Rebuttal Letter

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This research is on the leveraging machine learning for early recurrence prediction in hepatocellular carcinoma: a step towards precision medicine. This study is innovative, and may have certain value in the early recurrence of hepatocellular carcinoma after surgery. The model's ability to stratify risk facilitates targeted postoperative strategies, showcasing its potential as a guide for personalized patient care. The limitations to this study include selection bias as the cohort of patients largely had liver disease secondary to hepatitis B, which leaves a large space to question the applicability of these outcomes to other aetiologies of liver disease. In the follow-up study, whether there is a better method to reduce this selection bias and predict the recurrence factors of hepatocellular carcinoma of different etiologies? For this study, are there any relevant diagrams to help clarify the construction of the model? Could you clarify the inclusion and exclusion criteria and clinical application conditions of this study in more detail?

Response:

To the first point raised: "In the follow-up study, whether there is a better method to reduce this selection bias and predict the recurrence factors of hepatocellular carcinoma of different etiologies?"

Further studies will need to be conducted with the RSF model using patients of different aetiologies of liver disease to validate its use across different demographics in predicting HCC recurrence and reduce selection bias.

To the second point raised: "Could you clarify the inclusion and exclusion criteria and clinical application conditions of this study in more detail?"

Out of 5,686 HCC patients undergoing curative resection at Eastern Hepatobiliary Surgery Hospital (January 2008 to December 2015), 4,376 met inclusion criteria. The inclusion criteria were patients with Child-Pugh A cirrhosis or B7 liver function, No extrahepatic metastases, and complete resection of macroscopic tumour with histological evidence of tumour free margins. Exclusions (n=1,310) were due to preoperative anticancer treatment, history of other malignancies, palliative surgery, loss to follow up within 2 months of surgery, and perioperative death. The training cohort comprised 3,370 patients (January 2008 to December 2013), internal validation cohort 1,006 patients (January 2014 to December 2015), and external validation cohort 382 patients from Mengchao Hepatobiliary Hospital of Fujian Medical University.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Dear Authors, Excellent editorial, kindly improve on these points : 1. How the Machine learning model was trained and how it's sensitivity, specificity and predictive value was objectively measured? 2. Make a tabulated format of difference between Random Survival Forest vs Cox Proportional Hazard mode for Hepatocellular Carcinoma. 3. Add few lines on the future role of AI in evaluating hepatic diseases. Thanks

To the first point raised: "How the Machine learning model was trained and how it's sensitivity, specificity and predictive value was objectively measured?"

The RSF model was constructed and used as a regression algorithm with faster training and lower estimation bias. This was achieved by using techniques of random forests such as feature and sample bragging. The model was constructed using fifteen factors including age, gender, aetiology, platelet count, albumin, total

bilirubin, alpha-fetoprotein, tumour size, tumour number, microvascular invasion, macrovascular invasion, Edmondson-Steiner grade, tumour capsular, satellite nodules and liver cirrhosis. As 200 survival trees were built, the prediction error was significantly low and at 500 trees constructed, the variable importance (VIMP) for all 15 features was also generated. Utilizing cut-off values (50th and 85th centiles) from the training cohort's risk index, RSF classified patients into low-risk, intermediate-risk, and high-risk groups, providing valuable insights for postoperative follow-up and adjuvant therapy. Kaplan-Meier analysis validated the stratification in all cohorts (P<0.0001). (Figure 1)

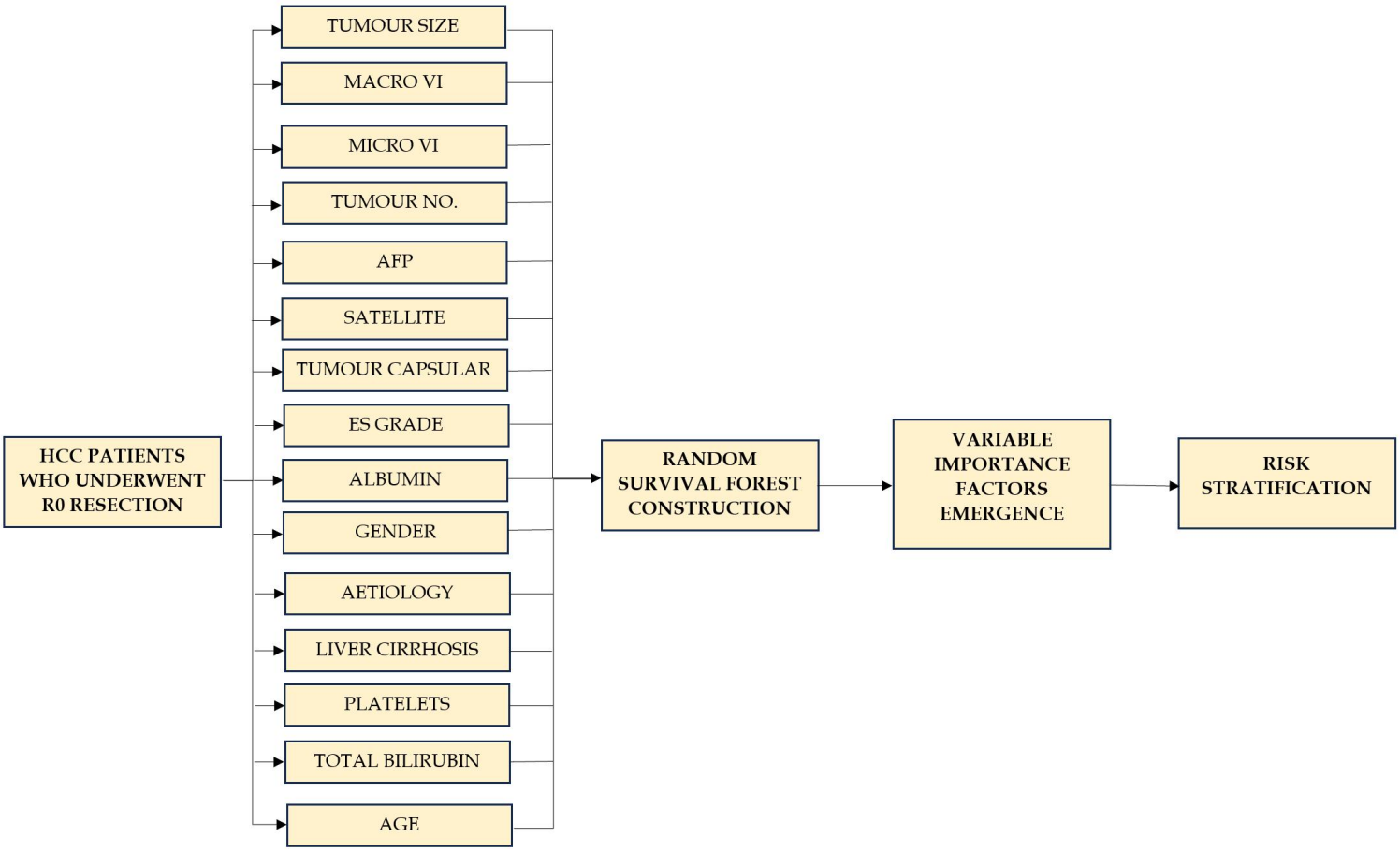

Figure 1: 15 factors used to construct RSF model in HCC patients who underwent R0 resection with variable importance factors emergence and risk stratification applied.

To the second point: "Make a tabulated format of difference between Random Survival Forest vs Cox Proportional Hazard mode for Hepatocellular Carcinoma."

Model performance was assessed across several methods including model discrimination, model calibration, clinical usefulness and overall performance. In training, internal, and external validation cohorts, RSF outperformed existing models with C-index values of 0.725, 0.762, and 0.747, respectively. Overall performance time-dependent Brier (2 years) were 0.147, 0.129, and 0.156. RSF excelled against ERASL model, Korean model, AJCC TNM stage, BCLC stage, and Chinese stage. Decision curve analysis (DCA) affirmed RSF's superior net benefit over other models. (Table 1)

Performance	**Cohort**	**RSF**	**ERASL**	**Korean**	**AJCC TNM**	**BCLC**	**Chinese**
Model Discrimination: (Harrell's C-Index)	Training	0.725	0.706	0.658	0.674	0.635	0.684
	Internal	0.762	0.726	0.672	0.711	0.646	0.709
	External	0.747	0.727	0.722	0.711	0.658	0.696
Overall Performance: Time-dependent Brier (2 years)	Training	0.147	0.156	0.174	0.160	0.167	0.161
	Internal	0.129	0.143	0.159	0.144	0.154	0.146
	External	0.156	0.162	0.161	0.169	0.180	0.176
Clinical Usefulness: Net benefit at threshold 50%	Training	0.166	0.154	0.093	0.139	0.137	0.137
	Internal	0.121	0.092	0.041	0.095	0.073	0.073
	External	0.206	0.190	0.222	0.185	0.154	0.154

Table 1: Comparison of RSF model performance vs. 5 other models following Cox proportional hazard (CPH) format to predict early recurrence.

Utilizing cut-off values (50th and 85th centiles) from the training cohort's risk index, RSF classified patients into low-risk, intermediate-risk, and high-risk groups. Kaplan-Meier analysis validated the stratification in all cohorts ($P<0.0001$).

To the third point raised: "Add few lines on the future role of AI in evaluating hepatic diseases":

The future role of artificial intelligence (AI) in evaluating hepatic diseases holds tremendous promise for revolutionizing diagnostic and treatment approaches. AI technologies, particularly machine learning algorithms, can analyze vast amounts of medical data, including imaging studies, laboratory results, and patient histories, to identify patterns and subtle anomalies that may escape the human eye. In hepatic diseases, AI can play a crucial role in early detection, risk assessment, and personalized treatment planning. Advanced imaging techniques, such as MRI and CT scans, can be enhanced by AI algorithms to provide more accurate and timely diagnoses of liver conditions. Machine learning models can also predict disease progression, helping healthcare professionals tailor interventions based on individual patient profiles.

(1) Science editor:

1 Scientific classification: Grade B and Grade B. 2 Language classification: Grade B and Grade B. 3 Specific comments: (1) Please provide the Language certificate. The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240. (2) Please add the author's contribution section. The format of this section will be as follows: Author contributions: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; Wang CL, Liang L and Fu JF wrote the paper. 4 Recommendation: Conditional acceptance.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade B (Very good)

To the first point raised: "Please provide the Language certificate. The English-language grammatical presentation needs to be improved to a certain extent. There

are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend"

Please note that this editorial was written entirely by native English language speakers.

To the second point raised: "Please add the author's contribution section. The format of this section will be as follows: Author contributions: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; Wang CL, Liang L and Fu JF wrote the paper."

Author Contributions: Ravikulan A and Rostami R reviewed paper and wrote editorial.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a table/figure (medical imaging) to the manuscript. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving

the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/, or visit PubMed at

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All articles cited in this editorial are PubMed indexed (PMID provided) and a literary search conducted on the keywords provided (Machine learning; Artificial intelligence; Hepatocellular carcinoma; Hepatology; Early recurrence; Liver resection) were initially used to form the basis of this editorial along with the paper it appraises.