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COVID-19-induced liver injury in infants, children, and adolescents

Bitar R *et al*. COVID-19 induced liver injury in children

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Abstract

Coronavirus disease 2019 (COVID-19) typically presents with fever and respiratory symptoms in children. Most children develop an asymptomatic and mild illness, with a minority of patients requiring specialist medical care. Gastrointestinal manifestation and liver injury can be part of the manifestations in children following infection. The mechanism of liver injury may include infection with severe acute respiratory syndrome coronavirus 2 that originates from direct viral tissue invasion, immune response, or medication effects that tend to manifest in mild liver dysfunction and a benign course in most children without pre-existing liver disease. However, non-alcoholic fatty liver disease, among other pre-existing chronic liver disorders, presents a higher risk for developing severe COVID-19 illness and poor outcomes. On the other hand, the broadness of the liver injury and concomitant manifestations is amalgamated with the severity of COVID-19 disease and is considered an independent prognostic factor. Respiratory, hemodynamic, and nutritional supportive therapies are the mainstay of management, emphasizing vaccination of children at increased risk of developing severe COVID-19 disease. This review describes liver manifestations in children with COVID-19, detailing its epidemiology, basic mechanisms, clinical expressions, management, and

prognosis among pediatric patients with and without pre-existing liver disease and patients with liver transplantation.

Key Words: Keywords: Child; Corona virus disease 2019; Gastroenterology; Hepatic dysfunction; Infection; Liver diseases; Severe acute respiratory syndrome coronavirus 2; Liver injury; Liver transplant

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Core Tip: Liver injury presenting with elevated levels of alanine aminotransferase and aspartate aminotransferase is common in children infected with the coronavirus disease 2019 (COVID-19) virus. The mechanism of liver injury is not fully understood and is likely secondary to the viral invasion of the liver, hepato-toxic medications, and the patient's immune-mediated response. Liver injury in children is generally mild and resolves spontaneously but is usually seen in children with more severe illnesses. In addition, children with underlying non-alcoholic fatty liver disease and children with chronic liver disease may have a higher risk of severe COVID-19 illness. Management of liver injury after COVID infection is supportive. Proactive vaccination may reduce the transmission of infection and the severity of the disease.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) typically presents with fever, weakness, myalgia, malaise, and pulmonary symptoms[1]. In addition, a significant percentage of those infected with the virus demonstrated gut manifestations such as loss of appetite, colic, and lose stool[2]. Similarly, hepatic involvement has been reported in many studies [3,4]. Previous waves of the severe acute respiratory syndromes encountered in the Middle East have shown more or less elevated serum transaminases and bilirubin and decreased serum albumin levels[5,6]. SARS-CoV-2 shares up to 80% genomic sequence similarity

with both viruses, and consequently, hepatic injury is an anticipated manifestation of COVID-19[7].

This review aims to describe the liver injury in children with COVID-19, detailing its epidemiology, underlying mechanisms, clinical manifestations, management, and prognosis. We will also describe liver involvement in high-risk groups, including children with pre-existing liver disease.

EPIDEMIOLOGY

Acute liver injury in adults and children with SARS-CoV-2 infection is defined as an elevation in the serum concentration of aminotransferases (transaminases). The spectrum of liver injury ranges from asymptomatic elevated serum transaminase levels to severe liver injury, with reports of acute-on-chronic liver failure in patients with underlying liver disease. Usually, 14%-53% of adult patients develop mild to moderate elevation of liver enzymes[8,9].

Abnormal transaminase levels have also been linked to the severity of COVID-19[9-13]. Higher morbidity and mortality have been witnessed in those COVID-positive and altered liver function, with liver injury being an independent prognostic factor of COVID-19[14,15]. A review by Bende *et al*[15] of post-acute COVID-19 syndrome of 97 subjects demonstrated increased liver stiffness, viscosity, and steatosis in around one-third of the patients, with significantly higher values in subjects with pulmonary injury compared to those without.

COVID-19 in children and adolescents may be asymptomatic or cause only mild symptoms. These include fever, cough, upper respiratory tract symptoms, diarrhoea, nausea, and vomiting. In a multinational, multicentre cohort study, 22% of patients had gastrointestinal symptoms, of whom 7% had no respiratory symptoms[16]. In early pediatric reports, the rate of transaminase elevation was 14%-50%[12,17,18]. However, these data may need to be more representative because transaminase levels and liver function tests were only reported in a small proportion of patients. In a study involving 280 children ≤ 17 years of age with COVID-19, the elevation of serum transaminases was

mild, with a prevalence of 29%, predominantly children < 3 years of age[19]. Those with chronic liver diseases have encountered more aggressive diseases with an increased risk of hepatic failure [20].

MECHANISMS OF LIVER INJURY

The causes of elevated liver transaminases in COVID-19 still need to be fully understood[21]. Some possible risk factors, illustrated in Figure 1, include:

Viral invasion of liver tissue

There is evidence that the virus infects the organ cells by exploiting the angiotensin-converting enzyme (ACE) 2 receptor, complied by intracellular replication. ACE2 receptors are found in the respiratory tissues, gut, liver, kidney, and heart. However, compared to its load in the lung of acutely infected children, studies described the viral load in the hepatic cells as low. Evidence of hepatic cell injury with a high level of serum transaminases has been found in > 70% of patients with severe COVID-19 diseases[22,23]. Moreover, the virus has also been isolated from many patients' stools, indicating the infections spread to the gastrointestinal tract and not exclusively the pulmonary cells[22,23]. This direct viral invasion of liver tissue and replication inside the hepatocytes can explain the resulting hepatic injury.

Medications

Another mechanism from which the liver of infected children with SARS-CoV-2 sustains an injury is the polypharmacy commonly used during the illness with the virus. Antiviral drugs, antibiotics, and steroids used to treat moderate and severe COVID-19 may also cause liver toxicity in their own right[24,25]. Antipyretics, such as paracetamol, do not play a significant role in COVID-19 Liver injury. Other drugs include chloroquine, isoniazid, antivirals, particularly anti-Human immunodeficiency virus medications (lopinavir/ritonavir), and biological agents such as tocilizumab, which might be considered potential co-factors in the pathophysiology of liver injury in children with

COVID-19[9,22,23]. In a study of 147 patients with COVID-19-induced liver injury, the prevalence of hepatic injury was the same as in those with normal or impaired liver function when treated as outpatients. However, it was observed to be higher in those patients who received hospital care and with a higher rate of utilization of ritonavir[26].

The immune response

The resulting immune response is immature in infants and children with COVID-19 infection, and while it is mild in most patients, it can be severe. Hepatic injury caused by the SARS-CoV-2 virus in children is associated with systemic and local inflammatory responses of varying severity. During the acute stage of the infection, the immune system attempts to limit the reproduction of the virus through both immediate and delayed immune responses by producing specific antibodies against it. When exaggerated, this immune-mediated response can damage the hepatic tissue in children with more aggressive and prolonged diseases[1]. The inflammatory markers include cytokines, T helper 17 cells, cytotoxic DC8 T cells, interleukins 1, 2, and 6, serum ferritin, tumor necrosis factor, interferon, and other mediators[9], as well as C-reactive protein, are commonly elevated. In some patients, this may result in a "cytokine storm", leading to rapid clinical deterioration with multiple organ failures and endothelial dysfunction, further aggravating liver damage[2,26-32]. Endothelial dysfunction is associated with the stimulation of neutrophil extracellular traps through immunological mechanisms[19], causing the development of microthrombi in the lungs, manifesting the pulmonary symptoms of SARS-CoV-2[33]. The liver is similarly affected, and hepatic damage may be accelerated by a hypercoagulative disease state, which can involve other organs and tissues. Autopsy reports have confirmed the presence of hepatic sinusoidal congestion and micro thrombosis[20,27].

Acute liver injury is also a prominent feature of multi-system inflammatory diseases in children, occurring as a late complication of SARS-CoV-2 infection[34]. The exact mechanism still needs to be fully understood. Some researchers suggest an abnormal immune response to the SARS-CoV-2, similar to Kawasaki disease[35], or immunoglobulin

G antibodies enhancement of monocytes and cytotoxic CD8+ T cells[8], with downregulation of neutrophil and lymphocyte functions[6,7]. The pediatric multi-system inflammatory syndrome temporally associated with COVID-19, also known as a multi-system inflammatory syndrome in children (MIS-C), is a persistent acute febrile illness progressing to multi-organ dysfunction, conferring over a 2-fold increased risk of elevated serum transaminases. Although affected children often have an underlying medical condition, such as obesity, immunocompromised state (including malignancy), or CLD[36], it may also occur in previously healthy children and adolescents[37]. A few weeks after contracting SARS-CoV-2, affected children present with either a Kawasaki-like picture, shock, or macrophage activation syndrome, usually warranting admission to the pediatric intensive care unit (PICU). Clinical presentation includes fever and multi-organ involvement, including gastrointestinal, cardiovascular, mucocutaneous, and neurological symptoms, with laboratory evidence of severe inflammatory activity and coagulopathy[38,39]. Although liver involvement is reported, it occurs as part of intense multi-organ involvement[24,25].

CLINICAL MANIFESTATIONS

Acute Manifestations

Liver injury in children infected with COVID-19 is reflected by elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels in 13% to 50% of patients[12,18,24,25,40]. AST levels > 50 UI/L are observed in 20%-50% of cases, and ALT levels > 45 UI/L in up to 35%[12,40]. Abnormal serum bilirubin levels may also occur but to a lesser extent than transaminase increases. Raised alkaline phosphatase and gamma-glutamyl transferase levels are rarely observed. Liver injury is generally mild and resolves over time, and severe liver dysfunction is uncommon. Abnormal transaminase levels have also been linked to the severity of COVID-19, with liver injury occurring in 58.8% of patients with moderate and 66.7% of those with severe disease[10,11,41]. Other studies demonstrated elevated liver enzymes to be seen more often (40%-60%) in those with a severe illness compared to asymptomatic or patients with mild disease (18%-

25%)[9,12,13]. In a meta-analysis and systematic review, significantly higher levels of aminotransferases and significantly lower albumin levels were more common in severe cases of COVID-19[42].

Severe acute liver injury

Severe acute liver injury, defined as serum ALT values five times above the upper limit of normal[9,36,43], is commonly associated with severe COVID-19 infection, shock, respiratory compromise, higher serum inflammatory markers, and longer overall length of stay in hospital[20]. However, acute liver failure (ALF) is rare and is more common in patients with severe illness and multi-organ dysfunction [20,22]. In one published case report, an early teenager died with acute fulminant hepatic failure secondary to COVID19 infection. However, a similar child's live was rescued with liver transpnat[44,45].

Chronic manifestations

Post-COVID-19 cholangiopathy: This proliferative cholangiopathy is associated with the lymphocytic portal and parenchymal infiltration after excluding other possible causes, such as adenovirus infection. It occurs several weeks or more after full recovery from asymptomatic or mild acute infection[40]. Two clinical patterns of presentations have been described: ALF in infants and acute hepatitis with cholestasis in older children. The group with hepatitis and cholestasis showed an excellent response to systemic steroids, while patients with ALF needed LT.

Secondary sclerosing cholangitis: Secondary sclerosing cholangitis (SSC) has been described in adults following COVID-19 as prolonged cholestasis with severe cholangiopathy. Unlike children, it occurs mainly in patients who have been through a complex and critical course of COVID-19 requiring admission to an intensive care unit (ICU), with a mean time from COVID-19 disease to the diagnosis of cholangiopathy of 118 d (range 138-319). Compared to adults, ultrasound findings include strictures of intrahepatic bile ducts along with intraluminal sludging and casts formation[44,46]: biliary

duct dilatation, periportal oedema, gallbladder wall oedema, and thickening are more common in children.

Adult patients with post-COVID-19 cholangiopathy and SSC show progressive disease unresponsive to treatment with ursodiol therapy, with those most severely affected requiring LT. Corticosteroids, immunomodulators, or immunosuppressant therapies have not been studied in affected patients.

Special considerations

Obesity and Non-alcoholic fatty liver disease: In a meta-analysis, a number of 285004 children, infected with the novel virus, 9353 (3.3%) suffered from one or more than one other morbidity with obesity was documented as one of the morbidities encountered. Among 507 obese children, 64 had either severe COVID-19 or required ICU admission, with a calculated risk of severity of 2.87 (95%CI, 1.16-7.07)[46]. Obesity is thus the most common comorbidity reported in children with severe SARS-CoV-2 infection[20,47-50]. Although the proportion of patients with non-alcoholic fatty liver disease (NAFLD) in published obese cohorts remains unknown, children with NAFLD, especially those with obesity, should be considered a risk group for severe COVID-19[20].

Immunosuppressive therapy

The link between Immune deficiency and severe gastrointestinal and liver involvement has not been proven [47,52,53]. Furthermore, some immunosuppressive medications even mitigate severe COVID-19. These include calcineurin inhibitors, which potentially inhibit coronavirus replication [54]. European surveillance disproved any link between the use of calcineurin inhibitors and severe SARS-CoV-2 infections [55]. Moreover, drugs with antimetabolic activities such as mycophenolic acid reported to interfere with the virus activity, in laboratory studies [56]. In addition, the regular use of immunosuppressants did not produce a severe form of the disease[57,58]. In a study involving 180 children with an LT, 30 required non-ICU hospital admission (median 5 d), three required ICU admission.

However, non of them required inotropes or invasive ventilatory support[20]. Children on post-transplant immunosuppressive regimens have been shown to experience mild disease, similar to the general paediatric population[58-60].

MANAGEMENT

While liver involvement is commonly associated with COVID-19 infection in children, most cases demonstrate mildly abnormal liver function, which usually normalises without any specific treatment[9].

Supportive therapy

Like most other viral illnesses with inflammatory liver involvement, the management of COVID-19 infection is supportive. It includes stabilisation of vital signs, fluid and electrolytes correction, and ensuring adequate liver oxygenation. Avoiding hypo-perfusion and hypoxia (especially in patients with respiratory distress) is essential. Liver recovery will likely be enhanced with the ongoing improvement of the systemic inflammatory status. Some patients might require poly-pharmacotherapy depending on the severity of their lung injury and the other organs involved. Avoidance of hepatotoxic medications is crucial. All specific virus-targeted therapies are employed exclusively in clinical research trial settings[13].

Nutritional therapy

Nutrition is essential, especially in children with a prolonged critical illness. They are at higher risk of developing malnutrition, associated with increased morbidity and mortality. Hence, early oral or nasogastric tube feeding is recommended. It is preferred to parenteral nutrition, except in patients with severe gastrointestinal dysfunction. During the acute phase, the energy requirements do not need to exceed resting energy expenditure. Based on the tolerance and the patient's general condition, the European Society of Pediatric and Neonatal Intensive Care recommends a gradual increase toward

the target caloric need. Enteral nutritional support must be maintained as long as required until adequate oral intake is reliably attained to support physical and nutritional rehabilitation[61,62].

Children with pre-existing CLD and LT recipients

Infected patients with underlying primary liver diseases and other metabolic liver diseases will continue to receive treatment for their underlying condition[9]. Elevated liver enzymes shouldn't be a reason to discontinue antiviral treatment as far as liver function is monitored[10]. Post-liver transplant patients are advised to continue their immunosuppressants and modulator medications as normal.

The COVID-19 pandemic has profoundly impacted transplantation worldwide, both donor's and recipients' viral transmission and healthcare resources[59]. There is no indication for delaying or interrupting oncological treatments, withdrawing immune suppression, or postponing any required treatments to those patients with liver-transplant [57].

PROGNOSIS

Mortality is higher in COVID-19 children with deranged hepatic function and the proportion of liver injury is directly related to the poor prognosis[14]. A literature review of 12 studies with a total of 6976 patients, whose laboratory tests were obtained at admission significantly showed higher levels of transaminases and low albumin levels that were more common in severe cases of COVID-19[42]. In a meta-analysis of 12 studies with a total of 5135 COVID-19 subjects with collected data on raised AST and outcomes, increased AST values were associated with three times more risk of poor effects (pooled odds ratio: OR, 2.98; 95%CI, 2.35-3.77; $P < 0.00001$)[63]. Similarly, ten studies documented reported elevated ALT and outcomes, including 5091 patients, showed a marked increase in poor outcomes (pooled OR: 1.73; 95%CI: 1.32-2.27; $P < 0.0001$). Furthermore, a meta-analysis of four studies with a total sample size of 485 patients demonstrated that those

with acute liver injury had higher odds of poor outcomes with a pooled OR of 1.68 (95%CI, 1.04-2.70; $P = 0.03$)[63].

Studies of COVID-19 outcomes among children with CLD are limited. Data from adult patients have reported mixed results and occasionally conflicting conclusions, making it difficult to determine a prognosis[64-66]. An earlier meta-analysis of 17 studies with a sample size of 8800 COVID-19 patients revealed that chronic liver disease did not significantly affect the outcomes (pooled OR, 0.96; 95%CI, 0.71-1.29; $P = 0.78$)[63]. A similar conclusion was also reached in a review where there were no major differences in COVID-19 severity and mortality between patients with liver disease and those without[67]. However, given the limitations of these studies, their results must be cautiously interpreted.

A more recent and comprehensive meta-analysis of 40 studies with 908032 participants concluded that CLD is markedly affected clinical outcomes among COVID-19 patients[68]. For disease severity, the pooled OR was 2.44 with 95%CI of 1.89-3.16; for mortality, it was 2.35 (95%CI, 1.84-3.00). Subgroup analysis indicated that NAFLD, metabolic-associated fatty liver disease, and cirrhosis had the highest odd ratios of 5.6, 3.2, and 3.09 for COVID-19 severity. In other studies, cirrhosis was implicated as a significant risk factor for hospitalization, intensive care admission, and mortality. Mortality among cirrhotic patients was 32% compared to 8% among non-cirrhotic patients[69]. Other reports have also confirmed a higher risk of COVID-19 severity and mortality in CLD patients, up to four and two times, respectively, compared with those without CLD[63,70]. In children, a systematic review and meta-analysis inferred that those with COVID-19 have preserved effector and immunosuppressive components, and encountered a milder disease compared to adults [33].

Most children with MIS-C achieve full clinical recovery with a death rate of < 1%. However, in those where the clinical course was severe and required intensive care interventions for ALF, the possibility of death was 11 times more than in those without these complications[71].

PREVENTION

Preventative measures should be implemented for vulnerable patients at risk of exposure to SARS-CoV-2, as they may develop severe illness.

General public health measures

General measures for distancing, maintain good hygiene and avoiding contamination with the virus are important for the general public as well as for children with underlying liver condition

Vaccinations

Children suffering from CLD and/or LT are recommended to get the COVID-19 vaccination, which is generally safe in this group[72]. However, CLD among adults with non-cirrhotic compensated cirrhotic or decompensated cirrhotic was associated with lower rates of development of positive SARS-CoV-2 neutralizing antibodies compared with healthy individuals (77 *vs* 90 percent)[73]. Other studies suggested that patients with liver disease who received COVID-19 vaccination have a negligible risk of infection and COVID-19-associated mortalities[74]. Likewise, children awaiting a liver transplant also would need to be prioritized for receiving Covid vaccine. The type of vaccine would depend on the active strain of the virus as well as the chance to choose from different vaccines as per the local infectious disease department recommendations and regardless of whether there is enough time prior to the transplant to allow the child to receive the 2 doses or not as in certain vaccines protocols [75]. Routine serology tests to check for the Covid19 virus antibodies are not indicated[72].

CONCLUSION

The spectrum of liver injury in children with COVID-19 ranges from being asymptomatic with elevated serum transaminase levels to severe liver injury, with reports of acute-on-chronic liver failure in patients with underlying liver disease. The aetiology is multifactorial. Most children demonstrate a mild self-resolving liver injury; the level of

severity of the damage is linked to how severe the infection is with COVID-19 disease and is considered an independent prognostic factor. Treatment is supportive and, in rare patients, requires LT. Children with underlying NAFLD and other pre-existing chronic liver disorders present a higher risk of developing severe COVID-19 illness and poor outcomes.

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