Author's response to reviews

Title: Descriptive epidemiology of chronic liver disease in North-Eastern Italy: an analysis of multiple causes of death

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Author's response to reviews: see over
Dear Editor,

I submit a revised version of the manuscript entitled “Descriptive epidemiology of chronic liver disease in North-Eastern Italy: an analysis of multiple causes of death”, which I hope is now suitable for publication in Population Health Metrics.

In the revised manuscript changes addressing referees’ comments are highlighted (but not minor changes due to language editing); a point-by-point response to the comments is provided below.

I look forward to hear from you soon.

Best regards,

Ugo Fedeli
Referee 1

Comment 1 - Major Compulsory Revision

…. it is necessary to turn this into an answerable, policy-relevant question such as “To what extent do routine mortality data underestimate the burden of mortality from chronic liver disease of different aetiologies?”. The answers are largely in the paper but it would benefit from a sharper focus throughout. This would help to focus the discussion and conclusions too.

Answer

In the new Table 1 numbers are reported for the three selection strategies of ICD-10 codes applied only to the underlying cause of death, or to all diseases mentioned in the death certificate (see also Answer to Referee 2, Major Compulsory Revision 2). This allowed to focus Background, Discussion and Conclusion of the revised manuscript on the underestimation of chronic liver diseases (CLD) by routine mortality data (routine statistics are based on codes of Selection Strategy 1 as the underlying cause of death).

Comment 2 - Major Compulsory Revision

… It is not easy to see how the expansion of the CLD diagnoses impacts on the cases included. This could most easily be addressed by expanding table 1 and using numbers instead of percentages. What I want to know is the number of additional cases with a mention of alcohol or hepatitis are included when moving from the most restrictive of the three strategies.

Answer

The suggested change has been performed in the revised paper. Table 1 has been expanded and re-arranged: in each cell numbers as well as percentages are reported; codes included in selection strategies 1 and 2 have been slightly modified (see also Referee 2, Discretionary revisions 1 and 2); for each group of codes numbers identified by searching only the underlying cause and all diseases mentioned in the certificate are both reported. There has been a minor change in crude rate computation (in the old version a provisional population was used in Table 1 and final data in Table 2; this has been corrected in the revision).

Comment 3 - Minor Essential Revision

The paper requires considerable editing, with a number of words used inappropriately, such as “relevant”, which I take to mean “substantial

Answer

The suggested correction has been made. The manuscript has been revised by a native English speaker.

Comment 4 - Discretionary Revision

I felt that the list of alcohol-related causes that was included was overly restrictive. Why not also X45 (alcohol poisoning), W78-9 (inhalation of gastric contents), and I42.6 (alcoholic cardiomyopathy) (and maybe also pancreatitis?)
The adopted list of alcohol-related causes is somewhat restrictive. We tried to add other less used alcohol-related codes: E24.4 (Alcohol-induced pseudo-Cushing's syndrome), G31.2 (Degeneration of nervous system due to alcohol), G62.1 (Alcoholic polyneuropathy), G72.1 (Alcoholic myopathy), L42.6 (Alcoholic cardiomyopathy), K29.2 (Alcoholic gastritis), K85.2 (Alcohol-induced acute pancreatitis), T51 (Toxic effect of alcohol, which should be accompanied by alcohol-related external causes codes such as X45); instead we felt that W78-9 (inhalation of gastric contents) is not specific because related also to other diseases, i.e. neurological disorders. However, by adding the above mentioned codes, only six additional CLD deaths identified by selection strategy 2 could be attributed to alcohol. This finding is briefly summarized in Discussion of the revised paper.

Comment 5 – Discretionary Revision
I am not sure that the geographical analysis adds much but do not feel strongly about this

Answer
We acknowledge that the geographical analysis is not the main finding of the paper (maybe represented by Table 2). However a useful suggestion for future research could be to explore spatial differences in the etiology of CLD by multiple causes of death analysis, and therefore we chose to maintain the geographical analysis.

Comment 6 – Discretionary Revision
Although the policy implications are touched upon, this could be developed further.

Answer
The implications of HCV-related mortality data have been expanded in Discussion of the revised paper.
Referee 2

**Major Compulsory Revision - 1**

My biggest concern with the design of this paper is the vague distinction among the definitions of an underlying cause of death, disease related cause of death, and comorbid disease at the time of death. I do not believe this was made clear or appropriately addressed in the paper.... I recommend ..... paying particular attention to the choice of the following words; underlying, related, attributed.

**Answer**

In the revised version the use of words has been made clear: the term attributed has been deleted; the term underlying refers to the single cause selected by international rules for mortality statistics; the term related is used when the disease is mentioned in any part of the death certificate. Such use of terms is made explicit in Methods of the revised paper.

Overlapping terminologies and differences in death certificates by country contribute to some intricacy. According to coding instructions of the US National Center for Health Statistics, the certifier is requested to report in Part I as the first condition the immediate cause of death (e.g., cardiac arrest), thereafter antecedent conditions (e.g., liver failure), and as the last condition the underlying cause of the sequence of events (e.g., liver cirrhosis); in Part II should be mentioned any other significant disease which unfavorably influenced the course of the morbid process and thus contributed to the fatal outcome. However, the term “underlying cause” refers not only to the disease identified as such by the certifier, but also to the cause of death resulting from internationally adopted algorithms and usually reported in death statistics (the latter use is adopted in the manuscript); such disease generally corresponds to the underlying cause stated in Part I; however it could be also another disease reported in Part I or Part II, or a derived condition. As a further intricacy, Part I of the death certificate is reversed in Italy with respect to the US: first is reported the underlying cause, and last the immediate cause of death. As a consequence, we avoided the use of first/last reported cause through the paper.

**Major Compulsory Revision - 2**

Generally, however, causes reported besides the underlying cause of death are comorbid conditions not necessarily causal to the death at the time of death. While, exploring these conditions for the purpose of discerning, in this case, the etiology of chronic liver disease (CLD) (hepatitis, alcohol, etc...) is appropriate, assuming all cases that report CLD in the death certificates are CLD-related deaths will lead to bias in the mortality estimates. I recommend ..... estimate and compare to your current results CLD mortality using the underlying and first reported condition only (using ICD codes in strategy 2)

**Answer**

In the new Table 1 numbers are provided for deaths identified by searching codes of the three selection strategies only in the underlying cause, or in any position of the death certificate.

In theory, all diseases reported in death certificates had a role in causing or contributing to death. In the real word, a CLD could be probably present but not mentioned in the death certificate (e.g., in a subjects dying from hepatocellular carcinoma); or could be mentioned together with many other conditions although not really contributing to death (in this latter case, the analysis of multiple causes could correspond to a prevalence of disease at
In Figure 1 it can be seen that a relevant proportion of deaths with an underlying cause different from CLD is represented by primary liver cancer deaths; underlying causes different from liver diseases are selected in about one third of deaths identified with strategy 1 and 2. For these latter deaths, it must be remarked that due to ageing of the population in the Veneto Region about one fourth of deaths in males and half in females occur in the ≥85 yrs age class; in these elderly people it is often difficult to identify on a clinical ground a single real cause of death, and the multiple causes analysis could uncover the role of comorbidities in the fatal process. These comments have been summarized in Discussion of the revised paper.

In the Table below we report some supplementary data (not included in the manuscript), that in our opinion support this interpretation: CLD codes were searched according to strategy 2 only in the underlying cause, whereas alcohol or HCV etiology were ascertained using all diseases reported in the certificate; results are compared with those of the manuscript (age collapsed in two classes). It can be seen that:

i) the pattern by etiology is consistent, with alcohol being the main etiologic factor in males (while negligible in older females) and HCV in females (especially in the elderly)

ii) there is a sharp increase both in alcohol-related deaths and in HCV-related deaths when searching CLD codes among all causes reported in the certificate

iii) such increase tends to be greater in the older age class (see comments above)

iv) such increase tends to be greater for HCV-related deaths; as a consequence the share by etiology of total CLD deaths tends to be higher for alcohol and lower for HCV when restricting CLD codes only to the underlying cause

<table>
<thead>
<tr>
<th></th>
<th>HCV-related</th>
<th>Alcohol-related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td><strong>Strategy 2 applied only to the underlying, HCV and alcohol codes searched in all causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 75 yrs, n (% CLD deaths)</td>
<td>149 (15%)</td>
<td>86 (22%)</td>
</tr>
<tr>
<td>Age ≥ 75 yrs, n (% CLD deaths)</td>
<td>78 (20%)</td>
<td>273 (50%)</td>
</tr>
<tr>
<td><strong>Strategy 2, HCV and alcohol codes searched in all causes (paper-Table 2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 75 yrs, n (% CLD deaths)</td>
<td>429 (18%)</td>
<td>216 (28%)</td>
</tr>
<tr>
<td>Age ≥ 75 yrs, n (% CLD deaths)</td>
<td>336 (25%)</td>
<td>775 (52%)</td>
</tr>
</tbody>
</table>

**Minor Essential Revision - 1**

Background Paragraph 1: Report the actual mortality rate for HCC instead of stating “very high”

*Answer*

The mortality rate is now reported in the revised paper.

**Minor Essential Revision - 2**

Background Paragraph 1: Change the semi-colon to a period

*Answer*

The change has been made in the revised paper.
Methods Paragraph 1: Last sentence is long and confusing. Revise
Answer
In Methods of the revised paper the sequence of diseases in death certificates and the selection of the underlying cause of death by standard international rules are more clearly illustrated.

Methods Paragraph 2: List the ICD codes used in the third strategy
Answer
The codes are now reported in the text of the revised paper.

Methods Paragraph 5: “Share of total CLD deaths”. I am assuming the share by etiology. The phrase needs revision to make clear to the reader.
Answer
The suggested change has been made in the revised manuscript.

Results Paragraph 4: Delete “already” in “already in the 45-54”
Answer
The suggested change has been made in the revised manuscript.

Results Paragraph 4: The phrase, “And further increased in subjects ≥65 years especially among females, reaching levels higher than in males above 75 years” is not clear as phrased now. Needs revision. I am assuming the male to female ratio decreased. I am not clear to what increased since the prior sentence reported a peak at ages 45-54.
Answer
The paragraph has been rearranged in the revised manuscript: mortality rates reached high values at ages 45-54, and further increased in subjects ≥65 years especially among females, with a male to female ratio falling below the unity.

Results Paragraph 4: The phrase “Due to limited numbers, in all analyses deaths with multiple etiology are listed both among HCV and alcohol-related CLD” needs revision for grammar and structure.
**Answer**

The sentence has been rearranged in the revised manuscript: the few deaths with mention of both alcohol and HCV are analyzed both among HCV and alcohol-related CLD.

**Minor Essential Revision - 9**

Table 1: I am not clear as to what the category “no etiology” exactly refers to. Is it those cases where neither hepatitis nor alcohol was reported or no causes whatsoever were identified? If the former, I recommend changing the category name to “Other” which includes metabolic diseases, unidentified causes, etc…

**Answer**

No etiology refers to cases where neither hepatitis nor alcohol was reported; the category name has been changed to “other/not reported” in the revised Table

**Discretionary Revision - 1**

Selection of ICD codes for identifying CLD cases remains variable across the literature. The selection code choice is generally dependent on the characteristics of the database at hand, a wider net for databases with major under-reporting and vice-versa. I suggest adding I85 (esophageal varices) and K76.6 (hepato renal syndrome) to code selection 2 as both are complications related to liver cirrhosis and are fairly specific. K71.7 (Toxic liver disease with fibrosis and cirrhosis of the liver) and K72.1 (Chronic hepatic failure) are also appropriate.

**Answer**

Selection strategies 1 and 2 have been slightly changed in the revised manuscript (see also the following answer): strategy 1 has been limited to codes K70, K73, and K74, to more strictly adhere to conventional liver cirrhosis mortality statistics and to more clearly illustrate differences between underlying and multiple causes of death analysis. In strategy 2 code K76.0 has been removed; code K76.7 (hepato renal syndrome) has not been included because in our database it is associated also to hepatic failure due to other site cancers metastatic to the liver. The inclusion of additional codes I85, K71.7, and K72.1 to strategy 2 leads to only 39 additional deaths retrieved (with respect to 5,941 in the new Table 1). The referee’s comment on the opportunity to modulate selection of codes based on the characteristics of the database at hand has been introduced in Discussion of the revised paper.

**Discretionary Revision - 2**

I would raise concerns related to K76.0 (Fatty change of the liver) as part of the first 2 selections strategies. This condition is fairly common and generally benign. I recommend estimating the percent contribution of this etiology to the mortality estimate in order to ascertain there is no bias. A similar concern is related to including B15 (Acute hepatitis A) in selection strategy 3.

**Answer**

Fatty change of the liver (K76.0) was removed from selection strategies 1 and 2; this code is not frequently reported in death certificates. The selection strategy 3 is the broader one reported in the recent literature [McDonald 2010], and the inclusion of some codes could
therefore be questionable. However, in the present paper this strategy is adopted mainly to set a reference for a very sensitive but unspecific selection of codes. Anyway, B15 is very rarely reported in death certificates, and no additional CLD death was retrieved (no death with B15 and without any other liver disease code).

*Discretionary Revision - 3*

It is important to note that, as per ICD rules, hepatocellular carcinoma (HCC) deaths are not counted toward CLD deaths. While HCC is generally a complication of CLD, reported mortality estimates for CLD exclude HCC deaths. The following comments pertain to the ICD code selection number 3.

*Answer*

The referee’s comment has been added in Discussion of the revised paper: it is true that in mortality statistics HCC deaths are not counted in CLD deaths, but HCC deaths without mention of CLD represent a true problem of CLD mortality underestimation even in multiple causes of death analyses. For selection strategy 3, see also the previous answer.