

**Manuscript ID:** 70889

**Title:** Risk of venous thromboembolism in children and adolescents with inflammatory bowel disease: a systematic review and meta-analysis

**Journal:** World Journal of Gastroenterology

## **Response to Reviewers' comments**

Dear Dr. Ma,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,

## **Reviewer #1**

*The presented manuscript “Risk of venous thromboembolism in children and adolescents with inflammatory bowel disease: a systematic review and meta-analysis” is interesting and well-written, it raises an important medical question and would be of interest to researchers and physicians, however, I have some minor comments.*

**Response:** We thank the Reviewer for the positive and encouraging comments, the manuscript was modified according to the comments below.

*1. Please, use a larger font for figures 2-5, with the current one it is not possible to read!*

**Response:** We thank the Reviewer for the kind reminding. We now use larger fonts in the figures.

*2. For all Figures it is necessary to add in footnotes full forms of every inscription.*

**Response:** The Reviewer is right. It was revised according to the comment.

*3. Please, add a List of abbreviations.*

**Response:** We thank the Reviewer for the kind reminding. We added a list of abbreviations at the end of the main text.

*4. The association with VTE subtypes deserves much better and deeper discussion.*

**Response:** We thank the Reviewer for the comment. We tried to expand the discussion about that. Still, the literature contains more suppositions than actual evidence.

## **Reviewer #2**

*1. The title was complete and engaging and well written*

**Response:** We thank the Reviewer for the positive and encouraging comments.

*2.The keywords are basically three to five, here are 7 cords that need to be reduced*

**Response:** We thank the Reviewer for the kind reminding. We now have five keywords.

*3It is stated in the method that it has been used to extract data from cohort studies and clinical work, but in the abstract it is only written observational studies. Please correct the contradiction between these two sections.*

**Response:** We thank the Reviewer for the comment. We revised the Abstract accordingly.

*4.The introduction was appropriate, but newer references should be used if new studies are available*

**Response:** We thank the Reviewer. We revised the references when possible.

*5.Please describe the search strategy in more detail*

**Response:** We thank the Reviewer. We now provide a detailed search strategies for PubMed, Embase, Cochrane Central as supplemental materials.

### **Reviewer #3**

*Unfortunately I suspect a serious flaw in the presented analysis. The Authors claim the application of odds ratio (OR) to find the incidence IBD-VTE. Let's mark cases with IBD and VTE as a; Cases with IBD and without VTE as b; Cases without IBD but with VTE as c; Cases without IBD neither VTE as d; Then  $OR=(a/c)/(b/d)$  and if  $OR=1$  IBD does not affect odds of outcome (VTE) if  $OR>1$  IBD is associated with higher odds of outcome (VTE) if  $OR<1$  IBD is associated with LOWER odds of outcome (VTE) For the most analysed cases OR is not presented. However, 95 %*

*confidence interval is calculated based on OR. So OR is ALWAYS within CI range. For the majority of presented analysis CI lower and upper limit are below 1 and close to 0 e.g. 95 % CI: 0.01-0.03. It means  $OR < 1$  so IBD lowers odds of VTE. My conclusion is opposite to presented in the article but it is based on results presented there. I would suggest to widen the references by the items based on statistics, present some exemplary calculations (also for lower and upper limit of OR), explain why  $p=0.1$  is assumed as important (the most statisticians assume max  $p=0.05$  for stitistic importance of the results). Referring to the title of the article, it should be presented, discussed how the results of OR, CI can be understood in terms of RISK (the core term in the title). Then discussion and conclusions can be different.*

**Response:** We thank the Reviewer for the comment. The risk of VTE in IBD was estimated by ES (p) and the corresponding 95% confidence interval (CI), this is different from OR. Because of the nature of the included studies, we performed the meta-analysis based on both the effect size and odds ratios. Since the effect sizes are all  $>0$  and the ORs are all  $>1$ , we conclude that the risk of VTE is increased in IBD. In addition, because the event incidence (p) was relatively small ( $0 < P < 0.2$ ), the double arcsine method was also used for data conversion and showed similar results ( $P=0.03$ , 95% CI: 0.02–0.04, Figure S1). Statistical heterogeneity among studies was calculated using Cochran's Q-test and the  $I^2$  index. An  $I^2 >50\%$  and Q-test  $P < 0.10$  indicated high heterogeneity, and the random-effects model was used; otherwise, the fixed-effects model was applied. P-values  $< 0.05$  were considered statistically significant.

### **Science editor**

*The study performed a systematic review and meta-analysis, and concluded that IBD had a higher risk of VTE. This manuscript is well written and designed. Meanwhile, the conclusion is also informative. Few concerns raised by reviewers should be addressed in order to improve this manuscript.*

**Response:** We thank the Science Editor. We revised the manuscript according to the Reviewers' comments.

**Company editor-in-chief**

*I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.*

**Response:** We thank the Editor-in-Chief. All tables are three-line tables. The rows are aligned. Returns were not used to align the text in the tables.