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Title: Health care utilization differences between First Nations and the general population with inflammatory bowel disease: a retrospective cohort study from Saskatchewan, Canada
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Reviewer 1
General comments (author response in bold)

1. This paper starts with a great literature review – with many interesting health services papers for Indigenous groups with various conditions. I was curious about the relationship between this paper and reference #12 and reviewed that source. The current paper is from the same group, using the same data, during a similar time frame, and yet that information was not mentioned by the authors. I can see that this paper builds on the work reported in reference 12, and I am not concerned about duplicate publication. I was surprised by the lack of clarity regarding the relationship to reference #12. From my exploration, it appears that both are part of "Understanding and Advocating for miyo-māhcihowin Among Indigenous Peoples Living With IBD". More transparency would be helpful on the relationships between these two papers by the same authors. I also suggest cleaning up language that appears to position this paper as if it is independent, e.g., on page 5 of 23 line 20-21 "In a recent study from Saskatchewan, researchers reported …" should be "In our … we reported …". Line 57 on page 5 of 23 is also awkward given these are the same people working on the same data.
Thank you very much for your feedback and recommendations. We adjusted the introduction section to make a better connection with our research team and the work published in reference #12 (see pages 4 and 5).

Methods:

2. It would be good to let the readers know the strength of the data being accessed, particularly that they accessed data from a single-payer system, so the data was inclusive. However, I also wonder if there were services funded by Health Canada that were not captured, such as services provided by medical clinics on-reserve.
Statements were included in the data sources section of the methods (page 5) to give additional details of the Saskatchewan administrative health databases. We also clarified that these databases capture records of all hospitalizations and medications claims in the province and specified that on-reserved outpatient visits might not be captured in the physicians' claims dataset. However, this data limitation does affect our study outcomes; for example, all gastroenterologist outpatient visits occur out of reserve and are captured in the data.

3. I note that the authors use the same case definition as they used in the Pena-Sanchez et al (ref. 12) paper which is a strength but fail to draw the connection. I would like to see these details added in the methods sections.
We added a statement in the data sources section of the methods (page 5) to highlight that our research team previously used this case definition to determine the epidemiology of IBD among FNs in Saskatchewan.

4. I did not see a sample size calculation and have some queries related to the stratified analyses. I presume these were set a priori however on page 8 line 10, the authors state that 2008 is used as the dividing line between pre- and post-biologics, which concerns me for two reasons. First, it suggests the analysis was not specified a priori. Second, while I agree that this justified a good division point for the FN cohort, it may not be an equally good transition point for the GP. I also wonder if the sample size was set with sufficient power to do the stratified analyses, as 116 FN cases seem small once broken down for all the stratified analyses.
Thank you for the observation. We decided to remove the pre- and post-biologic stratification of the manuscript given that it was an exploratory analysis, and our study might not have enough power for this specific stratification. Further studies with bigger sample sizes could reconsider a pre- and post-biologic era analysis.

5. Results: I agree with the key findings presented related to hospitalizations. Those results appear solid. The sensitivity analysis with alternative case definitions is a strength and supports the robustness of the main analysis. I wonder if the lower rates of medication claims (HR 0.52) and 5-aminosalicylic acid claims (HR- 0.56) may be related to missing data from federally funded services. This needs to be clarified so that there is confidence in the interpretation of these results. I wonder if the stratified analyses would be better positioned as exploratory.
The Saskatchewan administrative databases capture all outpatient prescription medication claims in provincial pharmacies. Medication claims are captured regardless of provincial/federal coverage and of who paid for the claim. This detail was included in the data sources section of the methods (page 5).

Discussion:

6. I have questions about lines 37 to 41 on page 10: “Taken together, these results suggest that FNs with IBD are not receiving appropriate treatment for their disease resulting in increased rates of adverse outcomes, in particular hospitalizations.” It seems like a bit of a leap from my read. Perhaps the connections to support this could be strengthened.
We revised the discussion section and adjusted this sentence on page 9.

7. I commend the authors for their efforts to include the perspectives of patients. I am particularly interested in how the patient partners interpreted the findings. It has been my experience that there is often a different interpretation than what the statistics would suggest and that patient partners can be extremely helpful in teasing that out, but I do not see evidence of the patient voice in the discussion.
A new section was included in the interpretation section (page 9) highlighting the perspectives and recommendations of the Indigenous patient and family advocates.

8. Tables and Figures: In Table 1 the term “matched cohort” is confusing. The pooled cohort (both Indigenous and Non-Indigenous) is presented under that heading. The 2.5-year difference in length of follow-up caught my eye, but was not discussed in the paper. It seems to me that much shorter follow-up would result in fewer medications. I like the use of bolding to denote significant results. Were all of these comparisons planned a priori and should there be adjustments for multiple comparisons? Again, I see the value in the exploration but do not want to put too much weight on results if they are exploratory.

The title of Table 1 was revised. In the revised manuscript, we consider the follow-up difference between the groups in the interpretation section (page 8). In addition, we reconsidered and removed the pre- and post-biologic comparisons as previously mentioned in point #4.

References

9. Some references need minor corrections. E.g., ref #6 C Open should be CMAJ Open
This typo was adjusted.

Overall, a very good paper that needs some tightening up before publication. The comprehensiveness of the prescription data is most important.

Reviewer 2
General comments (author response in bold)

General Comments:

Overall, this paper this is a retrospective study aims to compare health care utilization for First Nations with IBD to the general population with IBD for incident IBD cases only. This is an important question to help us understand better IBD in Canadian First Nations. I appreciate the inclusion of the patient/families in this project.

The findings of this study that FN have higher hospitalization and lower IBD prescription utilization is interesting. However, in the sub-analysis by era the findings are not consistent. Further, I am concerned about the potential confounders of IBD type, northern residence, and disease severity. Further, as this is a chronic disease, health care utilization of prevalent cases may be more important and an explanation as to why only incident cases were included should be clarified.
Thank you very much for your feedback and suggestions. We decided to include incident IBD cases in this study to have precise and comparable data since the date of IBD diagnosis. The use of an incident cohort let us measure of critical variables at IBD diagnosis (e.g., age, area of residence, income quintile, etc.) which we considered in the data analysis. After this study, further research initiatives could consider larger incident cohorts (interprovincial data) and potentially using prevalent cohorts.

Specific Comments:

a) Table 1 – please show analysis to compare the groups, to show baseline differences/similarities. (Eg. It appears that FN were more likely to be from the North and the GP from the South, and FN are more likely to have UC compared to the GP.) Are there potential differences in health care between northern and southern Saskatchewan that may be confounding these results?
We evaluated if region of residence (i.e., Regina/Saskatoon and surrounding areas, Northern, and Southern Saskatchewan) confounded the associations identified in this study. Although, the inclusion of this variable in the final models did not change the regression estimates of the other variables in more than 10%. Furthermore, we rea not aware of major differences in the care provided across

these regions beyond those related to be living in rural and remote areas of Saskatchewan.

b) How comprehensive are the data sources? I am in particularly interested in prescription medication claims as not all patients have medication coverage (may be paying out of pocket or accessing compassionate programs). Please clarify.
The data sources are quite comprehensive in Saskatchewan. Specifically, the prescription medication claim data captures all prescription claims that occurred in Saskatchewan pharmacies regardless of how and who paid the claim. We adjusted the data sources section in the methods (page 5) to clarify this point.

c) In the methodology, it states that only incident cases were included, but this is not in the aims of the study. Please clarify why only incident cases were studied, as this is a chronic disease with lifelong costs. Further, the analysis focuses on pre- and post-biologic eras but this is not mentioned in the aims of the paper.
As mentioned before, we used an incident cohort to measure critical variables at IBD diagnosis (e.g., age, area of residence, income quintile, etc.) which we considered in the data analysis. In addition, we removed the pre- and post-biologic analysis given that it was an exploratory analysis and have power limitations. Further studies could consider prevalent IBD cohorts and complete a pre- and post-biologic era analysis with a larger sample size.

d) Table 2 – which comparisons were different?
Table 2 was revised as per suggestions of the Journals' statistician. The revised table presents now only the frequencies. The Cox models consider follow-up differences to determine statistically significant differences.

e) For the medication use/Rx data, please clarify why you combined UC and CD, as 5ASA are often effective in mild-moderate UC but have limited efficacy in Crohn's.
We evaluated 5-ASA prescription claims in the full IBD group, as well as stratified by UC and CD. Interestingly, higher hazard rates of 5-ASA claims were observed among both FNs with UC and CD in comparison with individuals from the general population with IBD, see Table 3.

f) Presumably, the outcome Rx claims for IBD would include biologics, IM, and 5-ASA); is it fair to say that the differences in Rx claims is driven by the differences in 5ASA prescriptions? What about corticosteroids Rx, why were these not included in the IBD prescriptions?
The group differences in IBD prescription claims could be driven by the 5-ASA claims. Therefore, we presented the overall medication IBD claims, and the claims for each group (i.e., 5-ASA, immunomodulators, and biologics) to give an overall and detailed picture. On the other hand, we did not include corticosteroids because these medications are used for a wide variety of conditions not only IBD. Oral corticosteroid dependency after IBD diagnosis could be considered as a more specific IBD outcome in further studies with a larger sample size.

g) While the overall data (table 3) showed a fewer IBD prescriptions and higher IBD hospitalizations, the pre- and post-biologic associations do not support this. Table 4 (pre-biologic) shows decreased Rx and similar hospitalizations, and Table 5 (post-biologic) shows higher hospitalization and similar prescriptions (except the unadjusted HR for biologics).

As mentioned before, we removed the pre- and post-biologic analysis given that we have power limitations. Tables 4 and 5 were removed from the revised manuscript.

h) It would be good to know disease severity in this patient population, as 5ASA medications are appropriate in the treatment of mild-moderate UC, while biologics are used for moderate to severe disease. Is this information available from prior studies? While disease severity is acknowledged as a potential confounder for utilization, it should also be acknowledged for medications as well.
We acknowledge that disease severity is a potential confounder for health care utilization and prescription medication claims. We adjusted the limitations section accordingly (page 10).

i) The discussion is quite long and yet not all of it is relevant to the aims of this study (eg. Lessons learned from working with IPFA's – this may warrant a separate paper).
We revised and summarized the interpretation section.