

Peer Review File

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Reviewer A:

The authors aim to develop a novel frailty index in cirrhosis. Their results indicated that Frailty Index, which is a modification of Carolina Frailty Index, may predict 2-year mortality and exhibit superior predictive ability in combination with CTP compared with CTP alone. They also identified several key determinants of proposed novel Frailty Index. However, several issues should be exploited as following:

1. The manuscript needs further English editing since some phrases and sentences are confusing. For instance, Page 4 line 53, “It is similar to the well-described state of”; Page 5 line 68, “missing data more than 26-items”; Page 8 line 116 “(both robust and pre-frail are non-frail)”; Page 10 line 134 “(AUC)”; Page 14 line 199 “Complex potential mechanisms driving fall risk in cirrhosis as follows:” etc.

Reply: We appreciate the informative comments and have substantially revised our original manuscript. We believe phrases and sentences used in the revised manuscript have improved. Please check for our improvement.

2. Page 4 line 50, the author should state the shortcoming of existing frailty index, such as FFC or SPPB, if possible.

Reply: The Fried Frailty Criteria (FFC) uses five criteria to determine the level of frailty: weight loss, exhaustion, low physical activity, slowness, and weakness. The first three criteria are measured with self-report questions, while slowness and weakness are assessed with the performance-based measures of walk time and handgrip strength. A recent review showed a dramatical variation in how these criteria are assessed between studies (Theou et al. Ageing Research Reviews. 2015; 21:78–94). These differences cause variations in frailty prevalence estimates and

predictive ability (Drey et al. Gerontology. 2011; 57(1): 11-18). When screening large populations, performance-based measures can be difficult to conduct because they are time consuming and costly, and often require well-trained assessors. Therefore, many researchers use questionnaires or a single question instead of performance-based measures. (Page 6 line 74-82)

3. It should be normative regarding the use of “health defect” or “health deficit” across the manuscript.

Reply: We appreciate the informative comments and we have standardized the phrase to “health deficit”. Please check for our correction. (Page 4 line 41)

4. Page 6 line 77, Carolina Frailty Index should be expressed in its abbreviation form.

Reply: We appreciate the informative comments and we have changed the Carolina Frailty Index to CFI. (Page 9 line 112)

5. Page 9 line 129, that author should specify the median survival of cirrhosis in frail and non-frail group.

Reply: We appreciate the informative comments. The Kaplan-Meier survival curves (Figure 2) showed significant distinction in 2-year mortality between frail and non-frail group ($p = 0.001$), however the median survival is not available, because the mortality is less than 50%.

6. The Discussion section should be re-organized according to the main findings of current manuscript. Notably, Page 11 line 158-162 preferentially move to the very beginning of Discussion section.

Reply: We appreciate the informative comments and we have moved these sentences to the beginning of Discussion section. (Page 13 line 190)

7. Page 11 line 158, “physical strength” is better changed to “physical frailty

components”.

Reply: We appreciate the informative comments and have changed “physical strength” to “physical frailty components”. (Page 14 line 193)

8. Page 11 line 162-168 should be removed, since no relevant results have been addressed.

Reply: We appreciate the informative comments and have removed these sentences.

9. Page 13 line 185, the phrase “there is always nothing they can do to reverse their MELD or CTP score” is confusing, please improve the statement and adding reference if applicable.

Reply: The MELD and CTP scores focus on physiological parameters which are calculated through creatinine, bilirubin and other indicators, while no effective ways are always anticipated to reverse MELD or CTP score. On contrast, frailty may be a modifiable risk factor that could respond to the intensive nutritional support and exercise. Please check for indicative references as follows: Laube et al. Liver Int. 2018; 38: 2117– 28. (Page 16 line 227-230)

10. Page 20 line 301, non-frail and frail group are supposed to be defined in detail.

Reply: We appreciate the informative comments and have added the sentence of “we defined the Frailty Index that less than 0.07 as robust, 0.07-0.38 as pre-frail and more than 0.38 as frail, we classified robust and pre-frail as non-frail phenotype for analytic convenience”. (Page 25 line 361)

11. All the titles of tables should be given out of the table frame.

Reply: The raised comments are really appreciated. We have changed all of the tables.

12. The title of Table 3 should be “Univariate and multivariate analysis to predict 2-Yr mortality in cirrhosis”

Reply: The raised comments are really appreciated. We have changed this title to “Univariate and multivariate analysis to predict 2-Yr mortality in cirrhosis” in the Table 3.

Reviewer B:

Frailty occurs commonly in cirrhotic patients, and several researchers have explored its role in predicting the short-term prognosis of patients. In the present study, the authors reported a self-reported frailty index and its association with short and intermediate term mortality of cirrhotic patients, which provide some novel and helpful information. However, several questions regarding the manuscript need to be further clarified:

1. It would be better the authors provided the duration of liver cirrhosis and presence of esophagogastric varices bleeding upon presentation, as they may be a influence factor of mortality.

Reply: We really appreciate the precious comments and suggestions from the reviewer. We understand that the duration of liver cirrhosis may be an influential factor of mortality, however some patients may not go to the hospital for the diagnosis of cirrhosis until they develop into decompensated cirrhosis such, so the duration of cirrhosis may be inaccurate. In addition, we have analyzed the complications of cirrhosis, it suggested that there are no statistical difference in esophagogastric variceal hemorrhage between the alive and deceased groups ($p>0.05$) (Table 1).

2. Was there any association between frailty index and MELD/CHILD-PUGH Score?

Reply: Scores such as the MELD and CTP can assist prognostication, yet by focusing on physiological parameters they fail to completely capture the elements contributing to a patient's clinical status. Mounting evidence has supported an important role of physical functioning in patient outcomes. Frailty has been increasingly recognized in medical literature over recent years, including in hepatology where it is identified in nearly half of cirrhotic patients. It is a complex construct consisting of multi-systemic

physiological decline and increased vulnerability to stressors. In our study, we build two multivariate models to analyze the independent risk factors for 2-year mortality in cirrhosis. The results showed that Frailty Index and CTP (model 1), Frailty Index and MELD (model 2) are independent risk factors, it seems that Frailty Index is characterized differently from CTP and MELD.

3. Several spell errors are there, for example, Page Line 55 "hereafter" should be "thereafter", etc.

Reply: We appreciate the informative comments and have revised our original manuscript. We believe phrases and sentences used in the revised manuscript have improved. (Page 7 line 90)

4. Line 133, the authors should clarify "In univariate analysis, Frailty Index was an independent risk factor", a risk for what? 90-day, 1-year or 2-year mortality?

Reply: We really appreciate the informative comments from the reviewer. We have changed this sentence to "In univariate analysis, Frailty Index was an independent risk factor for 2-year mortality in cirrhosis". (Page 12 line 170)