PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Liver cirrhosis in England-an observational study. Are we measuring its burden correctly?
AUTHORS	Ratib, Sonia; West, Joe; Fleming, Kate

VERSION 1 - REVIEW

REVIEWER	Kittiyod Poovorawan Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Thailand
REVIEW RETURNED	31-Aug-2016

GENERAL COMMENTS	The manuscript entitled “Liver cirrhosis in England-an observational study. Are we measuring its burden correctly?”. This is a study to determine the accuracy of diagnostic coding from National Statistics death registry on the burden of liver cirrhosis in England and Wales, from 1968 to 2011. Authors have retrospectively analyzed big secondary data on cirrhosis and determined the difference in mortality rates and incidence of liver cirrhosis based on different diagnosis code system. The major strength of the study is the large number of cases and very long period of time. However, there are some limitations of the study according to the database such as under-diagnosis of cirrhosis (if unrelated to death), lack of other data associated with the burden of cirrhosis such as admissions, cost of treatment, etc. Overall, the study clearly point out the practical point, potential utilization and limitation of this kind of database. Comments 1. Introduction: Authors should describe in more detail about system of healthcare database and public health system in England. If possible compare with other country in Europe or other regions in the world. This information will benefit for the readers and enhance utilization of the study. 2. Results: Mortality rates and incidence rates of cirrhosis was standardized with 2011 population. Authors should also demonstrate overview in dynamic change of the population from 1968, and further discuss of any impact on the outcome. 3. Discussion: Authors should discuss potential effect of other factors over the time on incidence and mortality (such as improvement in treatment and care of chronic liver disease, disease prevention and control, etc.). 4. Discussion: most of coding was limited cause of cirrhosis to alcohol, but chronic viral hepatitis is also major cause of cirrhosis globally. Authors should discuss more about room for improve coding system to specificity etiology of cirrhosis (e.g. chronic viral

	hepatitis B and C) in discussion part.

REVIEWER	Fausto Edmundo Lima Pereira Professor of Pathology . Centro de Ciências da Saúde-Universidade Federal do Espirito Santo. Vitória ES. Brazil
REVIEW RETURNED	15-Sep-2016

GENERAL COMMENTS	We call the attention of authors to page 9 , line 7 : Change (Table 1) to (Supplementary Table 1).

REVIEWER	Ramon Bataller University of North Carolina at Chapel Hill, USA
REVIEW RETURNED	06-Nov-2016

GENERAL COMMENTS	The aims of the current study were to demonstrate that (i) exclusive reliance on mortality rates may not reveal the true burden of liver cirrhosis, and (ii) diverse use of diagnostic coding may produce misleading estimates in England. The authors demonstrate that overall mortality rates underestimate the incidence of liver cirrhosis by at least three-fold. Although the study is relevant from a public health point of view, I have several concerns. 1. While the manuscript is interesting (i.e. it demonstrates that the real burden of cirrhosis is underestimated by using mortality data), I think it would be more suitable to a specialized public health journal. 2. The main conclusion of the study (i.e. “Liver cirrhosis mortality rates varied greatly by definition of disease”) is confusing and is hard to interpreted by the general reader. 3. The definitions of liver cirrhosis based on the codes are not fully accurate, since many patients with chronic liver disease may have early stages. Moreover, they may overlook mortality due to alcoholic hepatitis (not in patients have underlying cirrhosis) and hepatocellular carcinoma. 4. The differences between mortality and equivalent incidence should better explained. Patients with cirrhosis due to alcohol and NAFLD often have important co-morbidities and it is conceivable that mortality and incidence rates are quite different. 5. As quoted by the authors, a potential limitation is the fact that codes may have changed over time. This should be explained in more detailed by the authors.

REVIEWER	Ruosha Li UTHealth
REVIEW RETURNED	01-Jan-2017

GENERAL COMMENTS	Poisson regression was used for regression analysis. Please conduct a diagnosis of over-dispersion. The negative-binomial regression may be more flexible in handling count data.

	Regarding ``the standardised incidence rates were between 3- and 6-fold that of mortality", this appears to be one main point of the paper. It is desirable to present the point estimates (and CI, if possible) for the ratio between the two types of rates. Please report the sample size of the analytic data. For the difference between three definitions, could you identify the main causes of the difference from the data? (to explain the difference between 8.8, 5.4 and 5.1 in more detail).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Poovorawan, K
Mahidol University, Clinical Tropical Medicine

Please leave your comments for the authors below
The manuscript entitled “Liver cirrhosis in England-an observational study. Are we measuring its burden correctly?”. This is a study to determine the accuracy of diagnostic coding from National Statistics death registry on the burden of liver cirrhosis in England and Wales, from 1968 to 2011. Authors have retrospectively analyzed big secondary data on cirrhosis and determined the difference in mortality rates and incidence of liver cirrhosis based on different diagnosis code system. The major strength of the study is the large number of cases and very long period of time. However, there are some limitations of the study according to the database such as under-diagnosis of cirrhosis (if unrelated to death), lack of other data associated with the burden of cirrhosis such as admissions, cost of treatment, etc. Overall, the study clearly point out the practical point, potential utilization and limitation of this kind of database.

*Thank you very much for your comment and appreciating both the strengths and limitations of our work. Thank you also for taking *time to consider our work and your helpful comments below. We have responded to all of them.

Comments
1.Introduction: Authors should describe in more detail about system of healthcare database and public health system in England. If possible compare with other country in Europe or other regions in the world. This information will benefit for the readers and enhance utilization of the study.
*Thank you for your helpful comment. We have now added this extra information to the Introduction:

*“In the UK, as in many Northern European countries, patients with suspected liver cirrhosis may be diagnosed by their primary care *physician, or more commonly are referred to a secondary care specialist who will then pass on information to the primary care *physician. Our research group has therefore used linked primary and secondary routine healthcare databases in order capture the *incidence of cirrhosis as comprehensively as possible. [3]”

2.Results: Mortality rates and incidence rates of cirrhosis was standardized with 2011 population. Authors should also demonstrate overview in dynamic change of the population from 1968, and further discuss of any impact on the outcome.
*Thank you for your comment. It is in order to take account of the fluctuating nature of the underlying population in terms of age and *sex distribution that we have provided our estimates standardised to the 2011 population. Whilst we acknowledge that there are *other factors which may have contributed to population change we are unable to adjust for these and have adopted the pragmatic *approach that is common in most demographic / epidemiological papers examining disease trends over time.

3.Discussion: Authors should discuss potential effect of other factors over the time on incidence and mortality (such as improvement in treatment and care of chronic liver disease, disease prevention and control, etc.).
*Thank you for your helpful comment. Our premise was to see whether differential coding itself could be a potential explanation for *the trends in disease seen and whether the use of mortality or incidence figures appears to more accurately represent the burden *of disease. We do agree that we should add in the discussion that the difference in incidence and mortality could be due to *improvement in treatment over time, and this means that with improving treatment mortality becomes an even worse proxy *measure of burden. We have therefore added this sentence on page 13:

*"Finally, differences in incidence and mortality could be partially due to improvement in treatment and care of chronic liver disease, if *anything this means that with improving treatment mortality becomes an even worse proxy measure of burden."

4.Discussion: most of coding was limited cause of cirrhosis to alcohol, but chronic viral hepatitis is also major cause of cirrhosis globally. Authors should discuss more about room for improve coding system to specificity etiology of cirrhosis (e.g. chronic viral hepatitis B and C) in discussion part.

*Thank you for bringing this to our attention. We have now added a sentence on page 14 to address the fact that specific codes for *chronic hepatitis B (ICD10 B18.1) and chronic hepatitis C (ICD10 B18.2) could be used by future researchers when considering the *burden of cirrhosis. Whilst some people with viral hep will develop cirrhosis it is most certainly not all:

*"We acknowledge that specific ICD10 codes for chronic viral hepatitis such as chronic hepatitis B (B18.1) and chronic hepatitis C (B18.2) have not been considered by researchers in the field. Inclusion of these codes could also be considered when developing a *broad definition of cirrhosis."

Reviewer: 2
Pereira, Fausto Edmundo
Universidade Federal do Espirito Santo

Please leave your comments for the authors below
We call the attention of authors to page 9 , line 7 : Change (Table 1) to (Supplementary Table 1).

*Thank you for bringing this error to our attention we have now made this change.

Reviewer: 3
Bataller, Ramon
University of North Carolina at Chapel Hill

Please leave your comments for the authors below

The aims of the current study were to demonstrate that (i) exclusive reliance on mortality rates may not reveal the true burden of liver cirrhosis, and (ii) diverse use of diagnostic coding may produce misleading estimates in England. The authors demonstrate that overall mortality rates underestimate the incidence of liver
cirrhosis by at least three-fold. Although the study is relevant from a public health point of view, I have several concerns.
*Thank you for taking time to consider our work and your helpful comments below. We have

responded to all of them.

1. While the manuscript is interesting (i.e. it demonstrates that the real burden of cirrhosis is underestimated by using mortality data), I think it would be more suitable to a specialized public health journal.
*We agree that our work falls under the category of public health. However, the BMJ Open does include work specifically related to *public health and also has a broad scope which will allow our work to be read by a range of clinicians and researchers. Publishing *our study in the BMJ Open will therefore increase the impact of our findings across different fields.

2. The main conclusion of the study (i.e. “Liver cirrhosis mortality rates varied greatly by definition of disease”) is confusing and is hard to interpreted by the general reader.

*Thank you for your helpful comment. We have now amended he conclusion accordingly on page 2:
*“Mortality rates underestimated the incidence of liver cirrhosis by at least three-fold between 1998 and 2009 and varied with *differing definitions of disease. Mortality data should not be used exclusively as an indicator for the occurrence of liver cirrhosis in *the population. Routinely collected healthcare data are available to measure occurrence of this disease. Careful consideration *should be taken when selecting diagnostic codes for cirrhosis.”

3.The definitions of liver cirrhosis based on the codes are not fully accurate, since many patients with chronic liver disease may have early stages. Moreover, they may overlook mortality due to alcoholic hepatitis (not in patients have underlying cirrhosis) and hepatocellular carcinoma.
*Thank you for your comment. We agree that people with chronic liver disease may have early stages of cirrhosis. That is why we *have mentioned in our Discussion (on page 14) that broad codes may be more appropriate if sensitivity is more important than *specificity in the context of the research question being answered.

4.The differences between mortality and equivalent incidence should better explained. Patients with cirrhosis due to alcohol and NAFLD often have important co-morbidities and it is conceivable that mortality and incidence rates are quite different.
*We apologise that we have not been clear. We are trying to show that measuring the occurrence of cirrhosis is higher when *counting the number of people newly diagnosed with the condition rather than just counting the number deaths due to cirrhosis *which to date has been the standard practice. The key message of our paper is that reliance on mortality data alone (which others *have done for several decades both in the UK and for the purposes of international comparisons 1,2,3) may lead to an *underestimate of the occurrence of cirrhosis. This finding has implications for the NHS as it may well be under resourced and *unable to cope with future demand on hepatology clinics given the current sharp rise of cirrhosis in the UK.

5.As quoted by the authors, a potential limitation is the fact that codes may have changed over time. This should be explained in more detailed by the authors.
*Thank you for your comment. We would like to bring to our attention that we have provided an explanation on pages 11 and 12:
*“The change in rate of specific causes of death over time could be due to the use of different ICD versions throughout the study *period rather than a true change. For example, the sharp increase in the number of liver disease deaths (definition) 1, after 1979, *when ICD-9 came into use; followed by a reduction in the rate of change from 2001 onwards when ICD-10 came into place. This *phenomenon has been reported by others.[20] Coding phenomenon also occurs when doctors change the way they select codes *on death certificates. For example, over time doctors may be more likely to use codes for alcoholic liver disease even in the *presence of alcoholic cirrhosis. This may explain the increase in deaths coded as alcoholic liver damage in contrast to the fall in *deaths coded

for alcoholic cirrhosis, which we report in this study."

Reviewer: 4
Li, Ruosha
University of Texas Health Science Center at Houston

Please leave your comments for the authors below
Poisson regression was used for regression analysis. Please conduct a diagnosis of over-dispersion. The negative-binomial regression may be more flexible in handling count data.
*Thank you for your helpful suggestion. We have conducted a diagnosis of overdispersion using the likelihood ratio test of alpha and *found high overdispersion ($p<0.001$) for all models. We have therefore used the negative binomial modelling instead of Poisson *models to determine average annual increase in mortality.
Regarding ``the standardised incidence rates were between 3- and 6-fold that of mortality", this appears to be one main point of the paper. It is desirable to present the point estimates (and CI, if possible) for the ratio between the two types of rates.
*Thank you for your comment. We did not plan a priori to establish the ratio of these rates using statistical modelling. We are just *describing narratively how the incidence and mortality rates vary.

Please report the sample size of the analytic data.
*We apologise that we omitted the sample size of the incidence cohort. We have now inserted this on page 6. For the ONS data, the *number of deaths varies from year to year, and from diagnosis to diagnosis, as can be seen in Table 1.

For the difference between three definitions, could you identify the main causes of the difference from the data? (to explain the difference between 8.8, 5.4 and 5.1 in more detail).
*Thank you for your comment. The difference in rates is most likely due to the fact that definition 1 includes codes related to *alcoholic liver disease such as K70.9 (Alcohol liver disease) whereas the other two definitions do not. K70.9 contributed to 40% of *'Definition 1'deaths in 2008, i.e. it was the most common cause of death in 2008. We have now made this clearer on page 13:

*"The second implication of our findings is the necessity of careful consideration of disease definition. We have shown that the *inclusion of patients who died from chronic liver diseases introduced an overestimate of cirrhosis mortality rates, by about 60%, *comparing definitions 1 and 3 (8·8 per 100,000 vs. 5·4, respectively). Definition 1 included codes related to alcoholic liver disease *such as alcoholic fatty liver disease (K70.0) and alcohol liver disease (K70.9) (the latter contributed 40% of 'Definition 1' deaths in *2008) , as well as autoimmune diseases which were not included in Definition 3. With respect to alcoholic liver disease, some *patients with this condition can fluctuate between alcoholic fatty liver and alcoholic hepatitis and not actually completely progress to *cirrhosis, and if they stop…"

VERSION 2 – REVIEW

REVIEWER	Ruosha Li, PhD UTHealth
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	The authors have addressed my comments on Poisson regression and interpretation.