

11/6/2018

Dear Editors,

We appreciate an opportunity to revise our manuscript (Manuscript NO: 42713). We reviewed each comment carefully and major revision was made to our manuscript. We believe we made considerable improvement to our manuscript. We thank all comments by peer-reviewers and the Board of editors for the time spent on this manuscript.

Please find response to peer-reviewer's comments in italics for the detail of changes.

This revision was made with all coauthors and all coauthors approved this final form of manuscript. Please see below for the detail of the response. The Copyright agreement form signed by each author remains valid.

Thank you again for your consideration.

Sincerely,

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Reviewer 1 (02860590):

1. Title: The title is long. Could the authors reduce the title and focus on an accurate reflection of the contents of the manuscript.

Thank you for your suggestion. We have now changed the title to shorter one entitled "Temporal Trends of Cirrhosis Associated Conditions."

2. The major limitation of this study consists in considering transjugular intrahepatic portosystemic shunt or TIPS as a complication of cirrhosis. In fact, "transjugular intrahepatic portosystemic shunt (TIPS) is the percutaneous creation of a conduit from the hepatic vein to the portal vein that is used to manage consequences of portal venous hypertension (i.e., variceal hemorrhage and refractory ascites)" (Suhocki PV et al., 2015). Thus, the complications of cirrhosis are, for example, variceal haemorrhage and refractory ascites. Please, clarification should be provided for this matter.

We agree with the Reviewer that the use of the term "complications" to include TIPS is misleading, so we changed the term to "conditions" rather than complications such that the use of TIPS be included in the list of associated conditions.

3. In the sentence "These ICD-9 codes have been validated in literature except HC secondary to viral hepatitis" (page 6, study population). The sentence is generic and the overlapping between acute and chronic complications of hepatopathy could be analyzed together.

Thank you for the suggestions. We analyzed a primary diagnosis related to hospitalizations. Thus, our analysis is based on acute conditions rather than chronic conditions. We added a sentence on page 6 to clarify. We considered to include secondary diagnosis of cirrhosis associated conditions, but we were concerned that this may skew the results, as not all providers list all secondary diagnosis at discharge. Also, some providers include codes if there are

histories of these conditions. For example, if someone is receiving lactulose/rifaximin for hepatic encephalopathy even though this is not the reason the patient is hospitalized, some provider would include this as secondary diagnosis.

4. Did the authors have the careful to evaluate the cases of severe viral acute hepatitis associated with complications such as hepatic encephalopathy? Please, clarification should be provided for this matter.

Thank you for your suggestion. Although we included ICD-9 code with viral hepatitis with hepatic coma to help capture possibly more severe viral acute hepatitis, given the limitation of claims database which often don't have accurate detailed data to help risk stratify the disease severity, we feel that the data don't allow us to accurately account for the impact of severe viral acute hepatitis. We added comments regarding this concern, and we acknowledged the limitation of ICD-9 codes study.

Reviewer 2 (00006208):

Strong points -

There are few studies on the economic burden of complicated liver diseases - Important number of patients studied, evaluation period of more than 10 years -the study includes several complications of cirrhosis not often studied like hepatic encephalopathy -the comparison of virus / non virus complications, especially EH is useful -comparison of hospitalizations costs for cirrhosis complications with all-cause of hospitalization costs, makes it possible to show a relative increase cost of cirrhosis complications

Thank you for pointing out strong points. We greatly appreciate your interest and taking the time to carefully review our manuscript.

Weak points –

1. Purely descriptive study, few attempts to explain the findings. For example, the increased costs targeted to serious EV, EH and SBP complications suggest that hospitalized patients are more severe, more numerous, or that specific treatments are more expensive. To be documented

We agree and appreciate with your suggestion. Our study is limited by the use of aggregate claims data that have limited clinical details. Therefore, we were limited to the descriptive study that could only show aggregate temporal trends. Although we agree with you that those patients can have more severe disease, increasing numbers, or increasing cost related to treatment such as introduction of antiviral agents for hepatitis C, we are afraid that these statements would be assumptions which are not supported by our data. Thus, we tried not to add too much speculative comments in our manuscript without supportive evidence. We humbly request the Reviewer to accept our revised manuscript without making these speculative comments.

2. There is no notion of length of hospital stay, and the design of the study does not allow studying the rehospitalizations following the first severe complication which impacts largely public health costs. This point is important as outpatient management to decrease rehospitalizations may reduce the costs (development of "Alternative models of care to reduce unplanned hospital admissions" (Morales BP, Digestive and Liver Disease 50 (2018) 76-83?) and costs for first severe complications of cirrhosis are just one aspect of the financial burden.

As per length of stay (LOS), we adjusted some of the data based on LOS. We made figure 3 to explain the trends about LOS for ease of visualization. We totally agree with your statement regarding readmission, and we wish we had readmission data. Instead, we presented previously conducted study in HC regarding re-admission rates as we also thought readmission was important part of explanation.

3. Difficult to distinguish what is related to a better accuracy of the coding or to an increase of the epidemiological incidence of the cases

From our study nature, it is not possible to clearly distinguish coding behavior versus increase in actual numbers. We acknowledged this limitation in the manuscript as reporting bias.

4. The impact of costs is seen through the first event and has not been designed to identify readmissions, major causes of additional costs. See point 2°

The data we have access to does not include readmission data and previous studies suggested high re-admission rates. We hope to address this in our future studies.

5. The serious complications of cirrhosis identified are not exhaustive and especially those that impact the prolongation of hospitalization. In particular, the coding used does not identify refractory ascites, an essential complication responsible in itself for prolonged periods of hospitalization (KJ Fagan, Internal Medicine Journal 2014) even if there is a link between unscheduled hospitalization, ascites and infection.

We agree that our list is not inclusive of all complications related to cirrhosis. Due to the nature of NIS database and ICD-9 codes, it is difficult to identify non-specific infection in cirrhosis which is not SBP. Doing this as a secondary diagnosis would lead to double or triple counting of the patients and we will lose accuracy of numbers. Cirrhosis is not the only cause of ascites and getting data for unspecified ascites may leads to counting patients who does not have cirrhosis.

6. One of the temporal modifications observed in the field of EH in connection with viral diseases will be totally modified after 2014 due to new hepatitis C antiviral drugs. Need for a photograph 2014 -2019

We greatly appreciate this insightful comment. *We mentioned this possibility on page 10. Introduction of ICD-10 codes happened in 2015 and HCUP does not provide all the data for 2015 at this point, we cannot add data beyond 2014 at this time. In addition, comparison of ICD-9 and 10 codes would be extremely difficult as coding changed dramatically as ICD-10 codes became more specific.*

7. The time of hospitalization for TIPS should be supported according to the cause: TIPs of rescue or early tips for HD or refractory ascites but obviously one runs up against the limits of the coding (the prognosis of the patients is not the same in the different situations)

We agree with the Reviewer that knowing the clinical indications for TIPS would be helpful to better understand our observation, due to the nature of NIS database and utilization of procedure code for TIPS, it is not possible to distinguish causes. We understand that this is a limitation of our study. We are hoping that our descriptive study can aid future prospective study. We added sentence to limitation section. We humbly request the Reviewer to accept our data as is, with the understanding of our limitation.

8. Also, the declining mortality of HE according to the evolution of practices outside of rifaximin should be discussed?

L-ornithine-L-aspartate use for hepatic encephalopathy has been suggested (Khungar, Clin Liver Dis. 2012;16(2):301), however, this is not a standard of care in the U.S., and rarely used. We are not sure if we can apply this fact to our data. Although we appreciate your comment, we would like to refrain from discussing this topic in our manuscript to maintain our message simpler and less speculative.