PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	ECONOMIC BURDEN OF CIRRHOSIS IN CATALONIA:A POPULATION- BASED ANALYSIS
AUTHORS	Miquel, Mireia; Cleries, Montserrat; Vergara, Mercedes; Vela, Emili

VERSION 1 – REVIEW

REVIEWER	Patrizia Pontisso University of Padua, Italy
REVIEW RETURNED	28-Jun-2017

GENERAL COMMENTS	The Authors have addressed a sanitary relevant problem, consisting in the evaluation of healthcare resource use and expenditures in patients with advanced liver disease. The population-based approach is worth and the regional health data obtained include detailed information on healthcare units, prescription and billing for services of the unselected population of cirrhotic patients residing in the Catalonia Region. The results are interesting and potentially useful for health care planning in the field of liver diseases. Minor comments: It is unclear how the authors could weight unplanned hospitalizations in private hospitals (5.2%) while they stated that information from private health centers was not available for analysis (page 7, line 3). The second sentence of "Limitations" in the discussion section should be better explained (..administrative data ..can lead to misdiagnosis). Several typing errors must be corrected (e.g pacients, poblational...)

REVIEWER	Hsiang, John C Changi General Hospital, Department of Gastroenterology and Hepatology
REVIEW RETURNED	11-Jul-2017

GENERAL COMMENTS	This is a population study from Catalonia, Spain on the healthcare cost expenditure of cirrhotic patients of various stages. This is a good study but this study does have few biases which needs to be addressed. 1.The authors split the groups into three (compensated, previous decompensation, and recent decompensation) - these were based on whether patient has had an hepatic event in 2012 or not. The authors did not take account into those who died in 2012 - this is important because this rate will undermine the mortality and morbidity, and even the cost impact of those in previous and recent decompensation group. - This is called 'immortal bias' where those who didnt die in year 2012 are continued to be analysed in the study and those who died, are excluded in the study. Therefore it is iimportant the authors discuss the % of patients who are excluded, and the cost impact of these. 2. The authors have made statements in the paper which needs to be backed up by quoting p-values and show some statistical data - eg. page 11, line 41-45 - "...of women decreased with worsening disease (44.8% in the Compensated group, 33.8% in the Previous decompensation group, and 33.4% in the Recent decompensation group). Is there p value to support this in the main text? 3. page 12, line 3 to line 10 - confusing and hard to understand statement 4. similarly in page 12, line 12 to line 17 - simply stating the mortality rates and says this is three times more than group 1 is not very scientific - please back it up with statistical analysis 5. mortality rate is higher in the recent decompensation group - however, this rate is affected by many factors including, age of the group, the gender composition, and the higher proportion of comorbidities. Suggest to do age- and sex-adjusted mortality rates 6. Similarly the hospitalisation rates and the costs should be adjusted to age/cormorbidities. Even without knowing whether patient decompensated recently or previously or not - 7. page 12, line 28 - 'pacients' rather than patients... please review the manuscript for grammatical errors and spelling errors. 8. page 15, line 37 - the authors mentioned ROC for expenditure is 0.88 - but what is the clinical relevance of this? There is no other data mentioned elsewhere in the manuscript regarding ROC. Please remove this or expand on discussion on the predictive model that the authors set out to do.

REVIEWER	Richard Woodman Flinders University Australia
REVIEW RETURNED	02-Oct-2017

GENERAL COMMENTS	The abstract should include that an objective was to describe the point/period prevalence. Check for English grammar e.g. repeated use of "in function" rather than "as a function of" and spelling e.g. Page 15 line 57 "poblational study". It would be useful if more information about CHSS could be provided e.g. when it was established and is it a passive or active surveillance system? Does it provide comprehensive (100%) coverage of all hospital admissions and or other healthcare visits? Are the recorded diagnoses primary or primary and secondary? A reference for the statement regarding public versus private hospitalisations (page 7 line 12) should be provided. What was the entry date for the cohort i.e. how far back prior to December 2012? (page 8 line 12). The logistic regression includes only patients that survived and results may therefore be biased. A sensitivity analysis should be performed that includes all patients. This can be done if for those that died, their costs could be extrapolated to give costs per year and then these patients can be classified according to the 85th percentile of cost - as for the other patients that survived. This is important given that a large % (19.4) of the recent decompensation group died. It would be helpful if a list of all variables considered for inclusion in the logistic regression were stated in the methods. This would allow readers to see which variables were not predictors. Page line 34. Quantitative variables should be described as continuous variables. Qualitative variables should be described as categorical variables. How was the goodness of fit (calibration) for the logistic regression assessed? Were interactions included in the model to ensure adequate fit? The study was not approved by an Ethics committee. Although there is no risk regarding patient confidentiality, can the authors justify why studies of this type do not require any kind of approval (even e.g. low risk approval). Patient confidentiality is not the only aspect that Ethics committees must consider. Is the prevalence reported on page 12 line 27 a period prevalence or point prevalence? i.e. for the whole year of just 31st December. It would be helpful to the reader if the term period prevalence or point prevalence were used. The units for each of the Figures given in Table 3S are unclear. (Stating x100 is also not helpful). The limitations of excluding patients that died is not addressed in the discussion. These patients may have contributed considerably to costs. Are the costs therefore an underestimate?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Patrizia Pontisso
Institution and Country: University of Padua, Italy
Please state any competing interests: None declared

Please leave your comments for the authors below

The Authors have addressed a sanitary relevant problem, consisting in the evaluation of healthcare resource use and expenditures in patients with advanced liver disease. The population-based approach is worth and the regional health data obtained include detailed information on healthcare units, prescription and billing for services of the unselected population of cirrhotic patients residing in the Catalonia Region.

The results are interesting and potentially useful for health care planning in the field of liver diseases.

Minor comments:
a. It is unclear how the authors could weight unplanned hospitalizations in private hospitals (5.2%) while they stated that information from private health centers was not available for analysis (page 7, line 3).

A:--> Thank you for pointing out this shortcoming. We have explained this issue in the manuscript, page 7, line 13

b. The second sentence of "Limitations" in the discussion section should be better explained (..administrative data ..can lead to misdiagnosis)

A:.--> We have explained this better. (main text page 24 line 1 to 6)

c. Several typing errors must be corrected (e.g pacients, poblational...)

A:--> Sorry about that. The revised manuscript has been reviewed by a native English speaker with extensive experience in scientific texts.

Reviewer: 2
Reviewer Name: JH
Institution and Country: C
Please state any competing interests: None declared

Please leave your comments for the authors below
This is a population study from Catalonia, Spain on the healthcare cost expenditure of cirrhotic patients of various stages.
This is a good study but this study does have few biases which needs to be addressed.

1.The authors split the groups into three (compensated, previous decompensation, and recent decompensation) - these were based on whether patient has had an hepatic event in 2012 or not. The authors did not take account into those who died in 2012 - this is important because this rate will undermine the mortality and morbidity, and even the cost impact of those in previous and recent decompensation group.

- This is called 'immortal bias' where those who didnt die in year 2012 are continued to be analysed in the study and those who died, are excluded in the study. Therefore it is important the authors discuss the % of patients who are excluded, and the cost impact of these.

A:-->You are right that immortality bias can be a serious problem. To avoid "immortal bias" during 2012 we included only the patients alive on 31/12/2012 to analyze what happened during 2013. We are sorry this was not clear in the original manuscript. We have stated it clearly in the revised text (page 7, line 20).
According to Levesque et al. (1) "Immortal bias refers to a period of follow-up during which, by design, death or the study outcome cannot occur…immortal time typically arises when the determination of an individual's treatment status involves a delay or wait period during which follow-up time is accrued… This wait period is considered immortal because individuals who end up in the treated or exposed group have to survive (be alive and event free) until the treatment definition is fulfilled".

This situation does not occur in our study: the start date of follow-up for all patients is 12/31/2012 while the definition of the variable "decompensation" includes only events prior to the start date of the follow-up. That is, in our study, all of the events we studied may occur (for all study participants) from day 1 of follow-up.

Levesque L. et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010;340:b5087

2. The authors have made statements in the paper which needs to be backed up by quoting p-values and show some statistical data - eg. page 11, line 41-45 - "...of women decreased with worsening disease (44.8% in the Compensated group, 33.8% in the Previous decompensation group, and 33.4% in the Recent decompensation group). Is there p value to support this in the main text?

A:--> Sorry about that. Although the p-value was reported Table 1, we neglected to include it in the main text. (corrected: page 12, line 5)

3. page 12, line 3 to line 10 - confusing and hard to understand statement

A:-->Sorry about that. We have rewritten this part to make it easier to understand (page 12, line 10 to line 13)

4. similarly in page 12, line 12 to line 17 - simply stating the mortality rates and says this is three times more than group 1 is not very scientific - please back it up with statistical analysis

A:-->We have rewritten this part, as suggested: Page 12, line 14 to line 17

5. mortality rate is higher in the recent decompensation group - however, this rate is affected by many factors including, age of the group, the gender composition, and the higher proportion of comorbidities. Suggest to do age- and sex-adjusted mortality rates.

6. Similarly the hospitalisation rates and the costs should be adjusted to age/cormorbidities. Even without knowing whether patient decompensated recently or previously or not –

A:-->Both points (5 and 6) are true. However, the main objective of the study was not to analyze mortality or hospitalization but to evaluate the use of health resources. Therefore, we have focused on the risk factors of having higher expenses.

Furthermore, mortality in patients with cirrhosis depends largely on hepatic failure and neither age, sex, or comorbidities are major determinants. Proof of this is that all prognostic scores in cirrhosis (either child or MELD) evaluate only liver-disease-related parameters, and age, sex, and comorbidities are not included.

We have added, as supplementary material, the tables 4S (Multivariable logistic regression analyzing factors associated with mortality) and 5S (Multivariate logistic regression analyzing factors associated with being hospitalized. These tables show how, once adjusted for the other factors, the likelihood of dying and having some urgent hospitalization increases considerably for patients who have had a recent liver decompensation.

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7. page 12, line 28 - 'pacients' rather than patients... please review the manuscript for grammatical errors and spelling errors.

A:--> Sorry about that. The revised text has been reviewed by a native English speaker with extensive experience in scientific texts.

8. page 15, line 37 - the authors mentioned ROC for expenditure is 0.88 - but what is the clinical relevance of this? There is no other data mentioned elsewhere in the manuscript regarding ROC. Please remove this or expand on discussion on the predictive model that the authors set out to do.

A:--> Thanks for pointing this out. Following Reviewer 3's suggestion, we have expanded on this in the discussion. (main text: page 16, line 2 to line 4)

Reviewer: 3
Reviewer Name: Richard Woodman
Institution and Country: Flinders University Australia
Please state any competing interests: None declared

Please leave your comments for the authors below
1.The abstract should include that an objective was to describe the point/period prevalence.

A:--> Thank you. We have specified this objective in the abstract. (main text: in page 3, line 5 and 6)

2.Check for English grammar e.g. repeated use of "in function" rather than "as a function of" and spelling e.g. Page 15 line 57 "poblational study".

A:--> Sorry about that. The revised manuscript has been reviewed by a native English speaker with extensive experience in scientific texts.

3. It would be useful if more information about CHSS could be provided e.g. when it was established and is it a passive or active surveillance system? Does it provide comprehensive (100%) coverage of all hospital admissions and or other healthcare visits? Are the recorded diagnoses primary or primary and secondary?

A:--> We have provided more information about CHSS (main text: from page 6, line 19 to page 7, line 4)

4. A reference for the statement regarding public versus private hospitalisations (page 7 line 12) should be provided.

A:-->Sorry for the confusion. All the data came from CatSalut, and this has been clarified in the revised text (page 7, line 12)

5. What was the entry date for the cohort i.e. how far back prior to December 2012? (page 8 line 12).

A:--> The entry date was December, 31 2012. We have modified the main text to make this clearer (page 7, line 20)

6. The logistic regression includes only patients that survived and results may therefore be biased. A sensitivity analysis should be performed that includes all patients. This can be done if for those that died, their costs could be extrapolated to give costs per year and then these patients can be classified according to the 85th percentile of cost - as for the other patients that survived. This is important given that a large % (19.4) of the recent decompensation group died.

A:-->We understand your concerns. However, extrapolating data of patients who died to the whole year would greatly overestimate the costs, as the consumption of resources tends to be extremely high at the end of life. We have added a comment to address this point in the limitations section (page 19, line 18 to page 20 , line 24).

Patients who died during the study period were excluded from the assessment of predictors of increased expenditure. Although this exclusion could lead to bias, it is also true that the cost of these patients after their death was zero. Therefore, the inclusion of dead patients in the analysis could lead to a possible bias in the calculation of the odd ratios of risk factors and, consequently, to errors in interpretation when diseases with high mortality are analysed. For example, a particular tumour could appear as a protective factor for expenditure even though antineoplastic treatments are expensive.
In the other hand, extrapolating data of patients who died to the whole year -as suggested by the reviewer- will largely overestimate the costs of this patients, as consumption of resources tend to be extremely high at the end of life.
Regarding the possible solutions for this bias, we opted for the simplest solution and we analysed only patients alive throughout the year. This strategy has two main advantages: simplicity and robustness. In contrast to several similar strategies, each of which introduces some sort of bias, we believe it is better to use the simplest and easiest strategy to explain and understand the data. Moreover, the strength of this work is that as it is a population-based study with real data, there is no need for methodological sophistication when a simpler strategy can be used.

7.It would be helpful if a list of all variables considered for inclusion in the logistic regression were stated in the methods. This would allow readers to see which variables were not predictors.

A:-->Thank you for this suggestion. We have been cautious in the selection and introduction of variables in the predictive models taking into account the study aims. In the current study, we did not intend to carry out an exploratory study of possible risk factors, but rather to show the importance of multi-morbidity and the power of population-based risk assessment tools in patients with cirrhosis. Thus, we have tested only variables that, a priori, showed a possible clinical relevance. We believe that the messages generated by the study are not affected by the multiple tests performed
In the main text, in the “Assessment of predictors of increased expenditure” section we list the predictors (page 10, line 1 to 4): Predictors assessed were age, sex, co-morbidities included in the Charlson Index, previous healthcare utilization, and a novel population-based health risk assessment tool deployed in Catalonia, the Adjusted Morbidity Grouper , which is used to calculate an individual’s morbidity burden.

8 Page line 34. Quantitative variables should be described as continuous variables. Qualitative variables should be described as categorical variables.
A:-->You are right. We have changed in the text (page 10, line 24 and page 11, line 1)

9.How was the goodness of fit (calibration) for the logistic regression assessed?

A:-->Calibration (Hosmer-Lemeshow test) of the model analyzing factors associated with expenditure higher than the 85th percentile
(see the grafic in reviewers comments)

10. Were interactions included in the model to ensure adequate fit?

A:-->No interactions were evaluated in the models, but it is not unreasonable to think that many of them would appear as significant. As previously mentioned, the main focus of our research was to explore if morbidity groupers can contribute to stratification of patients with cirrhosis. In this regard, our interest has been to keep predictive modelling simple and intuitive.
We understand the question raised by the reviewer. But, we have tried to use clinical criteria in our statistical analysis to avoid overadjustments and generation of spurious interactions that might end up introducing high complexity in the predictive models, thus hindering their interpretation and the message we want to convey--that morbidity groupers are useful for enhancing risk assessment and stratification of patients with cirrhosis. That is why we aimed to quantify the total economic impact of cirrhosis in relation to hepatic decompensation and to determine the distribution of costs in treating patients with this condition.

11.The study was not approved by an Ethics committee. Although there is no risk regarding patient confidentiality, can the authors justify why studies of this type do not require any kind of approval (even e.g. low risk approval). Patient confidentiality is not the only aspect that Ethics committees must consider.

A:-->We had consulted our ethics committee secretary, who informed us that approval was not required under Spanish law. We have clarified this issue in the revised manuscript (page 11, line 13 to 18)

12. Is the prevalence reported on page 12 line 27 a period prevalence or point prevalence? For the whole year of just 31st December. It would be helpful to the reader if the term period prevalence or point prevalence were used.

A:-->Thank you for this suggestion. It's a point prevalence. We have clarified this in the main text (page 20, line 12) .

13.The units for each of the Figures given in Table 3S are unclear. (Stating x100 is also not helpful).

A:--> Sorry. We have corrected this mistake. 3S

14 The limitations of excluding patients that died is not addressed in the discussion. These patients may have contributed considerably to costs. Are the costs therefore an underestimate?

A:-->The patients were not excluded for the evaluation of the overall healthcare expenditure, although they were excluded from the analysis of possible risk factors associated with higher expenditures (see point number 6). This has been clarified in main text (page 19, line 18)

VERSION 2 – REVIEW

REVIEWER	Patrizia Pontisso University of Padua, Italy
REVIEW RETURNED	07-Nov-2017

GENERAL COMMENTS	The Authors have positively addressed the points raised by the reviewer.