European Review for Medical and Pharmacological Sciences 2021; 25: 7543-7552

Effects of direct-acting antiviral therapy for patients with advanced hepatocellular carcinoma and concomitant hepatitis C—A population-based cohort study

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Abstract. – OBJECTIVE: We analyzed real-world data to elucidate the effects of anti-Hepatitis C virus (HCV) direct-acting antiviral (DAA) therapy on survival in patients with advanced hepatocellular carcinoma (HCC) and concomitant HCV infection treated with sorafenib.

MATERIALS AND METHODS: This population-based retrospective cohort study used the Taiwan National Health Insurance Research Database and the Registration System for Patients Treated with Oral Hepatitis C Antivirals to identify patients with advanced HCC and concomitant HCV infection who received initial targeted therapy (sorafenib) in 2018-2019. The overall survival (OS) of the DAA and non-DAA groups were compared using the Kaplan-Meier survival analysis. Propensity score matching was performed using a ratio of 1:4 to reduce confounding between the DAA and non-DAA groups.

RESULTS: The study included 1,684 patients (122 DAA and 1,562 non-DAA users) with HCC and concomitant HCV infection who used sorafenib for the first time in 2018-2019. The Kaplan-Meier survival analysis indicated that advanced HCC patients who used DAAs had longer OS compared to non-DAA patients. The mean survival times were 20.7 months for DAA and 12.5 months for non-DAA. Results obtained after propensity matching indicated a significant difference in OS between the DAA and non-DAA groups.

CONCLUSIONS: The analysis of big data from the Taiwan National Health Insurance Research Database revealed that advanced HCC patients on sorafenib benefited from DAAs as a treatment for HCV infection. Patients whose HCV infection was cured had better OS.

Key Words:
Advanced hepatocellular carcinoma (HCC), Direct-acting antiviral (DAA), Survival, Propensity score matching.

Introduction

Hepatitis C virus (HCV) infection has a global prevalence of 2%-4%. In Taiwan, approximately 400,000-700,000 people are infected with HCV, and 3%-4% of the population are HCV carriers[1]. HCV infection is the primary cause of chronic hepatitis-induced cirrhosis and hepatocellular carcinoma (HCC), with approximately 70%-80% of acute HCV-infected patients subsequently developing chronic HCV infection. The lack of pharmacological treatment will lead to the gradual development of liver fibrosis, which causes cirrhosis in 20% of HCV-infected patients within 20 years[2]. Every year, individuals with cirrhosis have a 1%-4% risk of producing HCC cells and a 4%-5% risk of developing hepatic decompensation[3].

Direct-acting antiviral agents (DAAs), also known as novel all-oral anti-HCV drugs, signify the beginning of a new era of HCV treatment[4]. In the past, less than 10% of patients who received conventional interferon (IFN)-based therapies achieved sustained virologic response (SVR), indicating the successful cure of the infection[4]. Since 2000, the combined use of long-acting IFNs (pegylated IFNs) with the oral antiviral agent

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ribavirin has effectively increased the cure rate to >50%[4]. With the advent of all-oral IFN-free regimens in 2013, a cure rate of >90% could be achieved in patients with differing levels of liver fibrosis[4]. SVR is associated with the reduction of hepatic decompensation-, transplant-, and liver-related mortality or overall mortality[5]. DAAs are also extremely safe, which which greatly benefit many HCV-infected patients, especially those with a high risk of advanced hepatic insufficiency or HCC[5]. However, there is currently no standard of care for the use of antiviral agents in treating HCV-related HCC.

SVR after surgery and local treatment increases the recurrence-free survival and overall survival (OS) rates in patients with HCV-related HCC[6]. Although individuals with HCV infection and concomitant HCC achieved poorer post-DAA treatment SVR compared with HCV-infected patients without HCC (regardless of the degree of cirrhosis), those who underwent curative HCC management showed a better response to DAA treatment[7], with patients having active HCC exhibiting a poorer response than those with inactive HCC[8]. Treatment with DAAs may also trigger immune changes, such as weakening of the cytotoxic effects of natural killer (NK) cells and mucosal-associated invariant T (MAIT) cells toward cancer cells. In addition, the increased frequency of regulatory T cells (Tregs) is not reversed even after HCV eradication, which suppresses the immune response and hinders the eradication of cancer cells[9,10]. Some previous studies[9,10] have reported the rapid development of new-onset HCC or early recurrence of HCC after DAA treatment; others have indicated that the successful treatment of HCV infection with DAAs does not increase the risk of new-onset HCC[5]. However, the effects of successful DAA treatment of HCV infection on the recurrence of early HCC in patients who received curative HCC treatment remain under debate. At present, there are no restrictions on the use of DAA treatment to prevent the deterioration of hepatic diseases in HCV-induced cirrhotic patients who have undergone surgical resection or ablation therapy for HCC[5]. However, HCV-induced cirrhotic patients who have been cured of HCV infection should be subjected to liver imaging and alpha-fetoprotein (AFP) testing twice a year to monitor for any recurrence of HCC[5].

For patients with mid-stage and advanced (Barcelona Clinic Liver Cancer [BCLC] stage B or C) HCC, relevant research has suggested that the treatment of cancer-related symptoms and hepatic decompensation should be prioritized rather than focusing on the improvement of hepatic function through DAA therapy[11]. If patients are classified as having BCLC-B/C due to the presence of liver dysfunction caused solely by HCV infection, they should be individually assessed to determine whether DAA treatment should be prioritized; they should also be adequately informed of all benefits and risks of using DAAs[11]. However, for patients whose BCLC stage is determined based on cancer-related symptoms or tumor burden and remains unchanged due to the use of DAAs, existing data do not support the routine use of DAAs for treatment as there is a lack of evidence demonstrating the therapeutic effects of DAAs in this patient population[11]. A previous study[12] offering a clinical perspective proposed that HCV-infected cancer patients should receive antiviral therapy unless they have the following contraindications: uncontrollable cancer, comorbidities resulting in a life expectancy of <12 months, the use of chemotherapy or immunosuppressants that cannot be temporarily suspended but may generate severe adverse interactive effects when used with antivirals, or Child-Pugh class B or C cirrhosis[12]. In particular, antiviral therapy for decompensated cirrhosis causes an increased risk of lactic acidosis, which may be further elevated with concurrent cancer therapy[12]. In addition, much debate has questioned whether HCV treatment should be administered before or after cancer treatment[12]. In general, the pros and cons of different sequences of treatment should be weighed on a case-by-case basis, and the benefits and risks of HCV treatment in patients with a limited life expectancy must also be comprehensively considered[13]. The American Association for the Study of Liver Diseases-Infectious Diseases Society of America HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C recommends that patients with a life expectancy of 12 months are unlikely to benefit from HCV eradication; therefore, palliative measures should take precedence in this setting, including for patients with decompensated liver disease and advanced HCC[14,15]. A previous study[16] indicated that, given a good prognosis, HCV eradication before sorafenib treatment could prolong the post-progression survival (PPS) in patients with advanced HCC (Child–Pugh class A disease) (8.5 months in the SVR group vs. 5.2 months in the non-SVR group, p=0.02) and OS (15 months in the SVR group *vs.* 9.3 months in the non-SVR group, p=0.014).

In response to the Glasgow Declaration on Viral Hepatitis launched in September 2015, in whi-

ch member states of the World Health Organization pledged to eliminate viral hepatitis by 2030, Taiwan formulated the Taiwan Hepatitis C Policy Guideline 2018–2025[17]. The goal of this guideline is to achieve the treatment of 250,000 HCV-infected patients with novel oral drugs between 2018 and 2025 in order to completely eradicate HCV by 2025[17]. Following the approval of the first DAA on September 16, 2015, several DAAs have received marketing authorization in Taiwan, and novel DAAs have been included as reimbursement items of the National Health Insurance (NHI) program of Taiwan since January 24, 2017. To optimize the allocation of limited resources and achieve maximum benefits, the National Health Insurance Administration (NHIA) has also launched the NHI Payment Implementation Plan for Novel All-Oral Hepatitis C Drugs and established the Registration System for Patients Treated with Oral Hepatitis C Antivirals to effectively manage and track patients' treatment status[17].

However, studies and real-world data on the therapeutic effects of DAAs in HCV-infected patients with concomitant advanced HCC are limited. In the present study, we analyzed real-world data to elucidate the effects of anti-HCV DAA therapy on survival in patients with advanced HCC and concomitant HCV infection treated with sorafenib.

Materials and Methods

We conducted a retrospective observational study. Using the Taiwan National Health Insurance Research Database and the Registration System for Patients Treated with Oral Hepatitis C Antivirals, we identified patients with advanced HCC and concomitant HCV infection who received initial targeted therapy (sorafenib) between 2018 and 2019. The use of DAAs among these patients was investigated, and the patients were followed up until December 31, 2020, to determine their survival status. Patients who used DAAs prior to sorafenib therapy were excluded. Since August 2012, the NHIA has reimbursed the costs of sorafenib treatment for metastatic or unresectable advanced HCC (Child–Pugh class A) in adult patients who have failed or are unsuitable for local treatment[18]. Therefore, the use of sorafenib therapy is regarded as an important factor for identifying patients with advanced HCC.

The main variable of the study was the use of DAAs, which was determined based on whether any of the following medications had been used: daclatasvir plus asunaprevir, glecaprevir/pibrentasvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir, sofosbuvir, sofosbuvir/velpatasvir, or the concomitant use of the last five medications with ribavirin. The outcome variable was OS; the index date was defined as the date of initiation of sorafenib therapy, while the end date was defined as the date of death or observation endpoint (December 31, 2020). The control variables included the patient's sex, age, comorbidities in the year prior to the use of sorafenib (hepatitis B virus [HBV] infection, cirrhosis, or metastatic cancer), and treatment received (radiofrequency tumor ablation, liver tumor resection, chemotherapy, or liver trans-arterial chemo-embolization [TACE]).

SVR was investigated in the present study to determine the differences in the survival of patients whose HCV infection had been cured after using DAAs. SVR was defined as the absence of detectable HCV RNA in the serum or a decrease in the serum HCV RNA level to undetectable levels (i.e., below the lower limit of detection of specific testing methods) at 12 weeks after completion of anti-HCV therapy.

Data processing and analysis were performed using SAS software. The differences in continuous and categorical variables were separately compared using the t-test and χ^2 test. The OS of the DAA and non-DAA groups were compared using the Kaplan–Meier survival analysis. Subsequently, survival curves were plotted, and the differences between the two groups were compared using the log-rank test. To reduce research bias caused by confounders and mimic randomization, propensity score matching was performed using a ratio of 1:4 to obtain generally similar distributions of control variables in the DAA and non-DAA groups. The variables included in the matching were the patients' sex, age, comorbidities, and treatment status in the previous year; the number of months between the time of initial diagnosis of HCV infection and the time of initial diagnosis of HCC; and the number of months between the time of initial diagnosis of HCC and time of initiation of sorafenib treatment. The probability for each patient in the DAA group was calculated using logistic regression, and four patients in the non-DAA group were matched based on similar probability values. Finally, a survival analysis was conducted on the matching results.

The protocol was approved by TMU-Joint Institutional Review Board (TMU-JIRB: No.: N202005012). Informed consent was not required considering the retrospective nature of this study.

Results

A total of 1,684 patients with HCC and concomitant HCV infection who used sorafenib for the first time between 2018 and 2019 were included in this study; 122 (7.2%) were DAA users, and 1,562 (92.8%) were non-DAA users. The study population's mean age was 68.5 years (standard deviation [SD]=10.0). Of all patients, 1,172 were men (69.6%), while 511 were women (30.3%). A total of 407 patients (24.2%) had a history of HBV infection, 1,051 (62.4%) had a history of cirrhosis, and 905 (53.7%) had been diagnosed with metastatic cancer (i.e., stage 4 cancer). The HCC treatment methods used included radio frequency tumor ablation (290 patients, 17.2%), liver tumor resection (161 patients, 9.6%), chemotherapy (326 patients, 19.4%), and liver TACE (931 patients, 55.3%). The mean interval between the time of initial HCV diagnosis and time of initial HCC diagnosis was 12.5 months (SD=29.0, median=0 months, first quartile [Q1]=0.5 months, and third quartile [Q3]=33.15 months). The mean interval between the time of initial HCC diagnosis and the time of initiation of sorafenib treatment was 24.6 months (SD=26.6, median=12.2 months, Q1=1.6 months, and Q3=45.7 months). Moreover, 1,378 patients (81.8%) died at the end of the observation period. Before matching, the distribution of HBV infection history, liver tumor resection, chemotherapy, and interval between HCC diagnosis and sorafenib use was significantly different between the DAA group and non-DAA group. After matching, the differences in all control variables were not significant. Table I shows the baseline characteristics of the study participants.

Results of the Kaplan–Meier survival analysis indicated that the OS of advanced HCC patients who used DAAs was longer than that of the non-DAA group. The mean survival times of the DAA and non-DAA groups were 20.7 months (SD=1.1 months, median=20.8 months) and 12.5 months (SD=0.3 months, median=8.3 months), respectively. The 6-month, 12-month, and 24-month survival rates of the DAA group were 86.9%, 70.5%, and 37.9%, respectively, while those of the non-DAA group were 59.1%, 38.2%, and 18.9%, respectively. Results of the comparison using the log-rank test revealed that the differences in survival rates of the two groups were significant (p<0.001; Table II and Figure 1).

Propensity score matching was performed using a ratio of 1:4 to reduce confounding between the DAA and non-DAA groups. Results obtained after matching also indicated a significant difference in OS between the DAA and non-DAA groups (Table II and Figure 2). To determine the effects of the HCV infection cure status of the DAA group on survival, a stratified analysis was performed on the DAA group. The results indicated that the median survival time of the cured, uncured, premature treatment termination, and untested after treatment completion subgroups was 23.9, 24.9, 5.7, and 5 months, respectively. The differences in OS were also significant (Table III).

Discussion

In the present study, we found that sorafenib-treated advanced HCC patients who received DAA therapy achieved better survival than those who did not use DAAs (median survival from the date of initiation of sorafenib: 19.7 months vs. 6.7 months, p<0.001). Our results also showed that patients in the DAA group whose HCV infection had been successfully cured achieved better survival (median survival=23.9 months). Although the survival analyses of HCV-positive advanced HCC patients in Western countries who used sorafenib and DAAs concomitantly have not yet been reported in the literature, our results are similar to those of related studies conducted in Japan and Taiwan. In a study by Kawaoka et al[16], 58 patients with advanced HCC (Child–Pugh class A disease) at a single medical facility in Japan who had used DAAs prior to sorafenib therapy were enrolled, of whom 27 were cured of HCV infection (SVR group) and 31 were not cured (non-SVR group)[16]. The results indicated that the SVR group had longer PPS and OS compared with the non-SVR group[16]. Therefore, the researchers contended that HCV eradication improved the hepatic function, which led to the preservation of hepatic function and allowed for the adoption of other treatment methods after sorafenib failure[16].

Another study of 168 HCV-positive advanced HCC patients with limited life expectancy who had been treated with sorafenib compared the differences in OS (the time from the initiation of sorafenib treatment to the time of death or loss to follow-up) and PFS between patients with detectable HCV RNA and those with undetectable HCV RNA[19]. The results indicated that the median OS of all patients was 232 days[19]. The undetectable HCV RNA group (32 of 45 patients were cured after receiving interferon therapy) had better OS (median=351 days) and prolonged time of progression from a Child–Pugh score of A–B, but

did not exhibit a significant difference in PFS[19]. Among the 51 patients with detectable HCV RNA at sorafenib initiation, 5 received DAA therapy while being treated with sorafenib. All 5 patients achieved better OS and PFS, which was indicative of the positive benefits of DAAs despite the small number of cases[19]. The results of this study demonstrate that HCV eradication before or after sorafenib therapy is beneficial to the preservation of hepatic function and prolongation of survival during the course of sorafenib treatment[19].

Some studies[20-22] investigating the effects of DAAs on survival in patients with various stages of HCC have reported results similar to those

Table I. Baseline characteristics of the study participants.

		Before matching			After matching		
	Total	DAA group	Non-DAA group		DAA group	Non-DAA group	
	n (%)	n (%)	n (%)	p	n (%)	n (%)	p
No. of patients	1684	122	1562		98	362	
Follow-up status				<.001			<.001
Survived	306 (18.2)	37 (30.3)	269 (17.2)		27 (27.6)	45 (12.4)	
Died	1378 (81.8)	85 (69.7)	1293(82.8)		71 (72.4)	317 (87.6)	
Age (M, SD)	68.5 (10.0)	67.0 (9.1)	68.6 (10.1)	0.090	68.1 (9.2)	66.9 (10.2)	0.301
Sex				0.539			0.810
Male	1172 (69.6)	88 (72.1)	1084(69.4)		70 (71.4)	263 (72.7)	
Female	511 (30.3)	34 (27.9)	477 (30.5)		28 (28.6)	99 (27.3)	
Comorbidities*							
HBV infection	407 (24.2)	14 (11.5)	393 (25.2)	<.001	13 (13.3)	65 (18.0)	0.272
Cirrhosis	1051 (62.4)	74 (60.7)	977 (62.5)	0.699	58 (59.2)	219 (60.5)	0.814
Metastatic cancer	905 (53.7)	74 (60.7)	831 (53.2)	0.104	58 (59.2)	218 (60.2)	0.853
HCC treatment*							
Radiofrequency tumor ablation	290 (17.2)	14 (11.5)	276 (17.7)	0.077	10 (10.2)	53 (14.6)	0.257
Liver tumor resection	161 (9.6)	18 (14.8)	143 (9.2)	0.045	13 (13.3)	45 (12.4)	0.835
Chemotherapy	326 (19.4)	33 (27)	293 (18.8)	0.026	21 (21.4)	95 (26.2)	0.330
Liver TACE	931 (55.3)	71 (58.2)	860 (55.1)	0.523	54 (55.1)	212 (58.6)	0.538
Interval between HCV infection and HCC (months) (M, SD)	12.5 (29.0)	12.6 (24.0)	12.4 (29.3)	0.929	13.7 (25.4)	12.6 (27.0)	0.714
Interval between HCC and sorafenib use (months) (M, SD)	24.6 (26.6)	14.9 (21.1)	25.4 (26.8)	<.001	15.2 (21.1)	15.4 (21.3)	0.931
SVR				<.001			<.001
Uncured	1568 (93.1)	7 (5.7)	1561(99.9)		7 (7.1)	361 (99.7)	
Cured	86 (5.1)	86 (70.5)	0 (0)		66 (67.3)	0 (0)	
Could not be determined	30 (1.8)	29 (23.8)	1 (0.1)		25 (25.5)	1 (0.3)	

*Data screened from the medical records of the year prior to the index date.
Direct-acting antiviral agent (DAA); hepatitis B virus (HBV); hepatitis C virus (HCV); trans-arterial chemo-embolization (TACE); sustained virologic response (SVR).

Table II. Results of the survival analysis of the unmatched and propensity scored-matched patients.

Group	Unmatched		Matched (1:4)	
	DAA group	Non-DAA group	DAA group	Non-DAA group
No. of patients	122	1562	98	362
Survival time (months)				
Mean (SD)	20.7 (1.1)	12.5 (0.3)	20.2 (1.2)	11.1 (0.6)
75th percentile (Q3)	34.9	18.9	34.9	15.3
Median (Q2)	20.8	8.3	**19.7**	**6.7**
25th percentile (Q1)	10.2	3.4	9.9	3.1
Survival rate				
6 months	86.9%	59.1%	86.7%	53.6%
12 months	70.5%	38.2%	68.4%	33.2%
24 months	37.9%	18.9%	35.6%	15.5%
Log-rank *p*	<.0001		<.0001	

Direct-acting antiviral agent (DAA).

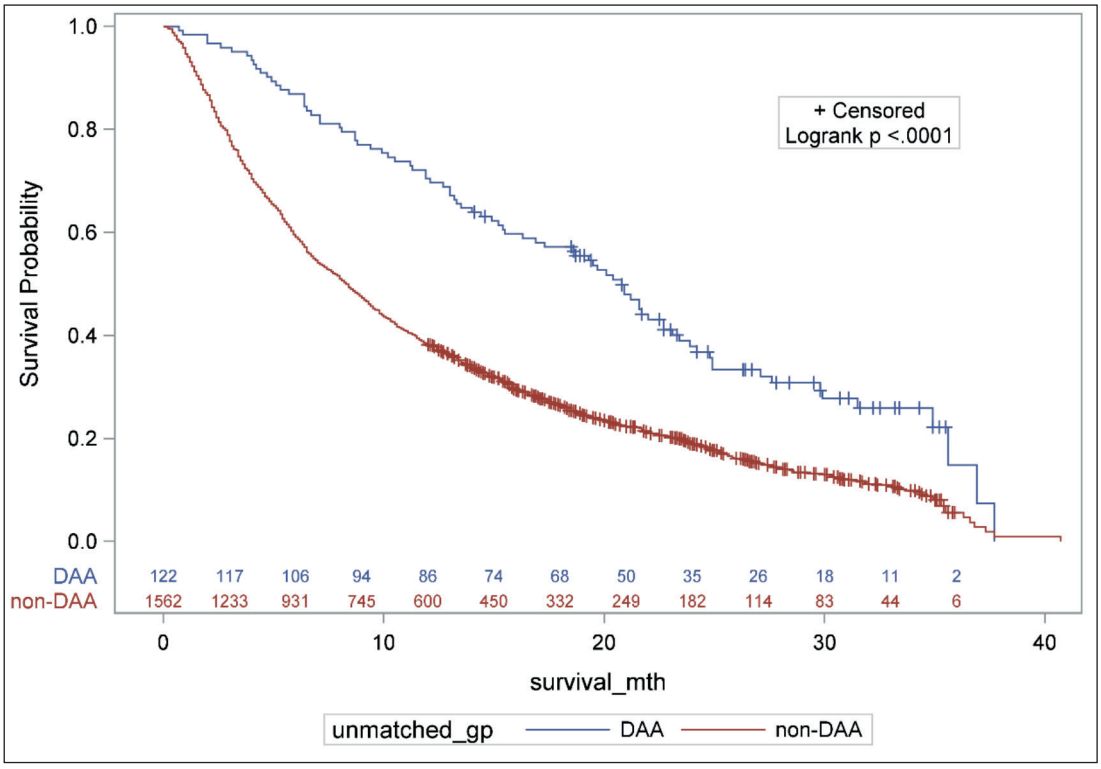

Figure 1. Kaplan-Meier survival analysis between the DAA and non-DAA groups in 2018-2019 (unmatched, total N=1684). DAA, direct-acting antiviral.

employing stratified analyses of DAA use in advanced HCC patients. This finding suggests that advanced HCC patients who have been cured of HCV infection after treatment with DAAs have a better survival rate[20-22]. In a multinational, multi-center retrospective observational study of 1,389 HCC patients with concomitant HCV infection from nine clinical centers in four

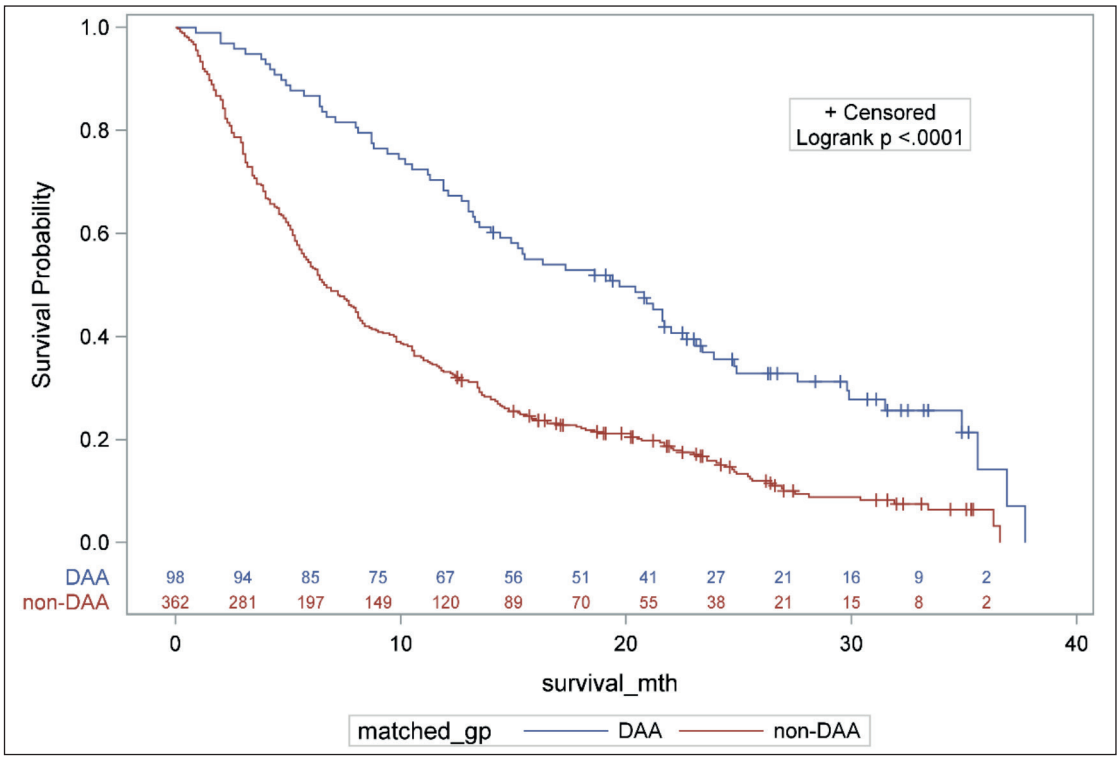

Figure 2. Kaplan-Meier survival analysis between the DAA and non-DAA groups in 2018-2019 (matched 1:4, total N=460). DAA, direct-acting antiviral.

countries (United States, Japan, Korea, and Taiwan)[18], patients cured of HCV infection before being diagnosed with HCC (post-SVR HCC: 301 patients) exhibited better clinical and tumor characteristics and longer OS[18]. Among patients who tested positive for HCV after HCC diagnosis (viremic HCC: 1,088 patients), those cured of HCV infection (239 patients) had better survival rates, which were greater than even those of the post-SVR HCC group[18]. The remaining 849 patients not cured of HCV infection showed the worst survival rates[18]. A stratified analysis based on HCC stage demonstrated that patients with BCLC stage B and BCLC stage C/D disease who had been cured of HCV infection after HCC diagnosis (SVR) showed significantly better OS than non-cured patients and those diagnosed with HCC after HCV eradication[18]. Rinaldi et al[23] conducted an updated literature review to understand the impact of SVR by DAAs on the risk of HCC; they also assessed risk factors and the role of epigenetics[23]. They found that SVR had no impact on HCC occurrence in the short to medium term but reduced the risk of HCC in the medium to long term. DAAs' direct role in the development of HCC was not demonstrated[23]. The hypothesized reduction in immune surveillance in response to the rapid clearance of HCV and changes in the cytokine pattern influencing early carcinogenesis remains to be elucidated[23].

Rinaldi et al[24] further evaluated early HCC occurrence and its risk factors in the HCV-infected population treated with DAAs. Their data suggested that early HCC occurrence appears more frequently related to Sofosbuvir-based therapy without Ribavirin which, indeed, seems to play a protective role on HCC onset[24]. Therefore, careful follow-up is required, especially in regimens including Sofosbuvir without Ribavirin[24].

A previous study[20] investigating the effects of SVR after DAA treatment on outcomes in 199 patients with various stages of HCC and concomitant HCV infection from two medical institutions in Taiwan (Taipei Veterans General Hospital and Chiayi Christian Hospital)[20] found that patients with BCLC stages B and C disease had SVR rates of 97.1% (68/70) and 77.8% (7/9), respectively. The results also indicated that high SVR was the primary predictor of relapse-free survival and OS; the use of DAAs did not increase the risk of HCC relapse or progression[20]. Another study[22] conducted at a single medical facility in Taiwan

Table III. Results of the stratified analysis of the DAA group based on HCV infection cure status.

Subgroup	Uncured, i.e., residual virus detected	Cured	Premature treatment termination	Untested after treatment completion
No. of patients	7	86	13	16
Follow-up status				
Died	4	52	13	16
Reached endpoint (survived)	3	34	0	0
Survival time (months)				
Mean (SD)	20.3 (2.7)	25.4 (1.1)	5.5 (1.1)	6.5 (0.8)
75th percentile (Q3)	.	35.6	7.1	7.9
Median (Q2)	24.9	23.9	5.7	5
25th percentile (Q1)	13	18.6	2	4.15
Survival rate				
6 months	100.0%	100.0%	46.2%	43.8%
12 months	85.7%	89.5%	7.7%	12.5%
24 months	57.1%	49.5%	0.0%	0.0%
Log-rank *p*	<.0001			
Degree of fibrosis (N, %)				
F0	0 (0)	1 (1.2)	0 (0)	0 (0)
F1	0 (0)	1 (1.2)	1 (7.7)	1 (6.3)
F2	0 (0)	6 (6.98)	1 (7.69)	0 (0)
F3	1 (14.29)	27 (31.4)	5 (38.46)	5 (31.25)
F4	6 (85.71)	51 (59.3)	6 (46.15)	10 (62.5)
Cirrhosis (N, %)				
No	2 (28.6)	33 (38.4)	4 (30.8)	9 (56.3)
Yes	5 (71.4)	53 (61.6)	9 (69.2)	7 (43.8)
Interval between sorafenib use and DAA use (months) (M, SD)	3.6 (4.3)	4.8 (4.5)	3.5 (3.6)	2.0 (2.8)
Interval between DAA use and follow-up endpoint (months) (M, SD)	16.8 (8)	17.5(7.5)	2.0 (1.4)	4.5 (1.2)

Direct-acting antiviral agent (DAA); Hepatitis C virus (HCV).

(Mackay Memorial Hospital) compared the effects of DAA use after HCC treatment in 107 patients with BCLC stage 0 to C disease. The results showed that patients who used DAAs had significantly longer OS (interval between confirmed HCC diagnosis and death or study cutoff date) and did not exhibit an increased risk of recurrence following curative HCC treatment[22].

In this study, among 122 patients in the DAA group, 86 (70.5%) were cured of HCV infection, 7 (5.7%) were not cured (HCV RNA still detectable at 12 weeks after the completion of DAA treatment), 13 (10.7%) discontinued DAA treatment prematurely, and 16 (13.1%) did not return to the hospital for testing after completing treatment. This finding indicates that concomitant DDA therapy and HCC treatment may be ineffective in certain advanced HCC patients and can have limited effects in retarding cancer progression or even accelerating cancer progression. If simultaneous improvement in hepatic function and the progression of HCC symptoms occurs, the benefits of DAAs may be diminished or totally negated[11]. HCV eradication may also possibly result in the suppression of the anticancer effects of immune cells[8]. These results reflect the uniqueness of each advanced HCC patient. Therefore, a detailed evaluation (e.g., physical fitness, degree of liver fibrosis and cirrhosis, or cancer burden) should be performed prior to the use of DAAs, and patients should be adequately informed about the benefits and risks of DAA treatment[11,14]. In the present study, the degree of liver fibrosis and presence/absence of cirrhosis did not cause significant differences in SVR among patients in the DAA group. This finding shows that SVR in advanced HCC patients using DAAs may be affected by other factors; thus, further research is necessary.

This study has some limitations. First, only the presence/absence of cirrhosis was determined, without the further identification of the degree of cirrhosis. Second, we were unable to collect the data on the clinicopathological characteristics that affected HCC patients' survival, such as TNM stage and tumor size[25]. However, as the use of sorafenib is restricted to advanced HCC patients with Child–Pugh class A disease under the NHI program and as this study only investigated patients who received sorafenib treatment, it is highly unlikely that those with cirrhotic cases developed severe cirrhosis.

Conclusions

The effects of DAA treatment on the survival of patients with advanced HCC and concomitant HCV infection were investigated by analyzing big data from the NHI database in Taiwan. The results indicated that advanced HCC patients who received sorafenib achieved survival benefits from the use of DAAs as treatment for HCV infection, with patients whose HCV infection had been cured having better OS.

Acknowledgments

The authors thank the National Health Insurance Administration (NHIA), Ministry of Health and Welfare (MOHW) for their financial support. No funding support was provided for preparing this manuscript.

Author Contributions

Hsin-Yun Tsai, Hui-Ping Chang, Chang-Jr Chen, Wan-Ling Hsu, Li-Ying Huang, and Po-Chang Lee contributed to the design and implementation of the research, the analysis of the results, and the writing of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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References

1) National Taiwan University Hospital (NTUH) e-news. Available from URL: https://epaper.ntuh.gov.tw/health/201806/project_3.html [accessed October 12, 2021].
2) Ministry of Health and Welfare (MOHW) news. Available from URL: https://www.mohw.gov.tw/cp-3159-24039-1.html [accessed October 12, 2021].
3) National Health Insurance coverage implementation plan for novel all-oral anti-HCV drugs (updated on May 26, 2021). Available from URL: https://www.nhi.gov.tw/Content_List.aspx?n=A4EFF6CD1C4891CA&topn=3FC7D09599D25979 [accessed October 12, 2021].
4) Ben AZ. Chronic hepatitis C infection—eradication of the virus. Harefuah 2014; 153: 392-393.
5) Roche B, Coilly A, Duclos-Vallee JC, Samuel D. The impact of treatment of hepatitis C with DAAs on the occurrence of HCC. Liver Int 2018; 38: 139-145.
6) Manthravadi S, Paleti S, Pandya P. Impact of sustained viral response postcurative therapy of hepatitis C-related hepatocellular carcinoma: a systematic review and meta-analysis. Int J Cancer 2017; 140: 1042-1049.
7) He S, Lockart I, Alavi M, Danta M, Hajarizadeh B, Dore GJ. Systematic review with meta-analysis: effectiveness of direct-acting antiviral treatment for hepatitis C in patients with hepatocellular carcinoma. Aliment Pharmacol Ther 2020; 51: 34-52.
8) Ji F, Yeo YH, Wei MT, Ogawa E, Enomoto M, Lee DH, Iio E, Lubel J, Wang W, Wei B, Ide T, Preda CM, Conti F, Minami T, Bielen R, Sezaki H, Barone M, Kiolly P, Chu PS, Virlogeux V, Eurich D, Henry L, Bass MB, Kanai T, Dang S, Li Z, Dufour JF, Zoulim F, Andreone P, Cheung RC, Tanaka Y, Furusyo N, Toyoda H, Tamori A, Nguyen MH. Sustained virologic response to direct-acting antiviral therapy in patients with chronic hepatitis C and hepatocellular carcinoma: A systematic review and meta-analysis. J Hepatol 2019; 71: 473-485.
9) Sung PS, Shin EC. Immunological mechanisms for hepatocellular carcinoma risk after direct-acting antiviral treatment of hepatitis C virus infection. J Clin Med 2021; 10.
10) Fiore V, Vidili G, Bagella P, Lobrano G, Muredda AA, Caruana G, Babudieri S, Madeddu G. Hepatocellular carcinoma development in a patient with HCV infection after eradication with direct-acting antiviral agents. WCRJ 2017; 4: e833.
11) Reig M, Cabibbo G. Antiviral therapy in the palliative setting of HCC (BCLC-B and -C). J Hepatol 2021; 74: 1225-1233.
12) Torres HA, Shigle TL, Hammoudi N, Link JT, Samaniego F, Kaseb A, Mallet V. The oncologic burden of hepatitis C virus infection: A clinical perspective. CA Cancer J Clin 2017; 67: 411-431.
13) Harrod E, Moctezuma-Velazquez C, Gurakar A, Ala A, Dieterich D, Saberi B. Management of concomitant hepatocellular carcinoma and chronic hepatitis C: a review. Hepatoma Research 2019; 5: 28.
14) AASLD, IDSA. AASLD/IDSA HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Clin Liver Dis 2018; 12: 117.
15) AASLD–IDSA. HCV guidance: Recommendations for testing, managing, and treating hepatitis C:

When and in whom to initiate HCV therapy. Available from URL: https://www.hcvguidelines.org/evaluate/when-whom [accessed October 12, 2021].
16) Kawaoka T, Aikata H, Teraoka Y, Inagaki Y, Honda F, Hatooka M, Morio K, Morio R, Kobayashi T, Nagaoki Y, Nakahara T, Hiramatsu A, Tsuge M, Imamura M, Kawakami Y, Chayama K. Impact of hepatitis C virus eradication on the clinical outcome of patients with hepatitis C virus-related advanced hepatocellular carcinoma treated with sorafenib. Oncology 2017; 92: 335-346.
17) White paper for the Taiwan Hepatitis C Policy Guideline 2018–2025. Available from URL: https://www.mohw.gov.tw/cp-4464-49019-1.html [accessed October 12, 2021].
18) NHIA. Drug Payment Guidelines–Chapter 9: Antineoplastic drugs (Updated on July 23, 2021). Available from URL: https://www.nhi.gov.tw/DL.aspx?sitessn=292&u=LzAwMS9VcGxvYWQvMjkyL3JlbGZpbGUvMC82MTM3L2NoYXA5XzExMDA3LnBkZg%3d%3d&n=Y2hhcDlfMTEwMDcucGRm&ico%20=.pdf [accessed October 12, 2021].
19) Yeh ML, Kuo HT, Huang CI, Huang CF, Hsieh MY, Liang PC, Lin IH, Hsieh MH, Lin ZY, Chen SC, Dai CY, Huang JF, Yu ML, Chuang WL. Eradication of hepatitis C virus preserve liver function and prolong survival in advanced hepatocellular carcinoma patients with limited life expectancy. Kaohsiung J Med Sci 2021; 37: 145-153.
20) Yeh ML, Liang PC, Tsai PC, Wang SC, Leong J, Ogawa e, Jun DW, Tseng CH, Landis C, Tanaka Y, Huang CF, Hayashi J, Hsu YC, Huang JF, Dai CY, Chuang WL, Nguyen MH, Yu ML. Characteristics and survival outcomes of hepatocellular carcinoma developed after HCV SVR. Cancers (Basel) 2021; 13.
21) Chi CT, Chen CY, Su CW, Chen PY, Chu CJ, Lan KH, Lee IC, Hou MC, Huang YH. Direct-acting antivirals for patients with chronic hepatitis C and hepatocellular carcinoma in Taiwan. J Microbiol Immunol Infect 2021; 54: 385-395.
22) Lin WC, Lin YS, Chang CW, Chang CW, Wang TE, Wang HY, Chen MJ. Impact of direct-acting antiviral therapy for hepatitis C-related hepatocellular carcinoma. PLoS One 2020; 15: e0233212.
23) Rinaldi L, Nevola R, Franci G, Perrella A, Corvino G, Marrone A, Berretta M, Morone MV, Galdiero M, Giordano M, Adinolfi LE, Sasso FC. Risk of Hepatocellular Carcinoma after HCV Clearance by Direct-Acting Antivirals Treatment Predictive Factors and Role of Epigenetics. Cancers (Basel) 2020; 12: 1351.
24) Rinaldi L, Perrella A, Guarino M, De Luca M, Piai G, Coppola N, Pafundi PC, Ciardiello F, Fasano M, Martinelli E, Valente G, Nevola R, Monari C, Miglioresi L, Guerrera B, Berretta M, Sasso FC, Morisco F, Izzi A, Adinolfi LE. Incidence and risk factors of early HCC occurrence in HCV patients treated with direct acting antivirals: a prospective multicentre study. J Transl Med 2019; 17: 292.
25) Liu H, Cen D, Yu Y, Wang Y, Liang X, Lin H, Cai X. Does fibrosis have an impact on survival of patients with hepatocellular carcinoma: evidence from the SEER database? BMC Cancer 2018; 18: 1125.