Reviewer’s report

Title: Mortality Among British Columbians Testing for Hepatitis C Antibody

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Reviewer: Ann-Sofi Duberg

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Mortality Among British Columbians Testing For Hepatitis C Antibody
Yu A, Spinelli JJ, Cook DA, Buxton JA, Krajden M.

This is a large register-based cohort study of all-cause and disease-specific mortality among individuals who underwent HCV testing between April 1992 and July 2004. The laboratory covers 95% of anti-HCV testing in British Columbia. The study population was divided according to HCV status, and mortality was compared with the general population (SMR) and also compared in between the subgroups of the cohort (Cox regression).

The study is unique because of the large cohort with time-dependent information on HCV-serological status enabling an interesting comparison between subgroups. As HCV-testing is an inclusion criteria there is a selection of a study population with higher mortality (also those with a negative anti-HCV test) than the general population which is demonstrated with the SMR analyses, and discussed. The results coincide with previous cohort studies of mortality in HCV patients but the comparisons between subgroups add further information.

There are a few questions needed to be clarified.

Considering the points in the reviewer guidelines:

1) The question posed by the authors is well defined.

2) Methods are appropriate and well described, but there are a few things to clarify.
   a. Data sources: I would like some more information about the death registry. Did you use the “underlying cause of death” (which I assume)? Is the cause of death based only on death certificates or is the death registry linked to other registers?
   b. Time dependent HCV serological groups: Were there any time-limit for next test or were two tests the same month enough to be classified as a MNR?
   c. Statistical methods, 1st paragraph, 2nd sentence, about the calculation of observed deaths: “…for each five year age group in the study cohort…”. Please clarify; I think you calculated the observed deaths for each serological group, not only the whole cohort.
   d. Statistical methods, 1st paragraph, 3rd sentence, about the calculation of expected deaths: Also here, I assume that you calculated expected deaths for
each serological group of the study population. More important, please clarify about the calculation: Did you just multiply the person-years with the BC population death rate – or did you multiply the calculated person-years for each 5-year age group in each serological group by the BC population death rate for each 5-year age group to get the correct number of expected deaths?

3) The data seem to be sound, I have one question on the results/study population

a. Results, Table 1: The numbers in the serological groups are hard to follow because individuals change groups. Could you please check over the numbers in the table! In the text (under Study population) you write that 8,914 were excluded due to 6-month lagging, in the table there are 16,924 removed because of lagging (could the change of groups give this difference??). Also, all individuals in the study population ought to be in the SNR or REAC group from the beginning (or?), but they are not. Could you please clarify!

4) The manuscript adheres to relevant standards.

5) Discussion and conclusion are balanced and supported by the data. Some comments:

a. To discuss: the reliability of the cause of death register

b. Discussion, 2nd paragraph, 4th sentence: the group with individuals whose 1st anti-HCV test was reactive was older (mean 10 years) and had been infected for a longer time which is the main reason for the higher risk of liver-related mortality, and another important factor, they had survived their drug-abuse... this could be discussed. In the middle of the 3rd paragraph there is some iteration on the higher risk of liver mortality in the REAC group.

c. Discussion, 8th paragraph, 2nd sentence: I don’t think you should use the word “seroconverters” when it comes to the public health implications. Why not write something like “In the short term, young drug addicts would likely benefit more from...” eventually you could include something like “here represented by the seroconverters”

d. Discussion, last sentence, you forgot “with”: “...associated with HCV acquisition”.

e. Conclusion, 1st sentence: “… HCV positive testers.” The word “testers” could be changed to something a little more formal, maybe “individuals”? Also, next sentence could be improved, more clear and concise.

6) Most limitations are clearly stated and discussed. A few comments:

a. As mentioned, the reliability of the cause of death register could be discussed.

b. The 6-month lagging: Selection bias due to a higher probability of HCV testing already sick (maybe dying) individuals could be reduced by introducing a lag time. The 6-month lagging should be discussed, this is the lag time used in several mortality studies, but for liver complications and death a longer lag time (12 months or even more) could be needed. There are some studies on this subject (#Törner A. et al. A proposed method to adjust for selection bias in cohort

7) Acknowledge, OK.

8) The title and abstract convey what has been found

Referring to the points above

Major Compulsory Revisions:
Points 2c, 2d and 3a.

Minor Essentional Revisions:
Points 2a, 2b, 5a, 5b and 6b.

Discretionary Revisions:
Points 5c, 5d and 5e.

**Level of interest:** An article of importance in its field

**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.