

## REVIEW

# Spectrum of COVID-19-induced liver injury in children

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**ABSTRACT**

Deranged liver functions, which mainly raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in 14%–53% of coronavirus disease 2019 (COVID-19) patients without known liver disease. Patients with the severe disease showed higher frequency and degree of liver dysfunction, while in milder cases the liver injury was transient. The mechanisms of hepatic injury include immune-mediated inflammation and hypoxic injury due to severe pneumonia and drug usage. It is also postulated that expression of the ACE2 receptor on cholangiocytes may predispose to cholestatic injury. In this study, it was aimed to review the spectrum of COVID-19-induced liver injury in children.

**Key words:** COVID-19, liver injury, children

**INTRODUCTION**


The main manifestations of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection include fever, dry cough, weakness, and breathing difficulty. Abnormal liver functions were frequently reported as extrapulmonary clinical features and almost one-half of patients experienced different degrees of liver function damage.<sup>[1,2]</sup> Deranged liver functions, mainly raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in 14%–53% of patients without known liver disease.<sup>[3,4]</sup> Patients with the severe disease showed higher frequency and degree of liver dysfunction, while in milder cases the liver injury was transient.<sup>[5]</sup> The mechanisms of hepatic injury include immune-mediated inflammation, hypoxic injury due to severe pneumonia and drug usage.<sup>[6]</sup> It is also postulated that expression of the ACE2 receptor on cholangiocytes may predispose to cholestatic injury.<sup>[7]</sup> Data on post-mortem liver biopsies are limited and demonstrates moderate microvascular steatosis and mild lobular and portal activity.<sup>[8]</sup> All drugs used in the treatment of coronavirus disease 2019

(COVID-19) have hepatotoxic potential at varying rates. Especially when these drugs are used together, this risk increases even more.<sup>[9,10]</sup> In one study, it was determined that liver function tests occurred in one out of every two patients during the treatment of COVID-19. It was determined that the drugs that increase liver enzymes the most and cause drug-induced liver damage are antibiotics more than favipiravir.<sup>[10]</sup> In this large multinational study including a cohort of 228 patients, SARS-CoV-2 infection produces acute liver injury in 43% of chronic liver diseases patients without cirrhosis. Additionally, 20% of compensated cirrhosis patients develop either acute on chronic liver failure or acute decompensation. Liver-related complications were seen in nearly half of the decompensated cirrhotics, which were of greater severity and with higher mortality.<sup>[11]</sup> Children under 18 years of age represented a minority hospitalized COVID-19 cases during the first year of the pandemic.<sup>[12,13]</sup> Their symptoms are usually milder.<sup>[14–16]</sup> Symptoms at presentation have been described in some studies;<sup>[17]</sup> however, it remains unclear how these symptoms group together into clinically identifiable phenotypes. Only 0.4% of severe cases are children.<sup>[18]</sup>

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Risk factors that lead to severe disease in children have been partly described including young age, obesity and underlying comorbidities, lymphopenia and elevation of other inflammatory biomarkers including high C-reactive protein (CRP).<sup>[19–21]</sup> Risk factors for pediatric intensive care units include MIS-C, elevated biomarkers of inflammation, asthma, moderate or severe liver disease, and heart disease.<sup>[22]</sup> Although symptoms of pulmonary involvement such as fever and cough are most common in patients with COVID-19, SARS-CoV-2 may lead to a systemic and multiorgan involvement picture including the gastrointestinal system. The liver is the second most frequently involved organ after the lung.<sup>[23]</sup> In this study, it was aimed to review the spectrum of COVID-19-induced liver injury in children.

## RISE IN LIVER TESTS AND COVID-19

Liver damage associated with the COVID-19 infection mechanism is not clearly understood. Damage directly viral systemic inflammation may be associated with infection, hypoxia and reperfusion dysfunction, multi-organ failure, which may be related to hepatotoxic effects of drugs used. Cytokine storms triggered by infection can cause damage to liver cells.<sup>[24]</sup>

Elevated serum transaminase enzyme values can be observed in some of the patients who present with symptoms of COVID-19. Elevated ALT and AST levels have been reported in 16% to 53% of patients.<sup>[25]</sup> In one study, patients with biochemical findings suggestive of hepatocellular or mixed-type liver injury at hospitalization were at risk of progression to serious illness during their hospital stay.<sup>[22]</sup> In a large series of patients with COVID-19 in China, it has been reported that 76.3% of the patients had elevated liver tests (AST, ALT, total bilirubin, gamma-glutamyl transferase (GGT), and this elevation occurred in 21.5% of the patients while they were hospitalized, especially in the first two weeks.<sup>[25]</sup> In studies conducted with some adults, it has been reported that 14.8% to 53.1% of ALT, AST and gamma-glutamyl transferase values may increase during the course of the disease along with a mild increase in bilirubin.<sup>[4,26]</sup> Based on these studies, we can say that the same situation may occur in children. Also, it was determined that a borderline increase was observed in ALT and AST values of 72 babies born to mothers with a diagnosis of COVID-19.<sup>[27]</sup> Studies have shown that the increase in biochemical markers of ALT and bilirubin is associated with poor prognosis in COVID-19.<sup>[28,29]</sup> In the study of Ma *et al.*, 11 (9.6%) children were found to have elevated ALT and it was determined that this increase was mostly concentrated in young children and infants.<sup>[30]</sup>

## COVID-19-RELATED LIVER DAMAGE IN CHILDREN

Comments on chronic liver disease (CLD) in a review article are as follows: It has been reported that COVID-19 is often associated with varying degrees of abnormal liver function tests, especially transaminases, which are usually transient and mild. Current evidence suggests that liver injury may result from direct pathogenicity of the virus, systemic inflammation, or toxicity from commonly used drugs in this subset of patients. SARS-CoV-2 infection in children is associated with minimal or no increase in liver enzymes, so the presence of abnormal liver function tests should trigger an evaluation for underlying liver disease. While CLD patients do not seem to be at greater risk of contracting the infection, those with cirrhosis, hepatocellular carcinoma, nonalcoholic fatty liver disease, autoimmune liver diseases or a liver transplant may be at greater risk for severe COVID-19.<sup>[31]</sup> People in all ages are susceptible to SARS-CoV-2 infection. However, infected children appear to have a milder disease course and a better prognosis than adults.<sup>[32]</sup> In fact, children have a special immune response system with distinct clinical features in COVID-19.<sup>[33]</sup> Qiu *et al.* analyzed 36 pediatric patients (aged 0–16 years) with laboratory-confirmed COVID-19 in three hospitals in Zhejiang and they recorded only 2 children with elevated liver enzymes.<sup>[12]</sup> Wang *et al.*, studied 31 cases of SARS-CoV-2 infection in children from six provinces in northern China and reported 22.2% of patients with elevated transaminases levels, being the highest value registered of ALT and AST 68 U/L and 67 U/L respectively.<sup>[34]</sup> Moreover, Zhu *et al.* analyzed the clinical features and outcomes of 10 neonates born to mothers with COVID-19 pneumonia and reported only two patients with abnormal liver function tests.<sup>[35]</sup> Since COVID-19 in children is associated with minimal or no increase in ALT and AST levels, The American Association for the Study of Liver Diseases (AASLD) suggests evaluating all children with abnormal liver enzymes for underlying liver diseases and do not assume COVID-19.<sup>[36]</sup>

## NEW THERAPIES FOR COVID-19 AND LIVER DISEASE

Unfortunately, the negative effects of many drugs that have to be used in COVID-19 patients have been ignored because COVID-19 suddenly came into our lives and there was no medicine to cure this disease, and many drugs have been tried to be used in the treatment. However, it is important to keep in mind that therapeutic agents can be hepatotoxic, especially in patients with underlying CLD. Lopinavir/ritonavir, an antiretroviral protease inhibitor, may cause transient and often asymptomatic elevations in serum aminotransferase levels.<sup>[37]</sup> Lopinavir-related risk of severe hepatotoxicity is low in patients with advanced liver disease, but lopinavir plasma trough levels are elevated and should therefore be used with caution. In

COVID-19 infected patients with hepatitis B virus (HBV) and hepatitis C virus (HCV), highly active antiretroviral therapy with lopinavir may result in exacerbation of the underlying CHB or chronic hepatitis C (CHC).<sup>[38]</sup> Hydroxychloroquine is not associated with liver abnormalities and is an extremely rare cause of clinically evident acute liver injury. No dose adjustment is required in patients with hepatic impairment.<sup>[39]</sup> However, high-quality clinical data showing a clear benefit of these agents for COVID-19 are lacking and hydroxychloroquine should be used with caution.<sup>[40]</sup> Tocilizumab, an interleukin-6 inhibitor, often causes mild serum elevations of aminotransferase and bilirubin, which are usually short-lived and asymptomatic.<sup>[41]</sup> Tocilizumab has been used safely and without worsening the disease.<sup>[42]</sup> Importantly, tocilizumab may increase the risk of reactivation of HBV; HBV screening is mandatory and antiviral prophylaxis should follow international guidelines when necessary.<sup>[43,44]</sup> Ivermectin, an antiparasitic agent, has been associated with minor, self-limiting elevations of serum aminotransferases and very rare instances of clinically significant liver injury.<sup>[45]</sup> Dosage adjustments are not required in patients with hepatic impairment. Remdesivir is a new nucleotide analog currently under investigation and has no experience with liver cirrhosis. Elevated transaminase levels have been reported in up to 22.6% of patients.<sup>[46]</sup> Similarly, there is no data available in patients with CLD about favipiravir, an RNA polymerase inhibitor that may also cause liver cytolysis.<sup>[47]</sup>

## RISKS OF COVID-19 PANDEMIC FOR CHILDREN WITH IMMATURE ORGANS

Growth and development are two main features observed in children that are not observed in adults.<sup>[48]</sup> Children show progressive developmental changes associated with the growth of organs and maturation of their functions.<sup>[49]</sup> Drug applications have an important place in terms of patient safety, and these applications are more riskier in children and infants.<sup>[50]</sup> Although an average drug dose is calculated for all age groups, the dose of the drug may differ for each child.<sup>[51]</sup> These differences are stated as changes in metabolic capacity in children, joint development, and differences in kidney and gastrointestinal function developments in the first 18 months.<sup>[52]</sup> Physiological development, including physical development and maturation of organs, transporters and enzymes in children, can cause variability in pharmacokinetic parameters. Therefore, pharmacokinetic measurements; it should relate to measures of growth, such as age, weight or body surface area.<sup>[53]</sup> Especially liver enzymes play an active role in reducing the toxicity of drugs by converting them to metabolites. However, enzymes are not formed in newborns. In the same newborns, enzymatic activities are higher in some cases compared to adults. This

situation significantly affects the type and dose of drugs to be given to the pediatric group.<sup>[54]</sup> Fewer pediatric pharmacodynamic studies than pharmacokinetic studies appear to be a serious problem for dose calculation in pediatrics.<sup>[55]</sup> As a result, the importance of pharmacokinetic and pharmacodynamic studies is more evident in the pediatric field.<sup>[56]</sup> Therefore, it is important to use the drugs more rationally for COVID-19 in children.

## DISCUSSION

More than 2 years into the COVID-19 pandemic, ongoing waves of infection challenge hospital resources and public health responses worldwide. Most children are asymptomatic or have mild symptoms after exposure to SARS-CoV-2 virus, including with the Delta and Omicron variants. Despite the low risk of severe COVID-19 in children, there has been an increase in the number of children requiring hospitalization and treatment as exposure to SARS-CoV-2 becomes near universal.<sup>[57]</sup> It turned out today that COVID-19 triggered many diseases. Studies have shown that many of these diseases, which prevent the living standards of people, many of which are fatal, can be frightening and anxiety-provoking.<sup>[58]</sup> One of the damages caused by COVID-19 is the deterioration of the liver system.<sup>[30]</sup> Public and public health officials, clinicians, and researchers have been highly concerned about the mortality rate and effect of the virus on patients with chronic diseases.<sup>[59]</sup> In addition to physical well-being, the COVID-19 pandemic affects behavioral and mental health. Restrictions make people feel isolated, lonely, stressed, anxious, and helpless. Individuals may have deep concerns about being in contact with someone who has COVID-19. Moreover, becoming ill or dying and losing a loved one results in stress due to grief and bereavement.<sup>[60,61]</sup> Therefore, addressing this issue can be a solution to many problems that children will experience. Since there are not enough studies on this subject, there is a need for research that addresses this issue and addresses the concerns of children and families. Chronic diseases can cause serious mental problems such as not accepting the disease, denial and anger in both the child and family members. This situation negatively affects the healing process of the disease. For this reason, children and family members should be handled together and solutions should be tried to find solutions to this issue.

## CONCLUSION

We can say that COVID-19 has a risk of causing liver damage, and it is important to consider the possibility of liver damage by the drugs used in the treatment of COVID-19. It should be noted that the dose calculation of the drugs used in the treatments to be used for

COVID-19, especially in children who are immature in terms of organ development and who are in a sensitive group, should be very carefully calculated and not every drug will be suitable for this group.

## DECLARATIONS

### Conflicts of interest

There is no conflict of interest among the authors.

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