Albumin-Bilirubin Grade as a Three-Month Survival Predictor in Hepatocellular Carcinoma Patients after Initial Transarterial Chemoembolization (ALBI Grade Predicting Survival in HCC Treated With TACE)

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ABSTRACT

One of hepatocellular carcinoma (HCC) therapeutic modality is transarterial chemoembolization (TACE). The albumin-bilirubin (ALBI) grade is amongst the newest of prognostic scores published to predict survival. The aim of this study was to analzye the ALBI grade as a three-month survival predictor in HCC patients after initial TACE. This was a retrospective analytic observational study identifying patients that underwent initial TACE from January 2013 to December 2017 in Dr. Soetomo General Hospital, Surabaya. Data were collected before treatment and analyzed to evaluate ALBI grade as a survival predictor. Out of 134 HCC patients, the subjects consisted of 100 (74.6%) male subjects and 34 (25.4%) female subjects. There were 25 (18.7%), 98 (73.1%), dan 11 (8.2%) subjects who were classified into to ALBI 1, ALBI 2, and ALBI 3, respectively, with a median ALBI score of -2.295. The ALBI grade was significantly associated with the three-month

survival variable ($p = 0.01$; CI 95%). Using the ROC curve, we have determined a new cut-off point. The group of ALBI score $\leq$ -2.27 had an odds ratio of 2.549 (CI 95% 1.232-5.273) for three-month survival. The ALBI grade was associated with three-month survival after initial TACE in patients with HCC.

Keywords: HCC, TACE, ALBI grade, survival

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INTRODUCTION

Hepatitis B infection was the most common hepatitis infection in Indonesia.[1] Hepatitis B diseases can lead to hepatocellular carcinoma (HCC).[2] Transmission of HBV is parenteral, in contact with blood or other body fluids.[3,4] In addition, intra-familial transmission is a potential source of HBV-infected patients.[5] HBV acquisition in early life is mostly asymptomatic but associated with a particular risk of developing chronic infection.[6]

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer in patients with chronic liver diseases and cirrhosis.[7] HCC is the sixth most common cancer wolrdwide, and also the third leading cause of cancer-related death.[8,9] Other causes that can develop HCC are non-alcoholic fatty liver disease, aflatoxin, alcohol, and genetic factors.[10]

Highest incidence of HCC is detected in Southeast Asia and sub-saharan district of Africa in which hepatitis B virus infection is endemic. Whereas, Hepatitis C virus (HCV) related HCC increases sharply in the United States.[11,12] Prevalence rate of HCC in developing countries are twice the number of that in developed countries. The mortality rate in Asia and Africa are 33.5 and 23.73 per 100.000 people, respectively.[13] The rate decreased to 2.8-4.7 per 100.000 people in the last decade.[14] In Indonesia, HCC is one of the most common cancer in several hospitals, and the prevalence inclines each year.[15]

The main therapy of HCC is tumor resection, but most patients are not suitable candidates for surgery because of the tumor size or the impairment of liver function. Other therapeutic modality for inoperable patients is transarterial chemoembolization (TACE), which is a procedure of

administrating cytotoxic and embolization to the cancer site.[16] Patients with HCC that can receive optimal benefit from TACE are those who are classified in the Barcelona Classification of Liver Cancer (BCLC) B stadium.[17]

The mechanism of TACE is a combination of transarterial embolization and regional chemotherapy to produce ischemic necrosis and slow tumour progression.[18,19] Several studies about TACE showed variable results on survival. One meta-analysis confirmed survival benefits of TACE and reported that the mean of the two-year survival percentage in the TACE group was higher than the control group (41% vs 27%), also the objective response related to TACE reached 35% (16-61%). On the other hand, a cochrane analysis of six studies did not obtain any advantage on survival between TACE and the control group.[19] This variability was thought to be caused by the heterogenicity of patients with HCC. Therefore, patient selection is a crucial matter for TACE procedure to succeed.[20] In selecting patient, various predictors that are related to survival after TACE, including laboratory parameters and scoring systems, had been studied. Of all the scoring systems tested, the albumin-bilirubin (ALBI) grade is acknowledged of having a better prognostic power compared to others.[21–23]

The ALBI grade is a new approach model to assess the prognosis of patients with HCC. This scoring system offers a simple, evidence-based, and objective method of assessing liver function that has been extensively tested in an international setting. The ALBI grade utilizes only the level of serum albumin and serum bilirubin, which eliminates the necessity of subjective variables, such as ascites and encephalopathy used in child-pugh scoring.[24] The aim of this

study was to analyze the ALBI grade as a survival predictor of three-month survival in HCC patients after initial TACE.

MATERIALS AND METHODS

This study used a retrospective analytic observation design and identified patients that underwent initial TACE from the 1st of January 2013 to the 31st of December 2017 in Dr. Soetomo General Hospital, Surabaya. Data on demography, laboratorium, and radiology were taken from patient's medical record. The diagnosis of HCC was based on the criteria from *American Association for the Study of Liver Disease* (AASLD). The exclusion criteria were incomplete data and if patient underwent second TACE before three month after the initial TACE. The decision of TACE was made by interdiscipline discussion with several considerations and was done in the radiointervention installation by a radiologist. Laboratorium data such as bilirubin serum and albumin serum were drawn before TACE to fulfill the study requirements. Before grouping patients into the ALBI grade, ALBI score must first be calculated using the formula of $= (\log_{10}$ bilirubin x 0.66) + (albumin x - 0.085). The ALBI score was then categorized into 3 ALBI grades, $\leq$ -2.60 (ALBI 1), > -2.60 to $\leq$ -1.39 (ALBI 2), dan > -1.39 (ALBI 3).

Statistical Analysis

Demographic data and clinical characteristic were presented descriptively, in frequency and percentage for categorical data. As for numerical data, authors used median or mean with standard deviation. All data were tested for normality using Shapiro-Wilk test. To analyze the association between two variables with nominal scales, chi-square test was used. If significancy was achieved, cross tabulation test was done to calculate odds ratio (OR). To compare differences between two groups, the Mann-Whitney U test was utilized because the data did not have normal distribution. Significancy was achieved if *p* value <0.05. All statistical analyses were undertaken using the SPSS program for Windows version 23.0.

RESULTS

The subjects' baseline characteristics are shown in Table 1. The total subjects of this study were 134 patients with HCC after initial TACE, consisting of 100 (74.6%) male subjects and 34 (25.4%) female subjects. The median age was 52 years with age ranging from 21 to 77 years. As many as 88 (65.7%) subjects had normal level of albumin serum, and the mean of albumin serum was 3.56 mg/dL. There were 47 (35.1%) subjects with eleveated total bilirubin, and the mean was 1.22 g/dL. After calculating the ALBI score, the mean was -2.18. According to the ALBI grade, the number of patients in the ALBI 1, ALBI 2, and ALBI 3 were 25 (18.7%), 98 (73.1%), and 11 (8.2%), respectively. After three months post initial TACE, the majority of subjects (64.2%) still survived.

Tabel 1: Baseline Characteristics

Characteristics	Result (n = 76)
Age (years)	52 (21-77)
Sex	
Male	100 (74.6)
Female	34 (25.4)
Albumin	3.56 ± 0.49
<3.5 g/dL	46 (34.3)
≥3.5 g/dL	88 (65.7)
Total Bilirubin	1.22 ± 0.74
0.2-1.2 mg/dL	87 (64.9)
>1.2 mg/dL	47 (35.1)
ALBI Score	
mean ± SD	-2.18 ± 0.52
median (range)	-2.295 (-3.18 - (-0.71))
ALBI Grade	
ALBI 1	25 (18.7%)
ALBI 2	98 (73.1%)
ALBI 3	11 (8.2%)
3-month Survival	
Survivor	86 (64.2%)
Non-survivor	48 (35.8%)

Data presented as mean ± SD, median (range), and number (%)

Table 2: Bivariate Analysis of ALBI Grade with 3-month Survival after TACE

Variables	Three-month survival		*P* value
	Survivor (n = 86)	Non-survivor (n = 48)	
Grade of ALBI			
ALBI 1	20	5	0.01
ALBI 2	63	35	
ALBI 3	3	8	

From bivariate analysis in Table 2, the ALBI Grade (*p* = 0.01; CI 95%) was significantly associated to the three-month survival variable. By comparing the groups in the ALBI grade as shown in Table 3, analysis resulted that some comparison was not significant, while others were significant but had a wide range of confidence interval. Authors then tried to analyze if there was any significant difference between the survivor and non-survivor groups, especially in regard to the ALBI score. Further analysis showed that the distribution of ALBI score (*p* = 0.003) differed significantly between the survivor and non-survivor groups. Following that result, ROC curve was used to determine a new cut-off point. Based on the curve, the new cut-off point was the ALBI score of -2.27. That cut-off point was utilized to establish new groupings in which would be analyzed to evaluate its association with the three-month survival variable. In Table 4, using the chi-square test, authors found that the new ALBI gradings were significantly associated with three-month survival (*p* = 0.011; CI 95%). The group with an ALBI score ≤ -2.27 had an odds ratio of 2.549 (CI 95% 1.232-5.273) for three-month survival, meaning that HCC patients having ALBI score below -2.27 had 2.5 times the tendency of surviving three months after initial TACE than the other group (ALBI score > -2.27)

Table 3: Bivariate Analysis of Groups in ALBI Grades with Three-month Survival after TACE

ALBI Grades	Three-month survival		*p* value	*Odds Ratio* (CI 95%)
	Survivor (n = 86)	Non-survivor (n = 48)		
ALBI 1	20	5	0.067	2.606 (0.910-7.466)
ALBI 2 & 3	66	43		
ALBI 1 & 2	83	40	0.008	5.533 (1.393-21.983)
ALBI 3	3	8		
ALBI 1	20	5	0.134	2.222 (0.767-6.437)
ALBI 2	63	35		
ALBI 2	63	35	0.017	4.800 (1.196-19.266)
ALBI 3	3	8		
ALBI 1	20	5	0.002	10.667 (2.049-55.516)
ALBI 3	3	8		

Tabel 4: Bivariate Analysis of the New ALBI Grade with 3-month Survival after TACE

Variables	3-month survival		*p* value	*Odds Ratio* (CI 95%)
	Survivor (n = 43)	Non-survivor (n = 44)		
New ALBI Grade, n				
ALBI score ≤ -2.27	52	18	0.011	2.549 (1.232-5.273)
ALBI score > -2.27	34	30		

DISCUSSION

In the current study, the ALBI grade was significantly associated to three-month survival after initial TACE. The result was similar to other studies which indicated that the ALBI grade was an accurate prognostic model for HCC patients undergoing TACE.[22] The ALBI grade as a potential survival predictor was reported to be a great model to represent liver function.[25] Even in high-risk HCC patients, the ALBI grade was an accurate metrics of survival.[21]

Besides the ALBI grade, the ALBI score itself was also a significant predictor of overall survival.[26] Afterwards, authors analyzed the ALBI score between the survivor and non-survivor groups, and the result showed that the median of ALBI score (*p*=0.003) differed significantly between the two groups. Using the ROC curve, authors obtained a new cut-off point of -2.27 from the ALBI score. By utilizing the new cut-off point, a significant association and odds ratio was gained. This result indicated that the ALBI score has a more distinctive feature than the ALBI grade with its original cut-offs.

In this study, most of the subjects were male (74.6%), and the median age was 52 years (range of 21-77 years). Several studies showed that the number of male subjects was higher than the female subjects with a variable ratio around 2:1 to 8:1.[27] Whereas, the median age was slightly different compared to studies held in China with median age of 55-59 years and Europe with median age of 63-65 years.[11]

Majority of subjects were included in the ALBI 2 group (73,1%). This result was similar to previous studies which subjects were mainly categorized as ALBI 2.[22,25] The median of ALBI score was -2.295, which was adjacent to the study in Taiwan with a median of -2.49.[25]

This study has several weaknesses. It was only a single centre study with retrospective design, and data were retrieved form medical records. This new cut-off point should be tested in future studies with bigger samples, more predictor variables, with a prospective cohort design, and also longer evaluation period to confirm its ability to predict survival.

CONCLUSION

In conlcusion, the ALBI grade was associated with three-month survival after initial TACE in patients with HCC. By using the ALBI score, we determined a more discriminating cut-off point for the population and concluded that patients with an ALBI score below the new cut-off point had better odds of surviving a three-month period after inital TACE.

CONFLICT OF INTEREST

The authors in this study declared that they do not have any conflict of interest with respect to this manuscript.

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