell.

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