

Date: 3 Jan 2022

To,

The Editor,

World Journal of Gastroenterology

Subject: Responses to reviewer's and editor's comments

Original Manuscript title: Epidemiological characteristics of Asian children with Inflammatory Bowel Disease at diagnosis: insights from a multi-centre registry network

Revised Manuscript title: Epidemiological characteristics of Asian children with Inflammatory Bowel Disease at diagnosis: insights from an Asian-Pacific multi-centre registry network

Manuscript ID: 72785

Dear Editors,

We thank and appreciate the efforts made by the journal editors and the reviewers in reviewing the manuscript and for their valuable comments. We also appreciate the opportunity given to us to revise and resubmit the manuscript. We have addressed all the comments raised by the reviewers and editors and have made the necessary changes in the manuscript text where applicable. The detailed point-by-point responses to the comments are appended below for ready reference. The revised manuscript with changes **highlighted in yellow** is uploaded in the online submission portal.

Thank you.



Corresponding author

Responses to Reviewers' and Editors' comments

Reviewer: 1

Specific Comments to Authors

Comment1: - This is one of the first multi-centric and international publication extensively dedicated to pediatric IBDs from Asia-Pacific regions. However, the title refers to “Epidemiological characteristics of ASIAN children....”. I think the authors should specify in the title that this study refers to a specific Asian region, namely the Pacific region of Asia, as specified several times in the main manuscript.

Reply: We have adjusted the title to specify that the network is an Asian-Pacific multi-centre disease registry

Edits in manuscript:

“Epidemiological characteristics of Asian children with Inflammatory Bowel Disease at diagnosis: insights from an Asian-Pacific multi-centre registry network”

Comment2: - In the introduction and/or in the discussion, I think the authors should emphasize the point that Asia (like Africa) are not necessarily true “low-prevalence regions”. Indeed, there are some regions of Asia where there is a lack of any type of study or report about pediatric IBDs, like Central Asia (as discussed in Pediatric Ulcerative Colitis in Kazakhstan: First Case Series from Central Asia and Current Clinical Management, Gastroenterol. Insights 2020, 11(2), 27-35; <https://doi.org/10.3390/gastroent11020006>), Nepal (as emerges from Epidemiology of Inflammatory Bowel Diseases in Nepal. Cureus. 2021 Jul 28;13(7):e16692. doi: 10.7759/cureus.16692.) or Afghanistan, for instance.

Reply: We have taken the above point and have accordingly emphasised in the Introduction section that there remains a large knowledge gap in the true epidemiological patterns in many Asian countries. Even within our participating sites, there may be variability in healthcare access in the rural regions and this limits the reporting of the true disease prevalence and incidence, included in the Discussion section

Edits in manuscript:

Introduction

“Yet in spite of these global trends, there remains a dearth of epidemiological literature for paediatric IBD in Asia, in particular the regions of Central, South and Southeast Asia. This begets the question whether these countries are truly ‘low prevalence’ in the absence of national IBD registries such as those established in Japan^[4] and South Korea^[5]. Apart from studies published out of these East Asian cohorts, current literature is mostly limited to single centre publications^[6-8] from countries in the Asia-Pacific region. Epidemiological data from these publications would only represent ‘the tip of the iceberg’ of the true burden of IBD and may not necessarily encapsulate recent regional epidemiological trends in disease incidence and behaviour.”

Discussion

“Lastly, the number of patients captured within our network may only represent ‘the tip of an ice-berg’. We acknowledge that access to healthcare services may be very limited in rural regions of the participating countries, and there may be an inevitable selection bias in recruiting patients living in the proximity of major Asian city centres (Singapore, Kuala Lumpur, Bangkok, Manila, Colombo, Chinese Taipei) where our participating sites are located. Hence, there could be a number of children with IBD who do not present to centres equipped with adequate disease knowledge and diagnostic capability, and thus remain undiagnosed.”

Comment3: - “The biostatistician is Yoko Wong who is listed as the second author of this manuscript”. I would suggest removing this sentence and, conversely, to clarify the specific authors’ contribution in the appropriate statement at the end of the manuscript or in the title page, according to the editorial rules of the manuscript.

Reply: As suggested, we have removed the statement from the manuscript. As for the specific authors’ contributions, they are listed in in the manuscript under ‘Authors’ contributions’ included on the title page of the manuscriptas originally submitted

Edits in manuscript:

Not applicable

Comment4: - the statistical methods need more detailed description

Reply: An expanded description of the statistical methods is added in the Methods section

Edits in manuscript:

Methods

“Statistical analysis was done through SPSS Version 27 whereby we compared presenting symptoms, biochemical indices and growth indices between the key phenotypic subgroups (Crohn’s Disease and Ulcerative Colitis); the overall effect of ethnicity on IBD phenotype and behaviour. Continuous variables (laboratory investigation values, anthropometric indices) were compared through the student’s t-test while most of the other outcomes (clinical findings, disease phenotype and behaviour) were classified as categorical variables/dichotomous outcomes and these were compared through the chi-square test. A p-value of less than 0.05 was deemed as a significant difference in outcomes, otherwise stated as ‘NS’ (non-significant). Whereby multivariate analysis was required in determining the effect of South Asian ethnicity on the incidence of perianal disease in Crohn’s Disease adjusting for inter-ethnic variability in disease phenotype, logistic regression was used to calculate an adjusted odds ratio.”

Comment5: - in the materials and methods, there is no ethical statement. The authors should report the number and date of all the IRB approvals, if appropriate, or at least the one received by the Singapore Clinical Research Institute, which is the site where the data were centralized.

Reply: Included a section with the suggested information (dates, approval letter number) in the Methods section

Edits in manuscript:

Ethics approval

“Ethics approval for the storage of anonymised clinical data on a multi-centre central data registry hosted by the Singapore Clinical Research Institute was granted by the National Healthcare Group (NHG) Domain Specific Review Board (Approval letter for study code NUH/2019-00060 dated 23rd January 2020), followed by a separate ethics approval for data extraction and analysis (Approval letter for study code 2019/00751 dated 20th October 2021 to 19th October 2022).”

Comment6: - In table 1, demographic information is completely missing: please, add it.

Reply: Tables 1 and 3 were mistakenly swapped. We apologize for the error. We have rectified the placement of Tables in the revised manuscript and accordingly, the Table 1 (Table 3 in the original manuscript) does include demographic details.

Edits in manuscript:

Table 1 and Table 3 in the revised manuscript

Comment7: - For the rest, figures and tables look all appropriate.

- The results are clear and appropriately described, overall.
- The discussion is also comprehensive; as previously mentioned, I would suggest adding some more comments about the epidemiological situation and mention about lack of knowledge on pediatric IBDs in other Asian regions.

Reply: Thank you for the constructive feedback. The lack of knowledge in other Asian regions is first mentioned in the Introduction subsequently also further discussed in the Discussion section

Edits in manuscript:

Introduction

“Yet in spite of these global trends, there remains a dearth of epidemiological literature for paediatric IBD in Asia, in particular the regions of Central, South and Southeast Asia. This begets the question whether these countries are truly ‘low prevalence’ in the absence of national IBD registries such as those established in Japan^[4] and South Korea^[5]. Apart from studies published out of these East Asian cohorts, current literature is mostly limited to single centre publications^[6-8] from countries in the Asia-Pacific region. Epidemiological data from these publications would only represent ‘the tip of the iceberg’ of the true burden of IBD and may not necessarily encapsulate recent regional epidemiological trends in disease incidence and behaviour.”

Discussion

“This is also consistent with rising trends observed in other Asian paediatric cohorts in Saudi Arabia^[16], Bahrain^[17], Japan^[18], South Korea^[19] and China^[20]. There still remains a knowledge gap on the epidemiological trends of PIBD in many parts of Asia, particularly

Central and South Asian regions, although recently published studies out of Kazakhstan^[21], India^[22] and Nepal^[23] reaffirm IBD as an emerging health issue.”

Comment8: - the conclusion should provide clear final messages and not only future perspective. Please, revise the conclusions accordingly.

Reply: The conclusions have been revised accordingly

Edits in manuscript:

Conclusions

“Our study presents epidemiological data from the largest multi-centre Asian-Pacific paediatric cohort to date, and reaffirms the rising trend of paediatric IBD across our registry, particularly in the past decade (2010-2019). We also report a substantially higher incidence of very-early onset IBD than European cohorts, and this is similarly observed in other Asian cohorts in mainland China and the Middle East. The unique multi-ethnic demographic composition of our cohort allows for distinct phenotypic differences to be seen between ethnicities, chiefly the over-representation of the Indian/South Asian ethnicity and its strong association with symptomatic perianal Crohn’s disease. Prospective follow-up data from this registry would also ascertain if any of these observed epidemiologic trends within this publication have implications on medium to longer term disease outcomes.”

Reviewer: 2

Specific Comments to Authors: General: In this study, the authors investigated the presenting features of PIBD in 7 pediatric gastroenterology centers across six Asia-Pacific regions between 1st January 1995 to 31st December 2019. The concept of this study is interesting and this study was well written.

Major comments:

Comment1: 1. Etiology of pediatric IBD may differ between South-East and East-Asian populations. Why did not authors investigate East-Asian populations?

Reply: The predominance of Southeast Asian centres and lack of East Asian (or West Asian) representation is now listed as a limitation. This is mitigated by the fact that there is ample published data from East Asian cohorts, allowing us to draw comparisons with our cohort's data

Edits in manuscript:

Discussion

“Another limitation was the predominance of Southeast Asian participating centres in our network, with the lack of East and West Asian representation. However, we were able to mitigate this as there already exists a substantial amount of published literature from established Japanese, South Korean and mainland Chinese cohorts as previously cited. Hence we were able to compare certain epidemiological features such as age of onset and the proportion of perianal disease as discussed above.”

Comment2: 2. As authors suggested, number of pediatric IBD is increasing. This findings may associate with number and rate of CT scanning and endoscopy for patients with diarrhea and abdominal pain.

Reply: We discuss this point which is often raised (in the Discussion section) as we try to explain the rapid rise in IBD incidence in Asia. We acknowledge that improved access to healthcare resources may *partly* explain the rise in incidence, although it cannot fully explain the continued rise in IBD incidence seen in countries where there is already excellent access to healthcare i.e. Japan/South Korea.

Edits in manuscript:

Discussion

Several other factors have been proposed as reasons for the observed rise in IBD incidence within the Asia-Pacific region, namely increased disease awareness amongst healthcare professionals, improved access to healthcare resources and better diagnostic modalities in rapidly industrialising areas. While such factors may account for part of the initial observed rise in incidence in the earlier decades, they do not sufficiently explain the sustained year-on-year rise in PIBD incidence seen in developed regions of our network^[6,24] as well as other highly industrialised regions in Japan and South Korea.

Reviewer: 3

Specific Comments to Authors: This is a well written concise article, discussing the important issue of IBD prevalence in the Asia -Pacific region, and the rise of disease prevalence in the last years.

Comment1: One question that should be addressed is the availability of medical services in those different countries and among these various populations, If medical services are not equally available it might cause a bias in the results, therefore this should be addressed, either by stating the medical services are equally available to all, or by describing the differences and how they affect the results

Reply: We acknowledge that variability in healthcare services may limit the full representativeness of our data , especially in rural regions of our participating countries. Hence we postulate in our discussion that our data likely represents ‘the tip of the iceberg’ in true disease burden and may under-estimate the true prevalence of IBD.

Edits in manuscript:

Discussion

“Lastly, the number of patients captured within our network may only represent ‘the tip of an ice-berg’. We acknowledge that access to healthcare services may be very limited in rural regions of the participating countries, and there may be an inevitable selection bias in recruiting patients living in the proximity of major Asian city centres (Singapore, Kuala Lumpur, Bangkok, Manila, Colombo, Chinese Taipei) where our participating sites are located. Hence, there could be a number of children with IBD who do not present to centres equipped with adequate disease knowledge and diagnostic capability, and thus remain undiagnosed. At the same time, there could be a number of adolescent IBD patients who are managed by adult gastroenterologists. The general lack of national chronic disease registries for PIBD in the respective countries of this network further adds to the challenges in obtaining complete epidemiologic data. These factors discussed suggest the true burden of PIBD in the Asia-Pacific region is very likely under-estimated.”

Comment2: minor language corrections: page 5 line 5 in the results section should be: An over-representation of the page 6 4th line from the bottom An over-representation page 16

top line: CD cohorts reporting even higher rates

Reply: These language corrections have been put in place

Edits in manuscript:

“An over-representation of the Indian/South Asian ethnic group was observed, accounting for 37.0% of the overall Singapore/Malaysia subcohort (6.8-9.0% Indians in census).”

“We affirm earlier findings for a sharp rise in PIBD incidence, with unique features of a very high incidence of VEO-IBD and an over-representation of the Indian ethnicity.”

“An earlier Singaporean paediatric cohort reported a 21.6% incidence of perianal disease amongst CD patients at diagnosis^[6] with mainland Chinese and South Korean paediatric CD cohorts reporting even higher rates of perianal involvement (42.4% Shanghai^[45], 47.1% ([perianal fistulising disease only] South Korean^[46]).”

Re-reviewer:

Specific Comments to Authors: Authors have well revised according to reviewer’s and editor’s comments.

Reply: Thanks for your comments.

Editorial comments

(1) Science editor:

Comment1: It is an interesting study of epidemiological characteristics of children with inflammatory bowel disease at diagnosis. This study affirmed earlier findings for a sharp rise in PIBD incidence, with unique features of a very high incidence of VEO-IBD and a over-representation of the Indian ethnicity. Indian CD patients were also significantly more likely to have symptomatic perianal disease. A higher prevalence of constitutional symptoms and higher inflammatory indices was also a presenting feature of CD. Data for Central and South Asia are included, but no data for East Asian countries are included. We suggest that the author can expand the scope of the later study, so that the results of this study will be more convincing.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Reply: The predominance of Southeast Asian centres and lack of East Asian (or West Asian) representation is now listed as a limitation. This is mitigated by the fact that there is ample published data from East Asian cohorts, allowing us to draw comparisons with our cohort's data.

Edits in manuscript:

Discussion

“Another limitation was the predominance of Southeast Asian participating centres in our network, with the lack of East and West Asian representation. However, we were able to mitigate this as there already exists a substantial amount of published literature from established Japanese, South Korean and mainland Chinese cohorts as previously cited. Hence we were able to compare certain epidemiological features such as age of onset and the proportion of perianal disease as discussed above.”

(2) Company editor-in-chief:

Comment1: 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. 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.

Reply: All the tables included are prepared as specified and formatted following the example given in the Format provided in the author instructions.

Edits in manuscript:

Not applicable