Liver Injury in Children with COVID-19: A Systematic Review

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Abstract:
Background: The rapid global spread of coronavirus disease 2019 (COVID-19) infection has become a major health issue with high morbidity and mortality rates. COVID-19 in children showed different unique presentations. Besides respiratory symptoms, a growing body of evidence indicates multi-organ manifestation, including liver involvement. In this regard, several data supported an association between COVID-19 infection and liver injury in adults, while on the other hand, there is compelling but currently limited evidence in children. In this systematic review, we summarize data of updated literature regarding the evidence of acute liver injury in children with COVID-19.

Methods: Online scientific articles were explored on PubMed and Google Scholar databases using keywords. The systematic review was performed under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Results: The literature search yielded 238 articles, of which 16 were identified as relevant to the topic and met the inclusion criteria. A total of 564 pediatric patients were confirmed positive for COVID-19 by PCR examination, involving 298 (52.9%) boys and 266 (47.1%) girls with an age range of 1 day - 17 years. Liver injuries have been reported in pediatric COVID-19 patients, with prevalence ranging from 1.5 to 52%.

Conclusion: SARS-CoV-2 virus infection in children shows a unique presentation. Several reports suggest that liver injury correlates with the severity of COVID-19 disease. Therefore, monitoring liver function in COVID-19 patients is important to assess the prognosis.

Keywords: acute liver injury, children, COVID-19, prognosis

Introduction
COVID-19 is a disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The prevalence of COVID-19 in children is substantial and with unique manifestations, which are diverse from COVID-19 cases in general adult population. COVID-19 was predominantly clinically manifested in the respiratory
tract at the beginning of the pandemic. However, recent data suggest that SARS-CoV-2 infection can cause systemic inflammation with multi-organ involvement, known as Multisystem Inflammatory Syndrome in Children (MISC). In addition, ACE2 receptor, the functional receptor for SARS-CoV-2 to enter cells, was expressed in several other organ systems, including the gastrointestinal, liver, bile ducts, kidney, cardiovascular, nervous system, and integument. This explains the emergence of extrapulmonary manifestations in COVID-19. Manifestations of liver involvement in pediatric COVID-19 is a relatively rare condition but often with a poor prognosis. Thus, it requires special attention.

The pathophysiology of liver injury in COVID-19 is thought to be due to virus, inflammation, hypoxic-ischemia/micro-thrombosis, and drugs. Several studies have reported signs of liver injury in COVID-19 patients, including increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), increased bilirubin levels, and prolongation of prothrombin time (PT). Case reports also show acute liver failure and fulminant hepatitis in patients with severe COVID-19. However, case reports of liver involvement in pediatric COVID-19 patients are limited and show heterogeneous results. Moreover, the correlation between liver involvement and the severity as well as prognosis of COVID-19 in children is still unclear. Therefore, this systematic review aims to determine the incidence of liver injury in pediatric patients with COVID-19 and its relationship to prognosis.

Methods

Literature Search

Online scientific articles were explored on PubMed and Google Scholar databases using keywords (MesH Term) of "SARSCoV-2," "COVID-19," "coronavirus," "children," "pediatric," "liver," "hepatitis," "liver injury," "alanine aminotransferase (ALT)", "aspartate aminotransferase (AST)", gamma-glutamyl-transpeptidase (GGTP)", "alkaline phosphatase (ALP)", "lactate dehydrogenase (LDH)", "bilirubin", "albumin", "international normalized ratio (INR)", "prothrombin time (PT)".

The inclusion criteria for research articles include publication in English; full text available; retrospective or prospective or cross-sectional observational study designs and case reports containing data on hepatic manifestations of COVID-19 in children; the age of the study subject <18 years and confirmed COVID-19. Meanwhile, the exclusion criteria were duplicate articles; only abstract available; review articles; systematic reviews; meta-analyses; comment articles; and letters to editors. The systematic review was performed under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1).
Data Extraction
Data contained in the articles were then extracted, including lead author, year of publication, country, type of study, number of subjects, age of subjects, gender, comorbid liver disease, clinical symptoms, laboratory findings, and association with severe COVID-19 symptoms. Data extraction was performed by a minimum of two authors independently. The data was recapitulated in an excel file by each investigator and then compared. The differences found would be resolved by a third author.

Results and Discussion
The literature search yielded 238 articles, of which 16 were identified as relevant to the topic and met the inclusion criteria. A PRISMA diagram that describes in detail the systematic search strategy is shown in Figure 1. The articles included retrospective studies, cohorts, case series, and case reports published in 2020-2021. A total of 564 pediatric patients were confirmed positive for COVID-19 by PCR examination, involving 298 (52.9%) boys and 266 (47.1%) girls with an age range of 1 day - 17 years. Recently, liver involvement has been reported in pediatric patients with COVID-19. Clinical manifestations include nausea, vomiting, drinking intolerance, anorexia, abdominal pain, and even jaundice. Meanwhile, the most frequently reported markers of liver injury include elevated alanine transaminase (ALT), aspartate transaminase (AST), and elevated bilirubin levels. Data reporting decreased levels of albumin, prothrombin time (PT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) are limited. Although not all studies reported ultrasonographic features, several reported normal liver and bile duct features, one patient with hepatomegaly and another with hepatomegaly secondary to hepatic steatosis. Characteristics of case reports and studies on the manifestations of acute liver injury in pediatric patients with COVID-19 are shown in Table 1.

Manifestations of Liver Injury in Pediatric COVID-19 Patients
COVID-19 infection in children shows unique and varied clinical manifestations. A large retrospective cohort study reported that the manifestations of COVID-19 in pediatrics included 16.5% with respiratory symptoms (cough, shortness of breath), 13.9% with gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), 8.1 % with skin symptoms (rash), 4.8% with neurological manifestations (headache), and 18.8% with non-specific symptoms (fever, weakness, muscle aches, joint pain, impaired smell, and taste). Although not as much as reported in adult patients, liver lacerations due to COVID-19 in pediatrics were recorded and characterized by significant abnormalities in liver enzyme levels.

Dooki et al. reported an increase in ALT (27.8%) and AST (38.9%) levels of 18 pediatric COVID-19 patients in Iran. Xia et al. also reported similar results, with an increase in ALT levels (>40 U/dL) in 25% of 36 pediatric patients with COVID-19.
Following other studies, Perez et al. showed that of 219 pediatric patients with COVID-19, the ALT levels were increased to >40 IU/dL in 105 (36%) subjects, in which 31% (n=69) in pediatric patients with COVID-19 and 51% (n=36) in children with MIS-C. Pediatric patients with MIS-C have a 2.3 times risk of an increase in ALT compared with non-MISC pediatric COVID-19 patients.5

A retrospective study involving 8 cases of children with severe or critically ill COVID-19 admitted to the PICU in Wuhan (aged two months to 15 years) reported elevated ALT levels in 50% of cases with normal bilirubin levels.12 A cohort study by Qiu et al. analyzed 36 pediatric patients (0-16 years) with confirmed COVID-19 at three separate hospitals in Zhejiang, China, found only two patients (5.5%) had elevated ALT and AST levels.13 A retrospective study of 77 pediatric patients with COVID-19 also noted the increased level of ALT in 1 case (1.5%), AST in 7 cases (10.3%), ALP in 7 cases (28%), while total bilirubin, direct bilirubin, albumin, and INR were normal.14 Other reports mentioned an increase in ALT and AST levels along with normal levels of bilirubin, albumin, PT, and INR in pediatric patients with COVID-19.15 Jiehao et al. showed a relatively low prevalence of manifestations of liver injury, with 1 in 10 pediatric patients with COVID-19 (10%).16

**Figure 1.** PRISMA diagram.
**Table 1. Prevalence and manifestation of liver injury in children with COVID-19**

<table>
<thead>
<tr>
<th>No</th>
<th>Author, Year</th>
<th>Country</th>
<th>Study</th>
<th>Number of subjects</th>
<th>Gender, Age</th>
<th>Clinical Manifestation</th>
<th>Marker of liver injury</th>
<th>Correlation with severity</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| 1  | Sgouropoulou V et al. (2021) | Greece | Case Report     | 1                 | Male, 5 years old | Nausea, vomiting                           | AST 526 IU/L (↑)  
ALT 1413 IU/L (↑)  
ALP 277 IU/L (↑)  
Total bilirubin 0.4 mg/dL (N)  
Direct bilirubin 0.15 g/dL (N)  
Albumin 4.6 g/dL (N)  
INR 1.35 (N)  
PT 15.1 s (N) | Not evaluated                                                                 | Increase of liver enzyme which is sign of severe acute liver injury correlated with SARS-CoV-2 infection in children |
| 2  | Cui Y et al. (2020)    | Iran    | Case Report     | 1                 | Male, 11 years old | Fever, jaundice, abdominal pain            | AST 1038 U/L (↑)  
ALT 1260 U/L (↑)  
Albumin 3.7 g/dL (N)  
Gamma GT 30 U/L (N)  
Total bilirubin 19.2 mg/dL (↑)  
Direct bilirubin 16 mg/dL (↑)  
CRP 29 mg/L (↑)  
Ammonia 186 mmol/L (↑)  
Lactate 56 mg/dL (↑)  
PT 29.4 s ; INR 3.8 (↑) | Not evaluated                                                                 | Fulminant hepatitis was reported in children with severe COVID-19                                             |
| 3  | Saeed et al. (2021)    | Iran    | Case Report     | 1                 | Male, 11 years old | Fever, jaundice, abdominal pain            | AST 2030 U/L (↑)  
ALT 690 U/L (↑)  
ALP 387 U/L (↑)  
Total bilirubin 35.4 (↑)  
Direct bilirubin 21.6 (↑)  
LDH 5660 (↑)  
PT 15.9 s ; INR 1.3 (↑) | Patient died due to fulminant hepatitis                                                                 | Acute liver injury with fulminant hepatitis occurred in children with severe COVID-19                           |
| 4  | Sica et al. (2021)     | Italy   | Case Report     | 1                 | Male, 14 years old | Dehydration, jaundice, diffuse abdominal pain, | ALT 143 IU/L (↑)  
AST | A new onset hepatic steatosis in children with SARS-CoV-2                                                                 | Non-alcoholic hepatic steatosis was reported in                                                              |
<table>
<thead>
<tr>
<th>Case ID</th>
<th>Author(s)</th>
<th>Country</th>
<th>Study Type</th>
<th>Age/Duration</th>
<th>Features</th>
<th>Laboratory Data</th>
<th>Imaging/Other Tests</th>
<th>Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Perez et al. (2021)</td>
<td>USA</td>
<td>Case series</td>
<td>Male, 16 years old</td>
<td>Jaundice, abdominal pain, nausea, non-bloody and non-bilious vomiting, low intake, dark urine</td>
<td>Increase of serum AST (655 U/L), total bilirubin/direct bilirubin (3.6/2.2 mg/dL), gamma GT (301 U/L), Albumin 5.0 g/dL (N), INR 1.1 (N)</td>
<td>Abdominal ultrasonography: normal liver and biliary duct</td>
<td>Acute hepatitis with clinical jaundice and cholestasis without biliary obstruction, associated with SARS-CoV-2 infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female, 17 years old</td>
<td>Fever for 4 days, acute onset of jaundice, dark urine</td>
<td>Increase of serum AST (154 U/L), total bilirubin/direct bilirubin (3.4/1 mg/dL), gamma GT (147 U/L), INR, albumin and platelet were within normal range. Ultrasonography: hepatomegaly (16.1 cm liver span) with normal echogenicity, without gallstone, sludging, or dilatation of the bile duct</td>
<td>Not evaluated</td>
<td>10% children with COVID-19 have significant</td>
</tr>
<tr>
<td>6</td>
<td>Cui Y et al. (2021)</td>
<td>China</td>
<td>Case report</td>
<td>Female, 55 days old</td>
<td>Jaundice</td>
<td>Increase of AST 100U/dL, ALT 84 U/dL, total bilirubin 33.7 mg/dL, direct bilirubin 25.2 mg/dL</td>
<td>Not evaluated</td>
<td>Abnormal liver function was found in infant with COVID-19</td>
</tr>
<tr>
<td>7</td>
<td>Jiehao et al. (2021)</td>
<td>China</td>
<td>Case series</td>
<td>3-131 months (mean 74 months)</td>
<td>No available data</td>
<td>Median value of ALT: 18.5 U/L (N), AST: 27.7 U/L (N), one patient</td>
<td>No available data</td>
<td>10% children with COVID-19 have significant</td>
</tr>
<tr>
<td>Study ID</td>
<td>Authors</td>
<td>Country</td>
<td>Study Type</td>
<td>Age Range</td>
<td>Sex Ratio</td>
<td>Laboratory Parameters</td>
<td>Liver Injury Incidence</td>
<td>Severe Liver Injury</td>
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<tr>
<td>8</td>
<td>Perez A et al. (2021)</td>
<td>USA</td>
<td>Retrospective study</td>
<td>2-21 years old</td>
<td>Female 1:1</td>
<td>ALT 100 U/L (↑) and AST 142 U/L (↑)</td>
<td>Increase of ALT &gt; 40 IU/L (mild to moderate liver injury) in 36% (n=105) of subjects; which is 31% (n=69) in children with COVID-19, and 51% (n=36) in children with MIS-C. Severe liver injury (ALT&gt;200IU/L) was reported in 8% COVID-19 and 4% MIS-C</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Dooki et al. (2020)</td>
<td>Iran</td>
<td>Retrospective study</td>
<td>Age under 18 years old</td>
<td>Fever, anorexia, malaise, nausea, abdominal pain</td>
<td>Increase of ALT in 5/18 (27.8%) patients Increase of AST in 7/18 (38.9%) patients</td>
<td></td>
<td>Patient with increase of liver enzyme was not correlated with severity of COVID-19 respiratory manifestation</td>
</tr>
<tr>
<td>10</td>
<td>Qiu et al. (2020)</td>
<td>China</td>
<td>Cohort study</td>
<td>0-16 years old</td>
<td>No available data</td>
<td>Increase of ALT in 2 patients (mild case) and AST in 3 patients (2 mild case and 1 mild case), 6 patients (severe case)</td>
<td></td>
<td>No available data</td>
</tr>
<tr>
<td>11</td>
<td>Sun et al. (2020)</td>
<td>China</td>
<td>Retrospective study</td>
<td>2 months-15 years old</td>
<td>No available data</td>
<td>Increase of ALT in 4 from 8 patients (50%) severe COVID-19 patient in ICU</td>
<td></td>
<td>No available data</td>
</tr>
<tr>
<td>12</td>
<td>Wang et al. (2020)</td>
<td>China</td>
<td>Retrospective study</td>
<td>44 (57.1%) male and 33 (42.9%) female, median age 10 years old</td>
<td>No available data</td>
<td>Increase of ALT in 1 case (1.5%), AST in 7 cases (10.3%) ALP in 7 cases (28%) Total bilirubin, direct bilirubin, albumin, and INR were normal</td>
<td>No significant difference in liver function in pneumonia compared to non-pneumonia group (p&lt;0.05)</td>
<td>Increase of liver enzyme in COVID-19 patient was not associated with pneumonia</td>
</tr>
<tr>
<td>No.</td>
<td>Authors</td>
<td>Country</td>
<td>Study Design</td>
<td>Number (Age)</td>
<td>ALT Data</td>
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<td>13</td>
<td>Xia et al. (2020)</td>
<td>China</td>
<td>Retrospective</td>
<td>20 1 day old to 14 years and 7 months old (median age 2 years old 1.5 months)</td>
<td>No available data</td>
<td>Increase of ALT (&gt;40 U/L) in 25% patients</td>
<td>No available data</td>
<td>Increase of ALT in children with COVID-19</td>
</tr>
<tr>
<td>14</td>
<td>Liu et al. (2020)</td>
<td>China</td>
<td>Retrospective</td>
<td>46 Infants less than 1 year old (IQR 2-7 months)</td>
<td>No available data</td>
<td>ALT (↑) in 11 patients (25%), and AST (↑) in 20 patients (45.45%). Albumin (↓) in 8 cases (18.18%). Bilirubin (↑) in 6 cases (13.64%)</td>
<td>Complication of liver injury in 20 (45.45%) moderate COVID-19 cases</td>
<td>Infants with SARS-CoV-2 infection have higher risk of liver injury compared to children and adult</td>
</tr>
<tr>
<td>15</td>
<td>Wang et al. (2020)</td>
<td>China</td>
<td>Retrospective</td>
<td>31 6 months-17 years old</td>
<td>No available data</td>
<td>Increase of ALT AST in 22% cases</td>
<td>No available data</td>
<td>Increase of ALT and AST in children with COVID-19</td>
</tr>
<tr>
<td>16</td>
<td>Tan et al. (2021)</td>
<td>China</td>
<td>Retrospective</td>
<td>20 7 years (1-12 years old)</td>
<td>No available data</td>
<td>Increase of AST in 10% cases</td>
<td>No available data</td>
<td>Increase of AST in children with COVID-19</td>
</tr>
</tbody>
</table>

Interestingly, a report mentioned that two pediatric patients with COVID-19 who had elevated ALT, AST, and bilirubin levels apparently had normal liver and biliary system ultrasound results. This indicates the presence of acute hepatitis with clinical jaundice without biliary obstruction in SARS-CoV-2 infection. Sica et al. demonstrated a new onset of hepatic steatosis in a 14-year-old boy patient with SARS-CoV-2 infection, which may be one of the sequelae of severe manifestations of COVID-19, known as MIS-C.

Fulminant acute hepatitis was also declared in an 11-year-old patient with severe COVID-19 and complaints of fever, persistent abdominal pain, and jaundice. Laboratory parameters found the AST levels of 2030; ALT 690 U/dL; ALP 387 U/dL; total bilirubin 35.4 mg/dL; direct bilirubin 21.6 mg/dL; LDH 5660; and the elongation of PT in 15.9 seconds and INR 1.3.

The acute liver laceration was found in confirmed COVID-19 infants aged 55 days, with recorded AST levels of 100 U/dL, ALT 84 U/dL, total bilirubin 33.7 mg/dL, and direct 25.2 mg/dL. Moreover, Zhu et al. mentioned that 2 of 10 newborns from mothers with confirmed COVID-19 had elevated liver enzyme levels. Manifestations of liver involvement in infants are thought to be associated with the tissues' immaturity and the liver's immune system.

From several case reports and studies in this systematic review, data on the prevalence of liver injury manifestations in children ranged from 1.5 to 50%. The clinical features include nausea, vomiting, decreased intake, abdominal pain, and jaundice. Meanwhile, the liver injury criteria used were increased AST and/or ALT up to 3 times the upper limit of expected values. However, several other studies used the criteria for an increase in ALT of >40 U/dL and AST of >37 U/dL. Elevated AST and ALT were more common than elevated bilirubin levels, prolonged INR, and decreased albumin levels. Data regarding radiological and histopathological features of the liver in pediatric patients with COVID-19 were limited. Post-mortem studies on COVID-19 patients with acute liver laceration showed steatosis, mild sinusoidal dilatation, and minimal lymphocytic infiltration. These features are not specific whether due to SARS-CoV-2 infection, hypoxemic conditions, or drug-induced. However, the sample contains viral inclusions in the nucleus and cytoplasm of hepatocyte cells. As the growing number of reports on liver involvement in COVID-19, the American Association for the Study of Liver Diseases recommends regular monitoring of transaminases in pediatric patients with COVID-19 who have mild elevated liver enzymes.
Pathophysiology of Acute Liver Injury in Pediatric Patients with COVID-19

The mechanism underlying the increase in liver enzymes in COVID-19 patients is multifactorial due to direct viral damage, inflammatory response, hypoxic conditions, or drug cytotoxicity. Some of these mechanisms can be seen in Figure 2.

Figure 2. Pathophysiology of liver injury in COVID-19. Several mechanism underlying the increase in liver enzymes in COVID-19 including direct viral damage, inflammatory response, hypoxic conditions, or drug cytotoxicity (Adapted from de Sousa Moreira JL et al. Pathophysiology and molecular mechanisms of liver injury in
Cell Damage due to Virus Infection

It is well known that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor to enter and invade host cells. Studies have reported that the ACE-2 receptor is expressed on hepatocytes, bile duct cells (cholangiocytes), and liver endothelial cells. Chai et al. stated that the expression of the ACE-2 receptor was higher in bile duct cells than in type II alveolar epithelial cells. This may be due to the important role of the bile ducts in immune defense and liver regeneration. Cytopathogenic effects cause viral liver damage. Wang et al. identified the appearance of hepatocytes infected with SARS-CoV-2, which showed the endoplasmic reticulum's expansion, mitochondrial edema, and decreased glycogen granules and associated with infiltration of CD4+ and CD8+ lymphocytes.

Hyperinflammation

Several studies have reported an increase in serum levels of proinflammatory cytokines in COVID-19 patients with abnormal liver function. This is consistent with the histopathological picture of liver tissue that shows moderate microvascular steatosis, increased lobular and portal activity, followed by T lymphocyte overactivity. The presence of SARS-CoV-2 infection in the respiratory system will induce local and systemic inflammatory reactions, by releasing proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF), that can cause a cytokine storm. IL-6 is a pleiotropic cytokine that has receptors in several cells in tissues or organs of the body, including the liver. The binding of IL-6 to receptors on the hepatocyte cells will activate inflammatory signals that will attract monocytes and lymphocytes, leading to inflammatory conditions and further liver tissue damage. Moreover, severe inflammatory conditions due to SAR-CoV-2 will result in an imbalance of the immune response, and the hemostasis function of the liver as a guard of immune tolerance will be disrupted. The dysregulation of the innate immune response in the liver causes the excessive production of proinflammatory cytokines by Kupffer cells, which in turn causes further inflammation.

Hypoxic-Ischemic

Severe COVID-19 infection with clinical manifestations of respiratory failure can cause tissue hypoxia, including liver tissue. Hypoxic hepatitis or ischemic hepatitis can be found in severe COVID-19 patients who experience cardiac, circulatory, or respiratory complications that cause impaired liver perfusion. Under conditions of systemic stress, a compensatory mechanism for decreased peripheral and splanchnic blood flow cause a decrease in blood flow to the liver, which results in hepatocellular hypoxia, especially in zone 3. Hypoxic and reperfusion injury mediated by reactive
oxygen species cause cell damage through the lipid peroxidase process. In addition, Kupffer cells can also produce proinflammatory cytokines in response to ischemia and trigger the activation and recruitment of polymorphonuclear leukocytes. This condition will cause further liver tissue damage, characterized by increased transaminases and LDH, which can improve when the hypoxic conditions are resolved.29

Drug-Induced Hepatotoxicity

Although several therapeutic agents are effective for COVID-19 infection, some have been reported to have hepatotoxic side effects.30 Among these are nucleoside analog antiviral agents, such as Remdesivir, that have caused liver enzyme elevations in COVID-19 patients. Lopinavir, an antiretroviral protease inhibitor, has also been reported to cause transient elevations in serum aminotransferase levels but is often asymptomatic. Tocilizumab, an IL-6 inhibitor, often causes mild elevations in serum aminotransferase and bilirubin levels, usually transient and asymptomatic. Ivermectin, an anti-parasitic agent and used as a therapeutic regimen for COVID-19, has been reported to be associated with transient elevations of serum aminotransferases, and very few reports of ivermectin-induced liver injury have resulted in dose adjustment for patients with hepatic impairment.31 Also, pediatric patients with COVID-19 often come with complaints of fever and are given Paracetamol. Paracetamol is said to be associated with liver damage due to its hepatotoxicity.30

Relationship between Liver Injury Manifestations and COVID-19 Severity and Prognosis

Reports regarding the relationship between the manifestations of liver injury with the severity and prognosis of COVID-19 infection in children are still inconclusive. Several studies have shown that COVID-19 patients with elevated liver enzyme levels do not correlate with more severe respiratory manifestations.10,32,33 Another study also reported no significant difference in the liver function of pediatric patients with COVID-19 with and without pneumonia (P > 0.05).14 However, Perez et al. noted that liver involvement in COVID-19 infection in children correlated with more severe clinical manifestations. The study also reported that pediatric patients with MIS-C had a 2.3-fold increased risk of ALT compared with those with COVID-19.5 A meta-analysis study concluded that patients with severe COVID-19 had a higher risk of developing liver injury manifestations. Although, the incidence in pediatric patients was lower than in adults. It is thought to be due to severe COVID-19, the presence of an inflammatory process, and massive tissue hypoxia that can increase the risk of liver damage.34

The prognosis of COVID-19 patients with manifestations of liver injury is still indecisive. A large-scale study reported elevated AST and/or ALT correlated
significantly with mortality and intensive care hospitalization.\textsuperscript{35} Another study also mentioned that the De Ritis ratio (serum AST and ALT) was significantly associated with mortality in COVID-19 patients.\textsuperscript{36} However, reports in pediatric patients are still finite. Perez et al. reported that pediatric COVID-19 patients with elevated ALT had more severe clinical manifestations and longer ICU stay (p<0.05).\textsuperscript{4}

Another interesting thing is that almost 10\% of COVID-19 patients show manifestations only in the digestive system. Patients with early digestive system symptoms were recorded to have delayed diagnosis, so they tend to progress to severe disease, critical conditions, and poor outcomes. Therefore, increasing attention to the manifestations of the digestive system in COVID-19 infection, especially for pediatric patients, is crucial. The American Association for the Study of Liver Diseases recommends regular monitoring of transaminases in pediatric patients with COVID-19 who have mild elevations of liver enzymes. Pediatric COVID-19 patients with jaundice, elevated ALT/AST over 500 U/mL, and new-onset liver decompensation should be investigated further in the hospital. Thus, it is expected that liver laceration in pediatric patients with COVID-19 can be reduced to improve outcomes and prognosis.\textsuperscript{34}

**Conclusion**

SARS-CoV-2 virus infection in children shows a unique presentation. Liver injuries have been reported in pediatric COVID-19 patients, with prevalence ranging from 1.5 to 52\%. Clinical manifestations include nausea, vomiting, abdominal pain, drinking intolerance, and jaundice. Elevated levels of ALT and AST are more frequently reported as a sign of liver injury. Several pathomechanisms of acute liver injury in COVID-19 have been proposed, including direct viral infection, inflammation, hypoxia-ischemia, and drug induced. In addition, several reports suggest that liver injury correlates with the severity of COVID-19 disease. Therefore, monitoring liver function in COVID-19 patients is important to assess the prognosis.

**Conflict of Interest**

None declared.

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**References**


