

Reviewer 1:

This manuscript aimed to support the concept that beta-blockers (BB) use in end stage liver disease was not associated with physical frailty. The goal appears to be clear, but there are some concerns that need to be clarified:

1. The acronyms in the abstract should be specified (MELD, BB). Furthermore the aim should be reformulated, adding survival among the objectives. Instead of "...Fatigue and weakness are commonly reported with beta-blocker use in the general population..", the Authors have to focus their attention on "frail phenotype or frailty index", such as cited in the title.

A list of abbreviations has been added to the manuscript and acronyms in the abstract were specified. The aim of the abstract was modified as suggested:

"Aim: To investigate beta-blocker (BB) use in patients with cirrhosis and determine their effects on physical frailty and overall survival."

2. The concepts of "Fatigue and weakness" should be replaced by more appropriate definition of frailty index. The introduction should be focused on frailty phenotype and exhaustion (Targeting Cognitive Frailty: Clinical and Neurobiological Roadmap for a Single Complex Phenotype. J Alzheimers Dis. 2015;47(4):793-813).

We have revised the manuscript so that the concepts of fatigue and weakness are used to report the side of beta-blockers, but that the aim of our analysis was to evaluate the association between beta-blockers and physical frailty.

Furthermore, we have revised the introduction of the manuscript to focus initially on physical frailty and how the investigation of the common side effects of beta-blockers might be particularly relevant to patients with frailty and cirrhosis. The introductory paragraph of our manuscript is now:

"Physical frailty is reported to be prevalent in patients with cirrhosis and has emerged as a critical determinant of outcomes in this population^[1-3]. Resulting from the loss of homeostatic balance of multiple physiologic systems including (but not limited to) musculoskeletal, inflammatory, endocrine, and neurocognitive, physical frailty has been operationalized using standardized instruments that measure multiple domains such as fatigue, weakness, slowness, weight loss, and low activity^[4]. Two of these physical frailty components, fatigue and weakness, overlap with the frequent side effects of non-selective beta-blockers."

3. The work lacks of an adequate background concerning the role of nonselective beta-blockers in cirrhotic patients with ascites; however, definitive evidence in this regard is still lacking; furthermore references should be updated (Curr Treat Options Gastroenterol. 2018 Jun;16(2):215-225. doi: 10.1007/s11938-018-0179-x. Frailty in Patients With Cirrhosis)

We have enhanced our introduction with the following sentence that also includes this updated reference:

“More recently, investigators have hypothesized that a “therapeutic window” exists during which a patient with cirrhosis might benefit from beta-blocker therapy for variceal prevention, with a patient losing benefit once they develop refractory ascites^[6, 7].”

4. The clinical description of the sample lacks of illness’s duration. The great debate about this topic led to an interesting “window hypothesis” for beta-blocker therapy, in which Krag et al. proposed that beta-blockers improve survival within only a narrow window in the natural history of cirrhosis and are either ineffective or harmful outside of this window (The window hypothesis: haemodynamic and non-haemodynamic effects of betablockers improve survival of patients with cirrhosis during a window in the disease. Gut. 2012;61:967–969)

Given the cross-sectional nature of this study, we only have information on beta-blocker use and the patient’s disease severity at a single time point. However, to investigate the Reviewer’s point in the best way that we could – particularly with respect to the window hypothesis – we considered the proportion of patients with refractory ascites. Only 3% of our cohort had refractory ascites, which provides evidence in support of the window hypothesis – perhaps our finding that beta-blocker use was associated with decreased risk of waitlist mortality was related to the fact that the vast majority of patients in our cohort were within their “therapeutic window”.

We have addressed both of these points in the Discussion section:

“ Since this was a cross-sectional study, we were only able to ascertain beta-blocker use at a single visit, but recognize that beta-blocker prescription could have changed during the course of the patient’s time on the waitlist.”

“The fact that the vast majority of our cohort did not have refractory ascites supports the concept of a “therapeutic window” for benefit of beta-blockers on mortality in patients with cirrhosis^[7].”

5. No reference was cited about dietary patterns.

We apologize in advance – but we must request clarification from the Reviewer regarding this comment, as it is not clear where we referenced dietary patterns in this manuscript.

Reviewer 2:

Kuo et al. have investigated beta blocker (BB) side effects on physical frailty in patients with cirrhosis. They found BB use was not associated with increased odds of frailty, exhaustion, or low physical activity. BB use was, however, significantly associated with a decreased adjusted risk of mortality. Thus, they claimed BB should not deter their utilization when indicated in patients with cirrhosis. This manuscript was interesting in general and well written.

Major comments are as below:

1. The authors dichotomize patients into BB users and non-users. The dose dependent effects should be investigated or discussed.

We agree that it would be interesting to investigate if there were dose dependent effects and we have added this analysis to the results section for the non-selective beta-blockers:

“There was no association between physical frailty and each unit increase in dosing of either propranolol [OR 1.00 (95% CI: 0.98-1.02)] or nadolol [OR 0.99 (95% CI: 0.92-1.08)].”

2. In considering recent debates on the BB usage in decompensated cirrhosis, the BB effects should be investigated or discussed in terms of severity of liver cirrhosis.

To address this point, we have added the following statements to the Discussion:

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“The fact that the vast majority of our cohort did not have refractory ascites supports the concept of a “therapeutic window” for benefit of beta-blockers on mortality in patients with cirrhosis^[7].”