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Association of Hepatoma Arterial-embolization Prognostic Score with Survival in Hepatocellular Carcinoma Patients undergoing Transcatheter Arterial Chemoembolization

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ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) ranked as the third leading cause of cancer-related deaths worldwide. Hepatoma Arterial-embolization Prognostic (HAP) score was suggested as a survival predictor for HCC patients undergoing Transcatheter Arterial Chemoembolization (TACE).

Objectives: This study aimed to analyse the association of HAP score with survival in HCC patients undergoing TACE.

Methods: This was survival analysis with longitudinal study. The Kaplan-Meier curve was used for survival analysis, while Cox Regression test was used to analyse univariate and multivariate association between HAP score and its components to survival.

Results: There were 100 patients HCC who underwent TACE at a tertiary hospital between January 2019 and September 2022. The overall survival (OS) median was 7 months, while the 12-months survival rate was 9%. The 12-months survival rates of HAP A, HAP B, HAP C and HAP D were 25%, 23.3%, 0 and 0, respectively. There was association between HAP score and 12 months' survival of HCC patients undergoing TACE (hazard ratio (HR) 3.187, 95% confidence interval (CI) 2.002–5.074, p<0.001).

Conclusions: HAP score has a prognostic value in predicting survival outcomes for HCC patients undergoing TACE.

Keywords: *Hepatocellular carcinoma, transcahteter arterial chemoembolization, prognostic score, survival rate, mortality*

1. INTRODUCTION

*H*epatocellular carcinoma (HCC) was the 7th most frequent cancer worldwide.[1] The biggest incidence was happened in hepatitis B endemic areas, such as sub-Saharan Africa and East Asia.[2] Not only tumor burden, liver function and performance score were required to determine its management but also multidiscipline team involvement.[3] Transcatheter arterial chemoembolization (TACE) was performed in Barcelona Clinic Liver Cancer (BCLC) B HCC patients who were not included in percutaneous ablation, resection nor transplant candidates. TACE was aimed to induce tumor necrosis dominated by arterial vascularization. TACE and non-TACE survival rates in the first year was 33.3% and 8.2%, respectively. [4-6]

There were many survival predictors in HCC patients undergoing TACE.[7] Hepatoma Arterial-Embolization Prognostic (HAP) score was one of these predictors. This score was consisted of hyperbilirubinemia, hypoalbuminemia, high titer alpha-fetoprotein (AFP) and large tumor size. Moreover, all the composing parameters of HAP score were included in tumor burden and liver function.[8]

In Indonesia, patients were coming at late stage of the HCC. Thus, definitive therapy was not given to them causing high mortality rate. This study was conducted to analyze association of HAP score with survival in HCC patients undergoing TACE. This study was expected to help clinician educating HCC patient undergoing TACE in order to predict their survival.

2. METHODS

This longitudinal study with survival analytical approach was conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from December 2021 to August 2024. All HCC patients undergoing TACE were considered eligible. The hospital is the primary referral hospital in Eastern Indonesia.

This study evaluated the survival of HCC patients undergoing TACE as independent variable. The dependent variables were HAP score and its composing parameters (hyperbilirubinemia > 1 mg/dL, hypoalbuminemia < 3.6 mg/dL, high titer AFP > 400 ng/mL and large tumor size > 7 cm). HAP score was defined as the sum of these parameters. Each positive parameter had score 1. The patients were categorized into four risk groups, HAP A (score 0), HAP B (score 1), HAP C (score 2) and HAP D (score 3 and 4) [8]. Survival rate was represented by percentage of individuals still alive after 12 months following first TACE.

The sampling procedure was total sampling. Patient records from January 1st 2019 to September 30th 2022 were obtained from the Division of Interventional Radiology, Department of Radiology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. HCC patients undergoing TACE aged ≥ 18 years were enrolled in this study. The exclusion criteria were patients with comorbidities and patients who can't be reached during observation time. Demographic and clinical data of all patients were collected, including sex, age, laboratory parameters and etiology. These data were assessed a week before TACE was done. Patient status was assessed with family report concerning of the disease and heath condition. The patients were followed 1 year after underwent TACE.

Categorical variables were presented as percentages and continuous variables as median and range. Survival analysis and overall survival were assessed using Kaplan-Meier survival analysis and log rank. Univariate and multivariate association between composing parameters of HAP score and survival were assessed using Cox-Regression test. Association between HAP score and survival were also assessed using Cox-Regression test. A $p < 0.05$ was considered statistically significant. All statistical analysis were conducted using SPSS version 29.0 for Mac (IBM Corp., Armonk, NY, USA).

3. RESULTS

Characteristics of the patients

A total of 100 patients diagnosed with HCC who underwent TACE were included in this study, as presented in Table 1. The majority of patients were male (77%), with a median age of 56.5 years. HBV infection was identified as the predominant etiological factor, accounting for 65% of cases. Pre-procedural laboratory assessments revealed three notable abnormalities, including elevated serum glutamic-oxaloacetic transaminase (SGOT) levels, with a median value of 85 U/L (range: 16–707), tumor size with a median of 8.25 cm (range: 1.7–18.8), and alpha-fetoprotein (AFP) levels with a median of 446 ng/mL (range: 1.4–1,557,756). Based on the HAP score stratification, 8% of patients were classified as HAP A, 30% as HAP B, 29% as HAP C, and 33% as HAP D.

Table 1. Demographic and clinical characteristics of the patients (N=100)

General characteristic	Frequency (%)
Sex	
Male Female	77 (77) 23 (23)
Age (years), median (range)	56.5 (23 – 85)
< 60 years ≥ 60 years	55 (55) 45 (45)
Etiology	
Hepatitis B Hepatitis C Non-hepatitis B hepatitis C	65 (65) 13 (13) 22 (22)
Pre-TACE laboratories	Median (range)
Hb (g/dL)	12.4 (8.0 – 18.9)

WBC (/µL)	7,485 (2,410 – 26,420)
PLT(/µL)	249,000 (42,000 – 601,000)
RBG (mg/dL)	113 (80 – 236)
Natrium (mmol/L)	138 (124 – 150)
Kalium (mmol/L)	3.9 (2.1 – 5.4)
Chloride (mmol/L)	101 (80 – 112)
BUN (mg/dL)	11.5 (3 – 23)
Creatinine (mg/dL)	0.99 (0.5 – 1.75)
SGOT (U/L)	85 (16 – 707)
SGPT (U/L)	48.5 (11 – 354)
Bilirubin (mg/dL)	0.77 (0.25 – 4.01)
Albumin (mg/dL)	3.5 (2.4 – 4.2)
Tumor size (cm)	8.25 (1.7 – 18.8)
AFP (ng/mL)	446 (1.4 – 1,557,756)
HAP score	Frequency (%)
HAP A	8 (8)
HAP B	30 (30)
HAP C	29 (29)
HAP D	33 (33)

AFP: Alpha-fetoprotein; BUN: Blood Urea Nitrogen; HAP: Hepatoma Arterial-embolization Prognostic; Hb: hemoglobin; PLT: platelet; RBG: random blood glucose; SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; TACE: transcatheter arterial chemoembolization; WBC: white blood cell

HCC Patients Undergoing TACE Survival

The cumulative survival curve for all subjects was presented in Figure 1. The 3-months, 6-months, 9-months and 12-months survival rates of this study were 72%, 53%, 16% and 9%, respectively. Median overall survival (OS) of this study was 7 months.

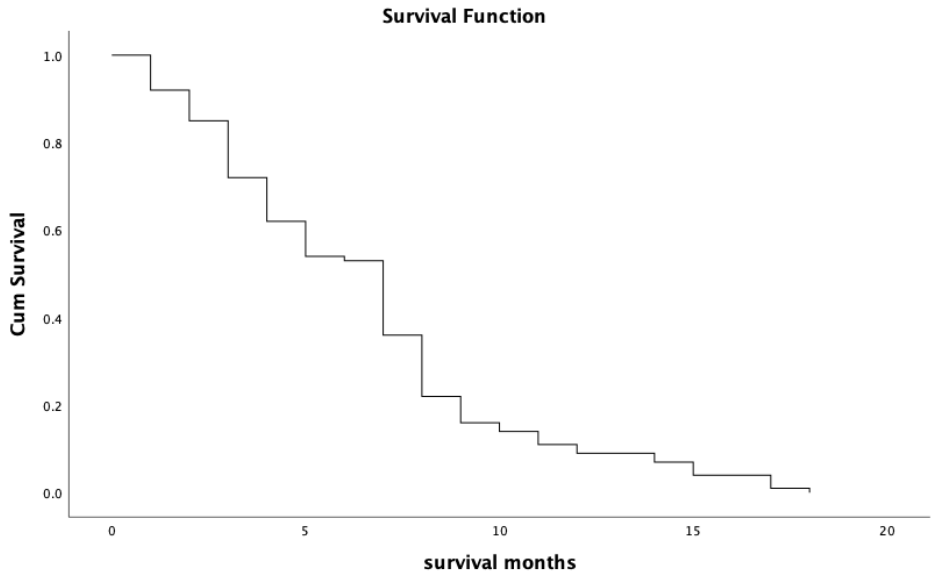

Figure 1. Kaplan Meier curve on survival outcomes of the HCC patients who underwent TACE.

HCC Patients Undergoing TACE Survival Based on HAP Score

Survival of the subject based on HAP score was presented in Figure 2. The 12-months survival rates of HAP A, HAP B, HAP C and HAP D were 25%, 23.3%, 0 and 0, respectively. Their median OS was 10 months, 8 months, 7 months and 3 months, respectively. A significant difference in survival was observed among HAP score groups (log-rank: $p < 0.001$), indicating a clear trend of decreasing survival with worsening HAP category (**Figure 2**).

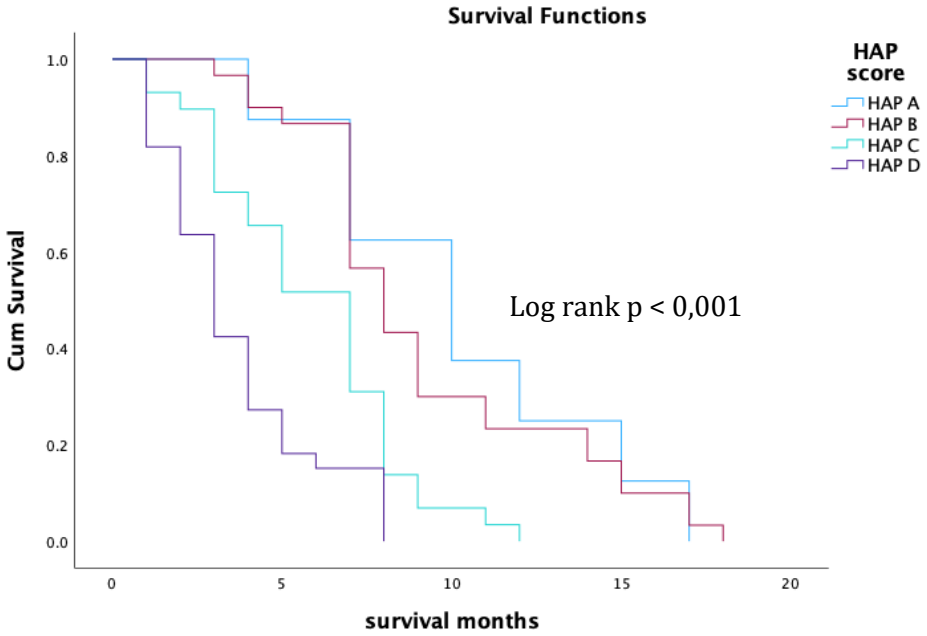

Figure 2. Kaplan Meier curves on survival outcomes of HCC patients who underwent TACE based on the HAP category.

Association between HAP score and Its Composing Parameters with Survival in HCC Patients Undergoing TACE

Univariate and multivariate analysis of HAP score's composing parameters and survival was presented in Table 2. There were association between HAP score's composing parameters and survival in HCC patients undergoing TACE except tumor size (p = 0.082). Multivariate analysis was assessed in the remaining parameters. AFP was the most associated parameter of survival (p < 0,001; HR 2.441; 95% CI 1.599 – 3.799).

Table 2. Association between HAP score's composing parameters and survival in HCC patients undergoing TACE

Parameters	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Bilirubin	2.123 (1.346 – 3.349)	0.001	2.413 (1.505 – 3.829)	< 0.001
Albumin	1.986 (1.293 – 3.051)	0.002	1.709 (1.111 – 2.629)	0.015
Tumor size	1.440 (0.954 – 2.173)	0.082	-	-
AFP	2.278 (1.510 – 3.435)	< 0.001	2.441 (1.599 – 3.799)	< 0.001
AFP: alpha-fetoprotein; CI: confidence interval; HR: hazard ratio				

Association between HAP score and survival in HCC patients undergoing TACE was presented in Table 3. There were association between HAP score and survival in HCC patients undergoing TACE (p < 0.001; HR 3.187; 95% CI 2.002 – 5.074).

Table 3. Association between HAP score and survival in HCC patients undergoing TACE

Variable	HR (95% CI)	*p*-value
HAP score	3.187 (2.002 – 5.074)	< 0.001
CI= confidence interval; HAP= hepatoma arterial-embolization prognosis; HR= hazard ratio		

4. DISCUSSION

Even though TACE was one of management modality in BCLC B HCC patients, there was still numerous variations in its survival.[9] This study reported its median OS was 7 months and its 12-months survival rate was 9%. These median and survival rates were low compared to other countries. These similarities were reported in two Chinese reports. Their median OS were 8 months and 7 months, respectively, while their survival rates were 39.4% and 18.5%, respectively. [6,10] This was due to the patients didn't include in resectable criteria.[11]

Different results were reported in one study from Japan and one study from Hongkong. Median OS was 20.5 months and 12-months survival rate was 76.7% were reported in study from Japan.[12] The 12-months survival rate was 31% reported in study from Hongkong.[13] A study in China reported early TACE after resection had better 5-year survival rate.[14] TACE performed before HCC definitive therapy was known as conversion therapy. This therapy intended to downstage tumor became resectable tumor. This caused by majority of HCC patients in China had a similarity as in Indonesia, as the time of diagnosis was in intermediate or late stage of cancer with big or multifocal lesions. This therapy was a novel strategy to extend the HCC survival.[15]

These differences were caused by the availabilities of supporting facilities to diagnose and management of HCC were still limited. These facilities were only available at few centers. Systemic therapies haven't been covered by government health insurance when these patients undergoing TACE yet. Furthermore, patients' travel distance was one of the reasons for low OS and survival rates. HCC surveillance also hadn't been implemented well in Indonesia. There was 75% of cirrhosis patients who was treated didn't undergo surveillance was reported in a study in Jakarta. [16,17]

Even though TACE could minimalize liver function deterioration and improve therapy response and survival, repeated TACE could also made liver function impairment and decreased patient survival.[18] These were caused by hypoxia-inducable factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) induced and activated by TACE.[19] Worse survival was also caused by worse condition of the patients, bigger tumor size worse deterioration of liver function when the patient came, microvascular invasion and longer observation duration.[11,13,20]

This study reported HAP C and HAP D had 0 of 12-months survival rate. A study in England stated HAP C and HAP D had worse prognosis. This group was unlikely had benefit from TACE. Besides, this group had better chance if got systemic therapy or best supportive care (BSC), aimed at improving patients' quality of life. [8, 21]

This study also assessed association between HAP score's composing parameters and survival. Even tough other studies reported tumor size was associated with survival, this study reported otherwise. Tumor size wasn't a poor prognosis survival predictor in HCC, but the microvascular was. Tumor recurrence was one of factors affecting survival, alas tumor size wasn't one of factors affecting tumor recurrence. [22-24]

Liver function deterioration was reflected on hyperbilirubinemia. It was associated with survival. Hyperbilirubinemia > 3 mg/dL was associated with higher mortality rate. Clinically aggressive HCC was seen in hyperbilirubinemia. This association was even depicted at small size tumor. Hyperbilirubinemia was caused by liver deterioration and HCC biological environment. [25-27]

Normal liver was reflected in normal albumin. Thus, albumin was used in many survivals prognostic scores. Low albumin level before therapy was poor prognostic for OS, disease free survival (DFS) and recurrence free survival (RFS) in HCC. It was associated with more malignant tumor and higher AFP level. Liver parenchymal destruction caused by more aggressive tumor, made growth and development of HCC. [28,29,30]

AFP > 400 ng/mL had 3 times fold increased risk of death. AFP was associated with more advance staging, bigger tumor size, more aggressive tumor and lower survival. AFP induced cell proliferation thus stimulated cell motility and became invasive. Wide tumor necrosis also symbolized by AFP. This was associated with tumor burden. Higher AFP level was associated with vascular invasion risk. It made HCC cell escaped from its host lymphocyte surveillance mechanism. It was occurred via FasL and TRAIL expression in HCC cells and TRAILR in lymphocytes. [8,19,31-33]

Association between HAP score and survival in HCC patients undergoing TACE was assessed to fulfill the main objective of this study. Tumor burden and liver function were independent survival predictor in HCC patients. HAP score itself had four parameters, specifically hyperbilirubinemia, hypoalbuminemia, tumor size > 7 cm, AFP > 400 ng/mL. These parameters were included in tumor burden and liver function. HAP score was suitable to use in HCC patient survival predicting that

didn't get resection therapy. This score particularly was used for early and intermediate stage HCC patient undergoing TACE.[19]

HAP score was calculated before TACE. Although there was association between HAP score and HCC patients undergoing second TACE after the first one survival, there wasn't any association between HAP score and HCC patients undergoing second TACE after the second one, and undergoing third TACE, either after the first, second or third one. TACE was an intervention affecting patient outcome based on its disease natural course. HAP score didn't have independent ability to evaluate the impact of changes in the outcome predictive value.[34]

The limitation of this study was this study was conducted in a tertiary hospital and didn't include portal vein involvement, tumor number, other therapy, performance score, hepatic encephalopathy, other score and BCLC stage in statistic test.

5. CONCLUSION

This study reported there was association between HAP score's composing factor except tumor size. Hyperbilirubinemia, hypoalbuminemia and higher AFP level were associated with survival. This study also reported there was association between HAP score and 12-months survival in HCC patients undergoing TACE. HAP C and HAP D had worse survival than HAP A and B group.

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