Oct 10, 2023

Submission ID: World Journal of Gastroenterology Manuscript NO: 87126

Title: " Global burden of inflammatory bowel disease 1990-2019: A systematic examination of the 2019 Global Burden of Disease and 20-year forecast levels "

Dear Editor,

We are very grateful to you and the reviewers for the comments on our manuscript entitled “Global burden of inflammatory bowel disease 1990-2019: A systematic examination of the 2019 Global Burden of Disease and 20-year forecast levels”. We considered the manuscript to be greatly improved as a result of your efforts. Based on your and the reviewers’ suggestions, we have addressed the comments point-by-point, and the modifications in the revised manuscript were highlighted with yellow color. Moreover, we have formatted the manuscript strictly according to the submission guidelines. We have checked the grammar and spelling of the manuscript and also asked a professional English language editing company to edit the manuscript (please see the yellow font in the revised manuscript). We believe that our revisions will satisfy you and the reviewers. On behalf of my co-authors, we would like to express our great appreciation to you and the reviewers.

Yours sincerely,

Shuixiang He

Response to Reviewer #1:

Comment: Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The projection and burden of IBD ,despite to some limitations as expressed in discussion are well analysed. As a grammar concern, you chose the word "publically" . but "publicly" is considered more correct in grammar sources. Still no revision is recommended.

Response: Thank you for your careful review and kind reminder. We feel so sorry for our carelessness. The grammar of the full manuscript was carefully checked and errors have been corrected. We have revised the article and corrected the word "publically" to" publicly" in the manuscript marked in yellow text (the Acknowledgements section). Thank you for your patience, the authors do appreciate your nice suggestion.

Response to Reviewer #2:

Comment: Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Well summarized Paper. Chengjun Li et al. is a comprehensive analysis of literature review on the burden of IBD from 1990 to 2019 at the global, regional, and national perspectives. The association and significance of various demographic indicators were first analyzed in different geographic areas. Further, they forecast the number and incidence rate of IBD for the next twenty years from 2019 to 2039 based on the R software and validated the reliability of the results anticipating providing new hypotheses for the management to alleviate the global burden of IBD. It is now clear that IBD is alarmingly evolving in young adults worldwide and now contemplated to be an emergent global disease. IBD, which encompasses Crohn's disease (CD) and ulcerative colitis (UC), was a known problem in industrial-urbanized societies attributed largely to a Westernized lifestyle, wealthy socioeconomic status and other associated environmental factors. However, its incidence and prevalence in low-in-come countries and/or developing countries is steadily rising attributed to the rapid modernization and Westernization of the population. In this,

paper the investigators collected the information on the incidence of IBD from the GBD study from 1990-2019 to calculate the AAPC and EAPC in ASR of IBD in different regions. The relationship between IBD and the HDI, SDI was analyzed. The Nordpred and BAPC models was also used to predict the prevalence trends of IBD by gender from 2019-2039. Globally, they found North America consistently has the highest IBD ASR, while Oceania consistently has the lowest. Meanwhile, East Asia had the fastest average annual growth in ASR (2.54%), while Central Europe had the fastest decline (1.38%). Countries with low ASIR in 1990 had faster growth in IBD, while there was no significant correlation in 2019. In addition, IBD grew faster in countries with low ASDR in 1990, while the opposite was true in 2019. Analysis of SDI and IBD ASR shows that countries with high SDI generally have higher IBD ASR. Finally, they report projections find a declining trend in the incidence of IBD from 2019-2039, but a gradual increase in the number of cases. There are data from 204 countries. The calculus is illustrated in 7 Figures and 1 Table including data from low-in-come nations herein presented. Fig. 1, A-C summarizes all. They concluded that in the face of global population growth and aging, early monitoring and prevention of IBD is particularly important to reduce the disease burden caused by IBD, especially for countries with a high incidence of IBD. The relationship between IBD and the Human Development Index (HDI) and Socio-Demographic Index (SDI),and predict the prevalence trends of IBD by gender from 2019-2039. This is a great paper supporting clinicians, in their adoption of new epidemiological guidance for IBD by establishing and fortifying key learning approaches maybe expected to change their methods as additional research becomes available. However, the greatest hope and assurance for IBD prevention and management depends largely on broadening, thus far, insufficient understanding of the molecular etiopathogenesis link between multifactorial interplay and chronic inflammation pathways.

Response: Thank you for appreciating our work and offering helpful comments.We strongly agree with your comments that the greatest hope and assurance for IBD prevention and management depends largely on understanding of the molecular etiopathogenesis link between multifactorial interplay and chronic inflammation pathways. We have summarized the findings from the latest relavent research on novel IBD therapies based on the molecular etiopathogenesis between multifactorial interplay and chronic inflammation pathways.

We summarized as follows:

IBD has been a multifactorial disease, and its specific pathogenesis still remains unclear. Current studies have found that IBD is associated with individual genetic susceptibility, environmental factors, gut microbiota dysbiosis, and immune responses [1]. Chronic intestinal inflammation is thought to be a consequence of immune system abnormalities [2]. The immune dysregulation involving multiple cytokines plays a significant role in the occurrence and progression of IBD. This includes an increased production of IL-17, IFN-g and TNF-a mediated by type 1 T helper cells (Th1) and Th17, as well as the dysregulation of Th2 cell responses [3]. The release of various inflammatory factors such as IL-6, IL-23 and IL-17 contributes to the amplification of inflammatory responses, inducing and exacerbating intestinal inflammation. Therefore, a better comprehension of the interactions between these cytokines and various immune cells will provide excellent opportunities for IBD prevention and therapeutic advances.

It has been reported that some certain medications of conventional IBD treatments have noticeable side effects, and their efficacy may diminish over time. In fact, a significant number of patients don't have a satisfactory response to these therapies[4,5]. Consequently, the search for new therapeutic strategies targeting alternative immunological pathways and inflammatory cytokines has intensified. New therapies targeting alternative pro-inflammatory pathways like IL-12/23 axis, IL-6 pathway or Janus Kinase inhibitors are on its way. Alternatively, some emerging oral substances that aim to stimulate canonical immune-modulating pathways, like the TGF-b pathway, have shown clinical efficacy. The inhibition of adhesion and migration of leukocytes into the inflamed intestinal mucosa has also received extensive attention. The use of engineering immune-modulating cells like mesenchymal stem cells (MSCs) or immune-regulatory cells like Tregs is a promising alternative approach [5]. New strategies for IBD are in development, and they are expected to expand its prevention and treatment options. It may be helpful for us to select appropriate therapeutic approach based on risk factors and clinical progression to maximize cost-effectiveness while minimizing adverse risks and side effects, such as infections or the suppression of other protective properties. We are in the opening of a new era in the treatment of IBD. A better understanding of the mechanisms, especially in immunology, and the continuous exploration of new therapeutic targets for IBD will provide excellent opportunities for the prevention, treatment, and management.

[1] **McGovern DP**, Kugathasan S, Cho JH. Genetics of Inflammatory Bowel Diseases. *Gastroenterology* 2015;**149:**1163-1176.e2. [PMID: 26255561 DOI: 10.1053/j.gastro.2015.08.001]

[2] **de Souza HS**, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol* 2016;**13:**13-27 [PMID: 26627550 DOI: 10.1038/nrgastro.2015.186]

[3] **Ordás I,** Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012;**380:**1606-1619. [PMID: 22914296 DOI: 10.1016/S0140-6736(12)60150-0]

[4] **Ding NS,** Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. *Aliment Pharmacol Ther* 2016;**43:**30-51. [PMID: 26515897 DOI: 10.1111/apt.13445]

[5] **Catalan-Serra I,** Brenna Ø. Immunotherapy in inflammatory bowel disease: Novel and emerging treatments. *Hum Vaccin Immunother* 2018;**14:**2597-2611. [PMID: 29624476 DOI: 10.1080/21645515.2018.1461297]

Response to Science editor:

Comment: The manuscript has been peer-reviewed, and it is ready for the first decision.

Response: Thank you for your kind reminder. We have answered the questions point-by-point in detail and made the modifications in the revised manuscript marked in yellow text. Thank you very much.

Response to Company editor-in-chief:

Comment: I have reviewed the Peer-Review Report, the 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. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". 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. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023. I recommend the manuscript to be published in the World Journal of Clinical Cases. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

Response: Thank you very much for your kind suggestion. We have uploaded the decomposable figures and organized them into a single PowerPoint file. For the tables, we have provided the standard three-line tables in accordance with the guidelines. All the figures are original ,and we have added the copyright information to the bottom right-hand side of the picture in PowerPoint. Furthermore, we have supplemented the Article Highlights section before the References section and added the latest cutting-edge findings at the end of the first paragraph of the Introduction section. The latest cutting-edge research has been focused on IBD personalized treatment, microbiota research, immunotherapy, digital health and remote monitoring, collaborative disease research, et al. We also summarized the findings of the latest cutting-edge research on IBD as follows.

1. Personalized Treatment: The latest research has begun to apply genomics to IBD therapy [1]. By

analyzing patient's genetics, researchers can determine which medication or treatment method is most effective for a particular individual.

2. Microbiota Research: Recent studies highlight the role of gut microbiota in pathogenesis of IBD and focus on the personalized approaches that modulate the gut microbiota to treat IBD [2]. This opens up the possibility of IBD treatments through microbiome adjustments, such as fecal microbiota transplantation.

3. Immunotherapy: Novel immunotherapies have shown promise in IBD treatment. For instance, specific antibody therapies targeting the anti-IL-12/23 axis, IL-6 pathway and TGF-b pathway, have demonstrated clinical efficacy in treating IBD patients [3,4].

4. Digital Health and Remote Monitoring: With the use of smartphone applications and remote monitoring devices, patients can easily track their symptoms, diet, weight, and other health data and share it with healthcare providers [5]. This digital health technology assists doctors in better managing patients' conditions and providing more personalized treatment recommendations.

5. Disease Collaboration Research: Increasingly, studies are focusing on the connections between IBD and other diseases. For example, research suggests some associations between IBD and conditions such as arthritis, dermatological diseases, and cardiovascular disorders [6,7]. These interdisciplinary research provide insights into common etiological factors and treatment approaches.

[1] **Kammermeier J**, Lamb CA, Jones KDJ, Anderson CA, Baple EL, Bolton C, et al. Genomic diagnosis and care co-ordination for monogenic inflammatory bowel disease in children and adults: consensus guideline on behalf of the British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition. *Lancet Gastroenterol Hepatol* 2023;**8:**271-286. [PMID: 36634696 DOI: 10.1016/S2468-1253(22)00337-5]

[2] **Qiu P**, Ishimoto T, Fu L, Zhang J, Zhang Z, Liu Y. The Gut Microbiota in Inflammatory Bowel Disease. *Front Cell Infect Microbiol* 2022;**12:**733992. [PMID: 35273921 DOI: 10.3389/fcimb.2022.733992]

[3] **Catalan-Serra I**, Brenna Ø. Immunotherapy in inflammatory bowel disease: Novel and emerging treatments. *Hum Vaccin Immunother* 2018;**14:**2597-2611. [PMID: 29624476 DOI: 10.1080/21645515.2018.1461297]

[4] **Turner D**, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: An

Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021;**160:**1570-1583. [PMID: 33359090 DOI: 10.1053/j.gastro.2020.12.031]

[5] **Nguyen NH**, Martinez I, Atreja A, Sitapati AM, Sandborn WJ, Ohno-Machado L, Singh S. Digital Health Technologies for Remote Monitoring and Management of Inflammatory Bowel Disease: A Systematic Review. *Am J Gastroenterol* 2022;**117:**78-97. [PMID: 34751673 DOI: 10.14309/ajg.0000000000001545]

[6] **Ashrafi M**, Kuhn KA, Weisman MH. The arthritis connection to inflammatory bowel disease (IBD): why has it taken so long to understand it? *RMD Open* 2021;**7:**e001558. [PMID: 33863841 DOI: 10.1136/rmdopen-2020-001558]

[7] **Argollo M**, Gilardi D, Peyrin-Biroulet C, Chabot JF, Peyrin-Biroulet L, Danese S. Comorbidities in inflammatory bowel disease: a call for action. *Lancet Gastroenterol Hepatol* 2019;**4:**643-654. [PMID: 31171484 DOI: 10.1016/S2468-1253(19)30173-6]

Thank you for your sincere suggestions, we have sent this revised manuscript to a professional English language editing company to polish the manuscript and provided a new language certificate. Thanks for your recommendation. We are sure that the quality of the English language of this manuscript will meet the requirements of this journal. We, all the authors, thank you very much.