

Dear Editor and Reviewers,

Thanks very much for taking your time to review this manuscript. I really appreciate all your comments and suggestions! Please find my itemized responses in below. The comments are reproduced (orange) and our responses are given directly afterward in a different color (black).

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** This review about the pathophysiological aspects of Covid-19 on children is summarised in an understandable format. It can be published.

Answer #1:

Thank you for your support and positive!

Reviewer #2:

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** Comments: “Recently, several studies have provided the results of abnormal liver tests in pediatric COVID-19. Alkan et al[19] found that 130 (44.2%) of 294 patients (age range: 14 days–18 years) with COVID-19 had abnormal liver function and most patients (33.3%) were characterized by elevated ALT, and other patients had elevated ALT (5.1%), ALP (6.6%), GGT (8.9%) and TBIL (3.8%). In addition, decreased albumin was also observed by Esmaili et al[20] and Liu et al[21]. In their studies, the proportion of decreased albumin in pediatric patients was 16.7%[20] and 18.2%[21], respectively. In general, the main manifestations of CRLI in children were mildly elevated ALT/AST and most research has confirmed this, for instance, Parri N et al[22] reported on 130 children (age range: 0–17 years) with COVID-19 in Italy, and 8/68 (11.8%) children had elevated ALT and 11/60 (18.3%) had elevated AST. The analysis by Du et al[23] showed that ALT and AST increased in 9 (5.0%) and 24 (13.3%) of 180 subjects (age range: 0–15 years), respectively, and 11 (6.3%) of 174 subjects showed increased ALP levels. Thus, the elevation of liver enzymes in pediatric patients is not significant, which may be due to the fact that COVID-19 is mainly mild in children. In addition, Sun et al[24] conducted a single center observational study of 8 children (age range: 2 months–15 years) with severe COVID-19 and the results showed that ALT was increased in 4 (50.0%) cases, but increased AST was not observed. It is possible that sometimes abnormally elevated

ALT/AST is not a sufficient indicator of liver injury” Comments:

1- The included literatures did not show that children who had COVID-19 necessitated admission to ICU and were on ventilators or liver support machine.

Answer #2-1:

The relevant literature support has been updated and added. (“Woodruff *et al*<sup>[65]</sup> investigated COVID-19 -associated hospitalization surveillance network of 14 states in US, they found that 691 (30.1%) patients required ICU admission and 122 (5.3%) patients needed invasive mechanical ventilation among 2293 hospitalized children (aged < 18 years). Moreover, other several researches also have showed 6% to 18% pediatric patients of COVID-19 required mechanical ventilation and 3% have died<sup>[66-71]</sup>.”)

2- There is no data on pathology of liver in children who had COVID-19, the available data are those on adults whom the undergone post-mortem histopathology and ultrastructure.

Answer #2-2:

I sincerely agree with you, and the lack of data in pediatric patients has been mentioned in this article, but the purpose of this article is to summarize the existing data and suggest possible etiology and pathology of pediatric COVID-19 related liver injury.

3- Children would have COVID-19 and get fast recovery; the mechanism is different from adults.

Answer #2-3:

For this point, mild symptoms in children are also mentioned in the INTRODUCTION of this paper, and the differences in mechanisms between children and adults, such as ACE2 expression, immunity, etc., are also repeatedly compared in this paper. Furthermore, the Table 2 has showed the frequencies of different COVID-19-related liver injury types in adults and children.

4- Research on COVID-19 in children has its critical ethical issue.

Answer #2-4:

Thank you for your reminding. This is an objective problem existing in the current research, and we have added and explained it. In addition, the factors affecting the study of COVID-19 cases in children also include the developmental characteristics of the SARS-CoV-2, which can be found in this article.

(“these conclusions have been drawn from a limited number of pediatric cases and there are serious ethical questions about research on children with COVID-19. Therefore, many conflicting views remain to be further explored,

for example: ...", "It is normal for these contradictions to emerge. As the short duration and wide coverage of the COVID-19 epidemic, the severity and complexity of clinical cases vary, and the criteria for inclusion and the outcome of patients are also different among case reports.")

5- The cited literature should be presented in detail, including duration of illness, admission to ICU, mortality.

Answer #2-5:

Thanks for your advice, but this is not our focus, we have elaborated and summarized the details of the cited literature related to the topic of this article (see the text and table). Since this is a Minireview, we think it's probably not necessary to go into too much detail.

6- Sample size of the published papers, adherence to ethical rules, type of study would be considered to evaluate the validity of the published papers.

Answer #2-6:

The literature we refer to is written by experts and scholars in related field, and all come from high-level journals, so these problems should not be worried.

7- The proposed hypothesis is invalid as it is not based on enough clinical data.

Answer #2-7:

The current research status and existing problems are also elaborated in this paper. Before more sufficient data are available, none of us can draw an accurate conclusion. The purpose of this paper is to summarize the existing results and put forward possible views.

We would like also to thank you for allowing us to resubmit a revised manuscript.

We hope that this manuscript is accepted for publication.

Sincerely,

Yang-Fang Yun