Editorial

Predictive scores for hepatocellular carcinoma: a race with no winners?

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Comment on: Wang Z, Fan Q, Wang M, *et al.* Comparison between Child-Pugh Score and albumin-bilirubin grade in patients treated with the combination therapy of transarterial chemoembolization and sorafenib for hepatocellular carcinoma. Ann Transl Med 2020;8:537.

Submitted May 15, 2020. Accepted for publication Jun 28, 2020.

doi: 10.21037/atm-20-3960

View this article at: http://dx.doi.org/10.21037/atm-20-3960

Cancer is a major public health problem with an estimated 18.1 million new cases and 9.6 million cancer deaths during 2018, worldwide (1). It is a heterogeneous group of diseases thus prediction models have been constructed to help clinicians in identifying subgroups of patients with different survival and therapy response. Identification of prognostic factors is crucial for planning treatment and stratification of patients enrolled in studies. In several cancers, discovery of biomarkers forecasting drug response has changed the treatment landscape. This revolution only partially involved hepatocellular carcinoma (HCC) for which identification of reliable predictive models and biomarkers is still controversial. Such gap is confirmed by the high number of staging and prognostic models proposed during the last 35 years (*Table 1*). HCC is a unique neoplasm developing mainly in cirrhosis and prognosis prediction is a complex task because it may be influenced by tumor burden, liver disfunction and complications of portal hypertension cirrhosis-related (17). Furthermore, such prediction should be dynamically evaluated being influenced by treatment and changing prevalence of cancer progression and liver failure. With this scenario, it is likely that a single score or system does not fit all clinical conditions.

To increase the complexity, it should be considered that scores are not universally applicable being influenced by characteristics of population used to identify prognostic variables. Okuda *et al.* formulated the first score combining tumor burden and liver function (2). However, the definition of tumor burden (less or more than 50% of liver volume) is too rough to be applied in clinical practice today. The widespread use of imaging identifies a rising number of small HCC and Okuda system is useless to classify these cases. To ameliorate the accuracy, the Cancer of the Liver Italian Program (CLIP) score evaluates also the variables cancer multifocality, AFP and portal thrombosis (3). But again, tumor morphology is roughly defined and CLIP is unsuitable to classify small tumors that may receive curative treatments. The French scoring system (GETCH) is few validated and barely used (4). Chinese University Prognostic Index (CUPI) introduced TNM stage to characterize tumor morphology. However, it performs better in advanced cases being developed from a patient cohort mainly with advanced HCC (6). The Japan Integrated Staging (JIS) and Stage Liver damage DEs-γ-carboxy-prothrombin (SLIDE) scores include TNM staging by Liver Cancer Study Group of Japan (7,8). JIS is simple and easily calculable whereas SLIDE incorporates indocyanine green and des-γ-carboxy-prothrombin tests not widely available. Tokyo score performs better in patients receiving curative treatments being developed from patients treated by percutaneous ablation (9). To reduce possible imaging-related bias, BALAD score and its modification were constructed using only serum biomarkers to characterize tumor burden and aggressiveness (10,14). Taipei score combines Child-Pugh score with total tumor volume, but external validation is lacking (11). The Model to Estimate Survival in Ambulatory HCC Patients (MESIAH) includes only objective parameters and the resulting score is continuous allowing an accurate stratification of patients independent by performed treatment or etiology (12,18). The model to

Table 1 Clinical scores and systems for predicting prognosis in HCC patients

Classification	Liver parameters	HCC morphobiology	Other	Stages
Okuda (2)	Albumin (<30 g/L), bilirubin (>3 mg/dL), ascites	Extension <50%; Extension >50%	/	1 to 3
CLIP (3)	Child–Pugh	Single + extension ≤50%	/	0 to 6
		Multinodular + extension ≤50% Massive or extension >50%, PVTT, AFP (≥400, >400 ng/mL)		
GETCH (4)	Bilirubin (<50, ≥50 μmol/L), ALP (<2, ≥2× ULN)	PVTT, AFP (<35, ≥35 ng/mL)	Karnofsky index (≥80, <80)	A: 0 points; B: 1–5 points; C: ≥6 points
BCLC (5)	Child–Pugh, portal hypertension	Tumor size (<2, ≤3, ≤5, >5 cm) Tumor number (1, ≤3, >3) PVTT	PS	0: Very early; A: Early; B: Intermediate; C: Advanced; D: End–stage
CUPI Index (6)	Bilirubin (<34, 34–51, >51 μmol/L), ALP (≥200 UI/L)	TNM stage, AFP (≥500 ng/mL)	No symptoms on presentation	Low risk: score ≤1; Intermediate: score 2–7; High: score ≥8
JIS (7)	Child–Pugh	TNM of LCSGJ	/	0 to 4
SLIDE (8)	Albumin (>3.5, 3–3.5, <3 g/dL), bilirubin (<2, 2–3, >3 mg/dL), PT (>80, 80–50, <50%), ascites (no, responsive, unresponsive), ICG–R15 (<15, 15–40, >40%)	TNM of LCSGJ	/	0 to 4
		DCP (<400, ≥400 mAU/mL)		
Tokyo (9)	Albumin (>3.5, 2.8–3.5, >3.5 g/dL), bilirubin (<1, 1–2, >2 mg/dL)	Tumor size (<2, 2–5, >5 cm)	/	0 to 6
		Tumor number (≤3, >3)		
BALAD (10)	Albumin (>3.5, 2.8–3.5, >3.5 g/dL), bilirubin (<1, 1–2, >2 mg/dL)	AFP (>400 ng/mL), AFP–L3 (>15%), DCP (>100 mAU/mL)	/	0 to 5
Taipei (11)	Child–Pugh	Total tumor volume (<50, 50–250, 250–500, >500 cm^3), Vascular invasion, AFP (≤400, >400 ng/mL)	/	0 to 6
MESIAH (12)	MELD, albumin	Largest tumor size (≤1, 1–2, 2–3, 3–5, 5–10, 10–15, 15–20, >20 cm)	Age	continuous
		Tumor number (1, 2, 3, 4, 5, >5)		
		AFP, vascular invasion, metastasis		
HKLC (13)	Child–Pugh	Tumor size (≤5, >5 cm); Tumor number (≤3, >3)	PS	I, IIa, IIb, IIIa, IIIb, IVa, IVb, V, Vb
		Intra/extrahepatic vascular invasion, Metastasis		
BALAD-2 (14)	Albumin (continuous), bilirubin (continuous)	AFP, AFP–L3, DCP	/	0.24 (risk 1), 0.24 to >−0.91 (risk 2), −0.91 to >−1.74 (risk 3) and ≤−1.74 (risk 4)
MESH (15)	Child–Pugh 5/≥6, ALP <200/≥200 IU/L	HCC in/out Milan Criteria	PS </≥2	0 to 6
		AFP </≥20 ng/mL		
		Vascular invasion, metastasis		
ITA.LI.CA (16)	Child–Pugh	ITA.LI.CA tumor staging (tumor size, tumor number, intra/extrahepatic vascular invasion, metastasis), AFP >1,000 ng/mL	PS	0 to 13

HCC, hepatocellular carcinoma; DCP, Des-γ-carboxy prothrombin; PVTT, portal vein tumor thrombosis; ICG-R15, indocyanine green 15-minute clearance retention rate; ALP, alkaline phosphatase; LCSGJ, Liver Cancer Study Group of Japan.

Table 2 Clinical scores for predicting prognosis of HCC patients treated with TACE

Classification	Liver parameters	HCC morphobiology	Treatment	Other	Stages/scores
ART (22)	Child-Pugh increase; AST increase >25%	Radiologic tumor response	TAE/cTACE/DEB-TACE Only retreatment	/	2 (0–1.5; >2.5)
HAP (23)	Albumin <3.6 g/dL, bilirubin >0.9 mg/dL	Tumor size >7 cm, AFP >400 ng/mL	TAE/cTACE	/	A, B, C, D
STATE (24)	Albumin g/L	Up-to-seven criteria	cTACE/DEB-TACE	C-reactive protein ≥1 mg/dL	</≥18 points
ABCR (25)	Increase Child-Pugh score ≥2	BCLC (A, B, C); AFP (>200 ng/mL); Radiologic response	cTACE; Only retreatment	/	–3 to +6
mHAP-II (26)	Albumin <3.6 g/dL, bilirubin >0.9 mg/dL	Tumor size >7 cm, Tumor number ≥2, AFP >400 ng/mL	cTACE	/	A, B, C, D
mHAP-III (27)	Albumin, bilirubin (continuous)	Maximum tumor size; Tumor number (1, 2–3, >3), AFP, No PVTT	cTACE/DEB-TACE	/	Individual prognostic estimation
SNACOR (28)	Child-Pugh (A, B)	Tumor size (<5, ≥5 cm), Tumor number (<4, ≥4), AFP (<400, ≥400 ng/mL), Radiologic response (CR + PR, SD + PD)	cTACE; Only retreatment	/	0–2, 3–6, 7–10
Six-and-twelve (29)	/	Tumor size + number	cTACE	/	≤6, 7–12, >12

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

estimate survival for HCC patients (MESH) incorporates commonly-used clinical variables that are dichotomized for easy calculation with a good discriminative capacity (15). The Barcelona Clinic Liver Cancer (BCLC) is the most widely used system and has been endorsed by EASL and AASLD as the standard staging system (2). Differently from other systems, it was constructed from results of studies not from variables derived by statistical analysis. BCLC system has some drawbacks as lack of discriminatory ability among B and C stages that include a heterogeneous population with varying degree of tumor burden, liver damage and survival probability. BCLC system gained popularity because it is simple and guide treatment allocation, being each stage connected to a treatment recommendation. However, this algorythm is too rigid to be applied as it is in daily clinical practice: it does not contemplate the use of combined treatments and in several cases stage migration strategy should be used (19). The Hong Kong Liver Cancer (HKLC) classification seems partially to overcome some problems of BCLC system allowing a better stratification of B and C stage patients in subgroups with different prognosis (13). It was constructed analysing patients predominantly HBV infected and recently validated in European patients with prevalent alcoholic and HCV etiology (20). As BCLC system, HKLC links any stage to a treatment recommendation, but some of suggested application as surgery and TACE for BCLC B and C stage patients needs to be validated before clinical application. Recently, a new system including a tumor staging and a prognostic score has been constructed, the Italian Liver Cancer (ITA.LI.CA) prognostic score (16). It seems to have better discriminative ability than BCLC and HKLC allowing a more accurate stratification of patients useful to select the best therapeutic strategy in the single case.

Unfortunately, at diagnosis only 30–40% of patients have early-stage disease and receive curative treatments. The majority are affected by unresectable or multifocal HCC and the most widely used treatment is transarterial chemoembolization (TACE) (21). This group of patients is extremely heterogeneous with varied tumor burden and survival. The high number of TACE treatments raised interest in formulating scores to improve selection of patients suitable for TACE and to avert over-treatment or procedural-related toxicity (*Table 2*). They may be divided in two groups: scores to guide the decision for first TACE and scores for TACE re-treatment. Among baseline scores, Hepatoma Arterial-embolisation Prognostic (HAP) was the first score constructed for predicting post-TACE

outcomes (23). It was modified with the introduction of variable multifocality (mHAP-II) (26) and with evaluation of variables as continuous parameters (mHAP-III) to increase the individual prognostic estimation (27). A web-based calculator for easy prediction of prognosis according to mHAP-III (http://www.livercancer.eu/mhap3.html) was constructed. Recently, a simple score based on tumor diameter and number, six-and-twelve score, was calculated in a large cohort of Asian patients with preserved liver function, but it lacks of validation (29). To identify patients unsuitable for the first TACE, an easy to calculate score, the selection for transarterial chemoembolisation treatment (STATE) score, was developed (24).

Among scores to predict retreatment, ART and ABCR scores differentiate two groups with different survival and risk of major adverse events after the second TACE (22,25). The sequential use of STATE and ART-score (START-strategy) was proposed to select patients who benefit from TACE. However, ART and ABCR predictive value was not confirmed in a large European cohort (30). The SNACOR score in addition to basal parameters included HCC response at imaging (28), but its predictive value was not confirmed in a European cohort (31).

In this issue of *Annals of Translational Medicine*, Wang *et al.* compared the prognostic value of ALBI model and Child-Pugh score in the specific setting of Child-Pugh A patients who received combined treatment with TACE and sorafenib (32). This therapy is used in clinical practice also if previous randomized clinical trials gave inconsistent results (33-36). The recently published TACTICS trial showed that TACE plus sorafenib as compared to TACE alone increased progression free survival (37). Assessment of liver function before administration of TACE and sorafenib is crucial because patients are exposed to hepatic toxic effects of both therapies. Usually clinicians grade liver function using Child-Pugh classification. It was formulated to evaluate outcomes in cirrhotic patients who receive surgery for portal hypertension but hides several drawbacks. For example, ascites and encephalopathy grade is subjective and cutoff points of biochemical tests are arbitrarily defined. Furthermore, Child-Pugh score works better in patients with liver failure who are excluded from treatment with TACE and sorafenib.

Albumin-Bilirubin (ALBI) grade model is a new tool to evaluate liver function that was formulated from analysis of large international databases (38). It has the advantage over Child-Pugh score of being derived by statistical analysis and not influenced by subjectivity. A nomogram for easy calculation was constructed and resulting linear predictor was categorized into three grades related to distinct prognostic groups. ALBI model performs better in Child-Pugh A patients as shown in studies of curative treatments for HCC (39,40). Therefore, we fully agree with the choice of using ALBI model in patients who receive sorafenib plus TACE combination.

In conclusion, there is none prognostic index universally applicable to HCC patients, but it should be selected on the basis of the characteristics of the population and of the planned treatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3960). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Tortora R, Guarracino M, Di Costanzo GG. Predictive scores for hepatocellular carcinoma: a race with no winners? Ann Transl Med 2020;8(19):1211. doi: 10.21037/atm-20-3960