May 26th 2022

Andrzej S Tarnawski
Editor-in-Chief
World Journal of Gastroenterology

Dear Editor,

Thank you for the decision letter informing us that our paper would have a chance of further enhancement for publication.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the *World Journal of Gastroenterology*. The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers' suggestions. The point-by-point responses to all comments has been prepared and given below.

Thank you for your kind processing and consideration of our revised manuscript. We look forward to hearing from you.

Sincerely,

Dr. Qian Cao

Inflammatory Bowel Disease Center of Sir Run Run Shaw Hospital,

College of Medicine Zhejiang University,

No. 3 East Qingchun Road, Hangzhou 310016, Zhejiang Province, China

Tel: +86 13588706896

Email: caoq@zju.edu.cn.

Reviewers' Comments:	Response	Revision in text
Reviewer #1:		
Reliable information regarding the use of IBD drugs and temporal changes herein in China is missing. For that reason the manuscript by Yao et al is of interest. The authors should be acknowledged for the great amount of work done by travelling through more than 3000 patient files given that there does not seem to be access to central registries covering all chinese IBD patients. In general the english language is OK needing polishing here and there. However before the manuscript can be recommended for publications a number of changes and considerations have to be made.	Thank you for your comments and suggestions. We have polished our language and carefully revised the manuscript accordingly.	
General points: As is noted in the manuscript the data is extracted from more than 3000 patient files from seven referral hospitals. In China more than 1,5 mio people are suspected to suffer from IBD so the patients investigated represents only 0,2% of the total IBD population. So even though the data stems from referral hospitals in various regions of China considerations as to whether the data is really representative must be made. I think this very important issue should be a part of the discussion.	Thank you for your suggestions. We agree with your opinion that the study population accounted for merely 0.2% of the total Chinese patients with IBD as estimated. Here, we have three considerations on population representation in our study: First, it is difficult to acquire complete data on the diagnosis, treatment, and prognosis of all IBD patients as there is lack of national registries covering all IBD patients in China. Instead, researchers usually conduct studies based on Hospital Information Manage Systems or databases, and increase the sample size by recruiting as many centers as possible. We hope a well-organized national IBD registry could be established in the near future to satisfy the need for larger clinical studies. Second, the 12 hospitals in this study are distributed throughout all the seven administrative regions in China, which were large IBD referral centers with diverse socioeconomic backgrounds. Therefore, the study population represents in-patients from Chinese referral centers to some extent, while extrapolation of medication trends to grass-roots hospitals remains unknown. Third, we found similar patterns in demographic and clinical characteristics by further comparing IBD patients in our study with those in other Chinese studies with large sample size [1,2], which also reflects the representativeness of our study to	Page 12, Line 8-19

	a certain extent. Considering all these factors together, we have revised the Discussion accordingly.	
General points: Infliximab is the only biologics which use is described. I assume this is because of the simple fact that no other biologics or small molecules were available in China. I think this should be the case should be noted very clearly in the manuscript as should the fact that reimbursement of the cost of biologics does not seem to be possible in China. This can of course affect the use of biologics and this deserves attention in the discussion section.	Thank you for your suggestions. Before 2020, infliximab was the only approved biological agent prescribed to IBD patients in China. In our study, patients were included with a definite diagnosis of CD or UC between January 1, 1999 and December 31, 2019. For this reason, infliximab is the only biological agent analysed in our study. In addition, insurance coverage of infliximab was not achieved until November 28th 2019, the day infliximab entered the national medical insurance. This policy will influence the decision making of IBD patients on whether to choose infliximab or other immunosuppressants, which may explain the drug discrepancy between patients from China and other countries. We have added statements to the Discussion accordingly.	Page 14, Line 4-9
General points: The period of follow up is very short (table 1). It should be explained why and the impact of this short period of follow up on the data and its interpretation should be discussed.	Thank you for your suggestions. We also found that the duration of follow-up was short. As seen in Table 1, the total median duration of follow-up was 1.6 years. There are two possible explanations: (1) The study population mainly stems from IBD referral centers and therefore many patients will go back to grass-roots hospitals for following treatment after acquiring definite IBD diagnosis and initial treatment strategies, which may result in loss to follow-up. (2) Due to the observational design, most information originated from medical records or databases. It would be a huge cost to follow such a large number of patients. Despite the short follow-up period, which may affect medication trend analysis, there were still more than 1,000 patients who were followed for more than three years, and our analysis towards long-term changes in treatment patterns provided a credible result, which can assist in clinial drug management. We have added statements to the Disscussion accordingly.	Page 12, Line 22-30 Page 13, Line 1-2
Specific comments: Introduction pg 1: IBD does not include but consists of UC and CD; I don´t know what is meant by "launched	Thank you for your suggestions. We have revised "Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC)" to "Inflammatory bowel diseases (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC)" to the Introduction accordingly.	Page 5, Line 21-24 Page 5, Line 26-27

succession" .	In the Introduction, we wanted to illustrate the fast development of IBD medications which launched in succession during past decades. We apologize for the typographic error of missing “in” between “launch” and “succession”. We have revised the statement accordingly.	
Specific comments: Materials and Methods pg 9: It should be stated clearly whether the population consists of incident or prevalent patients； If the Chinese consensus on IBD diagnosis differs from the rest of the world the differences should be described； The patients were excluded from analyses of treatment patterns if they had no prescriptions throughout follow up. Why this ? No medication is also part of a treatment pattern.	Thank you for your comments. Our population consists of incident patients who were diagnosed with CD or UC between January 1, 1999 and December 31, 2019. The Chinese consensus on IBD diagnosis was similar to that of the European Crohn’s and Colitis Organization (ECCO) consensus. We have revised the statement in the Study population section of Materials and Methods accordingly. We agree with your opinion that no prescription is also a treatment pattern. We focus more on periodic changes between different medications. Therefore, we have not included patients who had no prescription with either 5-ASA, CS, IMS, or IFX during the 3-year follow-up.	Page 6,Line 29-30 Page 7, Line 1-2
Specific comments: Results pg 12: How were the 957 patients included in the analysis for periodic changes in treatment patterns selected ? pg 13 The major differences in characteristics between included and excluded patients should be briefly mentioned in the text. The information given in figure 2 and table 3 is basicly the same. There is a lot of data in the manuscript. I think table 3 can be omitted. pg 14 51% of the patients ceased medical treatment after 1-3 month. This is really in contrast to the strategy applied world wide. This issue earns focus in the discussion pg 15 It seems surprising that patients having perianal surgery and thus complicated disease were less prone to be treated with infliximab. This should be discussed.	Thank you for your comments. By excluding 2452 patients who were followed for less than three years since diagnosis, and 201 patients with no prescription of either 5-ASA, CS, IMS, or IFX throughout follow-up, 957 patients were further included in the analysis for periodic changes in treatment patterns (Data shown in Figure 1). We have added a statement to the Baseline characteristics section of the Results. We have briefly described the major differences in characteristics between included and excluded patients in the analysis for periodic changes in treatment patterns in the Baseline characteristics section of the Results. In addition, while the previous Tables 3 and 4 provided us with more specific information about temporal changes in medications, we have omitted it from the manuscript and reformatted them as Supplymentary Tables 1 and 2, in case that helps. In our study, 51.6% of CD patients and 60.1% of UC patients ceased medical treatment within 1-3 months. We realized the contradicting results from our study with the current strategy applied worldwide. Our treatment data are mainly derived from IBD referral centers where patients may ceaced treatment after returning home with only one-month prescriptions. This may explained by the following reasons which reflect the specific situation in Chinese IBD management: (1) lack of	Page 9,Line 2-6 Page 9,Line 17-22 Supplementary Tables 1-2 Page 14,Line 16-25 Page 11,Line 11-17 Page 16,Line 2-6

	communication between referral centers and grass-roots hospitals during the early period of IBD treatment; (2) poor medication adherence at the patient level [3]; (3) knowledge gap between doctors and guidelines worldwide. We have added these statements in the Discussion. Among CD patients, We carefully assessed the factors impacting the initiation of different medications compared with the no prescription group and found that we have mistakenly stated them in the Results but data in the previous Table 7 was still correct. Specifically, patients having perianal surgerical history before diagnosis were more prone to be treated with infliximab (OR, 2.68; 95% CI, 1.92-3.73; p<0.0001). We have revised the manuscript and also discussed the possible reason for these results.	
Specific comments: Discussion Clearly the weakest part of the manuscript. In fact I think this section should be rewritten. In it's present stand it more or less just reflects a summary of the results presented instead of a discussion putting the important results into a context comparing the results with the data from the literature. This is of special importance in thius case since limited information regarding drug use i available from China and other Asian countries. This makes it highly relevant to compare the findings with findings from other parts of the world and with acknowledged guidelines (ECCO,AGA). There is much too few references in the present version of the discussion	Thank you for your suggestions. We have carefully revised the Disscussion.	Page 11-17
Specific comments: Figure 2 Panel A: Was there no use of 5-ASA in 1999 and 2000 ? Panel B: No steroid use in 2000 ? Figure 3: Simply too small, omit it and present the data only in the tabel or make a readable version	We have checked the original data, and there was no use of 5-ASA in 1999 and 2000, and no use of steroids in 2000 (Figure 2). To improve readability, we reorganized the previous Figure 3 by retaining the periodic changes in treatment pattern of the total cohort as Figures 3 and 4 and relegating those of Cohort I and II as Supplementary Figures 1-4. Moreover, we also renamed the previous Tables 5 and 6 as Supplementary Tables 3 and 4, and the previous Tables 7 and 8 as Tables 3 and 4, respectively.	Figures 2-4 Supplementary Figures 1-4 Tables 3-4 Supplementary Tables 3-4

Reviewer #2:		
Specific Comments: Authors have conducted a well designed retrospective study. The development of imaging techniques and biologic agents have made a big difference in therapy over the last 20 years. The findings of this study reflect this change, seen as an increase in the use of specific forms of therapy, better suited for the treatment of IBD. The figures and tables are presented in a good manner, making interpretation easy.	Thank you for your comments.	
Editorial office's comments	**Response**	**Revision in text**
(1) Science editor: In this retrospective study, authors presented a multi-center cohort study to depict temporal trends in long-term medication uses, and periodic changes in treatment paradigms in Chinese population. The study is well designed. However, the reviewers have raised a few major concerns that should be addressed: 1) The information given in figure 2 and table 3 is basically the same, keep only one that depict the information the best. 2) The entire discussion section should be rewritten, please do not repeat the results again in this section, but discuss the main finding in the context of current literature, as well as limitations of the study.	Thank you for your suggestions. We have provided point-by-point responses and carefully revised the manuscript.	
(2) Company editor-in-chief: 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	We have provided figures in a single PowerPoint file.	

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 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) 2022.		

[1] Liu J, Ge X, Ouyang C, et al. Prevalence of Malnutrition, Its Risk Factors, and the Use of Nutrition Support in Patients with Inflammatory Bowel Disease[J]. Inflammatory bowel diseases, 2022.

[2] Yang L, Song X, Chen Y, et al. Treatment Decision-making in Chinese Inflammatory Bowel Disease Patients[J]. Inflammatory bowel diseases, 2021.

[3] Tripathi K, Dong J, Mishkin B F, et al. Patient preference and adherence to aminosalicylates for the treatment of ulcerative colitis[J]. Clinical and Experimental Gastroenterology, 2021, 14: 343.