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MINIREVIEWS

Joint replacement and human immunodeficiency virus

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Abstract

The incidence of human immunodeficiency virus (HIV)-infected cases that need total joint replacement (TJR) is generally rising. On the other hand, modern management of HIV-infected cases has enabled them to achieve longevity while increasing the need for arthroplasty procedures due to the augmented degenerative joint disease and fragility fractures, and the risk of osteonecrosis. Although initial investigations on joint replacement in HIV-infected cases showed a high risk of complications, the recent ones reported acceptable outcomes. It is a matter of debate whether HIV-infected cases are at advanced risk for adverse TJR consequences; however, the weak immune profile has been associated with an increased probability of complications. Likewise, surgeons and physicians should be aware of the complication rate after TJR in HIV-infected cases and include an honest discussion of the probable unwelcoming complication with their patients contemplating TJR. Therefore, a fundamental review and understanding of the interaction of HIV and arthroplasty are critical.

Key Words: Human immunodeficiency virus; Arthroplasty; Infection; Joint replacement

Core Tip: The outcome and prevalence of complications are controversial among human immunodeficiency virus-infected cases who need arthroplasty. According to our literature review, total joint replacement procedures are recommended based on patient-specific factors such as viral load, $CD4^+$ T-cell count, clinical classification, history of intravenous drug addiction, and the patient's overall health. Optimization with antiviral drugs is also suggested before elective arthroplasty.

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INTRODUCTION

Human immunodeficiency virus (HIV) infection in humans was initially recognized in the early 1980s and documented as the reason for acquired immunodeficiency syndrome (AIDS). With an estimated 37 million affected people in 2015, the pandemic has grown to all corners of the world. Southern and Eastern Africa have tolerated the extreme impact of this problem, with 52% of the total infected people, 19 million cases, and more than 1 million new annual infections. The yearly occurrence of newly infected cases has decreased by 38%, from 2001 (3.4 million) to 2015 (2.1 million), with the successful advent and introduction of antiretroviral therapy (ART) programs in the last years[1,2]. AIDS-related expiries have also dropped from a high in 2005 (2.0 million), distinguished to be the topmost of the epidemic, to 1.1 million yearly in 2015, which means a reduction of about 45%[3].

The etiology varies according to highly active antiretroviral treatment (HAART) and disease-related mechanisms[4].

Femoral head osteonecrosis was initially reported in HIV-infected cases in the early 1990s - before the ART time. Several investigations have considered ART drugs as an independent factor for osteonecrosis development[5-7]. Therefore, HIV-positive individuals would need TJR at a much earlier age due to the osteonecrosis of the hip, in comparison to their counterparts who are affected by osteoarthritis and mostly are bilaterally involved[8].

Furthermore, a reduction in the density of bone minerals is more frequently seen in HIV-positive cases compared to non-infected controls[9,10]. The stimulation of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) is followed by an imbalance of the receptor stimulator of nuclear factor kappa-B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system, which eventually motivates bone resorption by osteoclasts and inhibits osteoclastic action. The cascade mentioned above in the long term accelerates osteopenia and would augment the probability of fragility fractures, particularly fractures of the femur neck in HIV-infected males[11].

It is controversial whether HIV-infected cases are at advanced menace for adverse TJR consequences; however, the weak immune profile may have been correlated to the increased probability of complications. Although initial investigations on hip and knee arthroplasty in HIV-infected cases showed a high risk of complications, the recent ones reported acceptable outcomes[12]. Despite the increasing number of the HIV-infected population, there is scarce literature investigating outcomes after TJR in infected ones. Periprosthetic joint infection (PJI) is one of the most prevalent causes of revision arthroplasties, and its underlying risk factors could be both non-modifiable and modifiable. Non-modifiable factors include chronic diseases such as cirrhosis, coagulopathies, kidney disease, and obstructive pulmonary as well as race, gender, and age[13,14]. Modifiable issues have been proven to increase early revision rates and complications and prolong the hospital stay. These factors include diabetes, smoking, opioid use, poor dentition, obesity, HIV, and *Staphylococcus aureus* colonization[14]. A bunch of risk factors may also have been developed in HIV-positive cases undergoing TJR[15]. Initial studies in orthopedic trauma patients infected with HIV showed a significant rate of postoperative infection rate[16,17]. Parvizi *et al* [18] demonstrated a similar finding in arthroplasty cases. However, their study involved patients with hemophilia, which may have been demonstrated as an independent risk factor for PJI[19,20]. Further investigations among non-hemophilic HIV-positive cases have displayed a remarkably lower rate of infection but a worryingly high rate of total complications[1].

Furthermore, Orthopedic Infections International Consensus in 2018 announced that HIV is an independent factor in increasing the risk of PJI[21]. However, the importance was reduced when HAART managed HIV-positive cases, and preoperative optimization was performed for them[21]. Therefore, identification and optimization of HIV-positive patients before surgery are mandatory to reduce the burden of already serious healthcare systems.

According to the above, a fundamental approach and understanding of the TJR and HIV interaction are inevitable. Therefore, we conduct a literature review on joint replacement in the HIV-positive group. Moreover, this minireview highlights the critical aspect of complications and outcomes.

CLASSIFICATION

Clinical staging methods help determine the prognosis and treatment for HIV-positive patients. Orthopedic surgeons who plan to operate on these patients must understand these systems well. The two most commonly used HIV classification systems were introduced by the Centers for Disease Control (CDC) and the World Health Organization (WHO). In 2014, the CDC released the modified definition of surveillance case for HIV infection[22]. This surveillance case explanation for HIV has been revised and combined into a sole case definition for people of every age. New multi-test algorithms, such as HIV-I and HIV-II detection criteria and direct detection of HIV infection, have been added to laboratory criteria to define an approved case. The surveillance case definition refers to monitoring the burden of HIV infection at the population level and planning for care and prevention, not for individual patient treatment decisions. A proven case of HIV infection is classified into five stages (0, 1, 2, 3, or unknown) (Table 1).

The CDC proposes three descriptive classifications based on the presence or absence of specific clinical symptoms (Table 2). The $CD4^+$ T-cell count further subdivides these three types. $CD4^+$ T-cell counts above 500/μL are categorized as types A1, B1, and C1. $CD4^+$ T-cell counts within 200/μL and 400/μL are A2, B2, and C2 categories. Infections in patients having $CD4^+$ T-cell numbers lower than 200/μL are classified as A3, B3, or C3.

Orthopedic surgeons mostly use the WHO staging system[23]. Patients are divided into four clinical groups using this classification system: Stage one patients are asymptomatic or accompanied by persistent generalized lymphadenopathy; patients with stage two present with a slight disease along with 10% weight loss and skin exhibition; those with stage three experienced moderate disease and weight loss of more than 10%, severe bacterial infections, and chronic diarrhea lasting more than a month; and patients with the last stage have a severe disease, AIDS, cryptosporidiosis, toxoplasmosis, HIV wasting syndrome, Kaposi's sarcoma, and pneumonia caused by *Pneumocystis jirovecii*.

PATHOPHYSIOLOGY AND ASSOCIATION BETWEEN HIV AND TJR

In HIV-infected persons, osteonecrosis is still the most common reason for TJR. Since the first case was reported in 1990, the annual osteonecrosis prevalence among HIV-infected ones has consistently grown, ranging from 0.08% to 1.33%[24,25]. Although the specific origin of osteonecrosis in HIV-positive people is unknown, various risk variables have been identified[26,27].

Alcohol, corticosteroids, hyperlipidemia, anticardiolipin and antiphospholipid antibodies, cigarette smoking, course of HIV infection, and antiretroviral therapy are some of the most common risk factors for changes in the bloodstream to the bone[26,27]. Although many researchers believe that the multiple effects of several factors that impair bone blood flow would lead to osteonecrosis, some investigators provide evidence that HIV infection alone can cause osteonecrosis[7,22,28]. According to a study by Ries *et al*[28], there was a much higher percentage of HIV-infected individuals with nontraumatic osteonecrosis without any identified risk factors than HIV-negative cases. Figure 1 demonstrates factors affecting joint replacement among HIV-infected patients.

Some factors stimulate osteonecrosis in both HIV-positive and -negative cases. Steroids alter bone metabolism and the growth of bone marrow stromal cells, resulting in fat penetration into the bone marrow and blockage of the bloodstream inside the bone. The cascade above increases intraosseous pressure. Moreover, steroids may cause acute fat embolization in capillary arteries[23-26], which are widely used to manage HIV-related diseases, such as pneumocystis pneumonia and also central nervous system toxoplasmosis[29-31]. Miller *et al*[29] also verified the abovementioned association and determined that even short-term consumption of a corticosteroid drug could significantly raise the incidence of osteonecrosis. Hyperlipidemia, a known subsequent event of HIV infection and HAART diets, is substantially implicated in atherosclerotic pathways and is known to be a causative agent in steroid-induced osteonecrosis. Several investigations have linked high serum cholesterol levels and the consumption of fat-reduction drugs to the pathogenesis of osteonecrosis[7,26,31].

HIV has a detrimental effect on the density of the bone mineral, and patients with HIV infection are prone to develop osteoporosis 3.7 times greater than non-infected people[1,32]. Consequently, there is an augmented fragility fracture risk in HIV-positive cases[1]. Low bone mineral density is associated with low $CD4^+$ T-cell count and long-term HIV infection[1]. Another reason for generated osteopenia is the constant inhibition of osteoblasts and activation of osteoclasts, which is a result of miss-balanced receptor activation of the nuclear factor kappa-B (RANK)/RANKL/OPG system[11,33]. This pattern is triggered by the virus, which causes activation of TNF-α and IL-1[10].

Increased levels of antiphospholipid antibodies and further thrombophilic factors are correlated with osteonecrosis in HIV-infected cases. Antiphospholipid antibodies are considered a risk factor for venous and arterial thrombosis and are generally found in HIV-infected patients. In a new investigation, the incidence of antiphospholipid antibodies in HIV-infected cases was predicted to be around 44%[34]. It is well known that these antibodies are involved in the progression of osteonecrosis in systemic lupus erythematosus patients, and similar processes have been suggested for HIV-infected cases[25,35].

Table 1 Classification of laboratory categories based on age-specific CD4+ T-lymphocyte count

Age on date of CD4+ T-lymphocyte test						
Stage	< 1 yr		1–5 yr		≥ 6 yr	
	Cells/μL	%	Cells/μL	%	Cells/μL	%
1	≥ 1500	≥ 34	≥ 1000	≥ 30	≥ 500	≥ 26
2	750-1499	26-33	500-999	22-29	200-499	14-25
3	< 750	< 26	< 500	< 22	< 200	< 14

Table 2 Classification clinical category

Clinicalcategory	Symptomatic conditions
A	Asymptomatic HIV infection, persistent generalized lymphadenopathy, acute (primary) HIV infection complicated by illness, or a history of acute HIV infection. Bacillary angiomatosis
B	Candida infection, cervical dysplasia, constitutional symptoms, hairy leukoplakia, herpes zoster, unexplained thrombocytopenic purpura, listeriosis, pelvic inflammatory disease, and peripheral neuropathy.
C	AIDS-defining diseases: Toxoplasmosis, Kaposi's sarcoma, Pneumocystis pneumonia

HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome.

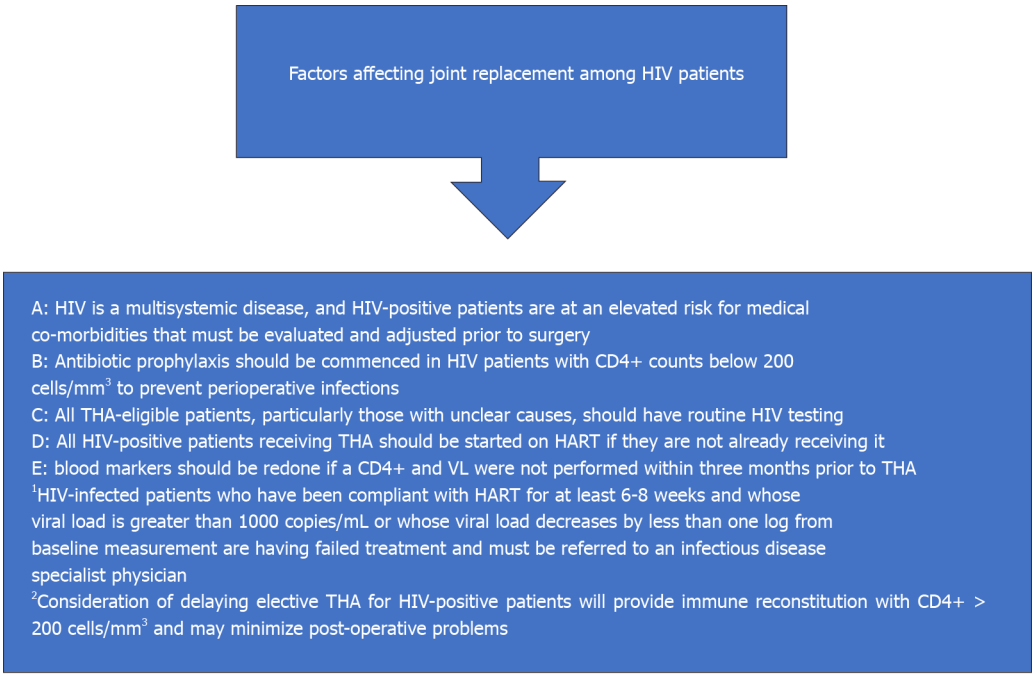

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Figure 1 Factors affecting joint replacement among human immunodeficiency virus-positive patients. HIV: Human immunodeficiency virus; THA: Total hip arthroplasty.

Recent studies have engrossed the role of antiretroviral therapies, mainly protease inhibitors, in the pathogenesis of osteonecrosis. Even though the precise processes of HAART that may play a role in osteonecrosis are unclear, the association of protease inhibitors and conventional osteonecrosis risk factors has been recognized[8,22,26]. Hypertriglyceridemia due to HAART has been widely cited as a potential cause of osteonecrosis. Through interactions with cytochrome P450, protease inhibitors may increase the effectiveness of steroid therapy. A study by Penzak *et al*[36] showed that treatment with ritonavir dramatically amplified the concentration of prednisolone in healthy cases. Several HIV-positive cases with osteonecrosis were reported before the introduction of HAART, suggesting that HIV treatment regimens could not be the primary cause of the disease. Osteonecrosis has a complex etiology and is highly prevalent among HIV-positive individuals, thus increasing the need for total joint arthro-

plasties in this patient population.

While the incidence of HIV infection is steadily increasing, broad access to HAART has upgraded from 25% in 2010 to 73% in 2021[37]. Increased access to HAART has reduced global AIDS-related mortality by 64% since its peak in 2004 and by 47% since 2010[37]. HIV and HAART are independently associated with joint pathology that ultimately requires joint replacement[4].

HAART should be started in all HIV-positive patients, regardless of clinical stage or $CD4^+$ T-cell count [1]. This is particularly significant for cases pending elective TJR. First-line HAART almost always consists of a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and an agent of a different drug class. Protease inhibitors (PIs) are believed to form the primary drug class that aids avascular necrosis (AVN) in the hip[4]. In addition, drugs containing tenofovir have been linked to the progression of osteopenia[1]. Remarkably, all first-line regimens in every corner of the world include tenofovir agents.

Due to osteodegenerative and renal complication of tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) was developed[38]. TAF continues to cause renal disease and bone loss, but to a lesser extent than TDF. The WHO recommended that integrase strand transfer inhibitors (InSTIs) replace PIs as the ideal first-line regimen. However, more than half of the global HIV prevalence is in East and South Africa, which cannot easily access InSTIs[38].

There are several side effects to HAART drugs, and the patient's diet should be monitored. There are significant drug interactions between anesthetic drugs and NRTIs and PIs that are usually prescribed for induction and sedation. TDF is nephrotoxic, so patients need to be checked for blood urea nitrogen; the urine protein-to-creatine ratio is sometimes assessed to evaluate their renal function[39]. Anemia and neutropenia are side effects of zidovudine. Thus, these patients need a complete blood count, white cell count, and differential amount[40].

EVALUATION AND PREOPERATIVE OPTIMIZATION

Different studies show how immune system impairment is a key factor in postoperative risk of infection and complications[41]. Any major disease which causes impaired immune system like diabetes mellitus, which results in impaired leukocyte function[42,43], and even malnutrition[44], can be risk factors for PJI[41].

$CD4^+$ T-cell count is an alternative indicator of immunological status, and the number of $CD4^+$ T cells less than 200 cells/mm^3 confirms the diagnosis of AIDS[39]. Optimistic monitoring of the patient's immune status is essential in managing HIV-infected patients undergoing HAART. The opportunistic infections-related prevalence, mortality, and morbidity are higher in patients with a CD4+ T-cell count of 200 cells/mm^3[45]. Patients with opportunistic infections and abandoned viral status should be recognized to reduce perioperative and postoperative complications[45]. Antibiotic prophylaxis should be initiated for all patients with a $CD4^+$ T-cell count < 200 cells/mm^3[45]. The guidelines recommend trimethoprim-sulfamethoxazole (TMP-SMX) as an effective treatment for opportunistic infections[45].

Viral load (VL) is a reliable indicator of treatment effectiveness and is influenced by patient adherence to HAART. Elective procedures should be delayed for those with higher VL[45]. If, after 6 to 8 wk of careful treatment, the VL is greater than 1000 copies/mL or less than one log below starting point, there is a viral failure[45].

Multiple systems can be affected by HIV, and patients should be thoroughly evaluated for perioperative risk classification before TJR. HIV-positive cases often suffer cardiovascular disease, nephropathy, liver disaster, neurological problems, and non-AIDS-related malignancies[46]. Evaluation of the patients mentioned before surgery should contain suitable blood work, nutritional status, and immune deficiency syndrome stage[47]. In HIV-positive patients, postoperative complications are mainly due to immunodeficiency, not the procedure itself. Therefore, a comprehensive evaluation is required to prevent anesthetic and surgery problems[45].

HIV-infected cases who developed advanced stages of the disease should also have their nutritional status evaluated since there is a higher risk for nutritional deficiencies and wasting[45]. Hypoalbuminemia is an independent risk factor for mortality in HIV-infected cases postoperatively compared to the non-infected control group[48].

Malnutrition is related to several problems following THA, such as delayed wound healing and prolonged wound damage, which increases the risk of infection[21]. If the diet is inadequate, dietary supplements may be necessary and should be consulted with a nutritionist[45].

On the other hand, compared to the HIV-negative control group, HIV-positive individuals are at higher risk for coronary artery disease, which may be due to persistent chronic inflammation[45]. HAART drugs have decreased the risk of perioperative cardiovascular problems[46].

HIV-infected patients treated with HAART have an increased incidence of insulin resistance, diabetes, and hypercholesterolemia. This may increase the risk of AVN in the femoral head and thus upsurge the need for TJR among HIV-infected cases. All HIV-infected patients should undergo a thorough clinical evaluation for lipodystrophy and fasting lipograms, mainly if they consume a HAART diet containing PI[45].

In HIV-positive patients, smoking is approximately 40% more prevalent than in the general population, and the probability of quitting is also lower[49]. This makes the patients susceptible to atherosclerotic developments, chronic lung disease, and postoperative respiratory infections[45]. Before elective surgery, the respiratory function should be evaluated in all HIV-infected smokers to determine their capacity for diffusion[45]. In addition, AIDS patients are susceptible to nosocomial invasive bacterial infections, and elective TJR should be delayed to optimize immune system reconstruction[45].

OUTCOMES OF TJR IN HIV-INFECTED PATIENTS

As the global number of HIV-infected cases rises, the need to evaluate the results of orthopedic treatment in them also increases. Due to the growing demand for these treatments, the consequences and complications of TJR among them are also receiving particular attention. In addition to functional implications, many of these studies have investigated the incidence of postoperative infections. Previously, HIV was known as an independent factor for infection after surgery. Therefore, the benefits and safety of elective surgery in these patients have been questioned. However, some recent investigations of TJR in HIV-infected patients have raised doubts about this theory.

The treatment algorithms for HIV-positive patients should be similar to algorithms used for non-infected cases, with two-step revision surgery. We suggest a long course of intravenous antibiotics: Up to 6 mo *vs* 6 wk. The medical condition of patients, especially their VL and CD4+ T-cell count, should always be considered.

Several studies focusing on the results of complete joint arthroplasty in HIV-infected cases have focused on hemophilic ones. Due to recurrent periarticular and intra-articular hemorrhage, people with hemophilia are at a much higher risk for joint degeneration. The risk of developing joint arthropathy increased with the higher rates of HIV infection in these people between 1979 and 1985 due to the application of polluted blood products. During that period, injection of infected factor VIII resulted in serum conversion in about 80% of hemophilia patients. Preliminary research conducted by Gregg-Smith *et al*[50] and Wiedel *et al*[51], evaluated the infection prevalence in HIV-infected hemophiliac cases who underwent complete knee arthroplasty before the extensive use of HAART. Wiedel *et al*[51], in a 1989 study, found an advanced rise in acute postoperative infections. The result, as mentioned earlier, was also confirmed by Gregg-Smith *et al*[50].

Hicks *et al*[52] and several other researchers confirmed that the growing risks are related to TJR in HIV-positive hemophiliacs, linking the probability of these problems to the number of $CD4^+$ T-cells. Hicks *et al*[52] evaluated the results of 102 TJR in 73 hemophiliac patients infected by HIV in a large multicenter retrospective study. The incidence of surgical site infection was 18.7% for initial surgeries and 36.3% for revision after an average five-year follow-up. About 62.5% of the infected group had a preoperative $CD4^+$ T-cell count of less than 0.2×10^9/L, while 16.7% were non-infectious. Ragni *et al*[19] found a similar increase in the rate of postoperative infections in HIV-positive hemophiliac patients with CD4+ T-cell counts of less than 0.2×10^9/L in patients who underwent knee and hip arthroplasty surgeries. An infection rate of 15% was observed in a retrospective analysis of 115 hemophilia clinics in the United States in 1995, which the authors highlighted was three times more likely than the risk of infection at surgical sites among HIV-negative arthroplasty patients.

In contrast, many current investigations could not confirm the extensive risk of problems in this population of patients after total joint replacement. For instance, Powell *et al*[53] evaluated the incidence of postoperative infections following total TJR of the knee and hip in HIV-negative and HIV-positive hemophilia patients between 1975 and 2002. Three of the 30 joints among HIV-infected cases developed primary joint infections, compared to two of the 21 non-infected groups. The perusal above did not show an elevated relative risk of surgical site infection in HIV-positive patients (relative risk = 1.49). The researchers concluded that TJR is a viable treatment choice for hemophilic patients with concomitant HIV infection.

The relative safety of the orthopedic procedures in HIV-positive hemophiliac patients was further supported by Unger *et al*[54], who evaluated 26 knee arthroplasties of 15 patients with HIV infection and type A hemophilia; all of them experienced an improvement in function after arthroplasty, and also during 6.4 years of follow-up, no infection occurred at the surgical site.

Subsequent research has evaluated the outcomes of TJR procedures in HIV-infected adults who are not hemophiliacs. For instance, Parvizi *et al*[18] conducted a study on total hip and knee arthroplasties in 21 infected cases and reported a significant incidence of postoperative complications. Twelve of 21 arthroplasties needed to be reconsidered at the subsequent evaluation due to recurrent infection. Furthermore, there was a significant relationship between the immunological status of patients and the probability of deep infection (six joints). The authors mentioned above discovered a significant prevalence of *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* among deep-seated infections[18].

In parallel to prior investigations, Habermann *et al*[55] have compared the incidence of total complications in non-hemophiliac infected cases and hemophiliac patients after TJR. However, they found no significant difference in functional outcomes[55].

Recently, Mahoney *et al*[56] conducted a study among non-hemophiliac HIV-infected patients who had total hip arthroplasty, demonstrating favorable functional results. Three years afterward, only one in 40 patients with a history of intravenous drug abuse had severe infection with antibiotic-resistant *Staphylococcus aureus*.

Moreover, further comorbidities associated with HIV, including intravenous drug abuse, negatively and significantly influence the clinical outcome of TJR surgery. On the other hand, Lehman *et al*[57] assessed the risk of PJI in HIV-infected patients and simultaneous infection from IV drug use (IVDU) following TJR. In the study mentioned above, patients with co-infection of HIV and IVDU had a more than 40% surgical site infection rate. Infections did not occur in four HIV-positive patients without comorbidities (IVDU, hemophilia). The findings of this study suggest an individual-based evaluation of the benefits and risks of TJR.

THA AND HAART IN HIV-INFECTED PATIENTS UNDERGOING TJR

The functional consequences of THA in HIV-positive individuals are controversial in the literature. There is still considerable debate about the relative efficacy and safety of TJR in these patients. It was traditionally believed that HIV infection was associated with an augmented complication risk, particularly infectious adverse effects. In addition, the growing use of HAART has reduced the related complications. HIV-infected patients who do not receive HAART are more prone to unfavorable outcomes. Parvizi *et al*[18] found a substantial complication rate among HIV-infected cases who had undergone total hip arthroplasty; it is worth mentioning that 80% of them did not receive HAART. This amount included 29% of PJIs[58]. The mean $CD4^+$ T-cell count for those who developed PJI was 239 cells/mm^3, while the mean for the entire study population was 523 cells/mm^3[58]. A similar result was displayed by Lehman *et al*[57]; they reported a PJI rate of 14.3% among HIV-infected cases receiving THA. It is worth mentioning that none of them were optimized by HAART.

Several studies have shown ambiguous functional results when comparing HIV-positive patients treated with HAART with the HIV-negative control group. Graham *et al*[59] conducted a survey among 43 THAs which had been performed on 29 HIV-positive patients in 2014; they reported no occurrences of dislocations, deep or superficial infections, or venous thrombotic events, either in late (> 6 wk) or early (< 6 wk) follow-ups. Significant postoperative functional benefits and tangible progress in the Harris hip scores were recorded. Between 1998 and 2010, likewise, Naziri *et al*[60] conducted a study among 9275 HIV-positive patients with THA to evaluate the outcomes of THA and compare it to the results of 2.7 million non-infected cases. The rates of minor and major complications in HIV-infected individuals were 5.2% and 2.9%, respectively, meaningfully higher than the respective rates of 4.8% and 2.7% in non-infected individuals. In addition, a longer duration of hospitalization was observed in the HIV-positive group[60].

Sadoghi *et al*[61] analyzed global registration data from New Zealand, Australia, Denmark, Finland, Norway, and Sweden, showing that aseptic loosening is the main reason for revising THAs, which accounts for 55.7% of them. PJI was the third cause of revision[61]. The onset of aseptic loosening does not appear to be due to HIV[1,46].

One- and five-year survival rates after THA surgery in HIV-positive patients are similar to those of non-HIV-positive patients[1]. Issa *et al*[62] evaluated the lifespan of prostheses after ten years; there was no difference in the survival of infected and non-infected cases. Moreover, Novikov *et al*[63] showed that a significant amount of revision THA (80%) happened during the first year after surgery. Still, the revision rate in the long-term analysis was similar to that among non-infected patients[1]. Although functional outcomes of infected cases optimized with HAART are equal to those of HIV-negative cases, a higher probability of PJI has been reported.

Previously, THA outcomes in HIV-positive individuals with simultaneous hemophilia[19] or IVDU [57] showed a high proportion of poor outcomes and late deep infections. In a comprehensive assessment of 722 THAs out of 25 research studies, Enayatollahi *et al*[58] found that PJI is significantly more prevalent among those with simultaneous HIV infection and hemophilia than in HIV-infected alone. The corresponding PJI rates were 10.98% and 2.28%, respectively. Nevertheless, before HAART, the frequency of PJI was up to 50%[58]. The onset of HAART coincided with a reduction in the incidence of THA infections in HIV-positive individuals[46,58]. Also, Youngman *et al*[64] found that the complication rate of HIV-positive patients who were not treated with the HAART and did not undergo THAs due to femoral head osteonecrosis is 12.5% higher than that of patients who were optimized with HAART.

ELECTIVE SURGERY

Given the increasing need for TJR and the HIV pandemic, it is essential to determine if a threshold should be proposed for elective arthroplasty. King *et al*[48] evaluated 30-d postoperative THA mortality in the United States retrospectively and found that HIV-positive patients had a higher mortality rate

(3.4%) than HIV-negative patients (1.6%). Regardless of $CD4^+$ T-cell count, the HIV-positive group had a higher mortality rate than the control group, even though lower $CD4^+$ T-cell count was correlated with a greater mortality rate[48]. There is a hypothesis that a $CD4^+$ T-cell count threshold of 200 cells/mm^3 is associated with a higher risk of postoperative complications, such as PJI. However, this has not been proven[1,46].

There is considerable evidence that HIV-positive cases, particularly the poorly controlled ones, are more susceptible to postoperative complications[46]. Serum markers should be monitored periodically, as the infection is perilous, mainly if $CD4^+$ T-cell counts decrease[46,65]. Many studies have not linked the $CD4^+$ T-cell count consistently and accurately. Dimitriou *et al*[1] reported that THA might be safely administered to HIV-positive patients regardless of their $CD4^+$ T-cell status, while Shah *et al*[46] suggested a $CD4^+$ T-cell count of more than 400 cells/mm^3 was essential for a safe THA. On the other hand, Sax *et al*[66] suggested that elective THA can be done in both groups of HIV-infected patients who are actively taking ART or not, and the complication rates are similar to those not infected by HIV.

Preoperative VL may be more important than $CD4^+$ T-cell count. A higher level of the virus may indicate unsuccessful surgery and require a referral to an infectious disease specialist. Horberg *et al*[47] conducted a retrospective study on more than 5000 HIV-infected individuals; they believed that VL > 30000 copies/mL was related to a 3-fold bigger chance of postoperative complications.

In a systematic evaluation, Shah *et al*[46] recommended a VL of 50 copies/mL before elective procedures. It is suggested that patients continue the HAART regimen, and full compliance is essential. If the subsequent studies show a decrease in $CD4^+$ T-cell count or an increase in VL, treatment mismatch or failure should be considered.

CONCLUSION

Currently, reports on HIV-positive patients and TJR afford contradictory information. While some authors reported significant complications and reconsideration rates following TJR on HIV-positive patients, most of these collections include a large proportion of HIV-infected cases with hemophilia. Thus, it is a critical confounder in the results described in prior studies. Future studies should evaluate the results of HIV-positive patients with no simultaneous disease to identify its risks, especially for patients with complete joint arthroplasty. Before surgery, we now examine each patient and try to optimize the general health of HIV-positive patients. Total joint replacement procedures are recommended based on patient-specific factors such as viral load, $CD4^+$ T-cell count, clinical classification, history of intravenous drug addiction, and the patient's overall health. The risks and frequency of perioperative problems should be made clear to patients. We expect TJR to improve the quality of life of these patients. In Figure 1, we have recommendations for better outcomes of TJR in HIV-positive cases.

FOOTNOTES

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MINIREVIEWS

Severe acute respiratory syndrome coronavirus 2 may cause liver injury *via* Na^+/H^+ exchanger

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Abstract

The liver has many significant functions, such as detoxification, the urea cycle, gluconeogenesis, and protein synthesis. Systemic diseases, hypoxia, infections, drugs, and toxins can easily affect the liver, which is extremely sensitive to injury. Systemic infection of severe acute respiratory syndrome coronavirus 2 can cause liver damage. The primary regulator of intracellular pH in the liver is the Na^+/H^+ exchanger (NHE). Physiologically, NHE protects hepatocytes from apoptosis by making the intracellular pH alkaline. Severe acute respiratory syndrome coronavirus 2 increases local angiotensin II levels by binding to angiotensin-converting enzyme 2. In severe cases of coronavirus disease 2019, high angiotensin II levels may cause NHE overstimulation and lipid accumulation in the liver. NHE overstimulation can lead to hepatocyte death. NHE overstimulation may trigger a cytokine storm by increasing proinflammatory cytokines in the liver. Since the release of proinflammatory cytokines such as interleukin-6 increases with NHE activation, the virus may indirectly cause an increase in fibrinogen and D-dimer levels. NHE overstimulation may cause thrombotic events and systemic damage by increasing fibrinogen levels and cytokine release. Also, NHE overstimulation causes an increase in the urea cycle while inhibiting vitamin D synthesis and gluconeogenesis in the liver. Increasing NHE3 activity leads to Na^+ loading, which impairs the containment and fluidity of bile acid. NHE overstimulation can change the gut microbiota composition by disrupting the structure and fluidity of bile acid, thus triggering systemic damage. Unlike other tissues, tumor necrosis factor-alpha and angiotensin II decrease NHE3 activity in the intestine. Thus, increased luminal Na^+ leads to diarrhea and cytokine release. Severe acute respiratory syndrome coronavirus 2-induced local and systemic damage can be improved by preventing virus-induced NHE overstimulation in the liver.

Key Words: Liver; Hepatocyte; Severe acute respiratory syndrome coronavirus 2; COVID-19; Na^+/H^+ exchanger; Sodium-proton pump

Core Tip: Severe acute respiratory syndrome coronavirus 2 readily infects the liver by angiotensin-converting enzyme 2. Increased angiotensin II causes Na^+/H^+ exchanger (NHE) overstimulation allowing the accumulation of Na^+ and Ca^{2+} in hepatocytes. Thus, hepatocytes are damaged and eventually die. Increased cytokine release increases fibrinogen levels, enhancing thrombotic events. Cytokine storms can be triggered by NHE overstimulation. Severe acute respiratory syndrome coronavirus 2-induced NHE overstimulation can change bile acid structure, which disrupts gut microbiota and can trigger cytokine storms. Liver damage from the virus can be considered the most important cause of disease progression and mortality.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide pandemic and multisystem organ involvement, resulting in immense hospital costs and mortality. Although the virus settles in the lungs and causes infection, it spreads to other organs expressing angiotensin-converting enzyme 2 (ACE2), such as the heart, liver, and kidney, *via* the neighborhood route, systemic blood circulation, or vascular endothelium[1,2]. Liver involvement is also often seen in the course of severe novel coronavirus disease 2019 (COVID-19) and may advance the progression of the disease[3]. Understanding how SARS-CoV-2 spreads to these organs and solving the damage mechanism in the organs will provide an outstanding opportunity to reduce the severity and mortality of the disease.

Intracellular pH plays a vital role in SARS-CoV-2 infection[4]. Physiologically, the pH of endosomes is low. Therefore, acidic pH leads to the autophagy of viruses and harmful substances[4]. However, SARS-COV-2 can smoothly escape autophagy by manipulating cellular autophagy[5] and cause infection at low intracellular pH by fusing with ACE2[6]. When the pH of the endosomes becomes alkaline, SARS-CoV-2 cannot infect the cell since the configuration of ACE2 changes[7]. Hydroxychloroquine, which makes the intracellular pH alkaline, has been used until its harmful effects appear in patients with COVID-19[8]. The primary regulator of intracellular pH in the liver and many organs is the Na^+/H^+ exchanger (NHE)[9,10]. In a previous study, NHE activity was high in the blood of patients with COVID-19[11]. NHE activation in COVID-19 has been associated with cytokine storms and organ damage[12]. Unraveling the unique relationship between NHE and SARS-CoV-2 may illuminate liver involvement, mortality, and progression of COVID-19. Therefore, we should solve the mechanism of possible SARS-CoV-2 and NHE interaction in liver tissue.

COVID-19 AND THE LIVER

The liver has many significant functions, such as detoxification, the urea cycle, gluconeogenesis, and protein synthesis. Many systemic diseases, hypoxia, infections, drugs, and toxins can easily affect the liver, which is extremely sensitive to injury. Systemic infection of SARS-CoV-2 or agents used in COVID-19 treatment can cause liver damage[13]. Liver enzyme elevation is seen in 16.1%-53.1% of patients with COVID-19[14]. Liver damage has been seen in approximately 20% of hospitalized patients with COVID-19[14]. Since hepatocytes express ACE2, SARS-CoV-2 can directly cause liver damage[15].

In COVID-19, gamma-glutamyl transferase (GGT) and alkaline phosphatase, which indicate cholestasis, increase. Aspartate aminotransferase (AST) and alanine transaminase (ALT), which are markers of hepatocyte damage, increase as well[16]. AST, ALT, GGT, and bilirubin indicate liver damage but also reflect the severity of COVID-19[13,17]. Liu *et al*[16] revealed that GGT and ACE2 share the same transcriptional machinery and speculated that GGT may indicate the *in vivo* expression level of ACE2. In addition, the finding of high bilirubin as a predictive marker for mortality in patients with COVID-19 reveals the importance of liver involvement in the disease[18,19]. On the other hand, the presence of microthrombus in most patients with COVID-19 and the fact that arterial thrombosis is

responsible for mortality indicate that liver involvement is more significant in COVID-19.

Fibrinogen, the precursor of fibrin, is synthesized in the liver. D-dimer, a fibrin degradation product, was elevated in many critically ill COVID-19 patients[20]. D-dimer levels correlate with total bilirubin, AST, and ALT levels in patients with COVID-19[21]. Baroiu *et al*[21] reported that D-dimer might be a predictive marker of abnormal liver function parameters and liver injury in patients with COVID-19. Therefore, in most patients with COVID-19, liver involvement may be responsible for mortality and the disease progression.

NHE AND ITS ISOFORMS

There are many ion pumps in plasma membranes. They provide signaling and stabilization of ion concentrations between intracellular and extracellular areas. NHE is one of the most important and has nine isoforms. These isoforms are localized in different tissues and cell types and have various functions depending on their localization. NHE1 is the cleaning form found in almost all tissues and is expressed abundantly in the liver. NHE2 is located in the stomach and intestines. Liver, intestine, and kidney tissues have NHE3. NHE4 is in the stomach and kidney. The brain has NHE5. NHE6-9 are found in intracellular organelles[22-24]. NHEs are involved in the etiology of several gastrointestinal and liver diseases[22].

NHE AND ITS FUNCTION IN THE LIVER

NHE is localized in the basolateral or sinusoidal membrane of hepatocytes[22]. The NHE, which provides the intracellular pH balance, is physiologically activated when the intracellular pH decreases and brings the intracellular pH to its physiological levels[25]. NHE causes the movement of Na^+ into the cell and H^+ out of the cell. As soon as the intracellular pH reaches physiological levels, the NHE activity reduces[12]. NHE provides the passage of Na^+ into the cell. The $Na^+/K^+/2Cl^-$ cotransporters cause the influx of Na^+, K^+, and Cl^- into the cell. Simultaneously, the $Cl^-/HCO3^-$ antiporter ensures the influx of Cl^- into the cell. Na^+/K^+-ATPase (NKA) pumps Na^+ outward while K^+ moves into the cell. Eventually, KCl increases in hepatocytes[25-27]. Na^+/Ca^{2+} Exchanger (NCE) provides intracellular Ca^{2+} balance[28]. These pumps work in harmony in the liver. Physiological NHE, NCE, and NKA activities are summarized in Figure 1.

In acute ischemic events, NHE activation increases intracellular pH and prevents hepatocytes from undergoing apoptosis[10]. Arginine vasopressin activates NHE in hepatocytes by calcium/calmodulin-dependent processes[29]. Stimulation of NHE is involved in hepatocyte regeneration and growth[25]. However, if the stimulus is increased, hepatocyte apoptosis due to intracellular Ca^{2+} accumulation increases[22,25].

Chronic cytokine or platelet-derived growth factor-mediated NHE stimulation causes hepatic stellate cell proliferation and fibrosis[30]. NHE3 is located in the apical membranes of the hepatocytes and cholangiocytes. NHE3 is responsible for maintaining the fluid content of bile acid[31]. Increased NHE3 activity leads to Na^+ loading and an increase in the concentration function of the gallbladder, resulting in gallstone formation[32-34].

PROLONGED NHE ACTIVATION

While NHE does significant work in physiological conditions, its continuous activation causes serious problems. During NHE physiological function, NCE pumps Na^+ into the cell and Ca^{2+} outward. As a result of NHE overstimulation, NCE activation stops, and reverse NCE becomes active due to increased Na^+ in the cell. While Ca^{2+} is pumped into the cell, Na^+ begins to be pumped outward. As a result, the concentration of Na^+ and Ca^{2+} in the cell increases. The NKA pump, which pumps K^+ inward and Na^+ outward, loses its function due to increased intracellular Na^+ and ATP depletion[4,12,35-37]. While edema occurs due to Na^+ accumulation in hepatocytes, Ca^{2+} overload causes hepatocyte apoptosis[38]. In the prolonged activity of NHE, continuous pumping of H^+ into the extracellular area causes some chain redox reactions, H^+ begins to influx into the cell, and the intracellular pH drops[4,12,29]. NHE overstimulation and its outcomes are summarized in Figure 1. NHE activation also increases the influx of lipids and free fatty acids into the cell. Free fatty acid influx further increases intracellular acidity, and concomitant Ca^{2+} overload accelerates apoptosis[36]. As a result of all these events, acute hepatocyte damage may progress from an advanced level to liver failure. Tanaka *et al*[39] found that NHE suppression inhibited the nuclear factor kappa B pathway and proinflammatory cytokine release, thus preventing fatal acute liver failure. In addition, there is a strong interaction between NHE and low-density lipoprotein receptors (LDLR), which may cause liver damage. Non-physiological LDLR excess gives rise to cholesterol overload in hepatocytes. Lipid deposition causes hepatomegaly in the chronic

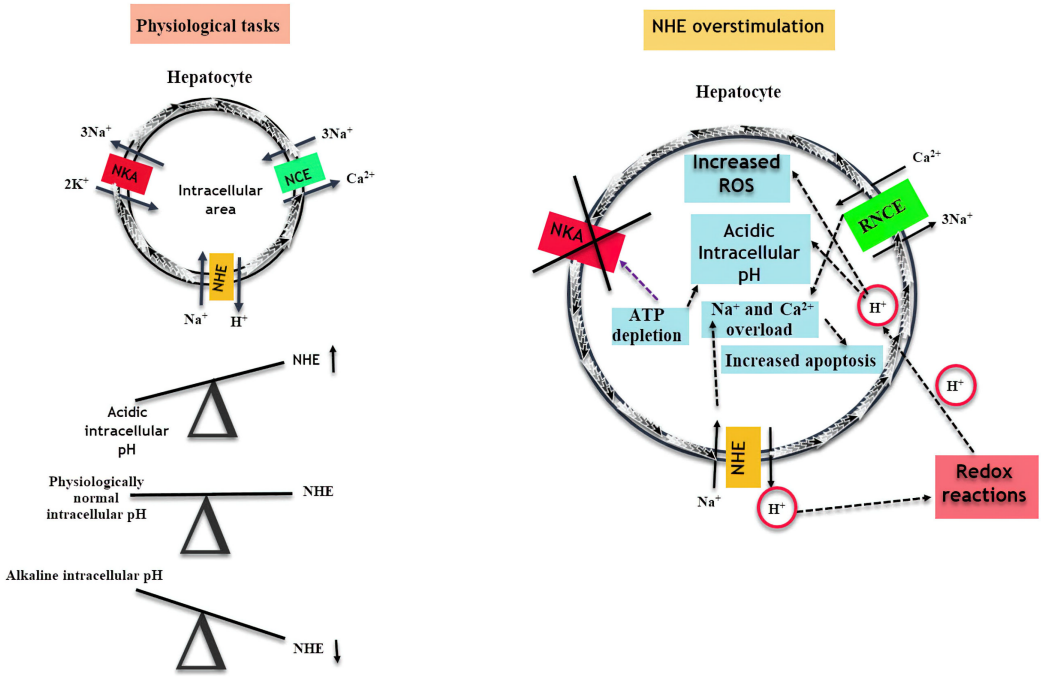

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Figure 1 Na^+/H^+ exchanger overstimulation and its outcomes. Physiologically, the Na^+/H^+ exchanger (NHE) causes Na^+ to flow inward and H^+ to flow outward. When the intracellular pH falls, NHE is activated, raising the intracellular pH to its physiological level. NHE activity decreases as the intracellular pH increases. When NHE is overstimulated, increased Na^+ in the cell activates the reverse Na^+/Ca^{2+} exchanger and Ca^{2+} flows inward. The increased H^+ in the extracellular area causes chain redox reactions and an inwards H^+ influx. Reactive oxygen species increase, and ATP depletion inhibits Na+/K+-ATPase. As a result, hepatocytes are damaged and eventually die. NCE: Na^+/Ca^{2+} exchanger; NHE: Na^+/H^+ exchanger; NKA: Na^+/K^+-ATPase; RNCE: Reverse Na^+/Ca^{2+} exchanger; ROS: Reactive oxygen species.

process[40]. Although hepatocytes are resistant to cholesterol loading, hepatocytes begin to die with prolonged lipid deposition[40].

SARS-COV-2 AND NHE INTERACTION

The alkalinity of the intracellular pH creates a barrier against SARS-CoV-2 infection. Therefore, this mechanism has been considered for COVID-19 treatment[6]. Hydroxychloroquine has been used for COVID-19 treatment since it makes the intracellular pH alkaline by inhibiting vacuolar H^+-ATPase[41]. Also, metformin converts endosome pH to alkaline *via* vacuolar H^+-ATPase[42-44]. At or slightly above the physiological NHE activation can shift the intracellular pH to alkaline, preventing ACE2-SARS-CoV-2 fusion. Using proton pump inhibitors in mild COVID-19 patients may worsen the course of the disease[45,46]. However, when the virus takes total control of the cells in patients with severe COVID-19, NHE overstimulation causes many detrimental effects as well as a decrease in intracellular pH.

Hitherto, it has not been determined whether SARS-CoV-2 directly affects NHE; however, NHE activity was elevated in the blood of patients with COVID-19[11]. SARS-CoV-2 can increase NHE activity by many mechanisms. SARS-CoV-2-infected mice, which have physiological angiotensin II levels, have been shown to have no damage in some of their tissues[47]. However, patients with severe COVID-19 have high angiotensin II levels[48]. ACE2 degrades angiotensin II and reduces its levels. When SARS-CoV-2 fuses with ACE2, the level of angiotensin II increases in the circulation and tissues since ACE2 cannot complete its task[4]. The liver has a local renin-angiotensin system that is not very important in physiological conditions, which is dissimilar to hepatic renin-angiotensin system that plays a significant role in pathological conditions[49,50]. Since the liver expresses ACE2, the virus increases the local angiotensin II level by binding to ACE2 in the liver. Angiotensin II is the substantial stimulus of NHE. Angiotensin II shows pro-oxidant, fibrogenic, and proinflammatory actions on the liver[51].

SARS-CoV-2 uses lipid rafts and cholesterol to fuse with ACE2 in membranes[52]. Lipid rafts play a remarkable role in the entry of SARS-CoV-2 into the cell[53]. In addition, there is a strong interaction among lipid rafts, cholesterol, and NHE. Therefore, the virus can activate NHE through cholesterol and lipid rafts[36]. The release of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 and increased oxidative stress by SARS-CoV-2 can also stimulate NHE[12]. Fibrinogen produced in the liver provides activation of NHE1 by inducing NCE[54]. Fibrinogen increase in COVID-19 can also initiate NHE activation.

SARS-COV-2 AND NHE IN THE LIVER

Since the liver has many vital functions, the virus infecting it will have many systemic consequences. Physiologically, NHE protects hepatocytes from apoptosis by making the intracellular pH alkaline[10]. However, NHE overstimulation can cause acute lethal liver damage[39]. Once the virus settles in the liver and infects hepatocytes, it can cause NHE overstimulation. The virus renders intracellular Ca^{2+} accumulation with reverse NCE activation after Na^+ accumulation in hepatocytes. Apoptosis is induced in hepatocytes and cell death. Liver enzymes such as AST and ALT increase due to parenchymal damage[55]. NHE overstimulation may also trigger a cytokine storm by increasing proinflammatory cytokines in the liver[12].

On the other hand, NHE1 plays a role in urea synthesis[56]. Increased H^+ extrusion increases urea synthesis[57]. The virus can increase the level of urea by NHE1 overstimulation. Increased urea in patients with COVID-19 indicates kidney damage[58]. However, urea may also be a marker of liver injury.

Gluconeogenesis in the liver is significantly reduced when the intracellular pH is lowered. Therefore, a hypoxic environment occurs[59,60]. In physiological conditions, NHE stimulates gluconeogenesis by increasing intracellular pH. NHE overstimulation decreases gluconeogenesis in the liver by reducing intracellular pH[61]. In patients with severe COVID-19, elevated blood glucose may be due to insulin resistance[61] or decreased insulin secretion related to NHE and proinflammatory cytokine-mediated pancreatic damage[62].

Other liver functions are vitamin B_{12} storage[63], iron storage[64], and vitamin D synthesis[65]. Vitamin D reduces acute liver injury[66]. Vitamin D is immunomodulatory, and low levels may worsen the progression of COVID-19[67,68]. Insulin-like growth factor-1 levels[69,70], which stimulate vitamin D synthesis in hepatocytes, was lower in COVID-19 patients[71]. While vitamin D increases circulating insulin-like growth factor-1 levels[72], insulin-like growth factor-1 inhibits NHE. Increased intracellular Ca^{2+} decreases vitamin D synthesis in the liver[73]. NHE-mediated hepatocyte injury in patients with COVID-19 may reduce vitamin D synthesis and worsen disease progression. Reduced intracellular pH leads to iron release from the liver[74], and excess iron causes local and systemic damage with the Fenton reaction[75]. Low intracellular pH caused by NHE overstimulation can lead to iron-mediated damage to cells in patients with COVID-19.

According to the LDLR mechanism we described earlier, the virus can cause lipid accumulation in the liver, leading to the fattening and enlargement of the liver and even loss of function[36]. Unfortunately, there is not enough information in the literature regarding the role of LDLR in patients with COVID-19. Although a study proved the opposite[76], Lange *et al*[77] reported that LDLR expression was higher in patients with COVID-19 than in healthy controls. Agirbasli *et al*[78] reported that LDLR-related protein 1, a member of the LDLR family, is increased in severe COVID-19. According to current findings, angiotensin II inhibits proprotein convertase subtilisin/kexin type 9[36], which disrupts LDLR[36]. Angiotensin II indirectly increases LDLR levels. In severe cases of COVID-19, increased angiotensin II may lead to NHE overstimulation and lipid accumulation in the liver. In addition, the virus needs cholesterol particles to form new virions after infecting cells[79]. Since the liver is the production and storage site of cholesterol, the virus can continue its life cycle in the liver for a lengthy time. Some studies have shown that high-density lipoprotein (HDL) binds to SARS-CoV-2[80]. Low HDL facilitates the virus binding to ACE2[80]; however, high HDL may play an active role in SARS-CoV-2 transfer from other infected tissues to the liver, as HDL is a cholesterol transporter of the liver.

The virus may settle in the liver and cause hepatocyte damage and multisystem disorder. Therefore, liver involvement may contribute significantly to mortality in COVID-19. There may be a close relationship between liver injury and fibrinogen and coagulation disorders in patients with COVID-19 [3]. As we know, fibrinolysis increases liver necrosis[81]. Initially, fibrinogen and D-dimer levels are elevated in patients with severe COVID-19, but their levels decrease over the following days[82]. Fibrinogen is an acute phase reactant primarily released from the liver, and interleukin-6 increases fibrinogen synthesis[83]. Since the release of proinflammatory cytokines such as interleukin-6 increases with NHE activation, the virus may indirectly cause an increase in fibrinogen and D-dimer. In severe cases of COVID-19, fibrinogen and D-dimer levels were low after 10 d.

NHE increases the tendency for thrombosis mainly through platelets[84]; however, it may also indirectly lead to a tendency for thrombosis through the liver. Prothrombin synthesized in the liver is converted to thrombin when fibrinogen is transformed into fibrin. Thrombin levels are high in patients with COVID-19[85]. Thrombin activates NHE in vascular smooth muscle cells[86]. Thus, the virus can cause damage to distant organs with the help of NHE-mediated proinflammatory cytokine release and thrombin.

While the virus causes a Na^+ load in the cell by NHE overstimulation, it overloads H^+ in the extracellular area[4]. As a result of the subsequent redox reactions, H^+ flows into the cell, and excessive ATP consumption by NKA results in hypoxia and ATP depletion in the cell[12]. Hypoxia and ATP depletion are prominent stimuli of heme oxidase[87,88]. Increased heme oxidase activation enhances carbon monoxide and bilirubin levels in the cell[89]. Carbon monoxide usually has a hepatoprotective effect, but sometimes it can also have a hepatotoxic effect[88]. Elevated bilirubin in patients with COVID-19 has been identified as a predictive marker for mortality rates[90]. Elevated bilirubin may

indirectly reflect NHE-mediated cell hypoxia in patients with COVID-19.

The elevation of alkaline phosphatase and GGT in COVID-19 patients suggests that SARS-CoV-2 changes the structure of bile acid and may lead to cholestasis[91]. NHE1 on the basolateral surface of the bile ducts regulates intracellular pH, while NHE3 on the apical surface regulates bile acid structure and fluidity[92]. Increasing NHE3 activity leads to Na^+ loading, which impairs the containment and fluidity of bile acid[32]. Bile acids play a primary role in maintaining gut microbiota composition[93]. We have recently described that disruption of NHE-mediated gut microbiota composition leads to cytokine release syndrome[12]. The virus disrupts the gut microbiota composition in the intestine and increases the release of proinflammatory cytokines like tumor necrosis factor-alpha. In addition, SARS-CoV-2 increases local angiotensin II levels by binding to ACE2. Unlike other tissues, tumor necrosis factor-alpha and angiotensin II decrease NHE3 activity in the intestine[12,94,95]. Thus, increased luminal Na^+ leads to diarrhea and cytokine release[12,96]. This event may play a role in triggering cytokine storms [12]. The virus can cause intestinal-associated cytokine release by changing the structure and fluidity of bile acid before it has intestinal involvement. It is not yet known whether the changed content of bile acid will play a role in transferring the virus to the intestine. Detailed studies are needed on this subject.

CONCLUSION

Physiological NHE activation protects the liver against acute injury, whereas NHE overstimulation causes severe liver injury. NHE overstimulation can lead to hepatocyte death. Also, it increases the urea cycle and inhibits of gluconeogenesis and vitamin D synthesis in the liver. NHE overstimulation may cause thrombotic events and systemic damage by increasing fibrinogen levels and cytokine release. It can also change the gut microbiota composition by disrupting the structure and fluidity of bile acid, thus triggering systemic damage. SARS-CoV-2-induced local and systemic damage can be improved by preventing virus-induced NHE overstimulation in the liver.

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MINIREVIEWS

Association between COVID-19 and chronic liver disease: Mechanism, diagnosis, damage, and treatment

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Abstract

As the outbreak evolves, our understanding of the consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (COVID-19) on the liver has grown. In this review, we discussed the hepatotropic nature of SARS-CoV-2 and described the distribution of receptors for SARS-CoV-2 (*e.g.*, angiotensin-converting enzyme 2) in the vascular endothelium and cholangiocytes of the liver. Also, we proposed mechanisms for possible viral entry that mediate liver injury, such as liver fibrosis. Due to SARS-CoV-2-induced liver damage, many COVID-19 patients develop liver dysfunction, mainly characterized by moderately elevated serum aminotransferase levels. Patients with chronic liver disease (CLD), such as cirrhosis, hepatocellular carcinoma, nonalcoholic fatty liver disease, and viral hepatitis, are also sensitive to SARS-CoV-2 infection. We discussed the longer disease duration and higher mortality following SARS-CoV-2 infection in CLD patients. Correspondingly, relevant risk factors and possible mechanisms were proposed, including cirrhosis-related immune dysfunction and liver decompensation. Finally, we discussed the potential hepatotoxicity of COVID-19-related vaccines and drugs, which influence the treatment of CLD patients with SARS-CoV-2 infection. In addition, we suggested that COVID-19 vaccines in terms of immunogenicity, duration of protection, and long-term safety for CLD patients need to be further researched. The diagnosis and treatment for liver injury caused by COVID-19 were also analyzed in this review.

Key Words: SARS-CoV-2; COVID-19; Chronic liver disease; Angiotensin-converting enzyme 2; Hepatotoxicity; Calcineurin inhibitors

Core Tip: In this review, we discussed the hepatotropic nature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and described the distribution of receptors for SARS-CoV-2 in the vascular endothelium and cholangiocytes of the liver. We proposed mechanisms for possible viral entry that mediate liver injury, such as liver fibrosis. Due to SARS-CoV-2-induced liver damage, many coronavirus disease 2019 (COVID-19) patients develop liver dysfunction. We discussed the longer disease duration and higher mortality following SARS-CoV-2 infection in chronic liver disease patients. Correspondingly, relevant risk factors and possible mechanisms were proposed. Finally, we discussed the potential hepatotoxicity of COVID-19-related vaccines and drugs.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On December 31, 2019, the World Health Organization first learned about this new virus from a set of cases of viral pneumonia reported in Wuhan, People's Republic of China. The most common symptoms of COVID-19 are fever, dry cough, and fatigue. In particular, symptoms of severe COVID-19 often present with dyspnea, loss of appetite, confusion, and high fever. Of those who develop symptoms, the majority (about 80%) do not require hospitalization to recover. About 15% of patients are severely ill and require oxygen; 5% of patients are critically ill and require intensive care.

Complications of death from COVID-19 may include respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and/or multiple organ failure, including heart, liver, or kidney damage. In particular, people aged 60 and older, as well as those with underlying medical conditions such as high blood pressure, cardiorespiratory problems, diabetes, obesity, or cancer, are at higher risk of developing severe COVID-19.

Currently, individual COVID-19 vaccines have been licensed for use by regulatory agencies in some countries, and many potential COVID-19 vaccine candidates are under development. This article analyzed and summarized COVID-19 from four aspects: Mechanism, diagnosis, damage, and treatment. Table 1 summarizes the analysis of these four parts.

MECHANISM

Our understanding of the hepatic consequences of SARS-CoV-2 infection and the resulting COVID-19 has evolved rapidly since the beginning of the pandemic[1]. Many reports showed that many COVID-19 patients had chronic liver disease (CLD) of varying degrees[2-5]. In particular, COVID-19-related liver injury refers to any liver injury that occurs in patients with COVID-19 during the course and treatment of the disease, regardless of pre-existing liver disease[6-8].

Several studies have shown that SARS-CoV-2 can bind to the host angiotensin-converting enzyme 2 (ACE2) receptor, allowing the virus to enter cells and actively replicate in the liver[9-11]. Notably, severe disease outcomes depend on the high affinity of the virus to ACE2[12]. ACE2 is expressed in multiple organs, such as the lung, gastrointestinal tract, and liver[13-15]. In the liver, ACE2 is expressed at a low level in hepatocytes, with a positive rate as low as 2.6%[16]. However, it is highly enriched (59.7%) in cholangiocytes, similar to the expression levels in the type II alveolar cells (primary target cells of SARS-CoV-2 in the lung)[17,18]. Therefore, the virus may directly infect bile duct cells but not hepatocytes[13]. Viral infection could lead to cholangiocyte apoptosis accompanied by mitochondrial swelling, endoplasmic reticulum expansion, reduction of glycogen granules, and extensive necrosis[19, 20].

SARS-CoV-2 infection can lead to severe host hyperimmunity in the lungs, triggering a life-threatening cytokine storm[21,22], a systemic inflammatory response syndrome driven by viral infection. Cytokine storm syndrome may induce a massive release of multiple proinflammatory cytokines and inflammatory markers[23], leading to tissue damage and multiple organ damage or failure, including the liver[24]. Cytokine storms caused by virus-induced excessive immune response may be one of the pathways of CLD[25,26].

Table 1 Summary of the mechanism, diagnosis, damage, and treatment of coronavirus disease 2019 in chronic liver disease patients

Feature	Conclusion of each part
Mechanism	SARS-CoV-2 can bind to the host ACE2 receptor, allowing the virus to enter cells and actively replicate in the liver. Severe disease outcomes depend on the high affinity of the virus to ACE2. In addition, SARS-CoV-2 infection can lead to severe host hyperimmunity in the lungs, triggering a life-threatening cytokine storm[21,22], a systemic inflammatory response syndrome driven by viral infection. This leads to tissue damage and multiple organ damage or failure. In addition, symptoms due to COVID-19 complications are underlying pathological mechanisms of extensive liver injury
Diagnosis	Liver biochemical abnormalities are common in COVID-19-related CLD patients. The main manifestations of patients with COVID-19-related CLDs are moderately elevated serum transaminase activity and elevated LDH levels. The severity of CLD during the COVID-19 course can be effectively judged by detecting serum transaminase, LDH, bilirubin levels, and albumin concentrations
Damage	Invasion of SARS-CoV-2 may lead to significant systemic disease; some can even develop severe lung disease, leading to respiratory compromise, which in turn may progress to multiple organ failure, coagulopathy, and death. Typically, COVID-19 patients are more vulnerable and susceptible to underlying metabolic diseases. In addition, SARS-CoV-2 can cause CLD by direct cytopathies, immune-mediated, hypoxia/ischemia, and microvascular thrombosis
Treatment	Immunosuppression therapy is meaningful for both COVID-19 and CLD. Therefore, immunosuppressive drugs should be evaluated during the co-occurrence of both disorders Common immunosuppressive drugs include calcineurin inhibitors and mTOR inhibitors. Medication side effects need to be considered during treatment, including increasing susceptibility to SARS-CoV-2 infection and secondary bacterial or fungal infection and prolonged viral clearance. In addition, currently prescribed drugs for COVID-19 are all metabolized in the liver, and these antiviral drugs may lead to abnormal liver function. Therefore, it is necessary to balance the management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19 and minimize the use and dosage of immunosuppressants to reduce the impact of liver damage

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; CLD: Chronic liver disease; LDH: Lactate dehydrogenase.

In addition, liver disease worsens because of COVID-19 complications, including coagulation disorders and cardiac and respiratory failure. These complications induced diffuse intravascular coagulation, ischemia, and hypoxia in the liver. All of these can lead to upregulation of fibrotic pathways, fatty acid oxidation, oxidative phosphorylation, and dysregulation of markers of immune activation. These are also the potential pathological mechanisms of extensive liver injury[27].

DIAGNOSIS

Liver biochemical abnormalities are common in COVID-19-related CLD patients, occurring in approximately 15%-65% of SARS-CoV-2 infected individuals[28-31]. The main manifestations of patients with COVID-19-related CLDs are moderately elevated serum transaminase activity and elevated lactate dehydrogenase (LDH) levels[32-35]. However, COVID-19 may cause damage to other organs, including the heart, bones, and kidneys. Skeletal muscle and myocardial injury can also lead to elevated serum transaminases and LDH levels[12,16]. In addition, hypoalbuminemia was reported to be a nonspecific marker of disease severity associated with poor COVID-19 prognosis[36]. Therefore, the severity of CLD during the COVID-19 course can be effectively judged by detecting serum transaminase, LDH, bilirubin levels, and albumin concentrations[37-40].

DAMAGE

Invasion of SARS-CoV-2 may lead to significant systemic disease involving the gastrointestinal tract, liver, biliary tract, and pancreas[12]. Most patients with SARS-CoV-2 infection are asymptomatic or have mild symptoms, including fever, cough, loss of smell, and headache[1]. However, approximately 15% of patients develop severe lung disease within 10 d, leading to respiratory compromise, which in turn may progress to multiple organ failure, coagulopathy, and death[41-43].

COVID-19 patients are more vulnerable and susceptible to underlying metabolic diseases, including hypertension, cardiovascular disease, type 2 diabetes, chronic lung disease, and metabolic syndrome[44,45]. In particular, people at high risk for severe COVID-19 are usually the elderly and those with comorbidities[37]. In addition, obese patients who frequently develop the metabolic dysfunction-associated fatty liver disease are also at high risk of developing severe COVID-19 due to the role of acutely active inflammatory pathways[19,38]. Infection with SARS-CoV-2 can increase the severity of viral hepatitis, and its clearance in patients is delayed. For those underlying undetected liver diseases, especially nonalcoholic fatty liver disease and cirrhosis, the prevalence of COVID-19 is significantly increased, and the prognosis will be worse[46]. For CLD patients, especially those with advanced liver disease, SARS-CoV-2 infection may seriously jeopardize survival and exacerbate liver failure in the case of the diminished liver reserve[47,48].

In conclusion, SARS-CoV-2 can cause CLD in the following aspects: Direct cytopathies (SARS-CoV-2 invades liver cells and causes cytopathic effects leading to liver dysfunction in COVID-19 patients); immune-mediated (SARS-CoV-2 infection leads to a disordered inflammatory response and increased proinflammatory cytokines, which in turn triggers severe liver dysfunction); hypoxia/ischemia (in severe COVID-19, multiple organ dysfunction can lead to hypoxia-related acute respiratory distress syndrome[49], hypotension[50], or congestive heart failure, which in turn leads to liver dysfunction); and microvascular thrombosis.

TREATMENT

CLD is common worldwide. The rapid spread of COVID-19 has resulted in infections in many patients with underlying CLD. Immunosuppression therapy is meaningful for both COVID-19 and CLD. Therefore, immunosuppressive drugs should be evaluated during the co-occurrence of both disorders. First, calcineurin inhibitors (CNIs), including cyclosporine or tacrolimus, are considered the basic drugs for immunosuppression in treating CLD[51]. They are often used with mycophenolate mofetil or everolimus to reduce plasma levels. Their use avoids the adverse effects of cyclosporin A binding to the intracellular receptor cyclosporine to form an active complex. This may inhibit the phosphatase activity of calcineurin. Second, immunosuppressants such as mycophenolate mofetil and CNIs have been shown to have antiviral activity against coronaviruses[52]. There is evidence that CNIs have direct antiviral effects. Cyclosporine can block replication of all coronavirus genera, including SARS-CoV. Similarly, mTOR inhibitors (*e.g.*, tacrolimus) have antiviral properties in addition to their immunosuppressive and antiproliferative effects. Glucocorticoids for COVID-19 have been shown to prevent the disturbances in the immune response that lead to the poor prognosis of COVID-19[53].

The side effects cannot be ignored, despite the indispensable role of immunosuppression therapy in COVID-19-related CLD. Immunosuppression induced by these drugs may increase susceptibility to SARS-CoV-2 infection[54] and secondary bacterial or fungal infection. In addition, it may also prolong viral clearance time[55]. Related research shows that patients using immunosuppressive drugs have an increased average risk of SARS-CoV-2 infection. Therefore, experience suggests that reducing mycophenolate mofetil or mTOR inhibitors remains beneficial for managing immunosuppression during SARS-CoV-2 infection. Patients who received thiopurines and glucocorticoids before the onset of COVID-19 had a higher risk of severe COVID-19 than CLD patients who were not receiving immunosuppressive therapy[56]. In particular, patients with severe COVID-19 infection may need to consider dose adjustment of steroids, CNIs, or mycophenolate mofetil to reduce the effect of liver injury.

In addition, currently prescribed drugs for COVID-19 (*e.g.*, oseltamivir, lopinavir/ritonavir, and chloroquine) are all metabolized in the liver. Although there is currently no recognized effective antiviral drug for COVID-19, nearly half of the critically ill patients were prescribed antiviral drugs such as oseltamivir, abidol, lopinavir, and ritonavir[57]. These antiviral drugs may cause abnormal liver function. In particular, patients with CLD, such as hepatitis B or C, may have elevated aminotransferase levels before treatment, which may increase the risk of drug-induced liver injury[46]. Therefore, attention should be paid to abnormal liver test indicators during the treatment process to reduce drug-induced liver injury[58].

In summary, the management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19 must be balanced. The effects of drugs on liver toxicity, steatosis, necroinflammation, fibrosis, and biological metabolism should be comprehensively considered when treating COVID-19. This is beneficial to avoiding serious drug-induced liver injury while exerting a sufficient immune response and antiviral effect[12].

Finally, although these patients have compromised immune responses, immediate and long-term protective responses through immunization may not be complete for the protective measure of vaccination. However, early vaccination against various pathogens, including SARS-CoV-2 in patients with CLD remains essential and effective[59]. A small number of patients have mild jaundice (slightly elevated bilirubin levels).

CONCLUSION

Above all, SARS-CoV-2 can bind to the host ACE2 receptor, allowing the virus to enter cells and actively replicate in the liver. Severe disease outcomes depend on the high affinity of the virus to ACE2. SARS-CoV-2 infection can lead to severe host hyperimmunity in the lungs, triggering a life-threatening cytokine storm[21,22], a systemic inflammatory response syndrome driven by viral infection. This leads to tissue damage and multiple organ damage or failure. In addition, symptoms due to COVID-19 complications are also underlying pathological mechanisms of extensive liver injury.

Liver biochemical abnormalities are common in COVID-19-related CLD patients. The main manifestations of patients with COVID-19-related CLDs are moderately elevated serum transaminase activity and elevated LDH levels. The severity of CLD during the COVID-19 course can be effectively judged by

detecting serum transaminase, LDH, bilirubin levels, and albumin concentrations.

Invasion of SARS-CoV-2 may lead to significant systemic disease, and some patients can even develop severe lung disease, leading to respiratory compromise, which in turn may progress to multiple organ failure, coagulopathy, and death. Typically, COVID-19 patients are more vulnerable and susceptible to underlying metabolic diseases. SARS-CoV-2 can cause CLD by direct cytopathies, immune-mediated, hypoxia/ischemia, and microvascular thrombosis.

Immunosuppression therapy is meaningful for both COVID-19 and CLD. Therefore, immunosuppressive drugs should be evaluated during the co-occurrence of both disorders. Common immunosuppressive drugs include CNIs and mTOR inhibitors. Medication side effects need to be considered during treatment, including increasing susceptibility to SARS-CoV-2 infection and secondary bacterial or fungal infection and prolonged viral clearance. In addition, currently prescribed drugs for COVID-19 are all metabolized in the liver, and these antiviral drugs may lead to abnormal liver function. Therefore, it is necessary to balance the management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19 and minimize the use and dosage of immunosuppressants to reduce the impact of liver damage.

FOOTNOTES

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MINIREVIEWS

COVID-19 in patients with pre-existing chronic liver disease – predictors of outcomes

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Abstract

Coronavirus disease 2019 (COVID-19) has affected patients with pre-existing chronic liver disease (CLD) in various ways. The maximum impact was seen on patients with underlying cirrhosis who have shown to have poor clinical outcomes in the form of increased risk of hepatic decompensation, acute-on-chronic liver failure, and even mortality. It is of paramount importance to identify various factors which are associated with unfavorable outcomes for prognostication and making informed management strategy. Many factors have been evaluated in different studies in patients with underlying CLD. Some of these factors include the severity of underlying chronic liver disease, comorbid conditions, age, and severity of COVID-19. Overall, the outcomes are not favorable in patients with cirrhosis as evidenced by data from various studies. The main purpose of this review is to identify the predictors of adverse clinical outcomes including mortality in patients with CLD for risk stratification, prognostication, and appropriate clinical management.

Key Words: Severe acute respiratory syndrome coronavirus 2; Cirrhosis; Predictors; Outcomes

Core Tip: Coronavirus disease 2019 (COVID-19) has been shown to negatively affect the outcomes of patients with chronic liver disease. Some of the major factors predicting poor outcomes and mortality as shown by various studies include old age (> 60 years) and presence of comorbidities like diabetes, hypertension, and obesity. Apart from these, the most important outcome measure is the severity of underlying chronic liver disease and in some cases the etiology of chronic liver disease. Another major predictor of outcome is the severity of COVID-19, with respiratory failure being a common cause of mortality. Further data is required to draw a definitive relation between these risk factors and outcomes in these patients.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related coronavirus disease 2019 (COVID-19) has wreaked havoc since its outbreak in late 2019. As per the most recent estimates, it has affected more than 575 million people worldwide[1]. It has adversely affected the health care system even in developed nations. Although the most common manifestations of COVID-19 are either asymptomatic infection or mildly symptomatic infection with fever, cough, and generalized weakness, some patients developed severe respiratory failure requiring mechanical ventilation and even death[2].

Patients with chronic liver disease (CLD) have been affected due to the COVID-19 pandemic, such as lack of routine services like variceal and hepatocellular carcinoma (HCC) screening, lack of physical follow-up to monitor the response to treatment like ascites, re-allocation of health care facilities for COVID-19 management, *etc.* An acute insult in the form of COVID-19 in a background of CLD may lead to further decompensation and increased morbidity and mortality. Therefore, in this review, we will summarize and identify the predictors of adverse outcomes in patients with CLD, which will help in prognostication, risk stratifying, and providing optimal care to the patients.

EPIDEMIOLOGY

COVID-19 is a systemic disease affecting multiple organ systems and gastrointestinal system (GI) involvement may be seen in a subset of patients. Studies have shown that nearly 20% of the affected patients had some abnormalities in liver function as reflected by elevated liver enzymes (20%) and elevated bilirubin (16%)[3]. About 35% of patients showed abnormal alanine aminotransferase or bilirubin levels, out of which 77% showed elevation to levels less than 5 times the upper limit of normal [4]. The prevalence of underlying CLD in COVID-19 patients was 3%-6.3% in various studies[5-8]. A meta-analysis of 73 studies with 24299 patients, showed that the prevalence of CLD in COVID-19 positive patients was 3%, which was similar to that among COVID-19 negative patients[3]. The differences in prevalence might be due to admission bias, sampling bias, and retrospective nature of studies.

A recent study showed that mortality rates among alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) affected patients increased significantly during the pandemic while the rate of mortality among patients with viral hepatitis remained similar to the pre-pandemic times[9]. A recent meta-analysis of 40 studies has shown that patients with CLD had a significantly higher risk of severe COVID-19 (pooled odds ratio [OR]: 2.44) and death (pooled OR: 2.35) as compared to COVID-19 patients without[10]. Hence, COVID-19 does affect patients with CLD and in some cases with adverse outcomes.

PATHOPHYSIOLOGY OF LIVER INVOLVEMENT IN COVID-19

The liver involvement in COVID-19 is multifactorial, including direct viral hepatotoxicity, immune-mediated liver injury, sepsis, hypoxemia, or drug-induced liver injury[11]. Direct hepatotoxicity is due to entry of SARS-CoV-2 into the liver through the binding of viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor on cholangiocytes. The expression of ACE2 is highest in cholangiocytes followed by sinusoidal endothelial cells and hepatocytes as shown in healthy livers by single cell RNA sequencing methods[12]. After entering the cell, the S protein is primed by a specialized serine

protease, transmembrane serine protease 2 (TMPRSS2), in the host cell[13]. Once inside the cell, SARS-CoV-2 causes activation of the mTOR pathway which inhibits autophagy of the viral particles. Thus, the viral particles evade the immune system and increase in number, exerting direct hepatotoxicity *via* mitochondrial dysfunction, ER stress, and activation of the intrinsic pathway of apoptosis as depicted in Figure 1[14].

The second hit in the pathogenesis of liver injury is secondary damage caused by cytokine storm. Infection with SARS-CoV-2 has been postulated to cause a massive surge in proinflammatory cytokine levels. The predominant cytokines implicated include interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and elevated levels of ferritin and CRP[15]. These proinflammatory cytokines result in cholestatic liver injury by causing downregulation of proteins and channels involved in uptake and secretion of bilirubin and bile salts similar to what is seen in sepsis-related cholestasis. Another postulated mechanism is decreased albumin synthesis due to IL-6 mediated suppression of C/EBP pathway[14]. TNF-α and IL-1 also activate and recruit macrophages to the liver and induce apoptosis of hepatocytes. These inflammatory cytokines also cause hypoxic liver injury by causing endothelial damage and inducing microvascular thrombosis[14]. Thus, various cytokines act in concert to cause liver injury reflected as biochemical alterations in liver function. Other mechanisms include hypoxemic injury secondary to type 1 hypoxemic respiratory failure and drug induced liver injury.

CHRONIC LIVER DISEASE AND COVID-19 OUTCOMES

Predictors of outcomes in chronic liver disease

Numerous studies across the globe have tried to identify the predisposing factors for poor outcomes of COVID-19 in patients with CLD as summarized in Figure 2 and Table 1. A summary of evidence available and the possible risk factors has been enumerated below.

Age: Increasing age is associated with a blunted immune response and multiple comorbidities, and thus may have an impact on the outcomes in patients with pre-existing CLD. Age more than 60 years had an adjusted hazard ratio (aHR) of 1.05 for mortality in cirrhotics with COVID-19[16]. Another study showed that the mortality increased from 6.1% in patients aged less than 50 years to 33.9% among those who were more than 65 years with an adjusted OR (aOR) of 7.2 in this group of patients[17]. Therefore, increasing age especially more than 60 years has been associated with increased mortality and risk of liver decompensation[16-18].

Ethnicity: African Americans with CLD were twice more likely to develop COVID-19 than Caucasians in a study[19]. Another study found that non-Hispanic blacks and Hispanics had higher chances of contracting COVID-19 in patients with CLD; however, they did not find any difference in outcomes of disease in different ethnicities[20]. Hispanics had more severe COVID-19 infection in patients with CLD [18]. Henceforth, Hispanics and blacks have been shown to have higher risk of contracting COVID-19 disease and having a severe course likely due to lower socioeconomic status, poverty, overcrowding, and inadequate access to health care services.

Etiology of CLD: Several studies have tried to relate the etiology of CLD with outcomes in COVID-19 patients. In the following sections, the determinants of outcomes are described according to etiology of CLD.

Alcohol

Alcohol is one of the most common etiologies of CLD. The pandemic led to a situation of social isolation and unemployment which lead to an increased consumption of alcohol in higher quantities[21]. A study found a higher rate of mortality among alcohol-related liver disease with an aHR of 1.79[22]. Kim *et al* [18] showed an aHR of 2.42 of mortality among alcohol-related liver disease. There was a three times increase in the monthly percent change of crude ALD-related mortality after February 2020 as compared to January 2017 to December 2017 in one study[23]. However, another study did not find alcohol as a poor outcome variable on multivariate analysis of retrospective data[24,25]. A recent study showed that the mortality among ALD patients was declining in the pre-pandemic era but increased fivefold during the pandemic[9]. Therefore, it seems that alcohol as an etiology increases the risk of adverse outcomes and mortality[26] in patients with COVID-19 and CLD as summarized in Table 2 and Supplementary Table 1.

NAFLD

NAFLD is rapidly becoming the most common cause of CLD across the world. It is considered to be the hepatic manifestation of metabolic syndrome and usually coexists with other components of metabolic syndrome. The COVID-19 pandemic showed a bidirectional relationship with NAFLD. Lockdown during the pandemic and lack of exercise lead to an increase in sedentary behavior and thus metabolic syndrome including NAFLD. Such patients had a more severe COVID-19 infection as evidenced by higher requirement of oxygen, mechanical ventilation, and prolonged intensive care unit (ICU) stay[27-

Table 1 Studies showing clinical outcomes of chronic liver disease in coronavirus disease 2019 and associated risk factors

Ref.	Type	Clinical outcomes	Predictors of outcomes
Iavarone *et al* [53]	Multicentric retrospective study of 50 cirrhotics	ACLF and *de novo* acute liver injury: 28%; 30-d mortality: 34%	Predictors of mortality: CLIF-OF (HR: 1.426); Moderate/severe respiratory failure (HR: 1.608)
Marjot *et al*[22]	Retrospective data from United Kingdom hospital network including 745 patients with CLD (386 with and 359 without cirrhosis)	Acute hepatic decompensation: 46%; ACLF: 50%; Mortality in cirrhosis, ACLF, and non-cirrhotics: 32%, 65%, and 8%	Predictors of mortality: ALD (OR: 1.79); Child-Pugh class: Child-Pugh A +2.0%, Child-Pugh B +20.0%, Child-Pugh C +38.1%. Predictors of decompensation: Child-Pugh class
Ge *et al*[16]	Data from the National COVID Cohort Collaborative (N3C) dataset of 6.4 million cases	3.31 times adjusted hazard of death in cirrhotics at 30 d than non-cirrhotics	Predictors of 30-d mortality: Age (aHR: 1.05 per year); Hispanic ethnicity (aHR: 1.20); Chronic hepatitis C (aHR: 1.27); ALD (aHR: 1.40); Modified CCI (aHR: 1.07 per point)
Elhence *et al*[24]	Retrospective analysis of 221 cirrhosis patients	Compensated cirrhosis: 8.1%; Acute decompensation: 62.9%; ACLF: 29.0%; MODS: 55.6%; Type 1 respiratory failure: 20.0%; Sudden cardiac arrest: 6.7%; GI bleeding: 3.3%	Predictors of mortality: Higher TLC [HR: 1.054]; Elevated creatinine [HR: 1.184]; MELD score [HR: 1.038]; Alkaline phosphatase [HR: 1.003]; COVID-19 severity [HR: 2.573]; ACLF on presentation (HR: 2.573)
Xiao *et al*[52]	Medical records collected from 23 Chinese hospitals	Decompensated cirrhosis: 57.5%; Mortality: 28.9%	Factors associated with mortality: Child-Pugh class (OR: 5.71); CURB65 (OR: 5.88)
Grgurevic *et al* [48]	4014 patients	Four times higher risk of 30-d mortality in cirrhosis	Predictor of 30-d mortality: Cirrhosis (HR: 2.95)
Mendizabal *et al* [17]	Prospective cohort of 96 cirrhosis patients	Mortality in cirrhotic: 47% *vs* 16% in non-cirrhotics; Acute decompensation: 61.4%; ACLF: 55.2%	Factors associated with mortality: Age > 65 yr (OR: 7.2); Male gender (OR: 1.8); BMI > 30 (OR: 1.7); Cirrhosis (OR: 3.1)
Kim *et al*[18]	Multicentre observational cohort study in 21 institutes in United States with 867 CLD cases (227 with cirrhosis)	Mortality: 25%; Hepatic decompensation: 7.7%; Hepatic encephalopathy: 34.3%; Ascites: 16.4%; Variceal bleed: 10.4%	Predictors of all-cause mortality: ALD (HR: 2.42); Hepatic decompensation at baseline (HR: 2.91); HCC (HR: 3.31); Increasing age (HR:1.44 per 10 yr); Diabetes (HR: 1.59); Hypertension (HR:1.77); COPD (HR:1.77); Current smoking (HR: 2.48)
Sarin *et al*[37]	Retrospective data from 13 Asian countries with228 patients [185 CLD without cirrhosis and 43 with cirrhosis]	ACLF: 11.6%; Acute decompensation: 9%; Mortality rate: 43% among decompensated cirrhotics	Predictors of sever liver injury: In CLD without cirrhosis, diabetes [57.7% *vs* 39.7%, OR: 2.1 (1.1-3.7)]; In cirrhotics, obesity [64.3% *vs* 17.2%, OR: 8.1 (1.9-38.8). Predictor of mortality: CTP score of 9 or more at presentation [AUROC 0.94, HR:19.2]
Xiang *et al*[54]	Retrospective cohort study of 267 patients	Severe COVID-19: 15%; High-flow oxygen support: 14%; Mechanical ventilator support: 4%; Death: 1	Predictor of severity: FIB-4 > 3.25

ACLF: Acute-on-chronic liver failure; ALD: Alcohol related liver disease; AUROC: Area under the receiver operator curve; BMI: Body mass index; COVID: Coronavirus disease; CLD: Chronic liver disease; CCI: Charlson's comorbidity index; CLIF OF: Chronic liver failure consortium organ failure; CLIF-C: Chronic liver failure consortium; COPD: Chronic obstructive pulmonary disease; CTP: Child-Turcotte-Pugh score; FIB-4: Fibrosis 4; HCC: Hepatocellular carcinoma; MELD Na: Model for end stage liver disease sodium score; MODS: Multiorgan dysfunction syndrome; NACSELD: North American Consortium for the Study of End-Stage Liver Disease.

Table 2 Clinical outcomes in patients with underlying alcoholic liver disease during coronavirus disease 2019

Ref.	Study	Outcomes
Deutsch-Link *et al*[23]	Retrospective analysis - pre (January 2017 to December 2017) and post-COVID era (February 2020)	Increase in the monthly percent change of crude ALD-related mortality: Males: 3.18 *vs* 0.96; Females: 3.8 *vs* 1.18
Yeo *et al*[26]	16813 patients with ALD before and 11625 during the pandemic	OR of death in ALD - 18.7 during the pandemic *vs* 0.995 in the pre-pandemic era

ALD: Alcohol related liver disease; COVID: Coronavirus disease; LT: Liver transplant; NASH: Non-alcoholic fatty liver disease; OR: Odds ratio; UNOS: United network for organ sharing.

30] (Table 3). Studies have demonstrated that patients with features of metabolic syndrome including higher body mass index (BMI) and waist circumference and presence of diabetes and hypertension had adverse effects on outcomes[29-31].

Patients with COVID-19 and underlying NAFLD have multiple associated comorbidities including diabetes, hypertension, dyslipidemia, and obesity. These factors have been independently associated with poor outcomes in patients with COVID-19[32,33]. Different studies have estimated different

Table 3 Studies evaluating outcomes and predictors of severity in non-alcoholic fatty liver disease with coronavirus disease 2019

Ref.	Type of study	Patients included	Outcomes	Predictors
Chang *et al* [27]	Retrospective study	3122 COVID-19 cases [FLI (fatty liver index) was calculated]	Severe disease: 223 (7.14%); Mechanical ventilation: 82 (2.63%); ICU admission: 126 (4.04%) High-flow oxygen therapy: 75 (2.40%); Death: 94 (3.01%)	FLI associated with severe complications from COVID-19 (aOR: 1.77)
Vrsaljko *et al*[28]	Prospective observational study	120 NAFLD patients (of 216 COVID-19 patients)	Patients with NAFLD had more high-flow nasal cannula or non-invasive ventilation (21.66%, *vs* 10.42%), longer duration of hospitalization (10 d *vs* 9 d), and more pulmonary thromboembolism risk (26.66% *vs* 13.54%)	Delayed time to recovery (HR: 0.64); Increased pulmonary thrombosis (OR: 2.15) among NAFLD patients
Velazquez *et al*[29]	Retrospective cohort study	359 NAFLD patients as per Dallas steatosis index (DSI) out of total 470 cases	Lower oxygen saturation levels; Higher D-dimer; Elevated LDH; Higher lymphocyte count among NAFLD	On multivariable analysis, NAFLD is a predictor of mortality (OR: 2.13)
Madan *et al* [36]	Retrospective observational case control study	289 NAFLD patients among 446 cases	Similar in-hospital mortality, ICU requirement, ventilatory support, and duration of ICU and hospital stay	Predictors of in-hospital mortality: High total leukocyte count (OR: 1.082); High FIB-4 (OR: 1.606)
Chen *et al* [34]	Retrospective single centre cohort study	172 patients with hepatic steatosis (HS) among 342 cases	19% of patients expired; > 50% required ICU admission	Increased intubation (aOR: 2.75); Vasopressor requirements (aOR: 1.22); ALT > 5 x ULN (aOR: 7.09)
Sarin *et al* [37]	Retrospective multinational cohort	113 NAFLD cases out of 228 cases (185 without cirrhosis and 43 with cirrhosis)	Higher risk of acute liver injury in obese cirrhotics *vs* normal weight patients (OR: 8.9)	Higher risk of liver injury: In non-cirrhotics, diabetes [57.7% *vs* 39.7%, OR: 2.1]; In cirrhotics, obesity, [64.3% *vs* 17.2%, OR: 8.1]
Li *et al*[31]	Observational study	Genome-wide meta-analysis (GWMA) of 3711 NAFLD cases and 426252 controls from United Kingdom Biobank data	No significant association of NAFLD and severe COVID-19 after adjusting for confounders	Predictors of severity: Body mass index (OR: 1.73); Waist circumference (OR: 1.76); Hip circumference (OR: 1.33)
Yao *et al* [30]	Retrospective study in China	86 COVID-19 patients with NAFLD	NAFLD patients with advanced fibrosis (NFS > -1.5) had more fever (81.6% *vs* 50%), shortness of breath (18.4% *vs* 0%), and severe disease (28.9% *vs* 2.1)	Predictors of severe disease: Diabetes (OR: 8.264); Advanced liver fibrosis [NFS > -1.5] (OR: 11.057)
Targher *et al*[35]	Retrospective study	94 NAFLD cases among 310 patients		Factors associated with severity: Increasing FIB-4 (aOR: 1.90); Increasing NFS (aOR: 2.57)

aOR: Adjusted odds ratio; ALT: Alanine transaminase; AST: Aspartate aminotransferase; COVID: Coronavirus disease; CLD: Chronic liver disease; FIB-4: Fibrosis 4; NFS: NAFLD fibrosis score; FLI: Fatty liver index; GWAS: Genome wide association studies; ICU: Intensive care unit; LDH: Lactate dehydrogenase; NAFLD: Non-alcoholic fatty liver disease; TLC: Total leukocyte count; ULN: Upper limit of normal.

prevalence of comorbidities in NAFLD. The prevalence of obesity, diabetes mellitus, and hypertension was 47%, 27%, and 31%, respectively, in NAFLD patients in a study, in which 27% of patients required non-invasive mechanical ventilation, 44% required ICU admission, and 27% were expired[29]. Another study showed that 69% of patients had hypertension, 43% had diabetes, 47% had dyslipidemia, 85% were overweight, and 52% were obese, and out of total 342 patients, > 50% required ICU admission and 19% were expired[34]. Thus, the presence of comorbidities is associated with poor outcomes in patients with NAFLD and COVID-19.

Advanced fibrosis in patients with NAFLD was associated with more severe COVID-19 and adverse outcomes with an almost two-fold increased risk of severity in patients with an FIB-4 score of more than 2.67[35,36]. Another study showed that presence of cirrhosis with diabetes was associated with poor outcomes in COVID-19 patients with higher risk of liver injury (OR: 2) and NAFLD was the most common cause of CLD in this study[37]. The rate of severe illness was significantly higher in patients with advanced fibrosis [NAFLD fibrosis score (NFS) > -1.5] compared to those with non-advanced fibrosis with an NFS < -1.5 (28.9% *vs* 2.1%, $P < 0.001$)[30]. Therefore, the underlying degree of fibrosis in NAFLD patients and various components of metabolic syndrome has been associated with poor outcomes as compared to those without significant fibrosis.

Hepatitis B

Patients with chronic hepatitis B (CHB) had a higher rate of ICU admission (HR: 1.86) and increase risk of mortality (HR: 3.19) among hepatitis B virus "e" antigen positive (HBeAg+) CHB cases as shown in Table 4[8,38,39]. Another study showed that although the mortality rate was higher among patients with hepatitis B, it was not statistically significant after adjusting for other factors[40]. The study had shown that patients with COVID-19 had a lower positive rate for CHB[41,42]. One of the postulated

Table 4 Studies showing outcomes and predictors of severity in hepatitis B virus-infected patients with coronavirus disease 2019

Ref.	Study	Patients	Results	Predictors
Yang *et al* [38]	Single centre retrospective study	Patients with HBV infection out of 2899 COVID patients. Resolved hepatitis B (n = 503); HBeAg (-) CHB/infection (n = 44); HBeAg (+) CHB/infection (n = 55); HBV reactivation (n = 6)	HBeAg (+) CHB/infection and HBV reactivation were associated with more abnormal liver function, severe disease, longer ICU stay, and death	Increased ICU admission (HR: 1.86) and mortality (HR: 3.19) in HBeAg (+) CHB/infection
Choe *et al* [40]	Nationwide population-based cohort study	676 chronic HBV infection cases (19160 COVID-19 cases)	Mortality in HBV infected *vs* non-infected patients with COVID-19: 8.2% *vs* 13.5%	No difference in mortality, ICU admission, or organ failure
Wang *et al*[8]	Multicentre retrospective cohort study	109 CHB and 327 non-CHB patients with COVID-19	CHB *vs* non-CHB patients: Severe disease (27.5% *vs* 12.84%) and more dyspnoea (55.05% *vs* 43.12%) and mechanical ventilation requirement (22.49% *vs* 7.95%) in CHB	Increased mortality in CHB patients (OR: 3.748). Predictors of mortality: AST; ALT; ALP; Bilirubin; LDH; Elevated D-dimer. Protective effect: ALB (HR: 0.13); ALB/GLO (HR: 0.123)
Yip *et al*[44]	Retrospective cohort study	Current (353) and past HBV infection (359) out of total 5639 COVID cases	Mortality in current HBV *vs* past HBV *vs* non-HBV infection: 2.3% *vs* 5.8% *vs* 2.2%	Acute liver injury associated with mortality (aHR: 2.45), more than current (aHR: 1.29) or past (aHR: 0.90) HBV infection
Kang *et al* [42]	Nationwide cohort study	7723 COVID-19 cases and 46231 controls	Lower SARS-CoV-2 positivity rate in CHB, after adjusting for comorbidities (aOR: 0.65)	Reduced SARS-CoV-2 positivity (aOR: 0.49) on antivirals
Liu *et al*[39]	Retrospective cohort study	347 COVID-19 patients (21 *vs* 326 with or without chronic HBV infection)	Severe COVID-19 in 30% *vs* 31.4% in the HBV *vs* non-HBV group	Similar SARS-CoV-2 clearance and severe COVID-19

ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COVID: Coronavirus disease; CHB: Chronic hepatitis B; GLO: Globulin; HBV: Hepatitis B virus; LDH: Lactate dehydrogenase.

reasons for this finding is that patients with CHB mount a reduced T cell mediated immune response termed as 'immune exhaustion' which may reduce the extent of cytokine storm seen in patients with COVID-19[41]. The major predictor of poor outcomes was positivity for HBeAg suggestive of active viral replication and ongoing liver injury in addition to liver injury inflicted by SARS-CoV-2[38]. Reactivation of hepatitis B virus (HBV) with anti-IL6 therapy (tocilizumab) was found to be 3.3% in a systematic review[43]. In short, patients with HBeAg positive CHB are more likely to have a poor outcome in terms of hospitalization requirement and mortality[44] and some specific treatment for COVID-19 will lead to reactivation of HBV like anti-IL6 antibody (tocilizumab).

Hepatitis C

Hepatitis C predominantly causes a chronic indolent infection. Various management aspects of hepatitis C have been impacted during the COVID-19 pandemic. The impact of COVID-19 on chronic hepatitis C depends on the extent and severity of underlying CLD as discussed previously. A study by Ronderos *et al*[45] showed an increased mortality among hepatitis C virus (HCV)-infected patients, and increasing age, elevated D-dimer, ferritin, and FIB-4 score were identified as predictors on multivariate analysis. However, more data are required to draw a conclusion regarding the effect of HCV infection on COVID-19, excluding the severity of liver disease.

Autoimmune hepatitis

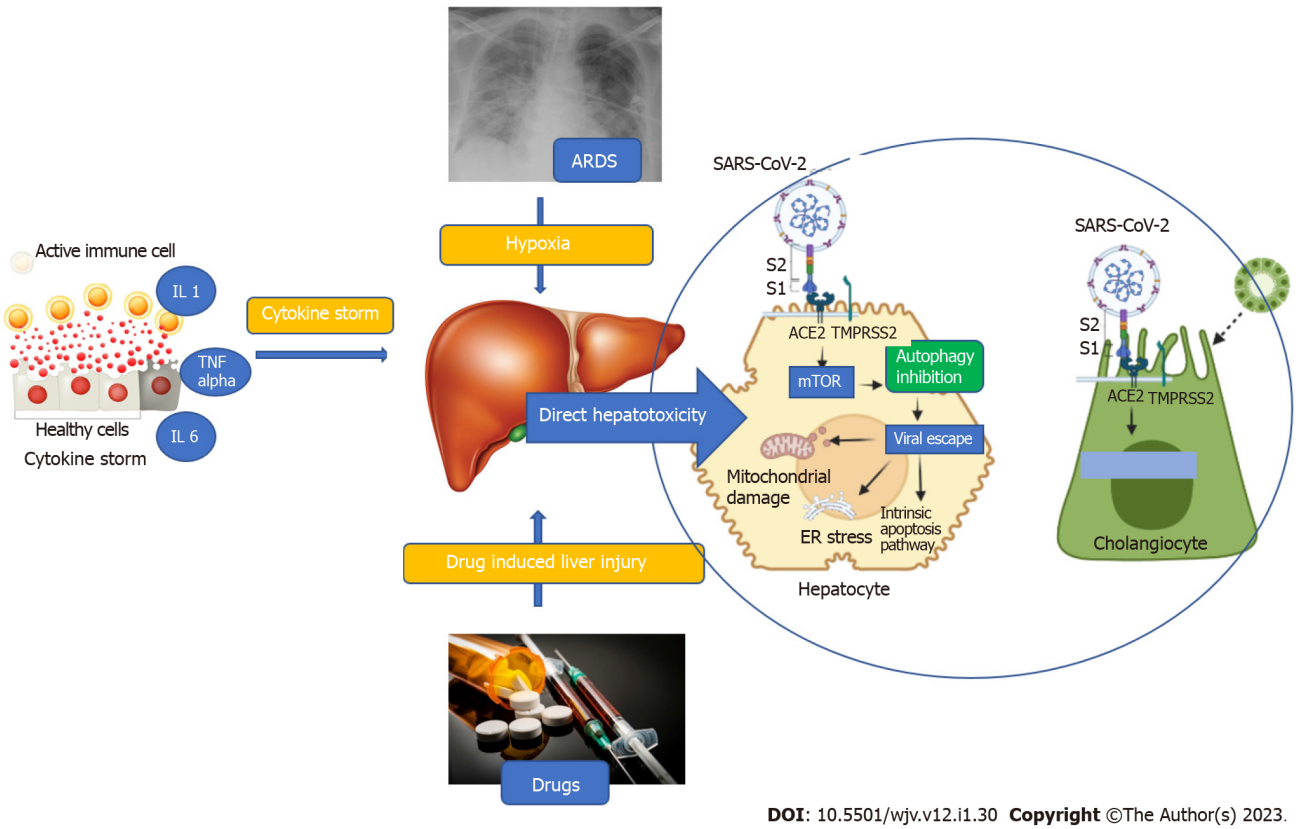
Autoimmune hepatitis (AIH) patients are a vulnerable group due to underlying liver disease, use of immunomodulators, and associated systemic diseases. Different studies have tried to identify the risk factors of severity and outcomes in these patients including those on immunosuppressants. Di Giorgio *et al*[46] demonstrated that the predictors of outcomes were same in AIH as in the general population, including increasing age and presence of comorbidities. Cirrhosis was the most important predictor of mortality among patients with underlying autoimmune liver diseases (OR: 17.46) in a study[47,48]. Among cirrhotics, outcomes worsened with progressive underlying liver dysfunction measured by increasing Child-Pugh-Turcotte (CTP) scores with an OR of mortality increasing from 42 to 69 in Child-Pugh classes B and C, respectively[49] (Table 5).

The effect of immunosuppressive treatment on outcomes in COVID-19 patients has shown some diverging results. A study by Efe *et al*[50] in 254 AIH patients showed that systemic glucocorticoids (aOR: 4.73), thiopurines (aOR: 4.78), mycophenolate mofetil (MMF) (aOR: 3.56), and tacrolimus (aOR: 4.09) were associated with a more severe COVID-19 course. The study showed that outcomes were worse in patients on steroids at a prednisolone equivalent dose of > 5 mg/d. Similarly, another study showed that baseline treatment with steroids, thiopurines, MMF, and tacrolimus were associated with a severe disease course[51]. Therefore, patients with AIH having cirrhosis and stage of cirrhosis reflected

Table 5 Studies evaluating outcomes and predictors in autoimmune hepatitis with coronavirus disease 2019

Ref.	Study	Patients	Results	Predictors of outcomes
Efe *et al* [47]	Multicentre retrospective study from 34 centres in Europe and the Americas	110 AIH patients	Acute liver injury: 37.1%	Predictor of severe COVID-19: cirrhosis (OR: 17.46); Immunosuppression not associated with severe COVID-19 (OR: 0.26)
Di Giorgio *et al*[46]	Phone based survey in tertiary centre	adult AIH patients: AIH (n = 97, 96%); PSC/AIH overlap (n = 2, 2%); PBC/AIH (n = 2, 2%); 4 patients had confirmed COVID	Severe COVID: 1; Death: 1	No difference in risk factors of mortality
Marjot *et al*[49]	Retrospective data from three international registries	70 AIH cases among 932 patients with CLD with COVID-19	No differences between AIH and non-AIH related CLD in Hospitalization (76% *vs* 85%); ICU admission (29% *vs* 23%); Death (23% *vs* 20%)	Factors predicting mortality in AIH: Age (OR: 2.16/10 yr); Child-Pugh class [B (OR: 42.48) and C (OR: 69.30)] cirrhosis
Efe *et al* [50]	Retrospective data from 15 countries	254 AIH patients	Hospitalization: 94 (37%); Death: 18 (7.1%)	Factors associated with COVID-19 severity: Systemic glucocorticoids (aOR: 4.73); Thiopurines (aOR: 4.78); Mycophenolate mofetil (aOR: 3.56); Tacrolimus (aOR: 4.09)

AIH: Autoimmune hepatitis; COVID: Coronavirus disease; CLD: Chronic liver disease; ICU: Intensive care unit; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.



DOI: 10.5501/wjv.v12.i1.30

Figure 1 Pathophysiology of liver involvement in coronavirus disease 2019.

by CTP score are predictors of adverse outcomes. The use of immunosuppressive drugs is also associated with worse outcomes among COVID-19 patients with AIH.

Severity of CLD: One of the most important determinants of clinical outcomes is the presence and severity of underlying cirrhosis as shown in various studies. There was an increasing risk of mortality with increasing CTP score ranging from additional +2% in Child-Pugh A to +20% in Child-Pugh B and +38% in Child-Pugh C. Similarly, another study showed that Child-Pugh score was associated with mortality[52]. CTP score of more than 9 was associated with a high mortality (HR: 19) in another study

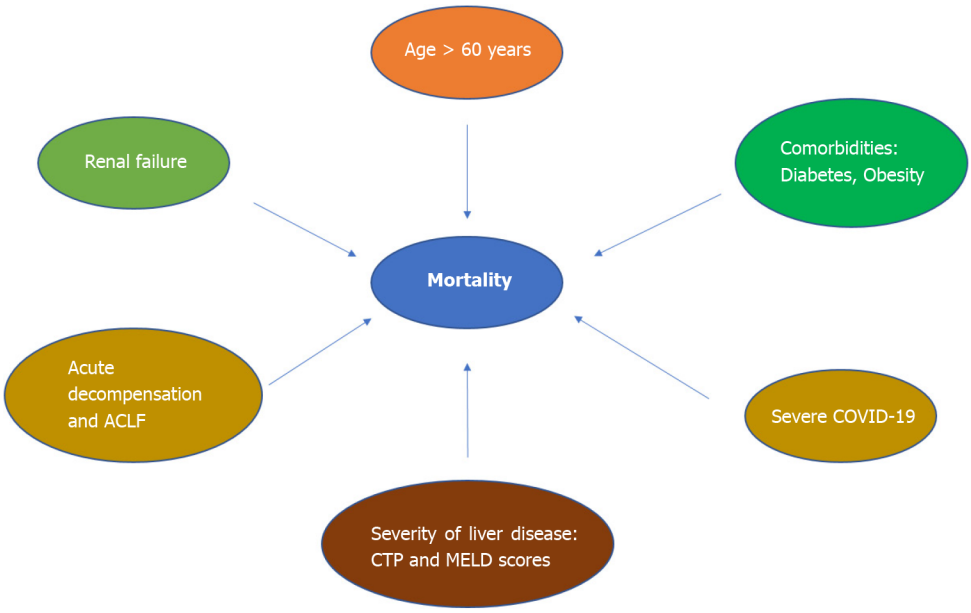


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Figure 2 Predictors of mortality in pre-existing chronic liver disease with coronavirus disease 2019. ACLF: Acute-on-chronic liver failure; CTP: Child-Turcotte-Pugh score; COVID-19: Coronavirus disease 2019; MELD: Model for end stage liver disease.

[37]. Mortality in cirrhotics increased with worsening chronic liver failure consortium score (HR: 1.42), which is an indicator of hepatic and extrahepatic organ failures[53]. Model for end stage liver disease (MELD) score more than 25 is associated with a two-fold increase in mortality as demonstrated by univariate analysis in a study from India[24]. Similarly, a study from Italy showed that MELD score more than 15 was associated with a higher mortality (HR: 5.18) at 30 d[53]. Various factors associated with adverse outcomes in cirrhosis are summarized in Table 1. Therefore, the currently available evidence suggests that increasing severity of underlying CLD is associated with poor outcomes including mortality.

Degree of liver fibrosis: A study from China showed that higher FIB-4 score, which is a marker of liver fibrosis, was associated with a more severe COVID-19 disease[36] with greater requirement of high flow oxygen, prolonged hospitalization, and even death[54]. They postulated that FIB-4 score could be a prognostic marker of disease outcomes but more data is required to increase external validity. Similar findings were seen in a meta-analysis which showed that elevated FIB-4 score was associated with severe COVID-19 and mortality[54]. Hence, the degree of liver fibrosis is an important determinant of disease outcome with higher degree of fibrosis being negatively associated with outcomes[55].

Comorbidities: Another predictor of mortality was the presence of comorbidities, with the most common being diabetes, obesity, dyslipidemia, and hypertension[16-18,37]. This may be due to a more severe COVID-19 infection seen in this subgroup of patients irrespective of the presence of cirrhosis. A prospective study showed that a BMI of more than 30 was associated with mortality[17]. Another study showed that diabetes and hypertension were predictors of mortality[18]. A study from Asia showed that diabetes was associated with severe liver injury without cirrhosis (OR: 2.1), as was obesity in cirrhotics (OR: 8.1)[37]. Therefore, the presence of comorbidities increases the severity of liver disease and has unfavorable outcomes.

Severity of COVID-19: Some studies showed that respiratory failure was the main cause of mortality among cirrhotic COVID-19 patients. Outcomes were poor for patients with higher CURB-65 (confusion, uremia, respiratory rate, blood pressure, age > 65) scores, substantiating the fact that respiratory failure was associated with mortality[44]. In this study, they observed that CURB-65 score was associated with a 5-fold increased risk of mortality[52]. Severe COVID-19 with respiratory failure was a significant predictor of mortality (HR: 2.5) in patients with chronic liver disease in another study[24]. Henceforth, more severe COVID-19 is associated with an increased risk of liver injury and mortality.

Biomarkers: A recent study evaluated the role of inflammatory biomarkers in risk-stratifying the patients with regard to liver injury and mortality in 221 COVID-19 patients[56]. They included CRP, IL6, D-dimer, and blood lymphocyte counts as inflammatory biomarkers, which were all significantly elevated in the patients who subsequently expired as compared to survivors. They found that patients who showed rising aspartate transaminase and alkaline phosphatase over time, as markers of liver

injury, had a higher mortality. These correlations attenuated with age. Thus, inflammatory biomarkers may serve as predictors of poor outcomes, but more studies are required for identification of biomarkers and their validation.

Miscellaneous factors: Some other factors affecting the severity and outcomes of COVID-19 have also been seen in some studies. As discussed previously, obesity and physical inactivity have been associated with worse outcomes. Recently, it has been shown that obesity, physical inactivity, and diet rich in simple sugars predisposes to chronic low-grade inflammation in the mucosal barrier along with microbial dysbiosis. This state of chronic inflammation has been shown to be associated with worse clinical outcomes in COVID-19 patients[57]. Similarly, obese individuals with excessive visceral fat have excessive proinflammatory adipokines that have been postulated to be associated with poor outcomes [57]. Extrapolating the role of inflammation, patients with CLD have low level endotoxemia with increased gut permeability which may be associated with unfavorable outcomes; however, concrete evidence for the same is lacking[58]. A summary of risk factors associated with poor outcomes is shown in Table 6.

PREDICTORS RELATED TO OUTCOMES OF UNDERLYING CHRONIC LIVER DISEASE

Acute decompensation and acute-on-chronic liver failure

In patients with CLD, acute decompensation and acute-on-chronic liver failure (ACLF) usually develop due to a precipitating factor, with infections being the most common such factor. COVID-19 may act as a trigger for such decompensation. Marjot *et al*[22] observed in their study that the major predictor of decompensation was Child-Pugh class, with a rate of decompensation of 30%, 56%, and 64% observed in Child-Pugh A, B, and C patients, respectively. Hepatic decompensation at baseline was associated with an increased mortality (HR: 2.91) in another study[18]. Acute decompensation developed in 9% and ACLF in 11.6% among 43 cirrhotic patients, and CTP score was the major predictor of mortality, with a CTP score of 9 or more at presentation associated with high mortality (HR, 19.2)[37]. Another study showed that acute decompensation developed in 62.9% and ACLF in 29% with a mortality as high as 72% among ACLF patients, with major predictors of mortality being MELD score, leukocytosis, elevated creatinine, and COVID-19 severity on multivariate analysis[24]. The mortality in grades 1, 2, and 3 ACLF patients was 56.3%, 50%, and 93.3%, respectively (P = 0.001) in the same study. In a prospective study of 96 cirrhotic patients, 61.4% developed acute decompensation and ACLF in 55% according to CLIF-C criteria. The major predictors of mortality were CLIF-C organ failure score (AUROC: 0.85) and MELD Na score (AUROC: 0.70)[17].

These observations suggest that SARS-CoV-2 infection may be a triggering factor for decompensation and subsequent ACLF in cirrhotic patients by triggering a pro-inflammatory cascade as discussed earlier. Possible factors that can be postulated could be a proinflammatory milieu, multi-organ dysfunction due to severe COVID-19, direct hepatotoxicity to a compromised liver, or sepsis. In summary, COVID-19 patients with underlying CLD are more prone to develop acute decompensation and may progress to ACLF. The major predictors of these outcomes are the baseline severity of liver disease reflected by CTP and MELD score, and the severity of hepatic and extra-hepatic organ failure as indicated by CLIF-C scores.

Upper gastrointestinal bleeding

The data on the rate and risk factors of variceal bleed in patients with COVID-19 positive patients with underlying CLD is scarce. Upper gastrointestinal (UGI) bleeding developed in 24/1342 (1.8%) of all patients admitted with COVID-19[24]. Most of bleeding episodes (88%) were variceal bleeding in patients with cirrhosis with no rebleeding or death at 5 d with medical management alone[24]. The same group also observed that the initial control of UGI bleeding was achieved in all patients with no one requiring an emergency endoscopy. Thus, emphasizing the utility of conservative management of variceal bleeding with endoscopic therapy is only needed on a case-to-case basis[25].

Another study from Hong Kong showed that although peptic ulcer bleeding was the most common cause of UGI bleeding both before (66.0%) and during (66.1%) the COVID-19 pandemic, there was a significant increase in the proportion of patients with UGI bleeding with variceal bleeding after COVID-19 (5.3% *vs* 10.5%, P < 0.01)[51]. Patients had significantly lower hemoglobin (7.5 *vs* baseline 8.3 g/dL) and higher requirement for blood transfusion (64.5% *vs* baseline 50.4%) but had similar rates of all-cause mortality (6.9% *vs* 7.1%) and rebleeding (6.7% *vs* 5.1%)[59]. There was no significant difference in the timing of endoscopy after admission or the percentage of patients requiring endoscopic hemostasis (77.3% *vs* 76.3%) before and during the COVID-19 pandemic[59]. Thus, patients with variceal bleeding in the COVID-19 pandemic have similar management principles as the pre-COVID-19 era.

HCC

The major impact of the COVID-19 pandemic on patients with HCC was multifactorial. A decline of

Table 6 Risk factors associated with adverse outcomes in coronavirus disease 2019 affected patients with chronic liver disease

Demographics	Etiology	Clinical parameters	Underlying disease severity	Biochemical parameters
Age > 60 yr; Hispanic and black ethnicity; Diabetes mellitus; Hypertension; Obesity	Alcohol; HBeAg positivity among CHB; AIH on immunosuppressants	Respiratory failure: CURB-65 score; Decompensation at baseline; ACLF at presentation	CTP score; MELD score; FIB-4 index	Elevated creatinine; Leucocytosis; AST levels; ALT levels; CRP

ACLF: Acute-on-chronic liver failure; AIH: Autoimmune hepatitis; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; CTP: Child-Turcotte-Pugh score; CURB-65: Confusion, Uremia, Respiratory rate, BP, age > 65 years, FIB-4: Fibrosis 4 score; MELD: Model for end stage liver disease.

26.7% in new HCC cases was reported during the pandemic compared to the pre-pandemic era[60]. Advanced BCLC stage and higher tumor burden at diagnosis were due to resource limitation and lack of physical appointments, and were associated with a higher incidence of spontaneous tumoral hemorrhage[61]. Delayed treatment initiation longer than 1 month (21.5% *vs* 9.5%; $P < 0.001$) due to re-allocation of services for the pandemic was reported[62]. Muñoz-Martínez *et al*[63] reported an increase in mortality rate proportional to advanced BCLC stage. Thus, the impact of COVID-19 on patients with HCC is predominantly due to delayed diagnosis, delayed presentation, delay in initiating treatment, and availability of imaging and locoregional or transplant facilities.

COVID-19 waves and impact on liver disease

Some studies identified the impact of different waves of the pandemic on liver disease. The waves of COVID-19 occurred due to mutations and spread of newer variants of the virus that evaded the immune response. The second wave was predominantly caused by delta variant[64]. Nawghare *et al*[65] showed that the second wave had more number of acute decompensations and the factors predicting outcomes were renal dysfunction and elevated D-dimer. Elhence *et al*[24] compared outcomes in the first wave to those in the second wave and reported that although the disease severity was more during the second wave but the mortality rate and duration of hospital stay were similar with no significant differences.

CONCLUSION

COVID-19 has a major impact on patients with pre-existing CLD in the form of severe COVID infections and worsening of underlying hepatic disease. The predictors of poor outcomes of COVID-19 patients with underlying CLD are multiple and have been different in numerous studies across the globe, with the most important predictor being presence of cirrhosis with outcomes progressively deteriorating with increasing severity of underlying liver dysfunction estimated by CTP and MELD scores. These are the subgroups of patients who are more prone to risk of decompensation, further decompensation, and ACLF.

The predictors may be related to demographic factors, with increasing age and black and Hispanic ethnicity being associated with poor outcomes. Another major predictor of the severity of COVID-19 is cytokine storm, which may even lead to multiorgan failure, with the liver being one of the organs involved. Other predictors include the presence of comorbidities, whose prevalence is estimated to be around 30%-50% in various studies, and these have been associated with poor outcomes even in the absence of underlying liver disease. Major comorbidities found in studies that are negatively associated with outcomes include diabetes mellitus, hypertension, and obesity. The COVID-19 pandemic also adversely affected routine services for patients with hepatitis B, hepatitis C, and HCC, which will have long-term impacts in the form of increased disease burden, delayed implementation of eradication programs, and poor outcomes in the times yet to come.

FOOTNOTES

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MINIREVIEWS

Commentary on COVID-19-induced liver injury in various age and risk groups

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Abstract

Towards the end of 2019, a new type of coronavirus, severe acute respiratory syndrome, emerged in the city of Wuhan in China's Hubei Province. The first occurrence was described as a case of pneumonia. Coronavirus disease 2019 (COVID-19) can progress primarily with symptoms varying from a mild upper respiratory tract infection to severe pneumonia, acute respiratory distress syndrome, and death. Determining the mechanisms of action of this virus, which can affect all systems including gastrointestinal, is vital for predicting the progression of the disease and managing its treatment. It is important to demonstrate the mechanisms of action of COVID-19 in patients without a previously known chronic or systemic disease. Although there is still no specific treatment for the virus, various algorithms have been created. As a result of the applied algorithms, the response to the treatment was satisfactory in some patients, while unexpected side effects occurred in some patients. It helps to clarify whether the unwanted effects that occur are due to the effect of the disease or the side effects of the drugs used in the treatment. There is currently increasing interest in COVID-19 interaction with liver tissue. Therefore, we would like to discuss the details of liver injury/dysfunction in the current literature.

Key Words: COVID-19; Liver injury; SARS-CoV-2

Core Tip: Coronavirus disease 2019 (COVID-19) can progress primarily with symptoms ranging from a mild upper respiratory tract infection to severe pneumonia, hepatic injury, and even death. There is currently increasing interest in COVID-19 interaction with liver tissue. We would like to discuss the details of liver injury/dysfunction in COVID-19 in the current literature.

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INTRODUCTION

Hepatotropic viruses replicate in their main target liver, which can be involved in these viruses' infections. The host is mostly afflicted as a consequence of the immune response to viruses like hepatitis A, hepatitis B, hepatitis C, and hepatitis E viruses which can be a known reason for hepatitis and liver damage[1]. In non-hepatotropic viral infections like severe acute respiratory syndrome (SARS), Epstein-Barr virus infection, *etc.*, it is known that the liver is mainly affected as a result of immune infiltrates and reactions that occur as a result of the virus-induced immune system response. The result of this effect can range from mildly irregular liver biochemistry to fulminant hepatic failure. The liver is also affected by infections such as adenovirus, cytomegalovirus, and other opportunistic viruses in people with immunocompromised and other immune system disorders[2].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is identified to result in severe acute respiratory syndrome through its host cell receptor, angiotensin-converting enzyme 2 (ACE-2). As a part of multi-organ involvement, cardiac, kidney, and liver injury can be seen[3]. The fact that coronavirus disease 2019 (COVID-19) is more important than diseases caused by many other viruses and needs to be investigated is its high mortality. In a meta-analysis of 3772 patients acquired from 326 studies examining SARS-CoV-2 and liver damage, it was demonstrated that there is a link between liver dysfunction and fatality[4]. Interestingly, besides the respiratory system, a significant proportion of SARS and COVID-19 patients showed signs of liver damage of varying degrees, the mechanism and effect of which have yet to be determined (Table 1).

PREVALENCE OF LIVER INJURY IN COVID-19

The prevalence of liver damage in COVID-19 patients differed from 16% to 29%. A meta-analysis showed that the rate of liver dysfunction among COVID-19 cases was 27.4%[5,6]. Fu *et al*[7] collected data from 355 patients in China and demonstrated that 39.6% of COVID-19 cases were afflicted with cholestasis, 51.9% with hypoproteinemia, and 39.0% with hepatocellular injury at presentation.

SUPPOSED MECHANISMS OF LIVER INJURY

The etiology of acute liver injury in COVID-19 patients remains unclear but is likely to be multifactorial (Table 1). It is supposed that it may be due to the direct invasion of hepatocytes by viruses, immune-mediated damage, the toxicity of drugs utilized in the treatment, hypoxia, ischemia, endothelial dysfunction, microthrombi formation, systemic inflammatory response syndrome, sepsis, or exacerbation of underlying liver disease[8].

ACE-2 receptors can be demonstrated in hepatic cholangiocytes and hepatocytes. These receptors make the gastrointestinal system a target for SARS-CoV-2 infection, which can vigorously infect and reproduce. The strong affinity of the SARS-CoV-2, particularly to cholangiocytes, results from a high binding rate to the ACE-2 receptor, which suggests that it is related to impaired hepatic function[9,10]. In a study, cell type-specific expression of ACE-2 was investigated in healthy liver tissues. The researchers showed that the virus can bind directly to ACE-2-positive cholangiocytes, but not hepatocytes. This finding suggests that liver abnormalities of SARS and COVID-19 patients are due to cholangiocyte dysfunction, not hepatocyte damage. What is confusing at this point is that in many studies conducted in China, elevation in aspartate aminotransferase (AST) instead of γ-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) indicates cholangiocyte and bile duct damage [11]. But it should be in mind that this occurs only infrequently on hepatocytes, nevertheless it may be upregulated on hepatocytes during periods of physiologic stress[12]. Myalgia or myositis are also common symptoms in COVID-19 patients. Therefore, it may be necessary to examine the elevations in lactate dehydrogenase and creatinine kinase in COVID-19. The AST elevations observed in this circumstance can be ascribed to some degree to muscle injury[13].

In addition, it is known that patients with COVID-19 have severe hypoxia, and this hypoxemia significantly affects all organs, including the liver. As a part of SARS-CoV-2 infection in severe acute respiratory syndrome, capability to trigger severe hypoxia that was recalcitrant to the management of high inspired fractions of oxygen and high mean airway pressures was observed. Hypoxic hepatic damage is noticeable by alanine aminotransferase (ALT)/AST elevations owing to oxygen imbalance.

Table 1 Events in the liver from a broad perspective of severe acute respiratory syndrome coronavirus 2 infection

Effect	Mechanism	Result	Outcomes and morphological changes
SARS-CoV-2 virus	Genomic translations and replication	More viruses in circulation	Inflammation features. Usually, the biliary intrahepatic tree and bile duct did not show any significant histological alteration. Actin smooth muscle antibodies existed in pericytes which were in portal vein walls and adventitial areas
Viral proteins of SARS-CoV-2	SIRS -> stimulate cytokine storm	Increased TNF-α, IL-6, IL-1β, IL-2, IL-8, CCL2, CCL3, CCL5, CXCL10 levels. Decreased ($CD4^+$) T cell and NK cell counts	Increase in the number of portal vein branches associated with lumen massive dilatation and focal periportal abnormal vessels. Portal vein endotheliitis (fragmented smooth muscle layer). Scattered portal and lobular lymphocytes. Extremely activated Kupffer cells with large cytoplasm containing necrotic debris
Hypoxia	Hypoxic ischemic injury of all organs and also liver	Decreased SpO2 levels, mitochondrial dysfunction, and hypoxic hepatocytes express higher ACE-2 levels	Partial or complete luminal thrombosis of the portal and sinusoidal vessels, focal portal vein parietal fibrosis, enlarged and fibrotic vessels. A diffuse network of sinusoids decorated by CD34 suggests a disturbed circulation of blood within the liver
Drugs (antivirals, immune stimulants)	Liver damage	Increase in ALT, AST, LDH, CRP, D-dimer, ferritin, and bilirubin levels and a decrease in albumin levels	Portal fibrosis, lobular and mild portal inflammation
Drugs and viral proteins	The cytopathic effect, oxidative imbalance	Apoptosis and steatosis	Small and/or large droplets of steatosis in hepatocytes

ACE-2: Angiotensin-converting enzyme 2; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SIRS: Systemic inflammatory response syndrome; TNF-α: Tumour necrosis factor-alpha; IL: Interleukin.

This shows that severe hypoxia may be one of the pathophysiological elements of hepatic injury in COVID-19[13,14].

Therapeutic agents, *e.g.*, hydroxychloroquine, immune modulators (tocilizumab, steroids, and anakinra), anti-retroviral drugs (remdesivir, favipiravir, and lopinavir), antibiotics (azithromycin and ceftriaxone), and antipyretics (paracetamol and ibuprofen), which are utilized in the management of COVID-19, also have hepatotoxic effects. Patients are recommended to have regular follow-ups who have management with single and/or combined use of these potential hepatotoxic drugs for possible hepatic injury[8,13].

The existence of viral particles in the feces of infected cases indicates that the gastrointestinal system is affected by SARS-CoV-2. This is another reflection that demonstrates the possible direct impact of SARS-CoV-2 on liver tissue, provided the close association between the bowel and the liver. The exact mechanisms of this suggested direct injury route are yet to be explained[15]. Even the gut microbiome is important at this point since ACE-2 is also expressed in the luminal intestinal epithelium. With the attachment of SARS-CoV-2 to the ACE-2 receptor, intestinal permeability and inflammation increase. All these events increase the risk of bacterial translocation, which leads to dysregulation of the gut microbiome and, *via* this pathway, to Gram-negative sepsis, through portal circulation[16]. This translocation is also partially responsible for liver damage in COVID-19 patients[17].

PATHOGENESIS

SARS-CoV-2 is a new positive-strand RNA virus from the beta coronavirus family and has a glycolipid envelope. The virus connects to the host's ACE-2 receptor to start an infection. The viral access and reproduction process begins. ACE-2 is existing in cardiomyocytes and most endothelial cells except for those lining the liver sinusoids, lungs, bile ducts, bowels, and kidneys[18]. The spike protein (S protein) is located on the SARS-CoV-2 surface that will attach to ACE-2. After binding to the cell membrane, the virus is detained when the viral envelope fuses with the host membrane. Moreover, the type 2 transmembrane serine protease, which is present in host target cells (predominantly alveolar epithelial type II cells), stimulates viral uptake. The viral genome accesses the cytoplasm and is converted to produce new virions. After the virus enters the cell by fusion with the host membrane, an antiviral immune response begins with the viral nucleocapsid proteins remaining on the cell surface. These viral nucleocapsid proteins are recognized by antigen-presenting cells. Viral antigens are passed to cytotoxic ($CD8^+$) and regulatory ($CD4^+$) T lymphocytes by major histocompatibility complexes, also known as human leukocyte antigens[19].

Viral-specific $CD8^+$ T cells stimulated as a response to viruses affecting organs other than the liver are thought to be involved in the manifestation of T cell-mediated hepatitis lacking viral antigens in the

liver. Even with the extrahepatic influence of viruses, liver damage can be seen when no virus is detected in the liver. Because most strains of these viruses infect only the epithelial cells of the airway and therefore viral antigens should not be existing in the liver. This phenomenon was detected by the effect of the influenza virus and defined as collateral damage[20].

Previous studies on viral infections other than SARS-CoV-2 are therefore important and show that the liver is involved in diseases not only by antigen-specific T-cell response activation but also by some clinical hepatic inflammation syndromes that are not easily explained. It is expected that lymphocytes are caught in the liver sinusoids and cause occlusion, reducing blood flow, and infiltrates consisting of inactivated lymphocytes are expected to increase liver damage. All of these and more may cause more liver damage with the effect of autoimmunity. Exacerbated inflammation in response to SARS-CoV-2 is also a cause of immune damage. The immense discharge of cytokines by the immune system in reaction to the viral infection can cause a cytokine storm and symptoms of sepsis that are the reasons for fatality in 28% of mortal COVID-19 patients[21].

OTHER ETIOPATHOGENETIC FACTORS IN LIVER DAMAGE INDUCED BY SARS-COV-2

Preexisting liver diseases

The relationship between chronic or dormant liver diseases and COVID-19 has been investigated in many studies. In the frequency of COVID-19, a higher number has not been determined in patients with previous liver disease, unlike the general population. Two to five percent of COVID-19 cases had known liver disease before contracting COVID-19. However, there is an opinion that there may be an increase in severe COVID-19 and death in chronic liver patients[5]. As liver damage increases, patients begin to worsen in their clinical condition and prognosis. Established hepatic diseases may have adversarial effects on COVID-19 prognosis, including severity, fatality, and need for mechanical ventilation[22].

Liver transplantation

After the liver transplantation in approximately 700 children with chronic liver disease, only three had SARS-CoV-2 infection and no lung or other system disease such as pneumonia was observed in these patients[23]. Also, in a different study that included data on 151 Liver transplant adults, six recipients fell ill with COVID-19, while three long-term liver transplant recipients died. Data from liver transplant recipients continue to be organized in the form of case reports[24]. It should be kept in mind that patients with liver transplantation receive immunosuppressive treatments and these treatments may initiate cytokine storms or increase viral spread with an asymptomatic course in mild COVID-19 infections[25].

Cholestatic liver disease

Considering the cells and organs where ACE-2 receptors are located, it is expected to be affected in cholestatic liver disease. The fatality rate was higher in patients with cholestasis[22].

Cirrhosis

The incidence of COVID-19 varies widely in patients with cirrhosis. In a study that analyses cirrhosis patients in China, it was reported that 5 of 16 cirrhosis patients died[26]. The reason can be cirrhosis-associated immune dysfunction. They are more likely to have poor outcomes from ARDS.

Other liver diseases

All liver diseases have interactions with COVID-19 resulting from their specific disorder[26]. Chronic low-grade inflammation known to be associated with metabolic dysfunction-associated fatty liver disease may worsen COVID-19 outcomes[22,27,28].

EFFECTS OF VARIOUS AGE AND RISK GROUPS ON LIVER INJURY

When the literature is examined, the striking point is that SARS-CoV-2 does not occur with the same clinical features in patients. Since the severity of the disease is also related to the liver, liver involvement is not the same in every patient. Liver injury varies in patients having previously known blood disease, susceptibility to thrombosis for portal/hepatic thrombosis or immunosuppression, *etc.*[29]. Risk factors such as age, gender, previous diseases, chronic or acute health status, various medications, coronary artery diseases, metabolic diseases, serologies for other viruses related to hepatitis, and other etiologies affect the severity of the disease[3,8].

Elevated liver enzymes were more frequent in males with severe COVID-19 than in females[30]. Also, male gender, older age, and lymphopenia were three important independent risk elements forecasting hepatic dysfunction among COVID-19 cases[7]. Additionally, a clinical study showed that pulmonary failure was related to poor prognostic indicators of hepatic failure[31].

When the pediatric group is examined, only scarcely data is in the pediatric literature. We believe that the reason for this may be a milder course or asymptomatic transmission of SARS-CoV-2 infection in children[32]. In the data of a study that examined SARS-CoV-2 infection by dividing it into two groups, the data of children who had COVID-19, the first group, and that of multi-system inflammatory syndrome in children and adolescents (MIS-C), the second group, were shared. Elevated ALT was found in 36% of the 291 patients, with 31% having COVID-19, and 51% having MIS-C. High levels of ALT in COVID-19 were accompanied by obesity, immune-compromised status, and chronic hepatic disease. Children with elevated ALT and MIS-C were more often boys. Children with MIS-C had a 2.3-fold augmented risk of high ALT compared to COVID-19. No relationship was detected between elevated ALT and fatality[29].

EFFECTS OF DRUGS ON COVID-19-INDUCED LIVER INJURY

With the onset of the pandemic, various guidelines have been published for the treatment algorithm for COVID-19. Some drugs have been removed from the list due to their side effects and benefits. Currently, no specific drug for the SARS-CoV-2 virus has been discovered, and studies on this subject are continuing. The effects of the commonly used medications on the liver are examined.

Remdesivir

Remdesivir is a nucleotide analog prodrug with antiviral activity against SARS-CoV-2. Recently, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) endorsed remdesivir for the management of cases admitted with severe COVID-19. The most common adverse drug reaction reported in hospitalized patients treated with remdesivir with a diagnosis of severe COVID-19 was elevations in liver enzymes. There is limited data on the number of patients exposed to remdesivir in clinical studies reporting severe hepatotoxicity or drug-induced liver injury[33].

Adverse effects reported in at least 5% of all patients in remdesivir trials were decreased glomerular filtration rate, a decline in hemoglobin level, decreased lymphocyte count, pyrexia, increase in blood glucose and creatinine level, transaminase elevations, *etc.*, whose rates were generally similar between remdesivir and placebo[34]. In general, when the adverse events in the remdesivir group and the placebo group were compared, adversarial events were detected in 102 (66%) of 155 remdesivir users and 50 (64%) of 78 placebo users. However, 18 (12%) patients in the remdesivir group and 4 (5%) patients in the placebo group had to be discontinued early due to side effects (including gastrointestinal symptoms, aminotransferase or bilirubin elevations, and worsening cardiopulmonary status), which is more frequent with remdesivir than with placebo. However, when we examined the liver enzymes in cases where treatment was required to be terminated, it was observed that there was an indication in only three (2%) patients in the remdesivir group due to the increase in aspartate aminotransferase[35]. In a more comprehensive study describing the drug-induced liver injury and liver disorders caused by remdesivir, the data were different. Among 387 events with remdesivir listed in VigiBase, 130 hepatic adverse events (34%) were described; they were the most frequent adverse drug reactions. One hundred and fourteen cases had elevated liver transaminases. A more pronounced correlation of the incidence of hepatic failure has been reported with the use of remdesivir compared with hydroxychloroquine, lopinavir/ritonavir, or tocilizumab (odds ratio, 1.94; 95% confidence interval, 1.54-2.45)[36].

Baricitinib and JAK (Janus kinase) inhibitors

Tofacitinib and baricitinib are immunomodulators that are thought to have potent antiviral effects through interference with viral entry. There is not enough data on the side effects on the liver in clinical trials[37].

IL-6 pathway inhibitors (e.g., tocilizumab)

Serious adverse events in the trials were not greater with IL-6 pathway inhibitors than with comparators. It has been discussed in some studies that these inhibitors may be associated with an increased risk of secondary infections[38]. Tocilizumab and baricitinib which are used widely in COVID-19 may also cause HBV reactivation[37].

Glucocorticosteroids

Glucocorticosteroids may result in hepatic steatosis (fatty liver) that can infrequently cause systemic fat embolism or cirrhosis as an adverse effect[39].

Non-steroidal anti-inflammatory drugs

The use of paracetamol was considered relatively safe after the especially beginning of the COVID-19 epidemic and the effect of ibuprofen on ACE receptors was revealed. Therefore, patients suffering from COVID-19 frequently consumed paracetamol for its antipyretic and analgesic effects[40]. It is known that the effects of paracetamol are generally dose-dependent. However, hepatotoxicity risk can be seen

at levels much lower than the expected dose, even at therapeutic doses. At this point, genetic characteristics and metabolic differences may be due to immune-mediated mechanisms[41].

Non-steroidal anti-inflammatory drugs (NSAIDs) impede cyclooxygenase (COX)-1 and COX-2. Significant and well-known common side effects are on the gastrointestinal and renal systems. There are cases of liver toxicity reported and frequently encountered in the literature[42]. Currently, there is no strong evidence about the safety of the use of NSAIDs in COVID-19 patients[43].

HISTOLOGICAL FINDINGS OF LIVER INJURY INDUCED BY SARS-COV-2

Hepatic histology in cases with COVID-19 is nonspecific, comprising moderate microvesicular steatosis with mild, mixed lobular and portal activity and focal necrosis. In a series of 48 autopsies, pathologic hepatic outcomes consisted of focal portal and lobular lymphocytic infiltrates and changes indicative of hepatic vascular participation[44]. In another study conducted with the liver samples of 40 patients who died due to COVID-19, hepatic involvement was observed in all of the patients. Macrovesicular steatosis was the most frequent (30 cases, 75%), followed by mild lobular necroinflammation and portal inflammation (20 patients each, 50%). Vascular pathology, including sinusoidal microthrombi, was rare and observed in six (15%) cases. PCR using hepatic tissue samples was positive in 11 of 20 cases tested, but quantifying viral load in the liver is lacking[45].

DIFFERENT LABORATORY FINDINGS INDICATIVE OF LIVER INJURY INDUCED BY SARS-COV-2

An increase in liver transaminases has been detected in approximately two-thirds of patients with severe COVID-19. The analysis demonstrated that the more severe the coronavirus infection, the greater the levels of ALT, AST, total bilirubin, ALP, and GGT, and the lesser the level of albumin[46]. Mean levels of AST and ALT over 400 U/L have been reported[47]. Low albumin has been associated with severe COVID-19. Nevertheless, it is uncertain if hypoalbuminemia is a risk element for severe COVID-19 or if hypoalbuminemia is a consequence of severe COVID-19[7,48]. Although they are rare, cases progressing from liver damage to ischemia have been reported[49]. Liver functional indexes of two-thirds of COVID-19 cases stay abnormal 14 d after discharge[7].

BRIEF SUMMARY OF OUR OPINION

COVID-19 is still a multisystemic disease with many unknowns. It is known today that it affects the liver, albeit indirectly, as it has on all systems. Due to its mortal course, the disease has been tried to be treated with rapidly created emergency treatments and algorithms. However, the effectiveness of these treatments, which are performed without knowing the effects of SARS-CoV-2 on the organs, is controversial. It is an already known fact that more studies are needed on the virus and the pathogenesis of COVID-19. However, the side effects of drugs should also be analyzed in detail. The treatment and algorithms of liver failure, especially seen in the severe patient group, are confusing. Things to do in liver involvement due to virus and liver effects that can be seen due to drug side effects may be completely different. While it is necessary to ensure that the liver recovers from the cytopathic effects of the virus with the least damage and continues to fight the disease, it should also be noted that liver failure can be triggered by the drugs applied for this. In these two different situations, different procedures need to be implemented. At this point, we think that histopathological data can be used as we have mentioned in detail in our article. We would like to draw attention to the fact that most of the histopathology data were made postmortem in the studies. We can suggest that liver biopsy should be performed in patients with appropriate clinical status before the treatment procedures are discontinued or changed, and histopathological and immunological examinations should be on the agenda. Although liver biopsy is an invasive and costly procedure, we think that the data obtained may be useful in explaining the liver pathologies of the patients, as well as in providing an idea about the side effects of drugs and in the follow-up of the patients.

CONCLUSION

Liver diseases in COVID-19 have been studied in different groups, from mild to severe and chronic. In light of these studies, our general opinion is that SARS-CoV-2 infection will be more fatal in the case of liver disease. We think that both the direct injury to the liver and other etiological factors including the drugs used have an effect. Exploring liver injury related to COVID-19 has an important role in the

estimation of fatality and might be used for the creation of prognostic tools to recognize cases with possible worse consequences.

FOOTNOTES

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SYSTEMATIC REVIEWS

COVID-19-related liver injury: Focus on genetic and drug-induced perspectives

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Abstract

BACKGROUND

Empirical use of potentially hepatotoxic drugs in the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is considered as one of the major etiopathogenetic factors for liver injury. Recent evidence has shown that an underlying genetic factor may also occur. Hence, it is important to understand the host genetics and iatrogenic-based mechanisms for liver dysfunction to make timely remedial measures.

AIM

To investigate drug-induced and genetic perspectives for the development of coronavirus disease 2019 (COVID-19)-related liver injury.

METHODS

Reference Citation Analysis, PubMed, Google Scholar and China National Knowledge Infrastructure were searched by employing the relevant MeSH keywords and pertaining data of the duration, site and type of study, sample size with any subgroups and drug-induced liver injury outcome. Genetic aspects were extracted from the most current pertinent publications.

RESULTS

In all studies, the hepatic specific aminotransferase and other biochemical indices were more than their prescribed upper normal limit in COVID-19 patients and were found to be significantly related with the gravity of disease, hospital stay, number of COVID-19 treatment drugs and worse clinical outcomes. In addition, membrane bound O-acyltransferase domain containing 7 rs641738, rs11385942 G>GA at chromosome 3 gene cluster and rs657152 C>A at ABO blood locus was significantly associated with severity of livery injury in admitted SARS-CoV-2 patients.

CONCLUSION

Hepatic dysfunction in SARS-CoV-2 infection could be the result of individual

drugs or due to drug-drug interactions and may be in a subset of patients with a genetic propensity. Thus, serial estimation of hepatic indices in hospitalized SARS-CoV-2 patients should be done to make timely corrective actions for iatrogenic causes to avoid clinical deterioration. Additional molecular and translational research is warranted in this regard.

Key Words: SARS-CoV-2; Liver injury; Genetic prospective; Drug-induced liver injury; Prognosis; COVID-19

Core Tip: Evidence highlights the multisystemic nature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Hepatic dysfunction is the primary extrapulmonary manifestation. In addition to the direct cytopathic effect of the virus, iatrogenic causes and genetic susceptibility are also postulated in the pathogenesis of hepatic damage in SARS-CoV-2 infection. Degree of liver toxicity in terms of altered biochemical indices were consistent with severity of coronavirus disease 2019 (COVID-19) illness and hospital stay. Hence, serial monitoring of hepatic indices in COVID-19 hospitalized patients may provide useful prognostic value to make timely corrective actions to avoid clinical deterioration.

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INTRODUCTION

Since the index case of coronavirus disease 2019 (COVID-19) infection was confirmed in the month of December 2019 in China[1], the upsurge of COVID-19 has led to devastating effects on global health[2]. Considering the incessant evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its impact on public health, SARS-CoV-2 variants were labelled as "variants of concern" (*e.g.,* Alpha, Beta, Gamma, Delta and Omicron) and "variants of interest" (*e.g.,* Eta, Iota, Kappa and Lambda) based on their attributes[3,4].

Each of the variants penetrates human cells by binding the cell surface receptor angiotensin converting enzyme (ACE) 2 *via* the spike protein subunit 1, while spike protein subunit 2 permits entry of the virus by enabling fusion of the virus envelope with the host cell membrane. This virus-cell fusion is facilitated by S protein priming by host cell proteases *viz* transmembrane protease serine 2 at a cleavage site (spike protein subunit 1/spike protein subunit 2), which is a polybasic furin cleft[3,4]. Fusion of the viral and cell membrane is followed by the entry of the virus inside the host cell to release the genetic material, *i.e.,* positive sense RNA. This RNA genome is the template for synthesis of new negative sense RNA with the help of RNA-dependent RNA polymerase. Newly synthesized RNA in turn facilitate the synthesis of positive sense RNA, which is responsible for the production of new cytoplasmic proteins, namely nucleocapsid protein and membrane protein. Nucleocapsid protein binds to freshly synthesized positive sense RNA, and membrane protein facilitates its assimilation into the endoplasmic reticulum (ER) to form nucleocapsids. These nucleocapsids are finally transferred to the cell membrane *via* the ER lumen and Golgi vesicle to the extracellular space *via* exocytosis[5,6].

These newly released virions infect the neighboring healthy cells and manifest COVID-19 with a diverse spectrum of symptoms, ranging from asymptomatic disease to severe symptoms, primarily associated with the respiratory system. However, emerging scientific evidence highlights the multisystemic nature of the disease, *i.e.,* involving extrapulmonary clinical manifestations such as myocardial infarction, neurological, ocular, dermatologic, gastrointestinal, kidney failure and liver dysfunction, owing to the tropism of the virus for ACE2 expressed in different human cells[7]. In fact, liver injury is the primary extrapulmonary manifestation, and the most common pattern is mild to moderate hepatocellular injury, observed in 14%-53% of the hospitalized patients with COVID-19. Furthermore, epidemiological studies have revealed that over one-half of infected patients with SARS-CoV-2 had deranged liver function tests characterized by abnormal levels of hepatic specific aminotransferases and other hepatic specific biochemical indices[8,9], while a small subset of patients was found with acute liver damage and fulminant hepatic failure[10,11]. Altered biochemical indices were more frequent in severely ill COVID-19 patients in contrast to patients presenting with mild to moderate illness[12,13].

In addition, certain therapeutic compounds can cause drug-induced liver injury (DILI)[14]. This was substantiated by the findings that toxicity was relieved after the cessation of these agents in *in vitro* and *in vivo* experiments[15,16]. These compounds include: (1) Antibiotics (azithromycin and ceftriaxone); (2) Antivirals [remdesivir (RDV), lopinavir (LPV)/ritonavir (RTV), favipiravir, umifenovir and triazavirin]; (3) Antimalarial [hydroxychloroquine (HCQ)]; (4) Adjuncts; (5) Steroids (dexamethasone); and (6) Immunomodulators [tocilizumab (TCZ)]. Overall, available data suggest that the spectrum of hepatic damage in SARS-CoV-2 infection may be accredited to the direct cytopathic effect of the virus through the ACE2 receptor, indirect involvement by systemic immune-mediated inflammation and by iatrogenic causes, *i.e.*, drug-induced[17,18].

Moreover, underlying genetic factors could also contribute to COVID-19-related liver abnormalities due to the occurrence in a subset of the patient population. In accordance with this, a substantial number of genetic-based and or association studies have addressed the genetic makeup of the host in regards to the predisposition to the development and progression of COVID-19-related liver injury to recognize the patient cohort for high clinical priority in terms of early or novel therapeutic interventions albeit with equivocal results.

Since there are limited data on the individual genetic susceptibility to SARS-CoV-2 infection-related liver abnormalities, a detailed understanding of the influence of specific genotypes will be crucial for clinical outcomes. In addition, substantial evidence from the scientific literature indicate that the degree of liver toxicity is due to a certain therapeutic regime employed in the treatment of SARS-CoV-2. Only a handful of researchers methodically and comprehensively explored the complete array of DILI in COVID-19 patients. Hence, it is worth reviewing the genetic and drug-induced perspectives on COVID-19-related liver injury. This review emphasized DILI in COVID-19 patients along with genetic insight into the development of SARS-CoV-2 infection-related liver injury by providing evidence from the most current pertinent publications using relevant keywords from online databases.

MATERIALS AND METHODS

Procedure adopted for relevant literature search

Using various electronic databases, namely Reference Citation Analysis, PubMed, China National Knowledge Infrastructure and Web of Science, our team carried out the relevant literature search using the following MeSH keywords: DRUG INDUCED LIVER INJURY AND COVID-19 OR DRUG INDUCED LIVER INJURY AND SARS-COV-2 OR DRUG INDUCED LIVER INJURY AND 2019 nCOV OR DRUG INDUCED LIVER INJURY AND CORONAVIRUS DISEASE with regards to drug-induced perspectives and COVID-19 AND LIVER INJURY AND POLYMORPHISM OR SARS-COV-2 AND LIVER INJURY AND POLYMORPHISM OR COVID-19 AND LIVER INJURY AND GENETIC INSIGHT OR SARS-COV-2 AND LIVER INJURY AND GENETIC INSIGHT for genetic insight of hepatic damage.

The criteria for inclusion were: Original articles; case series or reports; brief communication; or letters to the editor. However, articles were in English and published during between December 1, 2020 and April 30, 2022. The references of the articles from the initial search were screened to add any plausible relevant literature. However, studies with animal or cellular models were not included. Other criteria for exclusion were: Injury due to SARS-CoV-2 infection itself; and hepatic injury from herbal or dietary supplements. Finally, after eliminating duplicate articles, 31 (2 and 29 relating to genetic insight and DILI, respectively) out of 727 (14 and 713 articles, respectively, for genetic insight and DILI) articles were selected for review.

Document retrieval

By means of the aforementioned key words and in line with inclusion and exclusion criteria of the study, Sonagra AD, Dholariya S and Motiani A reviewed articles to ensure the fulfilment of inclusion criteria. Thereafter, Parchwani D and Singh R chose the articles to be finally included in the study. The authors then extracted the data: Author, site and sample size of study, stages of COVID-19, severity of disease, medication, outcome and/or DILI. All the mentioned information were extracted by standardized data extraction tables in duplicate.

RESULTS

A total of 8 studies on genetic insight and 279 studies concerning DILI were screened after removing the duplicate publications. Among the included studies, a total of 31 studies were considered suitable for the qualitative synthesis comprising 2 studies regarding genetic insight and 29 studies regarding DILI. Extraction of research articles (Figure 1) were performed as per the guideline prescribed in PRISMA statement 2020 and was done according to the published protocol (PROSPERO ID: CRD42022311838).

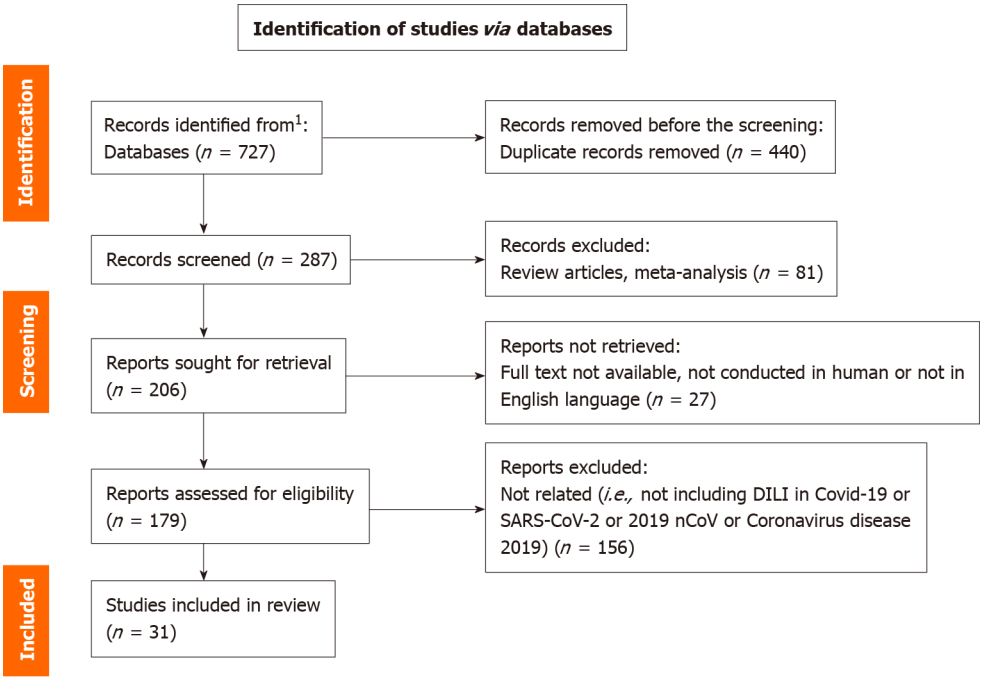

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Figure 1 Selection process of research studies from various databases according to PRISMA 2020. [1]Reference Citation Analysis, PubMed, China National Knowledge Infrastructure and Web of Science. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; DILI: Drug-induced liver injury; COVID-19: Coronavirus disease 2019.

Hepatoxicity of commonly used drugs used in the treatment of SARS-CoV-2

Medications and or therapies employed in COVID-19 management, such as RDV, LPV/RTV, ribavirin, TCZ, hydroxyl chloroquine sulfate, *etc* are potentially hepatotoxic, specifically in high doses[19], and their administration in the form of polypharmacy exponentially increases the risk of DILI. The hepatotoxicity information as described across the included studies are compiled herewith for most frequently used drugs in the therapeutic regime of COVID-19. Table 1 depicts the relevant information per study. The most frequently associated drugs with DILI were RDV, LPV/RTV, TCZ, HCQ (+/-) azithromycin, ceftriaxone, paracetamol and enoxaparin.

RDV: A broad-spectrum nucleotide analogue prodrug, primarily used for hospitalized patients with COVID-19 is known to inhibit viral RNA polymerases. RDV had the maximum DILI rate/administration. Screening of the World Health Organization safety reports database revealed a total of 387 adverse drug reactions (ADRs) reports of RDV by late 2021. Out of which the majority were hepatobiliary (61%) followed by 34% hepatic. The most common documented adverse liver outcome in different studies were elevated hepatic specific aminotransferase in the range of 15%-50%, hypoalbuminemia and hyperbilirubinemia[20]. Levels of aminotransferase elevation were more prominent in seriously ill patients, suggesting a possibility of occurrence of various adverse events due to severity and gravity of SARS-CoV-2 infection. Furthermore, studies also stated that in a subset of patients RDV treatment was discontinued on account of the abnormally high liver aminotransferase levels[20]. Chew *et al*[21] conducted a study in a sample of 834 COVID-19 hospitalized patients and reported that 12.6% (*n* = 105) of patients showed a > 5 upper limit of normal (ULN) of serum aspartate aminotransferase. Among the adverse lung events, TCZ and RDV were significantly associated with DILI on univariate analysis. Further, Delgado *et al*[22] conducted a retrospective observational study for the assessment of DILI by a pharmacovigilance program using laboratory signals. Out of 8719 patients admitted for COVID-19, 4.9% of patients developed DILI. The drugs commonly associated with DILI were HCQ, azithromycin, TCZ and ceftriaxone. Out of these, RDV had the highest incidence rate of 992.7 DILI per 10000 defined daily doses.

These adverse events were further corroborated by individual case reports/series. In one such report [23], after 2-d administration of RDV, a sharp elevation in the level of alanine aminotransferase (ALT) was observed, which was instantly corrected after discontinuing RDV. Correspondingly, in other reported cases[24,25], increased levels of liver enzymes were found in patients on RDV +/- HCQ, who were initially treated with LPV/RTV. In a case series reported in the United States, Carothers *et al*[26] suggested that administering acetyl cysteine had a positive impact on the overall health of the patient and reversed acute liver failure due to RDV with hepatic specific transaminase (ALT and aspartate aminotransferase) levels > 5000 IU/L and increased total bilirubin levels (3.1 mg/dL), serum ammonia (161 μmol/L) and international normalized ratio of 2.3.

Table 1 Drug induced hepatoxicity outcome and other relevant information in the included studies

Sr. No.	Ref.	Type of study	Location	Number of study participants	Medication	Outcome
1	Grein *et al* [20], 2020	Cross sectional/follow-up study	United States, Canada, Europe, Japan	53	Remdesivir	Elevation of liver enzymes in 12/53 patients
2	Goldman *et al* [76], 2020	Randomized, open-label, phase 3 trial	United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	397	Remdesivir	Elevated ALT in 26; elevated AST in 23; elevated bilirubin in 5
3	Wang *et al*[1], 2020	Randomized, double-blind, placebo-controlled, multicenter trial	China	158	Remdesivir	Elevated ALT in 2; elevated AST in 7, elevated bilirubin in 16, decreased albumin in 20
4	Antinori *et al* [77], 2020	Prospective (compassionate), open-label study	Italy	35	Remdesivir	Elevated transaminase in 15; elevated bilirubin in 7
5	Leegwater *et al*[23], 2021	Case study	Netherlands	1	Remdesivir	Elevated ALT, AST, ALP and GGT
6	Lee *et al*[24], 2020	Case series	South Korea	10	Remdesivir	Elevated ALT in 5; elevated AST in 5
7	Zampino *et al* [25], 2020	Case series	Italy	5	Remdesivir	Elevated ALT in 4; elevated AST in 4
8	Carothers *et al*[26], 2020	Case series	United States	2	Remdesivir	Elevated ALT, AST, bilirubin, INR, ammonia in both patients; elevated ALP in 1
9	Sun *et al*[27], 2020	Active monitoring study by hospital pharmacovigilance system	China	217	LPV/ritonavir, umifenovir	Elevated ALT in 30
10	Fan *et al*[28], 2020	Retrospective, single-center study	China	148	LPV/ritonavir	Elevated ALT in 27; elevated AST in 32; elevated GGT in 26; elevated ALP in 6; elevated bilirubin in 18
11	Cai *et al*[9], 2020	Cross-sectional study	China	417	LPV/ ritonavir, oseltamivir, interferon, NSAIDs, ribavirin	Elevated ALT in 167; elevated AST in 137; elevated GGT in 143; elevated ALP in 71; elevated bilirubin in 196
12	Jiang *et al* [29], 2020	Multicenter, retrospective, observational study	China	131	LPV/ritonavir	Elevated ALT in 45; elevated AST in 4; elevated bilirubin in 43
13	Serviddio *et al* [30], 2020	Case series	Italy	7	LPV/ritonavir, HCQ, azithromycin	Elevated ALT, AST, GGT in all patients
14	Guaraldi *et al* [32], 2020	Retrospective cohort study	Italy	179	Tocilizumab	No elevation of ALT or bilirubin was noted
15	Muhović *et al* [33], 2020	Case report	Montenegro	1	Tocilizumab	Elevated ALT and AST
16	Hundt *et al* [34], 2020	Retrospective observational cohort study	United States	1827	LPV/ritonavir, HCQ, remdesivir, tocilizumab	Elevated ALT in 1080 out of 1753; elevated AST in 1465 out of 1756; elevated ALP in 399 out of 1754; elevated total bilirubin in 284 out of 1747
17	Kelly *et al* [35], 2021	Retrospective analysis of hospitalized patients	Ireland	82	HCQ, azithromycin	Elevation of LFTs of more than ULN after 5 d therapy in 51/85 patients
18	Falcão *et al* [36], 2020	Case report	Brazil	1	HCQ	Elevated ALT and AST with normal bilirubin and GGT
19	Yamazaki *et al*[38], 2021	Case report	Japan	1	Favipiravir	Elevated ALT, AST, ALP, total bilirubin and LDH
20	Aiswarya *et al* [49], 2021	Observational prospective study	India	48	Remdesivir	No significant change in serum transaminases and LDH

22	Kaur *et al* [78], 2022	Case study	India	1	Remdesivir	Elevated ALT, AST and total bilirubin
23	Gao *et al*[79], 2022	Retrospective study	China	4010	Oseltamivir, arbidol, interferon, ribavirin, LPV/ritonavir, HCQ/CQ, antibiotics, antifungals, corticosteroids	395 out of 4010 developed DILI. 293 out of 395 received antibiotics, 25 out of 395 received antifungal, 42 out of 395 received oseltamivir, 52 out of 395 received ribavirin, 51 out of 395 received LPV/ritonavir, 47 out of 395 received interferon, 200 out of 395 received corticosteroid, 226 out of 395 received arbidol, 18 out of 395 received HCQ/CQ
24	Naseralallah *et al*[80], 2022	Retrospective study	Qatar	72	Azithromycin, HCQ, LPV	Elevated ALT and AST was implicated in 24 patients due to azithromycin, in 11 patients due to HCQ and in 11 patients due to LPV
25	Chew *et al* [21], 2021	Retrospective study	United States	834	Tocilizumab, remdesivir	105 out of 834 (12.6%) had elevated AST
26	Delgado *et al* [22], 2021	Retrospective observational study	Spain	8719	Remdesivir, hydroxy-chloroquine, azithromycin, tocilizumab and ceftriaxone	4.9% of 8719 patients developed DILI. Out of which remdesivir had the highest incidence of DILI per 10000 defined daily doses
27	Durante-Mangoni *et al* [81], 2020	Case report	Italy	4	Remdesivir	3 out of 4 patients had elevated AST and ALT
28	Wong *et al* [82], 2022	Self-controlled case series study	China	860	Remdesivir	334 (38.8%) out of 860 had acute liver injury
29	Montastruc *et al*[83], 2020	Multicenter study	France	387	Remdesivir	130 (34%) out of 387 developed liver injury

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; DILI: Drug induced liver injury; HCQ: Hydroxychloroquine; LPV: Lopinavir; LDH: Lactate dehydrogenase; GGT: Gamma-glutamyl transferase; ULN: Upper limit of normal; INR: International normalized ratio; LFT: Liver function test; NSAID: Nonsteroidal anti-inflammatory drug.

LPV/RTV: Among the therapeutic regimes of COVID-19, LPV/RTV is one of the most common contributors of the liver ADRs. A study of 217 patients reported that LPV/RTV was found to be associated with 63% of total ADRs, while other drugs (umifenovir, chloroquine and antibacterial drugs) contributed to 47% of ADRs[27]. Correspondingly, a study of 148 patients reported that 48% developed hepatic function abnormality after admission to the hospital[28]. They emphasized that among such patients, 57.8% of the patients were treated with LPV/RTV. In another study, the authors reported an abnormal liver function in 12.1% of patients with the addition of each collateral medication[29]. Moreover, combined use of LPV/RTV with arbidol (umifenovir) in patients who were not terminally ill had an elevated risk of liver injury up to 3.58 times in comparison to those patient cohorts whose treatment regimen did not include LPV/RTV. It was postulated that RTV, being an inhibitor of chromosome 3 gene cluster A4, could promote hepatic toxicity from azithromycin *via* drug-drug interactions (polypharmacy)[26]. Similarly, metabolic interactions between the two medications [LPV/RTV and arbidol (umifenovir)] were studied *in vitro* using human liver microsomes by Serviddio *et al*[30] and concluded that LPV/RTV significantly impedes arbidol metabolism ($P < 0.005$), which may be the cause of DILI.

In a study with 163 mild and 29 severe patients with COVID-19, the multivariate analysis suggested RTV as one of the independent risk factors (odds ratio = 4.75, 95% confidence interval: 1.89-16.55, $P < 0.001$) in COVID-19 patients with liver injury[31]. In contrast to most of the studies that reported moderate-to-severe elevations in serum aminotransferase levels in patients under LPV/RTV treatment, Cai *et al*[9] reported increased odds of liver injury by four-fold in the LPV/RTV treated group among the enrolled 417 COVID-19 patients in China. The most significant increases were gamma-glutamyl transferase activity and total bilirubin. Because the drug was not efficacious, it was discontinued from the COVID-19 treatment regimen.

TCZ: TCZ, an interleukin-6 receptor antagonist monoclonal antibody, is primarily used for severely ill COVID-19 patients to arrest the cytokine storm. Guaraldi *et al*[32] did not find any adverse effects on the liver function test in a retrospective study involving 1351 COVID-19 patients treated with TCZ. In the following line of evidence, Serviddio *et al*[30] published a case series from Italy and displayed substantially altered hepatic and lung function tests after administration of LPV/RTV, HCQ and azithromycin for 5-7 d. These patients showed an improvement in both liver and lung function after the use of TCZ within 3 wk. However, the first case reported of DILI due to the use of TCZ did not deny the possibility of serious hepatotoxicity when used with other hepatotoxic drugs. In this case, 1 d after TCZ adminis-

tration, the levels of serum transaminase increased up to 40-fold (aspartate aminotransferase of 1076 IU/L and ALT of 1541 IU/L)[33].

Another retrospective cohort study with 1827 patients conveyed that a positive correlation exists with usage of RDV, LPV/RTV, HCQ and TCZ and hepatotoxicity[34]. They observed peak hospitalization liver transaminase elevations more than 5 times the ULN.

HCQ with or without azithromycin: Most cases of DILI were reported for HCQ after its emergency use authorization for COVID-19 infection. Kelly *et al*[35] conducted an analysis in two groups of 134 patients. One group was treated with HCQ/azithromycin, while the other group was devoid of this targeted therapy. They reported no significant difference in the liver function tests between the two groups. On the contrary, a 10-fold elevation in levels of liver transaminases in the serum after HCQ administration was reported by Falcão *et al*[36]. They revealed that serum levels of hepatic enzymes rapidly declined after the withdrawal of HCQ from the treatment regimen.

Corticosteroids: Systemic corticosteroids, mainly dexamethasone, are widely used in patients with SARS-CoV-2 infections. However, an independent basis of hepatoxicity is uncommon. They are associated with minor, self-limiting elevations in serum aminotransferase. A study (n = 1040 COVID-19 patients) reported that the administration of corticosteroids was found to be correlated (adjusted odds ratio = 3.9) with development of acute liver injury on an independent basis (95% confidence interval: 2.1-7.2)[16].

Enoxaparin: Enoxaparin is associated with minor, self-limiting elevations in serum aminotransferase, but values > 5 ULN are uncommon. Sporadic cases of mild increases in serum bilirubin and alkaline phosphatase have been reported[37].

Favipiravir: A single study observed adverse liver events after favipiravir administration[38]. Authors of the study reported a COVID-19 patient who manifested bacterial pneumonia as a complication of COVID-19 during his hospital stay. The therapeutic regime of the patient was LPV/RTV combined with interferon β-1b. Following administration of favipiravir, liver transaminases and total bilirubin increased suggesting a cholestatic liver injury. The liver injury, in this case, may have been triggered by antibacterial treatment, which may have further deteriorated by treatment with a high dose of favipiravir.

Tang *et al*[39] found 17.31% (n = 3425) of patients exhibited DILI in a cohort of 19782 COVID-19 patients. The odds ratio for DILI was 2.99 (2.59-3.46), 5.39 (4.63-6.26) and 3.16 (2.68-3.73) when comparing LPV-RTV with all other drugs, RDV and HCQ/chloroquine, respectively. A single-center, open-label, parallel-arm, stratified randomized controlled trial completed by Panda *et al*[40] observed DILI in the form of elevated liver enzymes in 2 out of 67 participants who received a high dose of ribavirin.

Genetic insight towards SARS-CoV-2-induced liver injury

In the matter pertaining to a genetic propensity towards SARS-CoV-2 induced liver injury, in the United Kingdom Biobank cohort[41] an elevated risk score of genetic fatty liver disease (FLD) based on glucokinase regulator, membrane bound O-acyltransferase domain containing 7, patatin like phospholipase domain containing 3 (*PNPLA3*) and transmembrane 6 superfamily 2 human gene genetic variants was not found to be associated with a higher probability of developing severe SARS-CoV-2. Hence, this finding challenges the causal role for metabolic-associated FLD in COVID-19 and implies that genetic susceptibility to hepatic fat deposition does not, in and of itself, increase the risk of developing a severe form of the disease[41]. However, contrary to this, membrane bound O-acyltransferase domain containing 7 rs641738[42], rs11385942 G>GA at chromosome 3 gene cluster and rs657152 C>A at the ABO blood locus were significantly associated with the severity of livery injury in admitted SARS-CoV-2 patients[43,44]. Thus, the genetic basis of SARS-CoV-2-induced liver injury is not yet fully understood, and additional research is required to validate the involvement of any specific variant form. Table 2 depicts the commonly employed therapeutic drugs for COVID-19, with its hepatic side effects and 'Likelihood Score' by the LiverTox database[45].

DISCUSSION

The primary analysis of this review revealed that DILI is due to the large-scale use of drugs/off-label drugs in the prophylactic and therapeutic regimen of COVID-19, and the causal relationship of genetic susceptibility with hepatic damage in SARS-CoV-2 infected patients is incomprehensible. Hepatic damage may arise either through intrinsic or idiosyncratic mechanisms. The intrinsic pathway is predictable and has a short latency period. However, COVID-19-related liver injury (drug-induced and/or genetic-based) predominantly follows the idiosyncratic mechanism, *i.e.*, it is unpredictable with a variable latency period[19].

Table 2 Hepatoxicity and likelihood score of therapeutic agents of coronavirus disease 2019

Drug	Hepatotoxicity	Likelihood score
Remdesivir	A duration of 7-14 d of administration caused elevation of serum aminotransferases up to > 5 times of ULN. Elevation of > 5 times ULN were reported in 9% of patients but returned to normal after discontinuation. Prolonged and more severe effects were seen in critically ill patients with multiorgan involvement, pre-existing comorbidities and who had received combination therapy with other hepatotoxic agents like amiodarone	D
Lopinavir/ritonavir	A greater degree of rise in serum aminotransferase levels (> 5 times ULN) is mostly seen in association with immunodeficiency states. The pattern varies from hepatocellular to cholestatic or mixed type. Discontinuation leads to the normalization of enzyme levels. However, severe cases of acute liver failure or end stage liver disease are also reported with re-exposure of the drug	D
Tocilizumab	Reported to cause mild elevation of aminotransferases commonly, that is usually transient and asymptomatic, but rare instances of liver injury manifesting as jaundice and reactivation of hepatitis B are seen. ALT elevation (1-3 times ULN) was seen in 10%-50% of patients, which returned to baseline within 8 wk after stopping treatment. No effect on bilirubin or ALP levels were seen	C
Hydroxychloroquine	Clinically apparent liver injury is rare. In clinical trials for COVID-19 prevention and treatment, there were no reports of hepatotoxicity, and serum enzyme elevation was also low	C
Corticosteroids	Long-term use and high doses can result in hepatomegaly and steatosis. Can also trigger or exacerbate pre-existing or co-existing conditions like NASH, viral hepatitis or autoimmune hepatitis. Serum aminotransferase levels can rise up to 10-40 times ULN	A
Enoxaparin	4%-13% of patients showed mild elevation in serum aminotransferase levels. Rapid onset of liver injury symptoms after starting the drug (within 3-5 d) but rapid recovery (1-4 wk) after discontinuation of therapy is seen	E
Favipiravir	Pretreatment with other hepatotoxic drugs like lopinavir/ritonavir and IF-β 1B lead to an increase in liver transaminase and bilirubin levels by manifold suggesting cholestatic injury. Isolated use is not known to cause any severe liver injury	D

A: Well known hepatotoxicity; B: Highly likely hepatotoxicity; C: Probable hepatotoxicity; D: Possible hepatotoxicity; E: Unlikely hepatotoxicity. COVID-19: Coronavirus disease 2019; ULN: Upper limit of normal; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; NASH: Nonalcoholic steatohepatitis.

Drugs like LPV/RTV were associated with moderate to severe elevation (> 5 ULN) of hepatic specific aminotransferases in serum and exhibited a significantly (4 times) higher chances of liver injury[9]. The degree of hepatic damage varies widely, *i.e.*, from injury of hepatocytes to complete stagnation of bile acid secretion (cholestatic injury) or may be both in certain cases[45]. Correspondingly, medication of COVID-19 patients with LPV/RTV might exaggerate dysfunction of hepatic cells in particular to hepatitis B virus and hepatitis C virus infection cases[46]. However, the efficacy of LPV/RTV in SARS-CoV-2 patients is not fully understood and requires further evaluation[47,48]. In contrast, a study in China suggested out that administration of antibiotics, ribavirin and nonsteroidal anti-inflammatory drugs is not associated with a statistically significant risk of hepatic damage[9].

Likewise, studies evaluating the ADRs of RDV reported that it could lead to liver injury, barring one [49]. Liver injury caused by RDV manifested only after the 3rd d of its administration as elevated hepatic specific transaminases, coagulopathy and hepatic encephalopathy. N-acetyl cysteine is recommended for the management of acute liver failure induced by RDV and discontinuation of drug for progression to acute liver failure[26]. It was suggested that the following criteria should be considered for an immediate cessation of RDV treatment: Elevation of ALT > 5 times ULN or elevation of alkaline phosphatase > 2 times ULN; increased level of total bilirubin more than > 2 times ULN; immediate incidence of coagulopathy; or in cases where the patient's condition is deteriorating[50]. Thus, to diminish RDV-induced toxic effects, assessment of liver status must be completed before drug initiation, and continuous monitoring of the liver function test should be performed during the course of treatment.

However, the most contentious reports were of TCZ. A retrospective cohort study[32] and meta-analysis[47,48] reported that TCZ by itself is not associated with liver injury in COVID-19 patients. One study reported that TCZ had a positive effect on clinical and laboratory parameters caused by the use of LPV/RTV[30]. ALT levels fall within the normal range from > 5 times ULN after administration of TCZ. On the other hand, a study conducted by Muhović *et al*[33] reported that the hepatotoxic effects of TCZ were increased in cases of prior administration of antiviral drugs (LPV/RTV).

DILI in COVID-19 patients is often dependent on numerous factors. For instance, co-existing medical conditions (porphyria cutanea tarda, viral hepatitis and rheumatologic diseases) could increase the risk of developing toxicity due to recommended drugs[36]. Further, drug-drug interaction (*e.g.*, chloroquine and its derivatives combined with anti-rejection immunosuppressants[51]) can lead to detrimental effects. For example, the prevalence of liver damage was 15.2% in a sample size of 208 COVID-19 patients on RDV only, whereas it was 37.2% among 775 patients treated with RDV and LPV/RTV[52], substantiating the concept of polypharmacy.

Among included studies, one study reported that the grade of hepatotoxicity was not statistically different between the controls and cases, who were treated with HCQ and azithromycin[35]. Nevertheless, divergent findings are also frequently reported for HCQ and has been hypothesized that the presence of pre-existing inflammation (mild to moderate) might increase the risk of liver damage by HCQ (+/- azithromycin) in the doses that are not hepatoxic due to the production of cytotoxic metabolites from drug metabolism by inflammatory cells with the help of myeloperoxidase enzyme. Ivermectin (anti-parasite medication) and colchicine (anti-inflammatory agent) are well-tolerated and have been reported to reduce the severity, length of hospital stay and prevention of a cytokine storm[47,53,54], but efficacy of these drugs in the management of SARS-CoV-2 infected patients is still not fully understood[55,56]. Hepatotoxic effects are not well documented.

Mechanisms of DILI

Drugs employed in the management of SARS-CoV-2 infection (RDV, LPV/RTV, ribavirin, TCZ, HCQ or any other drugs) are metabolized by the hepatic cells. Liver damage with an associated increase of hepatic specific indices is predictable and has been corroborated and cited in the scientific literature[57-61] (Table 3).

Critical biochemical properties of anti-COVID-19 drugs that might lead to hepatotoxicity in susceptible hosts are lipophilicity, mitochondrial liability, generation of cytotoxic metabolites, their metabolic pathway in the liver and the ability to inhibit hepatic transporters[62]. Patients who died with severe COVID-19 had moderate microvesicular steatosis, a condition characterized by a variant form of hepatic fat accumulation and modest lobular and portal activity in their liver biopsies, suggesting that the liver injury may have been due to either viral- or drug-induced mechanisms. Steatosis in lieu of drugs occurs due to interference with β-oxidation of fatty acids, oxidative phosphorylation or both by certain drugs[63], resulting in the accumulation of free fatty acids, which are converted to triglycerides [64].

Clinical and murine studies have provided evidence that pre-existing medical conditions, *e.g.*, inflammatory diseases, increased blood pressure and diabetes mellitus, augment SARS-CoV-2 hepatic injury, possibly because of ACE inhibitors or angiotensin receptor blockers, which results in ACE2 upregulation[65,66]. The presence of pre-existing nonalcoholic FLD sensitizes hepatocytes to antipyretic agents containing acetaminophen[67].

Reduced and/or suppressed activity of the CYP family or cytochrome P450 (enzyme responsible for metabolism of xenobiotics) is also a plausible mechanism to alter the activity of liver cells[68]. CYPs are downregulated due to repressive effects exerted by interleukins and cytokines, which are upregulated during COVID-19 infection, leading to toxicity of several COVID-19 drugs[68]. Drug-drug interactions also play an important role in the development and progression of DILI, as exemplified by the clearance of umifenovir, which is compromised by concomitant use of LPV/RTV due to its inhibitory effect on cytochrome P3A[29].

A precedent of hepatic transporter inhibition by COVID-19 drugs to manifest the liver injury is reported by many studies with regard to LPV, a prominent blocker of multidrug resistance-associated protein-2. A study performed on rats reported the accumulation of taurocholic acid inside the liver cells following the 10-min exposure of rat liver cells to protease inhibitor (PIs) drugs, LPV and RTV, indicating that the Pis inhibit the efflux of bile salts from liver cells[69]. Experimental studies showed the inhibitory effect of Pis on multidrug resistance-associated protein-2[70,71]. Holmstock *et al*[70] also reached a similar conclusion using 5(6)-carboxy-2′,7′-dichlorofluorescein through confocal imaging. Another recent study by Khalatbari *et al*[72] focused on oxidative stress damage leading to hepatotoxicity and FLD due to Pis, LPV and RTV. They reported the interference of these drugs by ER-Golgi trafficking through inhibition of Ras converting CAAX endopeptidase-1 and any of its substrate, which in turn leads to development of fatty liver and cellular stress.

Additionally, exhaustion of P450 activity to metabolize large and multiple amounts of COVID-19 drugs as a treatment regimen can also be the cause of hepatoxicity. Simultaneously, studies reported that administration of certain drugs (LPV/RTV) assists in the reactivation of hepatitis B and C viruses and results in hepatoxicity[73]; administration of HCQ in patients with porphyria cutanea tarda leads to significant liver damage[73] due to the interaction of reactive metabolites of HCQ and the inflammatory response due to SARS-CoV-2 infection[74].

However, there is a deficit of uniformity and standardization of DILI due to a lack of reliable and exclusive evidence pointing towards the drugs used in the treatment of COVID-19. Moreover, there is considerable overlap and commonality in the presenting symptoms of hepatic damage due to COVID-19 infection per se and due to drugs given for its treatment. Increased vigilance on the part of the clinicians is warranted so that cases of severe liver damage suspected to be caused by the drugs can be reported and entered into the National/International database. The *R* value can be considered as a diagnostic approach for the pattern of liver injury (*i.e.*, $R > 5$ is considered hepatocellular DILI, $R < 2$ is considered cholestatic DILI, and $R = 2\text{-}5$ is considered mixed DILI; *R* value = ALT value/ULN divided by alkaline phosphatase value/ULN).

Table 3 Mechanism of hepatic damage in severe acute respiratory syndrome coronavirus 2 infection

Proposed main mechanism	Explanation
Direct cytotoxicity	Active SARS-CoV-2 replication in hepatic cells, which further binds to hepatic and biliary epithelial cells by angiotensin-converting enzyme 2 and damage them by direct infection[57]
Immunological damage	Severe inflammatory response generated by SARS-CoV-2 further damages hepatic cells by immune mediated pathogenesis[58]
Drug-induced	Antiviral drugs such as remdesivir, chloroquine and ritonavir are possibly hepatotoxic[59]
Reactivation of pre-existing liver illness	Increased risk to develop hepatotoxicity in the presence of pre-existing liver diseases. In addition, baricitinib also causes reactivation of hepatitis B virus infection[60]
Anoxia	Anoxia or hypoxia leads to respiratory failure in SARS-CoV-2, which further leads to hypoxic hepatitis[61]

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Genetic aspect of hepatic consequences of SARS-CoV-2 infection

Irrespective of the aforementioned drugs in the treatment regime, Machill *et al*[42] reported that patients with carrier genotypes of membrane bound O-acyltransferase domain containing 7 rs641738 polymorphism had significantly elevated bilirubin, ALT and alkaline phosphatase levels and decreased serum albumin levels during hospitalization. This points towards genetic susceptibility.

Dongiovanni *et al*[75] explored the polygenic risk score of hepatic fat content and genetic markers of liver fibrosis (PNPLA3 I148M variant). Both polygenic risk score of hepatic fat content and PNPLA3 I148M were found to be inherited independently of dysmetabolism at conception to gain a better understanding into the relationship between FLD, liver damage and COVID-19[23]. They reported that rs11385942 G>A at chromosome 3 gene cluster and rs657152 C>A at the ABO blood locus were significantly associated with the severity of liver injury in admitted SARS-CoV-2 patients[75]. In fact, although a greater ALT was related to a genetic propensity to FLDs during SARS-CoV-2, this was accompanied by reduced systemic inflammation or C-reactive protein levels and maintenance of hepatic production or circulating serum albumin levels in carriers with the PNPLA3 I148M variant. The protective impact of the non-secretor ABO phenotype against SARS-CoV-2 infection has yet to be explained; it depends on whether or not differences in membrane glycan shedding underlie differential tissue susceptibility such as the liver and lungs. Finally, it was observed that the risk of severe COVID-19 in hospitalized patients was not elevated by the use of genetics-based assessment, which is a reliable unconfounded all-time proxy of a tendency to and progression of FLD. Therefore, genetic propensity to obtain liver fat, despite aiding in liver injury, may unexpectedly defend against inflammation throughout SARS-CoV-2, suggesting that FLD predilection does not automatically lead to increased inflammation[43].

To summarize, the available evidence outlines that the degree of lipophilicity of drugs, inflammatory response to the antivirals, metabolization by CYP3A4 in the liver, interference of drugs with various transporters in the liver and molecules/proteins accountable for protection against the xenobiotics (*e.g.*, organic anion transporting polypeptide 1B1, p-glycoprotein, multidrug resistance-associated protein-2, breast cancer resistance proteins and ER-Golgi trafficking primarily by inhibiting Ras converting CAAX endopeptidase-1) are the underlying factors responsible for drug hepatotoxicity in SARS-CoV-2 infection treatment. Concurrently, drugs have a detrimental effect on bile salt export pump activity (an outflow transporter system responsible for excretion of waste and foreign substances from the hepatic cells) and thus becomes a central factor in the cholestasis process. In addition, robust shreds of evidence are lacking regarding the genetic predisposition to hepatic dysfunction in SARS-CoV-2 infection. Larger prospective studies are warranted in this regard.

CONCLUSION

Hepatic dysfunction in SARS-CoV-2 infection could be the result of an individual drug or due to interactions among more than one drug and may include a subset of the patient population that has a genetic propensity. Thus, serial estimation of hepatic indices in SARS-CoV-2 hospitalized patients, especially patients on treatment with drugs like RDV, LPV/RTV, favipiravir, HCQ and TCZ should be performed to take corrective actions for iatrogenic causes to avoid clinical deterioration.

Limitations

Nonetheless, our findings described here are only an assortment of studies and do not imply causation. Other limitations include the sample sizes that were comparatively small. The methodology adopted in

the included studies had a wide variation (as few studies only raised the probability of DILI rather than confirming the role of drugs with certainty). The therapeutic regimen, duration difference in the samples collected after hospital admission, the failure to record or the variation of the onset of disease/degree of liver injury and discrepancy in correcting different clinic and biochemical indices (sex, co-existing morbidities and age) varied between studies. The discrepancy in the measurement of liver indices and sub-classification of the cases was another limitation. Finally, only articles published in English were considered for analysis, which may have a local literature bias. In spite of all the aforementioned confines, the present review detailed important systematic data on the genetic susceptibility of liver damage and DILI in SARS-CoV-2 infection.

ARTICLE HIGHLIGHTS

Research background

Available data advocate that the spectrum of hepatic damage in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may be accredited to the direct cytopathic effect of the virus, indirect involvement by systemic immune-mediated inflammation and by iatrogenic causes, *i.e.*, drug induced. Empirical use of potentially hepatotoxic drugs in the management of SARS-CoV-2 infection is considered as one of the major etiopathogenetic factor for liver injury. Moreover, experimental and clinical evidence has shown that an underlying genetic factor may also be present. Hence, it is important to understand the genetics and iatrogenic-based mechanisms for liver dysfunction to make timely remedial measures.

Research motivation

To identify drug-induced liver injury in coronavirus disease 2019 (COVID-19) patients along with a genetic insight for the development of SARS-CoV-2 infection related liver injury to provide better care and timely management of critical patients.

Research objectives

To explore drug-induced and genetic perspectives in the development of SARS-CoV-2 infection related liver injury.

Research methods

A systematic literature search was carried out in multiple electronic databases: PubMed, Reference Citation Analysis, China National Knowledge Infrastructure and Goggle Scholar. The literature was screened using related MeSH keywords and relevant data. The inclusion criteria were English language articles published between December 1, 2020 and April 30, 2022. Reference lists from the articles in the initial search were screened to identify additional literature. There was no exclusion based on the study outcome and stage or severity of SARS-CoV-2 infection. However, studies with animal or cellular models were not included. Other criteria for exclusion were: injury due to SARS-CoV-2 infection itself; and hepatic injury from herbal or dietary supplements.

Research results

The primary analysis of this review revealed that DILI was due to the large-scale use of drugs/off-label drugs in the prophylactic and therapeutic regimen of COVID-19, and the genetic susceptibility underlying liver damage in COVID-19 patients is not yet fully understood. COVID-19-related liver injury (drug-induced and/or genetic-based) predominantly follows the idiosyncratic mechanism, *i.e.*, it is unpredictable with a variable latency period. In most commonly used drugs, the hepatic specific aminotransferases and other biochemical indices were elevated and were significantly associated with severity, hospital stay, number of COVID-19 treatment drugs and worse clinical outcomes.

Research conclusions

Hepatic dysfunction in SARS-CoV-2 infection could be the result of individual drugs or due to drug-drug interactions and may include a subset of the patient population with a genetic propensity. Thus, serial estimation of hepatic indices in SARS-CoV-2 infection hospitalized patients should be performed to make timely corrective actions for iatrogenic causes to avoid clinical deterioration.

Research perspectives

Additional prospective studies are warranted in this regard to justify drug-induced liver injury due to COVID-19 treatment along with the genetic predisposition, which should provide optimization of disease status.

FOOTNOTES

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