Author's response to reviews

Title: The high comorbidity burden of the Hepatitis C Virus infected population in the United States

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Author's response to reviews: see over
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Dear Drs. Holmberg, Das and Editors,

Re: The high comorbidity burden of Hepatitis C Virus infected population in the United States

Please find enclosed revised version of our manuscript for consideration to BMC Infectious Diseases. We have made revisions to the manuscript according to the Reviewer’s comments, which are appended below with our responses. All comments were very helpful and well-considered and we feel that the revision has made the manuscript more novel, stronger and clearer.

We hope that you will consider the possibility of this resubmission with these revisions made at this time. Thank you for your consideration and we look forward to hearing from you.

Yours sincerely,

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Major compulsory Revisions

1. 1st Para under “Co-morbidities associated with HCV disease (page 12) or 2nd para under “…not known to be associated with HCV disease (page 13)”. Many of the co-morbidities known or not known to be associated with HCV infection or treatment—such as back pain/problems (32.5%), joint disorders (29.3%), URIs, diarrhea etc-- are also very frequent in the non-HCV-infected population. So the major revision is to show, preferably in a Table, a comparison of selected conditions of interest among HCV and HCV-uninfected pop (with “N” of the uninfected pop).

Response: The comparison of selected conditions among HCV and HCV-uninfected population was in the original Table 2 that was submitted. It is the 4th column from the right. This shows the frequency of the comorbidity in the HCV uninfected population. With the exception of disorders of lipid metabolism, these comorbidities were more frequent in the HCV-infected population. The odds ratio (95% CI) shown in the last column, cases (HCV-infected) vs. controls (HCV-uninfected) shows the odds of the comorbidity being more frequent in HCV-infected cases compared to the non-infected controls. The odds ratio greater than 1.0 and the 95% CIs that do not overlap with 1.0 are statistically significant and indicate that these comorbidities are more common in the infected compared to the non-infected.

Minor Essential Revisions

2. Under limitations paragraph (last long para before “Conclusions”), the authors do a very good job talking about limitations of clinical coding data. They also need to address the bias of ascertainment (of sick patients and of patients taking antiviral meds) because of the way HCV-infected patients were selected (at least two medical facility notations of HCV).

Response: We have modified the referenced paragraph to the following for further clarification on bias ascertainment.

"Firstly, as we used a medical claims database, we did not have liver histology data to confirm stage of disease and we cannot exclude the possibility of ascertainment bias as the selection of cases required them to have at least two clinical codes for HCV diagnosis (e.g. patients with more advanced liver disease or on anti-viral treatment would have more clinical visits)."

Discretionary Revisions

4. “Box 1” and “Appendix A” can be put separately in electronic appendix.

Response: We appreciate the reviewer’s comment but we believe it is useful reference to guide the reader through the manuscript given the large amount of data that has been summarized.
REVIEWER: Gokul C. Das  
*Major Compulsory Revision:*

The major problems with this study are the following:

1. Although the authors attempted to estimate systematically the top 25 comorbid conditions in the US population, it appears as a biased selection of population within the US medical claim data base of integrated Health Care Information System based on medical coverage and submission of medical claims.

Response: We appreciate and agree with the reviewer’s comment. However, our results could be generalized to the privately insured population as 61% of those chronically infected with HCV have insurance and half of them were privately insured according to the NHANES, a population-based survey. We clarify the point that this is a biased selection of the population with the following modified sentence included in the last paragraph of the discussion section.

“Lastly, patients captured in a medical claims database may be a biased selection of the HCV population as it does not reflect the population who do not have access to healthcare, so estimates of these comorbidities should be extrapolated with caution to the general HCV population. However, our results could be generalized to the privately insured population. According to population-based data from the National Health and Nutrition Examination Survey (NHANES), 61% of those chronically infected with HCV had health insurance and among those insured, half of them had private health insurance [29].”

However, we do make the point that the population selected reflects a broader population that has not been used in previous studies that were limited to US veterans, dialysis, psychiatric and drug users.

“However, our study includes a much broader HCV population than previous studies, which were limited to select populations of US veterans [29-31], dialysis patients [32], psychiatric patients [33] and drug users [34].”

2. Again, it is only for a period of two years.

Response: The study was a cross-sectional study designed aimed at estimating the period prevalence of comorbidities for two years. We have clarified in the methods section under the sub-heading of *Statistical Analysis* that we were calculating a period prevalence

“The period prevalence of comorbidities during the 24-month study period was calculated.”

3. The prevalence of liver disease (other) came out as number one (37.5%) in the list of top 25 comorbid conditions. How the authors rule out that it is not the effect of HCV infection?
Response: We did not rule out that the effect of the prevalence of liver (disease) was not associated with HCV infection. Comorbidities comprised of both conditions and symptoms of HCV infection as described in the sub-section of “Disease Classification Systems” in the Materials and Methods section.

“HCV, HCV disease severity, and comorbidities (comprising both conditions and symptoms) were initially identified using the International Classification of Disease version 9 (ICD-9 codes) in IHCIS, and then further classified according to the Clinical Classifications Software (CCS) 2006 tool from the U.S. Agency for Healthcare Research and Quality [8]. The tool categorizes 12,000 ICD-9 codes into a manageable number of clinically meaningful categories to aid understanding patterns of diagnoses associated with particular illnesses.”

We clarify in the Results section that the other liver disease comorbidity is inclusive of HCV infection symptoms.

“Other liver diseases (37.5%) was the most common comorbidity (inclusive of symptoms) identified in this HCV population, and of these patients, 70% reported abnormal liver function, 26.7% elevated aminotransaminases, 13.8% abnormal serum enzyme levels, 10.7% ascites, and 9.0% hepatomegaly.”

4. Epidemiological study suggest that the incidence of type 2 diabetes is about 3 times more among chronically infected individuals and it is supported by HCV’s ability to induce insulin resistance, a hallmark of metabolic syndrome. Diabetes mellitus came out as number 23 in the list of comorbid conditions that does not provide me enough confidence about the design of statistical analysis and/or selection of study group.

Response: As reported in the last paragraph of the results, “the top ranking comorbidities among the overall HCV population were consistently identified in the top 25 comorbidities list of stratified groups of HCV treated, untreated, and controls populations, however with different prevalence and ranking orders (data not shown).”

Irrespective of rank, more importantly, the prevalence of diabetes was 1.5-fold higher among the HCV-infected (13.8%) compared to the HCV non-infected population (8.9%) in this study. This is lower than the 3-fold increase suggested by the reviewer but not unexpected. However, in our HCV-infected study population, the 13.8% are mainly those with diabetes without complication. If we included the population of diabetes with complications (<1%), which was a different comorbidity that was ranked lower, this prevalence would increase the prevalence with diabetes slightly.

It is possible that we under-estimate the effect of diabetes in the HCV-infected population if our HCV case definition is too strict as we required the individual to have at least two chronic HCV ICD-9 codes and 24-months of follow-up time. The inclusion criteria used may not adequately capture those who are chronically infected and also have diabetes. We have discussed the bias in case ascertainment as discussed above for Comment 2 of Scott Holmberg’s review.

However, this increased prevalence in the HCV infected vs. non-infected is consistent with a recent study using a nationally representative sample of the US population
(NHANES III) by (El-Kamary et al, 2011). The prevalence of diabetes in a chronic HCV infected population was 1.5% compared to 0.3% in the uninfected population. This prevalence is markedly lower than what was found in our study but reflects the difference in study population selection (general population vs. US managed care database). Although the prevalence of diabetes was 5-fold higher in the infected vs. non-infected, this difference in prevalence was not statistically significant.

5. Coinfection with other viruses, particularly HCV/HIV or HCV/HBV are very common (about 30%), this is also at the bottom of the list that make me uncomfortable with this analysis.

**Response:** We agree with the reviewer that coinfection with other viruses such as HCV/HIV and HCV/HBV can be as high as 30% when the denominator is an HIV-infected or HBV-infected population. However, the denominator used in this study was an HCV-infected population, and it would be expected that coinfection with HIV and HBV would be much lower.

For example, according to NHANES, a population-based survey in the US, the coinfection rate of HIV among an HCV-infected population was 2% (Stepanova et al, 2011). It would be expected that coinfection with HIV would likely to be even lower and under-represented in an insured population as people may not report their HIV status. Although the coinfection rate of HBV among an HCV-infected population is unknown in the US, it is estimated that HBV infection in the general population is 5.5% (McQuillan et al, 1999), so confection with HCV would be expected to be lower. In addition, globally, it has been estimated that the coinfection rate of HCV among an HBV population range from 7% to 15% (Peters MG, 2009), however these figures represent endemic areas of HBV infection (e.g. Southeast Asia) and not be representative of the US.

6. No information of genotypes, ethnic groups and ages associated with the comorbid conditions are provided.

**Response:** The limited data on genotypes and the lack of data on ethnic groups is an additional limitation of the IHCIS database. This is further clarified in the last paragraph in the discussion section.

“In addition, since data were limited (<1%) on HCV genotypes and unavailable for racial and ethnic groups in IHCIS, we were unable to match on these factors in our analyses although HCV disease is known to vary by genotype, between ethnic groups and have different treatment efficacy rates [28].”

The estimated prevalence was age-adjusted which provided a weighted average of the proportion of persons with the comorbid condition given the age of the study population. Therefore, we adjusted for age as a potential confounder of the prevalence of the comorbid condition and it provides a more accurate estimate.

**Minor Essential revisions**
Legends of Fig 1 needs more work for clarity.

**Response:** We have revised the Figure 1 legend to the following for more clarity:
“Figure 1. The proportion of HCV infected cases and HCV uninfected controls reporting comorbidities”

Discretionary Revisions:
While the objective of this study is highly significant in the field of HCV research, the selection of data base and analysis has limitation. An appropriate data base should be selected and both treated and untreated patient information with age and ethnicity should be included along with infected and uninfected population.

Response: We appreciate the comment that this work is highly significant in the field of HCV research. The limitations of using a US Managed Care database have been discussed at length in the discussion section and highlight the issues of using medical claims database for research. The IHCIS database is an administrative database that has been widely used for other HCV studies evaluating treatment patterns and adherence (Mitra et al, 2010) and for the evaluation of medical resource utilization and economic costs (Davis et al, 2011; Poordad et al, 2011). This study population also represents an insured population that would have access to treatment if comorbidities were able to be managed.

“Our study has several limitations. Firstly, as we used a medical claims database, we did not have liver histology data to confirm stage of disease and we cannot exclude the possibility of case ascertainment bias as the selection of cases required them to have at least two clinical ICD-9 codes for HCV diagnosis (e.g. patients with more advanced liver disease or on anti-viral treatment would have more clinical visits). In addition, since data were limited on HCV genotypes (<1%) and unavailable for racial and ethnic groups in IHCIS, we were unable to match on these factors in our analyses although HCV disease is known to vary by genotype, between ethnic groups and have different treatment efficacy rates [28]. Secondly, we relied on clinical coding for disease stage so the potential for misclassification of HCV diagnosis and liver disease stage cannot be ruled out. Thirdly, we cannot exclude the possibility of inconsistent coding or misclassification of comorbidities in our study; for example, COPD, which did not rank in our top 25 list, could have been misclassified under lower respiratory disease which ranked 5. Similarly, cutaneous conditions such as lichen planus and porphyria cutanea tarda which are commonly seen extrahepatic manifestations did not rank in the top 25, however, it is possible that these dermatologic conditions could be misclassified under allergic reactions [rank 18], which was mainly composed of unspecified dermatitis (65.9% of HCV patients with allergic reactions). In addition, given the cross-sectional design of this study, we were unable to establish the temporal sequence of events, i.e. whether a comorbidity, such as anemia deficiency, allergic reactions or eye disorders occurred prior to treatment, during treatment, or were treatment side effects. Lastly, patients captured in a medical claims database may be a biased selection of the HCV population as it does not reflect the population who do not have access to healthcare, so estimates of these comorbidities should be extrapolated with caution to the general HCV population. However, our results could be generalized to the privately insured population. According to population-based data from the National Health and Nutrition Examination Survey (NHANES), 61% of those chronically infected with HCV had health insurance and among those insured, half of them had private health insurance [29].” Despite these limitations, our study includes a much broader HCV population
than previous studies, which were limited to select populations of US veterans [30-32], dialysis patients [33], psychiatric patients [34] and drug users [35]; and represents an insured population that would have access to treatment if comorbidities were able to be managed.”

As discussed earlier, data on ethnicity are not available from IHCIS. However, the age distribution of HCV cases according to treatment status is presented in Table 1. The HCV non-infected controls were matched by age to HCV cases and have the same age distribution.

References


