Reply to: "The "six-and-twelve score" for TACE treatment: Does it really help us?"

Developing prognostic models for TACE in the setting of hepatocellular carcinoma: Is there a panacea?

To the Editor:

We sincerely appreciate Bourlière *et al.* for the external validation of our prognostic model in a French centre,[1] with essential results derived from a different setting.

Before interpretation of these results, we would like to clarify that our model is a continuous model in the first place, with linear predictor = largest tumour diameter + tumour numbers.[2] Only with this presentation can we achieve individualized outcome prediction, whereas "6" and "12" are cut-off values for quick stratified prediction. The use of cut-offs provides convenience yet sacrifices accuracy, as they underestimate heterogeneity within the strata (*e.g.*, tumour size + number being 2 and 6) but exaggerate the difference around the cut-off points (*e.g.*, 6 and 8).[3] In the findings of Bourlière *et al.*, it is somehow intriguing to see that G2 stratum, with twice the upper limit of tumour burden compared to G1 stratum, had similar median overall survival as the latter stratum (29 *vs.* 23 months).[1] A likely explanation is that a majority of patients in these 2 strata concentrated around the cut-off point, especially when 66% patients are multi-nodular, the sum of tumour size and number in G1 strata may easily exceed 3 and approach 6. This loss of information may account for the reduced performance and is the reason why we provided a nomogram for individualized prediction prior to stratified prediction with cut-offs. Therefore, for external validation, the continuous presentation of the model may be more accurate.

A more in-depth look into this question leads us to the matter of population. As we stated in our study, population is a determinant of the performance of the model. A well-performing model or staging system may become less effective in a totally different population. This problem becomes more intense in hepatocellular carcinoma (HCC), a disease with notorious heterogeneity among different populations, which is why the generalisation of most staging systems other than Barcelona Clinic Liver Cancer (BCLC) remains controversial,[4,5] and for BCLC staging, further refinements are still required.[6] Similarly, the tumour characteristics of this external cohort receiving transarterial chemoembolisation (TACE) were mainly multi-nodular (66%) with smaller diameters (32 [25–44] mm), unlike our cohort where single-nodular tumours predominated (57%) and tumour diameters were larger on average (61 [38–98] mm). This difference may have caused the reduced performance of our model in the external validation set. However, even with the information loss caused by the cut-off values and the small number of patients in G3 strata (only 2 patients), our model, utilising tumour burden parameters only and without liver function or performance status, exhibited similar performance as the BCLC staging system. This might indicate that tumour burden is still an essential predictor in this cohort representative of European patients. However, it must be noted that our "six-and-twelve" score is not developed to replace the BCLC staging system, but rather to refine it by further stratifying optimal TACE candidates with tumour burden heterogeneity that is unclassified by the BCLC system (Fig. 1). This stratification can provide referential criteria to define the target population for better clinical decision-making in future trial design. For example, patients with tumour burden >6 but ≤12 may be considered as a target population in trials involving TACE and other additional therapies such as loco-regional therapy, whereas those with tumour burden >12 may be candidates for trials comparing TACE alone and combined with systemic therapy.

Moreover, despite the result that liver function parameters are not predictors in our cohort, we also agree with Bourlière *et al.* that when populations differ, heterogeneity in liver function, aetiology, alpha-fetoprotein, and performance status, *etc.* will increase. These parameters might thus become more influential to survival after TACE and their addition to tumour burden criteria may improve predictive performance. Just like the situation with the HAP (hepatoma arterial embolization prognostic) score and its modified versions,[7–10] our model may not exhibit satisfying performance in its current form when greater multi-dimensional heterogeneity is introduced by a totally different HCC cohort. It can be expected that this deviation may be partly corrected by further external validation with a large sample size in different settings, and corresponding modification of the model to improve its performance, which is our next step. It will be hard to find a panacea to all the difficulties associated with developing prognostic models for a disease as heterogeneous as HCC, but we hope to get closer to it with improvements through trial and error.

In conclusion, we thank Bourlière *et al.* for their external validation. The generalisability of our model might be improved with further modifications derived from validations in different settings.

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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.

Authors' contributions

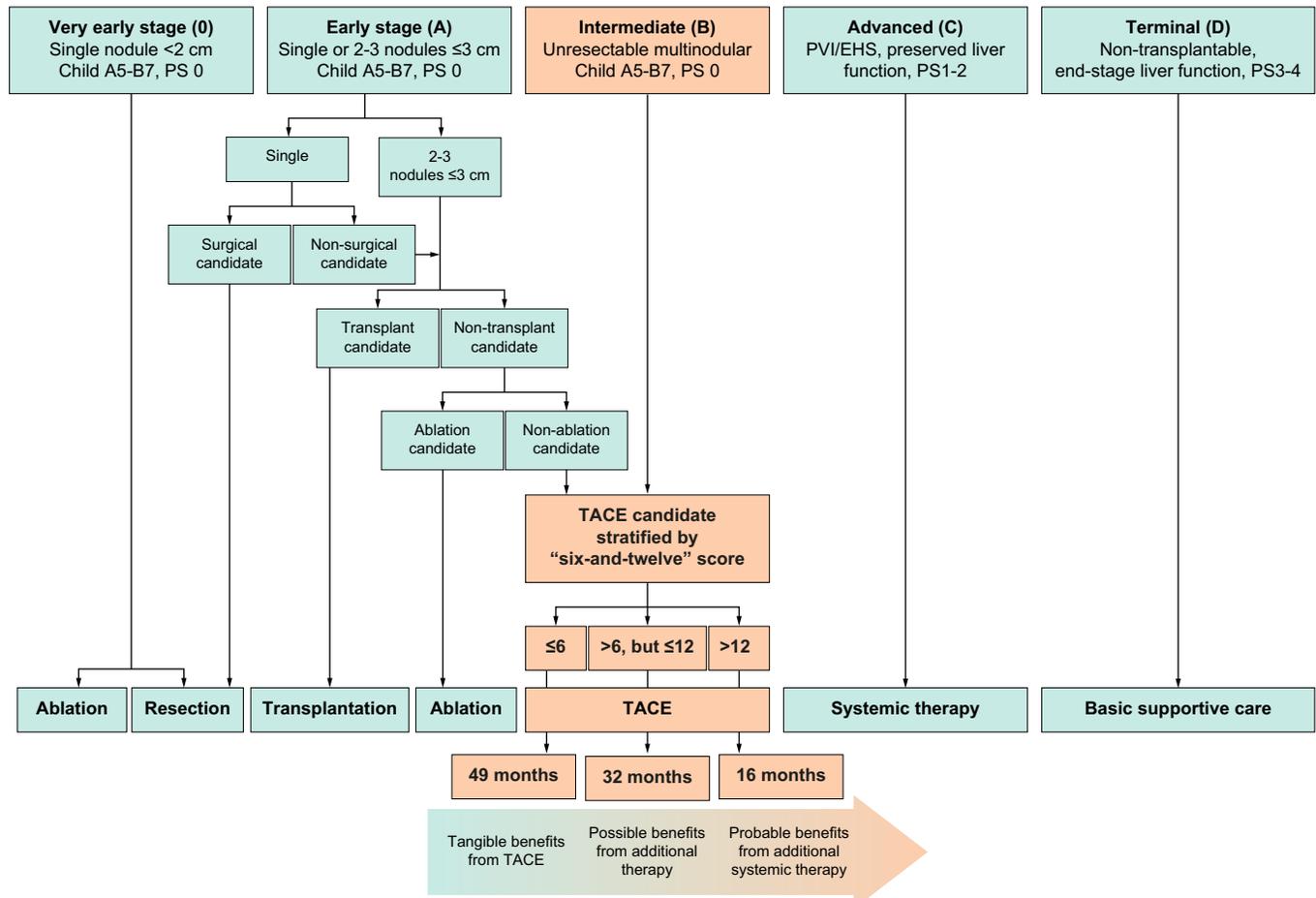Drafting and revision of the manuscript: QW, DX, WB, and GH.

Fig. 1. Possible role of "six-and-twelve" score in refining BCLC staging system. BCLC, Barcelona Clinic Liver Cancer; EHS, extrahepatic spread; PS, performance status; PVI, portal vein invasion; TACE, transarterial chemoembolisation.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.009.

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Author names in bold designate shared co-first authorship

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Qiuhe Wang[1]
Dongdong Xia[1]
Wei Bai[1]
Enxin Wang[1]
Guohong Han[1,*]

[1]*Department of Liver Disease and Digestive Interventional Radiology, National Clinical Research Centre for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, China*

*Corresponding author. Address: Department of Liver Disease and Digestive Interventional Radiology, National Clinical Research Centre for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, 15 West Changle Road, Xi'an, China. Tel.: +86 29 84771528; fax: +86 29 82539041.
E-mail address: hangh@fmmu.edu.cn