Elsevier Editorial System(tm) for Journal of Hepatology

Manuscript Draft

Manuscript Number: JHEPAT-D-18-02163

Title: Reply to Correspondence Concerning Models For Prediction Of Early Recurrence of HCC After Surgical Resection Of Hepatocellular Carcinoma

Article Type: Letter to the Editor

Corresponding Author: Professor Philip James Johnson,

Corresponding Author's Institution: University of Liverpool

First Author: Anthony W.H. Chan, FRCPA

Order of Authors: Anthony W.H. Chan, FRCPA; Sarah Berhane; Alessandro Cucchetti; Philip J Johnson

24th November 2018

Prof. Rajiv Jalan

Editor-in-Chief

Journal of Hepatology

Dear Prof. Jalan,

On behalf of all co-authors, we would like to submit a reply letter entitled "Reply to Correspondence Concerning Models For Prediction Of Early Recurrence of HCC After Surgical Resection Of Hepatocellular Carcinoma" to respond *four* Letters to the Editors commenting our recent paper concerning early recurrence after resection of Hepatocellular Carcinoma (HCC) (J Hepatol. 2018 Dec;69(6):1284-1293. doi: 10.1016/j.jhep.2018.08.027). Those four letters include

1. "Time to Recurrence, But Not Recurrence-free Survival, Should Be the Endpoint of Predicting Early Recurrence after HCC Resection" (JHEPAT-D-18-01944) by Wen-Tao Yan et al.
2. "Predicting early hepatocellular carcinoma recurrence after resection: a comment for moving forward" (JHEPAT-D-18-01803R1) by Xiao-Ying Zhang et al.
3. "Toward the universal scoring system in treatment for patients with hepatocellular carcinoma" (JHEPAT-D-18-01939) by Jiro Kusakabe et al.
4. "Factors Predicting Early Recurrence After Surgical Resection of Hepatocellular Carcinoma" (JHEPAT-D-18-01989) by Yao-Ming Zhang et al.

Thank you for your attention.

Yours sincerely,

Philip J Johnson, MD, FRCP

Professor in Translational Oncology

Institute of Translational Medicine

Department of Clinical Cancer Medicine

University of Liverpool

Reply to Correspondence Concerning Models For Prediction Of Early Recurrence of HCC After Surgical Resection Of Hepatocellular Carcinoma

Anthony W.H. Chan[1]

Sarah Berhane[2]

Alessandro Cucchetti[3]

Philip J. Johnson[4]

1. Department of Anatomical and Cellular Pathology, State Key Laboratory of Translational Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong
2. Department of Biostatistics, University of Liverpool, United Kingdom
3. Department of Medical and Surgical Sciences, University of Bologna, Italy
4. Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom

We are grateful to your correspondents [1-4] for their interest in, and comment on, our recent paper concerning early recurrence after resection of Hepatocellular Carcinoma (HCC).[5]

As Royston et al., have pointed out 'Surprisingly, there is no widely agreed approach to building a multivariable prognostic model from a set of candidate predictors'.[6] In building our prognostic models we have two guiding principles. Firstly, those variables involved should be readily available in all centers treating patients with HCC. Secondly, again as emphasized by Royston et al., the models should be 'transportable' 'i.e. broadly, if not universally, applicable'. To achieve these criteria, we need large cohorts from multiple centers, worldwide. With these two principles in mind we had to be pragmatic both in the variables used to develop the models and the datasets available to us for analysis. Thus, the price to pay, in most cases, for the large numbers is that we have to accept those cohorts that have already been collected. We are not in a position to specify exactly what variables are in the cohort, and we acknowledge that this not ideal. We are pursuing prospective studies to validate our models and collect other relevant variables not included in the original study.

The variables entering the final models

Like Zhang X.Y. et al., and Zhang Y.M. et al.,[3, 4] we found it surprising that macrovascular invasion (MaVI), a well-described risk factor for early recurrence after resection, was not in our final models. Had we considered MaVI in isolation (i.e. just in a univariate analysis), MaVI *was* a risk factor (HR 3.306, P<0.001). However, it was not an *independent* predictor in the multivariable analyses, a finding in agreement with other authors.[7, 8] When all identified risk factors are considered in a multivariable model, the presence or absence of MaVI does not add to the predictive utility of our model. Indeed, if we rebuild the model but exclude any one of the significant parameters (male gender, multiple tumors, tumor size or

AFP, except ALBI) then MaVI *does* enter the model.

Zhang Y.M. et al. questioned the high figure for microvascular invasion (MiVI) in the US series.[4] In our study we assumed that all patients with MaVI also had MiVI. We have confirmed the figures in the US series. The rate of MiVI in resected specimen was 44.6% (similar to that in Italy, 49.5%) and 28.6% for MaVI, giving the figure reported in Table 1 of 73.1%.

With regards to the inclusion of gender into our models,[4] we can only report what the analysis showed and recognize that multivariable models only relate to statistical associations and offer no insight into the underlying mechanism of the factors identified. In fact, Shim et al. also demonstrated that male gender was an independent risk factor associated with early recurrence in their cohort of 1085 patients.[8] Although it is unclear why male patients are prone to early recurrence, they may have more aggressive HCCs than female patients.[9]

Kusakabe et al. expressed concern that certain variables were excluded.[1] We have examined the effect of excluding the variables ALT, ALP, INR and positive margin on the performance of the ERASL-pre and ERASL-post models. Although the excluded variables modestly improved the fit of the model (LR test, P=0.0121 and P=0.0102), there was no further improvement in the survival prediction, as measured by Harrell's C index (P=0.064 and P=0.060). There was also no added enhancement in survival prediction when both models were rebuilt with the excluded variables added back in (P=0.107 and P=0.161).

All the variables in our study refer to the pre-operative assessment apart from MiVI which was only available after histological examination of the resected tumor and is only involved

in the post-operative model. We acknowledge that more accurate information about tumor size, number and MaVI might be forthcoming after visual inspection of the liver at the time of operation, but doubt that any changes will have a major impact on the model performance.

Issues surrounding the ALBI score

The ALBI score is an evidence-based and extensively validated refinement/simplification of the Child-Pugh score (CPS).[10, 11] Its performance is at least as good or, more often, better than the CPS.[12] Yan et al.,[2] expressed surprise that ALBI, a measure of liver function, entered our early recurrence models since liver function is usually considered to be a factor influencing *long term survival* after HCC resection and indeed we have previously confirmed this in relation to ALBI.[13] Hsu et al., also reported, in a study of over 1900 patients undergoing resection, that ALBI was an independent factor associated with early recurrence.[14] Why this should be so must remain speculative, but one possibility is that a fraction of 'early recurrences' may actually be 'de novo' tumor. Such cases might be expected to occur more frequently in patients with poor liver function in more advanced underlying chronic liver disease.

We acknowledge that, in principle, it is preferable to consider continuous variables in their continuous form rather than after categorization. In the event however, replacing the ALBI grade with the ALBI score did not improve the survival prediction of the model: ERASL-pre,(P=0.716 and P=0.422 respectively) and ERASL-post,(P=0.644 and P=0.913 respectively).

Again, a case for applying albumin and bilirubin as separate parameters in developing our models can be made. However, such an approach risks losing the conceptual basis of the

score as a measure of liver function and the same issue would arise in applying any composite score (e.g. CPS or tumor stage) in a multivariable model.

Issues concerning early deaths

A small percentage of patients (<10%) died before their recurrence status was known. In our study, that aimed to predict recurrence within the first two years of resection, we censored all deaths within this period. We believe this was the correct procedure but acknowledge, as Yan et al.,[2] point out, that this approach would be more appropriately labelled as 'time to recurrence' rather than 'recurrence free survival'.

Might the models suggest which sub-group of HCC patients would benefit from transplantation rather than resection?

As noted by Kusakabe et al.,[1] it is likely that at least those in the high risk ERASL group, would do better with transplantation although it will be difficult to design a study to formally predict the optimal potentially curative treatment. We have already shown that the 'cure fraction' after transplantation for HCC is 74.1% compared to only 24.1% in the cases undergoing resection.[15] In the near future we hope to be able to add a figure for 'likelihood of cure' at the individual patient level, to the ERASL model.

Conclusion

It is inventible that different researchers using different datasets and different statistical methodologies will arrive at different prognostic models. Like Kusakabe et al.,[1] we are aiming to develop an overarching model for HCC. To this end we have collected a database of around 150,000 cases with detailed clinical data and are starting to apply machine learning and artificial intelligence in addition to conventional statistical methodology. The only way to

arrive at a comprehensive and consistent model will be through large collaborative projects involving high quality datasets, preferably prospectively-collected. We hope the present study, and the lessons learnt therefrom, will be a significant step in the right direction.

References

[1] Kusakabe J, Firl DJ, Sasaki K. Toward the universal scoring system in treatment for patients with hepatocellular carcinoma. J Hepatol 2018.

[2] Yan WT, Quan B, Xing H, Wu MC, Yang T. Time to Recurrence, But Not Recurrence-free Survival, Should Be the Endpoint of Predicting Early Recurrence after HCC Resection. J Hepatol 2018.

[3] Zhang XY, Ou J, Chen JY, Li WW. Predicting early hepatocellular carcinoma recurrence after resection: a comment for moving forward. J Hepatol 2018.

[4] Zhang YM, Zhou ZT, Liu GM. Factors Predicting Early Recurrence After Surgical Resection of Hepatocellular Carcinoma. J Hepatol 2018.

[5] Chan AWH, Zhong J, Berhane S, Toyoda H, Cucchetti A, Shi K, et al. Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J Hepatol 2018;69:1284-1293.

[6] Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. BMJ 2009;338:b604.

[7] Huang S, Huang GQ, Zhu GQ, Liu WY, You J, Shi KQ, et al. Establishment and Validation of SSCLIP Scoring System to Estimate Survival in Hepatocellular Carcinoma Patients Who Received Curative Liver Resection. PLoS One 2015;10:e0129000.

[8] Shim JH, Jun MJ, Han S, Lee YJ, Lee SG, Kim KM, et al. Prognostic nomograms for prediction of recurrence and survival after curative liver resection for hepatocellular carcinoma. Ann Surg 2015;261:939-946.

[9] Yang D, Hanna DL, Usher J, LoCoco J, Chaudhari P, Lenz HJ, et al. Impact of sex on the survival of patients with hepatocellular carcinoma: a Surveillance, Epidemiology, and End Results analysis. Cancer 2014;120:3707-3716.

[10] Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550-558.

[11] Pinato DJ, Sharma R, Allara E, Yen C, Arizumi T, Kubota K, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 2017;66:338-346.

[12] Ho SY, Liu PH, Hsu CY, Chiou YY, Su CW, Lee YH, et al. Prognostic Performance of Ten Liver Function Models in Patients with Hepatocellular Carcinoma Undergoing Radiofrequency Ablation. Sci Rep 2018;8:843.

[13] Toyoda H, Lai PB, O'Beirne J, Chong CC, Berhane S, Reeves H, et al. Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. Br J Cancer 2016;114:744-750.

[14] Hsu HY, Yu MC, Lee CW, Tsai HI, Sung CM, Chen CW, et al. RAM score is an effective predictor for early mortality and recurrence after hepatectomy for hepatocellular carcinoma. BMC Cancer 2017;17:742.

[15] Pinna AD, Yang T, Mazzaferro V, De Carlis L, Zhou J, Roayaie S, et al. Liver Transplantation and Hepatic Resection can Achieve Cure for Hepatocellular Carcinoma. Ann Surg 2018;268:868-875.

***ICMJE disclosure form**

Click here to download ICMJE disclosure form: coi_disclosure.pdf