Author's response to reviews

Title: The occurrence of Urinary Tract Infection before development of Primary Biliary Cirrhosis: a case control study.

Authors:

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Author's response to reviews: see over
Responses to reviewers

Reviewer: Ikuko Haruta

Reviewer's report:

The authors studied OR of UTI and smoking as risk factors of PBC. There are already several reports about these (plus additional factors). So the findings in this report seemed to be not novel.

Thank you for your review.

We believe that replication of data adds to the strength of current findings. However, we also believe the results to be novel, as it is the first to demonstrate the order of events i.e. that Urinary Tract Infections preceded diagnosed Primary Biliary Cirrhosis.

1) Was ethnicity considered for characteristic of cases?
No we were unable to do so as no such data is available within the dataset.

2) In Table 1, smokers were classified never, ever and missing. How about current and former?
Within the database, we have to code smoking on the last record available. There is rarely a record of smoking at the point of diagnosis. Therefore to categorise as suggested is not possible within the data since at diagnosis the smoking status may have changed. We believe that the method chosen though imperfect is more accurate within this data.

3) Does ‘CI’ mean ‘95% CI’?
Thank you for your comment. Yes, it does. We have amended the manuscript to make this clearer.

4) Although authors commented about diabetes as a known risk factor for the development of UTI in page 7 and listed in the Table 1, there was no analysis and argument about diabetes in Discussion.

Although we do not further mention Diabetes in the discussion, we include it in the Results (Page 9, Line 182). Diabetes was not associated significantly with UTI in our model and its inclusion in the multivariate model did not significantly alter the effect estimates of UTI.
5) Page 13, line 267-268 is over speculation. Did authors studied about the cause of UTI? Was there any information that E. coli was dominant in these PBC patients’ urine culture, when they had been diagnosed as pyelonephritis? Any supportive data?

We agree entirely that the data to support the idea that this is specifically an E. Coli related phenomenon cannot be found in our study. It is for this reason that we somewhat labored the point that the diagnoses we are analyzing are proxies for the exposure we are interested in. We have amended the wording to make this more clear and added a reference to show that about 80% of UK urinary isolates are E.Coli.

6) Page 14, line 289, what do you mean ‘some laboratory’?

The laboratory evidence we refer to is elaborated upon in the following few lines of text.

7) The first time when authors wrote bacterial name, it should be written full spelling. (page 4, line 75; N. aromaticivorans, page 8, line 160 E. coli.) And E. coli should be expressed Italic (page p14, line 291 and 293).

Thank you for your comment, we have amended the paper to make correct this.

8) Page 13, line 274-276, ‘Secondary ... urothelial membrane’ is over speculation as well. Any evidence or referenced paper?

We have amended to clarify and added a reference to justify our assertion.

9) Is reference number 23, (Suppl A-837) published paper?

This is published as an abstract only.
Reviewer: Dimitrios Bogdanos  

Reviewer's report:

The report by Varyani et al determined whether urinary tract infections are more common in patients with primary biliary cirrhosis (PBC) prior to the diagnosis of the disease compared to controls with chronic liver disease. Their case control study is based on the UK General Practice Research Database (GPRD). These findings will help the ongoing debate as to whether urinary tract infection has a causal or casual relationship with this disease.

Their findings indicate that PBC is associated with UTI prior to diagnosis and that this association is stronger in younger PBC patients. Thus, it appears that in PBC patients before the age of 55, 31% had a prior diagnosis of UTI compared to 20% of age and sex matched controls.

The study is of interest. My view is that such methodological studies are needed to better understand the association of risk factors such as urinary tract infections or smoking with the development of PBC or other autoimmune liver diseases.

Thank you very much for your positive review of the study.

Major point

The Authors need to make clear that one of the limitation of their studies was that the control population of patients with chronic liver diseases was predominantly a population of male patients (60%) when that of PBC is strikingly a female population. Also, the control population with patients with chronic liver diseases was younger than that of PBC. These differences clearly affect the results given in cohorts not adjusted for age and sex as urinary tract infection is likely to be more frequent in older women.

The Chronic Liver Disease controls are younger and predominantly male when compared to the Primary Biliary Cirrhosis. Therefore we have performed a multivariate analysis taking into account age and gender as confounding factors (Ref: Table 2 and Table 3). Potential for residual confounding from these factors will be limited given that we have complete data for age and gender. Though therefore we agree there is confounding from these factors we believe we have dealt with it adequately and that it should not in any way invalidate the results of the final model presented.

Minor Points

The Authors need to give more details/brief description of the GPRD and a link to its website. The must also make clear in the abstract and methodology that GPRD is a UK database.

Several original and review articles discussing the role of E.coli infection in PBC and molecular mimicry studies involving E. coli and PBC-specific autoantigens are missing and should be included Dis Markers. 2010;29(6):301-11; Clin Rev Allergy Immunol. 2011 Feb 22; Clin Rev Allergy Immunol. 2009 Feb;36(1 ):30-9; Dig Liver Dis. 2003 Nov;35(1 1 ):801 -5; J Hepatol. 2004 Jan;40(1 );31 -9.
We are grateful for your suggestions and have added references.

Page 13, Discussion 268 & 269, it is molecular mimicry ...instead of .... molecular m i mockery

Thank you for your comment, this has been adjusted

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests