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Review Article

Impact of Liver Functions by Repurposed Drugs for COVID-19 Treatment

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Abstract

Liver injury is an important complication that may arise in patients suffering from coronavirus disease 2019 (COVID-19) and is accompanied by a transient increase of transaminases and/or other liver enzymes. Liver function test (LFT) abnormalities generally disappear when the COVID-19 resolves or hepatotoxic drugs are discontinued. The LFT abnormalities are associated with drug-induced liver injury (DILI), due to the overuse of antimalarials, antivirals, and antimicrobials. Studies have reported varying levels of these liver injuries in COVID-19 patients; however, most involve elevated serum aminotransferases. Hepatic dysfunction is significantly high in patients with severe illness and has poor outcome. Normally, the liver is involved in the metabolism of many drugs, including nucleoside analogs and protease inhibitors, which are currently repurposed to treat COVID-19. In addition to the manifestation of COVID-19, drugs implemented in its treatment may aggravate liver injuries. Thus, DILI should be considered especially in those COVID-19 patients with underlying liver disease. It was unclear whether the elevated liver enzymes have originated from the underlying disease or DILI in this population. Furthermore, it is difficult to establish a direct relationship between a specific drug and liver injury. Another possible effect of liver damage may due to inflammatory cytokine storm in severe COVID-19. Liver injury can change metabolism, excretion, dosing, and expected concentrations of the drugs, which may make it difficult to achieve a therapeutic dose of the drug or increase the risk of adverse effects. These repurposed drugs have shown limited efficacy against the virus and the disease itself; however, they still pose risk of adverse effects. Careful and close monitoring of LFTs in COVID-19 patients can provide early diagnosis of liver injury, and the risk of DILI could be reduced. Also, drug interactions in liver-transplanted patients should always be kept in mind for certain immunosuppressive therapies and their known signs of DILI. Altogether, abnormal LFTs should not be regarded as a contraindication to use COVID-19 experimental therapies if needed under emergent status.

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Introduction

Coronavirus disease 2019 (COVID-19) continues to affect our lives, yet there are still no specific antiviral therapies for it. Global efforts have been put forth to develop a vaccine against the causative pathogen, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), due to the knowledge that vaccines are the most efficient method against viruses. The routine strategy for creating such a vaccine includes exploration of mRNA, inactivated viruses, DNA and/or recombinant protein, and viral vectors. However, the time consumption requirement of around 18 months or more makes it even harder to develop an efficacious vaccine in a timely manner, although massive-scale efforts are underway. In the meantime, a number of drugs used for other diseases have been repurposed to tackle the COVID-19 pandemic, since this approach may be one of the quickest ways to discover an efficacious treatment for this new viral infection.

Since the SARS-CoV-2 shares extensive homology with SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV), effective therapies for these two viruses may also have therapeutic potential for the current SARS-CoV-2 outbreak.

Besides mainly targeting the respiratory system, SARS-CoV-2 attacks nearly all the other organs and systems, causing myocardial damage, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, and liver injury.[1] Liver injury is an important complication observed in COVID-19 patients. A ephemeral increase of transaminases and/or other liver enzymes may occur in COVID-19 patients within the range of 10.5–53.1%.[2,3] These abnormalities are generally self-limiting, mild to moderate increases, and mainly seen among symptomatic and severe COVID-19 patients.[3,4] Liver function test (LFT) abnormalities generally disappear when the COVID-19 infection resolves or hepatotoxic drugs are discontinued.[5]

Keywords: Liver injury; Hepatotoxicity; COVID-19; Antivirals; Aminotransferases; DILI.

Abbreviations: ADEs, adverse drug events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; COVID-19, coronavirus disease 2019; CPT, Child Pugh Turcotte; CYP, cytochrome P450 enzymes; DILI, drug-induced liver injury; GGT, gamma-glutamyl transferase; LFT, liver function test; LPV/r, lopinavir/ritonavir; OATP, organic anion transporting polypeptide; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; ULN, upper limit of normal.

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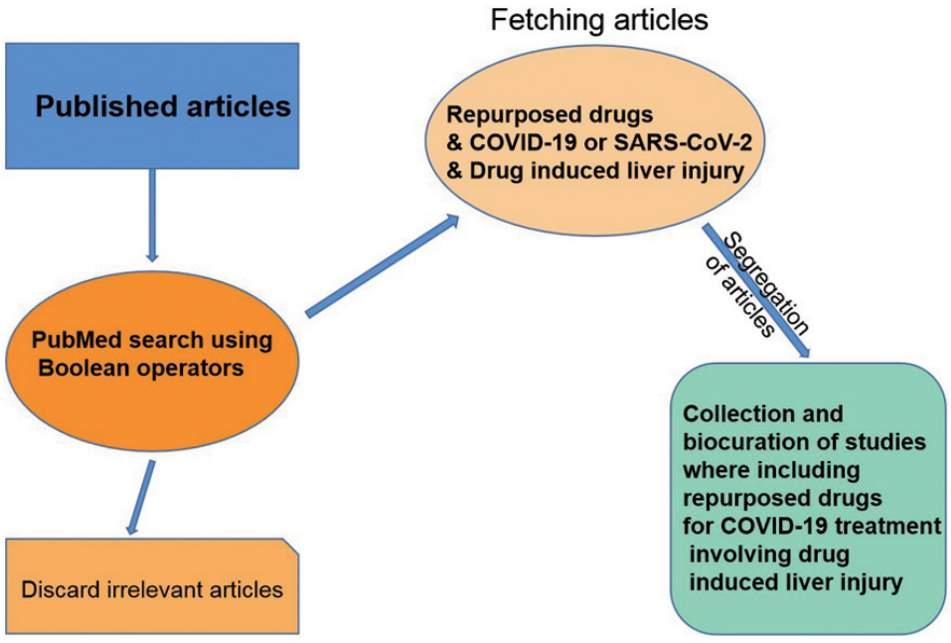

Fig. 1. Schema of literature fetching and filtering for repurposed drugs in treatment to COVID-19 with DILI. DILI, drug-induced liver injury.

Although the underlying mechanisms remain unknown, virus-induced inflammation, liver hypoxia and drug-induced liver injury (DILI) are three primary factors associated with hepatic injury.[6] LFT abnormalities associated with DILI due to the overuse of antimalarials, antivirals, and antimicrobials during COVID-19 necessitate special attention of the attending physicians.[7]

Rising levels of alanine aminotransferase (ALT) and aspartate transaminase (AST) are frequently indicative of hepatocellular damage, while this trend for alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) is associated with bile duct damage or cholestasis. Serum bilirubin levels indicate liver secretion capacity, while serum albumin level and prothrombin time indicate liver synthesis capacity. ALT and AST enzymes have wide tissue distributions. The AST enzyme is found in the liver, heart, kidney, brain, pancreas, and leucocytes; thus, isolated AST elevations usually indicate organ injury. ALT is also found in skeletal muscle, myocardium, lungs, and kidneys. Hence, minor AST and ALT elevations remain nonspecific, especially in severe illness with multiorgan injury, as in severe COVID-19. As expected, there is heterogeneity in the reported literature regarding the incidence and impact of liver injury in COVID-19.

We used "Boolean Operators" such as AND, OR and NOT to search relevant research articles/reviews from the PubMed for repurposed drugs applied as COVID-19 treatment. The repurposed drugs of chloroquine and hydroxychloroquine, remdesivir, ribavirin, umifenovir, and favipiravir are already being used in clinical trials to treat the COVID-19 patients. These drugs have been approved for a different indication and belong to diverse categories, such as antimalarial/antiparasitic, antiretroviral/anti-viral, or protective against rheumatoid arthritis. As described above, though a vaccine would be an ideal option for providing active immunity against the SARS-CoV-2, it is time-consuming. The repurposed drugs are the most viable option against SARS-CoV-2 currently. Hence, we searched, obtained and filtered the relevant articles in the literature, with the schema as shown in Figure 1.

We have searched the literature and screened published research articles to further investigation to determine which molecule the repurposed drug targets and their route of administration. Based on the literature survey, we divided the repurposed drugs that can be used for the trials to treat COVID-19 into four categories: (I) antimalarial/antiparasitic drugs; (II) drugs used for rheumatoid arthritis; (III) antiretroviral/antiviral drugs; (IV) others. Liver injuries were involved in each of these five categories. Altogether, a total of 106 articles/reviews (all in English language) containing "COVID-19 & drug-induced liver injury" were screened and selected for analysis, among which there were 44 reviews, 5 books and documents, 1 meta-analysis and 1 systematic review, and 55 other type articles, including clinical trials.

Liver and COVID-19

Studies have reported varying levels of liver injury in COVID-19 patients but mostly elevated serum aminotransferases.[8] Two to eleven percent of patients have existing chronic liver disease and 14–53% develop hepatic dysfunction, particularly in severe COVID-19. Hepatic dysfunction is significantly high in severe patients and associated with poor outcomes.[3]

In a study by Zhang *et al*.,[9] the mean level of ALT (37.9 vs. 21.2 IU/L), AST (38.9 vs. 24.4 IU/L), GGT (56.9 vs. 28.5 IU/L), and total bilirubin (14.1 vs. 10.3 mg/dL) was higher in severe COVID-19 patients than that in mild COVID-19 patients. Most of the LFTs in COVID-19 patients were found to be correlated with C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR) levels. Histological examination of the needle biopsy specimens reveals mild sinusoidal dilatation and minimal lymphocytic infiltration, while other specific damages are absent. In another study with 417 COVID-19 patients, 21.8% developed severe disease, 318 had abnormal LFTs and 90 had signs of liver injury during hospitalization.[10]

Goel *et al*.[7] showed that baseline and ≥3×upper limit of normal (ULN) transaminase elevations was present in 61.2% and 9.4% of patients at admission, respectively.

Furthermore, 72.1% and 22.4% of patients developed in baseline and ≥3×ULN elevated transaminases during the course of COVID-19, respectively. However, bilirubin and ALP elevations were less likely to be apparent at admission (11.4% and 12.6%, respectively) and through the course of the disease (17.7% and 22%). All LFT changes were correlated with inflammatory markers, while hyperbilirubinemia was correlated with elevated mortality. On the other hand, the effect of AST and ALT levels on mortality are different, with elevated AST being associated with mortality but ALT with survival.

A study reported that the hospitalized patients have a 76.3% abnormal LFTs and 21.5% have liver injury. Patients with severe pneumonia tended to have abnormal LFTs. The emergence of abnormal LFTs (3×ULN) was more common in the first 2 weeks of hospitalization. Lopinavir/ritonavir (LPV/r) treatment was found to be related to increased risk for liver injury.[10] In another study, it was reported that liver injury occurred in 14.8% of COVID-19 patients, mostly in severe cases. They also stated that liver injury occurred after administrating multiple drugs, such as LPV/r (18.6%), which are tightly associated with liver morbidity.[11] Huang *et al*.,[12] have reported that 30.7% of COVID-19 patients were diagnosed with nonalcoholic fatty liver disease (NAFLD) and 35.7% had abnormal LFTs, according to the clinical features of COVID-19 patients with NAFLD. The median ALT levels (35 IU/L vs. 23 U/L) and the elevated ALT (>40 U/L) (40.7% vs. 10.8%) were significantly higher in patients with NAFLD compared to those without, respectively. Multivariate analysis showed that age >50 years and concurrent NAFLD were independent risk factors of ALT elevation; however, the usage of interferon α-2b inhalation reduced the risk of ALT elevation.

Liver and Proposed Drugs of COVID-19

Effects of drugs on liver function

The liver is a principal site for the metabolization and elimination of chemical substances. Besides, it is involved in the metabolism of various drugs, including nucleoside analogs and protease inhibitors, which are currently repurposed for COVID-19 treatment. In addition to the manifestation of COVID-19, drugs implemented in its treatment may aggravate liver injury. Thus, DILI should be further evaluated especially for those patients with underlying liver disease.[13] It has remained unclear where the elevated liver enzymes originate from (either the disease or DILI) in this population. It has also been difficult to confirm the direct relationship between a specific drug and liver injury, due to the common combined use of antimalarials, antivirals, antimicrobials, and anticoagulants during COVID-19.[14] Finally, inflammatory cytokine storms in severe COVID-19 can result in liver damage.[13]

Some medications previously used to treat a variety of other diseases, i.e. antivirals (such as LPV/r, remdesivir, ribavirin, favipiravir, umifenovir), antimalarials (chloroquine and hydroxychloroquine), antimicrobials (azithromycin, interferons), and immunomodulators (corticosteroids, tocilizumab) have been the widely repurposed in the fight against COVID-19.[15] These drugs have a comparable risk for liver injury (Table 1).[10,11,16–37]

Cai *et al*.[10] demonstrated that patients under LPV/r had higher total bilirubin and GGT levels during hospitalization. In a study by Sun *et al*.,[16] evaluating adverse drug events (ADEs) in 217 COVID-19 patients, ADEs were associated with LPV/r and umifenovir, at rates of 63.8% and 18.1%, respectively; in addition, liver system disorders were the most frequently observed ADEs, after gastrointestinal disorders. In a meta-analysis,[17] the pooled incidence of DILI among COVID-19 patients was 25.4%; DILI occurred in 37.2% and 15.2% of COVID19 patients receiving LPV/r and remdesivir, respectively.

Interferon-β is produced by recombinant technology and is a cytokine with antiviral, immunomodulatory and antiproliferative properties. Interferon-β is available in three subtypes – 1a, 1b and pegylated β-1a – and all are approved for use in multiple sclerosis by either subcutaneous or intramuscular administration.[38] All forms of interferon-β may also induce liver injury, though most of such cases are mild and even asymptomatic. Interferon-related DILI is transient, with mild elevations in serum aminotransferases (ALT and AST), and with normal or mildly elevated ALP levels.[18] Whereas, LPV/r treatment had a higher rate of enzymes elevation (56% vs. 25%).[19]

LPV/r administration will induce moderate to severe elevations in serum aminotransferase levels (>5×ULN). Low-dose ritonavir has less impact on the frequency or severity of LFT elevations. Additionally, ritonavir has some properties similar to an enzymatic inhibitor and it can increase the serum level of co-administered drugs, resulting in a higher risk of hepatotoxicity.[18]

Hydroxychloroquine and chloroquine are antiviral/immune modulators that are used for the treatment and prophylaxis of malaria, rheumatoid arthritis, lupus erythematosus, photodermatosis, and liver amoebiasis. Hydroxychloroquine is metabolized by several CYP enzymes in the liver, with desethylhydroxychloroquine being an active metabolite. The USA's Food and Drug Administration's prescribing information cautions use in patients with existing liver disease and/or concomitant use with hepatotoxic drugs.[39,40] Hydroxychloroquine is known to accumulate in the liver.[41] and animal studies have shown that accumulation occurs rapidly, in the first 2 weeks of treatment.[42] However, hydroxychloroquine was found to have a low hepatic extraction ratio, indicating that a reduction in liver blood flow in cirrhosis may not directly result in increased exposure to the drug.[43] Hydroxychloroquine is also known to be hydrophilic,[44] and this should be a consideration in patients with ascites and decompensated cirrhosis. Based on these lines of evidence, hydroxychloroquine is regarded as a possible but rare cause of DILI.[18] Falcao *et al*.[20] reported a severe COVID-19 patient who showed a 10-fold increase of transaminases after using hydroxychloroquine, which returned to normal levels after withdrawal of the drug.

Remdesivir is a nucleotide analog for treatment of hepatitis C virus, used formerly.[45,46] Currently, data regarding hepatotoxicity of remdesivir is inadequate to draw firm conclusions. There was no liver injury in LiverTox,[18] and liver toxicity data were not reported in Ebola trials; however, abnormal liver enzyme profiles are common during Ebola infection, making it difficult to rule-out accompanying drug-induced liver toxicity.[47–49] The specificity of the cyano group in the remdesivir molecule allows for it to avoid inhibition by the host mitochondrial DNA polymerase and consequently limits the potential risk for lactic acidosis or mitochondrial toxicity. LFT elevations have varied widely among trials of remdesivir, accounting for 1% to 32% of participants.[21–23] LFT elevation rate was 23% among 53 patients, which led to remdesivir discontinuation in two patients, while bilirubin elevation was not detected in that trial.[24] Wang *et al*.[25] showed that hypoalbuminemia, hyperbilirubinemia, and AST elevation were present in 13%, 10%, and 5% of patients treated with remdesivir, respectively; also, in the remdesivir group, three patients discontinued treatment due to ALT elevation. Sabers *et al*.[50] reported that a patient presented with high liver enzymes (≥20×ULN) and had received remdesivir; eventually, the patient's liver enzymes improved through the course of the disease and they were discharged on day 10 of hospitalization.

Table 1. Changes in liver functions and liver enzymes in COVID-19 trials

Drugs	Toxicity	Type of toxicity		Reference
LPV/r	8.8%	ALT elevation (>3 ULN)		10
	4.8%	AST elevation (>3 ULN)		
	10.3%	GGT elevation (>3 ULN)		
	2.6%	Total bilirubin elevation (>3 ULN)		
	18.6%	Liver injury		11
	37.2%	Liver injury		17
	63.8%	Any adverse drug effect		16
	57.8%	Elevation is more than the ULN value (ALT, AST, ALP, GGT, and total bilirubin)		19
Umifenovir	18.1%	Any adverse drug effect		16
Remdesivir	15.2%	Liver injury		17
	3.4%	AST elevation		21
	2.3%	ALT elevation		
	7%	ALT elevation		22
	5.8%	AST elevation		
	32%	AST-ALT elevation		23
	23%	Increased LFTs		24
	10%	Hyperbilirubinemia		25
	5%	AST elevation		
	2%	ALT elevation leading to discontinuation of remdesivir		
Ribavirin Favipiravir	No data	Elevation in serum aminotransferases		18
	2.1-fold	ALT and AST elevation	CPT A	26–28
	2.0-fold		CPT B	
	3.7-fold		CPT C	
Hydroxychloroquine	10-fold	Elevation in transaminases		18,20
Azithromycin	1–2%	Elevation in serum aminotransferases		18
Interferons	25%	ALT and AST elevation, and mildly elevated ALP		18,19
Corticosteroids	N/A	No ADEs for short duration		18,32,33
Convalescent plasma (antibody)	N/A	No detailed information		28,34
Tocilizumab	Mild	Liver enzyme elevation		18,29–31
Acetaminophen	$48\%_{max}$	Dose-related hepatotoxicity		35–37

COVID-19, coronavirus disease 2019; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; LFT, liver function test; LPV/r, lopinavir/ritonavir; ULN, upper limit of normal; CPT, Child Pugh Turcotte; ADEs, adverse drug events.

There is a theoretical risk of P-glycoprotein interaction with remdesivir. Inhibition of P-glycoprotein with comedications reduces efflux of remdesivir from hepatocytes, raising cellular remdesivir concentration to supratherapeutic levels. However, the occurrence of this interaction is very low, because of remdesivir being the minor substrate of P-glycoprotein, as well as its short half-life.[51] In the recent case report by Carothers *et al*.,[52] the benefit of acetylcysteine continuous infusion was investigated in acute liver injury related to remdesivir. Both of the two patients investigated showed significant increases in transaminase levels with coagulopathy and encephalopathy in response to remdesivir therapy; the continuous infusion of acetylcysteine rapidly resolved the high transaminase levels in these patients.

Favipiravir is a type of RNA-dependent RNA polymerase (RdRp) inhibitor. It presumably acts as a nucleotide analog that selectively inhibits the viral RdRp or causes lethal mutagenesis upon embedding into the virus RNA.[53–57] Favipiravir, when used for the treatment of influenza, is administered at a dose of 1600 mg twice daily on day 1, followed by 600 mg twice daily on days 2–5. Besides being a treatment for influenza virus,[58] favipiravir has shown potent antiviral activity against other segmented negative-strand RNA viruses in both *in vitro* and *in vivo* studies.[59,60] Furthermore, some positive-strand RNA viruses can also be inactivated by favipiravir,[61,62] and the virus replication process can be interfered with by the drug's competition with purine nucleosides, as has been shown to consequently inhibit the viral RdRp of SARS-CoV-2.[26] Studies have also shown that

favipiravir administration provides better prognosis in COVID-19 patients in terms of disease progression and viral clearance.[27] ALT and AST elevation is just a possible adverse effect of favipiravir, however no data are available in cirrhosis patients.[28]

Tocilizumab is a monoclonal antibody against the interleukin-6 (IL-6) receptor, which is usually used to treat the cytokine storm that occurs in the advanced stages of the disease.[63] Though small series and case reports suggest its beneficial effects, it was not proven in randomized controlled trials.[29,64,65] Tocilizumab administration can lead to liver enzyme elevation but rarely to severe liver injury.[18] Recently, a patient with COVID-19 was reported on due to their transaminase levels increasing 40-fold after 24 h of initiation of tocilizumab administration.[66] Tocilizumab may pose a risk of hepatitis B virus (HBV) reactivation, thereby causing risk of indirect liver damage.[67] A study predicted that patients with severe COVID-19 and resolved HBV under immune modulator treatment had a low risk for HBV reactivation, and recommended that patients without antibodies to hepatitis B surface antigen (anti-HBs) be followed-up after discharge, if possible, and suggested that a short course of antiviral prophylaxis may be preferred. No hepatitis B surface antigen seroreversion was detected in their cohort and only two (3%) patients had detectable serum HBV-DNA.[30] In another study, liver injury was observed in COVID-19 patients with or without chronic HBV. Also, three patients experienced hepatitis B reactivation. Thus, monitoring of LFTs and HBV-DNA levels was recommended in COVID-19 patients treated with tocilizumab.[31]

Furthermore, membrane transporters localized on the cell membrane, especially those on tissues in the central organ for drug metabolism, such as the liver, can effectively influence pharmacokinetic characteristics and ADEs. Canalicular ABC transporters in hepatocytes, such as ABCC2/MRP2, ABCG2/BCRP, ABCB1/MDR1/P-gp and ABCB11/BSEP, mediate the extrusion of endo- and xenobiotics into the bile. P-gp, MRP2 and ABCG2 are multispecific transporters mediating the efflux of hydrophobic or partially detoxified amphiphilic compounds. MRP2 is the key transporter for bilirubin conjugates. The SLC-type transporter MATE1 in the hepatocyte canalicular membrane mainly transports cationic drugs, but also some zwitterionic and anionic molecules,[68,69] and mediates their biliary excretion. Inhibition of these drug exporters may cause elevated liver toxicity, such as cholestasis or DILI. All of the above repurposed drugs have various effects in inducing DILI through the special inhibition to transporters. A recent study showed that lopinavir and ritonavir, given in low micromolar concentrations, inhibited BSEP and MATE1 exporters as well as OATP1B1/1B3 uptake transporters. Ritonavir had a similar inhibitory pattern but also inhibiting OCT1. Specifically, remdesivir strongly inhibited MRP4, OATP1B1/1B3, MATE1 and OCT1. Favipiravir had no significant effect on any of these transporters.[70]

Corticosteroid is used in the treatment of a variety of inflammatory and autoimmune conditions. It is used at a wide range of doses, ranging from 0.5 to 80 mg daily.[71] Other glucocorticoids, including prednisolone, are used regularly for patients with significant liver disease in the treatment of autoimmune and alcoholic hepatitis, including for patients with cirrhosis, acute liver failure, ALT/AST >10×ULN and post-liver transplant.[72,73] Dexamethasone is metabolized in the liver via CYP3A4,[74] and has very limited influence in hepatic impairment, though its half-life is prolonged in severe liver disease.[71] Corticosteroid treatments are associated with hepatic steatosis, hepatic glycogenosis, and hepatic enlargement.[18] Corticosteroids can also promote hepatic gluconeogenesis, reduce peripheral use of glucose, and increase insulin levels consequently. Glucocorticoids have a pro-adipogenic function of increasing deposition of abdominal fat, and leading to glucose intolerance and hypertriglyceridemia. In addition, these drugs play a role in controlling liver metabolism and can lead to the development of hepatic steatosis.[32] But, in COVID-19 patients, this effect is unlikely to be significant given the very low dose (6 mg daily) and short duration.[33] Although toxicities that may arise in long-term use are not a problem for COVID-19 patients, it should be considered that there are short-term risks, such as HBV reactivation.[30]

Convalescent plasma has shown a potential therapeutic effect, with low risk for the treatment of severe COVID-19 patients.[34] At the same, there are still few experiences of convalescent plasma therapy in COVID-19 patients with chronic liver disease.[28]

Azithromycin is a macrolide antibiotic used in treatment of various infections, such as community-acquired pneumonia, bronchitis, soft tissue infections and uncomplicated genital infections due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The liver is the main site for metabolism of azithromycin and 50% is excreted unchanged in the bile, although some inactive metabolites are also found.[35] A previous study demonstrated that azithromycin has an association with a low rate of acute, transient, and asymptomatic elevations in serum aminotransferases, occurring in 1% to 2% of patients treated for short periods.[18] This drug can, thus, be exempted for further evaluation when used in COVID-19 patients, especially with low dose and short duration.

Ribavirin is a guanosine nucleoside analogue, approved for use in combination with direct acting antivirals or pegylated-interferon 2a or 2b for treatment of hepatitis C. In the treatment of hepatitis C, ribavirin is given orally and is dosed dependent on weight, ranging from 800 mg to 1200 mg daily. However, it has not been associated with serum aminotransferase elevations. Ribavirin treatment is usually used in COVID-19 patients with underlying liver disease; however, it is difficult to interpret increases in serum aminotransferase levels during therapy.[18]

Because of the fever and pain experienced by COVID-19 patients, several medicines agencies have warned physicians against the excessive use of non-steroidal anti-inflammatory drugs (NSAIDs), while the acetaminophen (paracetamol) was strongly recommended.[35] However, this recommendation could possibly result in the misuse of acetaminophen and consequently increase liver injury. Acetaminophen use is associated with generally mild ADEs, such as hepatitis, cholestasis, or other nonspecific liver enzyme elevation, but acetaminophen-induced hepatotoxicity is mostly estimated to account for 48% of acute liver injury diagnoses, providing caution for acetaminophen-caused dose-related hepatotoxicity.[36,37]

Another important point is the potential drug-drug interactions (DDIs) between the drugs used in patients with transplantation (such as tacrolimus and steroids) and COVID-19. These DDIs may also indirectly increase the risk of hepatotoxicity if the effect of the immunosuppressive or the COVID-19 drug were to become altered pharmacodynamically or pharmacokinetically.[75]

Clarify the liver injury by DILI vs. systemic inflammation from COVID-19

As described above, drugs implemented in the treatment may aggravate liver injury, which can occur besides the manifestation of COVID-19 or other underlying liver disease.[13] However, it was difficult to confirm the direct relationship between a specific drug and liver injury due to the combined use of all of above repurposed drugs during COVID-19.[14] According to the existing literature, we tried to conclude this complexity in order to caution the physicians

Table 2. Potential ADEs of repurposed drugs on liver in COVID-19 patients and non-COVID-19 patients

Drugs	COVID-19	Non-COVID-19	Reference
LPV/r	+	+++	10,16,17,18,19
	_	/	
Remdesivir	+	+	17,18,21–25,50,51,52
	–	/	
Ribavirin	+	+/−	18
	–	–	
Favipiravir	+	−/+	27,28
	–	–	
Umifenovir	+	+	16
	–	/	
Hydroxychloroquine	+	−/+	18,20
	–	N/A	
Azithromycin	+	−/+	18
	–	–	
Interferons	+	+/−	18
	–	/	
Convalescent plasma (antibody)	+	−/+	28,34
	–	N/A	
Corticosteroids	+	+/−	30,32,33
	–	–	
Tocilizumab	+	+/−	18,63,29,64,65,66,67,30,31
	–	–	
Acetaminophen	+	+++	35–37
	–	+/−	

Note: In COVID-19 column: with COVID-19(+), without COVID-19(−); in ADEs column: severe (+++), mild to Moderate (+), no ADEs (−), possible ADEs (+/−), possible no ADEs (−/+), with no report (N/A). COVID-19, coronavirus disease 2019; ADEs, adverse drug events.

and guide the drug use, and our findings are shown in Table 2.[10,16–25,50–52,27–37,63–67

Recommendation on drug use in liver injury

Liver injury can change metabolism, excretion, dosing, and expected concentrations of drugs, which may make it difficult to achieve an effective therapeutic dose or can increase the risk of ADEs.[76]

Acute liver injury has been commonly defined by the ULN of serum ALT, ALP, and serum concentration of total bilirubin based on the biological criteria, that is, elevation of ALT ≥5×ULN or ALP ≥2×ULN, or combination of ALT ≥3×ULN with a simultaneous total bilirubin concentration exceeding 2 ×ULN.[77,78]

Till now, the pharmacokinetics of remdesivir have not been evaluated in patients with hepatic injury. Hence, the hepatic function should be monitored in all patients before initiating and during daily treatment with remdesivir. Currently, remdesivir is not recommended in patients with ALT ≥5×ULN at baseline. It should be discontinued if ALT rises to higher than 5×ULN during treatment or if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, ALP, or INR, however, this therapy can be restarted if ALT is less than 5×ULN[79,80]

Since hydroxychloroquine commonly accumulates in the liver, it is recommended to monitor LFTs continuously and administrate it cautiously with concurrent hepatotoxic drugs.[81] It is also recommended that LFTs should be closely monitored for each patient while initiating tocilizumab; if ALT or AST are higher than 1.5×ULN, the treatment needs to be discontinued immediately.[82]

Since LPV/r is primarily metabolized by the liver, it is recommended to evaluate patient response and use with caution in case of liver injury. Although there is no need to reduce the dose for mild to moderate hepatic injury, frequent monitoring of LFTs is strongly recommended.[33] LPV/r administration has not been studied in patients with severe hepatic injury and its use is contraindicated.[83]

Azithromycin is eliminated predominantly in liver, and as such it should be used with caution due to its potential risk of hepatotoxicity and it should be avoided in patients with severe liver disease. A study has demonstrated that azithromycin pharmacokinetics do not differ consistently in patients with Child-Pugh A or B cirrhosis, in comparison with healthy volunteer; therefore, dosage modification is not required in these patient groups.[84] No difference in single-dose pharmacokinetics of ribavirin was noted in pa-

Table 3. Four categories of repurposed drugs for COVID-19 treatment and their detailed information

Drug category	Drug	Dose recommendation	Metabolism	Reference
I. Anti-malarial/ anti-parasitic drugs	Hydroxychloroquine	Maximum dosage based on minimal data and risk of hepatotoxicity	Major: CYP3A4/5, Minor: CYP2D6, CYP2C8	18,20
II. Drugs used for rheumatoid arthritis	Hydroxychloroquine			
	Tocilizumab	In patients with baseline ALT or AST >5×ULN, treatment is not recommended	Catabolic pathway	18,63,29,64,65,66,67,30,31
	corticosteroids	/	Hydroxylation via CYP3A4, followed by glucuronidation or sulfation	30,32,33
	Interferon-β	Caution if ALT >2.5×ULN, Dose reduction advised if ALT >5×ULN	Metabolized and excreted by liver and kidneys	18
	Azithromycin	Discontinue if signs of hepatic dysfunction	Liver: 35% to inactive metabolites	18
III. Anti-retroviral/anti-viral drugs	LPV/r	Use with caution in mild to moderate hepatic impairment and monitor for toxicities	CYP3A4/5, auto-induction own metabolism; stabilization after 10–16 days	10,16,17,18,19
	Remdesivir	Discontinuation: ALT >5×ULN or ALT elevation	*In vitro*: CYP2C8 CYP2D6, CYP3A4, OATP1B1, P-gp substrate	17,18,21–25,50,51,52
	Favipiravir	Dose adjustment should be considered	Extensive metabolism by hydroxylation (aldehyde oxidase and xanthine oxidase) to M1 and M2	27,28
	Ribavirin	Discontinue if progressive and clinically significant ALT rises, despite dose reduction, or accompanied by increased bilirubin	Intracellular phosphorylation by adenosine kinase to ribavirin mono-, di-, and triphosphate metabolites	18
IV. Others	Acetaminophen	/	/	35–37
	Convalescent plasma (antibody)	/	/	28,34

COVID-19, coronavirus disease 2019; ALT, alanine aminotransferase; AST, aspartate transaminase; LPV/r, lopinavir/ritonavir; ULN, upper limit of normal; CYP, cytochrome P450 enzymes; OATP, organic anion transporting polypeptide.

tients with mild, moderate, or severe hepatic dysfunction (Child-Pugh score A, B, or C).[85] Full-dose ribavirin can be used in severe hepatic dysfunction with caution; mild and moderate hepatic dysfunction associated renal impairment are suggested to make a proper dose reduction based on estimated glomerular filtration rate (eGFR).[33] Alteration of favipiravir dose is not recommended in mild and moderate hepatic impairment (Child-Pugh A and B), while it should be considered in severe hepatic injury (Child-Pugh C).[33]

Altogether, the detailed information of these repurposed drugs for COVID-19 treatment, including the family of the drug, the mode of action, and the possible mechanism by which it induces liver injury, are presented in the Table 3.[10,16–25,50–52,27–37,63–67]

Conclusion

Through the last year, COVID-19 devastated our health care systems and invoked an unprecedented need for new treatment options to heal its notorious manifestations. The scientific community is still far from finding a 'silver bullet' to overcome its detrimental effects; thus, some medications with limited *in vitro* activity against the eliciting virus are

being repurposed for its treatment. Those repurposed drugs have had limited efficacy against the virus and the disease itself; however, they still pose risk of adverse effects. Close monitoring of liver functions in COVID-19 patients can provide early diagnosis of liver injury, and reduce the risk of DILI as much as possible. A special caution should be given to those patients who are liver-transplanted, for drug-drug interactions occurring under certain immunosuppressive therapies. Abnormal liver tests should not be a contraindication against use of COVID-19 experimental therapies, if needed.

Limitations

Many measures have been applied against this virus during the pandemic, which have included officially approved Emergency Use Authorization (EUA) candidates and even some unofficial treatment methods. Among them, the repurposed old drugs have accounted for the majority in clinic, and most had been used before as anti-malarial/anti-parasitic, anti-retroviral/anti-viral, anti-cancer, or against rheumatoid arthritis drugs. Yet, there was no standard and systematic evaluation for their ADEs in COVID-19 patients, especially for their DILI aspects. As such, this review was limited by the ability to collect information on all of the repurposed drugs used worldwide. In-depth systematic exploration and discovery should be further improved for this topic.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Design of the work (JY) and writing of the manuscript (RZ, QW, JY). All authors have read and approved the final manuscript.

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