JOURNAL OF HEPATOLOGY

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

To the Editor:

We have read with interest the manuscript by Wang *et al.*,[1] wherein they propose a new scoring system named "six-and-twelve score" for patients with unresectable hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE). This prognostic index is simply calculated by the sum of tumor size and number. It determines 3 groups with different prognosis (G1, the sum ≤6; G2, the sum >6 but ≤12; G3, the sum >12). A survival benefit of more than 20 months can be expected for patients with HCC and an index ≤12, and more than 40 months for those with an index ≤6. The strengths of this study rely on: a) patient selection including only those with preserved liver function in the intermediate or early stages (when stage migration concept is applied); b) an appropriate methodology; c) the predictive ability of this new system outperforming other models published in recent years. As this new index was based on a large HCC population (n = 1,604), mainly related to hepatitis B virus infection (85%) and mostly Child-Pugh (CP) grade A (95%), we wanted to assess the reproducibility and the prognostic value of the current model in a multicenter French cohort of patients with HCC and the same tumor characteristics (n = 127), recently treated by conventional TACE (2015–2016). Median age of our population was 68 (60–73) years, 105 (83%) patients were male. All of our patients had cirrhosis, 104 of them had well-preserved liver function, CP grade A, and all other patients were CP B7 grade (n = 23) at baseline. HCCs were mainly related to hepatitis C virus infection (41%), alcohol use (41%) or non-alcoholic steatohepatitis (12%). Patients were Barcelona Clinic Liver Cancer (BCLC) stage B (n = 82) or stage A (n = 45); HCCs were mainly multinodular (66%), and the maximal size of the tumor was 32 (25–44) mm. The mean number of TACE sessions was 2.7 ± 1.8. After a median follow-up of 22.8 (14.5–38.4) months, similar to the study by Wang *et al.*, a total of 83 (65%) patients died. The median overall survival (OS) according to the six-and-twelve score was significantly different between the 3 groups: G1 (n = 59), 29 (25–51) months; G2 (n = 66), 23 (18–35) months; and G3 (n = 2), 12 (9–15) months (p (log-rank) = 0.0100). Median OS was also significantly different according to BCLC stages: BCLC stage A (n = 45), 51 (25–not reached) months; stage B (n = 82), 23 (18–27) months (p = 0.0026). In a similar way, median OS was significantly different according to the CP grade: CP A (n = 104), 27 (23–37) months; CP B (n = 23), 17 (14–30) months (p = 0.0165). Unlike in the study by Wang *et al.*, time-dependent area under receiver operating characteristic curve (AUROC) values and C-indices of the six-and-twelve score were not significantly different from those of BCLC staging system and CP grade within our cohort (Table 1).

It is of course a small sample size, but our results are not unexpected since few patients with HCC had a six-and-twelve index >12. It reflects a positive change in current practice of TACE treatment. Selection and discontinuation criteria are better defined,[2,3] and more alternative therapies including systemic agents[4] are available for patients in failure or refractory to TACE. As we have recently shown in a real life French cohort,[5] some patients with BCLC stage B HCC and a high tumor burden receive sorafenib at once.

Obviously, the prognostic performance of the six-and-twelve score was lower in our cohort than in Wang *et al.*'s study (3-year AUROC 0.56 [0.44–0.68] *vs.* 0.69 [0.65–0.74]). But this highlights the relevance of liver function in our population with more HCCs related to alcohol use. Median OS according to CP grade was significantly different. Conversely, liver function parameters were not identified as independent predictors in the Chinese cohorts.

Furthermore, TACE performance is based on nodule size and number but additional parameters might be helpful to optimize TACE efficacy, especially tumor morphology based on pre-therapeutic imaging, as recently demonstrated.[6] Non-nodular HCCs are predictive of satellite lesions[7] and microvascular invasion.[8,9]

Table 1. Comparison of time-dependent AUROC and C-index between the six-and-twelve model and BCLC system/Child-Pugh grade.

	1-yr AUROC (95% CI)	*p* value (*vs.* ref)	2-yr AUROC (95% CI)	*p* value (*vs.* ref)	3-yr AUROC (95% CI)	*p* value (*vs.* ref)	C-index (95% CI)	*p* value (*vs.* ref)
Six-and-twelve score	0.55 [0.39–0.70]	Ref*	0.58 [0.48–0.68]	Ref*	0.56 [0.44–0.68]	Ref*	0.63 [0.52–0.74]	Ref*
BCLC system	0.51 [0.39–0.63]	n.s.	0.58 [0.50–0.67]	n.s.	0.59 [0.49–0.69]	n.s.	0.65 [0.56–0.74]	n.s**
Child-Pugh grade	0.56 [0.45–0.66]	n.s.	0.55 [0.48–0.61]	n.s.	0.53 [0.46–0.60]	n.s.	0.57 [0.51–0.63]	n.s**

*Ref stands for the reference for the comparison.
**n.s., not significant at $\alpha = 0.05$ level.
AUROC, area under receiver operating characteristic curve.

Keywords: Hepatocellular carcinoma; Transarterial chemoembolization; Scoring system; Prognosis.
Received 11 May 2019; accepted 13 June 2019

TACE appears to be ineffective against small non-encapsulated HCC, or satellite lesions owing to their dual blood supply.[10]

In conclusion, we thank Wang *et al.* for their large well-designed study. The six-and-twelve score helps to define the limits of TACE and is useful for individual prognosis. However, evolution in our clinical practice and the availability of new therapeutic options likely make it less helpful for our patients.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

Marc Bourlière: Board member (Merck-Schering Plough, Gilead, Janssen, Vertex, Boehringer-Ingelheim, BMS, Roche, Abbvie, GSK), Speaker (Merck-Schering Plough, Gilead, Janssen, Vertex, Boehringer-Ingelheim, BMS, Roche, Abbvie, Novartis, GSK). Guillaume Pénaranda have no conflict of interest. Xavier Adhoute: Grant from Bayer. Jean-Pierre Bronowicki: Board member (Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, Bayer), Speaker (Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, Bayer). Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

MB, XA and JPB are physicians in charge of the patients.

JPB and XA collected the data and GP proceeded to statistical analysis.

MB and JPB wrote the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.014.

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