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COVID-19 and pediatric fatty liver disease: Is there interplay?

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Abstract

The rapid global spread of coronavirus disease 2019 (COVID-19) infection has become a major health issue with higher morbidity and mortality rates. Besides respiratory symptoms, a growing body of evidence indicates a variety of gastrointestinal manifestations including liver involvement. In this regard, several data supported an association between COVID-19 infection and liver injury in adults, while in children there is compelling but currently limited evidence. In particular, patients with COVID-19 have shown a higher risk of liver injury (mainly expressed as increased transaminase levels or hepatic steatosis). Conversely, a greater risk of more severe forms of COVID-19 infection has been observed in subjects with pre-existing chronic liver diseases. The dramatic interplay between COVID-19 and liver damage has been related to the inflammatory pathways chronically active in patients with nonalcoholic fatty liver disease and acutely in those affected by COVID-19, but other different pathogenic mechanisms have also been supposed. Of note, patients with previous metabolic comorbidities also had a higher risk of severe COVID-19 infection. This emphasizes the pathogenic interrelation of the inflammatory pathways with a dysregulated metabolic milieu in COVID-19 patients. Taking into account the prognostic role of fatty liver in COVID-19 patients and its intrinsic relationship with metabolic abnormalities even in childhood, a strict monitoring of this condition is recommended. We aimed to summarize the most recent evidence regarding the potential interplay between pediatric fatty liver and COVID-19.

Key Words: COVID-19; Children; Adults; Nonalcoholic fatty liver disease

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Core Tip: Both adult and pediatric data recently reported a liver involvement in

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coronavirus disease 2019 (COVID-19). Although several pathogenic mechanisms have been proposed, inflammatory pathways seem to play a pivotal role in the pathophysiology of liver damage in this viral infection. In particular, a complex and bidirectional relationship has been highlighted between fatty liver and COVID-19. Several data suggested this intriguing interplay by underscoring the need for an early close monitoring of this liver condition with an intrinsic greater cardiometabolic burden.

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INTRODUCTION

Since late 2019, the whole world has been suddenly disrupted by the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At the beginning of February 2021, this global acute pandemic produced more than 102 million worldwide confirmed cases and a total number of deaths to 2.2 million, representing an unprecedented healthcare challenge[1].

The pathogenic role of COVID-19 depends on binding of spike viral proteins to angiotensin I converting enzyme 2 (ACE-2) receptors facilitating the entry into the target cells[2-4]. Although mainly expressed in the respiratory tract, in particular in the nasopharynx epithelium, these receptors are also located in multiple sites such as the gastrointestinal tract and vascular endothelium[5-8]. Along with clinical respiratory symptoms, growing evidence supported a COVID-19 related gastrointestinal involvement[8-13]. COVID-19 positive adult patients might experience gastrointestinal symptoms due to the presence of ACE-2 receptors in the glandular cells of gastric, duodenal, and distal enterocytes that favor malabsorption, impaired intestinal secretion, and enteric nervous system activation[8,9,12,14]. The virus might also affect the liver through a direct viral translocation from gut or by an indirect mechanism involving systemic inflammation, pre-existing liver diseases, or drug-related liver damage[11,13-16].

Pediatric COVID-19 reports have shown both a milder course and a better prognosis of the disease in this population, probably due to the special immune response system pertaining to children. Gastrointestinal manifestations of the disease at this age are various and not uncommon, in particular in the early phase of the infection.

Nonalcoholic fatty liver disease (NAFLD) has become the most common worldwide chronic liver disease with an epidemic rate both in adults and children[17,18]. It has been largely recognized for its close relationship with insulin resistance and other metabolic features leading to an increased cardiometabolic risk from childhood to adulthood[19-23]. Nevertheless, NAFLD pathophysiology is still far from being fully clarified. To date, the "multiple hits" represents the most favored pathogenic hypothesis, including a role for several different factors (*e.g.*, inflammation, oxidative stress, gut axis, mitochondrial dysfunction, diet, hormones, and genetics)[24].

HOW CAN COVID-19 AFFECT THE LIVER?

The mechanism underlying the increase of liver enzymes seemed to be different between adult and pediatric patients, but further studies are needed for a better elucidation[25].

In adults, two mechanisms for liver injury have been postulated such as a possible role of ACE-2 receptor binding of the virus to the epithelial cells of the bile ducts or a dysregulated hepatic innate immune response, which represents the most probable hypothesis. No evidence supported the involvement of ACE-2 receptor in pediatric liver injury. Moreover, both interleukin (IL)-6 and IL-10 levels did not significantly differ between infected children with and without elevated liver enzymes[25]. Of

interest, the presence of a protective mechanism against liver involvement in children accounting for the mild increase of aspartate aminotransferase and/or alanine aminotransferase (ALT) compared to adults has been suggested. Zhou *et al*[25] reported a higher prevalence of liver involvement (expressed as abnormal liver enzymes) in children aged 0-3 years than in those aged > 3 years, by speculating that this finding might be related to a more pronounced liver immaturity.

The exact mechanism linking COVID-19 to pediatric fatty liver remains poorly known[8,11,25] (Figure 1). In fact, the low incidence of COVID-19 infection in children and its relatively asymptomatic course at this age make it difficult to better understand the pathophysiology of this concern[8,11]. To complicate matters, one of the most likely hypotheses supporting the abnormal liver enzymes in adults such as the inflammatory cytokine storm (including IL-6 and IL-10) seemed to not play a central role in pediatric COVID-19 related liver damage[25]. In fact, studies in infected children have demonstrated that levels of these cytokines are linked to greater severity of the disease, but no statistical differences of both IL-6 and IL-10 serum concentrations have been detected between patients with and without increased transaminases[25]. Moreover, the pediatric clinical practice to first give paracetamol for fever management did not exclude the potential link between liver injury (expressed as abnormal transaminase levels) and drug administration[25].

However, all these studies suffered from some limitations. The first was relatively small sample sizes. Lack of a more accurate laboratory assessment and of longitudinal data represented another limitation. Finally, lack of previous data about comorbidities or drug administration before the hospitalization needed to be mentioned.

Nevertheless, given the growing amount of data regarding liver involvement during this pandemic, the American Association for the Study of Liver Diseases recommends to regularly monitor the mild increase of transaminase in patients with COVID-19 and (mainly in children) to further evaluate for potential underlying liver diseases because of the uncommon presentation and the current paucity of data at this age[26].

FATTY LIVER AND COVID-19

Evidence in adulthood

A large body of evidence has shown an association between COVID-19 and NAFLD in adults (Table 1). Findings from adult studies reported that the prevalence of steatosis (mainly detected by ultrasound abdominal scan or computed tomography) in the confirmed COVID-19 cases was significantly higher than in healthy subjects, even after adjustments for gender and age[27].

Additional data suggested that male patients aged > 60 years, with higher body mass index, underlying comorbidities, and NAFLD were at higher risk of COVID-19 progression[28]. Another study reported no difference in terms of admission to intensive care unit and mortality between NAFLD and non-NAFLD patients. Mortality was associated to male gender (similarly to non-NAFLD patients) and a pronounced inflammatory response (including high ferritin and early weaning score as main predictors). The latter might account for the presence of a dysregulated hepatic innate immune response, one of the most acclaimed mechanisms postulated for liver injury. In addition, NAFLD patients were significantly younger at presentation and showed an increased risk of severe COVID-19 in both genders, specifically in males[29].

Interestingly, taking into account the new definition of metabolic-associated fatty liver disease (MAFLD), authors investigated the potential relationship between COVID-19 infection and MAFLD patients[30-32]. MAFLD patients had a greater risk of disease progression, longer viral shedding times, and a higher probability of liver dysfunction from admission to discharge than patients without MAFLD[30-32]. Sharma *et al*[32] found that younger patients (aged < 60 years) with MAFLD showed an increased severity of COVID-19 disease. Overall, a significant association between MAFLD and younger presentation of COVID-19 was found[31,32].

Notably, as observed in NAFLD subjects, the direct relationship of MAFLD with COVID-19 infection emphasizes the relevance of the metabolic milieu in this viral condition, by pointing out the role of dysregulated hepatic innate immunity to trigger liver damage[29-32]. Moreover, overwhelming evidence supported the association of COVID-19 infection severity (defined as the occurrence of any of the following parameters: arterial PaO₂/FiO₂ ≤ 300 mmHg, SpO₂ ≤ 93%, ≥ 30 breath per minute) with both NAFLD and/or MAFLD, even after full adjustment for common cardiometabolic

Table 1 Main findings regarding the association between fatty liver disease and coronavirus disease 2019 in adults

Ref.	Study design	Population	NAFLD	Main findings
Mahamid <i>et al</i> [34]	Retrospective case-control study, SZMC, Jerusalem	71 hospitalized patients with COVID-19 infection, both genders, age \geq 18.0 yr (mean age 51.0 ± 21.7), 22 NAFLD, 49 non-NAFLD	CT within hospitalization or recently made	Significant association between NAFLD and severity of COVID-19 even after adjustments for obesity, hypertension, metabolic syndrome, diabetes, and smoking. This association was independent of metabolic syndrome and/or its components. NAFLD patients have an increased risk of severe COVID-19 in both genders, in particular in males (Male: $P = 0.001$ Female: $P = 0.002$)
Ji <i>et al</i> [28]	Retrospective case-control study. Patients of two COVID Hospital in China	202 patients with COVID-19 (hospitalized and follow-up within 12 mo of the diagnosis). Median age 44.5 (34.8-54.1), 163 patients with stable disease (37.6% of patients with NAFLD), 39 patients with progressive disease (25.8% of patients with NAFLD)	NAFLD defined as hepatic steatosis index: $8 \times (\text{ALT}/\text{AST}) + \text{BMI} (+2 \text{ if type 2 diabetes, } +2 \text{ if female}) > 36$ and/or US	Male patients aged > 60 yr, with higher BMI, underlying comorbidities, and NAFLD were associated with COVID-19 progression. Patients with NAFLD had higher risk of disease progression, longer viral shedding times, and higher likelihood of abnormal liver function from admission to discharge than patients without NAFLD
Zhou <i>et al</i> [31]	Cohort study, Asian ethnicity	55 MAFLD patients with COVID-19 were 1:1 matched by age (± 5 yr), sex, and BMI (± 1 unit) to COVID-19 patients without MAFLD. Age < 60 yr	CT	The presence of MAFLD was associated with severity of COVID-19 even after full adjustment (age, sex, smoking status, obesity, diabetes, hypertension) and a trend to increased duration of hospitalization. MAFLD patients had higher levels of CRP, ALT, AST, GGT, fasting blood glucose, and triglycerides
Medeiros <i>et al</i> [27]	Retrospective case-control study. Radiology Departments of Hospital Beneficiencia Portuguesa, San Paolo-Brasil	316 patients clinically suspected of having COVID-19 infection: -n.204: RT-PCR positive; -n.112: RT-PCR and chest CT negative pattern. Age > 18 yr	CT: Attenuation value of ≤ 40 HU, measured in the region of interest (commonly in the right hepatic lobe) in non-enhanced phase	Higher prevalence of steatosis in affected patients, even after adjustments for sex and age
Forlano <i>et al</i> [29]	Retrospective cohort study. Imperial College Healthcare NHS Trust (London, United Kingdom)	193 hospitalized, adult patients with COVID-19 infection and CT imaging, NAFLD: 61 (31%); Non-NAFLD: 132 (66%), excluded: 5 (3%)	US or CT dated within 1 yr from the admission for COVID-19 or a known diagnosis of NAFLD. FIB-4 index for fibrosis	No difference in terms of admission to ICU and in mortality between NAFLD and non-NAFLD patients. NAFLD patients were significantly younger at presentation
Gao <i>et al</i> [30]	Cohort study. Four hospitals in China	130 nondiabetic patients with COVID-19: 65 MAFLD and 65 controls were 1:1 matched by age (± 5 yr) and sex	CT	MAFLD presence in nondiabetic patients was associated with a 4-fold increased risk of severe COVID-19, even after adjusting for age, sex, and coexisting comorbidities. The risk of severe COVID-19 increased with increasing numbers of metabolic risk factors
Targher <i>et al</i> [33]	Retrospective cohort study. Four hospitals in China	310 hospitalized, adult patients with COVID-19 infection	CT: FIB-4 index and NFS used to categorize liver fibrosis in low, intermediate, or high	In patients with MAFLD the presence of intermediate or high fibrosis (FIB-4 or NFS) was associated with a higher risk of severe COVID-19, even after adjusting for sex, obesity, and diabetes
Sharma <i>et al</i> [32]	Review	Adult patients	CT/FIB-4 index and NFS	Patients with MAFLD had higher risk of disease progression, longer viral shedding times, higher likelihood of abnormal liver function, and 4-6-fold increased risk of severe disease than patients with no MAFLD. Younger patients (age < 60 yr) were also at greater risk for increased severity of COVID-19

ALT/AST: Alanine aminotransferase/aspartate aminotransferase; BMI: Body mass index; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; CT: Computed tomography; FIB-4: Fibrosis-4; GGT: Gamma-glutamyl transferase; ICU: Intensive care unit; MAFLD: Metabolic-associated fatty liver disease; NAFLD: Nonalcoholic fatty liver disease; NFS: Nonalcoholic fatty liver disease fibrosis score; NHS: National Health Service; RT-PCR: Real-time reverse transcription polymerase chain reaction; US: Ultrasound.

risk factors such as obesity, hypertension, metabolic syndrome, diabetes, and smoking [30,33]. Hence, this association was found to be independent of metabolic syndrome and/or its components[33]. In particular, MAFLD presence in nondiabetic patients was associated with a 4-fold increased risk of severe COVID-19, even after adjusting for age, gender, and coexisting comorbidities, and the risk was even higher with increasing numbers of metabolic risk factors[30]. Moreover, the presence of intermediate or high fibrosis was also linked to a higher risk of severe COVID-19, even after adjusting for gender, obesity, and diabetes[34].

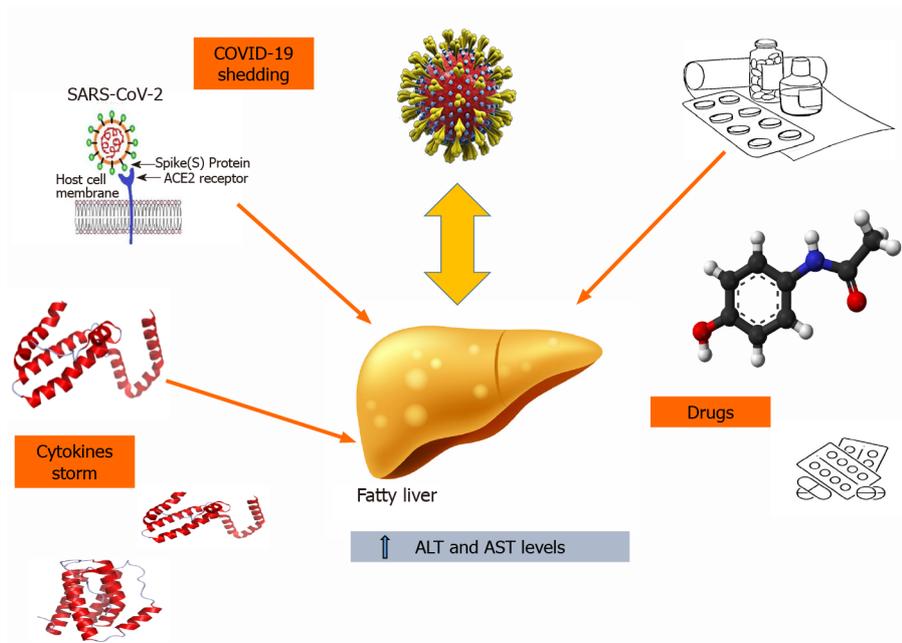


Figure 1 Potential mechanisms linking coronavirus disease 2019 to pediatric fatty liver. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COVID-19: Coronavirus disease 2019.

Evidence in childhood

Compared to adult findings, evidence in children is currently limited but in line with the aforementioned association (Table 2). In fact, data from 6 pediatric case-series studies and a review reported that liver involvement, defined as an increase of ALT and/or aspartate aminotransferase, was rare and mild ($< 2 \times \text{ULN}$) [35-41]. In contrast to adults, Zhou *et al* [25] found no gender difference in children with COVID-19 and elevated liver enzymes.

Pediatric studies examining different variables such as demographic data, clinical and laboratory features, chest imaging results, treatments, and clinical outcomes of the patients with COVID-19 showed a prevalence of possible liver involvement from 6% to 50% [25,35-41].

A retrospective analysis including eight severe or critically ill patients with COVID-19 (aged 2 mo-15 years) admitted to the intensive care unit of the Wuhan Children's Hospital reported a mild increase of ALT levels in half of the population, while total bilirubin levels in all patients were normal [36]. Similarly, a retrospective study of 20 pediatric patients with COVID-19 infection showed increased ALT levels ($> 40 \text{ U/L}$) in 25% of cases [37]. A slight prevalence (6%) of elevated liver enzymes in confirmed-COVID-19 Chinese patients (aged 0-16 years) was also described in a cohort study [35]. In addition, it provided evidence for a minor liver involvement compared to adults with COVID-19 (18%), children with severe acute respiratory syndrome (48%), and children with influenza A (7%) [35].

It has been observed in children that both critically ill patients admitted to the intensive care unit and mild patients (defined as the presence of upper respiratory symptoms or asymptomatic infection, positive real-time reverse transcription polymerase chain reaction test for SARS-CoV-2, and no abnormal radiographic and septic presentation) rarely showed abnormal liver enzymes [35,36]. In these studies, all the patients underwent an antiviral treatment, therefore the possibility that transaminase abnormalities were drug-induced cannot be ruled out [35,36]. Moreover, it should be noted that the most common symptoms at admission were cough and fever, usually treated with paracetamol, of which an incorrect administration might also influence transaminase levels [41].

CONCLUSION

Gastrointestinal symptoms have been largely described in COVID-19 infected patients. Indeed, the wide presence of ACE-2 receptors through the entire gastrointestinal tract has been considered to be responsible for the spectrum of gastrointestinal manifest-

Table 2 Main findings regarding the association between fatty liver disease and coronavirus disease 2019 in children

Ref.	Study design	Population	NAFLD	Main findings
Qiu <i>et al</i> [36]	Cohort study. Three hospitals in Zhejiang Province, China	36 pediatric patients (aged 0-16 yr) with laboratory confirmed COVID-19 infection; mild cases (<i>n</i> = 17); moderate cases (<i>n</i> = 19) compared with adults with COVID-19 (<i>n</i> = 175); Children with SARS (<i>n</i> = 44); Children with H1N1 influenza (<i>n</i> = 167)	Increased liver enzymes	Elevated ALT in two patients (mild cases) and AST in three patients (two mild and one moderate case), 6% of cases with elevated liver enzymes, 18% of cases with elevated liver enzymes, 48% of cases with elevated liver enzymes, 17% of cases with elevated liver enzymes
Sun <i>et al</i> [37]	Retrospective analysis. Intensive Care Unit, Wuhan Children's Hospital	8 severe or critically ill COVID-19 patients admitted to the ICU. Age: 2 mo-15 yr	Increased liver enzymes	Elevated ALT levels in 4 out of 8 patients. Total bilirubin level in all patients was normal
Wang <i>et al</i> [39]	Retrospective study. Children from six provinces (autonomous region) in northern China.	31 cases of COVID-19. Age: 6 mo-17 yr	Increased liver enzymes	Elevation of liver enzyme (22%)
Xia <i>et al</i> [38]	Retrospective study. Wuhan Children's Hospital	20 COVID-19 pediatric patients. Age: 1 d-14 yr, 7 mo (median age: 2 yr and 1.5 mo)	No NAFLD screening. CT was performed for pneumonia	Elevated ALT (> 40 U/L) in 25% of cases
Jiehao <i>et al</i> [40]	Case series. Children's Hospital in Shanghai, Hainan, Hefei in Anhui province, and Qingdao in Shandong province	10 patients aged 3-131 mo (mean: 74 mo). Male: female 1:1.5	No NAFLD screening. CT was performed for pneumonia	Median ALT: 18.5 U/L, AST: 27.7 U/L. One patient had ALT: 100 U/L and AST: 142 U/L
Tan <i>et al</i> [41]	Retrospective study. North Hospital of Changsha First Hospital	10 children with confirmed COVID-19 infection. Mean age of 7 yr (1-12 yr)	Increased liver enzymes	Elevated AST in two patients

ALT/AST: Alanine aminotransferase/aspartate aminotransferase; CT: Computed tomography; COVID-19: Coronavirus disease 2019; H1N1: Influenza A; ICU: Intensive care unit; NAFLD: Nonalcoholic fatty liver disease; SARS: Severe acute respiratory syndrome.

ations including abdominal pain, nausea, vomiting, or less commonly fatty liver and acute hepatitis. In particular, liver involvement has been reported both in adult and pediatric affected patients with a higher prevalence in the former population[7,42,43]. Several pathogenic mechanisms have been hypothesized to explain liver damage, but its exact pathophysiology is still under debate[42,44]. First, it could be considered as a consequence of the "cytokine storm" resulting in an aberrant immune system reaction with an excessive inflammatory response, as observed in many affected subjects. Moreover, liver injury might represent a side effect of the administered drugs or a secondary effect of the hypoxia consequent to failure of other organs such as heart and lung. On the contrary, a direct viral effect is unlikely, as supported by the scarce evidence of an increase of the classical markers of biliary tract involvement such as gamma-glutamyl transferase and alkaline phosphatase in affected patients in the face of a large hepatic expression of ACE-2 on cholangiocyte surfaces[6,45].

Of concern, liver damage in patients affected by COVID-19 seems to be enhanced by the intrinsic chronic activation of inflammatory pathways in NAFLD, potentially worsening outcomes in subjects with previous coexisting metabolic diseases[7,8]. Moreover, patients with pre-existing chronic liver diseases have been found to be at higher risk to develop more severe forms of COVID-19 infection.

NAFLD expressed as hepatic steatosis and/or elevated liver enzymes represents one of the most common liver abnormalities reported during this pandemic, in particular in pediatric patients[7]. Studies reported an overall prevalence of mild liver enzyme increases of almost 25% in COVID-19 infected children. Although different pathogenic mechanisms than adults have been supposed, further studies are required to better clarify the pathophysiology of abnormal liver enzymes in children with COVID-19.

The potential prognostic role for NAFLD as well as its intrinsic close relationship with metabolic traits require a close monitoring of fatty liver in these patients.

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