

## Responses to reviewer comments

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### **Retrospective study**

**Title:** The prognostic significance of hepatic encephalopathy in patients with cirrhosis treated with current standards of care

**Authors:** Anuj Bohra<sup>1</sup>, Thomas Worland<sup>1,2</sup>, Samuel Hui<sup>1</sup>, Ryma Terbah<sup>1,2</sup>, Ann Farrell<sup>1</sup>, Marcus Robertson<sup>1,2,3</sup>

<sup>1</sup> Department of Gastroenterology, Monash Health, Clayton, Australia

<sup>2</sup> Department of Gastroenterology, Austin Health, Heidelberg Australia

<sup>3</sup> Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Victoria, Australia

### **Reviewer 1**

**This retrospective study was performed in 3 Australian Centers, and despite being retrospective had a methodology that minimized this problem. One question: Why did the authors included patients with non-HCC neoplasia? Would this inclusion not compromise survival outcomes?**

**Response:** Patients with HCC neoplasia were excluded from the study due to the potential increased risk of HE and the expected decrease in survival outcomes in the absence of a liver transplant.

We elected to include patients with non-HCC neoplasia in the study as in the vast majority of cases the malignancies were stable and/or indolent and unlikely to significantly influence survival outcomes. In addition, we felt including these patients enabled us to analyze a “real-world” cohort of patients with cirrhosis and

hepatic encephalopathy, in which a significant percentage of patients would be expected to have non-HCC malignancy. This is reflected in the patient outcomes whereby in the mean follow-up period only 2% patients had a cause of death related to malignancy and there is no significant difference to the transplant-free survival probability if these patients are removed.

If the editors feel it is more appropriate to exclude patients with non-HCC malignancy we are happy to facilitate this.

### **Reviewer 2**

**We suggest, if possible, to discuss the factors that cause hepatic encephalopathy (HE): are they specific or common with other complication of cirrhosis, as portal hypertension, ascites, etc.? I think that HE represent a multi-factorial complication in the frame of cirrhosis, correlated with an advanced disease. Differently, it could be supposed that HE is a proper metabolic complication, caused by a simple impairment of one or multiple biochemical functions , correlated with a volumetric decrease in liver functioning parenchyma, or with an superimposed external aggression. In this case the test of green indocyanine could be a good prognostic index. This could be useful to better understand the importance of an early diagnosis of HE and of a long-term treatment.**

**Response:** We agree that the factors that cause and/or precipitate HE are very important. In the results section and in Table 3, we have detailed the precipitating factors for the acute episode of HE, which were identified in the majority of cases. In relation to the cause of HE, we have added a paragraph to the discussion highlighted in yellow, emphasizing that HE most commonly occurred in the setting of other complications of decompensated cirrhosis in our cohort, consistent with the reviewer's suggestion. The exact pathophysiology of HE remains controversial; whether HE represents a complication of cirrhosis or an independent metabolic complication is an extremely important topic however it is beyond the scope of this study. In addition, the diagnosis of HE and whether early diagnosis of low-level HE can influence prognosis is a very important clinical question, however our study

design did not enable us to analyze this specifically.