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REVIEW ARTICLE

The Impact of COVID-19 and COVID-19 Vaccination on Detection, Assessment, and Management of Suspected Acute Drug-Induced Liver Injury Occurring during Clinical Trials: Consensus Recommendations from the IQ DILI Initiative

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Abstract
While the acute impact of the coronavirus disease 2019 (COVID-19) pandemic has waned, implications for clinical trials remain. In particular, guidance for evaluation of elevated liver tests due to COVID-19, its treatments, and COVID-19 vaccination is lacking. The IQ DILI Initiative, composed of experts from academia, regulatory agencies, and industry herein propose recommendations to address this gap. Extensive literature review was conducted and structured discussions were held between IQ DILI industry members, regulators, and academic experts in hepatology and DILI. Liver-related manifestations in nonhospitalized patients with COVID-19 are highly varied. Evidence of liver injury may occur after COVID-19 symptoms resolve and testing is negative. Treatments for COVID-19 may cause liver injury or alter pharmacokinetics. COVID-19 vaccination has been associated with rare but clear hepatotoxicity, typically consistent with drug-induced autoimmune-like hepatitis, although other presentations, severity, latency, and time to resolution have been reported. Liver injury occurred with mRNA and viral vector vaccines, and in individuals with and without underlying autoimmune or liver diseases. Drug developers and investigators should be aware of the potential liver-related manifestations related to COVID-19, its treatments, and COVID-19 vaccination, as this may impact study eligibility and causality assessment during a trial. COVID-19 testing should be considered part of DILI causality assessment, as a positive test may prevent premature termination of the investigational drug. Since clinical trial participants may not consider vaccinations in their medical history, specific inquiry about their receipt is important when liver tests are abnormal during screening and as part of DILI causality assessment.

1 Introduction

1.1 COVID-19 Pandemic and the Liver—What We Know and What Gaps Remain

Coronavirus disease 2019 (COVID-19), the illness due to infection with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), was declared a worldwide pandemic in March 2020 [1]. The US Food and Drug Administration (FDA) responded promptly with the release of several regulatory guidances on COVID-19, which contained recommendations for the conduct of clinical trials performed during the pandemic [2, 3]. The hepatology community rapidly compiled manuscripts on the manifestations of COVID-19-associated liver abnormalities and made recommendations on the management and treatment of patients with chronic liver disease (CLD) during the pandemic [4, 5]. In the USA, 11 May 2023 marked the end of the Federal COVID-19 Public Health Emergency declaration [6].

The initial challenges pertaining to the execution and performance of clinical trials due to the pandemic have largely been overcome and the liver-related manifestations occurring in acutely ill hospitalized patients with COVID-19 have been defined and will not be addressed in this manuscript. However, COVID-19 remains an important public health issue with continual emergence of variants and high rates still being reported by the Centers for Disease Control and Prevention (CDC) in many states [7]. In addition, long COVID-19, which is now a recognized clinical entity, can also be associated with liver abnormalities. As such, many questions remain and gaps exist as to the best practices to adopt in clinical trials specifically related to liver

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Key Points

Acute COVID-19 infection and long COVID should be considered for individuals who present with liver test elevations at screening in clinical trials, even in the absence of respiratory symptoms.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) testing is recommended as a routine part of second-line DILI causality assessment, regardless of the presence of symptoms consistent with COVID-19, for new onset of liver test elevations during the clinical trial.

Evaluate COVID-19 vaccination as a potential cause of DILI, if liver tests are elevated within 90 days of receipt.

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test abnormalities due to or associated with COVID-19, its treatment, and/or vaccination. These include how to assess and manage elevated liver tests, as liver disorders associated with COVID-19 may impact eligibility criteria and the assessment of liver test elevations occurring during the clinical trial.

1.2 IQ-DILI

The IQ DILI Initiative was launched in June 2016 within the International Consortium for Innovation and Quality in Pharmaceutical Development (also known as the IQ consortium) to reach consensus and propose best practices on topics related to DILI [8]. The IQ Initiative is a science-focused, not-for-profit organization addressing scientific and technical aspects of drug development and is composed of 44 pharmaceutical and biotechnology companies (https://iqconsortium.org/). The IQ DILI Initiative is an affiliate of the IQ Consortium, composed of 17 IQ member companies, focused on establishing best practices for diagnosing, monitoring, managing, and preventing DILI.

1.3 Methods and Scope of this Manuscript

To provide meaningful guidance to sponsors and investigators involved in clinical trials, members of the IQ DILI Initiative have developed a number of recommendations to address the lack of specific guidance on COVID-19 and COVID-19 vaccination when designing eligibility criteria and when evaluating a new onset of elevated liver tests occurring during a clinical trial.

This publication is based on an extensive literature review of PUBMED, Embase, and MEDLINE utilizing the keywords DILI, SARS-CoV-2, COVID-19, COVID-19 vaccination, liver, and clinical trials. Consensus recommendations were achieved after numerous structured discussions between IQ DILI members and academic and regulatory experts. The levels of evidence and strength of each consensus statement have not been formally rated. These recommendations are based on the expert opinions of the authors and do not imply regulatory guidance or mandate.

It is conceivable that future pandemics may have similar characteristics to COVID-19, and as such, many of the approaches suggested herein could serve as a precedent for assessing the impact of other similar emerging viruses as they relate to liver injury on trial eligibility and the detection and management of suspected DILI. However, it is important to underscore that while transient liver abnormalities can occur with any acute viral illness, individual liver-related virus-specific injury phenotypes may differ, and as such, impact best practices in their assessment and management.

2 Liver Injury Due to SARS-CoV2 Infection

2.1 Mechanisms of Hepatotoxicity Due toSARS-CoV2 Infection

While a full discussion of the mechanisms of SARS-CoV-2-associated liver injury is beyond the scope of this manuscript and has been reviewed in detail elsewhere [9], this section will summarize some leading theories (Fig. 1). SARS-CoV-2 binds to use the angiotensin-converting enzyme 2 (ACE-2) receptor to enter host cells [10–12], after a priming step of the viral spike protein domain by transmembrane protease serine 2 (TMPRSS2) [10–12]. ACE-2 receptors are expressed on the cell surface of hepatocytes, cholangiocytes, and liver progenitor cells [13–16]. TMPRSS2 is also found on liver progenitor cells [15]. Autopsy studies have isolated SARS-CoV-2 viral antigens directly from the liver and bile [17–22]. With these findings, one postulated mechanism of viral-induced liver injury has been direct SARS-CoV-2-induced cytopathic hepatotoxicity. Other factors causing and/or contributing to liver injury are indirect effects arising from SARS-CoV-2 infection. Another well-described effect of the virus during acute infection is the induction of a massive systemic immune response or cytokine storm, driven by increased immune cell production of interleukin (IL)-6, IL-2R, IL-10, and tumor necrosis factor alpha (TNF-α) [23]. In a cohort of 96 patients admitted to an Austrian hospital for COVID-19, biomarkers of systemic inflammation IL-6, C-reactive protein (CRP), and/or ferritin correlated with the height of AST elevation (determined to be of liver origin), suggesting that the immune response to

COVID-19 disease can cause or exacerbate liver injury [24]. Elevations in alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), and alkaline phosphatase (ALP) have been reported to occur later in the acute course of COVID-19 illness [24, 25]. The reasons for these delayed effects were not explained. It is important to underscore that these data were obtained from hospitalized patients with severe infections and may not translate into the milder outpatient liver abnormalities that may be more applicable to patients enrolling in clinical trials. Other indirect factors that have been noted to lead to liver abnormalities include immune-mediated damage, anoxia, and reactivation of a preexisting chronic liver disease, e.g., autoimmune hepatitis or hepatitis B virus (HBV) reactivation [16, 26, 27].

Liver injury due to SARS-CoV-2 virus may occur due to direct effects of viral entry into hepatocytes mediated by ACE2 and subsequent activation of cell death and apoptosis. Alternate indirect mechanisms of injury can involve T-cell activation and downstream immune/vascular effects such as (1) activation of monocytes and macrophages resulting in a cytokine storm of inflammatory agents such as IL-6, IL-10, CRP; (2) inflammatory effects on neutrophils and vasculature leading to abnormal coagulation and ischemia reperfusion injury; and (3) reactivation of chronic viral hepatitis and subsequent hepatocyte death. Image created for this publication [28].

ACE2 Angiotensin-converting enzyme 2, *CRP* C-reactive protein, *IL-6* interleukin-6, *IL-10* interleukin-10, *SARS-CoV-2* severe acute respiratory syndrome coronavirus type 2

2.2 COVID-19-Associated Presentation of Liver Injury

COVID-19-associated liver injury was initially broadly described as "any liver damage occurring during disease course and treatment of COVID-19 patients, with or without pre-existing liver disease" [25, 29–31]. Most publications describing COVID-related liver manifestations occurred in acutely ill hospitalized patients with numerous comorbidities. Liver injury in these critically ill patients occurred in up to 67% of cases and was typically associated with numerous contributory or confounding factors such as sepsis, ischemia, multiple organ dysfunction, immune-mediated injury due to systemic inflammatory response syndrome, direct hepatotoxicity of the virus, and the use of hepatotoxic medications [16, 32–37]. This group of patients will not be discussed further in this manuscript as they would not be eligible for enrollment in a clinical trial of a study drug for a non-COVID-19 indication.

Over the last few years, individual case reports and case series of liver injury associated with mild-to-moderate nonhospitalized patients who had COVID-19 have been

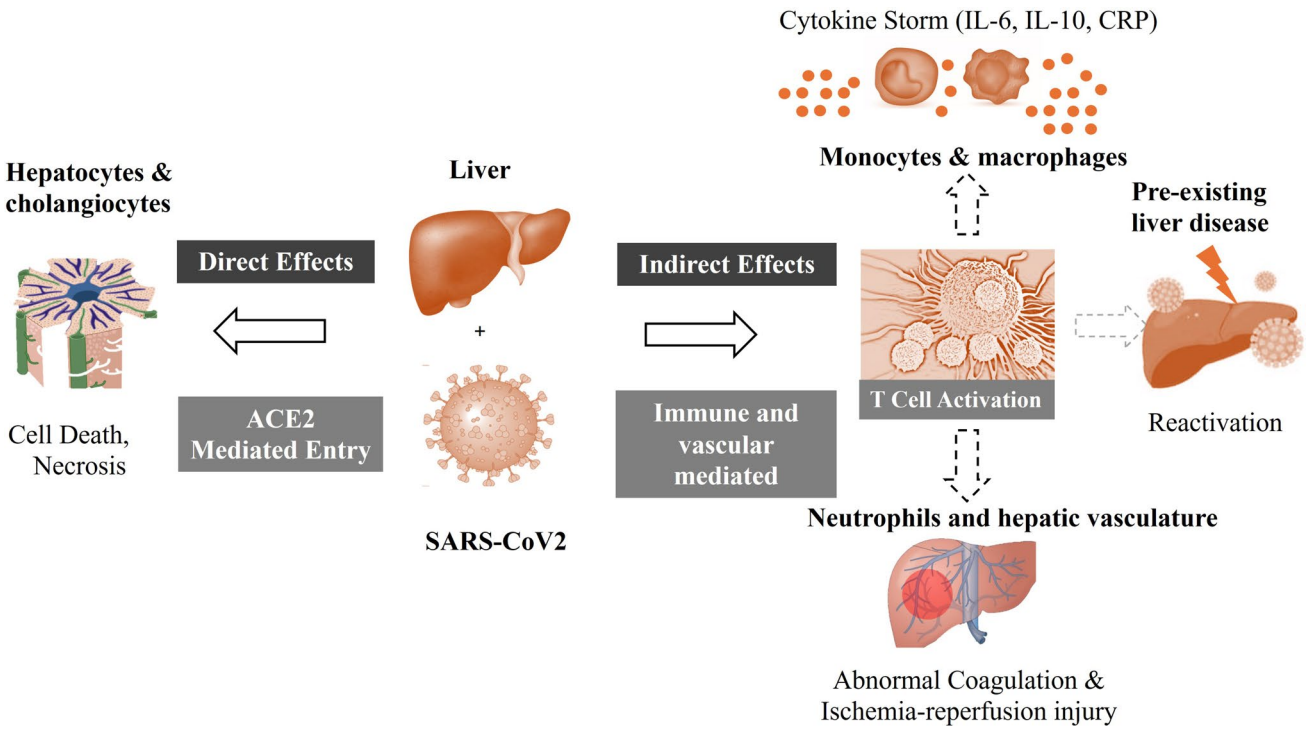

Fig. 1 Mechanisms of Liver Injury in COVID-19

described. Overall, up to 11% of patients with COVID-19 have liver comorbidities and 14–53% show elevated aminotransferase levels during illness progression [38]. Liver injury is mild, transient, and resolves without intervention in most cases. However, it is important to emphasize that such injury may impact clinical trial eligibility, and should be an essential component of causality assessment when investigational products are being assessed for DILI. Importantly, some cases have atypical presentations and thus do not fit the current broad definition of "COVID-19-associated liver injury." Examples include liver test elevations without the occurrence of respiratory symptoms, liver test elevations after resolution of respiratory symptoms, and/or liver test elevations after the polymerase chain reaction (PCR) test has become negative [39–42]. As such, it is important for both investigators and sponsors to be aware of the diverse liver-injury phenotypes associated with COVID-19 that may occur during the clinical trials that are described below and summarized in (Table 1).

2.2.1 Acute Hepatitis

Liver tests consistent with acute hepatitis (elevated aminotransferases) may occur early after infection and importantly, there have been reports of acute hepatitis as the initial presentation of COVID-19, even in the absence of respiratory symptoms [41, 42]. In other instances, acute hepatitis may appear as long as 3 weeks after a positive reverse transcription (RT)-PCR test and subsequent resolution of symptoms. The degree of elevation of aminotransferases can range from mild (ALT or AST > 1.0–3.0× ULN) to severe, reaching values as high as 30× ULN [43]. Overall, however, it appears that acute hepatitis associated with mild-to-moderate COVID-19 infection is uncommon.

2.2.2 Secondary Sclerosing Cholangitis (SSC)

SSC is a chronic cholestatic hepatobiliary disease characterized by extensive stricturing and dilatation of the intra- and extra-hepatic bile ducts that can lead to cirrhosis and its complications [44]. Case reports and case series have emerged describing hospitalized patients with severe COVID-19 who develop SSC. This is also known as secondary cholangitis of critically ill patients (SC-CIP), and is possibly due to ischemic injury to the bile ducts [45–47]. There have also been case reports of SSC in severely ill patients with COVID-19 supported with respirators who have been sedated with continuous or repeated intravenous (IV) ketamine infusions [48–50]. Many patients with SC-CIP described in the literature rapidly progressed to liver transplantation. Other patients have had prolonged cholestasis, with persistent elevations of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) lasting months to longer than 1 year despite recovery from COVID-19 [46, 51]. It is notable that SSC has been reported most commonly in patients with underlying liver disease, particularly metabolic-dysfunction-associated steatotic liver disease/metabolic-dysfunction-associated steatotic hepatitis (MASLD/MASH) [52].

2.2.3 Portal Vein Thrombosis (PVT)

Various arterial and venous thromboembolic disorders have been described in patients with COVID-19, including PVT, as the virus is considered to cause endothelial dysfunction [53]. In a review of publications of patients with COVID-19 and PVT, the interval between COVID-19 infection or RTR-PCR positivity and PVT onset ranged from 3 to 42 days [54]. The most common presentation was abdominal pain and distension, and PVT was more common in patients with underlying cirrhosis. Liver tests were typically normal or only mildly elevated. However, if a clinical trial is being conducted for a liver indication, a rapid deterioration of the underlying liver disease may be observed with signs of hepatic decompensation. In such a scenario, it would be important to determine whether PVT due to COVID-19 is a more likely alternative cause rather than exposure to the study drug during assessment of liver injury causality.

2.2.4 Autoimmune-Like Hepatitis (AIH)

Autoimmune-like hepatitis is a heterogeneous immune-mediated inflammatory condition of the liver that can lead to cirrhosis. Cases of AIH hypothesized to have been triggered by SARS-CoV-2 have been reported [55–60]. Although uncommon, it is nevertheless important to be aware of this potential occurrence after a resolved COVID-19 infection when differentiating de novo AIH potentially due to the study drug versus other causes. Time from COVID-19 infection resolution to appearance of elevated aminotransferases as high as > 20× ULN with associated serum autoantibodies and sometimes with elevations of TBIL, GGT, and/or ALP have been reported up to 1 month after respiratory symptoms had resolved. Histology, when performed, supported the diagnosis of AIH (e.g., interface hepatitis, plasma cells). Most cases resolved completely with corticosteroid treatment.

2.2.5 Acute Liver Failure (ALF) and Acute on Chronic Liver Failure (ACLF)

There have been few case reports of ALF attributed to mild COVID-19 [61–66]. There is a single case report of ACLF occurring in a patient with cirrhosis due to primary biliary cholangitis (PBC)/AIH overlap syndrome who subsequently

Table 1 Patterns of liver injury in patients with non-severe/mild COVID-19

Presentation	Onset	Clinical features	Biochemical Abnormalities	References
Acute hepatitis	• May occur 3 weeks after positive PCR and 1 week after symptom resolution	• Aminotransferase elevations • Respiratory symptoms may be absent	• Mild – severely elevated AST (2-30x ULN) and ALT (3-30x ULN)	Wander et al. [41], Bongiovanni et al. [42], Osario Martinez et al [40], Khan et al. [43]
Secondary sclerosing cholangitis (SSC)	• SSC detected months (median of 91 days) after COVID-19 diagnosis when patients are negative for COVID-19 • Reported in severely ill COVID-19 patients on respirators that are on continuous/repeated IV ketamine infusions	• Most patients present with jaundice and cholestasis. • Some report pruritus, abdominal pain or fever	• ALT and AST mildly increased (2-3x ULN) • Marked elevation of Bilirubin (8-10x ULN), GGT (20-25 x ULN) and ALP (8-10x ULN)	Hunyady et al. 2022, Wendel-Garcia et al. [48], Lee et al. [49], Henrie et al. [50]
Portal Vein Thrombosis (PVT)	• PVT mostly occurs during acute infection, but can also appear during convalescence (3-42 days after RT-PCR positivity). Can occur in patients without liver disease	• Most common presentation is abdominal pain/ distension. • Sometimes fever or nausea and vomiting	• Low platelets, leukocytosis • High CRP (3-30x ULN) • Liver enzymes and bilirubin normal to ~<3x ULN	Kheyrandish et al. [54]
Autoimmune-like Hepatitis	• 1 month after COVID-19 positivity and resolution of respiratory symptoms	• Can present with jaundice • Responsive to immunosuppressive therapy.	• Elevated AST (6-20x ULN) and ALT (6-20x ULN) and TBIL (~ 25x ULN) • Positive autoimmune serology and high serum IgG levels	Kabaçam et al. [56], Hong et al. [55], Rajendiran et al. [58]
Long COVID	• Onset can be after 3 months and persist as long as 20 months	• Fatigue and dyspnea, muscle weakness, muscle and joint pain,	• Elevated ALT, GGT, and ALP • Exact elevations and time course not described. • Ferritin and ESR increased with high ALT	Costa de Lima et al. [39]
Acute Liver Failure/Acute on Chronic Liver Failure	• After Mild COVID-19 infection	• May lead to death		Khawaja et al. [61], Melquist et al. [62], Gurala et al. [63], Sarkar et al. [66], Weber et al. [64], Tanaka et al. [65], Chen et al. [67]
Nonspecific enzyme elevations	• ALT/AST increase early in the course of COVID-19 which may be followed by cholestatic liver test elevations.	• Respiratory symptoms typically absent	• Elevated ALT and AST followed by ALP and GGT	Herta et al. [68], Lei et al. [70]

Clinical presentations summarized in this table are as described in the referenced literature

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *GGT* gamma-glutamyl transferase, *PVT* portal vein thrombosis, *RT-PCR* reverse transcription polymerase chain reaction, *SSC* secondary sclerosing cholangitis, *TBIL* total bilirubin, *ULN* upper limit of normal

died due to liver failure [67] considered to have been triggered by a mild COVID-19 infection.

2.2.6 Nonspecific Liver Test Elevations

It has been noted that hepatocellular enzymes increase early during COVID-19, which may be followed by cholestatic liver test elevations [42, 68–70].

3 COVID-19 Liver Injury in Special Populations

3.1 COVID-19 in Patients with Chronic Liver Disease

Patients with chronic liver disease (CLD), especially those with aminotransferase levels > 3× ULN, TBIL > ULN or if there is evidence for cirrhosis, are typically excluded from participation in clinical trials performed for nonliver disease indications. However, such patients may enter clinical trials for drugs being studied specifically for a liver disease indication, such as MASH, alcohol-associated hepatitis, or a phase 1 hepatic impairment study. Patients with chronic liver disease who become infected with SARS-CoV-2 have been found to have an increased risk of morbidity and mortality compared with patients without underlying liver disease and have a higher risk for severe COVID-19 infection [71, 72]. MASLD-associated metabolic comorbidities, such as type 1 diabetes mellitus (T1DM), obesity, and hypertension, have been shown to put patients at increased risk for a progressive course of COVID-19-related disease [73–75].

3.2 Liver Injury in Pediatric Patients with COVID-19

When children become acutely infected with SARS-CoV-2 they are typically asymptomatic or may have only mild symptoms. Liver manifestations of long COVID-19 in infants and children, while rare, do occur, and thus it is important to be aware of these manifestations. Liver tests have been reported to be "slightly elevated" with a hepatocellular pattern in approximately 20–50% of cases and occurred most frequently in those less than 3 years old [76–79]. In addition, like adults, when underlying CLD was present, liver injury from COVID-19 was associated with an increased likelihood of liver-related morbidity and mortality.

A retrospective case series from Israel described five children who presented with two different phenotypes of serious liver injury after being diagnosed with COVID-19 [80]. The first pattern describes two previously healthy infants 3 and 5 months of age, who presented with acute liver failure requiring liver transplantation. Neither infant had respiratory or other symptoms commonly associated with COVID-19, although both tested positive. Massive necrosis with cholangiolar proliferation and lymphocytic infiltrate was described in the liver explant. The second liver-related phenotype occurred in three children, two of 8 years of age and one of 13 years of age, who presented with hepatitis and cholestasis several months after a diagnosis of COVID-19. Two children had a liver biopsy that showed lymphocytic portal and parenchyma inflammation and with bile duct proliferations. All three children were started on steroid treatment with subsequent improvements of liver enzymes. All patients had an extensive causality assessment without an alternative etiology identified. Such presentations during pediatric clinical trials should raise suspicion of COVID-19 as an etiology of new onset of liver test elevations.

3.3 Long-COVID-19-Associated Liver Injury

The World Health Organization (WHO) defines long COVID or "post COVID-19 condition" as persistent symptoms usually occurring 3 months from onset in individuals with past confirmed or probable SARS-CoV-2 infection and persisting for at least 2 months that cannot be explained by an alternative diagnosis. It occurs in more than 10% of people who had SARS-CoV-2 [81]. Some patients with long COVID-19 may have elevated liver tests, although the prevalence is currently not known and may be underestimated, as many of these patients are incorrectly diagnosed with MAFLD/MASH. In a study of 243 Brazilian patients who developed long COVID-19, elevations in liver tests occurred for as long as 20 months following acute illness. However, the degree of elevation and/or fluctuation, if any, during this time was not described [39]. Analyses conducted comparing liver outcomes 1 year and beyond post-COVID-19 infection demonstrated an increased incidence of abnormal hepatobiliary tests and MASLD compared with a healthy control population that occurred independently of disease severity [82, 83].

Abnormal liver tests due to long COVID-19 may decrease over time, which may confound evaluation of efficacy in liver-related trials, as these reductions may be incorrectly attributed to study drug efficacy. It is unknown whether liver tests fluctuate with long COVID or if, once they resolve, remain normal. Indeed, more data are required to better understand the course of liver-related blood test elevations in patients with long COVID.

4 Liver Injury Due to COVID-19 Treatments

Another cause of liver injury in patients with COVID-19 are the medications used to treat COVID-19. This often does not present a problem in the clinical trial setting since subjects with significant symptoms from intercurrent COVID-19 infection will likely have study drug paused or permanently discontinued. In cases in which it has been determined that

the benefits of continued study participation outweigh the risks, liver tests should be monitored more frequently. Nirmatrelvir/ritonavir (Paxlovid™) has been associated with aminotransferase elevations, clinical hepatitis, and jaundice. The package insert states that "caution should be exercised when administering Paxlovid™ to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis, especially those with advanced liver disease patients with Child-Pugh-C" [84]. While treatment with Paxlovid™ should not be withheld, it is important for investigators to be aware of this rare but possible cause of a new onset of liver abnormalities. Additionally, ritonavir is one of the most potent inhibitors of CYP3A4. The potential for drug–drug interactions must be considered in this setting, both for its potential impact on metabolism of the study drug and its metabolites, as well as its impact on other drugs used by the study participant.

Other treatments for COVID-19 have also been implicated in liver injury. In a trial comparing remdesivir treatment for either 5 or 10 days, severe grade 3 ALT/AST elevations were reported in 4–6% of patients, and grade 4 AST/ALT elevations in up to 3.6% of patients, necessitating treatment discontinuation [85]. There has even been a case report of remdesivir-associated acute liver failure [86].

Importantly, since the outbreak of COVID-19 in December 2019, there has been a sharp rise in the use of complementary and alternative medicines (CAMs) [87]. While CAMs are often prohibited in clinical trials, patients may either inadvertently or purposely be using them. For example, the prevalence of CAM use in a phase 1 oncology clinical trial was 51%, and 23% of those patients did not fully disclose their CAM use to their physicians [88]. Thus, the use of CAMs and their potential interactions with COVID-19 treatments should also be considered as part of causality assessment for new elevations of liver tests during clinical trials.

5 Liver Injury Due to COVID-19 Vaccination

5.1 Mechanisms of Hepatotoxicity Due to COVID-19 Vaccines

Although rare, hepatotoxicity has been temporally related to administration of many vaccines, (e.g., hepatitis A, hepatitis B, influenza, and rabies virus vaccines) [89–96]. In addition, the influenza (H1N1), hepatitis B, and human papilloma virus vaccines have all been associated with autoimmune reactions possibly due to immune-mediated cross-reactivity and molecular mimicry [97]. Thus, it is not surprising that there are case series and case reports of SARS CoV-2 vaccine-associated liver injury (SVALI). These reports began to appear shortly after the advent of safe and effective vaccines against SARS-CoV-2 in Dec 2021, even though no cases of DILI were seen during their clinical development [98]. The exact mechanism of SARS-CoV-2 vaccine-induced liver injury is not known. The most common types of COVID-19 vaccines in the USA contain mRNA that encodes the SARS-CoV-2 spike (S) protein. The entry of S protein in the human body elicits a strong stimulus to innate immunity, which results in cellular activation, leading to proinflammatory cytokine and chemokine production. Due to molecular similarity between S protein and liver specific proteins, an activated immune system may lead to destruction of liver proteins [99].

A systematic review of the literature was conducted on histologically confirmed COVID-19 vaccination-related immune-mediated liver injury (ILI) [100] and included a total of 13 publications [101–113], identifying 12 patients with signs of ILI on liver biopsy samples. More than a quarter of these patients had underlying chronic liver disease, and jaundice was the most common symptom. The most frequent histologic finding was severe portal lymphoplasmacytic infiltration with interface hepatitis. In addition, eosinophilic infiltrates were found in one-third of patients, which is consistent with DILI. Approximately a quarter of patients had preexisting autoimmune diseases including AIH, primary sclerosing cholangitis (PSC), and Hashimoto's thyroiditis. Approximately 90% of these individuals were treated with and responded to steroids.

5.2 COVID-19-Vaccine-Associated Presentation of Liver Injury (Table 2)

The US DILIN reported 16 high causality cases of liver injury following COVID-19 vaccination. Median latency was 16 days but ranged from 1 to 47 days, and 75% of these patients presented with a hepatocellular pattern of liver injury. Median ALT was 497 U/L and more than one-third of patients presented with elevated bilirubin. Only 12% had elevated immunoglobulin G levels, while antinuclear antibody and smooth muscle antibody were detectable in 27% and 36% of patients, respectively. Eight patients had liver histology demonstrating either an acute hepatocellular or mixed/cholestatic pattern of hepatotoxicity [114]. A total of 37% of patients were treated with corticosteroids, with 88% resolving within 6 months.

A report of 11 cases from a single center [115] included 2 who had histologic evidence of nonspecific inflammation without steatosis or fibrosis and 1 with evidence of cholestasis. Latency was up to 12 weeks. Guardiola and colleagues utilized the Indiana University Health Enterprise Data Warehouse [116] to analyze the frequency and pattern of liver injury, defined as ALT > 200 U/L, ALP > 250 U/L, and/or TBIL > 2.5 mg/dl repeated twice within 12 weeks after the first or second SARS-CoV-2 vaccination.

After all other causes of potential causes of hepatotoxicity were excluded [117–119], they identified 177 cases among 470,274 patients, and thus concluded that liver injury was rare (0.038%). They found that there was no difference in the incidence of hepatotoxicity between the different types of vaccines received (m-RNA-based versus viral vector). In addition, the average time to injury was between 29 and 45 days, and the liver injury pattern was hepatocellular in 45%, cholestatic in 35%, and mixed in 20%. Finally, they found that the peak mean AST, ALT, ALP, and TBIL values were 800 IU/L, 553 IU/L, 405 IU/L, and 3.1 mg/dl, respectively.

A case series of more than 2 million adults investigated the risk of SVALI following BNT162b2 and CoronaVac, utilizing vaccination records obtained from the Department of Health Hong Kong Special Administrative Region, China [120]. This report concluded that most post-vaccination acute liver injury was mild without an increased likelihood of new-onset chronic liver disease and that incidence of acute liver injury following COVID-19 vaccination was very low.

The Spanish Registry for Autoimmune and Cholestatic Diseases [121] described 47 cases between February 2021 and February 2022 of SARS CoV-2 vaccine-associated liver injury, which demonstrated elevated aminotransferases within 90 days of either the initial or booster dose. As these patients were not prospectively monitored after vaccination, liver injury was identified by symptomatic presentation: jaundice (42.1%), asthenia (34.2%), abdominal pain (28.9%), nausea (13.1%), or incidentally (19.1%). Approximately 25% of patients had a past nonliver related autoimmune disorder and approximately 15% had previous AIH. In total, 36.2 % of cases occurred after the priming dose, with the remainder occurring after the first (46.8%) or second booster (17%). The majority of patients with SVALI after a booster had been exposed to a mRNA vaccine, the most common type of vaccine used in Spain. Median time from vaccine to diagnosis of liver injury was 22 days, with a range of 11–41 days. Liver injury tended to be more severe after the booster dose. Most patients were considered to have non-severe acute hepatitis (80.9%), $n = 6$ had acute liver injury with liver dysfunction defined as INR > 1.5, and $n = 3$ had acute liver failure, defined as both INR > 1.5 and hepatic encephalopathy. All patterns of liver injury occurred, with hepatocellular being most frequent (80.9%), followed by mixed (12.8%) and cholestatic (6.4%). The pattern of SVALI did not differ between type of vaccine. Median AST and ALT levels were ~1000 IU/mL, TBIL 4.7 mg/dL. Immunoglobulin (Ig)G was elevated in 63.8% of cases and 68.1% had a positive autoantibody, most commonly ANA; 70% of patients had a liver biopsy that was consistent with AIH in most cases, with 9.1% of cases consistent with DILI (eosinophilic infiltrates), with one case of immune-allergic in origin and one case that was nonspecific. A total of 28% of patients

Table 2 Liver-Related Injury following COVID-19 Vaccination

Mechanism	Clinical Manifestation	Lab Abnormalities and Histology	References
• Exact mechanism unknown • May be related to innate immune response to SARS-CoV-2 spike (S) protein • No difference in m-RNA-based vs viral vector	• Very rare event (Incidence <0.05%) • Liver injury onset can range from 1 to 90 days after vaccination. • More common after booster or subsequent doses. • Jaundice, nausea and fatigue most common symptoms. • Pattern of injury most commonly hepatocellular but can also be mixed or cholestatic. • More common in patients with pre-existing autoimmune disease or chronic liver disease	• Elevated ALT (10-15x ULN), AST (~20x ULN), ALP (~4x ULN) and TBIL (~3x ULN) in some cases • Autoimmune markers (IgG, ANA,SMA) present ~12–36% • Biopsy: portal lymphoplasmacytic infiltration with interface hepatitis most common. Eosinophilic infiltrates also common.	Fontana et al. [114], Shiffman et al. [115], Guardiola et al. [116], Efe et al. [99], Barreira-Díaz et al [121]

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *ANA* antinuclear antibody, *AST* aspartate aminotransferase, *IgG* immunoglobulin G, *SARS-CoV-2* severe acute respiratory syndrome coronavirus type 2, *SMA* smooth muscle antibody, *TBIL* total bilirubin, *ULN* upper limit of normal

who had the next booster dose had a relapse of liver injury, but all cases were mild.

An international case series from 18 countries [99] identified 87 cases of COVID-19-vaccination-related liver injury by retrospectively reviewing vaccinated patients who subsequently developed ALT or AST $\geq 5 \times$ ULN) and/or ALP $\geq 2 \times$ ULN or ALT/AST $\geq 3 \times$ ULN with a bilirubin $\geq 2 \times$ ULN. In total, 28% of patients had autoimmune disorders before liver injury onset. SVALI occurred most commonly after the Pfizer-BioNTech (BNT162b2) vaccine (59%), followed by the Oxford-AstraZeneca (ChAdOX1 nCoV-19) vaccine (23%), and least commonly with the Moderna (mRNA-1273) vaccine (18%). The study authors did not compare vaccine safety profiles or suggest a difference between vaccine types, but instead attributed differences to vaccination strategies and vaccine availability between countries. SVALI was diagnosed after the first vaccine in 46% and after the second dose in 54%. Median time from vaccination to the onset of liver injury was 15 (range 3–65) days. Three patients had mild SVALI after the first dose of vaccine with a more severe liver injury with the second dose of the same vaccine, and 92% were symptomatic, with the most common symptoms being fatigue (75%), nausea (63%), and jaundice (39%). The pattern of liver injury was hepatocellular (84%), mixed (10%), and cholestatic (6%). Antinuclear antibodies were present in 67%. Approximately half of the cases had a liver biopsy, of which 77% were reported to be consistent with either probable or definite AIH. New-onset immune-mediated liver injury due to SVALI as opposed to a flare or unmasking of an underlying AIH was suggested in most of these cases, as none had a relapse once immunosuppressive therapy was discontinued. A total of 14% of patients had preexisting liver disease. Spontaneous resolution was common, steroid response was good, and prognosis favorable. Three patients had mild liver injury after the first vaccination but more severe liver injury following the second dose of the same vaccine and one had immune-medicated liver injury requiring a liver transplant. There was no difference in incidence of SVALI by vaccine type. The mechanisms and clinical presentation of SVALI associated with COVID-19 vaccination are summarized in Table 3.

6 Impact on DILI Assessment and Management during Clinical Trials

6.1 DILI in Clinical Trials in the Context of COVID-19 and COVID-19 Treatments

6.1.1 Screening and Eligibility Criteria (Fig. 2)

Patients with signs and symptoms of acute COVID-19 infection are routinely excluded from clinical trials for multiple reasons, including confounding trial results, protection of study participants and staff, and potential need to interrupt the study for the symptomatic participant due to progressive infection. Symptomatic individuals should be tested for SARS-CoV2 using an RT-PCR or viral antigen test and excluded from clinical trial participation until symptoms resolve. RT-PCR testing has been shown to have substantially greater sensitivity for the detection of SARS-CoV2 compared with rapid viral antigen testing (RAT), especially for strains related to Omicron SARS-CoV2 variants, and should be considered a preferred method for ruling out active viral infection in symptomatic individuals with negative RAT results unless the longer turnaround time makes this impractical [122]. A test of cure is not usually required since patients may have persistently positive tests for up to 90 days following initial infection but are not considered contagious [123]. Isolation can generally be discontinued after 5 days for mild cases and 10 days for more severe cases provided the patient's clinical condition is improving [124]. Retesting is recommended using an antigen test or nucleic acid amplification test in the case of a moderately to severely immunocompromised patient. Utilization of serology tests is not useful for diagnosing acute infection since a large portion of the population has been vaccinated with vaccines containing spike protein, which will result in seroconversion for most common tests, regardless of acute infection. The screening of asymptomatic individuals prior to study entry is complicated by a lag between infection and viral detection. It should be noted that the mean incubation period after exposure ranges from approximately 5 to 9 days [125]. Antigen tests are less sensitive than nucleic acid tests, leading to false negative results, a potential delay in turnaround time (particularly for global trials), and the need for repeat testing that complicates the logistics and duration of the screening period. Additionally, given the relatively low prevalence of such infections in patients presenting for entry into clinical studies, COVID-19 antigen tests are not recommended. Another important consideration is the broad immune activation lasting approximately 4–6 weeks produced by both acute SARS-CoV2 infection and vaccination (see section on vaccination). This may confound any study biomarkers intended to assess investigational product activity. Thus, unless the underlying clinical condition warrants urgent treatment with an investigational product, such as when treatment options have been exhausted, it is best to postpone participation in trials for several weeks to avoid confounding the interpretation of study results and drug relatedness assessments.

Finally, it is important to be aware that COVID-19 may have long-term effects on drug metabolism [126] .

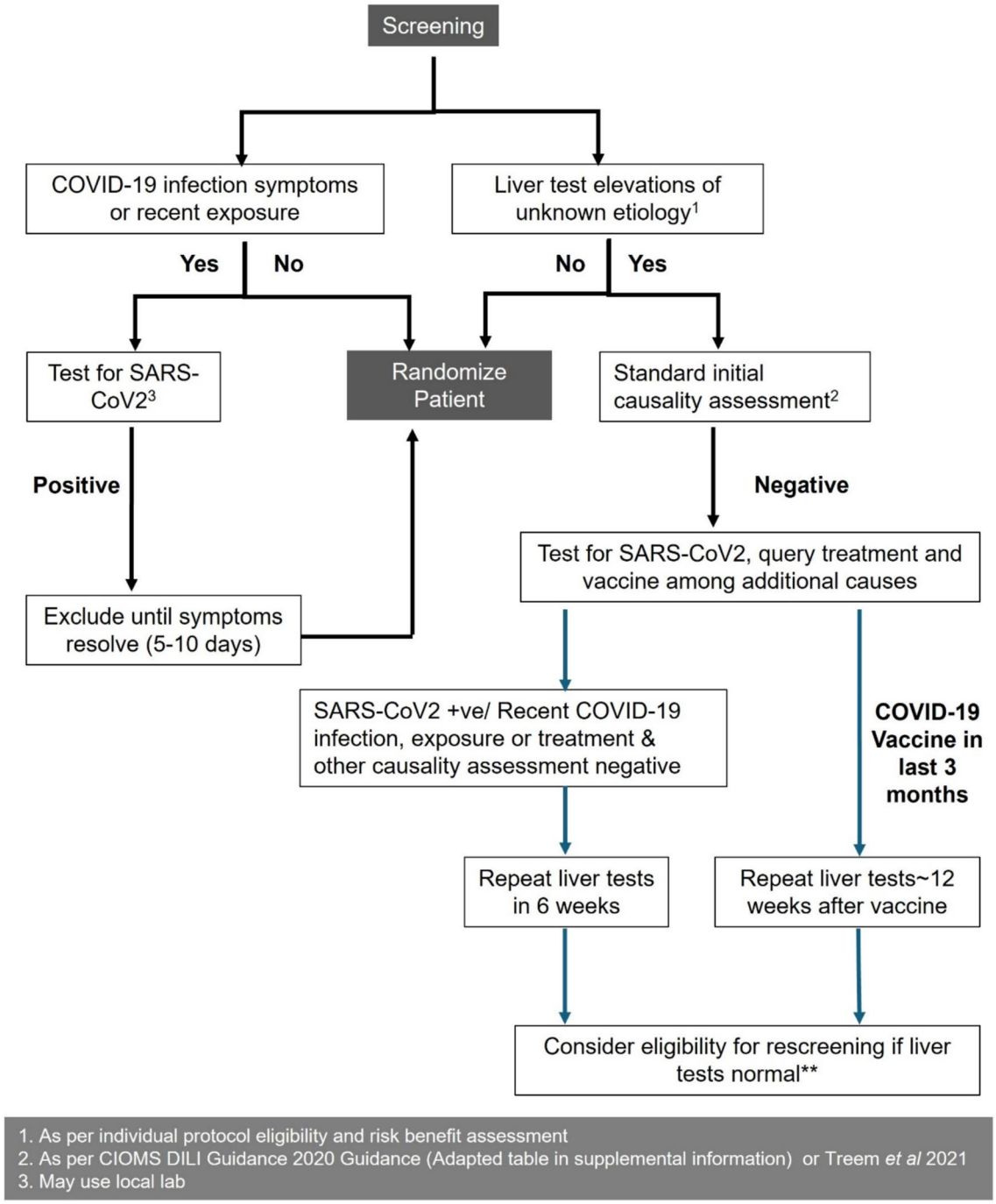

Fig. 2 Algorithm for Screening for Suspected Liver Injury in Relation to COVID-19 Infection, Treatment, and Vaccination [127, 128]. *SARS-CoV-2* severe acute respiratory syndrome coronavirus type 2

6.1.2 Detection, Monitoring, Causality Assessment, and Management of DILI

Once enrolled in a clinical trial, a patient who becomes infected with SARS-CoV-2 should be managed individually and continued administration of the investigational product should depend on considerations of the potential for the study drug to produce significant immunosuppression, which could impact resolution of COVID-19 and the potential impact of COVID-19 treatment on the trial intervention and patient safety. An individual benefit–risk assessment should be conducted by the investigator to determine whether to continue the investigational therapy. Factors to be considered include the urgency for treatment of the underlying condition

and the impact of treatment interruptions, the half-life and pharmacodynamics of the investigational product, and the nature of the immune defect associated with the investigational product. Data should be collected and reported to the sponsor on comorbidities and risk factors, treatments administered, especially as some are potent inhibitors of CYP3A4 as noted above, supplemental oxygen administration, and patient outcomes. This will allow a thorough assessment of the impact of the investigational product on study outcomes and to interpret missing data and/or confounding variables on outcomes and endpoint data [129]. When unexpected liver test elevations occur or worsen during the clinical trial, SARS-CoV2 testing using RT-PCR should be performed as a routine part of a second-line DILI causality assessment regardless of the presence or absence of symptoms consistent with COVID-19. To expedite the diagnosis, consideration should be given to local lab testing. The prevalence of COVID-19 in the population being studied and in the various study/site locations should be considered while determining the sequence of evaluating alternate etiologies.

6.2 DILI in Clinical Trials in the Context of COVID-19 Vaccination

While vaccinations for COVID-19 can produce an immune perturbation, the benefit–risk remains positive in favor of vaccination during most trials. Generally, the study duration does not justify delaying appropriate initial and booster vaccination. Vaccinations have, however, been reported to be associated with a low frequency of liver test elevations, which must be kept in mind during study observations. For studies of immunomodulatory agents, deferring study entry for approximately 1 month after completing the vaccine series is advisable when possible. This should permit the broad immune activation associated with COVID-19 vaccines to subside sufficiently to avoid interference with study endpoints and afford some level of protection against severe COVID-19. However, the deferral time for study entry should be customized for specific immuno-activating or suppressing treatments and patient populations and justified scientifically by a sponsor in the protocol.

7 Consensus Recommendations for DILI in the Context of COVID-19, Its Treatment, and COVID-19 Vaccination during Clinical Trials

7.1 Assessment at Screening

1. Routine testing for COVID-19 is not necessary during screening in individuals without respiratory symptoms and with normal liver tests. Those exhibiting COVID-19 respiratory symptoms should be tested for SARS-CoV-2 and excluded from clinical trial participation until symptoms resolve.
2. A RT-PCR or viral antigen test should be used for initial testing. Retesting is recommended with an antigen test or nucleic acid amplification test in the case of a moderately to severely immunocompromised individual. Since the RT-PCR test is typically more sensitive than the viral antigen test in detecting Omicron and other SARS-CoV-2 variants, it should be performed in those with negative viral antigen test results, unless the longer turnaround time makes this impractical.
3. For individuals who present with liver test elevations at screening, acute COVID-19 infection and long COVID should be considered after initial competing etiologies have been ruled out (Appendix 1). For the above individuals, acute COVID-19 infection and long COVID should be considered even in the absence of past or present respiratory symptoms.
4. To expedite a COVID-19 diagnosis, consideration should be given to local lab testing.
5. If liver tests are elevated during screening, specific inquiry as to receipt of a COVID-19 vaccine and its timing is advised, as patients may not consider receiving a vaccine as part of their medication history.

7.2 Eligibility Criteria

1. For studies evaluating liver disease treatments, consider exclusion of patients with a history of COVID-19 in the past 6 months who have unexplained elevations in liver tests during screening depending upon the length of the trial and indication under evaluation.
2. Patients with a past medical history of severe acute COVID-19 who have a cholestatic pattern of liver test elevations at screening require a full workup to determine the etiology prior to inclusion in a clinical trial. Patients diagnosed with secondary sclerosing cholangitis should be considered for exclusion depending upon the length of the trial and the type of treatment and the indication under evaluation.
3. For studies of immunomodulatory agents, deferring study entry for approximately 1 month after completing the COVID-19 vaccine series is advisable.

7.3 Causality Assessment and Management of Liver Test Abnormalities During Clinical Trial (Fig. 3)

1. If liver tests remain elevated in a setting of a recent COVID-19 infection, perform causality assessment described in first round of diagnostic testing as per CIOMS DILI Guidance (Adapted Table in Supplementary Information 1) or Treem et al., 2021 [127, 128]

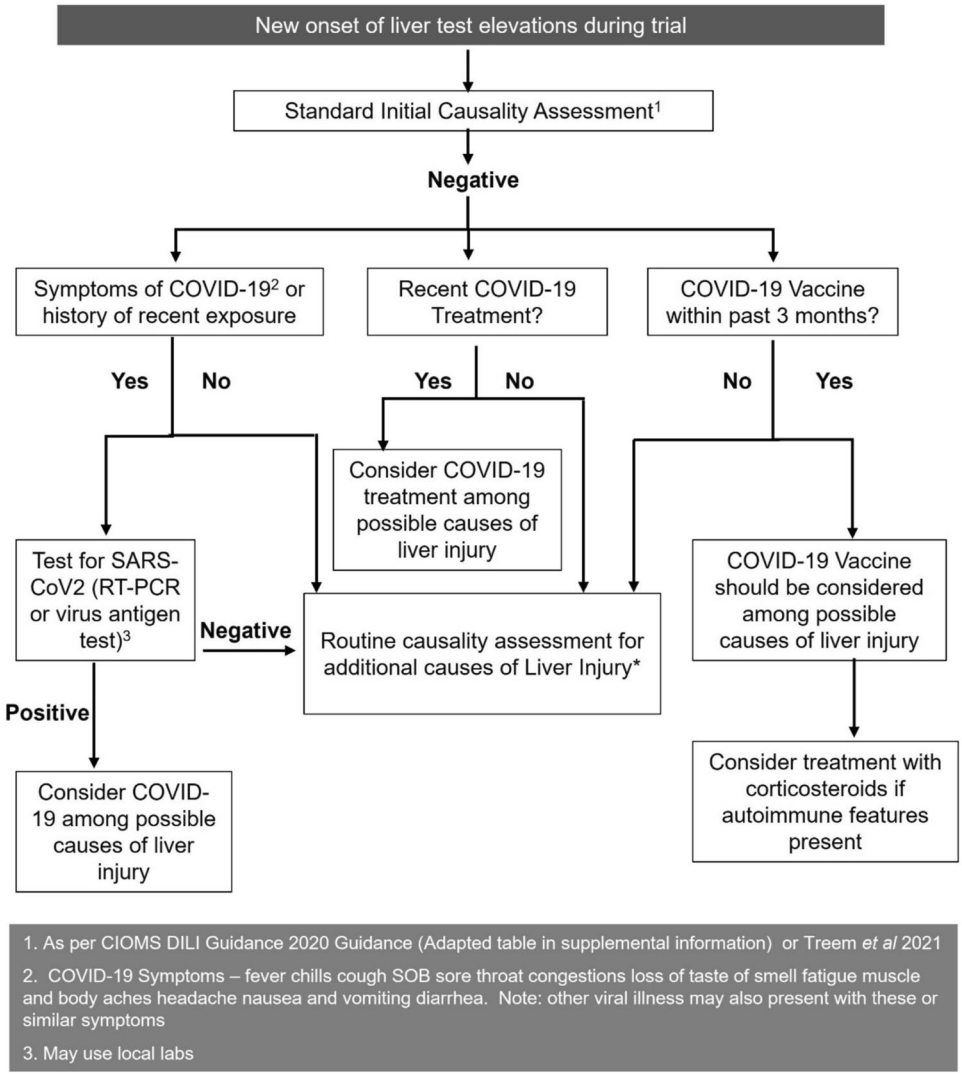

Fig. 3 Algorithm for causality assessment for suspected liver injury in relation to COVID-19 infection, treatment, and vaccination [127, 128]. *RT-PCR* reverse transcription polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus type 2

2. If liver tests are elevated in the setting of possible long COVID, repeat liver tests in 6 weeks. The time course and nature of liver test fluctuations in long COVID has not been well characterized, and more data need to be generated in this regard.
3. SARS-CoV2 testing is recommended as a routine part of a second-line DILI causality assessment in all clinical trials, regardless of the presence of symptoms consistent with COVID-19.
4. If a study participant tests positive for COVID-19 as part of the DILI causality assessment, or had a recent history of COVID-19, even if acute symptoms have resolved and COVID-19 test is now negative, COVID-19-related liver injury should be considered as a possible cause of the new onset of liver test elevations.
5. Study sponsors, investigators, and study staff should become familiar with the diverse liver injury presentations that can occur as a consequence of COVID-19.
6. If liver tests are elevated after a COVID-19 vaccination without an alternative etiology, it is recommended to repeat liver tests at 12 weeks after the date of vaccination, and at intervals as clinically indicated on the basis of severity of liver-related abnormalities.
7. The temporal relationship between COVID-19 vaccination and new onset of elevated liver tests should be evaluated and considered as a potential cause of acute DILI during the course of the trial.
8. Treatment of SVALI with corticosteroids, especially when autoimmune features are present, is recommended (Fig. 3).

8 Knowledge Gaps and Conclusions

While the COVID-19 pandemic is no longer a public health emergency, the potential effect of the virus, its treatments, and its vaccines on the liver continues to impact clinical

trials. It is important that the specific COVID-19-related factors discussed herein be taken into consideration in the differential diagnosis of patients presenting with liver abnormalities during screening, as well as those with a new onset or worsening of liver tests occurring during the clinical trial. Sponsors and investigators need to be aware of the varied liver-related presentations of COVID-19, with emphasis on the fact that signs of liver injury can occur even in the absence of respiratory symptoms or weeks after a positive RT-PCR test and subsequent resolution of symptoms.

Recommendations to delay or exclude patients or to remove a patient from the clinical trial apply only to specific situations and are dependent on the type of liver injury, the indications being studied, the treatments being assessed (e.g., immunomodulatory agents), and the individual benefit–risk assessment. While it is clear that COVID-19 can be associated with liver test abnormalities, clinical features of the course of COVID-19, including time to resolution, likelihood of progression to chronicity, magnitude of liver test elevation, and fluctuation over time, have not been clearly defined. This is a research gap that needs to be addressed. Better characterization of these factors will enhance causality assessment to differentiate the study drug from the infection and minimize premature study drug discontinuation.

While SVALI is rare, many gaps remain in our knowledge. For example, it is unknown whether liver test elevations can occur after the fourth or fifth annual COVID shot. Answers to such questions can only become clear with time and further assessment. It should be underscored that there are multiple factors that should be considered when evaluating each individual patient in a clinical trial. As such, a more personalized approach to DILI evaluation will yield the best benefit–risk balance. In this manner, premature drug pauses or discontinuations may be avoided.

Future pandemics may have similar characteristics to COVID-19, and as such, many of the approaches suggested herein may serve as a precedent for assessing the impact of another virus as it relates to liver injury on trial eligibility and DILI causality assessment.

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Consent to Participate Not Applicable.

Consent for Publication Not Applicable.

Availability of Data and Material Not Applicable.

Data sharing Data sharing is not applicable to this article as no datasets were generated or analysed.

Software applications or Custom codes Data sharing is not applicable to this article as no datasets were generated or analysed.

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