COVID-19 ISSUES RELATED TO LIVER DISEASE IN PEDIATRIC POPULATION

Lorena Mihaela Manole[1,2], Laura Mihaela Trandafir[2,3*], Laura Florescu[2,3*], Roxana Şerban[4], Otilia Iftinchi[2], Roxana Mihaela Popescu[5], Oana Raluca Temneanu[3]

1. "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, România
I.O.S.U.D
3. Mother and Child Department
4. Department of Morfo-Functional Sciences II
5. Department of Radiology
2. "Saint Mary" Emergency Children Hospital Iaşi, România

COVID-19 ISSUES RELATED TO LIVER DISEASE IN PEDIATRIC POPULATION (Abstract) : Objective : Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has had a significant impact on global health, economy, and society. While COVID-19 primarily affects older individuals and those with underlying health conditions, children generally experience milder symptoms or are asymptomatic. Liver injury caused by COVID-19 is a common complication, but often goes unnoticed in children. This review aims to analyze published studies on liver injuries related to COVID-19 specifically in pediatric patients. Material and Methods : A comprehensive search of medical databases was conducted to identify relevant articles published up to May 2023. Results : A total of 141 articles were identified, and 21 articles were included in this review after careful selection. COVID-19-related liver injury can occur during the disease progression or as a result of treatment. Discussions : The mechanisms underlying liver injury include direct toxic effects of COVID-19 on liver cells, inflammatory immune response, hypoxia-mediated injury, and drug-induced liver injury. Abnormal liver enzyme levels, such as elevated ALT, AST, ALP, GGT, TBIL, and reduced albumin, indicate liver injury in COVID-19 patients. Autopsy findings in pediatric cases reveal specific pathological changes associated with COVID-19, including lung abnormalities and liver congestion. Conclusions : Liver damage in children with COVID-19 is often underestimated, and further research will enhance our understanding of these aspects is crucial for effective prevention and management strategies in pediatric cases of COVID-19. Key-words : COVID-19, SARS-COV-2, LIVER ISSUES DAMAGE, CHILDREN, PATHOGENESIS

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a serious condition defined by World Health Organization as an infectious disease caused by Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-Cov-2) (1). This pandemic had a catastrophic impact on world health, economic stability (2), social consequences and is still causing effects in population of all ages, including the pediatric one. COVID-19 primarily affects older individuals and those with underlying health conditions (3). The severity of the infection shows a logarithmic and linear relationship with age for individuals over 30, meaning the risk of fatality increases significantly with each passing year. Instead, children have a lower likelihood of contracting the virus and typically experience either no symptoms or mild to moderate illness (4).

An additional concern arises of the clinical effects of COVID-19, that are variable in patients that can be asymptomatic, to the ones that develop the severe forms of disease (5) and progressively encompassing more than just respiratory manifestations, extending to systemic diseases as well. Apart from triggering acute

respiratory distress syndrome (6), COVID-19 also causes damage on vital organs like the liver, gastrointestinal tract, kidney, heart, and nervous system and can determine fatal outcomes (7). While the primary target of SARS-CoV-2 is the respiratory tract, the liver is often significantly affected, particularly in severe and critical cases (8). Because of the general predisposition of severe cases in adults, the existing studies does not detail many information regarding pediatric cases. Nevertheless, there were a global widespread and the infections of children was through family contacts, which played a crucial role in disease transmission. Meta-analyses have revealed that liver damage is prevalent in children, but frequently goes unnoticed (9). Numerous studies have highlighted that children with COVID-19 may experience gastrointestinal symptoms such as vomiting, nausea, diarrhea, abdominal pain and elevated liver enzymes, mirroring the symptoms observed in adults with gastrointestinal involvement (9). However, it is important to note that variations exist in pediatric digestive tract involvement and liver injury across different age groups, countries, and regions (9). The aim of this review is to analyse the actual published studies in the scientific literature and focus directly towards pediatric patients with liver injuries related to COVID-19. Also, our main objective is to summarize the most relevant information about the clinical, the investigations and the pathogenesis of COVID-19 related liver issues in children and to understand the possible complications that can affect children's quality of life.

MATERIAL AND METHODS

Within this review, we conducted a meticulous analysis of the most significant published studies, encompassing original research papers and reviews, present in the scientific literature. The literature search process involved querying electronic internationally recognized databases, PubMed, Medline, and Web of Science, to identify relevant articles for our analysis. The papers published up to May 2023 in each author's field of expertise were searched with the following keywords : COVID-19, SARS-CoV-2, liver issues, children, pathogenesis. The resulting draft was discussed among authors to provide a theoretical point of view and the final version was then communicated and approved by all the co-authors.

RESULTS

A total of 141 articles were identified through databases. The articles in extenso were studied and analyzed to be according to the topic of this review. After a careful survey we identified 21 articles with the specific subject, which were included in this review.

DISCUSSIONS

COVID-19-related liver issues or injury refers to the occurrence of hepatic damage in patients infected with SARS-CoV-2, whether it develops during the progression of the disease or as a result of treatment, regardless of the patient's pre-existing liver injury status (10). As stated by Sivandzadeh GR et al. (11), there is an observed higher risk of liver injury in adult men compared to women, while the cumulative incidence of liver injury tends to be lower in pediatric patients.

Yun YF et al. (12) classified the etiology of COVID-19-related liver injury into three categories :

- The direct pathway encompasses the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptors present in the liver or bile duct, leading to direct toxic effects.
- The indirect pathway involve an inflammatory immune response and hypoxia, which contribute to liver injury in COVID-19 cases.
- Additionally, liver injury can also arise as a result of COVID-19-related treatments, such as mechanical ventilation and the use of antiviral drugs.

In the direct pathophysiological mechanism, according to the recent studies, genomic sequencing, as well as phylogenetic and structural analyses, have provided confirmation that SARS-CoV-2 possesses the capability to bind to the ACE2 present on host cells. This binding process, facilitated by the spike protein of the virus, enables membrane fusion and subsequent viral invasion (13). While ACE2 is prominently expressed in alveolar cells, it is also distributed across various organs in the body, including the liver (14). Consequently, the direct pathological mechanism underlying COVID-19-related liver injury is attributed to the virulence of SARS-CoV-2, wherein the virus can bind to ACE2 receptors on liver endothelial cells, leading to toxicity and subsequent damage to hepatocytes (15,16).

In contrast to adults, children tend to exhibit milder symptoms of liver injury related to COVID-19, possibly due to lower ACE2 expression, less maturity, and weaker functional affinity (i.e., binding capability) to SARS-CoV-2. However, it has no value that ACE2 expression decreases with age, resulting in higher levels of ACE2 in children compared to adults (12). Therefore, apart from its ability to facilitate viral infections, further investigation is required to explore the distribution of ACE2 in different age groups and the organ damage (12). Chai et al. (17) found that ACE2 expression is higher in cholangiocytes than hepatocytes, implying that SARS-CoV-2 may preferentially bind to ACE2 on cholangiocytes, potentially impacting liver health and suggesting that COVID-19-related liver abnormalities may be influenced by cholangiocyte damage rather than hepatocyte injury (18).

Indirect pathophysiological mechanisms that contribute to liver injury in COVID-19 patients are : inflammatory immune response (dysfunction of innate and adaptive immune responses, multisystem inflammatory syndrome in children, complement dysfunction) and hypoxia-mediated liver injury. The immune response plays a vital role in protecting the body from damage, but an excessive inflammatory immune response (IIR) can lead to systemic diseases. Studies have shown that the systemic IIR induced by SARS-CoV-2 is intricately linked to liver injury (12). Dysfunctional innate (natural killer cells and natural antibodies) and adaptive immune responses (memory T and B cells) mediate the liver damage caused by COVID-19. The innate immune system detects the virus through pattern recognition receptors, triggering the production of interferons and pro-inflammatory cytokines. However, the virus can block innate immune signaling, leading to excessive cytokine production and inflammation (19-22). Multisystem inflammatory syndrome in children (MIS-C), a complication of SARS-CoV-2 infection, can lead to liver injury. MIS-C presents with various symptoms (persistent acute fever, abdominal pain, diarrhea, rash, lymphadenopathy, appendicitis, peritonitis) with the risk of progression to multiorgan dysfunction (23,24). Complement dysfunction is another mechanism of liver injury in COVID-19. The complement system, part of the immune system, can become overactive or dysfunctional during SARS-CoV-2 infection, leading to systemic inflammation, contribute to the hypercoagulable state and damage to other organs (25). Additionally, hypoxia-mediated liver injury can occur due to the decreased oxygen supply caused by acute respiratory distress syndrome and respiratory failure in patients with SARS-CoV-2 (6,26).

The treatment of COVID-19 can sometimes lead to liver injury in patients, particularly in pediatric cases. Mechanical ventilation, which is often required in severe COVID-19 cases (27), can contribute to liver injury. The use of ventilation support may lead to increased pulmonary vascular resistance and reduced right ventricular activity, causing liver congestion and ischemic hepatitis (28). Additionally, drug-induced liver injury is another concern in COVID-19 treatment. Drugs used to treat COVID-19, such as remdesivir, lopinavir/ritonavir, dexamethasone, tocilizumab, and hydroxychloroquine, can potentially cause liver enzyme elevation in pediatric patients (29). Monitoring liver function and considering the impact of these drugs on the liver are crucial in the treatment of children with COVID-19. Further research is needed to develop more suitable and safer treatment options for pediatric cases.

An investigation by Xu Y et al (30). conducted on children with COVID-19 and liver injury revealed that, when compared to adults, these young patients manifest a less severe clinical progression and fewer noticeable radiological and laboratory alterations.

COVID-19 can lead to varying degrees of liver injury, which can be observed through abnormal increases in alanine aminotransferase (ALT > 40 U/L) and aspartate aminotransferase (AST > 40 U/L) levels, accompanied by mild elevations in alkaline phosphatase (ALP > 135 U/L), gamma-glutamyl transferase (GGT > 49 U/L), total bilirubin (TBIL > 17.1 μmol/L), and a decrease in albumin levels (< 3 g/dL) (31-32).

Examining autopsy findings in pediatric cases is crucial for gaining insights into the pathophysiology and clinical manifestations of COVID-19. According to a recent study, overall observations revealed the presence of pericardial and pleural effusion, hepatosplenomegaly, cardiomegaly, enlarged kidney, and enlarged brain (7). The lungs displayed various abnormalities, including diffuse alveolar damage

(78.3%), fibrin thrombi (43.5%), hemorrhage (30.4%), pneumonia (26%), congestion and edema (26%), an angiomatoid pattern (17.4%), and the presence of alveolar megakaryocytes (17.4%). In the liver, centrilobular congestion was observed in the majority of cases (60%), along with micro/macrovesicular steatosis (30%) and arterial/venous thrombi (20%) (7). These autopsy findings shed light on the specific pathological changes associated with COVID-19 infection in pediatric patients.

CONCLUSIONS

Given the ongoing rapid global spread of SARS-CoV-2, it is imperative to enhance our comprehension of the fundamental aspects of transmission, the severity of infection and how to prevent the evolution towards serious forms of the disease or long-term sequelae. This knowledge plays a vital role in informing and guiding effective measures in response to the pandemic. To summarize, our review indicates that digestive system symptoms and liver damage in children are frequently underestimated. Consequently, additional clinical and experimental research is warranted to gain a deeper understanding of the impact of digestive system involvement on the progression of COVID-19 in children and the underlying mechanisms involved.

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REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19). URL : https : //www.who.int/health-topics/coronavirus#tab=tab_1. [data accesării, mai 2023].
2. Warner S, Richter A, Stamataki Z, *et al*. Understanding COVID-19 : are children the key ? *BMJ Paediatrics Open* 2021 ; 5 : e001063. doi : 10.1136/bmjpo-2021-001063.
3. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021 ; 19 : 141-154 doi : 10.1038/s41579-020-00459-7.
4. O'Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, Fontanet A, Cauchemez S, Salje H. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* 2021 ; 590 : 140-145 doi : 10.1038/s41586-020-2918-0.
5. Nakanishi T, Pigazzini S, Degenhardt F, Cordioli M, Butler-Laporte G, Maya-Miles D, et al. The Journal of Clinical Investigation Age-dependent impact of the major common genetic risk factor for COVID-19 on severity and mortality. 2021.
6. Swenson KE, Swenson ER. Pathophysiology of Acute Respiratory Distress Syndrome and COVID-19 Lung Injury. *Crit Care Clin* 2021 ; 37 : 749-776.
7. Khairwa A, Jat KR. Autopsy findings of COVID-19 in children : a systematic review and meta-analysis. Forensic Science, Medicine and Pathology. 2022 Sep 1 ; 18(4) : 516–29.
8. Hu WS, Jiang Y, Shu W, Zhao R, Cao JM, Wang DP. World Journal of Gastroenterology Liver injury in COVID-19 : A minireview. World Journal of Gastroenterology. 2022 ; 28(47).
9. Wang J, Yuan X. Digestive system symptoms and function in children with COVID-19 : a meta-analysis. Medicine 2021 ; 100 : 11.
10. Sun J, Aghemo A, Forner A - Valenti L. COVID-19 and liver disease. Liver int. 2020 ; 40(6) : 1278–1281.
11. Sivandzadeh GR, Askari H, Safarpour AR, Ejtehadi F, Raeis-Abdollahi E, Vaez Lari A, Abazari MF, Tarkesh F, Bagheri Lankarani K. COVID-19 infection and liver injury : clinical features, biomarkers, potential mechanisms, treatment, and management challenges. World J Clin Cases. 2021 ; 9(22) : 6178–6200.
12. Yun YF, Feng ZY, Zhang JJ. COVID-19 and liver dysfunction in children : Current views and new hypotheses. *World J Hepatol* 2023 ; 15(3) : 353-363.
13. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020 ; 579 : 270-273.
14. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004 ; 203 : 631-637 .
15. Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020 ; 73 : 807-816.

16. Spearman CW, Aghemo A, Valenti L, Sonderup MW. COVID-19 and the liver : A 2021 update. *Liver Int* 2021 ; 41 : 1988-1998.
17. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Lan F. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. 2020 Preprint. Available from : BioRxiv : 931766 .
18. Banales JM, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol* 2019 ; 16 : 269-281.
19. Abel AM, Yang C, Thakar MS, Malarkannan S. Natural Killer Cells : Development, Maturation, and Clinical Utilization. *Front Immunol* 2018 ; 9 : 1869.
20. Ochsenbein AF, Zinkernagel RM. Natural antibodies and complement link innate and acquired immunity. *Immunol Today* 2000 ; 21 : 624-630.
21. Aoshi T, Koyama S, Kobiyama K, Akira S, Ishii KJ. Innate and adaptive immune responses to viral infection and vaccination. *Curr Opin Virol* 2011 ; 1 : 226-232.
22. Cao X. COVID-19 : immunopathology and its implications for therapy. *Nat Rev Immunol* 2020 ; 20 : 269-270.
23. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic : an observational cohort study. *Lancet* 2020 ; 395 : 1771-1778.
24. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. *Circulation* 2020 ; 142 : 429-436.
25. Vitiello A, La Porta R, D'Aiuto V, Ferrara F. Pharmacological approach for the reduction of inflammatory and prothrombotic hyperactive state in COVID-19 positive patients by acting on complement cascade. *Hum Immunol* 2021 ; 82 : 264-269.
26. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet* 2021 ; 398 : 622-637.
27. Qiu H, Tong Z, Ma P, Hu M, Peng Z, Wu W, Du B ; China Critical Care Clinical Trials Group (CCCCTG). Intensive careduring the coronavirus epidemic. *Intensive Care Med* 2020 ; 46 : 576-578.
28. Fuhrmann V, Jäger B, Zubkova A, Drolz A. Hypoxic hepatitis - epidemiology, pathophysiology and clinical management. *Wien Klin Wochenschr* 2010 ; 122 : 129-139.
29. Venturini E, Montagnani C, Garazzino S, Donà D, Pierantoni L, Lo Vecchio A, Nicolini G, Bianchini S, Krzysztofiak A,Galli L, Villani A, Castelli-Gattinara G ; Italian SITIP-SIP SARS-Cov-2 pediatric infection study group. Treatment ofchildren with COVID-19 : position paper of the Italian Society of Pediatric Infectious Disease. *Ital J Pediatr* 2020 ; 46 : 139.
30. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potentialevidence for persistent fecal viral shedding. *Nat Med* 2020 ; 26 : 502-505.
31. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19) : What do we know till now ? *Arab J Gastroenterol* 2020 ; 21 : 3-8.
32. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L.COVID-19 : Abnormal liver function tests. *J Hepatol* 2020 ; 73 : 566-574.

**** Corresponding author***

Laura Mihaela Trandafir
e-mail: trandafirlaura@yahoo.com

Laura Florescu
e-mail: lauraflorescu60@yahoo.com