

Replies to reviewer comments

Reviewer #1:

The study has included patients of hepatic hydrothorax in cirrhosis of liver. The authors have assessed baseline characteristics including 12-month overall and transplant free survival. I have few comments.

1. The methods should include how pleural fluid analysis was interpreted. The values of SPAG, pleural fluid protein etc should be included as per standard guidelines.

Reply: We have provided the additional detail in the methods section: Pleural or ascitic fluid was sent for analysis at the discretion of the treating team according to indication and specimen viability, and where available, serum pleural ascites gradient (SPAG) or serum ascites albumin gradient (SAAG) values were obtained.

2. Infections are one of the most common cause of acute decompensation in cirrhosis. SBP and SBE are most common sites of infection. Therefore, Patients having spontaneous bacterial empyema on first diagnosis of HH should be given. Additionally, readmissions due to SBE should also be given in results.

Reply: Due to the retrospective nature of the study and the fact that thoracentesis was performed in a variety of locations (including the emergency department, intensive care unit, hospital wards and radiology) by a number of different treating teams, there is significant heterogeneity in pleural fluid analysis depending on what tests were ordered. In addition, some thoracentesis procedures were performed prior to the diagnosis of hepatic hydrothorax being made and thus pleural fluid protein and microscopy/culture/sensitivity were not routinely sent for analysis.

Comprehensive pleural fluid analysis is available for 31% of patients in the study and thus this was not included in the survival analysis. We have added this information to the results section and updated the limitations section of the discussion to include this as a limitation. Spontaneous bacterial empyema was detected in 10 instances of HH requiring admission and this has been added to the results.

3. In patients who had readmissions, compliance to salt restriction, diuretic therapy and adequate follow up should be given to determine whether it was a therapy failure or patient non-compliance which was adding to HH recurrence.

Reply: This is a very good point. Due to the retrospective nature of this study, factors associated with treatment failure or re-hospitalisation were difficult to discern and it is not possible to accurately determine in what percentage of patients non-compliance was a major reason for diuretic inefficacy. Typically major issues with compliance, where ascertained, would be documented in the patient notes however this is not standardised. We have added this to the limitation section of the discussion

Reviewer #2:

Permit me to express my gratitude for giving me the opportunity to review the manuscript entitled "Natural history and outcomes of patients with liver cirrhosis complicated by hepatic hydrothorax" by Romero S. et al. The manuscript deals with a multi-center retrospective cohort study of cirrhotic patients regarding an interesting topic, namely that of hepatic hydrothorax (HH). Interestingly, the authors conclude that smoking and acute kidney injury are of independent prognostic value regarding overall survival in HH. The methodology is sound, while the statistical analysis is adequate. Discussion is clear, and limitations are presented in a comprehensive manner.

Except some minor errors (e.g. Page 12, Line 2: Amend "dose of diuretics used were similar" for "dose of diuretics used was similar"), grammar and syntax are proper.

Under these circumstances, I would propose acceptance for publication as is.

Reply: Thank you for your kind assessment. We have corrected the error mentioned.

Reviewer #3:

1. The author used the Cox proportional hazards regression survival model to analyze the time of onset of HH to death and transplant-free survival, so would it make more sense to use a competing risk model?

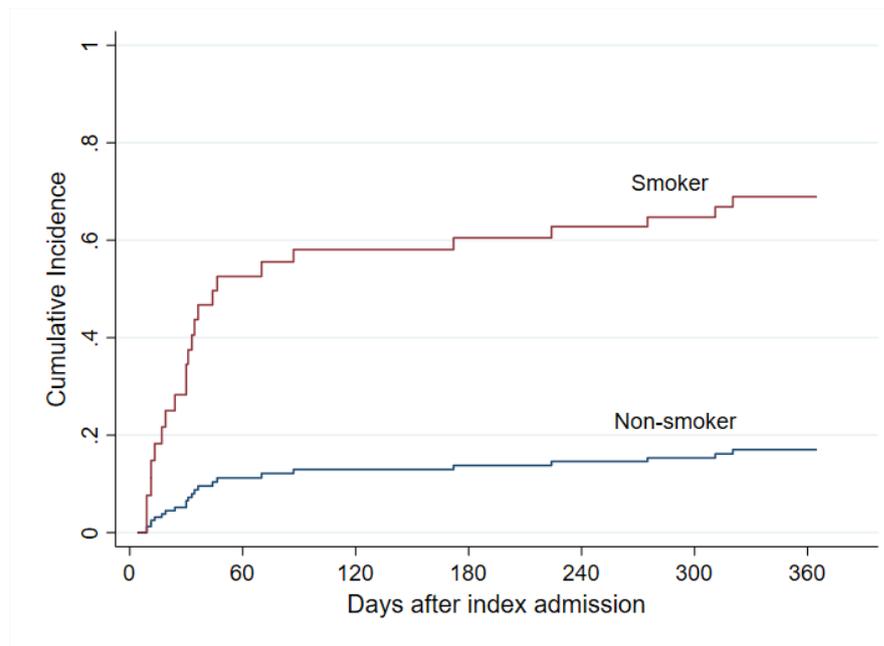
Reply: It is arguable that a competing risks model is superior to a cause-specific Cox regression by which liver transplant events are censored rather than treated as competing events. It is potentially problematic because not all patients in this cohort were on the active transplant waiting list throughout the entire duration of the follow-up period. For this reason, we initially reported both the transplant-censored estimates (overall survival) and the transplant-free estimates (transplantation is considered part of the composite endpoint along with death, rather than a competing event) as summarised in Figure 1.

Nonetheless, if we ran a competing risks (Fine-Gray subdistribution proportional hazards) regression with the same covariates with the assumption that all patients were on the transplant waiting list, the results were similar and the conclusions unchanged.

Smoking subhazard ratio (SHR) = 6.26 (95% CI: 2.75 - 14.3), $p < 0.001$

AKI subhazard ratio (SHR) = 2.60 (95% CI: 1.25 - 5.36), $p = 0.01$

The effect of smoking can be illustrated in the graph below showing the cumulative incidence function from the Fine-Gray analysis. We have included this information as a supplementary figure.



2. The author indicated that “Within 12-months of the index admission, 22 (26%) patients had 1 readmission, 9 (11%) had 2 readmissions, and 12 (14%) had ≥ 3 readmissions.” We surmised that a total of 43 patients had readmission. But then the authors describe “Overall, 63 (75%) patients had at least 1 readmission within 6 months.” what do you mean?

Reply: We apologize, this was a typing error. The reviewer is correct that 43 patients had readmission. We have replaced the previous statement with, “In the 43 patients who required readmission, the median time interval between the index admission and the first readmission was 32 days (IQR, 12-74 days).”

3. Also, author described “a further 62 procedures were performed on 33 of 84 (40%) readmitted patients.” It is rather difficult to understand.

Reply: The original statement was, “Thoracocentesis was performed in 53 of 84 (63.1%) patients during the index admission and a further 62 procedures were performed on 33 of 84 (40%) readmitted patients.” We were attempting to

describe the burden of thoracentesis in this patient cohort. We have replaced the previous statement with, “Thoracentesis was performed in 53 of 84 (63%) patients during the index admission. A further 62 thoracentesis procedures were performed in 33 of 43 patients who required one or more readmissions. On average, the probability of receiving another thoracentesis was 77% during each readmission episode.”

3. The author indicated that “No overall survival benefit from TIPS insertion was demonstrated, but transplant-free survival was higher (hazard ratio, 0.13; 95% CI: 0.02–0.96), as no patient who had TIPS insertion underwent LT.” Could you provide responsiveness after TIPS, there were studies showing that Better clinical response after TIPS were associated with longer survival after TIPS. (Dhanasekaran R, West JK, Gonzales PC, Subramanian R, Parekh S, Spivey JR, Martin LG, Kim HS. Transjugular intrahepatic portosystemic shunt for symptomatic refractory hepatic hydrothorax in patients with cirrhosis. *Am J Gastroenterol*. 2010 Mar;105(3):635-41. pii: ajg2009634. doi: 10.1038/ajg.2009.634. PubMed PMID: 19904245.)

Reply: The study by Dhanasekaran et al suggested better outcomes for those who responded to TIPS. It was an older study (1992 to 2008) of 73 patients who received TIPS. Their 60-day survival from of 78% was similar to ours but their 12-month survival of 48% was much lower than ours despite all patients in their study receiving TIPS. That study also did not include a comparator group (patients who did not receive TIPS), so it was hard to be confident that a similar conclusion can be drawn if mortality of a more contemporary cohort is lower (era effect).

Due to the small number of patients who underwent TIPS in our study (n=10) and the lower overall mortality compared to the report by Dhanasekaran et al, there may be a type 2 error in determining the potential benefit of TIPS on transplant-free survival. Thus, we have added a brief mention of this in the study limitations.

In order to assess if TIPS may have provided clinical benefit apart from survival, we describe the readmissions, thoracentesis, or ascitic drainage procedures in patients who received TIPS. Four patients had a single readmission post-TIPS, of which 3 occurred <30 days and one at 6 months post-TIPS. Thoracentesis was performed in 3 of 4 of these readmitted patients, and ascitic drainage in 1 of 4 of these readmitted patients. Due to these low frequencies and different timing of TIPS, we cannot provide a meaningful statistical comparison with patients who did not have TIPS.

4. Please add references for acute kidney injury.

Reply: We have added the following reference for acute kidney injury and updated the methods section:

Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplements*. 2012;2(1):1-138.

Re-reviewer:

no more comments

Reply: Thanks for your comments.