Format for ANSWERING REVIEWERS

October 24, 2023

Dear Editors,

On behalf of all the authors, I would like to thank you for your consideration of this paper. In the revised manuscript you will find the changes that we made in response to the Reviewers. In this response to reviewer letter we also indicated how we have dealt with the Reviewers' comments.

Please find enclosed the edited manuscript in Word format.

Name of Journal: World Journal of Hepatology

Manuscript NO:

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Perioperative score for elderly patients with resectable hepatocellular carcinoma

Maria Conticchio, Riccardo Inchingolo, Antonella Delvecchio, Francesca Ratti, Maximiliano Gelli, Massimiliano Ferdinando Anelli, Alexis Laurent, Giulio Cesare Vitali, Paolo Magistri, Giacomo Assirati, Emanuele Felli, Taiga Wakabayashi, Patrick Pessaux, Tullio Piardi, Fabrizio di Benedetto, Nicola de'Angelis, Javier Briceño, Antonio Rampoldi, Renè Adam, Daniel Cherqui, Luca Antonio Aldrighetti, Riccardo Memeo

Invited Manuscript: 03358964

The manuscript has been improved according to the suggestions of reviewers and Editorial Office's

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: Thank you for the opportunity to review this manuscript. The paper is about a proporsal for a risk score based on perioperative risk factors associated with 90 and 180-day mortality in elderly patients with HCC who were elegible for liver resection. This multi-center study

provides an insight in a fragile and specific population where surgeons should pay special attention to past medical history, size of the largest HCC and the use of MELD score. Kindly find my comments below:

1. Major revision:

- Although not an strict criteria to select the number of variables to include in a given model, 4 risk factors were finally included in the logistic regression model and 20 events occurred. I suggest the authors should explain how overfitting influences their study.

A: The statistical method chosen to underline possible variables which influenced he 20 events included the associations between baseline pre-operative variables with six-month mortality were evaluated using a univariate Cox proportional-hazards model. A score point system was derived from the multivariable Cox proportional-hazards model including univariate predictors with $p<0.05$. For a dichotomous risk factor, the estimated regression coefficient was rounded to the nearest integer. For a non-dichotomous risk factor, continuous or discrete, the estimated regression coefficient was multiplied by observed values, rounded to the nearest integer and rescaled to assign zero points to the lowest risk-category. Hazard Ratios (HRs) with their 95% confidence intervals (CI) were reported. The discriminative ability of the models was assessed using the Harrell's concordance index (C-index

- The paper states that ASA and comorbidity >2 are risk factors for mortality. However, ASA inherently is a measure of the overall health status of the patient where comorbidity(ies) can be compensated or not. I recommend to check for multicollinearity. Can the authors clarify how they approached this potential overlap in their analysis?

A:

- In Figure 2. The curves show significant AUC for the risk groups, however the p-value is pooled. I suggest to present results pairwise.

A: figure 2 came from our statistical program which followed the previous analysis. Then it results less understandable otherwise.

- In the Study design section, size of lesion, was it measured using CT scan/ MRI or pathology report? I would consider explaining in detail the source of the data.

A: ''calculated on the preoperative imaging''

Minor revision:

- In the Introduction section: "Liver resection represented the mainstay treatment in resectable HCC". Liver resection, ablation and liver transplant are still the mainstay treatments for HCC according to current guidelines and specific case scenarios.

A: corrected in the text

- In the Discussion section: " 'Up to 7 criteria´after, more usefull...". The correct spelling would be useful.

A: corrected in the text

- Table 2. the variable Sizeofbiggestle~m should say "Size of largest lesion (mm, cm)"

A: corrected

- In Table 3. Score point system: Comorbidity>2 Values (Sí) it should say (Yes).

A: corrected

Some questions for the authors:

- Would you suggest to other therapeutic approaches like I want to commend the authors for their important contribution to the HPB field. With this paper I consider many answers raised on whether operate an elderly patient can tolerate surgery and approach to a near-zero mortality can be achieved. Thank you again for the opportunity to review this paper.

A: thank you for the suggestions

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. The authors collected data of 11 hepato-biliary centers during a 10-years period. A multicentric, retrospective study was performed in the HCC resection patients aged 70years or older. The topic is interesting, but the writing is poor.

2. The analysis found that ASA score, high rate of comorbidities, MELD score and size of biggest lesion had independent correlations with increased 90- and 180-day mortality

3. Preoperative clinical index in Methods and Materials and Results should be indicated in addition to diagnosis criteria and detection methods which should be unified in different centers

A: unfortunately the multicenter nature or this work does not allow to erform preoperative clinical index

4. There are spelling errors in the manuscript and Tables 1 to 3, "Up to7 criteria'24 after", "more usefull in the context of liver transplantation", "Sizeofbiggestle~m", "There were several predictive of 30d mortality after liver resection for HCC11,12,13,14,15....Conversely Lee et al in a nationwide cohort study recognized the PALBI score had an higher sensitivity and specificity than MELD or ALBI score16."

A: corrected in the text

5. All abbreviations are not marked in full name in the manuscript and Tables, ALAT? OH? Major HTC? CHILD A? B? C? OH? I did not find the Figures legend.

A: corrected

6. The analyses were conducted using STATA software. It seemed not sufficient to draw the conclusion. It should better to try the R software.

A: unfortunately our statistician does not work with R software, even if we know it work better for this kind of analysis

Finally, we wish to thank the Editors and the Reviewer for their comments that helped us to increase

the value of our paper.

Thank you again for publishing our manuscript in the *World Journal of Hepatology*

Sincerely yours,

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