Validation of the Hepatoma Arterial Embolization Prognostic Score in European and Asian Populations and Proposed Modification

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BACKGROUND & AIMS: **Transarterial chemoembolization (TACE) is used to treat hepatocellular carcinoma (HCC), but it is a challenge to predict patient survival. The hepatic arterial embolization prognostic (HAP) score has been shown to predict which patients will have shorter survival times and should not undergo TACE. We aimed to validate this scoring system in a prospective study of patients in Europe and Asia.**

METHODS: **We evaluated the prognostic accuracy of the HAP score in estimating overall survival (OS) of 126 patients with HCC who received TACE in the United Kingdom or Italy (training set) from 2001 through 2013. We also analyzed data from 723 patients treated in Korea and Japan (validation set), including 79 with newly diagnosed HCC, who underwent TACE in Korea or Japan from 2004 through 2013. Response to TACE was determined based on computed tomography analysis. OS was calculated from the time of the first TACE until death or the last follow-up evaluation.**

RESULTS: **OS was associated with hypoalbuminemia, α-fetoprotein level greater than 400 ng/mL, and tumor size greater than 7 cm at diagnosis ($P < .01$), but not a bilirubin level greater than 17 umol/L ($P > .05$), in both data sets. The lack of association between OS and bilirubin level was confirmed using receiver operating characteristic analysis. We developed a modified version of the HAP score, based on the level of albumin and α-fetoprotein and tumor size, which predicted OS with increased accuracy in the training and validation cohorts.**

CONCLUSIONS: **In a multicenter validation study, we developed a modified version of the HAP that predicts survival of patients with HCC treated with TACE in Europe and Asia. This system might be used to identify patients with HCC most likely to benefit from TACE in clinical practice.**

Keywords: Outcome; Liver Cancer; Therapy; Hepatic; AUROC.

The prognosis of patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE) is notoriously variable. In patients with fully compensated hepatic function, liver-confined HCC, and good performance status the 2-year survival rates approach 63%,[1] deteriorating, however, by half when the disease becomes symptomatic or spreads to the portal vein.[2]

The hepatoma arterial-embolization prognostic (HAP) score recently was qualified as a prognostic tool that classifies patients into 4 strata based on hypoalbuminemia, bilirubin level of 17 mmol/L or greater, α-fetoprotein level of 400 ng/mL or greater, and tumor size greater than 7 cm at diagnosis.[3] Given the limited survival of patients with an increased HAP score, it has been suggested that TACE should be avoided in the poor prognostic group. However, this recommendation, which

Abbreviations used in this paper: **BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HAP, hepatic arterial embolization prognostic; HCC, hepatocellular carcinoma; HR, hazard ratio; mHAP, modified hepatic arterial embolization prognostic; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OS, overall survival; TACE, transarterial chemoembolization.**

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Table 1. Demographic and Clinical Characteristics of Patients With HCC Treated With TACE: Training and Validation Data Sets

Baseline characteristic	Training data set (n = 126)	Validation data set (n = 723)
Age, *y*	69 (33–84)	73 (34–89)
Sex		
Male	95 (75)	392 (70)
Female	31 (25)	165 (30)
Risk factors for chronic liver disease		
Hepatitis C virus infection	52 (41)	454 (63)
Hepatitis B virus infection	16 (13)	127 (18)
Ethanol excess	52 (41)	134 (19)
Others	13 (10)	4 (4)
Child–Turcotte–Pugh class		
A5	47 (38)	355 (50)
A6	50 (40)	187 (26)
B7	18 (14)	100 (14)
B8	8 (6)	47 (6)
B9	3 (2)	28 (3)
Missing	-	6 (1)
BCLC stage		
A	47 (38)	270 (37)
B	67 (53)	390 (54)
C	12 (9)	63 (9)
Performance status (ECOG)		
0	119 (94)	692 (96)
1	7 (6)	31 (4)
CLIP score		
0–2	114 (90)	NA
>2	12 (10)	
Maximum tumor diameter, *cm*		
≤7	103 (82)	477 (86)
>7	23 (18)	80 (14)
Portal vein invasion (segmental)		
Absent	121 (96)	525 (94)
Present	5 (4)	32 (6)
Albumin level, *g/L*	37 (14–49)	37 (20–50)
Total bilirubin level, *umol/L*	19 (4–124)	14 (3–70)
ALT level, *IU/L*	48 (10–348)	37 (4–277)
AST level, *IU/L*	56 (16–365)	49 (6–303)
ALP level, *IU/L*	262 (62–563)	345 (108–1220)
AFP level, *ng/mL*	15 (4–130.000)	28 (1–974.820)
INR	1.1 (1.0–1.4)	1.0 (1.0–2.0)
Platelet count, $\times 10^9$/L	115 (26–446)	115 (14–1653)
Number of TACE procedures		
1	66 (52)	199 (27)
2	28 (22)	156 (22)
≥3	32 (26)	289 (40)
Missing		79 (11)
Prior treatments		
First-line TACE	77 (61)	239 (43)
Resection	8 (6)	73 (13)
Transplantation	1 (1)	0 (0)
Radiofrequency ablation	27 (21)	221 (40)
Systemic treatment	13 (10)	24 (4)
Modified RECIST response after TACE		
Complete response	27 (21)	218 (40)
Partial response	55 (43)	95 (17)
Stable disease	20 (16)	56 (10)
Progressive disease	21 (17)	179 (32)
Missing	4 (3)	9 (2)
HAP score		
A	22 (17)	259 (36)
B	46 (37)	236 (33)
C	41 (32)	173 (24)
D	13 (11)	55 (7)
Missing	4 (3)	-
mHAP score		
A	45 (36)	317 (44)
B	52 (41)	298 (41)
C	20 (16)	86 (12)
D	5 (4)	22 (3)
Missing	4 (3)	-

NOTE. Data are n (%) or median (range).
AFP, α-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIP, Cancer of the Liver Italian Program score; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio.

potentially could optimize the provision of TACE in HCC, has not been validated in independent confirmatory studies including patients of diverse ethnicities. We sought to validate the prognostic accuracy of the HAP score in independent patient cohorts from Europe and Asia.

Materials and Methods

Patient Population

Our study population consisted of a training data set of 126 patients, including 64 patients who had undergone TACE at Imperial College, London (UK), between 2001 and 2012, and a second subgroup of 62 patients from the academic Liver Unit in Novara (Italy), treated between 2004 and 2013.

The validation set consisted of 723 patients, including 79 with newly diagnosed HCC referred to St. Mary's Hospital Catholic University of Korea (Incheon), prospectively recruited between June 2011 and July 2012, and a further 644 consecutive patients with unresectable HCC treated with TACE at the Kinki University Faculty of Medicine (Japan) between January 2004 and August 2013. The radiologic response to TACE was based on modified Response Evaluation Criteria in Solid Tumors (mRECIST)[4] on contrast-enhanced computed tomography scan, 6 to 8 weeks after TACE. In all institutions TACE was administered conventionally on demand until achievement of complete response. Overall survival (OS) was calculated from the time of the first TACE to the time of death or the last-documented follow-up evaluation. Patients were staged according to the Barcelona Clinic Liver Cancer (BCLC) and Cancer of the Liver Italian Program scores as previously described.[5]