

Direct-acting Antiviral Therapy Improves the Outcome of Chronic Hepatitis C/intermediate-stage B Hepatocellular Carcinoma Patients

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Abstract. *Background/Aim:* The benefit of direct-acting antiviral therapy (DAA) in chronic hepatitis C (CHC) infected patients who received curative treatment for early-stage hepatocellular carcinoma (HCC) is well known, but is unclear for intermediate stage HCC. *Patients and Methods:* CHC patients with Barcelona Clinic Liver Cancer (BCLC) stage B HCC receiving chemoembolization were identified. Univariate, multivariate analyses, and Kaplan–Meier curve were used to identify factors associated with survival outcomes. *Results:* Among 113 included patients, the median survival of DAA treated group (n=14) and non-treated group (n=99) were 40.1 months and 22.9 months, respectively. Multivariate analysis showed that Eastern Cooperative Oncology Group (ECOG) score, DAA, and serum albumin were key independent factors associated with overall survival. Moreover, the time-to-complete remission (TTCR) was improved in the DAA treated group. *Conclusion:* ECOG, DAA, and serum albumin were prognostic factors for CHC/intermediate-stage HCC patients. DAA was also a beneficial factor for TTCR.

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Key Words: Direct-acting antiviral (DAA), hepatocellular carcinoma (HCC), hepatitis C virus (HCV), transarterial chemoembolization (TACE).

Primary liver cancer ranks sixth in cancer incidence (841,000 new cases) and fourth in cancer-related mortality (781,000 cases) globally. Hepatocellular carcinoma (HCC) is the most common primary liver cancer and comprises over 80% of all liver tumors. Several known risk factors are linked to development of HCC including chronic viral infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV), heavy alcohol intake, type 2 diabetes, obesity/fatty liver disease, aflatoxin contaminated foodstuffs, hereditary hemochromatosis, alpha1-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, and Wilson's disease (2). These diseases also lead to hepatic fibrosis and cirrhosis. Furthermore, pre-existing cirrhosis is observed in over 80% of HCC patients.

The Barcelona Clinic Liver Cancer (BCLC) staging classification demonstrates the best predictive efficacy for HCC survival and is used as the universal practice guideline to determine the HCC treatment strategy. For BCLC stage B patients, transcatheter arterial chemoembolization (TACE) is one of the common treatments.

Chronic hepatitis C (CHC) infection is the second most common cause of HCC globally, which accounts for 10~25% of cases in Taiwan, and is the most common cause of HCC in Western countries. There are over 184 million people infected with HCV worldwide. CHC is associated with 20~30-fold increased risk for HCC. For HCV related cirrhosis, the annual incidence of HCC rate is around 3-5% and the 5-year cumulative risk ranges from 5~30%. Studies have shown that liver related morbidity and mortality can be reduced after CHC patients have achieved sustained viral response (SVR). As medicine advances, HCV treatment has evolved from pegylated interferon (Peg-IFN) to direct-acting antiviral (DAA) combination regimens which can achieve over 95% SVR with a low number of adverse events. Current guidelines recommend antiviral treatment for all CHC patients who do

not have comorbidity-related decreased life expectancy. The goal of antiviral treatments is to eradicate CHC infection and reduce its complications including cirrhosis, hepatic decompensation, HCC and mortality.

It is controversial whether DAA treatment for CHC decreases recurrence of HCC or improves HCC outcome. Reig *et al.* reported that 19 out of 58 HCV DAA-treated patients who had complete tumor response after anti-HCC treatment had a high tumor recurrence rate of 27.6%, within a median follow-up of 5.7 months. Similar findings were observed by Conti *et al.* and Ravi *et al.* who reported 28.81% and 9.1% HCC recurrence within 6 months after DAA treatment, respectively. Later studies reported otherwise. Singal *et al.* observed that DAA-treated and untreated patients had HCC recurrence rate of 42.1% and 58.9%, respectively; Cabibbo *et al.* showed no significant difference of HCC recurrence in DAA treated and untreated groups (HR=0.70; 95%CI=0.44-1.13; $p=0.15$).

Furthermore, the role of DAA therapy has not been clearly defined in patients with active intermediate/advanced stage HCC undergoing anti-HCC treatment. The 2020 American Gastroenterological Association (AGA) expert review on DAA and HCC reported that there was insufficient data regarding DAA therapy in patients with active intermediate or advanced stage HCC. Most of current studies were conducted on patients with earlier stage HCC (BCLC 0/A) who can receive curative treatment such as resection, local radiofrequency ablation, and transplantation. The benefit of DAA in CHC patients with intermediate/advanced stage of HCC is not clear. In this retrospective study, we examined the hypothesis that DAA treatment could improve outcomes in CHC patients with HCC BCLC stage B.

Patients and Methods

Study design and selection of patients. A retrospective cohort study of CHC patients CHC with HCC BCLC Stage B receiving TACE at the Linkou medical center of Chang Gung Memorial Hospital between 2010 to 2019 was conducted. This study was conducted in accordance with the ethical standards of our Institution's review board and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Medical records were reviewed to identify appropriate patients to be included in the study. Baseline demographics and characteristics, including tumor status, tumor number, largest tumor size, tertiary portal vein invasion, and previous surgery/ablation were recorded.

All patients had confirmed CHC with positive hepatitis C virus (HCV) RNA test. Diagnosis of HCC was made either pathologically or clinically. Clinical diagnosis was based on characteristic radiologic findings of arterial hypervascularity and venous or delayed phase washout under dynamic multiple detector computed tomography (MDCT) or contrast-magnetic resonance imaging (MRI). For those unable to be diagnosed clinically, liver biopsy was performed for pathological diagnosis (18). HCC staging was assessed according to the modified BCLC classification in 2019

American Association for the Study of Liver Diseases (AASLD) HCC practice guideline. Among 113 patients with CHC/HCC, 14 patients had received DAA for HCV eradication.

TACE treatment. TACE was performed as the current standard treatment for patients with intermediate stage HCC. Hepatic arterial angiography was performed to identify the target artery of HCC. Doxorubicin 20-60 mg (depending on the tumor size) mixed with 5-20 ml of lipiodol emulsion was infused through the target artery. Further, Gelfoam injection for target artery embolization was performed until no tumor stain was seen on angiography.

TACE treatment response and follow-up. Multiphase CT/MRI was performed 6-10 weeks after each TACE treatment. Treatment response was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Patients were followed until the time of death or loss to follow-up. For patient with complete response after TACE, serum alpha-fetoprotein (AFP) and abdominal ultrasound were monitored every 3 months. In the presence of newly suspected lesions or elevated AFP, further CT/MRI were performed for diagnosis of HCC recurrence.

DAA treatment. Depending on the DAA availability in Taiwan, different regimens were used. Achieving SVR was defined as undetectable HCV RNA at 12 weeks after completing DAA treatment.

Statistical analysis. Statistical analyses were performed using IBM SPSS statistic software, version 23 (IBM Corporation, Armonk, NY, USA). For the descriptive statistic, categorical data were expressed in number and percentage, whereas the continuous data were presented in mean with standard deviation or median with range. Median overall survival (OS) was calculated in months. Kaplan-Meier curve was used to evaluate the survival curves. Relevant baseline variables were analyzed using Cox regression hazard model to identify the factors associating with OS, time-to-complete response (TTCR), and progression-free survival (PFS). Statistically significant variables ($p<0.05$) in univariate analysis were further included in the multivariate analysis.

Results

Baseline characteristics of patients. A total of 113 CHC patients who were also diagnosed as HCC BCLC stage B, were included in the study. The basic characteristics of patients are listed in Table I. The mean age was 67.2 ± 9.3 years, and 76 of the patients were males. The group was predominantly cirrhotic Child-Pugh A (103/113, 91.2%). Sixty patients had tumor number ≥ 3 , largest tumor size mean of 3.2 ± 1.7 cm. All patients had received ongoing TACEs for HCC as the standard of care according the BCLC guideline, 14 patients also received DAA treatment for HCV eradication.

Subgroup characteristics. We subdivided the 113 patients into two groups, DAA treatment group and non-treatment group (Table I). When the demographic findings of the two groups were compared, the DAA treatment group had statistically significant better Eastern Cooperative Oncology Group (ECOG)

Table I. Basic clinical data of 113 HCV/HCC patients receiving TACE treatment.

Variables	All	HCV tx, n=14	HCV untx, n=99	p-Value
Gender, male, %	76 (67.3%)	9 (64.3%)	67 (67.7%)	0.802
Age, years, mean±SD	67.2±9.3	69.9±7.1	66.8±9.5	0.237
<60		1 (7.1%)	27 (27.3%)	
≥60		13 (92.9%)	72 (72.7%)	
ECOG, PS ≥1, %	30 (26.5%)	0 (0%)	27 (27.3%)	0.043
Cirrhosis, yes, %	103 (91.2%)	10 (71.4%)	92 (92.9%)	0.078
Alcoholism, yes, %	22 (19.5%)	0 (0%)	22 (22.2%)	0.05
Previous OP/ablation, yes, %	38 (33.6%)	3 (21.4%)	35 (35.4%)	0.306
Tertiary PV invasion, yes, %	7 (6.2%)	0 (0%)	7 (0.07%)	0.309
Ascites, yes, %	19 (16.8%)	1 (0.07%)	18 (18.1%)	0.306
DAA therapy, yes, %	14 (12.4%)	14 (100%)	0 (0%)	<0.001
Tumor number, ≥3, %	60 (53.1%)	11 (78.6%)	49 (49.5%)	0.042
Largest size of tumor, cm, mean±SD	3.2±1.7	3.8±3.0	3.1±1.4	0.226
AFP, ng/ml, median, range	28.0 (2.1-12900.0)	18 (3.0-1030.8)	28.0 (2.1-12897.9)	0.445
<100		11 (78.6%)	70 (70.7%)	
≥100		3 (21.4%)	29 (29.3%)	
Albumin, g/dl, mean±SD	3.5±0.5	3.9±0.4	3.4±0.5	0.001
<3.5		3 (21.4%)	57 (57.6%)	
≥3.5		11 (78.6%)	42 (42.4%)	
Bilirubin, mg/dl, mean±SD	1.2±0.7	1.1±0.8	1.2±0.7	0.408
≤1.5		12 (85.7%)	82 (82.8%)	
>1.5		2 (14.3%)	17 (17.2%)	
Prothrombin time, sec, mean±SD	12.4±1.6	13.0±2.3	12.3±1.5	0.157
≤12		4 (28.6%)	50 (50.5%)	
>12		10 (71.4%)	49 (49.5%)	
Creatinine, mg/dl, mean±SD	1.0±0.4	0.8±0.3	1.0±0.4	0.142
≤1.0		11 (78.6%)	70 (70.7%)	
>1.0		3 (21.4%)	29 (29.3%)	
AST, U/l, mean±SD	75.0±57.3	43.6±24.6	79.5±59.2	0.027
≤40		6 (42.9%)	22 (22.2%)	
>40		8 (57.1%)	77 (77.8%)	
ALT, U/l, mean±SD	61.3±47.4	33.9±25.7	65.2±48.5	0.02
≤40		10 (71.4%)	32 (32.3%)	
>40		4 (28.6%)	67 (67.7%)	
WBC, 10 ⁹ /l, mean±SD	5.1±2.1	5.6±2.0	5.0±2.1	0.283
NLR, mean±SD	2.9±4.6	2.5±1.7	2.9±4.9	0.758
Hemoglobin, g/dl, mean±SD	12.3±1.8	12.8±1.7	12.2±1.8	0.302
Platelet, 10 ⁹ /l, mean±SD	122.6±57.5	138.9±92.5	120.3±50.9	0.26
<100		5 (35.7%)	36 (36.4%)	
≥100		9 (64.3%)	63 (63.6%)	
Survival, median, range	25.1 (1.4-158.3)	40.2 (12.7-117.7)	22.9 (1.4-158.3)	
Progression, median	16.5+/- 21.3	13.5+/- 12.3		

Tx: Treated; untx: untreated; SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; PS: performance status; OP: operation; PV: portal vein; DAA: direct acting antiviral; AFP: alpha-fetoprotein; AST: aspartate transaminase; ALT: alanine transaminase; WBC: white blood cell; NLR: neutrophil/lymphocyte ratio. Significant p-Values are shown in bold.

performance status, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT). Notably, none of the DAA-treated patients had a history of alcoholism. However, they had significantly more numbers of HCC.

CHC DAA treatments and the overall survival. Out of 113 patients, 14 patients had received various DAA treatments with durations ranging from 8~24 weeks. Two started DAA prior to TACE treatments, and the rest were treated by DAA

in parallel with TACE treatment. Thirteen achieved SVR12 (13/14, 92.9%). Only patient number two had HCV reactivation. The clinical and virological data are listed in Table II. The overall survival in the DAA-treated patients was significantly longer than that in untreated patients as shown in the Kaplan–Meier curve ($p=0.005$; Figure 1). The median survival was 22.9 months in the untreated CHC/HCC patients and 40.2 months in the DAA-treated patients, respectively (Table I).

Table II. Clinical and virological data of 14 DAA-treated HCV/HCC patients who harbored active HCC tissues and received TACE.

Case	Age	Gender	Cir ^a	Child-Pugh	MELD	HCV RNA (•10 ⁶ IU/ml)	HCV geno-type	DAA regimen ^b	Treatment duration (weeks)	Tumor number size (cm)	Largest tumor (ng/ml)	AFP
1	70	F	Y	A6	8	1.381	2a	SOF+RBV	12	3	2.72	29.4
2	63	F	Y	B7	8	5.201	1b	3D+RBV	8	3	1.8	1033.8
3	65	M	Y	A5	7	7.499	2b	SOF/VEL	12	4	1.4	<2.0
4	75	M	Y	B9	16	5.029	1b	SOF/LED+RBV	12	4	1.5	<2.0
5	78	F	Y	A6	8	0.361	1b	SOF/LED	12	4	1.4	34.3
6	61	M	Y	A5	7	5.113	6	SOF+RBV	12	3	5.8	5.3
7	76	M	N	A5	6	7.635	1b	SOF/LED	12	>4	7.1	3.8
8	78	F	Y	A5	7	1.446	1b	SOF/LED	12	>4	4.7	188.0
9	75	M	Y	A5	9	0.721	1b	DAC/ASU	24	3	2.4	76.4
10	80	M	N	A5	8	0.028	1b	SOF/LED	12	>4	12.3	6.5
11	65	M	Y	A6	7	1.554	1b	3D	12	2	4.2	779.1
12	69	F	Y	A5	10	0.040	1b	SOF/DAC	24	3	1.7	53.8
13	58	M	N	A5	8	0.038	1b	3D	12	2	3.5	5.1
14	66	M	Y	A5	10	7.567	2a+b	SOF+RBV	12	2	3.3	3.0

^aCir: Clinical cirrhosis, defined as presence of esophageal varices or FibroScan stiffness value >18 kPa; Y: yes; N: no. ^bSOF: Sofosbuvir; RBV: ribavirin; 3D: dasabuvir/ombitasvir/partaprvir/ritonavir; VEL: velpatasvir; LED: ledipasvir; DAC: daclatasvir; ASU: asunaprevir.

Prognostic factors associated with survival outcomes.

Univariate and multivariate analyses by cox proportional hazard model were used to assess various prognostic marks of CHC/HCC. Among the 113 CHC patients with intermediate stage HCC, several factors, including ECOG performance status, tertiary portal vein invasion, DAA therapy, and serum albumin, were identified to be associated with OS by the univariate analysis (Table III). In multivariate analysis, patients with poor ECOG, graded as ECOG ≥1, had increased hazard on survival (HR=1.982, 95%CI=1.082-3.630, p=0.027). Significantly lower risk of death was observed in patients who received DAA treatment (HR=0.133, 95%CI=0.018-0.976, p=0.047) and those with serum albumin level higher than 3.5 ng/ml (HR=0.457, 95%CI=0.229-0.912, p=0.026).

Our univariate analysis revealed that male sex, bilirubin, AST, ALT, white blood counts (WBC), and DAA therapy significantly impacted TTCR (Table IV). Further multivariate analysis showed that bilirubin (HR=0.436, 95%CI=0.203-0.933, p=0.032), ALT (HR=0.983, 95%CI=0.966-1.000, p=0.048), and WBC (HR=0.746, 95%CI=0.581-0.958, p=0.022) were independent adverse factors influencing TTCR. In addition, DAA treatment was a good prognostic factor for TTCR (HR=3.137, 95%CI=1.334-7.378, p=0.009).

For the PFS (Table V), univariate analysis identified previous HCC treatments, tumor size, AFP, WBC, and platelet counts (PLT) as significant factors. However, multivariate analyses further showed previous HCC treatments (HR=2.291, 95%CI=1.394-3.766), AFP (HR=1.021, 95%CI=1.004-1.039), and WBC (HR=1.180,

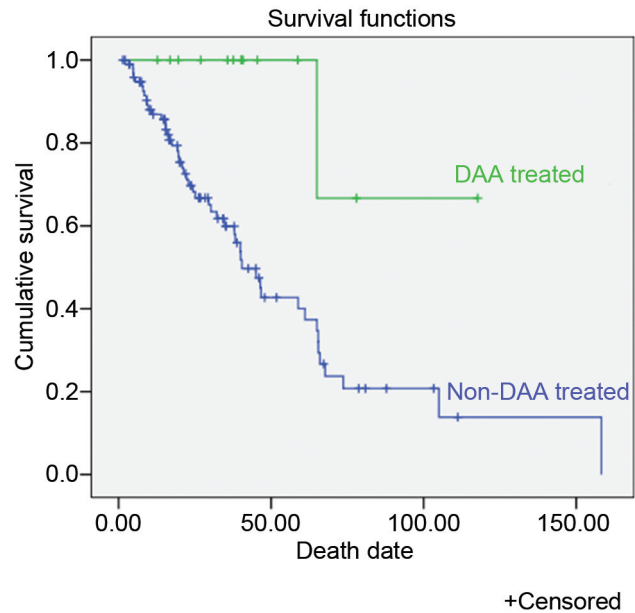


Figure 1. Kaplan–Meier curve of overall survival between direct-acting antiviral (DAA)-treated and non-DAA treated patients.

95%CI=1.056-1.319) were associated with increased risk for tumor progression.

Discussion

Current guidelines only advice DAA therapy in CHC/HCC BCLC stage 0/A patients who had received curative HCC

Table III. Cox proportional hazard analysis for overall survival.

Variables	Univariate		Multivariate	
	HR (95%CI)	<i>p</i> -Value	HR (95%CI)	<i>p</i> -Value
Gender, Male=1	0.882 (0.486, 1.599)	0.679		
Age, per year	1.017 (0.984, 1.051)	0.317		
ECOG, performance score ≥ 1	1.987 (1.103, 3.580)	0.022	1.982 (1.082, 3.630)	0.027
Cirrhosis, Yes=1	5.220 (0.719, 37.896)	0.102		
Alcoholism, Yes=1	1.086 (0.540, 2.183)	0.817		
Previous operation/Ablation, Yes=1	1.670 (0.947, 2.945)	0.077		
Tertiary PV invasion, Yes=1	3.065 (1.079, 8.707)	0.036	2.405 (0.807, 7.170)	0.115
Ascites, Yes=1	1.237 (0.575, 2.662)	0.586		
Anti-HCV DAA treatment, Yes=1	0.100 (0.014, 0.725)	0.023	0.133 (0.018, 0.976)	0.047
Tumor number, ≥ 3 as 1	0.882 (0.503, 1.548)	0.662		
Largest tumor size, per cm	0.990 (0.8009, 1.211)	0.919		
AFP, per 100 ng/ml	0.992 (0.973, 1.012)	0.426		
Albumin, per g/dl	0.321 (0.167, 0.617)	0.001	0.457 (0.229, 0.912)	0.026
Bilirubin, per mg/dl	1.166 (0.793, 1.715)	0.434		
Prothrombin time, per sec	0.934 (0.763, 1.142)	0.503		
Creatinine, per mg/dl	0.811 (0.409, 1.612)	0.551		
AST, per U/l	1.003 (0.999, 1.007)	0.192		
ALT, per U/l	0.998 (0.992, 1.005)	0.614		
WBC, per $10^9/l$	1.069 (0.924, 1.238)	0.368		
Neutrophil/Lymphocyte ratio, per fold	1.031 (0.984, 1.079)	0.197		
Hemoglobin, per g/dl	0.958 (0.815, 1.127)	0.606		
Platelet, per $10^9/l$	1.000 (0.995, 1.005)	0.925		

ECOG: Eastern Cooperative Oncology Group; PV: portal vein; HCV: hepatitis C virus; DAA: direct acting antiviral; AFP: alpha-fetoprotein; AST: aspartate transaminase; ALT: alanine transaminase; WBC: white blood cell. Significant *p*-Values are shown in bold.

treatments. It is unclear whether DAA therapy impacts prognosis of patients with intermediate stage HCC. Our retrospective study showed that ECOG, DAA therapy, and serum albumin were independent prognostic factors for intermediate stage HCC/CHC patients. We also found that DAA therapy has a positive effect on TTCR. In contrary, male sex, higher bilirubin, ALT, and WBC were associated with poor TACE treatment response. In patients who had previous HCC treatments, higher AFP and WBC were indicators of poor progression-free survival.

Similar to data recorded in various types of malignancy and diseases, it is not surprising that performance status (PS) and hypoalbuminemia are significant indicators of survival outcomes. Patients who have worse PS tend to be frail and are less likely to tolerate rigorous anti-cancer therapy. They are prone to have less favorable outcomes than patients with better PS. Thus, this is probably also the reason that PS is one of the three assessing components for the BCLC HCC staging. Serum albumin is not only an indicator of nutrition status, it is also a liver function parameter that is included in several scoring criteria such as the Child-Pugh Scoring system and Albumin-Bilirubin (ALBI). Our univariate and multivariate analyses showed comparable results.

In the newly established 10th Annual Asia-Pacific Primary liver cancer Expert (APPLE) consensus, it has been stated

that liver function preservation is as important as achieving high objective response for the treatment of intermediate-stage of HCC. CHC induced liver inflammation causes deterioration of liver functions and results in limited HCC treatment options. Studies have shown that eradication of HCV can improve liver function, promote fibrosis regression, prevent cirrhosis progression, and reduce risk of liver decompensation, which further result in decreased liver-related mortality. Current guidelines recommend HCV eradication for all patients except for those with limited life expectancy. The benefits of HCV clearance with DAA therapy after curative treatments have been extensively studied in HCC BLCL stage 0 and A patients. However, data regarding whether anti-HCV treatment should be initiated on intermediate or later stage HCC is currently unknown. Our rationale is that if HCV clearance can be achieved with DAA therapy, liver dysfunction may be reversed, which might further improve survival even in HCC BCLC stage B patients. Our study showed that DAA therapy had a beneficial effect on overall outcome. It is known that TACE is the standard treatment for intermediate stage HCC, whereas systemic therapy is the treatment of choice for those refractory to TACE. Furthermore, a recent randomized multicenter prospective study conducted by Kudo *et al*.

Table IV. Cox proportional hazard analysis for time-to-complete response.

Variables	Univariate		Multivariate	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Gender , Male=1	0.434 (0.214, 0.880)	0.021	0.678 (0.313, 1.468)	0.324
Age, per year	1.003 (0.966, 1.042)	0.874		
ECOG, performance score ≥1	1.159 (0.519, 2.589)	0.718		
Cirrhosis, Yes=1	1.070 (0.325, 3.517)	0.911		
Alcoholism, Yes=1	0.733 (0.282, 1.904)	0.523		
Previous operation/Ablation, Yes=1	0.972 (0.460, 2.056)	0.941		
Tertiary PV invasion, Yes=1	0.045 (0.000, 21.752)	0.325		
Ascites, Yes=1	0.956 (0.368, 2.485)	0.927		
Anti-HCV DAA treatment, Yes=1	3.828 (1.806, 8.111)	<0.001	3.137 (1.334, 7.378)	0.009
Tumor number, ≥3	0.825 (0.412, 1.652)	0.587		
Largest tumor size, per cm	0.917 (0.719, 1.170)	0.488		
AFP, per 100 ng/ml	1.008 (0.985, 1.031)	0.521		
Albumin, per g/dl	1.445 (0.710, 2.939)	0.310		
Bilirubin, per mg/dl	0.434 (0.195, 0.965)	0.041	0.436 (0.203, 0.933)	0.032
Prothrombin time, per sec	0.982 (0.797, 1.210)	0.867		
Creatinine, per mg/dl	0.545 (0.163, 1.822)	0.324		
AST, per U/l	0.989 (0.979, 0.999)	0.029	1.005 (0.993, 1.018)	0.425
ALT, per U/l	0.982 (0.969, 0.994)	0.005	0.983 (0.966, 1.000)	0.048
WBC, per 10 ⁹ /l	0.787 (0.640, 0.968)	0.023	0.746 (0.581, 0.958)	0.022
Neutrophil/Lymphocyte ratio, per fold	0.915 (0.781, 1.073)	0.276		
Hemoglobin, per g/dl	0.887 (0.742, 1.059)	0.185		
Platelet, per 10 ⁹ /l	0.994 (0.987, 1.001)	0.080		

ECOG: Eastern Cooperative Oncology Group; PV: portal vein; HCV: hepatitis C virus; DAA: direct acting antiviral; AFP: alpha-fetoprotein; AST: aspartate transaminase; ALT: alanine transaminase; WBC: white blood cell. Significant p-Values are shown in bold.

showed that combination treatment with TACE plus sorafenib in unresectable HCC significantly improved progression free survival compared to TACE alone. However, poor liver function and its related complications may hinder eligibility to TACE treatments or systemic therapy. It is important to preserve liver function in these patients to maintain their eligibility for not only subsequent systemic therapy after TACE failure/refractory HCC but also for new combination therapy with TACE and systemic therapy. In this respect, it is strategic and critical to treat HCV with DAA in patients with BCLC stage B HCC.

In patients receiving TACE, tumor response based on mRECIST especially initial complete response (CR) can predict a longer survival benefit. Our study revealed that DAA therapy has a positive effect on TTCR. This may be the reason DAA could improve OS and further support the use of DAA in HCV patients with BCLC stage B HCC.

Ng *et al.* found that female gender tends to have HCC survival advantage over male which is likely due to the differences in tumor nature between genders. On the other hand, underlying differences in gene expression in opposite sex may also play a role. Liu *et al.* identified that Family with sequence similarity 83 (FAM83D) over-expression was observed significantly more in male and was associated with

worse outcomes. These findings may provide possible explanations why the TACE treatment response was worse in male patients in the present study.

Studies have shown that poor liver function reserve, high-dose chemotherapeutic agents, and history of multiple embolization procedures increased risk of acute liver failure after TACE. Jeon *et al.* also demonstrated higher total bilirubin levels increased risk of acute hepatic failure after TACE. In our study, higher bilirubin and ALT levels were associated with decreased response to TACE. Both higher levels of bilirubin and ALT were indicators of poor liver dysfunction. Patients with higher bilirubin and ALT levels may be less tolerant to higher dosage of TACE due to higher risk of post-TACE irreversible liver parenchymal injury or even liver failure, thus affecting treatment outcome and leading to a less favorable response.

Tumor progression from previously treated residual HCC and/or repeated tumor recurrence after TACE may be associated with increased malignant potential of the tumor nature. Sustained liver parenchymal injury from previous locoregional treatments may further adversely affect progression-free survival as was seen in our analysis.

Several reports have identified AFP as an independent factor for HCC recurrence. Chen *et al.* have identified the

Table V. Cox proportional hazard analysis for progression free survival.

Variables	Univariate		Multivariate	
	HR (95%CI)	<i>p</i> -Value	HR (95%CI)	<i>p</i> -Value
Gender , Male=1	1.266 (0.776, 2.065)	0.345		
Age, per year	0.992 (0.967, 1.017)	0.515		
ECOG, performance status \geq 1	1.057 (0.623, 1.792)	0.837		
Cirrhosis, Yes=1	1.232 (0.565, 2.684)	0.600		
Alcoholism, Yes=1	1.168 (0.663, 2.057)	0.591		
Previous operation/Ablation, Yes=1	1.713 (1.077, 2.781)	0.023	2.291 (1.394, 3.766)	0.001
Tertiary PV invasion, Yes=1	1.666 (0.669, 4.153)	0.273		
Ascites, Yes=1	1.138 (0.624, 2.078)	0.673		
Anti-HCV DAA treatment, Yes=1	1.464 (0.786, 2.728)	0.230		
Tumor number, \geq 3 as 1	1.249 (0.798, 1.956)	0.330		
Largest tumor size, per cm	1.230 (1.078, 1.404)	0.002	1.137 (0.969, 1.335)	0.116
AFP, per 100 ng/ml	1.021 (1.004, 1.039)	0.017	1.021 (1.004, 1.039)	0.015
Albumin, per g/dl	1.178 (0.734, 1.891)	0.498		
Bilirubin, per mg/dl	0.878 (0.617, 1.251)	0.472		
Prothrombin time, per sec	0.974 (0.836, 1.136)	0.737		
Creatinine, per mg/dl	0.867 (0.489, 1.538)	0.625		
AST, per U/l	1.000 (0.996, 1.004)	0.995		
ALT, per U/l	1.000 (0.996, 1.004)	0.866		
WBC, per $10^9/l$	1.192 (1.084, 1.311)	<0.001	1.180 (1.056, 1.319)	0.004
Neutrophil/Lymphocyte ratio, per fold	1.027 (0.987, 1.069)	0.192		
Hemoglobin, per g/dl	1.034 (0.909, 1.178)	0.608		
Platelet, per $10^9/l$	1.004 (1.000, 1.008)	0.038	1.002 (0.998, 1.007)	0.351

ECOG: Eastern Cooperative Oncology Group; PV: portal vein; HCV: hepatitis C virus; DAA: direct acting antiviral; AFP: alpha-fetoprotein; AST: aspartate transaminase; ALT: alanine transaminase; WBC: white blood cell. Significant *p*-Values are shown in bold.

pro-oncogenic role of AFP in HCC progression (44). It is therefore not surprising to observe that higher AFP levels are an unfavorable prognostic factor of PFS in the present study.

Previously, studies have revealed the association between the pro-tumor and anti-tumor inflammatory effects of immune response with elevated WBC and neutrophil-lymphocyte ration (NLR) in different cancers. In our study, elevated WBC and NLR are both associated with unfavorable outcomes. However, NLR did not reach statistical significance, only WBC was found to be a significant factor for TTCR and PFS.

A previous study reported a lower SVR rate with DAA therapy in active HCC compared to inactive HCC (85.5% vs. 93.7%). In the present study, we achieved a much higher SVR of 92.9% in patients with BCLC stage B HCC. However, this may be due to the fact that we had a very small sample size of 14 patients who received DAA.

Our study had several limitations. First, it was a retrospective evaluation from a single medical center in Taiwan. The study population had little heterogeneity. The fact that the entire study cohort was ethnically Taiwanese could contribute to potential selection bias. This may limit the applicability of the results as it is unclear whether similar results would be observed in different ethnic groups. Second, the sample size of 14 patients who ultimately received DAA

therapy was small. This limits the statistical power of the study results. However, this was an anticipated problem as the current guidelines do not support the use of DAA for HCV eradication in HCC BCLC stage B patients. Lastly, of the 14 patients treated by DAA, 12 were Child-Pugh A (85.7%). We could not draw conclusions on the benefits of DAA treatment in HCC BLCL stage B patients who had more advanced liver disease. Currently, Child-Push B/C score is listed as contraindication of some DAA therapies.

In conclusion, we demonstrated that DAA therapy was associated with improved OS and TTCR in CHC-intermediate stage HCC. Moreover, we demonstrated that ECOG, higher serum albumin, and DAA therapy are independent predictors of survival in CHC-HCC patients.

Conflicts of Interest

All Authors declare no conflicts of interest regarding this article.

Authors' Contributions

Conception and design: Chau-Ting Yeh; Administrative support: Wey-Ran Lin, Chau-Ting Yeh; Provision of study materials or patients: Wei-Ting Chen, Cheng-Chun Lin, Wey-Ran Lin, Chau-Ting Yeh; Collection and assembly of data: Changhan Shao; Data

analysis and interpretation: Changhan Shao, Paul P Shao; Manuscript writing: All Authors; Final approval of manuscript: All Authors.

Acknowledgements

The Authors would like to thank the members of the Liver Research center for their diligent data collection.

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Received February 3, 2021
Revised February 18, 2021
Accepted February 19, 2021