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OPEN PEER REVIEW

Gastrointestinal Manifestations in Children with Immunodeficiency Referred to a Tertiary Hospital

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1 Original submission

3 comments · 9 Nov 2024 – 15 Dec 2024

Referee 1 Reviewer

MAJOR REVISION 9 Nov 2024

Dear AE,
There are some comments that need to be checked and addressed by the authors:

1. Remove “a cross-sectional study” from the title.
2. Include the exact time and location in the abstract.
3. I didn’t find any statistical analysis in this study.

Kind Regards

Associate Editor

MAJOR REVISION 10 Dec 2024

Dear EIC,
Based on the reviewers' comments, this manuscript needs major revision.

Have all patients diagnosed with Primary Immune Deficiency undergone WES?
Have all patients with PID undergone endoscopy and colonoscopy? Even patients without gastrointestinal symptoms?
What percentage of patients with PID have gastrointestinal involvement at this center?
The criteria for performing endoscopy and colonoscopy should be mentioned.

Kind Regards
AE

Editor-in-Chief

MAJOR REVISION 15 Dec 2024

Dear Author,
We have reviewed your manuscript carefully. This is to inform you that this manuscript needs major revision.
Kind Regards
EIC

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Point-by-Point Reply to Reviewers

Thank you for your valuable feedback on our manuscript. Below, we address each of your points completely.

Response to Reviewer 1:

1. Remove “a cross-sectional study” from the title.

- Response: We appreciate this suggestion and have revised the title to remove the phrase "a cross-sectional study." The updated title now reflects the content of the manuscript more accurately.

2. Include the exact time and location in the abstract.

- Response: Thank you for this important point. We have added the specific time frame and location of the study to the abstract. The revised abstract now includes: "Participants were selected from medical records from Mofid Children's Hospital, Tehran, Iran, from 2011 to 2022, a tertiary care hospital for pediatrics with immunodeficiency disorders."

3. I didn’t find any statistical analysis in this study.

- Response: Thank you for your comment. As this study primarily aimed to describe the gastrointestinal manifestations in children with immunodeficiency, the analysis was entirely descriptive. We have now clarified this in the manuscript, emphasizing that frequencies and percentages were used to summarize demographic, clinical, endoscopic, histopathologic, and imaging findings. This approach aligns with the study's objective of characterizing patterns rather than testing hypotheses.

Response to Associate Editor's Comments:

1. Do all patients diagnosed with Primary Immune Deficiency have WES?

Response: Thank you for your question. Yes, all patients included in this study underwent Whole Exome Sequencing (WES) as part of their diagnostic evaluation. This uniform approach ensured a comprehensive assessment of potential genetic etiologies in this cohort of children with immunodeficiency. We have added this detail to the manuscript for clarity.

2. Have all patients with PID undergone endoscopy and colonoscopy? Even patients without gastrointestinal symptoms?

- Response: Upper endoscopy and colonoscopy were performed on 14 and 11 patients, respectively (see Figure 1). Notably, these procedures were conducted based on clinical judgment and indications rather than the presence of gastrointestinal symptoms alone.

3. How many percent of patients with PID have gastrointestinal involvement at this center?

Response**:** I thank you for your valuable comment on the discussion part. Thank you for your insightful comment. Based on our data, GI involvement in patients with PID was observed in 25 patients (58%) and CID in 18 (42%). We have clarified this point in the revised manuscript and updated the results to highlight the prevalence of GI manifestations among PID patients. The authors have gone through the discussion once again and added more information on the subjects you have mentioned. Additionally, we performed a thorough analysis based on the symptoms in each CID and PID disease and added Table 3 along with a section in the result in which we presented the new data. We have revised the paper and the changes in the discussion section are defined in yellow highlight.

4. The criteria for performing endoscopy and colonoscopy should be mentioned.

- We agree that specifying the criteria for performing endoscopy and colonoscopy is essential for understanding our methodology. The criteria for performing these procedures in our study were based on the clinical presentation and symptoms as outlined in the *Textbook of Gastroenterology, 5th Edition* by Yamada et al. Upper endoscopy was performed for patients presenting with dysphagia, abdominal pain, or a positive *Helicobacter pylori* test. Colonoscopy was indicated for patients with elevated fecal calprotectin, blood in stool, or stool samples containing more than five red or white blood cells, as well as symptoms such as rectal bleeding, mucus in stool, and chronic diarrhea. This information has been added to the revised methods section for clarity.

Response to Assistant Reviewer Comments

1. Include explicit eligibility criteria and a detailed description of the setting.

-Response: The study included children diagnosed with primary immunodeficiency disorders, specifically combined immunodeficiency (CID) and severe combined immunodeficiency (SCID), who underwent gastrointestinal evaluations at Mofid Children's Hospital, a tertiary care facility in Tehran, Iran, from 2011 to 2022. Exclusion criteria encompassed incomplete medical

records, absence of GI diagnostic procedures, and underlying chronic gastrointestinal conditions unrelated to immunodeficiency.

2. Discuss potential biases and how they were addressed.

- Response: The study acknowledges selection bias due to its retrospective design and reliance on data from a single center, which may not represent the broader pediatric population. All eligible cases were included to mitigate this, and strict inclusion/exclusion criteria were applied. Information bias was addressed by using standardized data collection forms, while confounding variables were minimized by excluding patients with unrelated chronic gastrointestinal diseases.

3. Provide a rationale for the sample size and detail the statistical methods used.

- Response: The sample size of 43 was determined through a census of all available medical records of children diagnosed with immunodeficiency disorders during the study period. Statistical analysis was conducted using SPSS software (version 25.0)

4. Address limitations and discuss the generalizability of the findings.

- Response: Limitations include the retrospective nature of the study and its single-center design, which may restrict generalizability to other populations or settings. The focus on specific immunodeficiencies may also limit applicability to other types of primary immunodeficiencies. Future multicenter studies are recommended to enhance the generalizability of findings across diverse populations.

5. Include information on funding sources and potential conflicts of interest.

- Response: The study did not receive any external funding sources, and there are no reported conflicts of interest among the authors.

2 Revision 1

3 comments · 25 Jan 2025 – 2 Feb 2025

Referee 1 Reviewer

ACCEPT 25 Jan 2025

Dear AE,
All of the comments have been carefully addressed by the authors, and this manuscript is now recommended for publication.
Kind Regards

Associate Editor

ACCEPT 27 Jan 2025

Dear EIC,
As suggested by the reviewers, this manuscript is ready to be considered for publication.
Kind Regards
AE

Editor-in-Chief

ACCEPT 2 Feb 2025

Dear Authors,
This is to inform you that your manuscript has been accepted for publication.
Kind Regards
EIC