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ORIGINAL ARTICLE

경동맥화학색전술 불응성인 Child-Pugh Class A 간세포암 환자의 간기능 악화에 대한 위험인자

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Risk Factors for Liver Function Deterioration after Transarterial Chemoembolization Refractoriness in Child-Pugh Class A Hepatocellular Carcinoma Patients

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Background/Aims: A switch to systemic therapy, such as sorafenib, should be considered for hepatocellular carcinoma (HCC) patients refractory to transarterial chemoembolization (TACE). On the other hand, treatment changes are difficult if the liver function worsens to Child-Pugh B or C. Therefore, predicting the risk factors for non-responsiveness to TACE and deteriorating liver function may be helpful.
Methods: Newly diagnosed Child-Pugh A HCC patients who underwent TACE from January 2012 to June 2018 were included. After 1 year, this study evaluated whether there was a treatment response to TACE and whether the Child-Pugh class had worsened.
Results: Among 121 patients, 65 were refractory and 56 responded to TACE. In multivariable logistic regression analysis, the tumor size, tumor number, and albumin at the time of the diagnosis of HCC were significant prognostic factors for the treatment response to TACE. Among 65 patients who presented TACE-refractoriness, 27 showed liver function deterioration from Child-Pugh class A to class B or C after TACE. In multivariable logistic regression analysis, bilirubin at the diagnosis of HCC was a significant prognostic factor for liver function deterioration. A predictive algorithm based on the regression equations revealed a sensitivity, specificity, positive predictive value, and negative predictive value of 74.1%, 74.5%, 45.5%, and 90.9%, respectively, for TACE-refractoriness and liver function deterioration.
Conclusions: The prognostic model incorporating the tumor size, tumor number, albumin, and bilirubin at the diagnosis of HCC may help identify patients who show a poor response to TACE and aggravation of liver function after TACE, who may benefit from early switching into systemic therapy before liver function aggravation. **(Korean J Gastroenterol 2020;75:147-156)**

Key Words: Carcinoma, hepatocellular; Chemoembolization, therapeutic

INTRODUCTION

A majority of hepatocellular carcinoma (HCC) cases are often inoperable at the time of diagnosis because of the poor liver function, portal hypertension, multiplicity of tumors, portal vein tumor invasion, inability to secure a sufficient resection

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margin, old age, and severe comorbidities.[1] Transarterial chemoembolization (TACE) is the most commonly used non-surgical treatment modality for these patients, as shown in the global HCC BRIDGE ('bridge to better outcomes in HCC') study, which was a multiregional, large-scale, longitudinal cohort study.[2] Although many studies have demonstrated that TACE can increase survival compared to conservative treatment, TACE often has to be repeated, and it is difficult to obtain complete cure.[3-5] The development of untreatable progression of HCC, in which TACE can no longer be considered, is regarded as TACE refractoriness or failure.[6-8] Recent practice guidelines on HCC have defined TACE refractoriness in different ways.[6] On the other hand, in the case of TACE refractoriness, the majority of guidelines recommend switching to another treatment, such as sorafenib.[6,9-12]

Among patients with TACE refractoriness, switching to another treatment would not be an issue if Child-Pugh class A could be maintained without a deterioration of the liver function. On the other hand, it is difficult to switch treatments if the liver function worsens to Child-Pugh class B or C after TACE. No clear recommendations for systemic therapy, such as sorafenib, have been made for Child-Pugh class B or C patients, and poor outcomes were reported in the GIDEON trial.[13-15] Therefore, this retrospective study examined the risk factors in patients who did not respond to TACE and had a deteriorated liver function to predict which patients will experience these conditions using statistical methods.

SUBJECTS AND METHODS

1. Patients and methods

This was a retrospective cohort study. The Konkuk University Medical Center HCC registry was screened from January 2012 to June 2018. From this registry, 407 patients who received TACE as an initial treatment were identified. Among them, 286 patients who met the following exclusion criteria were excluded: 1) patients treated with TACE at other hospitals; 2) patients who had a short-term follow-up period (<6 months); 3) patients who had double primary cancer; 4) patients who were treated concurrently with radiofrequency ablation or hepatectomy; and 5) patients who were Child-Pugh class B or C. Finally, 121 Child-Pugh class A patients were included in

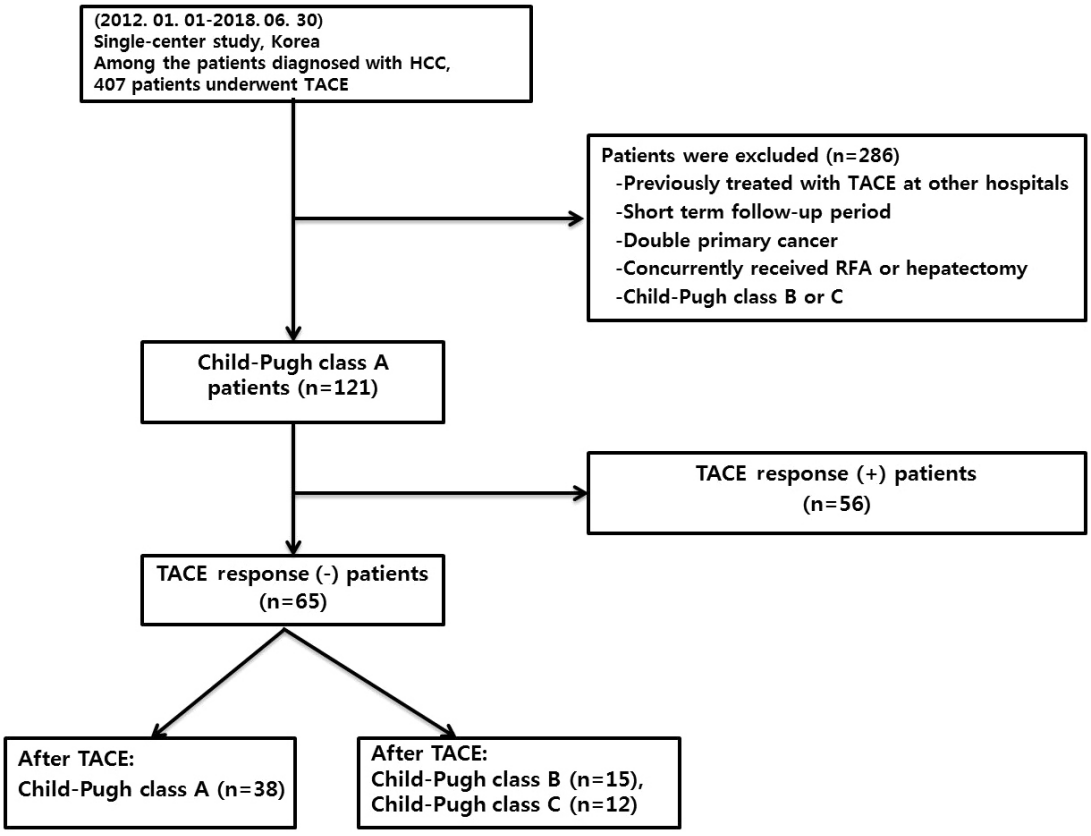


Fig. 1. Patient flow diagram. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

Table 1. Baseline Characteristics of All the Patients (n=121) with HCC and Child-Pugh Class A Liver Function First Treated by TACE and Comparisons of the Patients according to the TACE Response

Variable	Total	With TACE response (n=56)	Without TACE response (n=65)	p-value
Age (years)	65.1 (58.0-74.0)	66.6 (68.0-72.8)	63.9 (55.5-76.0)	0.336
Male	84 (69.4)	37 (66.1)	47 (72.3)	0.458
Diabetes mellitus	45 (37.2)	20 (35.7)	25 (38.5)	0.755
BMI (kg/m^2)	23.2 (20.7-26.1)	23.8 (21.0-26.3)	23.1 (20.6-26.0)	0.222
Alcohol (g/day)	1.8 (0.0-54.0)	27.6 (0.0-54.0)	32.4 (0.0-54.0)	0.929
Etiology of HCC				0.527
HBV	65 (53.7)	30 (53.6)	35 (53.8)	
HCV	23 (19)	9 (16.1)	14 (21.5)	
Alcohol	23 (19)	12 (21.4)	11 (16.9)	
Other	10 (8.3)	5 (8.9)	5 (7.7)	
Final follow-up state				<0.001
Died	25 (20.7)	5 (8.9)	20 (30.8)	
Ongoing follow-up	61 (50.4)	42 (75.0)	19 (29.2)	
Lost to follow-up	35 (28.9)	9 (16.1)	26 (40.0)	
Tumor size (cm)	2.5 (1.6-5.3)	2.9 (1.5-3.6)	4.7 (2.0-6.4)	0.006
Number of tumors	2.0 (1.0-3.0)	1.7 (1.0-2.0)	2.9 (1.0-5.0)	<0.001
Portal vein thrombosis	8 (6.6)	1 (1.8)	7 (10.8)	0.067
Liver cirrhosis	113 (93.4)	53 (94.6)	60 (92.3)	0.724
Platelet (×10^3/μL)	130.0 (86.0-166.0)	137.3 (97.5-159.3)	125.0 (76.0-168.5)	0.229
Albumin (g/dL)	3.8 (3.4-4.1)	3.9 (3.6-4.3)	3.62 (3.3-4.0)	0.003
Total bilirubin (mg/dL)	0.9 (0.6-1.2)	0.9 (0.9-1.2)	1.0 (0.6-1.3)	0.682
AST (U/L)	50 (33.5-67.0)	55.8 (30.0-66.8)	62.6 (36.5-68.5)	0.231
ALT (U/L)	34 (22.0-45.0)	32.3 (21.0-44.0)	41.5 (22.0-48.0)	0.437
BUN (mg/dL)	14.5 (12.5-17.6)	15.0 (12.6-17.0)	15.5 (12.5-18.0)	0.457
Creatinine (mg/dL)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	0.843
Na (mmol/L)	139.0 (136.0-141.0)	138.9 (137.0-140.8)	138.1 (136.0-141.0)	0.427
Prothrombin time (INR)	1.1 (1.0-1.2)	1.1 (1.0-1.1)	1.1 (1.0-1.2)	0.052
AFP (ng/mL)	14.1 (5.7-102.1)	201.5 (4.3-44.1)	14,799.6 (8.8-384.8)	0.004
PIVKA II (mAU/mL)	54.8 (21.5-313.0)	357.6 (19.6-168.2)	5,216.2 (24.0-721.0)	0.036
MELD score	8.0 (7.0-9.0)	8.1 (7.0-9.0)	8.6 (7.0-10.0)	0.010
Modified UICC				0.023
Stage I	22 (18.2)	15 (26.8)	7 (10.8)	
Stage II	43 (35.5)	22 (39.3)	21 (32.3)	
Stage III	38 (31.4)	16 (28.6)	22 (33.8)	
Stage IV	18 (14.8)	3 (5.4)	15 (23)	
BCLC stage				0.030
Very early stage (0)	8 (6.6)	13 (23.2)	6 (9.2)	
Early stage (A)	14 (11.6)	16 (28.6)	13 (20)	
Intermediate stage (B)	25 (20.7)	15 (26.8)	25 (38.5)	
Advanced stage (C)	72 (59.5)	10 (23)	21 (32.3)	
Terminal sate (D)	2 (1.7)	2 (3.6)	0 (0)	
Child-Pugh				0.031
Score 5	74 (61.2)	40 (71.4)	34 (52.3)	
Score 6	47 (38.8)	16 (28.6)	31 (47.7)	

Values are presented as median (interquartile range) or n (%).

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; Na, sodium; INR, international normalized ratio; AFP, alpha-fetoprotein; PIVKA II, protein induced by vitamin K absence-II; MELD, model for end-stage liver disease; UICC, Union for International Cancer Control; BCLC, Barcelona Clinic Liver Cancer.

this study (Fig. 1).

The Institutional Review Board of the Konkuk University Medical Center reviewed and approved this study (IRB No: 2019-08-038). Because the study was based on the retrospective analysis of existing administrative and clinical data, the Institutional Review Board waived the requirement of informed patient consent.

2. TACE response evaluation and follow-up

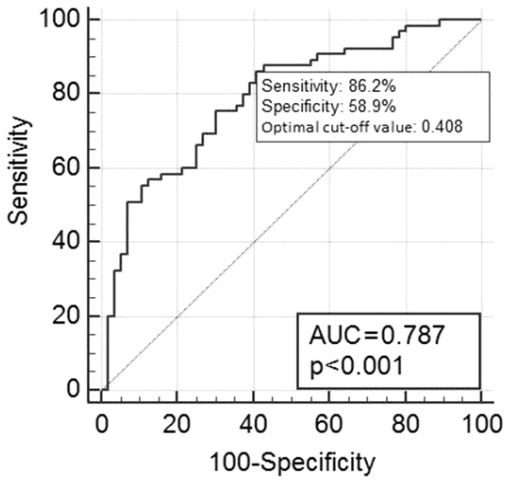
One year after TACE, this study evaluated the response according to the 2018 Korean guidelines for the management of HCC and the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[6,16] The 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of HCC evaluated TACE refractoriness are as follows.

After two or more on-demand sessions of TACE within 6 months after the first session of TACE, 1) an objective response was absent (complete or partial response), or 2) there was a new appearance of vascular invasion or extrahepatic spread.[6] According to the mRECIST criteria, a complete response was defined as the disappearance of any intratumoral arterial enhancement in all target lesions, and a partial response was defined as at least a 30% decrease in the sum of the diameters of the viable (contrast-enhanced in the arterial phase) target lesions.[16]

In addition to evaluating the TACE response, laboratory and clinical data were also collected 1 year after TACE. Using these data, the Child-Pugh score 1 year after TACE was calculated.

3. Statistical analysis

According to the response to TACE, comparisons were performed using an independent t-test or Mann-Whitney U-test for the continuous variables, and a chi-square test or Fisher's exact test for the categorical variables, where appropriate. The prognostic factors for TACE refractoriness and liver function deterioration after TACE were selected by logistic regression. Covariates with a p-value <0.25 from univariate analysis were included in multivariable analysis. A prognostic model was



Non-response score
=0.186×(HCC size)+0.408×(HCC No.)-1.25×(Alb)+3.298

Fig. 2. ROC curves and equations of the multivariable logistic regression of TACE refractoriness. AUC, area under the curve; HCC, hepatocellular carcinoma; Alb, albumin; ROC, receiver operating characteristic; TACE, transarterial chemoembolization.

Table 2. Prognostic Factor Analysis for the TACE Refractoriness by Logistic Regression

Characteristic	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age (years)	0.977 (0.945-1.010)	0.169		
Male	0.746 (0.343-1.619)	0.458		
BMI (kg/m^2)	0.936 (0.843-1.040)	0.221		
Portal vein thrombosis	0.151 (0.018-1.265)	0.081		
Tumor size (cm)	1.238 (1.067-1.437)	0.005	1.204 (1.018-1.424)	0.030
Number of tumors	1.642 (1.235-2.184)	0.001	1.503 (1.117-2.023)	0.007
Albumin (g/dL)	0.321 (0.142-0.686)	0.004	0.287 (0.120-0.685)	0.005
Platelet (×10^3/μL)	0.996 (0.990-1.003)	0.244		
Na (mmol/L)	0.933 (0.838-1.040)	0.209		
Prothrombin time (INR)	23.864 (0.870-654.732)	0.060		
AFP (ng/mL)	1.000 (1.000-1.001)	0.232		
PIVKA II (mAU/mL)	1.000 (1.000-1.000)	0.245		

TACE, transarterial chemoembolization; OR, odds ratio; CI, confidence interval; BMI, body mass index; Na, sodium; INR, international normalized ratio; AFP, alpha-fetoprotein; PIVKA II, protein induced by vitamin K absence-II.

made for both clinical outcomes using a regression equation, respectively, and the optimal cut-off values for the above clinical two outcomes were calculated on the area under the receiver operating characteristic curve (AUROC). Finally, these two prognostic models were applied sequentially to select the poor prognosis group, in which the patients were likely to show not only TACE-refractoriness but also liver function deterioration after TACE. Statistical analyses were performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). In the statistical

Table 3. Baseline Clinical and Tumor Characteristics according to Liver Function Deterioration after TACE among the Patients Who Showed TACE Refractoriness

Variable	Remained in Child-Pugh class A (n=38)	Worsened to Child-Pugh class B or C (n=27)	p-value
Age (years)	65.2 (57.5-75.3)	62.0 (49.0-76.0)	0.351
Male	29 (76.3)	18 (66.7)	0.392
Diabetes mellitus	16 (42.1)	9 (33.3)	0.474
BMI (kg/m^2)	23.5 (20.8-26.5)	22.5 (19.8-25.3)	0.242
Alcohol (g/day)	25.1 (0.0-43.2)	42.6 (0.0-72.0)	0.136
Tumor size (cm)	4.4 (2.1-5.6)	5.2 (1.6-9.4)	0.920
Number of tumors	2.8 (1.0-6.0)	2.9 (1.0-4.0)	0.632
Portal vein thrombosis	4 (10.5)	3 (11.1)	1.000
Liver cirrhosis	34 (89.5)	26 (96.3)	0.393
Platelet (×10^3/μL)	126.1 (76.8-161.3)	123.4 (73.0-179.0)	0.859
Albumin (g/dL)	3.7 (3.4-4.0)	3.5 (3.1-4.0)	0.207
Total bilirubin (mg/dL)	0.8 (0.5-1.0)	1.2 (0.9-1.4)	<0.001
AST (U/L)	58.0 (35.8-60.0)	69.1 (38.0-86.0)	0.082
ALT (U/L)	38.8 (22.0-42.3)	45.2 (26.0-59.0)	0.196
BUN (mg/dL)	16.1 (13.3-17.9)	14.7 (11.1-18.1)	0.214
Creatinine (mg/dL)	0.9 (0.8-1.0)	0.8 (0.6-1.0)	0.285
Na (mmol/L)	137.7 (136.0-140.0)	138.7 (136.0-141.0)	0.260
Prothrombin time (INR)	1.1 (1.0-1.2)	1.2 (1.0-1.3)	0.024
AFP (ng/mL)	19,298.5 (8.9-231.0)	8,467.9 (7.3-963.4)	0.331
PIVKA II (mAU/mL)	867.1 (23.5-403.3)	11,337.3 (24.0-2147.0)	0.372
MELD score	8.1 (7.0-9.0)	9.2 (8.0-11.0)	0.023
Modified UICC			0.628
Stage I	3 (7.9)	4 (14.8)	
Stage II	12 (31.6)	9 (33.3)	
Stage III	15 (39.5)	7 (25.9)	
Stage IV	8 (21.1)	7 (25.9)	
BCLC stage			0.948
Very early stage (0)	1 (2.6)	1 (3.7)	
Early stage (A)	2 (5.3)	1 (3.7)	
Intermediate stage (B)	9 (23.7)	5 (18.5)	
Advanced stage (C)	26 (68.4)	20 (74.1)	
Terminal sate (D)	0 (0)	0 (0)	
Child-Pugh			0.038
Score 5	24 (63.2)	10 (37.0)	
Score 6	14 (36.8)	17 (63.0)	

Values are presented as median (interquartile range) or n (%).

TACE, transarterial chemoembolization; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; Na, sodium; INR, international normalized ratio; AFP, alpha-fetoprotein; PIVKA II, protein induced by vitamin K absence-II; MELD, model for end-stage liver disease; UICC, Union for International Cancer Control; BCLC, Barcelona Clinic Liver Cancer.

hypothesis test, a p-value <0.05 was considered significant.

RESULTS

1. Baseline characteristics

Table 1 lists the baseline characteristics of the included patients. Of the 121 patients, 69.4% were male, and the median age was 65.1 years. The major cause of the underlying liver disease was a HBV infection (53.7%). The HCC classification was performed according to the Barcelona Clinic Liver Cancer (BCLC) staging; 6.6% of patients were classified as BCLC 0, 11.6% as BCLC A, 20.7% as BCLC B, 59.5% as BCLC C, and 1.7% as BCLC D. Sixty-one percent of the patients had a Child-Pugh score of 5 points; the other 38.8% of patients had a score of 6 points.

2. Risk factors for TACE refractoriness

Among the 121 patients with Child-Pugh class A, 56 patients were evaluated as having a treatment response to TACE; the other 65 patients did not. Table 1 lists the characteristics of the patients with and without a TACE response. The patients without response to TACE had larger tumor sizes (p=0.006), greater tumor numbers (p<0.001), poorer liver function (more patients had a Child-Pugh score of 6 and a lower albumin level), higher AFP levels (p=0.04), and higher protein induced by vitamin K absence-II (p=0.036) than those with no response to TACE.

Univariate logistic regression analysis for predicting the refractoriness to TACE showed that the tumor size, tumor number, and albumin level at the initial diagnosis of HCC were statistically significant predictive factors. Multivariable analysis was performed and included all covariates with p<0.25 from univariate analysis; these were age, gender, BMI, portal vein thrombosis, platelet count, sodium, INR, tumor size, tumor number, and albumin level. Among these variables, the tumor size, number of tumors, and albumin levels were identified as significant factors predicting the TACE refractoriness (Table 2). Based on predictive factor analysis, a regression equation was constructed, and the non-response risk was calculated as follows: non-response score=0.186×(tumor size [cm]) +0.408×(tumor number)-1.25×(albumin [g/dL])+3.298. This predictive model for the TACE refractoriness showed an AUROC value of 0.787 and an optimal cut-off value of 0.408. According to this cut-off value, the TACE refractoriness could be predicted, showing a sensitivity and specificity of 86.2% and 58.9%, respectively (Fig. 2).

3. Liver function deterioration after TACE refractoriness in Child-Pugh class A HCC patients

Of the 65 patients, who did not respond to TACE, 38 patients remained in Child-Pugh class A, and 27 patients worsened to Child-Pugh class B and C (Fig. 1). The patients with a liver function that deteriorated to Child-Pugh class B or C had significantly higher values for the following variables compared to the Child-Pugh class A patients: total bilirubin (p<0.001), PT (INR) (p=0.024), Child-Pugh score (more patients had a Child-Pugh score of 6, p=0.038), and model for end-stage liver disease (MELD) score (p=0.023) (Table 3).

Univariate logistic regression analysis for predicting a deterioration in the liver function showed that the total bilirubin and INR were statistically significant prognostic factors. Multivariable analysis, which included all covariates with

Table 4. Prognostic Factor Analysis for Liver Function Deterioration after TACE by Logistic Regression

Characteristic	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age (years)	0.980 (0.942-1.019)	0.313		
Male	1.611 (0.539-4.817)	0.393		
BMI (kg/m^2)	0.916 (0.791-1.060)	0.239		
Alcohol (g/day)	1.008 (0.997-1.020)	0.145		
Albumin (g/dL)	0.515 (0.184-1.438)	0.205		
Total bilirubin (mg/dL)	10.441 (2.511-43.410)	0.001	10.441 (2.511-43.410)	0.001
BUN (mg/dL)	0.926 (0.820-1.045)	0.213		
Prothrombin time (INR)	115.984 (1.728-7,786.880)	0.027		
PIVKA II (mAU/mL)	1.000 (1.000-1.000)	0.177		

TACE, transarterial chemoembolization; OR, odds ratio; CI, confidence interval; BMI, body mass index; BUN, blood urea nitrogen; INR, international normalized ratio; PIVKA II, protein induced by vitamin K absence-II.

p<0.25 from univariate analysis, was performed; these were age, gender, BMI, alcohol (g/day), albumin, BUN, protein induced by vitamin K absence-II, total bilirubin, and INR. Of these, only the total bilirubin was identified as a significant prognostic factor of a deterioration in the liver function (Table 4). The predictive model, including total bilirubin, presented an AUROC value of 0.774 and an optimal cut-off value of 0.82 mg/dL. According to this cut-off value, liver function deterioration could be predicted with a sensitivity and specificity of 81.5% and 68.4%, respectively (Fig. 3).

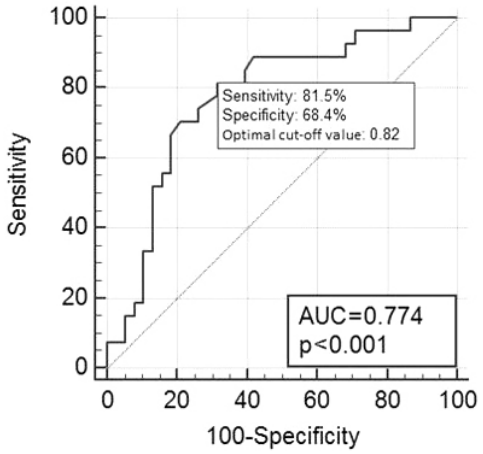


Fig. 3. Total bilirubin ROC curves of the univariable logistic regression of liver function deterioration. AUC, area under the curve; ROC, receiver operating characteristic.

4. Prediction of nonresponsive patients with reduced liver function

Using the above two predictive models, this study could determine how predictable the TACE refractoriness and the deterioration to Child-Pugh class B and C after TACE. Among the 121 patients, 44 patients were expected to have no TACE response and liver function deterioration (Fig. 4). The sensitivity, specificity, positive predictive value, and negative predictive value were 74.1%, 74.5%, 45.5%, and 90.9%, respectively (Table 5).

5. Subgroup analysis

The Supplementary Material summarizes the statistical

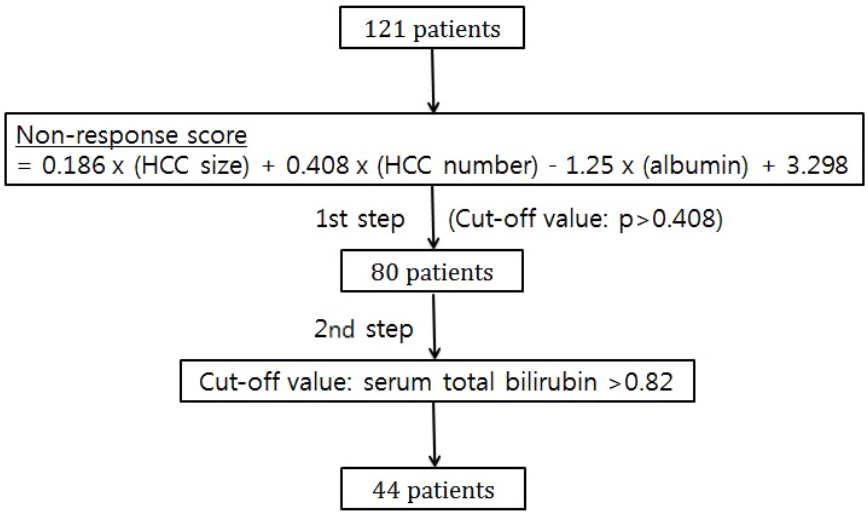


Fig. 4. Prediction of patients with reduced liver function without a response after TACE using the regression formula. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Table 5. Calculation of the Prediction of Patients with Reduced Liver Function without a Response after TACE Using the Regression Formula

	No response and liver function deteriorated to Child-Pugh class B or C	
	Positive (n=27)	Negative (n=94)
Calculation using regression formula		
Positive (n=44)	True positive (n=20)	False positive (n=24)
Negative (n=77)	False negative (n=7)	True negative (n=70)

Sensitivity=74.1%, specificity=74.5%, positive predictive value=45.5%, negative predictive value=90.9%.
TACE, transarterial chemoembolization.

analysis of 99 patients, excluding those with BCLC stage 0 and stage A (Supplementary Table 1-5 and Supplementary Fig. 1-3). In contrast to the whole cohort, the tumor number and albumin were significant prognostic factors for TACE refractoriness, but the tumor size was not. Bilirubin was the only significant prognostic factor for liver function deterioration after TACE, which is the same as the whole cohort.

Subgroup analysis of BCLC stage 0-A and stage B patients is also provided in Supplementary Material (Supplementary Table 6, 7). Only baseline charicteristics were performed because the statistical reliability of the comparative analysis was low due to the small number of patients.

DISCUSSION

Determining and predicting the TACE refractoriness is meaningful for obtaining effective treatment by rapidly changing from TACE to another treatment. Several studies have predicted the refractoriness of TACE in different ways.

The Assessment for Retreatment with Transarterial chemoembolization (ART) score, which was designed by Austrian researchers, assessed the response to TACE using a combination of AST increase, Child-Pugh score increase, and radiologic tumor response after TACE.[11] Similarly, a group from the United Kingdom developed the hepatoma arterial-embolization prognostic (HAP) score, which was used as a model for predicting the prognosis using albumin, AFP, maximum tumor diameter, and serum bilirubin levels before TACE.[17] Although these studies recommend rapid changes to other treatments for patients who do not respond to TACE, the treatment is limited in patients with a deteriorated liver function who become Child-Pugh class B or C. Moreover, there is no clear evidence for the use of systemic therapy, such as sorafenib in patients with Child-Pugh class B and C, and even in Korea, where the Health Insurance Review and Assessment Service restricts treatment to only Child-Pugh A patients.[13-15] Therefore, it is important to predict patients who will not respond to TACE and in whom the Child-Pugh score will deteriorate and to determine what risk factors are present.

This study was a retrospective cohort study conducted over six and a half years in a single institution with patients newly diagnosed with HCC who underwent TACE. The patients were evaluated for their TACE response at 1 year after TACE based on the mRECIST criteria and 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of HCC.[6,16] At the same time, 1 year after TACE, and the Child-Pugh score was calculated to determine if the liver function had deteriorated.

In this study, albumin and tumor size, which showed significant results in the HAP study mentioned above, were also statistically significant among the variables predicting the refractoriness to TACE (Table 3).[17] The modified HAP score, which did not include bilirubin, predicted the actual prognosis better than the original HAP score.[18] In this study, similar conclusions were found in that there was no significant difference in bilirubin between the two groups according to the response to TACE (p=0.682) (Table 2).

In addition, several studies have been conducted to identify the risk factors that worsen the liver function after TACE.[19,20] Studies in Hong Kong showed that the bilirubin level, PT, pre-TACE Child-Pugh class, and cisplatin dose were statistically significant.[19] Similarly, a study in Taiwan showed that the pre-TACE Child-Pugh class and the amount of lipiodol used were significant.[20] In this study, although there were limitations in that values other than the bilirubin levels were not statistically significant in multivariable logistic regression, the ROC curve analysis showed a sensitivity of 81.5% and an area under the curve value of 0.774. Interestingly, bilirubin was excluded as a predictor of TACE reactivity, but only bilirubin was included as a risk factor for liver function deterioration after TACE.

Using the calculations in Fig. 4, which predicted a deterioration to Child-Pugh class B and C among patients who did not respond to TACE, 20 out of 27 patients were predicted (sensitivity 74.1%) (Table 5). Using this prediction method, patients who are expected to be refractory to TACE and have a high likelihood of experiencing a deteriorating liver function might consider a rapid switch to other treatments, such as sorafenib, before their liver function deteriorates in reality. A Japanese study introduced the concept of early switching to sorafenib-regorafenib sequences in patients who easily become refractory to TACE.[21] In addition to previous Japanese studies, this study also predicted a group of patients with a high likelihood of a deteriorating liver function, enabling early switching prior to a deterioration of the liver function.[21] In addition, among the 77 patients who were negative according to the predictive formula, 70 patients actually had a TACE response or had a liver function maintained in Child-Pugh

class A, indicating a high negative predictive value of 90.9% (Table 5). In these patients, repeated TACE is expected to produce effective treatment results.

Only a few years ago, sorafenib was the only effective first-line systemic therapy available to patients refractory to TACE.[22,23] On the other hand, several options for systemic therapy have become available in recent years.[24] Lenvatinib proved to be non-inferior to sorafenib in the REFLECT study and was approved as a first-line therapy.[25] In addition, regorafenib was approved as a second-line therapy in patients who experienced no effect of sorafenib in the RESORCE study.[26] In addition, cabozantinib, ramucirumab, nivolumab, and pembrolizumab were also in clinical trials in advanced HCC patients.[23,24,27] Because of these diverse therapeutic options, patients, who are more likely to be unresponsive to TACE and whose liver function is predicted to deteriorate, require a rapid switch to other treatments.

This study had some limitations. This study was a retrospective analysis of Korean patients and was a single-center study. Detailed information of the factors that could influence the TACE outcome was difficult to analyze because of a lack of information, such as tumor vessel distribution, level of lipiodol uptake, and selective level of embolization.[28,29] Moreover, the response of the tumors to TACE was analyzed by multiple radiologists rather than by one radiologist. In addition, this study included BCLC stage 0 and stage A, which is contrary to the recommendations of the BCLC guidelines. On the other hand, a number of patients with BCLC stage 0 or A receive TACE as the initial treatment in real world scenarios.[2]

The analysis results differed slightly according to all stages of BCLC in this study; the Supplementary Material presents the statistical values of the patient groups, except those with BCLC stages 0 and A. In particular, the tumor size included in the analysis of BCLC patients at all stages was not statistically significant, except for patients with BCLC stages 0 and A (Supplementary Table 1-5 and Supplementary Fig. 1-3). Therefore, further studies involving a larger patient cohort with BCLC B are needed. In addition, because the intention was to use the same variables both in TACE-refractoriness and liver function deterioration, some important clinical factors, such as alcohol intake and the status of a HBV infection, were not included in the predictive model for liver function deterioration.

Finally, this study had a limitation in that the follow-up period was 1 year. This study focused on finding the risk factors at the time of initial TACE because patients with unresponsive treatment after TACE and deteriorated liver function have difficulty in switching to systemic therapy. The survival curves of the 27 patients who did not respond to TACE and whose liver function deteriorated and those of the remaining patients were calculated using the Kaplan-Meier method (Supplementary Fig. 4). At 12 months, there was already a 25.5% difference in survival between the two groups. In addition, the survival gap increased further after 12 months. Therefore, in this paper, a follow-up period based on 12 months was set. Based on this period, patients for whom TACE is expected to be ineffective can switch to another treatment before aggravation.

Despite these limitations, this study is applicable when considering the relatively small number of variables, and these simplified methods would be helpful when attempting to predict the TACE responsiveness and the deterioration of liver function in clinical practice. This study analyzed those two factors together, while most studies analyzed mainly the reactivity to TACE or the deterioration of liver function separately. In addition, other studies focused mostly on the groups, in whom the main etiology of HCC was alcohol or HCV.[11,17,18] On the other hand, it is significant that this study was aimed at Korean patients, in whom HBV was the main etiology of HCC.

In conclusion, a method of predicting the refractoriness to TACE and the deterioration of liver function after TACE was developed, with 74.1% sensitivity and a 90.9% negative predictive value. In this way, repeated TACE is expected to produce effective treatment results in people who do not fulfill those criteria, whereas those who do not respond to TACE and who are likely to experience deterioration of liver function might consider rapid switching to other treatments.

REFERENCES

1. Sotiropoulos GC, Lang H, Frilling A, et al. Resectability of hepatocellular carcinoma: evaluation of 333 consecutive cases at a single hepatobiliary specialty center and systematic review of the literature. Hepatogastroenterology 2006;53:322-329.
2. Park JW, Chen M, Colombo M, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 2015;35:2155-2166.
3. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003;37:429-442.

4. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology 2004;127(5 Suppl 1):S179-S188.
5. Ogasawara S, Chiba T, Ooka Y, et al. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. Oncology 2014;87:330-341.
6. Korean Liver Cancer Association, National Cancer Center. 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. Gut Liver 2019;13:227-299.
7. Yamanaka K, Hatano E, Kitamura K, et al. Early evaluation of transcatheter arterial chemoembolization-refractory hepatocellular carcinoma. J Gastroenterol 2012;47:343-346.
8. Kim HY, Park JW, Joo J, et al. Severity and timing of progression predict refractoriness to transarterial chemoembolization in hepatocellular carcinoma. J Gastroenterol Hepatol 2012;27:1051-1056.
9. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339-364.
10. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
11. Sieghart W, Hucke F, Pinter M, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57:2261-2273.
12. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821-829.
13. Hollebecque A, Cattan S, Romano O, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. Aliment Pharmacol Ther 2011;34:1193-1201.
14. Kim JE, Ryoo BY, Ryu MH, et al. Sorafenib for hepatocellular carcinoma according to Child-Pugh class of liver function. Cancer Chemother Pharmacol 2011;68:1285-1290.
15. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. J Hepatol 2016;65:1140-1147.
16. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.
17. Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol 2013;24:2565-2570.
18. Pinato DJ, Arizumi T, Allara E, et al. Validation of the hepatoma arterial embolization prognostic score in European and Asian populations and proposed modification. Clin Gastroenterol Hepatol 2015;13:1204-1208.e2.
19. Chan AO, Yuen MF, Hui CK, Tso WK, Lai CL. A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. Cancer 2002;94:1747-1752.
20. Hwang JI, Chow WK, Hung SW, et al. Development of a safety index of transarterial chemoembolization for hepatocellular carcinoma to prevent acute liver damage. Anticancer Res 2005;25(3c):2551-2554.
21. Kudo M. A new era of systemic therapy for hepatocellular carcinoma with regorafenib and lenvatinib. Liver Cancer 2017;6:177-184.
22. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-1314.
23. Kim DY. New systemic therapies for advanced hepatocellular carcinoma. Korean J Gastroenterol 2019;73:10-15.
24. Dika IE, Abou-Alfa GK. Treatment options after sorafenib failure in patients with hepatocellular carcinoma. Clin Mol Hepatol 2017;23:273-239.
25. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.
26. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.
27. Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019;380:1450-1462.
28. Chung JW. Recent advance in international management of hepatocellular carcinoma. J Korean Med Assoc 2013;56:972-982.
29. Miyayama S, Yamashiro M, Ikuno M, Okumura K, Yoshida M. Ultraselective transcatheter arterial chemoembolization for small hepatocellular carcinoma guided by automated tumor-feeders detection software: technical success and short-term tumor response. Abdom Imaging 2014;39:645-656.