Master of Philosophy

Validation of Prognostic Impact of ADV Score for Hepatocellular Carcinoma Resection: Analysis Using Korea Liver Cancer Registry Database

The Graduate School
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Department of Medicine

Choi, Jin-Uk

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Supervisor : Hwang, Shin

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Choi, Jin-Uk

Department of Medicine

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This certifieds that the dissertation of

Chol, Jin-Uk is approved

Ahn, Chul-Soo

Committee Chair Dr.

Hwang, Shin

Committee Member Dr.

Jung, Dong-Hwan

Committee Member Dr.

Department of Medicine

Ulsan, Korea

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Abstract

Background: We aimed to validate the prognostic power of the ADV score (alpha-fetoprotein [AFP], des-γ-carboxyprothrombin [DCP], tumor volume [TV] score, calculated as AFP [ng/mL]×DCP [mAU/mL]×TV [mL] and expressed in $\log_{10}$) for predicting patient survival after hepatocellular carcinoma (HCC) resection.

Methods: This study included 1390 patients with HCC registered in the Korea Liver Cancer Registry. Patients underwent hepatic resection between 2008 and 2012 and were followed up until December 2016. They were divided into 4 groups according to the number of tumors and preoperative treatment.

Results: There was no significant correlation among AFP, DCP, and TV values ($r^2 \leq 0.04$, $p<0.001$). In group 1 with single naïve tumor (n=1154), patient stratification with ADV 1log-interval and cutoffs of 5log, 7log, and 10log showed great prognostic contrast ($p<0.001$). In group 2 with multiple naïve tumors (n=170), patient stratification with ADV 1log-interval and above-mentioned 3 cutoffs also showed great prognostic contrast ($p<0.001$). In group 3 (n=50) and group 4 (n=16) with pretreated tumors, patient stratification with ADV 1log-interval and above-mentioned 3 cutoffs showed a noticeable prognostic contrast ($p \leq 0.031$). The ADV score based on preoperative findings also showed great prognostic contrast in 1106 patients preoperatively diagnosed as having single naïve tumor ($p<0.001$). Confining patients to tumor-node-metastasis stage I and II (n=1072) as well as Barcelona Clinic Liver Cancer stage 0 and A (n=862), ADV cutoffs showed further prognostic stratification.

Conclusions: This validation study strongly suggests that the ADV score is an integrated surrogate marker for postresection prognosis in HCC. The ADV score is primarily applicable to patients with single naïve HCC and can be expanded to those with multiple or pretreated HCCs.

Medical Subject Headings : ADV score, AFP, DCP, TV, HCCs

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and leading causes of cancer-related deaths worldwide. Hepatic resection (HR) is considered the first-line treatment in patients with preserved hepatic function; however, tumor recurrence occurs frequently and unpredictably after HR (1).

We previously demonstrated that the score derived from the multiplication of α-fetoprotein (AFP), des-γ-carboxyprothrombin (DCP or proteins induced by vitamin K antagonist or absence-II), and tumor volume (TV) (AFP-DCP-TV score or simply ADV score) is an integrated surrogate marker of postresection prognosis in solitary HCCs (2) and regarded as a quantifiable parameter reflecting tumor aggressiveness.

The prognostic role of the ADV score for HCC resection has been validated in single-center and multicenter studies (2-4); however, most patients in these studies belonged to a single high-volume institution where the ADV score had been originally developed. Thus, it is necessary to externally validate the clinical impact of the ADV score in high-volume multicenter cohorts.

In this study, we assessed the prognostic impact of the ADV score in patients who underwent HCC resection and were registered in the Korea Liver Cancer Registry (KLCR) database.

Patients and Methods

Study design

The Ministry of Health and Welfare of Korea initiated a nationwide cancer registry in 1980, called the Korea Central Cancer Registry. In concordance with the Korea Central Cancer Registry, the Korean Liver Cancer Study group established the KLCR as a nationwide HCC cohort. Totally, 4354 patients with HCC were registered in the KLCR database from January 2008 to December 2012 and were followed up with the Korea Central Cancer Registry until December 2016.

Of these patients, we selected 1439 who underwent HR. Thereafter, we excluded patients who lack data on important clinical or laboratory parameters, including tumor size, tumor number, preoperative AFP value, and preoperative DCP value. We also excluded those who underwent liver transplantation after HR because transplantation can change the postresection prognosis. Finally, we selected 1390 patients as the whole study cohort.

The 1390 total patients were divided into 4 groups according to precedent HCC treatment and number of tumors on pathologic evaluation: naïve single tumor group (group 1, n=1154), naïve multiple tumor group (group 2, n=170), treated single tumor group (group 3, n=50), and treated multiple tumor group (group 4, n=16). Patients who underwent locoregional HCC treatment once before HR were classified into the treated tumor groups regardless of the treatment response because such treatments change the values of the parameters of the ADV score. Patients who had received multiple sessions of locoregional HCC treatment were excluded because of their small number and complex recurrent patterns.

This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review board of Asan Medical Center.

The primary aim was estimating overall patient survival according to the ADV score, and the secondary aim was determining the cutoff values of the ADV score for clinical application.

Treatment

Because the KLCR database does not provide information on the types and extents of HR, we simply described surgical resection of HCC as HR. Any treatment for postresection recurrence, including various locoregional treatments and systemic chemotherapy but excluding liver transplantation, was permissible. The general principles of treatment for recurrent HCC are described elsewhere (1, 5).

ADV score

The values of AFP and DCP measured before HR were used. TV was calculated from the maximal tumor diameter under an assumption that the tumor is spherical. Multiplication of AFP (ng/mL), DCP (mAU/mL), and TV (mL) yields the ADV score, which is expressed in the logarithmic scale ($\log_{10}$ is simply presented as log) (2).

If there were multiple HCC tumors, total TV was estimated as the TV of the largest tumor multiplied by the number of tumors. This TV weighted by the number of tumors is greater than the actual total TV, thus providing some weighted prognostic value from

the number of tumors.

Data collection

Clinical parameters were collected, including age, sex, presence of chronic illness such as hypertension or diabetes mellitus, suspected etiologies of HCC such as viral hepatitis or heavy alcohol intake, Child-Pugh score and classification, model for end-stage liver disease score, Barcelona Clinic Liver Cancer (BCLC) stage at the time of HR, and tumor-node-metastasis (TNM) stage based on preoperative imaging and pathologic findings. Collected laboratory parameters included platelet, serum sodium, albumin, total bilirubin, creatinine, alanine aminotransferase, AFP, and DCP levels and international normalized ratio. Other clinical or laboratory parameters were excluded owing to insufficient data in the registry.

Statistical analysis

Numerical data are presented as means with standard deviations or as medians with ranges. Continuous variables were compared using Student's *t*-test, and incidence variables were compared using the chi-square test or Fisher's exact test. Overall survival period was computed from the day of HR until the most recent follow-up or death. Survival time and rate were estimated using the Kaplan-Meier method; differences between groups were assessed using the log-rank test. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 22; IBM, Armonk, NY, USA).

Results

Patient demographics

All 1390 patients were classified according to the number of tumors and preoperative HCC treatment; their clinicopathologic features are summarized in **Table 1**.

The primary liver diseases were hepatitis B virus infection in 1007 patients (72.4%), hepatitis C virus infection in 85 (6.1%), non-hepatitis B virus non-hepatitis C virus in 45 (3.2%), alcoholic liver disease in 125 (9.0%), and unknown (missing data) in 128 (9.2%).

In patients belonging to the single naïve tumor group (group 1), the preoperative imaging diagnosis (n=1141) was a single tumor in 1069 patients (93.7%), 2 tumors in 57 (5.0%), and 3 or more tumors in 15 (1.3%).

Patients in the treated tumor groups (groups 3 and 4) underwent HR 164.7±276.1 days (median 54 days) after HCC treatment (radiofrequency ablation in 9, transarterial chemoembolization in 55, and transarterial radioembolization in 2).

During the follow-up period of 50.0±24.9 months (median, 47.1 months), 315 of 1390 patients (22.7%) died of HCC recurrence (n=292, 92.7%) and other causes (n=23, 7.3%). Overall patient survival curves of the 4 groups are presented in **Fig. 1**. The survival rate in group 1 was higher than that in the other 3 groups ($P<0.001$); however, it was similar among the other 3 groups ($P=0.85$).

Table 1. Clinical features of 1,390 patients who underwent hepatic resection for hepatocellular carcinoma according to tumor number and preoperative treatment

Group	Treatment-naïve group			Preoperative treatment group		
	Single tumor (Group 1)	Multiple tumors (Group 2)	p-value	Single tumor (Group 3)	Multiple tumors (Group 4)	p-value
Patient number	1154	170		50	16	
Age (yrs)	56.8±10.3	56.3±11.0	0.47	56.5±11.9	53.9±10.0	0.44
Sex (Male / Female) (n)	918 / 236	138 / 32	0.62	14 / 10	13 / 3	0.17
Diabetes mellitus (n)	253	39	0.77	10	3	0.61
Hypertension (n)	383	60	0.59	13	4	0.61
Performance status			0.005*			0.59*
0	840	111		28	8	
1	110	25		11	4	
2	6	4		2	0	
Not available	198	30		9	4	
Background liver disease (n)			0.77**			0.36**
HBV	833	123		39	12	
HCV	67	15		3	0	
NBNC	42	1		1	1	
ALD	101	17		4	3	
Not available	111	14		3	0	
Preoperative blood laboratory profiles (mean±SD)						
Albumin (g/dL)	4.20±0.46	4.10±0.54	0.011	3.90±0.51	3.93±0.28	0.82
Creatinine (mg/dL)	0.95±0.73	0.87±0.18	0.17	0.91±0.35	0.82±0.20	0.32
Sodium (mmol/L)	140.1±3.9	139.6±2.9	0.13	139.5±2.6	139.1±2.1	0.43
ALT (IU/L)	44.5±61.2	50.9±74.8	0.22	53.7±64.2	55.0±34.1	0.94
Total bilirubin (mg/dL)	0.94±1.08	0.95±1.08	0.88	1.02±0.86	0.76±0.31	0.24
Prothrombin time (INR)	1.13±0.52	1.05±0.10	0.69	1.08±0.11	1.08±0.08	0.99
Platelet count (10^3/μL)	172.6±69.8	181.4±71.4	0.13	171.9±65.6	162.6±57.4	0.62
AFP (ng/mL) at operation						
Mean ± SD	2265.3±13737.4	3562.8±18036.4	0.27	5215.6±3877.7	488.4±1482.4	0.49
Median	19.6	31.7		13.2	59.9	
DCP (mAU/mL) at operation						
Mean ± SD	1610.1±7105.9	2696.6±9237.9	0.075	2738.2±8239.2	2192.9±7112.1	0.81
Median	67	177		64	50	
ICG-R_{15} (%)	11.9±8.6 (n=917)	12.0±8.0 (n=142)	0.98	11.9±9.5 (n=25)	12.6±8.5 (n=8)	0.87

MELD score	7.91±2.19	7.59±1.78	0.073	8.2±2.3	7.5±1.0	0.25
CTP class			0.22			0.76
A	1120	162		49	16	
B	34	8		1	0	
Preoperative imaging finding	(n=1141)	(n=169)		(n=48)	(n=15)	
Maximal tumor diameter (cm)	4.05±2.77	4.95±3.45	<0.001	4.63±2.90	3.87±2.54	0.63
Mean tumor number (n)	1.09±0.42	2.23±1.11	<0.001	1.52±1.18	1.80±1.08	0.42
Total tumor volume (mL)	123.3±399.3	508.2±1510.7	<0.001	151.7±283.8	139.7±245.8	0.88
Postoperative pathology finding						
Maximal tumor diameter (cm)	4.18±2.93	5.09±3.63	<0.001	4.93±3.06	4.01±2.33	0.27
Mean tumor number (n)	1.00±0.00	2.55±1.01	<0.001	1.00±0.00	2.69±1.20	<0.001
Total tumor volume (mL)	121.2±350.8	669.1±2051.5	<0.001	148.0±287.9	187.5±299.1	0.64
ADV score (log_{10})						
Preoperative	5.04±2.07	5.99±2.24	<0.001	5.42±2.26	4.99±2.10	0.53
Postoperative	5.06±2.11	6.10±2.23	<0.001	5.44±2.35	5.60±2.39	0.81
BCLC stage			<0.001***			0.94***
0	78	2		2	1	
A	726	56		21	6	
B	70	51		6	3	
C	187	44		16	4	
D	0	0		0	0	
Not available	93	17		5	2	
Postoperative TNM			<0.001****			<0.001****
T1N0M0	159	0		7	0	
T2N0M0	899	14		39	2	
T2N0M1	3	0		0	0	
T2N1M0	4	0		0	0	
T3N0M0	88	129		4	12	
T3N0M1	0	1		0	1	
T3N1M0	1	0		0	0	
T3N1M1	0	1		0	0	
T4N0M0	0	21		0	1	
T4N0M1	0	1		0	0	
T4N1M0	0	3		0	0	
Postoperative TNM stage			<0.001*****			<0.001*****
I	159	0		7	0	
II	899	14		39	2	
III	88	129		4	12	
IV-A	5	24		0	1	
IV-B	3	3		0	1	

AFP, alpha-fetoprotein; DCP, des-γ-carboxyprothrombin; ADV, AFP-DCP-tumor volume; ICG-R_{15}, indocyanine green retention test at 15 minutes; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; TNM, Tumor-Node-Metastasis; BCLC, Barcelona Clinic Liver Cancer.

* status 0 vs. status 1+2

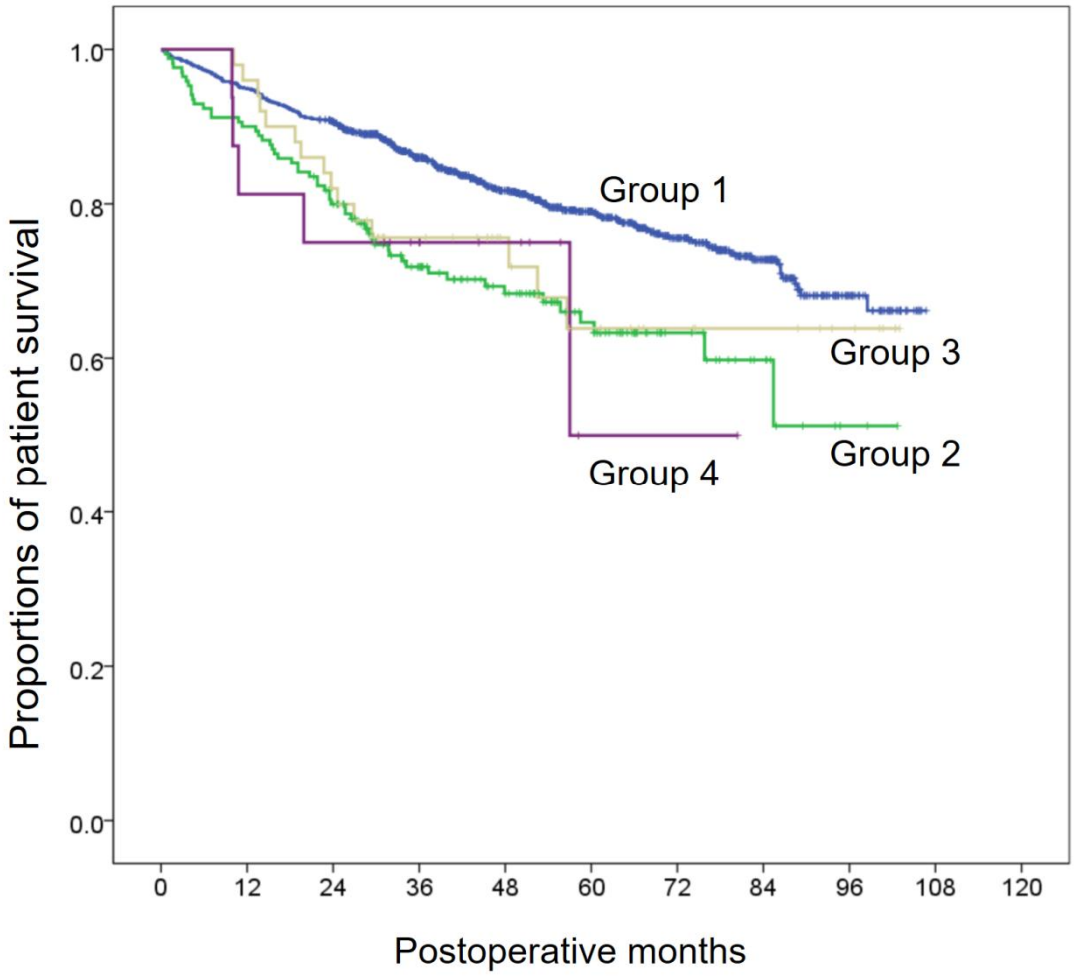
** HBV vs. others

*** stage 0+A vs. B+C+D

***** stage I+II vs. III + IV-A + IV+B

**** stage T1N0M0 + T2N0M0 vs. sum of others

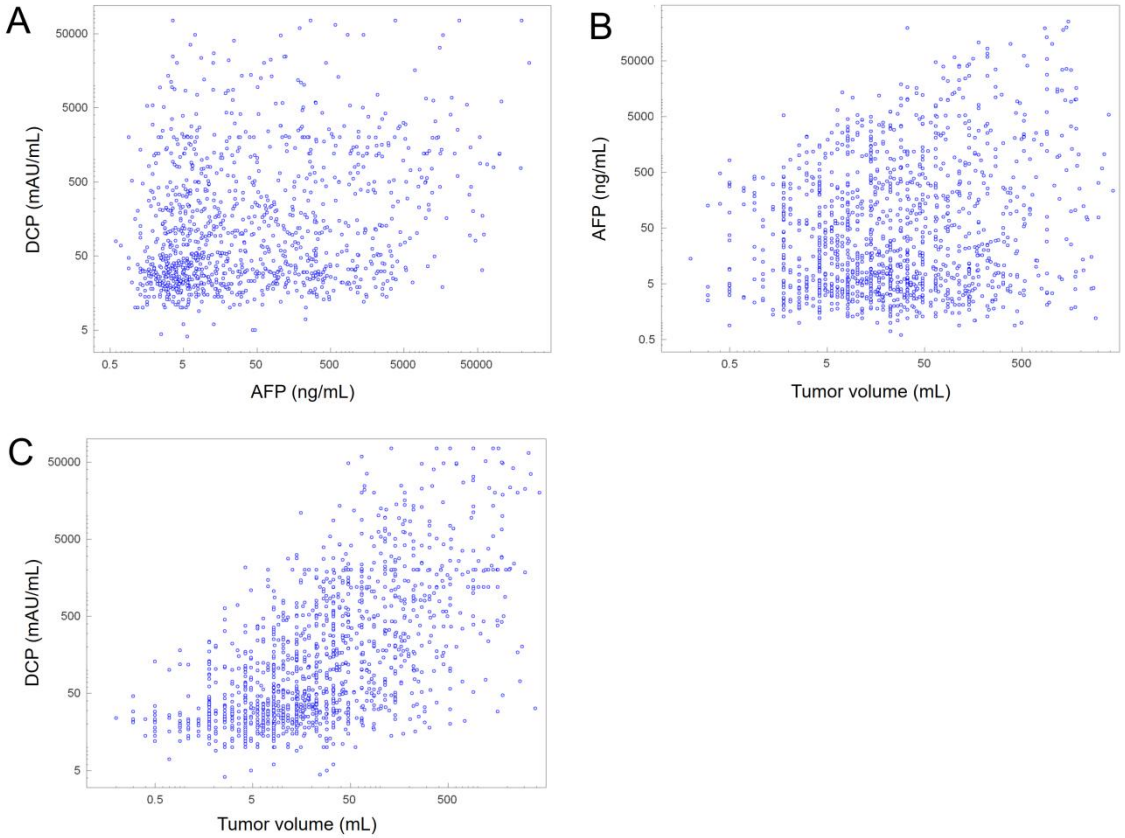
Figure 1. Comparison of overall patient survival curves according to the number of tumors and preoperative treatment for hepatocellular carcinoma.



Relationship between tumor size and tumor markers

In 1154 patients belonging to the naïve single tumor group (group 1), the association of AFP, DCP, and TV is presented in 2-dimensional scatter plots (**Fig. 2**). There was no significant correlation between the following combinations: AFP and DCP (r^2=0.040, r=0.200, p<0.001), TV and AFP (r^2=0.016, r=0.126, p<0.001), and TV and DCP (r^2=0.037, r=0.192, p<0.001). These results indicate that AFP, DCP, and TV are independent parameters.

Figure 2. Two-dimensional scatter plots for the correlation of α-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP), and tumor volume (TV). (**A**) DCP vs. AFP. (**B**) TV vs. AFP. (**C**) TV vs. DCP.



Patient survival according to postoperative ADV score in patients with a single naïve HCC

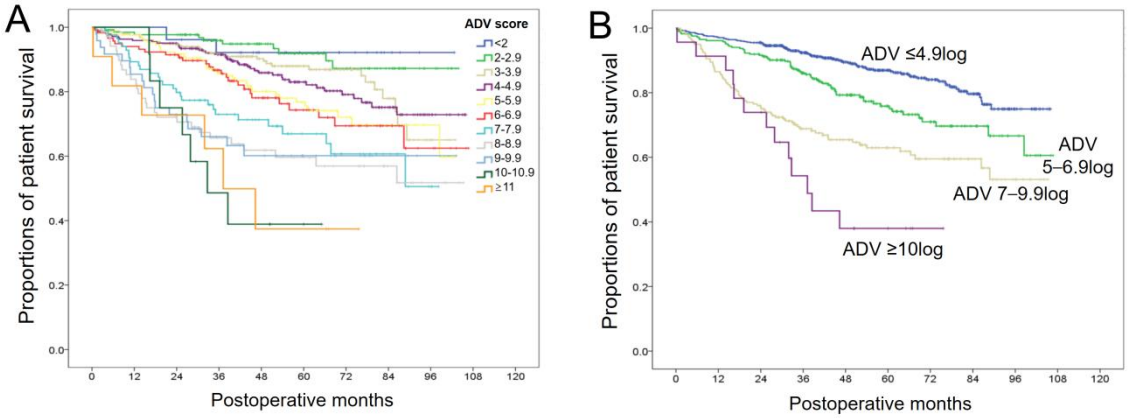
Of 1154 patients with single naïve tumor in group 1, 239 (20.7%) died during the mean follow-up period of 51.3±24.8 months (median, 48.2 months). Their 1-, 2-, 3-, and 5-year overall survival rates were 94.9%, 90.6%, 86.0%, and 79.0%, respectively (**Fig. 1**).

The ADV scores were stratified by an interval of 1log (10-fold). The distribution of ADV scores was as follows: <2log in 26 (2.3%), 2–2.9log in 129 (11.2%), 3–3.9log in 248 (21.5%), 4–4.9log in 243 (21.1%), 5–5.9log in 168 (14.6%), 6–6.9log in 117 (10.1%), 7–7.9log in 84 (7.3%), 8–8.9log in 68 (5.9%), 9–9.9log in 48 (4.2%), 10–10.9log in 12 (1.0%), and ≥11log in 11 (1.0%) patients.

The overall patient survival rate in each group was closely correlated with the ADV score ($p<0.001$), in which the 5-year survival rates were 92.1% in ADV <2log, 91.9% in ADV 2–2.9log, 87.9% in ADV 3–3.9log, 83.0% in ADV 4–4.9log, 76.8% in ADV 5–5.9log, 74.3% in ADV 6–6.9log, 66.9% in 7–7.9log, 59.6% in ADV 8–8.9log, 60.1% in ADV 9–9.9log, 38.9% in ADV 10–10.9log, and 37.4% in ADV ≥11log (**Fig. 3A**).

Through cluster analysis, the ADV scores were stratified as ADV ≤4.9log, ADV 5–6.9log, ADV 7–9.9log, and ADV ≥10log, showing great prognostic contrast ($p<0.001$, **Fig. 3B**).

Figure 3. Comparison of overall patient survival curves in group 1 patients. (**A**) Comparison according to the ADV scores of 1log intervals. (**B**) Comparison in 4 subgroups with cutoffs of 5log, 7log, and 10log.



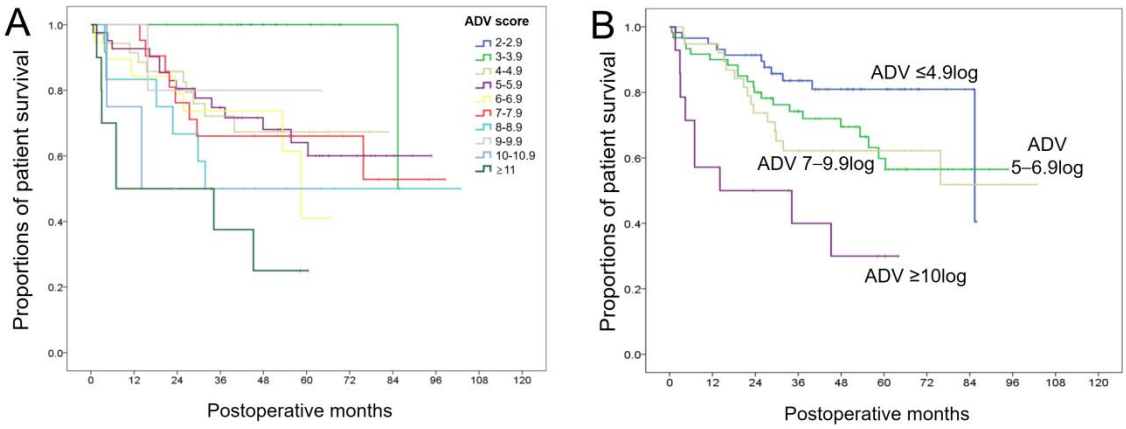
Patient survival according to postoperative ADV score in patients with multiple naïve HCCs

In 170 patients with multiple naïve tumors in group 2, 56 (32.9%) died during the mean follow-up period of 43.0±23.9 months (median, 40.8 months). Their 1-, 2-, 3-, and 5-year overall survival rates were 94.9%, 90.6%, 86.0%, and 79.0%, respectively (**Fig. 1**).

The overall patient survival rate in each group was crudely correlated with the ADV score ($p<0.001$), in which their 5-year survival rates were 100% in ADV 2–2.9log (n=5), 100% in ADV 3–3.9log (n=17), 67.3% in ADV 4–4.9log (n=35), 64.0% in ADV 5–5.9log (n=41), 40.93% in ADV 6–6.9log (n=19), 66.0% in 7–7.9log (n=21), 50.0% in ADV 8–8.9log (n=12), 80.0% in ADV 9–9.9log (n=5), 50.0% in ADV 10–10.9log (n=5), and 25.0% in ADV ≥11log (n=10) (Fig. **4A**).

Through cluster analysis, the ADV scores were stratified as ADV ≤4.9log, ADV 5–6.9log, ADV 7–9.9log, and ADV ≥10log, showing a noticeable prognostic contrast ($p=0.001$, **Fig. 4B**).

Figure 4. Comparison of overall patient survival curves in group 2 patients. (**A**) Comparison according to the ADV scores of 1log intervals. (**B**) Comparison in 4 subgroups with cutoffs of 5log, 7log, and 10log.

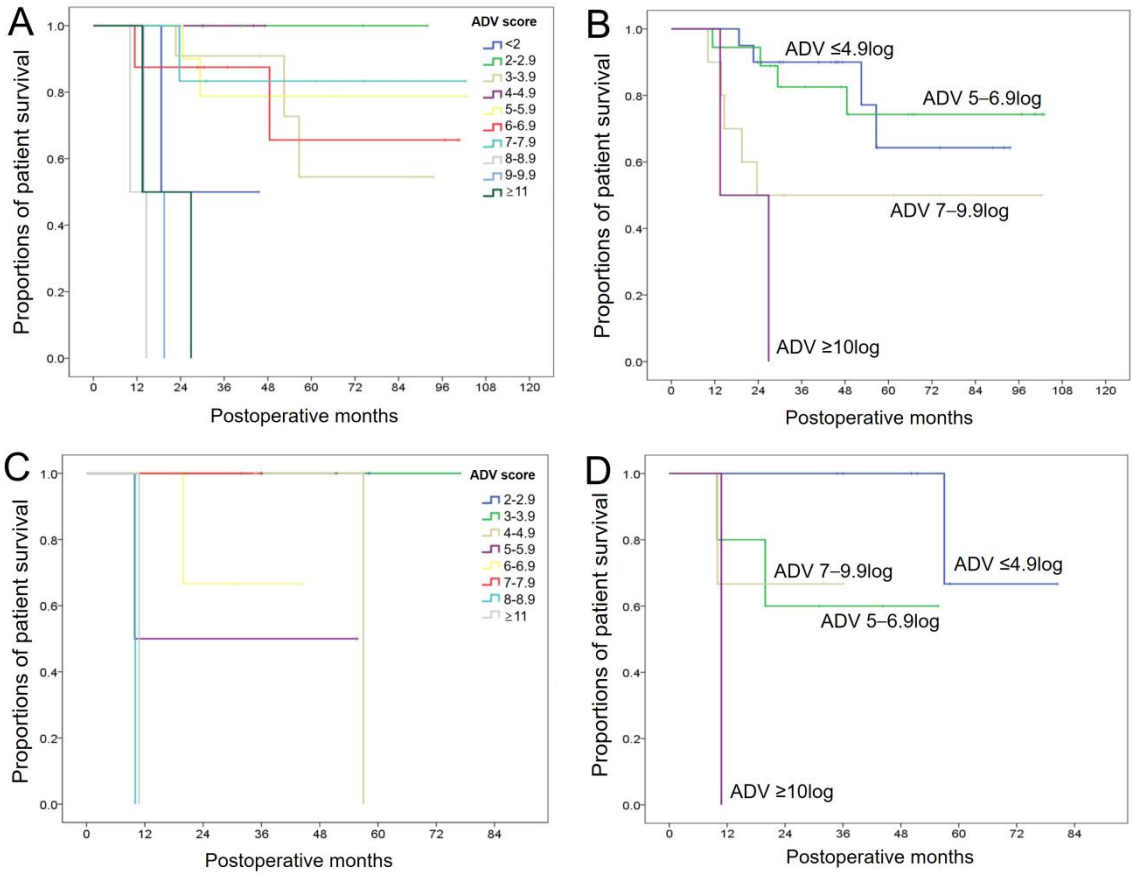


Patient survival according to postoperative ADV score in patients with treated HCCs

In 50 patients with a single treated tumor in group 3, 15 (30.0%) died during the mean follow-up period of 48.5±28.5 months (median, 44.1 months). Their 1-, 2-, 3-, and 5-year overall survival rates were 96.0%, 82.0%, 75.6%, and 63.9%, respectively (**Fig. 1**). The overall patient survival rate in each group was crudely correlated with the ADV score (p=0.003, **Fig. 5A**). Through cluster analysis, the ADV scores were stratified as ADV ≤4.9log, ADV 5–6.9log, ADV 7–9.9log, and ADV ≥10log, showing a significant prognostic contrast (p=0.007, **Fig. 5B**).

In 16 patients with multiple treated tumors in group 4, 5 (31.3%) died during the mean follow-up period of 38.6±20.0 months (median, 36.0 months). Their 1-, 2-, 3-, and 5-year overall survival rates were 81.3%, 75.0%, 75.0%, and 50.0%, respectively (**Fig. 1**). The overall patient survival rate in each group was crudely correlated with the ADV score (p=0.017, **Fig. 5C**). Through cluster analysis, the ADV scores were stratified as ADV ≤4.9log, ADV 5–6.9log, ADV 7–9.9log, and ADV ≥10log, showing a significant prognostic contrast (p=0.031, **Fig. 5D**).

Figure 5. Comparison of overall patient survival curves. (**A** and **B**) Comparison according to the ADV scores of 1log intervals and in 4 subgroups with cutoffs of 5log, 7log, and 10log in group 3 patients. (**C** and **D**) Comparison according to the ADV scores of 1log intervals and in 4 subgroups with cutoffs of 5log, 7log, and 10log in group 4 patients.



Prediction of patient survival using the ADV score based on the preoperative finding in patients diagnosed as having single naïve HCC

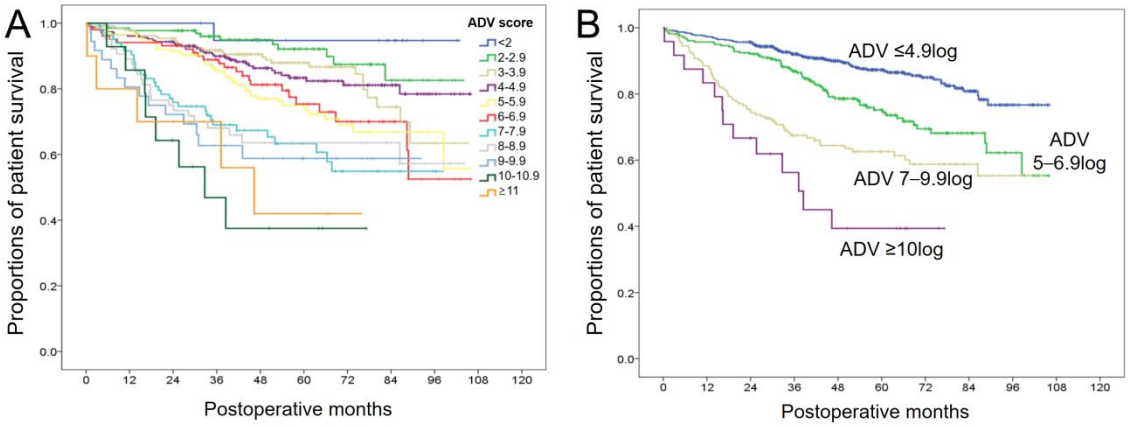
Of 1106 patients diagnosed as having single naïve tumor in the preoperative imaging study, 227 (20.5%) died during the mean follow-up period of 50.9±24.5 months (median, 47.5 months). Their 1-, 2-, 3-, and 5-year overall survival rates were 95.1%, 90.7%, 85.9%, and 79.0%, respectively.

The ADV scores were stratified by an interval of 1log (10-fold). The distribution of the ADV scores was as follows: <2log in 20 (1.8%), 2–2.9log in 133 (12.0%), 3–3.9log in 238 (21.5%), 4–4.9log in 230 (20.8%), 5–5.9log in 176 (15.9%), 6–6.9log in 102 (9.2%), 7–7.9log in 83 (7.5%), 8–8.9log in 64 (5.8%), 9–9.9log in 36 (3.3%), 10–10.9log in 14 (1.3%), and ≥11log in 10 (0.9%) patients.

The overall patient survival rate in each group was closely correlated with the preoperative ADV score ($p<0.001$), in which the 5-year survival rates were 94.7% in ADV <2log, 92.1% in ADV 2–2.9log, 87.9% in ADV 3–3.9log, 83.4% in ADV 4–4.9log, 74.9% in ADV 5–5.9log, 75.4% in ADV 6–6.9log, 63.3% in 7–7.9log, 63.6% in ADV 8–8.9log, 58.8% in ADV 9–9.9log, 37.5% in ADV 10–10.9log, and 42.0% in ADV ≥11log (**Fig. 6A**).

Through cluster analysis, the ADV scores were stratified as ADV ≤4.9log, ADV 5–6.9log, ADV 7–9.9log and ADV ≥10log, showing a high prognostic contrast ($p<0.001$, **Fig. 6B**).

Figure 6. Comparison of overall patient survival curves according to the ADV score based on preoperative findings. (**A**) Comparison according to the ADV scores of 1log intervals. (**B**) Comparison in 4 subgroups with cutoffs of 5log, 7log, and 10log.

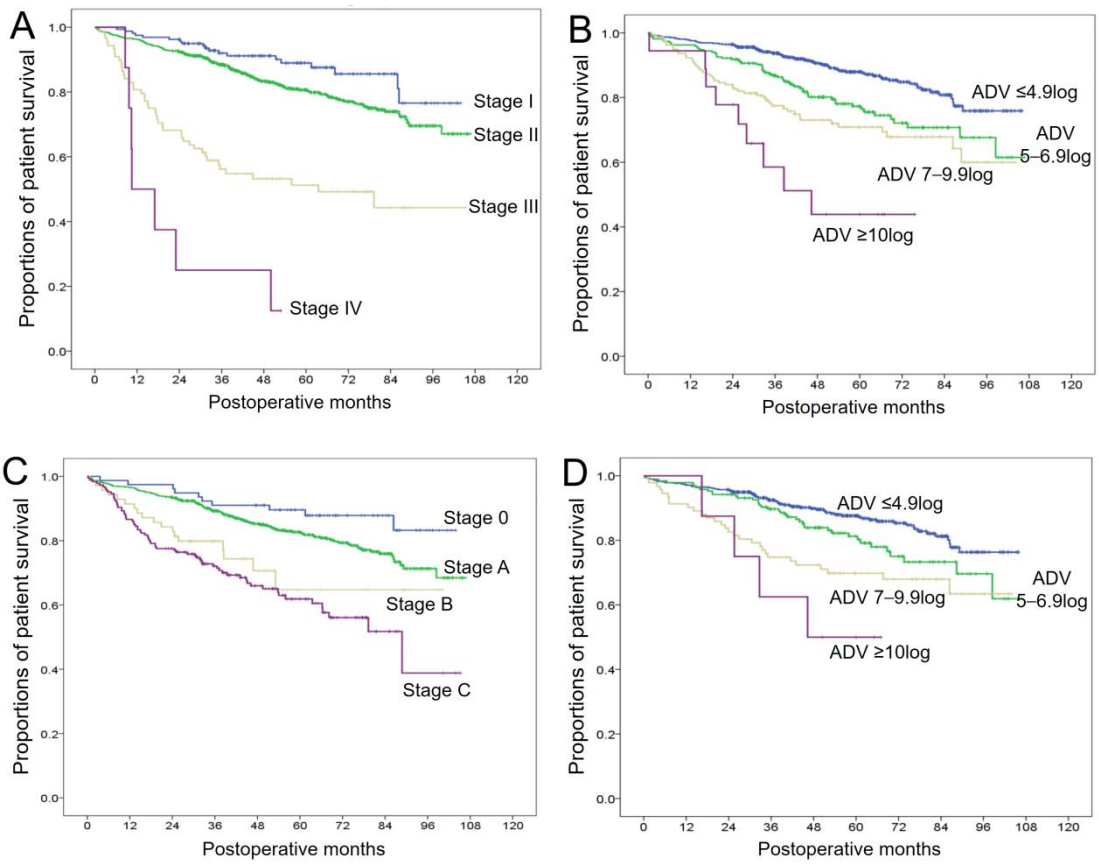


Survival analysis with postoperative TNM stage and BCLC stage in patients diagnosed as having naïve HCC

In 1324 patients belonging to groups 1 and 2, survival analysis with the postoperative TNM stage showed a highly noticeable prognostic contrast ($p<0.001$, **Fig. 7A**). However, 1072 of 1324 (81.0%) patients had TNM stage I and II disease; there was a relatively low prognostic difference between stage I and II ($p=0.034$). When confining to the 1058 patients belonging to TNM stage I and II, stratification with the ADV score increased the prognostic contrast ($p<0.001$, **Fig. 7B**).

In 1324 patients belonging to groups 1 and 2, survival analysis with the BCLC stage also showed a highly noticeable prognostic contrast ($p<0.001$, **Fig. 7C**). However, 862 of 1324 (65.1%) patients had BCLC stage 0 and A disease, and there was a marginal prognostic difference between stage 0 and A ($p=0.074$). When confining to the 862 patients belonging to BCLC stage 0 and A, stratification with the ADV score increased the prognostic contrast ($p<0.001$, **Fig. 7D**).

Figure 7. Comparison of overall patient survival curves according to the tumor staging system and ADV score in group 1 and 2 patients. (**A**) Comparison according to the tumor-node-metastasis (TNM) staging system. (**B**) After confining patients to TNM stage I and II: comparison of 4 subgroups with ADV cutoffs of 5log, 7log, and 10log in group 3 patients. (**C**) Comparison according to Barcelona Clinic Liver Cancer (BCLC) stage. **(D**) After confining patients to BCLC stage 0 and A: comparison of 4 subgroups with ADV cutoffs of 5log, 7log, and 10log in group 3 patients.



Discussion

It is difficult to predict postresection prognosis in patients with HCC because carcinogenesis and tumor biology in these patients are highly complex and heterogeneous. There are several clinically important individual predictors that can be used before HR (e.g., tumor size, tumor markers, and 18-fluoro-deoxyglucose positron emission tomography findings) and after HR (microvascular invasion [MVI]), as well various tumor staging systems for HCC (5-11).

The HCC tumor size has been accepted for a long time as one of the most important prognostic factors (1, 12, 13). The expression of tumor markers, such as AFP and DCP, is highly variable in HCC, as this study shows. Thus, to enhance the prognostic impact of tumor markers, multiple tumor markers need to be integrated in a single score, such as the sum of the number of positive tumor markers or multiplication of AFP and DCP with different cutoff values (14-18). However, the prognostic impact of these tumor markers is still not sufficiently high. Some specific imaging findings of gadoxetic acid-enhanced magnetic resonance imaging and 18-fluoro-deoxyglucose positron emission tomography indicate poor prognosis, but their prognostic impact is still debated.

MVI has been considered one of the most important prognostic parameters; however, because it is a pathologic finding, it is difficult to predict the status of MVI before HR. Many studies have predicted MVI using imaging findings (liver dynamic computed tomography, gadoxetic acid-enhanced magnetic resonance imaging, and 18-fluoro-deoxyglucose positron emission tomography), tumor markers (AFP, DCP, and next-generation DCP), and their combination (14-24). The ADV score was also used for predicting MVI in a previous study, in which the area under the receiver-operating characteristic curve was as high as 0.788 (2). These preoperative diagnostic

approaches resulted in a significant increase in the discriminatory power for predicting MVI; however, their role is limited in clinical practice.

To overcome the demerits of individual prognostic parameters, we developed the ADV score as an integrated surrogate marker for postresection prognosis in HCC and as a quantifiable parameter reflecting tumor aggressiveness (2). ADV score-dependent prognostic stratification was validated in 1 single-center study and 1 multicenter study (3, 4), in which the ADV score was highly correlated with the postresection prognosis. The present study also demonstrated that the ADV score was proportionally correlated with patient survival. Considering that 92.7% of mortality cases were directly associated with HCC recurrence in this study, the ADV score must be proportionally correlated with tumor recurrence, as shown in previous studies (2-4, 25).

The ADV score was originally developed for patients with single naïve HCC. To our knowledge, this is the first study to evaluate the prognostic impact of the ADV score in patients with multiple HCCs. Although the number of patients with multiple tumors was not large in this study, we believe that the ADV score is reliably correlated with the postresection prognosis. To apply the ADV score to multiple HCCs, the total TV was estimated as the TV of the largest tumor multiplied by the number of tumors. This calculation method results in a significantly larger total TV than the arithmetical summation of the TVs of individual tumors. We believe that the ADV score calculated using a TV weighted by the number of tumors can partially compensate for the high prognostic impact of tumor multiplicity. The prognosis of patients with multiple naïve HCCs with ADV score <4log was comparable to that of patients with single naïve tumor; however, outcomes worsened rapidly along the stepwise increase in the ADV score beyond 4log. Thus, the calculation of total TV in multiple tumors requires further

refinement.

The value of the ADV score can be significantly disturbed by preoperative locoregional treatment. We previously studied the prognostic impact of the ADV score in patients with downstaged or recurrent HCCs after preoperative locoregional treatment (3). Unless complete radiologic or pathologic response occurs, some viable tumor portions remain, thus enabling the calculation of the ADV score. Our previous study demonstrated that the ADV score was still valid for preoperatively treated single HCCs (3). In contrast, the prognostic impact of preoperative locoregional treatment cannot be simply estimated because it can change the tumor biology. We previously reported that transarterial chemoembolization for small single HCCs adversely affects the postresection prognosis irrespective of the pathologic response up to 95% necrosis, and even the prognostic benefit from complete tumor necrosis is limited to the downstaging effect (26, 27). Such adverse effects may be associated with residual tumor cells with worsened tumor biology (3, 27, 28).

The ADV score enables predicting the postresection prognosis quantitatively. However, ADV scores with tenths-place value or 1log-interval stratification have too many and too narrow zones to allow physicians and surgeons to intuitively estimate the prognosis. Thus, some cutoff values are needed to apply the ADV score in clinical practice.

We previously reported that the reliable ADV score cutoff in single naïve HCC was 4log for tumor recurrence and 5log for patient survival (2, 3). In this study, we adopted 3 cutoffs (5log, 7log, and 10log), by which our patients were stratified into 4 groups. We believe that patients with ADV ≤5log gain the most benefit from HR and those with ADV ≥10log gain the least benefit. Thus, we suggest using these 2 ADV cutoffs (5log and

10log) for patient survival.

The KLCR database provides preoperative imaging findings on tumor size and number, which enabled us to calculate the ADV score based on the preoperative finding. The results in patients with single naïve tumor on preoperative imaging were comparable to those from the postoperative ADV score. This is not surprising because the diagnostic accuracy for tumor size and number is high enough with the combination of dynamic computed tomography and contrast-enhanced magnetic resonance imaging (29). Such preoperative prognostic prediction is often helpful to decide the plan for HR, especially with respect to the extent of resection. We previously showed that anatomical HR is superior to non-anatomical HR in patients with an ADV score ≤4log for tumor recurrence and in patients with an ADV score ≤5log for patient survival regardless of preoperative treatment. Thus, even an HCC with a lower ADV score is eligible for aggressive surgical resection (3, 4).

There are various tumor staging systems for HCC; each system has its unique merits and limitations. In groups 1 and 2 in this study, the TNM staging system showed a highly noticeable prognostic contrast; however, 81% of the patients belonged to stage I and II, and there was no prognostic difference between these 2 stages. Such a low power of discrepancy is less helpful in clinical practice. In contrast, additional application of the ADV score resulted in noticeable enhancement of prognostic contrast. This ADV score-derived enhancement was repeatedly seen in patients with BCLC stage 0 and A. We also showed that the ADV score combined with MVI, 18-fluoro-deoxyglucose positron emission tomography findings, or gene signature test can enhance the prognostic predictive power of individual parameters (2, 4, 25). These findings indicate that the ADV score can be an additional predictive parameter

combined with various HCC staging systems or other individual risk factors.

This study has some limitations. This is a retrospective single-country cohort study in a hepatitis B virus-endemic area. It is necessary to validate the ADV score in other geographic regions before our results can be extended to patients with HCC of various causes. Another major limitation is the lack of recurrence analysis because detailed information on tumor recurrence is not obtainable from the KLCR database. However, the survival status of all patients was followed up completely together with the government-led Korea Central Cancer Registry.

In conclusion, this external validation study strongly suggests that the ADV score is an integrated surrogate marker for postresection prognosis in HCC. We believe that the ADV score is primarily applicable to patients with a single naïve HCC and can be expanded to those with multiple or pretreated HCCs.

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국문 요약

배경: 우리의 연구 목표는 간세포암 절제에 있어 ADV score (alpha-fetoprotein [AFP], des-γ-carboxyprothrombin [DCP], tumor volume [TV] score, 점수의 계산은 다음과 같이 AFP [ng/mL]×DCP [mAU/mL]×TV [mL] and expressed in log_{10} 각 수치의 곱을 log scale로 변환하여 계산한다) 가 가지는 예후 평가의 효용성 입증에 있었다.

연구방법: 연구에는 Korea Liver Cancer Registry (KLCR) 에 등재된 1390명의 환자들을 대상으로 이루어졌다. 연구환자들은 2008년에서 2012년 사이 간세포암으로 간절제술 을 받았으며 수술당시 종양의 개수와 수술 전 처치의 유무에 따라 총 4 그룹으로 나누어 분석하였다.

결과: ADV score를 구성하는 AFP, DCP 그리고 TV간에 통계학적으로 유의한 연관성은 없었다 ($r^2 \leq 0.04$, $p<0.001$). 수술 전 처치를 받지 않은 단일 종양 그룹 (그룹1, n=1154)의 환자들은 ADV score의 절단값을 5log, 7log 그리고 10log 로 나누어 분류했을 때 예후에 있어 통계적으로 큰 차이를 보였다 ($p<0.001$). 수술 전 처치를 받지 않은 다발성 종양 그룹 (그룹2, n=170) 에서도 같은 결과를 보였다 ($p<0.001$). 수술 전 종양에 대해 비수술적 치료를 받은 단일, 다발성 종양 그룹 (각 그룹3, n=50 그룹4, n=16)의 경우에도 비슷하게 예후에 있어 차이를 보였으나 통계학적으로는 그룹 1, 2에 비해 유의성이 떨어졌다 ($p \leq 0.031$). TNM stage (tumor-node-metastasis stage) I과 II 및 BCLC stage (Barcelona Clinic Liver Cancer stage) 0과 A 의 환자들만 분석했을 때, ADV score의 절단값은 충분한 예후 평가 도구로서의 가치를 보였다.

결론: 이 연구는 ADV score가 간세포암의 절제 이후 예후 평가의 도구로서 이용 될 수 있다는 가능성을 보여주었다. 또한 ADV score의 적용은 수술 전 처치를 받지 않은 단일 종양 그룹 뿐 아니라 수술전 처치를 받은 다발성 종양 그룹에서도 가능하다.

핵심어 : ADV score, AFP, DCP, TV, HCCs