

## Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-21-2136>

### *Reply to Reviewer A.*

**Comment:** In this letter to the editor, the authors have commented about human albumin treatment. They have well summarized the current concepts and indications of albumin infusion, gave appropriate rationales of their comments. In conclusion, restrictive human albumin infusion strategy might be more reasonable for cirrhotic patients.

**Reply:** Thanks for your comment.

**Changes in the text:** None.

### *Reply to Reviewer B.*

In this letter to the Editor, W Chen and L Zhang attempted to explore the differential impact between restrictive and liberal human albumin (HA) infusion strategies on the clinical outcome of patients with decompensated liver cirrhosis (DLC). By keeping the focus on the RCT by China L et al. [N Engl J Med 2021; 384(9): 808-17], here, the authors identified a high daily dosage of HA infusion and a prone heterogeneity within the liberally treated study population as potential reasons for HA infusion leading to more severe or life-threatening serious adverse events than standard care.

**Minor remarks:**

In further support of their discussion about the HA dose- and/or study population-related outcomes, the authors may choose to consider/mention that

**Comment 1:** the “proper” dose of HA in hepatorenal syndrome treatment has still not been well established [Garcia-Martinez R et al. Hepatology 2013; 58:1836–1846.].

**Reply 1:** Thanks for your comment. You are right that the proper dosage of human albumin hepatorenal syndrome and other complications of liver cirrhosis has still not been well established. We have added the related content in the revised manuscript.

**Changes in the text:** Please see the highlights by yellow in Page 2, Lines 4-5 in the revised manuscript.

**Comment 2:** ideally, central blood volume monitoring (e.g., by the serial measurement of the level of central venous pressure) can help to prevent circulatory overload by optimizing the fluid balance and helping to titrate the dose of HA [Clinical Practice Guidelines for the management of patients with

decompensated cirrhosis; EASL, J Hepatol 2018; 69(2): 406-60)].

**Reply 2:** Thanks for your comment. Your comments are very valuable. We have added these words.

**Changes in the text:** Please see the highlights by yellow in Page 2, Lines 19- 21 in the revised manuscript.

**Comment 3: contradictory findings between 2 RCTs as to the effectiveness of improving circulatory and kidney function by long-term HA administration in patients with DLC are also likely related to different doses of HA and/or the heterogeneity of the study populations. Caraceni P,et al. [Lancet 2018; 391(10138): 2417-29, “already cited by in this manuscript”] vs. Sola E et al. [J Hepatol. 2017;66:S11].**

**Reply 3:** Thanks for your comment. We have added the RCT by Sola E et al. in the revised manuscript.

**Changes in the text:** Please see the highlights by yellow in Page 2, Lines 35-38 in the revised manuscript.

*Reply to Reviewer 3.*

**Comment:** The authors adopted the articles to mention the dose-effect of albumin infusion for liver cirrhosis patients. Some meta-analyses<sup>1,2</sup> related to the time duration of providing albumin; however, the results were not inconsistent. The possible reasons would like to be various on the dose and frequency.

Until now, there was still no comprehensive systematic review or meta-analysis to document the effect on high- doses (3g/dL) and standard- doses (2.5g/dL). The data relating to the albumin and some factors in the health insurance database may be used to examine the outcome of using albumin in the future.

Therefore, I think the issue is important, but I have no confidence totally to agree with the opinion of authors related to the effect of liberal or restrictive Albumin infusion strategy in Liver cirrhosis.

1 Ashour, A. A., Atta, M. A., Sadek, K. W., Obaid, K. R., Ashour, M. A., Ashour, A., ... & ElZouki, A. N. (2021). Albumin administration in patients with decompensated liver cirrhosis: a meta-analytic update. *European Journal of Gastroenterology & Hepatology*, 33(4), 479-486.

2 Sandi, B. B., Leão, G. S., de Mattos, A. A., & de Mattos, Â. Z. (2021). Long-term albumin administration in patients with cirrhosis and ascites: A meta-analysis of randomized controlled trials. *Journal of Gastroenterology and Hepatology*, 36(3), 609-617.

**Reply:** Thanks for your comment. You are right. The time duration of human albumin in cirrhosis and its complications remains controversial. We have added these two meta-

analyses in the revised manuscript. Indeed, we primarily suggested that the effect of human albumin should be dependent upon its dosage and time duration.

**Changes in the text:** Please see the highlights by yellow in Page 2, Lines 4-5 in revision manuscript.