

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 54189

Title: Hepatobiliary manifestations in children with inflammatory bowel disease: A single-center experience in a low/middle income country

Reviewer's code: 03478404

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: Egypt

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Reviewer chosen by: Le Zhang

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The most important aspect of this manuscript is (trying to) reporting on hepatobiliary conditions in children with IBD, in a country with low/middle income. Reports from low and middle income countries are quite rarely published. Other than that, the paper has many limitations and its scientific quality is low. The English language (spelling, grammar and style) requires major revision. The Editing Certificate by Springer Nature should not have been released. The quality of the English language in this paper is very poor. Comments: A. Abstract: A1. Background and also in Core Tip: The authors wrote “exponential increase in the reported incidence of inflammatory bowel disease (IBD) in infants, children and adolescents”. According to the definition, infants are also children, as well as are the teenagers. Children = people under 18 years of age. Please correct (also in the Introduction). A2. Methods – please insert the period when the study was carried out. A3. Results: very mixed up. Please clarify first symptoms (we are clinicians) and then results of investigations. What “The two patients who had cholestatic jaundice”? They were not mentioned before. We only know that 2 of them had direct hyperbilirubinemia. In the end, what were the diagnoses in the 13 patients? Just 1 primary sclerosing cholangitis (PSC) and 1 PSC/ Autoimmune hepatitis (AIH) overlap syndrome? And 10 with possible fatty infiltration? Why do not use the term of fatty liver disease? Anything particular? Please clarify. Were there only 3 with elevated liver enzymes??? And what type of enzymes? Transaminases? GGT? Please insert this and correct. What was the diagnosis in the 13th patient then? And please revise the English language all over the manuscript. A4. Conclusion: The authors wrote: “The most common hepatobiliary disorders in our children with IBD were found to be abnormal biochemical liver function tests, fatty infiltration and PSC. Please explain: abnormal biochemical liver function tests (as you call them) were found in 3 or 3 + 2 (not clear if

those with elevated enzymes had also direct hyperbilirubinemia). Then – 10 had „so called” fatty infiltration. Did they also have modifications of enzymes? And 2 had PSC? Please clarify. 2 cases out of 13 represent the most frequent? What about viral hepatitis? Side effects of medical therapy? Elevated liver enzymes do not represent a manifestation. The authors wrote „Those hepatobiliary manifestations in paediatric patients in LMIC might be relatively more common than in industrialized countries.” But we do not have diagnosis in these children. Only 2 clear diagnoses: 1 primary sclerosing cholangitis (PSC) and 1 PSC/ Autoimmune hepatitis (AIH) overlap syndrome. Elevated liver enzymes do not represent a diagnosis. Fatty infiltration considered at sonography cannot be considered a diagnosis. B. Introduction: B1. Please add as references for the “increase in the reported incidence of inflammatory bowel disease (IBD) in infants, children and adolescents” (again, please use only children) the following recent ones: - S E Roberts, K Thorne, N Thapar, I Broekaert, M A Benninga, J Dolinsek, E Mas, E Miele, R Orel, C Pienar, C Ribes-Koninckx, M Thomson, C Tzivinikos, S Morrison-Rees, A John, J G Williams. A systematic review and meta analysis of paediatric inflammatory bowel disease incidence and prevalence across Europe, Journal of Crohn's and Colitis, 28 February 2020; <https://doi.org/10.1093/ecco-jcc/jjaa037>. - Sýkora J, Pomahačová R, Kreslová M, Cvalínová D, Štych P, Schwarz J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. World J Gastroenterol. 2018;24(25):2741–2763. doi:10.3748/wjg.v24.i25.2741. B2. Why do you consider British Columbia being a LMIC (reference 7 – which is only an abstract and not referring to any population)? Maybe you wanted to use the reference “Foster A, Jacobson K. Changing incidence of inflammatory bowel disease: environmental influences and lessons learnt from the South asian population. Front Pediatr. 2013;1:34. Published 2013 Nov 6. doi:10.3389/fped.2013.00034. B3. The authors wrote “Collaboration and shared decision making among IBD clinicians, paediatric hepatologists/gastroenterologists,...”. IBD

clinician is or it should be a gastroenterologist! B4. „The aim of the present study is to assess the prevalence and aetiology“...but etiology was not provided by the authors! B5. The other aim: „and compare them with those in some industrialized nations“ – was not clearly discussed. C. Materials and methods. C1. Study design – Even here, the period when the study was performed is not mentioned. Just that there were 6 months. When? It is very important. More worryingly, from the “Institutional Review Board Approval Form”, we see that the date of the approval was 11/4/2011. Approximately 9 years ago. Therefore, when was the study carried out? C2. In any case, why only 6 months? If extended, it could have had more patients included! C3. Assessment and evaluation: It is to appreciate that the authors considered “Symptoms suggesting HB manifestations of IBD (jaundice, abdominal distension, pruritus, manifestations of portal hypertension)”. However, in the Abstract they started with laboratory results. Besides, since we are clinicians, please do not write that jaundice is a symptom; it is a sign! Please mention in detail what manifestations of portal hypertension you did consider. D. Results: D1. Table 1 has no relevance, the symptoms/signs suggesting IBD are not important here. Results should focus on hepatobiliary conditions. D2. Symptoms/signs presented here should be mentioned in the Abstract as well (mentioned in Table 2). Please correct in Table 2 – Complaints – Dark coloured urine is not a complaint! Please replace the term “Complaints”. D3. Table 3 has no relevance. Why is therapy important, since there were no side effects of medication? In any case, please correct “Infleximab” to Infliximab. At least, the name of the medication should be correct. D4. What do you mean by the subtitle “Outcome data”? D4. In this “Outcome data”, we learn that 1 patient had HCV hepatitis and many other aspects that should be inserted properly in the Abstract. D5. Table is not useful at all. Everything is normal. Or, if pathologic, then the Table is not correctly presented to be understood. Please revise. D6. Figure 1 is adjusted to appear shiny. Please insert an original figure. D7. Figures showing histopathology are of good

quality. E. Discussion: E1. Reference 19 – ESPGHAN Position Paper on Nutrition is not properly used here. E2. This paragraph discuss a lot about presenting symptoms/signs, family history, association with FMF etc , which are not the objective of this study. They have no purpose here. E3. This Discussio appears very flimsy, as there are not many findings to report. Therefore, the comparision with data from industrialized nations (one of the aims of this paper) does not appear clearly. F. Conclusion: Definitely, this should be corrected: “The most common hepatobiliary disorders in children with IBD are abnormal biochemical tests of liver function”. Abnormal biochemical tests of liver function do not define any disorder. The aim was to establish the etiology. G. Suggestion for further research: I do not see the point of inserting here „Health education for parents and patients should be performed to raise the knowledge of the nature of disease and treatment”. The same for the following sentence: „Genetic research includes very early-onset IBD and similar cases in families.” This paper should focus on hepatobiliary diagnoses associated with IBD. H. This study did not mention its limitations: single-centre experience, extremely small number of patients – especially given that it was a cross-sectional study; just 2 with clear diagnosis. I. Article highlights: All paragraphs included here are long and just repeating what was already said. Nothing to the point. It should be entirely rewritten. Please make them shorter and crispier. J. STROBE statement was not checked, just inserted.

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Reviewer's code: 00503587

Position: Editorial Board

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: New Zealand

Author's Country/Territory: Egypt

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

this MS reports the patterns of potential liver disease in a small group of children with IBD

SPECIFIC COMMENTS

1. 48 children were included. was this the full number of patients available at the centre over this time? or were some children with IBD excluded
2. Were all the children evaluated with liver chemistry (and other tests)? in those shown to have abnormal tests, were these assessments only at the time of the study, or did this include any time since diagnosis until the current time?
3. A number of children has altered liver chemistry, which is not a diagnosis but merely a description. This could reflect any number of causes. Were other causes considered in these children (drug-related, nutrition-related, coeliac disease, other conditions etc etc). The authors should focus on the group of children who were actually diagnosed with a specific IBD-associated liver condition
4. In the ABSTRACT, the word exponential is somewhat dramatic. Unless the authors have data that demonstrates this specifically, the word should be deleted or amended
5. egyptian should be Egyptian
6. The comment about IC after mention of IBDU is not appropriate or required. IC refers to the situation where the diagnosis of IBD can still be classified after full examination of the removed colon
7. the word "affection" is mis-used and should be removed and replaced (involvement?)
8. the INTRO is too long and should be shortened
9. The phrase "The aim of the present study is to assess the prevalence and" should read: The aim of the present study was to assess the prevalence and"
10. The METHODS (and elsewhere) refers to "liver function tests". the only tests of hepatic synthetic function listed are albumin and INR. The other tests are not functional tests. The term "liver chemistry" should be used instead here and elsewhere
11. the term "*Saccharomyces cerevisiae*" needs to be presented in italics
12. Were other conditions such as CMV, EBV, Alpha-1-anti-trypsin, coeliac disease etc also considered?
13. The comment about ERCP and MRCP in the methods section is a result



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and must be amended accordingly 14. The RESULTS section needs subheadings 15. The authors describe the presenting features of the 48 children. Is this relevant to the presence or absence of IBD-associated liver disease? 16. The presentation of current medications should be presented differently 17. The RESULTS section is hard to read and follow with many small comments. suggest extensive revision and reformatting of these results (with focus on actual diagnoses) 18. The DISCUSSION could also be shortened and focused more. 19. The ARTICLE HIGHLIGHTS section is very long 20. The TABLE TITLES/LEGENDS should be expanded and enhanced 21. Are TABLES 2 and 3 required? these are basic data that could be just in the text of the results. Further, there is no need to include the presence of portal hypertension... 22. Are Figures 1 and 3 required? these do not provide unique information. If Figure 2 is retained, it should contain arrows to guide the reader to key aspects.

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Title: Hepatobiliary manifestations in children with inflammatory bowel disease: A single-center experience in a low/middle income country

Reviewer's code: 02451447

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: Egypt

Manuscript submission date: 2020-01-14

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors tried to study the hepatobiliary involvement by IBD in children population in low/middle income country. The topic is good but there are limitations of this study.

1. The spelling and grammar errors should be corrected before submission. Also please change the spelling to American style due to the country where the journal will be published.
2. The authors declare that their hospital is the largest paediatric tertiary care centre in the country. The authors should have more patients and the study was enrolled 48 patients in a short period (6 month). I would recommend to study for a longer period, for example 3 years. In this way the data will be more convincing, and will demonstrate well the hepatobiliary involvement by IBD children.
3. As to Figure 2, I would recommend one panel will be enough. You don't have to show 8 panels.
4. As to Figure 3, the title "...showing the criteria of PSC ", the use of "criteria" is inappropriate. Fig. 3A1 is a good picture showing pathologic features of PSC, but Fig. 3A2 trichome stain does not reveal any evidence of onion-skin fibrosis and I don't believe it was from the same portal tract of Fig. 3A. The description of Fig. 3B1 is inaccurate and I am not sure what you wanted to indicate. Did you mean this overlap syndrome? Fig. 3B, I doubt it is extensive portal fibrosis as the authors described, and it did not show features of PSC or overlap syndrome. Please ask the pathologist to review these pictures carefully.
5. For these 2 patients with PSC or PSC/AIH, are the UC or Crohn's patients? Please clarify.
6. The authors declare to study etiology, but I did not see any result for that.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 54189

Title: Hepatobiliary manifestations in children with inflammatory bowel disease: A single-center experience in a low/middle income country

Reviewer's code: 03478442

Position: Peer Reviewer

Academic degree: FEBG, MD, PhD

Professional title: Professor

Reviewer's Country/Territory: Greece

Author's Country/Territory: Egypt

Manuscript submission date: 2020-01-14

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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This is a well written manuscript including presentation of hepatobiliary manifestations in children with inflammatory bowel disease in the authors' center and a concise review of the literature on the subject. The findings are not surprising but more or less expected by the available literature on the subject, however the authors present their own experience honestly and with enough details and information provided. Suggestions. There are some minor language or typing errors which should be corrected with a careful inspection of the manuscript. The last part describing the research methods and conclusions should be incorporated into the text to have the standard format of manuscripts.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 54189

Title: Hepatobiliary manifestations in children with inflammatory bowel disease: A single-center experience in a low/middle income country

Reviewer's code: 00503587

Position: Editorial Board

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: New Zealand

Author's Country/Territory: Egypt

Manuscript submission date: 2020-01-14

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Thank you for revising your manuscript taking into account the comments of the reviewers. There remain errors of English language that should be corrected the methods section of the abstract contains the numbers of subjects: these are results and must be moved accordingly Some of the sections have been improved with the revisions conducted so far. Further revisions (esp Intro and Discussion) could further enhance flow and readability

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's Country/Territory: Greece

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
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SPECIFIC COMMENTS TO AUTHORS



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The manuscript has been significantly improved by the authors, but still some grammar and language mistakes exist and those should be corrected by a native English speaker.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Professional title: Associate Professor

Reviewer's Country/Territory: United States

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors made some improvement of this revised manuscript. Comment: 1. There are still significant grammar and language mistakes exist throughout the manuscript. Please correct these by a native English speaker who knows medicine, since this paper is submitted to a scientific Journal. I pointed there are spelling and grammar errors in my last comments, but the authors did not answer instead of giving “?”. 2. One of the reviewers (00503587) has suggested that the word "affection" is mis-used and should be removed and replaced. And the authors replied “has been revised”. However, “affection” is still used in this paper! For example, it is used 2 times in the Abstract, one time on the Core tips and 2 times in the main text. 3. I don’t think LMIC abbreviation can be used as Key word. 4. The Abstract: The authors should not put the data which should be in the “Results” session in the “Methods” session. 5. From a GI/Liver pathologist’s view, I do not see “diffuse bile ductular proliferation” in Fig 3. A1. I would recommend make the description of these 3 figures as simple as possible. For example, A1: periductal concentric “onion-skin” fibrosis; A2: Masson's trichrome stain highlighting the “onion-skin” fibrosis. I don’t think Fig. 3B is needed. Also you already know A2 is not H&E stain, but why still say “All photos H&E, Original magnification x400”?

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Manuscript submission date: 2020-01-14

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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I can see that some improvements were done by the authors. Reviewers made pertinent comments; however, only some of the suggestions were considered by the authors. On the other hand, the authors wrote they corrected some aspects, but in fact they did not. It is not only the very poor quality of the English language, but also the poor relevance of this paper for practice. This paper included only 48 patients studied in 2013. The study could have been improved by adding more patients. I am sure that, being such an important GI centre in Egypt, since 2013 many other patients were diagnosed with IBD. Why publish in 2020 a paper about patients diagnosed in 2013? What do we learn from this paper? Only 3 patients had definite cause of hepato-biliary manifestations. Conclusion of the Abstract mentions "The commonest hepatobiliary disorders in our children with IBD were found to be abnormal biochemical liver function tests...." Well, it would be dangerous for doctors and medical practice to read that "abnormal biochemical liver function tests" do not require further investigations. Elevated liver enzymes do not represent a manifestation. Abnormal biochemical tests of liver function do not define any disorder. The authors' answer was to look at reference 9. It is not relevant. As I initially said, the most important aspect of this manuscript was (trying to) reporting on hepatobiliary conditions in children with IBD, in a country with low/middle income. But, it was not properly done. In "Answering Reviewers", the authors said that they reported honestly. This is not of help. Any paper is supposed to report on honest data. Also, "Article Highlights" is still too long. The "Audio file" can hardly be heard.