



Reply to: Correspondence concerning “Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection”

To the Editor:

We are grateful for the interest in, and comment on,^{1–4} 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 2 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 2 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 *et al.*, and Zhang *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 1 of the significant parameters (male gender, multiple tumors, tumor size or alpha-fetoprotein, except albumin-bilirubin [ALBI] score) then MaVI does enter the model.

Zhang *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 in 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 1,085 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 alanine aminotransferase, alkaline phosphatase, inter-

national normalized ratio 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 (likelihood-ratio 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 preoperative assessment apart from MiVI which was only available after histological examination of the resected tumor and is only involved in the postoperative 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 performance of the model.

Issues surrounding the ALBI score

The ALBI score is an evidence-based and extensively validated refinement/simplification of the Child-Pugh score.^{10,11} Its performance is at least as good or, more often, better than the Child-Pugh score.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 1,900 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.* Child-Pugh 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 2 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 subgroup of patients with HCC 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 after liver transplant, 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 inevitable 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 collected prospectively. We hope the present study, and the lessons learnt therefrom, will be a significant step in the right direction.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying [ICMJE disclosure](#) forms for further details.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2018.11.026>.

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