

Peer Review File

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Reviewer A

Work by Gao et al is a descriptive study about COVID-19 infections in children during the Omicron predominance period. It is mostly well written; however, I would recommend an English review, especially regarding the semantics of some sentences.

Also, I have some serious concerns about the internal validity of this work, which is why I am making these recommendations. I will list them below:

Comment 1. The authors do not specify the study design, simply describing it as a "retrospective observational study." However, it is important to define the specific type of study we are reading. Was there any follow-up of the patients? Were they observed at only one time point? The authors do not make this clear in any part of the text.

Reply 1: The study design has been denoted in the title and the Method section. Most of the patients were followed up to 3 months post-discharge.

Changes in the text: None.

Comment 2. In the "Research Subjects" section (which I find an unusual title and would suggest replacing with "Study Population"), there is a sentence that reads, "Patients with missing data including demographic characteristics, laboratory and/or genetic tests, or clinical outcomes were excluded from the study." However, as strongly recommended by STROBE, there is no flowchart provided (making it impossible to assess how many patients were considered and what the percentage of missing data was), and there is no mention of whether the missing information was missing completely at random (MCAR) or missing at random (MAR), which could indicate bias.

Reply 2.1: The "Research Subjects" has been replaced by "Study population" according to your suggestion.

Reply 2.2: Because only a small proportion of patients with missing data were excluded, the risk of bias most likely were not increased. A patient's inclusion flow chart was provided depicting the procedure of patient's exclusion and inclusion accordingly.

Changes in the text: Page 5, Line 13; and Page 6, Line 24.

Comment 3. I did not see any mention of a sample size calculation. Additionally, the authors do not make it clear what the primary outcome or main objective of the study is. They simply mention that they will measure "prognosis." However, "prognosis" is

not a variable, and it could refer to any of the measured variables in the study. It was unclear to me what the authors' objective or research question was in this work. Even though they mention in the last paragraph of the introduction, "This study analyzed the clinical characteristics of children infected with the Omicron variants to provide an evidence-based reference to potentially utilize for improving diagnosis and treatment, based on the obtained effects of treatment, and help in formulating scientific epidemic prevention and control strategies," this statement is very vague about the authors' hypothesis.

Reply 3.1: The sample size was limited by the size of the existing dataset and all the eligible patients during the study period have been screened for potential inclusion.

Reply 3.2: The primary and secondary study endpoints have been described in the Methods section. (see Page 5, Line 26-31)

Changes in the text: Page 5, Line 30-31.

Comment 4. The authors mention the random selection of patients for performing sequencing, but why was this measurement not performed on all patients? And how is this measurement linked to the other variables studied? I do not see a reason why this result is included in this paper.

Reply 4: The sequencing tests were used for the identification of Omicron variant. However, this test was not a routine practice in our hospital and therefore was not performed for every patient.

Changes in the text: None.

Comment 5. In the Data Collection section, the authors do not mention who performed it. Was it double-checked? Was there any approach for identifying potential inconsistencies? How do we know if the collection was accurate?

Reply 5: The data were collected independently by 2 investigators and the discordances were solved by consensus.

Changes in the text: Page 6, Line 9-11.

Comment 6. How did the authors detect non-normal variables? The Statistical Analysis section was very short.

Reply 6: The Shapiro-Wilk test was used to detect the normality of continuous variables. The Statistical Analysis section has been revised accordingly.

Changes in the text: Page 6, Line 15.

Comment 7. In the Results section, the authors mention the use of traditional medicine treatment. What were the criteria for using these treatments? Why were these treatments included? They are not usually recommended in any international guidelines.

Additionally, I do not understand why the authors included this data. Were they suggesting that these treatments influenced better outcomes? It is not possible for me to make this inference, as the authors suggest in the Conclusions section.

Reply 7: The efficacy of traditional Chinese medicines for COVID-19 has been proven in a lot of studies, although the mechanism of action of these drugs is still unclear. The administration of traditional medicines was a routine therapy in COVID-19 patients based on the theory of traditional Chinese medical (TCM) and the expert consensus on the diagnosis and treatment of patients with COVID-19 in China.

Changes in the text: None.

Comment 8. The Study Limitations section is very short and does not address several potential biases and inconsistencies.

Reply 8: The Limitation section has been revised according to your suggestions.

Changes in the text: Page 10, Line 20-24.

Reviewer B

The authors retrospectively evaluated the clinical picture of children admitted to Tianjin Binhai Hospital in November 2022 with omicron variants.

Comment 1: Similar studies have been reported worldwide with larger sample sizes; nothing is novel about this study. In addition, the process for obtaining and withdrawing participant consent was not described. It is unclear when each symptom or laboratory data were obtained, and whether participants had co-infections or complications is not stated.

Reply 1.1: This study exclusively included Chinese children under 14 years, and the traditional Chinese medicines were included in the therapy regimen.

Reply 1.2: The participant consents were obtained from the statutory guardians of the included children.

Reply 1.3: The symptoms or laboratory data of the patients were obtained after admission and no co-infections or complications were observed during the hospital stay and follow up.

Changes in the text: None.

Reviewer C

The children infected with Omicron variant are at risk of progressing to severe disease. In the manuscript “Analysis on the clinical features of children infected with the SARS-

CoV-2 Omicron variant- a retrospective observational cohort study”, authors analyzed the clinical characteristics of children infected with the Omicron variant to provide evidences for the prevention, diagnosis and treatment of the Omicron variant infection in children.

Couple questions are required to be answered before it will be accepted.

Comment 1: In the text, it was better to describe the traditional Chinese medicine in detail.

Reply 1: The patient treatment regimens regarding TCM have been described in the Results section. See Page 7, Line 28-33; and Page 8, Line 1-11.

Changes in the text: None.

Comment 2: It was advised to add related reference (DOI: 10.21037/atm-20-3192) about the children infected with SARS-CoV-2.

Reply 2: The related reference you mentioned has been added and the references list of the original manuscript have been re-numbered accordingly.

Changes in the text: see the References section.

Comment 3: What were the differences between adults and children infected with SARS-CoV-2 Omicron variant? Please state in the introduction.

Reply 3: The differences between adults and children infected with SARS-CoV-2 Omicron variant have been described in the Introduction section. See Page 4, Line 21-26.

Changes in the text: None.

Comment 4: How to determine the children infected with SARS-CoV-2 Omicron variant? Please state clearly in the methods.

Reply 4: The infection was confirmed by positive results for SARS-Cov2 RNA in real-time PCR assay of a nasopharyngeal swab and gene sequencing results.

Changes in the text: Page 5, Line 20-22.

Comment 5: The patients were collected from November 19 to November 30, 2022. The period was so short. Whether the SARS-CoV-2 Omicron variant was disappeared after November 30, 2022? Please state clearly.

Reply 5: The SARS-CoV-2 Omicron variant was disappeared after November 30, 2022.

Changes in the text: None.

Comment 6: The total percentages of thrombocytopenia were 6.3%. what were the possible causes? Please state in the discussion.

Reply 6: The pathophysiology of thrombocytopenia in COVID-19 is hypothetically caused by the impaired hematopoietic stem cells and megakaryocyte maturation due to an increase of specific inflammatory cytokines. The reasons for thrombocytopenia have been discussed in the discussion section.

Changes in the text: Page 9, Line 31-33; and Page 10, Line 1.

Comment 7: 1 patient had elevated D-dimer. Why to detect D-dimer? Please state in the discussion.

Reply 7: D-dimer level is one of the measures used in patients to detect thrombosis and therefore was monitored during the hospital stay. Measuring the level of D-dimer and coagulation parameters from the early stage of the disease can also be useful in controlling and managing of COVID-19 disease. The reasons for D-dimer monitoring have been stated in the Discussion section.

Changes in the text: Page 10, Line 1-6.

Comment 8: Whether the treatments for adults or children infected with SARS-CoV-2 Omicron variant were different? Please state in the discussion.

Reply 8: Compared with adults, children have fewer comorbidities and therefore are less likely to progress to critical illness. The treatment measures for children are mainly symptomatic treatment. The therapy regimen has been described in the Results section.

Changes in the text: None

Reviewer D

Comment 1: First, the title is not complete please consider to add management and prognosis, as well as the research settings such as pediatric inpatients.

Reply 1: The title has been revised according to your suggestions.

Changes in the text: Page 1, Line 2-3.

Comment 2: Second, the abstract needs some revisions. The background did not indicate the potential clinical significance of this research focus and the knowledge gaps on this focus. The methods did not describe the inclusion of subjects, the assessment of clinical characteristics, treatment, and prognosis outcomes, as well as how the data were analyzed. The results need more data on the treatment and prognosis of the subjects. The conclusion needs more detailed comments for the clinical implications of the findings such as how to manage such cases and why the prognosis is good.

Reply 2: The Abstract section has been revised according to your suggestions.

Changes in the text: Page 3, Line 1-33.

Comment 3: Third, the introduction of the main text is inadequate, because the authors did not review what has been known on the clinical characteristics, treatment, and prognosis of pediatric patients with SARS-CoV-2, the difficulties in the managing of such cases, and what the knowledge gaps are. The potential clinical significance of this study should be clearly clarified.

Reply 3: The Introduction section of the main text has been revised according to your suggestions.

Changes in the text: Page 4, Line 1-33.

Comment 4: Fourth, in the methodology of the main text, please accurately and correctly describe the clinical research design of this study, i.e., a case series? I do not think a retrospective cohort study is correct because of the small sample size. Please describe the research settings to indicate the representativeness of the sample. Please also clearly define the prognosis outcomes and how the treatment data were collected. The prognosis outcomes need to be defined in detail such as the antiviral treatment outcomes and the negative conversion rate of the SARS-CoV-2. In discussion, please compare the current findings with those from the studies on SARS-CoV-2 alpha and other variants.

Reply 4: The Methods, Results and Discussion sections have been revised accordingly.

Changes in the text: see the revision traces in the corresponding sections.