Reviewer's report

Title: Trends in all cause and liver-related hospitalizations in people with hepatitis B or C: a population-based linkage study

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Reviewer: Ann-Sofi Duberg

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Trends in all cause and liver-related hospitalizations in people with hepatitis B or C: a population-based linkage study. Gidding FG, Dore GJ, Amin J, Law MG.

This is a large record linkage study (probabistically linked) where the size is a major strength. Some of the results concerning the HCV infected population have been recently published (reference 22). Now the aim was to compare the overall burden and trends in hospitalization rates in people notified with HBV or HCV infection in New South Wales (NSW), Australia. The hypothesis is not presented.

The two study cohorts differ from each other and from the reference NSW population, the HCV cohort with drug users and the HBV cohort with immigrants from Asia, this could cause problems when comparing the cohorts. Material and methods are appropriate but some methodological issues should be explained and discussed – see below!

The discussion and conclusion focus too much on the improved therapy for HBV infection. As the authors couldn’t link to treatment records they should be more careful in their conclusions about the effect of treatment. Improved HBV therapy could possibly contribute but probably together with other factors to be discussed. The aim of the study was to compare the burden and trends, could you discuss the results from some other points of view?

All together I think the study is of interest to demonstrate the burden and trends in hospitalization rates in the HBV and HCV infected population – though the results for the all cause hospitalisations is probably more related to life style than to the HBV/HCV infections.

More detailed comments by manuscript section:

(Major compulsory revisions marked with *1, *2, *3…)

INTRODUCTION

First sentence: “…infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)…”

Second paragraph, 2nd sentence: Is this a presentation of your study or hypothesis? As you don’t have treatment information the results of the study will only be able to suggest an effect of improved therapy (not provide evidence).
 According to the aim this is a study of the burden and trends in hospitalization rates, could you introduce something more on trends, for example the increasing burden of HCV?

Some older references on HBV therapy could be left out. The long-term effect of HBV therapy is not completely understood yet. Lamivudine and adefovir could reverse decompensated liver disease caused by HBV, but with drug resistance came relapse of liver decompensation. Consider if references 14-15 are too old. Entecavir and tenofovir will probably improve the long-term outcome – we will see in the future…

**METHODS**

**Data sources**

In this section I miss information on the HBV infections included, acute and/or chronic infections? Not until the end of the discussion part you mention that only chronic HBV infections were included. How did you differentiate acute/chronic HBV infections?

**Exclusions**

First sentence: “within 14 days of diagnosis” - which diagnosis? I assume you mean the HCV or HBV diagnosis but that should be clarified (HBV/HCV/HIV/principal diagnosis?).

*1 Could you explain why you chose only 14 days for the exclusion of admissions? Have you made any analyses to decide this time interval? Do you know if excluding admissions for 14 days reduced most of the bias?

Last sentence: admissions for extracorporeal dialysis were excluded. Did you ever think of excluding these individuals (not only the admissions) from the analyses? These patients often have a nosocomial HCV infection and are high consumers of health care (related to the kidney disease).

*2 Did you consider excluding or giving details about the admissions for diagnostic liver biopsies (if liver biopsy is a reason for inpatient care in Australia)? Probably more HCV than HBV patients have been admitted for liver biopsies – this could bias the comparison of liver diagnosis admissions.

**Statistical analyses**

Second line: again… “14 day after diagnosis” – which diagnosis?

*3 To calculate the SHRs you have used the hospitalization rates for the NSW population including the HCV and HBV infected individuals (I assume). This is probably negligible for the “all cause” hospitalizations. However, for the liver and liver cancer hospitalizations the admissions in the study population could have major impact on the NSW population rates, resulting in too high expected and too low SHRs, especially in the HBV cohort. Could you make a rough estimate of the annual number of liver/ liver cancer admissions in the HBV/HCV group and what percentage they constitute of the annual liver admissions in the NSW population,
and discuss the impact on the results.

Ethics?

RESULTS

Description of cohorts
Did you have information on country of origin (for table 1)?

All cause hospitalizations
Second paragraph, 2nd sentence (and Fig.1), “all disease cohorts had a secondary peak in less than 30 years old”, were there enough individuals age <30 y in the co-infection cohorts to draw conclusions from the higher rates in the younger age groups? Were the higher SHRs in the younger age groups statistically significant in the co-infection cohorts?

*4 Last paragraph: As liver related admissions constitute only about 2% of the all cause admissions the decline is probably unrelated to the HBV and/or HCV infection. For the discussion section: What is the situation in the NSW population? Is there a decline over years? Reduction in hospital beds? Other explanations? Maybe a result of bias, excluding only 14 days after notification will probably result in too high hospitalization rates the first months and then a decline. How many of the patients were notified during the study period 2000-2006 (with risk of introducing this type of bias)?

Non alcoholic liver disease

(*3) See comment under statistical analyses! Could the SHRs (especially for HBV) be too low as the NSW population rates include the HCV and HBV infected population?

First paragraph, 2nd sentence, 2nd part “…accounted for a higher proportion of all and liver disease-related hospitalizations”. Please clarify the meaning of this sentence, do you mean proportion of all cause hospitalizations and of all liver hospitalizations in each cohort? You have not presented what you mean by liver disease-related hospitalisations, which ICD codes did you include?

DISCUSSION

*5 Second paragraph: The discussion on the divergent trends in non-alcoholic liver hospitalizations in the HCV and HBV cohort focus too much on HBV therapy. Improved HBV therapy could possibly contribute but probably together with other factors. As you can’t link to treatment records you should be more careful in your conclusions about this. You discuss this again on page 11, this discussion is interesting but dominates, try to shorten. The aim of the study was to compare the burden and trends. What about the increase in the HCV-cohort? Is the HCV-epidemic also in NSW reaching the point when many HCV patients have been infected for 30-40 years with a high risk of liver complications, demonstrated as an increase in the trend analysis? According to the all cause admissions a decrease seems to be the general trend, maybe as a result of a
change in society, (maybe a reduction in hospital beds?) or as a result of bias (see comment “all cause hospitalisations”).

You don’t mention the limitations with the registers, for example the coding not always being perfect (how could the physician responsible of the coding discriminate non-alcoholic and alcoholic liver disease in patients with HCV and drug abuse?).

Page 11, 2nd paragraph, line 4 and 5, the spelling of tenofovir.

Conclusions
The aim was to study the burden and trends, the conclusion should focus on your findings, with some possible explanations.

Non alcoholic liver admissions constitute 1% of all admissions, then it’s very hard to believe that improved HBV treatment would have any significant impact on widening the HBV/HCV gap in hospital related morbidity overall. For non-alcoholic liver disease HBV treatment could possibly contribute but I think your conclusion is too certain.

Table 2
Could you please clarify what you present in the column “% Liver disease admissions”, is this the percentage of all liver admissions in each cohort? If so, what is included in all liver diseases (ICD codes)? Obviously not only non-alcoholic liver disease and primary liver cancer, please clarify!

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

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