AUTHORS' RESPONSES TO REVIEWERS' COMMENTS

Title: Cohort study to assess geographical variation in cholangiocarcinoma treatment in England

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Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The topic is very interesting and the statistical method is quite rational. However, I have some questions as follows:
AUTHORS' RESPONSE: We thank the Reviewer for their time and attention, and their conclusion to accept our paper pending minor revision. Below we have sought to provide a point be point response to each of the Reviewer's comments.

Major:
1) as a clinician, I pay more attention to the survival data. The authors should first make clear whether the treatment options could influence the survival of patients, considering that they enrolled patients between 2014 and 2017, which means sufficient follow-up
AUTHORS' RESPONSE: We believe treatment options can indeed influence the survival of cholangiocarcinoma patients, as has been well described in multiple trials and clinical studies of treatments that have been proven to improve overall survival. The follow up time period is sufficient in that the overall prognosis for most patients is poor, with only a minority of patients surviving more than 3 years from diagnosis. We have amended the Intro section accordingly in paragraph 2.

2) the results in the "Abstract" are too simple to reach the conclusion in the "Abstract" and the "core tip", and more details should be added;
AUTHORS' RESPONSE: We do not understand what the Reviewer means by the results being too simple. The key results, numbers and confidence intervals are given in the abstract as per usual practice in original data publications. The conclusion offers possible explanations to explain the results and the core tip is an accurate summary of the data. We have altered the wording in the abstract results and conclusions and the final sentence of the core tip to try to make clearer how the quoted results link to our main finding of geographic variation in the treatments received. Please can the Reviewer further clarify if these changes show we have correctly interpreted their comment and what if any further changes they think we should make?

3) the authors pay attention to the association between treatment options and patients and tumour, but another factor, local medician condiction, is not underpined.
AUTHORS' RESPONSE: In the Materials and Methods section we specify clearly that multiple co-morbidities were indeed taken into account, including the Charlson co-morbidity score, which is a well validated method of estimating the risk of death from comorbid disease and has been widely used as a predictor of long-term prognosis and

survival in epidemiological studies for many years. Other co-variates assessed included were age at diagnosis, gender, area income deprivation quintile, prior liver disease (including chronic hepatitis C or B, primary biliary cholangitis, autoimmune hepatitis, haemochromatosis, alcoholic liver disease, or non-alcoholic liver disease, cirrhosis. The final results presented are those **after adjustment for all measured characteristics** (as specified in every section of the Results section). We would be grateful if the reviewer could clarify what is meant by *'medician condiction'*, in order that we may be able to better respond to this comment.

4) the percentage of patients receiving non specific treatment in the the European Reference Network for the Study of Cholangiocarcinoma was 20%, but it was 50%. the authors should explain why?
AUTHORS' RESPONSE: The European Reference Network for the Study of Cholangiocarcinoma used data from self-selected expert centres where patients had been referred from other hospitals. It is a snapshot of expert care in those hospitals who chose to send in their data. These centres are large expert referral centres and the data is not therefore reflective of "real world" overall public healthcare, which our study is. Our study involved the entire NHS (National Health Service, Public, Government funded Hospitals) National Dataset, so all patients from all NHS hospitals were included. In real world practice, not all patients diagnosed locally are referred on to an expert centre, as it may be decided locally that the disease is too far advanced, or other reasons. We state this point in the Introduction (paragraph 3). In light of the Reviewer's comments, we have also added new text to discuss this in the Discussion (paragraph 5).

5) in the European Reference Network for the Study of Cholangiocarcinoma, around 20% did not receive any specific cancer therapy, but best supportive care only. To the best of knowledge, the beat support care is also an option for patients; and therefore, i wonder if 50% of CCA patients in England did not receive any treatment including the best support care
AUTHORS' RESPONSE: In our study, 50% of patients did not receive <u>cancer-specific</u> care, by which we mean surgery, systemic treatment (such as chemotherapy) or stent insertion. Our assumption is that these patients <u>would</u> <u>have</u> received best supportive care in keeping with national cancer guidelines and usual NHS clinical practice. We have clarified that this study looked at cancer-specific treatments only, in the text in our revision – please see Introduction (paragraphs 3&4) and discussion (paragraph 1) **.**

Minor:
1) in the "Introduction", the author stated that "CCA comprise the second most common form of primary liver cancer worldwide, after hepatocellular carcinoma" in Line 15-16, but I think it is not appropriate. eCCA could not be cateroried into primary liver cancer.
AUTHORS' RESPONSE: We agree and have amended the text accordingly, to clarify that **intra**hepatic CCA is a primary liver cancer (not eCCA) – Introduction (paragraph 1).

2) in the "Introduction", the authors underlined the differences amongst the three sub-types, but I think it should be weakened and more common characteristics might be appropriate here
AUTHORS' RESPONSE: In the 1st para of the Introduction we state that *"The CCA sub-types exhibit some differences in their respective clinical presentations, risk factors, routes to diagnosis and clinical management, as well as exhibiting distinct epidemiological, clinical, molecular and genetic*

characteristics". This is a simple and factually correct statement and is adequately referenced. The second para goes on to state the common characteristics of **all** CCA, e.g. high mortality, late presentation, lack of known risk factors and common themes to treatment. So we do not understand how the Reviewer wants us to change the text. We have added the word "All" to the 1st sentence of the 2nd paragraph of the Introduction to emphasise that this paragraph talks about characteristics common to all CCA. We hope this response will satisfy the Reviewer. If not, can they please be more specific as to how they think the text here can be improved?

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This manuscript by Jose et al is a retrospective cohort study to "assess geographical variation in cholangiocarcinoma treatment in England". Due to cholangiocarcinoma (CCA) being a rare disease with heterogenous subtypes that is tough to diagnose and manage, the authors aimed to investigate how treatments differ in various locations within England. Three datasets were utilised in this study, namely, The National Cancer Registration Dataset (NCRD), Hospital Episode Statistics and the Systemic Anti-Cancer Therapy Dataset. Patients diagnosed within the four-year period between 2014 and 2017 were studied. The three end-points of interests were 1. Potentially curative surgery for all patients 2. Systemic therapy and 3. Stent insertion. The authors concluded that "Substantial regional variation in treatment could be due to differences in case-mix, clinical practice or access to specialist expertise".
AUTHORS' RESPONSE: We thank the Reviewer for their time and attention, and their conclusion to accept our paper for publication.

EDITORIAL OFFICE'S COMMENTS:

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. 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/.

AUTHORS' RESPONSE: We thank the editor for the suggestion to use the RCA tool. Upon searching for the terms "cholangiocarcinoma treatment" in the RCA tool we were provided

a list of 37 articles, and unfortunately none of the recent or high impact index articles were found to be relevant to our research question. Upon an updated search of the Pubmed database, we found two further reviews and two research studies to be relevant to our research question. We have therefore included the research studies in our revised draft (References 11 and 29) in the introduction (paragraph 3) and the discussion (paragraph 5).