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Validation of Hepatoma Arterial Embolization Prognostic (HAP) Score in Egyptian Patients with Hepatocellular Carcinoma

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ABSTRACT

Background: *Hepatoma Arterial Embolization prognostic (HAP) score has recently emerged as an overall survival predictor for hepatocellular carcinoma (HCC) patients after treatment with transarterial chemoembolisation (TACE). It depends on serum bilirubin, albumin, alpha-fetoprotein (AFP) and tumor size. We evaluated the utility and validity of HAP score in a cohort of Egyptian patients with HCC who underwent TACE.*

Methods: *Our study included 416 Egyptian patients with HCC who underwent TACE at National Liver institute, Menoufia University, Egypt from January 2013 to May 2015. Child-Turcotte-Pugh (CTP), BCLC Staging as well as HAP score were calculated. Overall survival was assessed with a minimum follow up period of 12 months.*

Results: *Patients were mainly males (83.7 %) with a mean age of 58 ± 8.1 years, 267 (64.9%) patients had Child A cirrhosis, 143 (34.7%) had Child B cirrhosis and only one (0.2%) patient had Child C cirrhosis. Ten patients (2.4%) were in BCLC stage 0, 63 patients (15.1%) were in BCLC stage A, 335 patients (80.5%) were in BCLB stage B, 7 patients (1.7%) were in BCLC stage C and only one patient (0.2%) was in BCLC stage D. Fifty-one patients (12.3%) had a HAP score of 0, 129 (31%) had a score of 1, 164 (39.4%) had a HAP score of 2 and 72 (17.3%) had a HAP score of >2. Patients with HAP 0, HAP 1, HAP 2 and HAP >2 had a median survival of 53, 23, 22, 14 months respectively, showing a significantly shorter survival with more advanced score. Survival probability was 37.2%, 26.1%, 9.2% and 7.3% for patients with HAP score 0, 1, 2 and >2 respectively, with a P value 0.001.*

Conclusion: *HAP score is useful in survival prediction after TACE in HCC patients and can be used for proper patient selection to improve outcome after TACE.*

Keywords

Hepatoma Arterial Embolization, Hepatocellular Carcinoma, Prognostic score, Transarterial chemoembolisation.

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the fifth of the most frequent cancers and the second of the leading causes of deaths due to cancer in males [1]. In women, it is considered the seventh most common cancer and the sixth of the leading causes of deaths related to cancer [2]. In Egypt, the frequency of liver-related cancers in hospital-based studies is increasing over time [3]. Several staging systems were developed for classification of HCC patients but none has specifically been developed for predicting outcomes of therapy [4]. Transarterial chemoembolization (TACE) and bland Transarterial embolization (TEA) has become the most popular modality for treatment of unresectable hepatocellular carcinoma (HCC) [5-7]. However, patients who are candidate for TACE or TEA includes a wide spectrum in terms of liver function and extent of tumor, and this may explain the large differences in individual series reported survival [8]. Kadalayil and his colleagues identified a simple, pragmatic, and reliable prognostic system that was based on the four most statistically significant predictors of overall survival (OS) on multivariate analysis (albumin, bilirubin, AFP and tumor size). Patients were assigned one point for each of the

four parameters (Albumin < 3.6 g/dl, AFP > 400 ng/ml, Bilirubin > 1 mg/dl, Size of the largest tumor > 7 cm). The HAP score was defined as the sum of these values, accordingly patients were classified into 4 risk groups according to their HAP score, HAP A, B, C and D (scores 0, 1, 2 and >2 respectively) [9].

Our study evaluated the validity and utility of Hepatoma Arterial Embolization prognostic score (HAP Score) to predict survival after TACE in Egyptian patients with HCC.

Patients and Methods

Patients with a confirmed diagnosis of HCC who attended the oncology clinic at National Liver Institute, Menoufia University, Egypt, from January 2013 to May 2015 were identified. A total 416 patients who received TACE as the primary treatment were enrolled. All patients were subjected to full history taking including patient's demographics, etiology of liver disease, performance status and complete laboratory tests including complete blood count, International Normalized Ratio (INR), liver & renal function tests, serum AFP level, hepatitis markers (HCV Ab, HBsAg, HBc total Ab) and HCV RNA PCR. Abdominal ultrasonography, triphasic abdominal CT and/or dynamic MRI were performed stressing on liver and spleen size, texture, focal lesion, portal vein diameter and patency and presence of ascites. BCLC staging was assessed. HAP, Child Turcotte Pugh (CTP) as well as Model for End stage Liver disease (MELD) scores were calculated.

Patients were followed up from the time of enrollment to the date of death or date of data collection if they remained alive with minimum follow up period of 1 year. Overall survival (OS) was determined. OS is defined as the time from the date of TACE initiation until the date of death or last follow-up.

Diagnosis and definition: The diagnosis of HCC was based on the presence of hepatic focal lesion(s) larger than 1 cm in abdominal ultrasonography that showed the characteristic vascular enhancement pattern of HCC (hypervascular in the arterial phase and showing washout in the portal venous or delayed phase) with a 4-phase multidetector CT scan or a contrast enhanced dynamic MRI). For patients with atypical vascular enhancement pattern, a second contrast enhanced dynamic imaging or histopathological confirmation was needed [10-11].

HAP Score was calculated for all patients within three days of the procedure. Patients were assigned one point for each of four parameters (Albumin <3.6 g/dl, AFP >400 ng/ml, Bilirubin >1 mg/dl, Size of the largest tumor >7 cm). The HAP score was defined as the sum of these values, accordingly patients were classified into 4 risk groups according to their HAP score, HAP A, B, C and D (scores 0, 1, 2 and >2 respectively) [9]. According to BCLC recommendations all our patients were treated with TACE based on doxorubicin (Adriamycin) and lipiodol, and polyvinyl alcohol (PVA) was used as the embolic particle at the angiography unit of the National Liver Institute. TACE was repeated if there was persistant tumor vascularity, if there were no emergent contraindications and the patient tolerated the procedure.

Statistical analysis

The analysis was done with Statistical Package for Social Sciences (SPSS version 20.0; IBM Corp., Armonk, NY). Quantitative data were shown as mean, standard deviation (SD) and range. Qualitative data were expressed as frequency and percent. Patient and tumor characteristics were assessed and expressed as Median (interquartile range [IQR]) or n (%). Survival analysis was estimated by the Kaplan–Meier method. Median survival times and their 95% confidence intervals (CIs) were reported wherever possible. The survival difference between each group was assessed using the log-rank test. Cox regression model was used to give adjusted hazard ratio and 95% confidence interval of the effect of the different risk factors. Survival probability: the number of patients that survived beyond specific time. Survival probability calculated at 2 years for HAP score classes. P-value was considered statistically significant when it is less than 0.05.

Results

A total of four hundred and sixteen patients who received TACE were included in our study. Most of them were males (83.7% male, 16.3% female). Their Mean age was 58.7 ± 8.1 years, ranging from 32 to 83 years old. Two hundred and fourteen (51.4%) patients were smokers, 111(26.6%) were diabetics and 88 (21.2%) were hypertensive. Only 3.8% of our patients received antiviral treatment. Table 1 summarizes the Lab data of the studied groups. The higher proportion of our cohort was Child Pugh grade A, 271 (65.1%) patients, while 144 patients (34.6%) were Child B and 1 patient (0.2%) was Child C at presentation. Their MELD score ranged from 6 to 20, Mean ± SD (10.33 ± 2.8). Two hundred thirteen of our patients had single focal lesion, while 203 had multiple focal lesions. According to BCLC staging systems, ten patients (2.4%) were in the very early stage (BCLC 0), 63 patients (15.1%) were in the early stage (BCLC A), 335 patients (80.5%) were in the intermediate stage (BCLB B), 7 patients (1.7%) were in the advanced stage (BCLC C) and only one patient (0.2%) was in the terminal stage (BCLC D). HAP Score just prior to the procedure was calculated to all patients. Fifty-one patients (12.3%) were HAP A, 129 (31.0%) were HAP B, 164 (39.4%) were HAPC and 72 (17.3%) were HAP D.

Lab data		Mean ± SD Range	
		no	%
HBsAg (no = 416)	Negative	107	25.7
	Not available	309	74.3
HCV Ab (no=416)	Negative	3	0.7
	Positive	215	51.7
	Not available	198	47.6
ALT (IU/ml)		52.2 ± 34.4 5.0 - 206	
AST (IU/ml)		65.8 ± 46.3 4 - 300	
Alkaline Phosphatase (IU/ml)		137.4 ± 82.1 10.0 - 350	
GGT (IU/ml)		101.9 ± 57.8 34 - 211	

Hb (mg/dl)	12.5 ± 1.8 7.0 – 17.4
WBCs (/cmm)	5.5 ± 2.6 1.60 - 22
Platelets (/cmm)	115.9 ± 68.4 33.0 - 622
Total Bilirubin (mg/dl)	1.40 ± 0.7 0.30 – 4.2
Direct Bilirubin (mg/dl)	0.66 ± 0.51 0.09 – 3.0
Albumin (g/dl)	3.4 ± 2.3 1.60 – 4.9
Prothrombin concentration (%)	75.5 ± 15.8 0.84 - 108
INR	1.2 ± 0.2 0.80 – 2.0
Urea	34.7 ± 15.1 11.0 - 127
Creatinine (mg/dl)	0.91 ± 0.26 0.30 - 2.40
AFP (IU/ml)	1471.0 ± 7826.9 1 – 106370

Table 1: Lab data of the studied groups.

The mean survival time for patients with HAP scores A, B, C, D was 49.16, 34.2, 22.44 and 19.63 months respectively and the median survival time was 53, 23, 22 and 14 months respectively. The overall mean survival time 31.98 months and overall median survival 21 months (Table 2). The survivalprobability was 37.2 %, 26.1 %, 9.2 % and 7.3% for patients with HAP score 0, 1, 2 and > 2 respectively. Kapplen-meier plots stratified by HAP score showed statistically significant difference (P value =0.001) (Figure 1).

HAP SCORE	Mean (months)	Median (months)
A (0)	49.16	53
B (1)	34.20	23
C (2)	22.44	22
D(>2)	19.63	14
Overall	31.98	21

Table 2: Comparison of HAP score stages regarding mean and median survival.

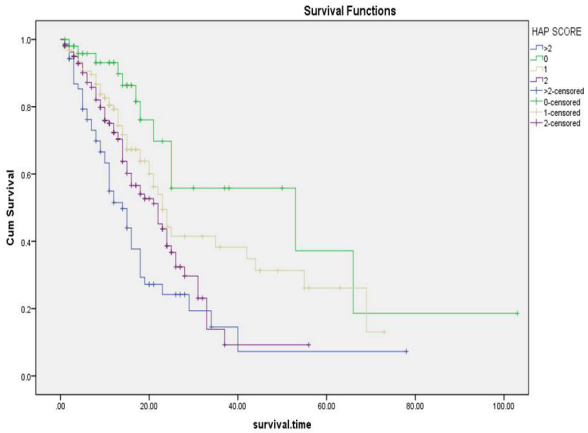

Figure 1: Comparison of survival between HAP score stages.

On the other hand, there was no statistically significant difference between patients with single versus multiple focal lesions regarding survival (p value = 0.450) (Table 3, Figure 2). In univariate survival analysis, age, serum bilirubin, serum albumin, serum AFP level and tumor size were the factors associated with prognosis (all p values < 0.05). Cox regression multivariate analysis revealed that age is a statistically significant independent factor affecting patient survival with p value<0.00 and hazard ratio (HR=1.1). Also, AFP>400, serum albumin <3.6, bilirubin >1, tumor size >7 cm are independent predictors of patient survival with p value (0.01, 0.02, <0.001, <0.001 respectively and HR 95% CI (1.48, 1.53, 1.78, 1.76 respectively) (Table 4).

No of focal lesions	Mean				Median	
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error
			Lower Bound	Upper Bound		
Multiple	25.910	2.072	21.850	29.971	22.000	2.401
Single	37.455	4.272	29.083	45.828	21.000	1.353
Overall	31.989	2.813	26.476	37.503	21.000	1.303

Table 3: Comparison of Mean and median survival time of patients classified according to tumor number (single or multiple).

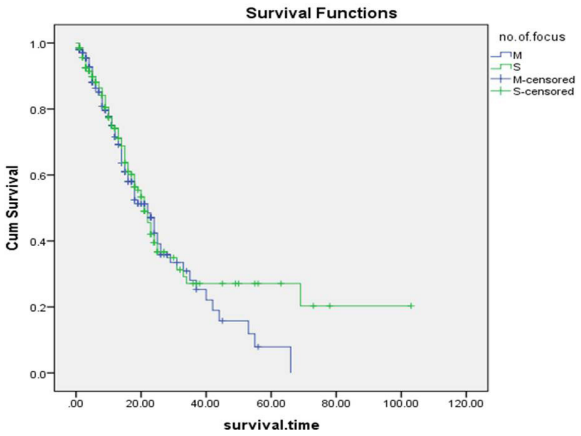

Figure 2: Comparison of survival of patients classified according to tumor number (single or multiple).

	*HR	P value
Age	1.1	<0.001
Total bilirubin >1	1.78	<0.001
Albumin<3.6	1.53	0.02
AFP>400	1.48	0.01
Tumor size > 7 cm	1.76	<0.001

Table 4: Cox regression analysis for factors affecting patient's survival. *HR=hazard ratio.

Discussion

Staging systems are used to define HCC prognosis and allocate treatment. The best staging system can stratify patients according to their survival time and is useful and reliable for comparing the

curative treatments and their effects on HCC [12]. According to the BCLC staging classification, TACE is the only recommended treatment option for patients with BCLC-B HCC. However, this stage includes a heterogeneous patients group that will not have the same survival benefits after TACE. Due to the lack of a standard treatment methodology and patient selection criteria for TACE, there are no firm conclusions about the efficacy of the procedure for BCLC-B & C HCC patients [13]. HAP score was first developed and validated by Kadalayil et al. at 2013. They found that serum bilirubin, albumin, AFP and tumor size were the most statistically significant predictors of survival with cut-off value: 1mg/dl for bilirubin, 3.6mg/dl for albumin, 400ng/ml for AFP, 7cm for size of dominant tumor [9].

The present study was designed to evaluate validity and utility of Hepatoma Arterial Embolization score (HAP score) in Egyptian patients with HCC. Our study was a retrospective study, conducted on 416 patients who attended the HCC clinic at National Liver Institute, from January 2013 up to May 2015 and underwent TACE. Demographically, most of our HCC patients were in their 5th decade of life with a mean age (58.7 ± 8.1) which is the expected time needed for development of HCC on top of cirrhotic patients with progressively increased incidence of HCC occurrence with advanced age in all populations, reaching a peak at 70 years [14]. HCC was more prevalent in males in this study (83.7% males versus 16.3% females) which comes in accordance with most HCC studies which suggested that the relatively low incidence of HCC in females during their reproductive years might be due to hepatic production of high levels of 2-methoxyestradiol. Consequently, the growth of hepatocellular carcinoma in females is delayed significantly as compared to males [15].

HAP score was calculated for patients: 12.3% were HAP A, 31.0% were HAP B, 39.4% were HAP C, 17.3% were HAP D. Patients followed up for survival for at least one year, median survival for HAP score A, B, C, D was found: 53.0, 23.0, 22.0,14.0 months respectively with overall median survival 21 months. Comparison of survival probability at 2 years among HAP score stages was found: 37.2%, 26.1%, 9.2%, 7.3% for HAP score A, B, C and D respectively, so there was significantly statistical difference among HAP score classes regarding probability of survival (P value 0.001). This was in agreement with a study in the United Kingdom on 431 patients with HCC who received TACE at a liver centre between 2005 and 2012. They reported that progression free survival (PFS) was 30.3, 19.5, 15, 6.2 months for HAP score A, B, C, D respectively with p value < 0.005 and concluded that there was a trend to longer survival with lower HAP scores and the HAP score predicts outcomes in patients with HCC undergoing TACE/TAE [16]. This is also in agreement with Pinato and his colleagues in a study on 660 patients from Japan and Korea that integrated and compared the assessment for re-treatment with TACE (ART) and HAP scores for their accuracy in prediction of overall survival (OS). They found that ART and HAP scores are independent predictors of OS (p<0.01) with a better prognostic accuracy of HAP over ART score [17].

COX regression analysis of parameters of HAP score with survival was done. There was statistically significant difference between patients with AFP ≥400 and patients with AFP <400 regarding survival (p value=0.01). There was also statistically significant difference between patients with serum bilirubin >1 and patients with serum bilirubin ≤1 regarding survival (p value <0.001). This finding disagreed with a study by Pinato et al. who found lack of association between overall survival (OS) and bilirubin level, and developed a modified version of the HAP score (mHAP) based on tumor size and serum levels of α-fetoprotein and albumin which predicted OS with increased accuracy in the validation and training cohorts [18].

Patients were classified according to size of focal lesion or the largest lesion if the patient had 2 or more focal lesions into <7cm or ≥7 cm.There was statistically significant difference between patients with size of largest ≥7 cm and patients with size of largest tumor <7 cm regarding survival (p value <0.001). These results are in agreement with Grieco et al. who found in multivariate analysis that tumor diameter <3 cm, absence of PVT, low AFP and low bilirubin level were significantly independent predictor of survival in patients with early-intermediate HCC having non-surgical therapy [19].

There was statistically significant difference between patients with serum albumin < 3.6 and patients with serum albumin ≥ 3.6 regarding survival (p value=0.02). These results was in agreement with Ikeda et al. who found that HCC patients treated by Transcatheter Arterial Embolization with serum albumin ≥3.5 g/dl, age < 60 years, α-fetoprotein < 400 ng/ml were significantly associated with favorable survival [20]. Cox regression analysis clarified that age is statistically significant independent factor affecting patient survival (P value <0.001), (HR =1.1). When performing statistical analysis according to tumor number; we found that there was no statistically significant difference between patients with single and patients with multiple focal lesions regarding probability of survival (p value =0.450). This is in disagreement with Park et al. in a study on 280 Korean patients with HCC treated with TACE; tumor number ≥ 2 was selected as an independent unfavorable prognostic factor. So, a modified HAP-II (mHAP-II) score was established by adding tumor number ≥ 2 [21].

As the four components of HAP scoring system (albumin, bilirubin, AFP and tumor size) were significantly affecting survival in this study, while tumor number showed no impact; the original HAP score is more accurate in our cohort than both versions of modified score. HAP score was assessed by Kohla et al., in prediction of hepatic decompensation after TACE and they found no statistically significant difference between HAP score classes this may be due to small number of patients (102 patients), but univarite analysis showed that low baseline albumin and high AFP was predictive of hepatic decompensation after TACE [22].

Conclusion

In conclusion, HAP score is a useful tool to predict survival

after TACE in Egyptian patient with intermediate stage HCC predominantly HCV induced cirrhosis.

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