Original Article
Comparable benefits of HCV eradication by direct acting antivirals and interferon-based therapy in patients with hepatocellular carcinoma undergoing surgical resection

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Abstract: Whether direct-acting antivirals (DAA) provide comparable survival benefit with interferon (IFN)-based therapy remains unclear. The aim of this study was to compare the outcomes after achieving SVR by IFN-based and DAA therapy after resection of HCV-related hepatocellular carcinoma (HCC). Consecutive 285 patients receiving curative resection for HCV-related HCC were retrospectively enrolled, including 103 (36.1%) and 69 (24.2%) patients with IFN-based and DAA therapy, respectively. Factors associated with recurrence, overall survival (OS) and hepatic decompensation-free survival were evaluated. The SVR rate of DAA was 95.7% in HCC patients. During a median follow-up period of 49.6 months, 102 (35.8%) patients died and 63 (24%) developed hepatic decompensation. By multivariate analysis, SVR by DAA or IFN-based therapy was not associated with early or late HCC recurrence. Achieving SVR (by IFN-based therapy: HR=0.321, P<0.001; by DAA: HR=0.396, P=0.011), BCLC stage B-C (HR=1.914, P=0.024), FIB-4 score >3.25 (HR=1.664, P=0.016) and microvascular invasion (HR=1.603, P=0.048) were independent predictors of OS. Achieving SVR (by IFN-based therapy: HR=0.295, P<0.001; by DAA: HR=0.193, P=0.002), BCLC stage B-C (HR=2.975, P=0.001), GGT >70 U/L (HR=1.931, P=0.015) and cirrhosis (HR=2.035, P=0.007) were independent predictors of decompensation-free survival. The benefit of achieving SVR was consistently observed in cirrhotic and non-cirrhotic patients, and in patients with and without HCC recurrence. In conclusion, achieving SVR by either DAA or IFN-based therapy provide comparable and significant reduction of mortality and hepatic decompensation after surgical resection of HCV-related HCC. DAA therapy should be prescribed for all HCC patients after curative surgical resection.

Keywords: Hepatitis C virus, hepatocellular carcinoma, resection, survival, direct-acting antivirals

Introduction

Chronic hepatitis C (CHC) is a leading cause of hepatocellular carcinoma (HCC), which is the fourth leading cause of cancer-related death globally [1, 2]. For patients with HCC diagnosed at early stage, surgical resection is the primary treatment choice for patients with compensated liver function, which may provide better overall outcomes and higher chance of long term cure [3, 4]. However, the 5-year recurrence rate after curative resection of HCC remains higher than 60% [5], and the 5-year survival rate was reported to be 52-63% in patients with hepatitis C virus (HCV)-related HCC [6, 7]. Furthermore, hepatic decompensation after curative resection of HCV-related HCC, which may occur in 10% of patient at 1 year and 44% at 5 years, still contributes to long-term mortality after successful treatment of early HCC [7].

HCV eradication by interferon-based (IFN-based) therapy has been proven to reduce recur-
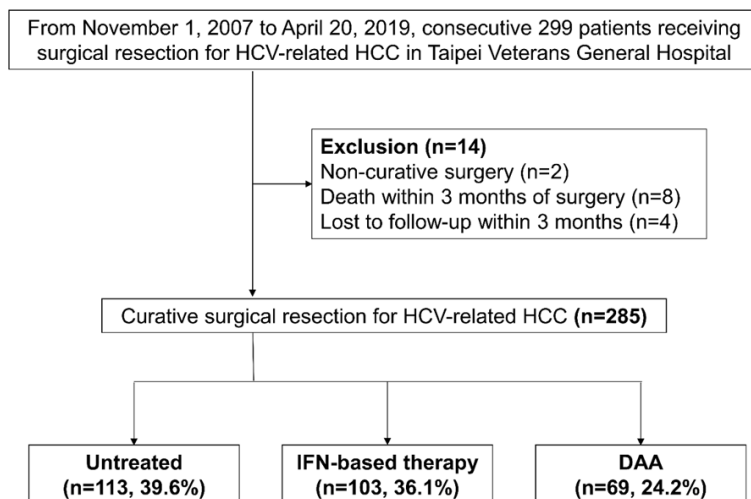
Figure 1. Flow diagram of patient enrollment and grouping.

rence and prolong survival in patients with HCV-related HCC after curative treatment [8-11]. Recent advent of IFN-free direct-acting antivirals (DAAs) has introduced high sustained virological response (SVR) rates, even for patients with HCC [12, 13]. In patients with HCV-related cirrhosis, eradicating HCV by DAA has been reported to improve survival and reduce the incidence of HCC development [14, 15]. In patients with HCV-related HCC, previous studies showed that the risk of HCC recurrence after DAA therapy was similar to that observed in IFN-treated or treatment naïve controls [11]. Although DAA therapy had no significant suppression effect on HCC recurrence, recent studies showed that DAA therapy may improve survival in HCC patients undergoing curative treatment [16-18]. The improvement in survival by DAA might be caused by the reduction in hepatic decompensation after surgery [16]. Whether DAA therapy had comparable benefits to IFN-based therapy in reducing mortality and hepatic decompensation after surgical resection remains unclear. The aim of this study was to compare the outcomes of patients who achieved SVR by IFN-based and DAA therapy after curative surgical resection for HCV-related HCC.

Material and methods

Patients

From November 1, 2007 to April 20, 2019, consecutive 299 patients undergoing surgical resection for HCV-related HCC in Taipei Veterans General Hospital were reviewed retrospec-

tively (**Figure 1**). The inclusion criteria were as follows: age above 20 years old, HCC undergoing surgical resection, and positive anti-HCV. The exclusion criteria were as follows: patients with non-curative resection, combined hepatocellular-cholangiocarcinoma, or died or lost to follow-up within 3 months of surgery. Prior to surgical resection, HCC was diagnosed according to the diagnostic criteria of the American Association for the Study of Liver Diseases (AASLD) by contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) [3, 19], and was confirmed pathologically after surgery. After surgery, patients were followed every 2-3 months with measurement of serum alpha-fetoprotein (AFP), ultrasonography, CECT or MRI. HCC recurrence was confirmed by CECT or MRI.

This study complied with current ethical guidelines and standards of the Declaration of Helsinki, and has been approved by the Institutional Review Board, Taipei Veterans General Hospital (IRB number: 2020-07-011BC).

Outcome assessment

Sustained virological response (SVR) was defined as achieving undetectable HCV viral load at 24 or 12 weeks after the end of IFN-based or DAA treatment, respectively. Early and late recurrence were defined as tumor recurrence developed within or beyond 2 years, respectively, after the surgery [20]. Overall survival (OS) was defined as the time from surgical resection to death. Hepatic decompensation was defined as the occurrence of hyperbilirubinemia (total bilirubin >2 mg/dL), variceal bleeding, ascites, or hepatic encephalopathy [16]. Decompensation-free survival was defined as the time from surgical resection to the date of hepatic decompensation. Twenty-three patients with incomplete information of hepatic decompensation were excluded from analysis of decompensation-free survival.

To address the immortal time bias caused by the varied antiviral-surgery interval in the co-

hort, we adjusted the overall survival and decompensation-free survival, which was calculated from the date of antiviral therapy to death or hepatic decompensation [21].

Laboratory tests and liver histology

The clinical parameters including age, gender, body mass index (BMI), Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh score, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), creatinine, albumin, total bilirubin levels, platelet counts and AFP levels were recorded. Serum AFP was measured by chemiluminescent microparticle immunoassay (ARCHITECT AFP assay, Abbott Ireland Diagnostics Division, Sligo, Ireland). The biochemistry tests were performed using systemic multi-autoanalyzer (Technicon SMAC, Technicon Instruments Corp., Tarrytown, NY). Anti-HCV was detected by enzyme-linked immunosorbent assay (anti-HCV; Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, USA HCV). HCV RNA was quantified by either Abbott Real Time HCV assay (with detection limit of 12 IU/mL) or Cobas TaqMan HCV Test v2.0 (Roche Diagnostics GmbH, Mannheim, Germany, with detection limit of 15 IU/mL). HCV genotype was determined by commercially available assay (Cobas HCV GT, Roche Diagnostics GmbH, Mannheim, Germany).

An Albumin-Bilirubin (ALBI) grade and fibrosis-4 index (FIB-4) score were calculated as previously described [22, 23]. Histological features, such as tumor size, tumor number, Edmonson histological grade, microvascular invasion, hepatic steatosis, Ishak inflammation scores and Ishak fibrosis grades [24] were obtained.

Statistical analysis

All the statistical analysis was performed using the IBM SPSS Statistics V22 (IBM, Armonk, NY). Descriptive statistic values were shown as median (interquartile range, IQR) or as mean ± standard deviation when appropriate. Continuous variable was compared by Mann-Whitney U test or Kruskal-Wallis test. Categorical variable was compared by Pearson chi-square analysis or the Fisher exact test. We used the Kaplan-Meier method to estimate survival rates, and log-rank test to compare survival curves between different groups. Cox proportional-hazards model was used to analyze the prognostic factors. Factors with P<0.1 by univariate analysis were included in the multivariate analysis by forward stepwise Cox proportional-hazards model. A two-tailed P<0.05 was considered statistically significant.

Results

We screened 299 patients with HCV-related HCC undergoing surgery. After excluding the 14 ineligibles, 285 patients were eventually analyzed, including 113 patients without antiviral treatment, 103 patients who received IFN-based treatment and 69 patients who received DAA treatment (**Figure 1**). The baseline characteristics of the 285 patients were shown in **Table 1**. The mean age at the time of surgery was 67 years. Majority of the patients were infected with HCV genotype 1 (52.7%) and 2 (42.3%). The median time from surgical resection to antiviral therapy was 3.8 months (IQR: -14.6 to 20.5 months). Nearly half of the IFN-based therapies were conducted before surgery, while majority of the DAA therapies started after surgery. Compared with the IFN-based therapy group, patients in the DAA group were significantly older, female predominant, had significantly higher HCV RNA, AST levels, lower platelet counts, and comprised of a lower proportion of patients with microvascular invasion and higher proportion of patients with poorer hepatic functions in terms of lower albumin levels, higher Child-Pugh score, ALBI grade and FIB-4 score. In 113 untreated patients, 9 of the 24 (37.5%) patients with available HCV viral load data had undetectable HCV RNA. SVR was achieved in 80 (77.7%) and 66 (95%) patients receiving IFN-based therapy and DAA, respectively.

Predictors of early and late recurrence

During the median follow-up of 49.6 months, 158 (55.4%) patients developed recurrence of HCC after curative surgical resection, including 101 (35.4%) and 57 (38.3%) patients with early and late recurrence, respectively. In order to study the impact of SVR on early recurrence, patients who achieved SVR after two years of surgery (n=36) were sorted as untreated, while patients who achieved SVR within the first two years after surgery (n=58) were excluded from the analysis of early recurrence. Similarly, 23 patients whose SVR were achieved after two

Table 1. Baseline characteristics of the 285 patients with HCV-related HCC receiving curative surgical resection

	Untreated (n=113, 39.6%)	IFN-based therapy (n=103, 36.1%)	DAA (n=69, 24.2%)	P
Age (years)	69.3±9.3	64.4±8.7	67.5±8.7	<0.001*
Sex (male), n (%)	76 (67.3)	70 (68.0)	33 (47.8)	0.013*
BMI (kg/m²)	24.1±3.9	24.9±3.7	24.5±3.1	0.192
Child-Pugh score 5/6/7, n (%)	72/41/0 (63.7/36.3/0)	91/11/1 (88.3/10.7/1.0)	50/19/0 (72.5/27.5/0)	0.001*
HCV RNA (Log IU/mL)†	4.74 (1.17-5.90)	4.87 (3.17-6.02)	5.80 (5.10-6.51)	<0.001*
HCV genotype 1/2/3/6†	0/4/0/1 (0/80/0/20)	15/17/0/0 (46.9/53.1/0/0)	22/9/2/1 (64.7/26.5/5.9/2.9)	0.010
Antiviral-surgery interval, months	-	1.4 (-53.0-5.4)	12.8 (2.5-44.0)	<0.001*
Antiviral before surgery, n (%)	-	55 (53.4)	12 (17.4)	<0.001*
Antiviral after surgery, n (%)	-	48 (46.6)	57 (82.6)	
0-12 months after surgery	-	37 (35.9)	24 (34.8)	<0.001*
12-24 months after surgery	-	5 (4.9)	9 (13.0)	
>24 months after surgery	-	6 (5.8)	24 (34.8)	
Sustained virological response	-	80 (77.7)	66 (95.7)	<0.001*
Achieved before surgery	-	41 (39.8)	10 (14.5)	<0.001*
Achieved after surgery	-	39 (37.9)	56 (81.2)	
0-12 months after surgery	-	27 (26.2)	20 (29.0)	0.003*
12-24 months after surgery	-	5 (4.9)	8 (11.6)	
>24 months after surgery	-	7 (6.8)	28 (40.6)	
BCLC stage 0/A/B/C, n (%)	7/89/11/6 (6.2/78.8/9.7/5.3)	11/81/7/4 (10.7/78.6/6.8/3.9)	5/54/8/2 (7.2/78.3/11.6/2.9)	0.787
Tumor size (cm)	3.46±1.93	3.77±2.77	4.09±3.33	0.004
Multiple tumors (>1), n (%)	20 (17.7)	18 (17.5)	17 (24.6)	0.434
AFP (ng/mL)	20.7 (6.9-244.5)	18.3 (5.3-148.6)	12.4 (5.9-67.7)	0.251
Albumin (g/dL)	3.77±0.40	4.11±0.43	3.89±0.41	<0.001*
Total bilirubin (mg/dL)	0.71±0.27	0.76±0.37	0.81±0.36	0.411
Albumin-Bilirubin (ALBI) score	-2.510±0.350	-2.791±0.373	-2.583±0.386	<0.001*
ALBI grade 1/2, n (%)	45/68 (39.8/60.2)	72/31 (69.9/30.1)	34/35 (49.3/50.7)	<0.001*
Platelet count (10⁹/L)	152±54	156±55	135±58	0.018*
ALT (U/L)	62.5±45.4	70.1±64.5	67.7±48.0	0.511
AST (U/L)	59.4±38.9	54.4±40.9	68.1±47.2	0.018*
GGT (U/L)	68.3±78.6	54.6±52.6	56.5±43.8	0.190
Creatinine (mg/dL)	1.04±0.57	0.88±0.21	1.23±1.78	0.048
FIB-4 score <1.45/1.45-3.25/>3.25, n (%)	5/44/64 (4.4/38.9/56.6)	12/56/35 (11.7/54.4/34.0)	1/25/43 (1.4/36.2/62.3)	<0.001*
Histological features, n (%)†				
Edmonson histological grade 1/>1	6/106 (5.4/94.6)	14/88 (13.7/86.3)	9/60 (13.0/87.0)	0.089

Microvascular invasion	73 (66.4)	66 (64.7)	30 (43.5)	0.005*
Presence of steatosis	47 (48.5)	37 (40.2)	19 (29.7)	0.060
Ishak inflammation scores >6	26 (23.9)	17 (16.8)	5 (7.2)	0.017
Ishak fibrosis grade 5-6 (cirrhosis), n (%)	49 (43.4)	53 (51.5)	39 (56.5)	0.200
Median follow-up, months	42.1 (21.2-68.2)	65.8 (28.7-90.8)	49.0 (34.6-81.6)	0.003
Early recurrence, n (%)	46 (40.7)	30 (29.1)	25 (36.2)	0.204
Late recurrence, n (%)	19 (36.5)	21 (35.6)	17 (44.7)	0.632
Death, n (%)	61 (54.0)	32 (31.1)	9 (13.0)	<0.001*
Hepatic decompensation, n (%)[†]	34 (35.8)	21 (21.4)	8 (11.6)	0.001

Quantitative measures are expressed as mean with standard deviation, median (interquartile range) or relative frequency (%). *P* value represents the comparison of the variables among the untreated, IFN-based therapy and DAA groups. *$P<0.05$ between IFN-based therapy and DAA groups. †Available baseline HCV RNA data, n=146; available HCV genotype, n=67; available histological features: Edmonson histological grade, n=283; microvascular invasion, n=281; hepatic steatosis, n=253; Ishak inflammation score, n=279; Ishak fibrosis grade, n=285. Eligible for hepatic decompensation analysis, n=262.

Table 2. Univariate and multivariate analyses of factors associated with early recurrence within 2 years after surgery

		Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	>60 vs ≤60	1.141	0.711-1.830	0.585			
Sex	Male vs female	1.052	0.705-1.571	0.803			
BMI (kg/m^2)	>27 vs ≤27	0.769	0.471-1.256	0.294			
BCLC stage	B-C vs A	2.314	1.430-3.743	0.001	2.862	1.649-4.969	<0.001
Child-Pugh score	>5 vs 5	1.292	0.840-1.989	0.244			
ALBI grade	2-3 vs 1	1.330	0.900-1.965	0.153			
HCV RNA (IU/mL)	>8×10^5 vs ≤8×10^5	1.110	0.622-1.892	0.700			
Achieving SVR[*]	Non-SVR or untreated	1		0.088			NS
	Interferon-based	0.438	0.210-0.913	0.027			NS
	DAA	0.935	0.341-2.564	0.896			NS
Tumor size (cm)	>5 vs ≤5	2.292	1.506-3.490	<0.001	2.694	1.671-4.344	<0.001
Tumor number	>1 vs 1	1.867	1.207-2.887	0.005			NS
AFP (ng/mL)	>7 vs ≤7	1.782	1.092-2.907	0.021			NS
Bilirubin (mg/dL)	>1.2 vs ≤1.2	1.326	0.709-2.481	0.377			
Albumin (g/dL)	>3.7 vs ≤3.7	0.705	0.476-1.044	0.081			
Creatinine (mg/dL)	>1.2 vs ≤1.2	1.004	0.571-1.766	0.988			
Platelet count (10^9/L)	>120 vs ≤120	0.934	0.612-1.426	0.753			
ALT (U/L)	>80 vs ≤80	1.218	0.804-1.847	0.352			
AST (U/L)	>80 vs ≤80	0.957	0.592-1.547	0.856			
GGT (U/L)	>70 vs ≤70	1.619	1.068-2.454	0.023			NS
FIB-4 score	>3.25 vs ≤3.25	1.200	0.812-1.774	0.361			
Histological grade	>1 vs 1	1.578	0.766-3.251	0.216			
Microvascular invasion	Presence vs absence	1.667	1.085-2.559	0.020			NS
Steatosis	Presence vs absence	0.732	0.475-1.127	0.156			
Ishak inflammation score	>6 vs ≤6	1.061	0.628-1.790	0.825			
Ishak fibrosis grade	5-6 vs ≤4	0.951	0.644-1.405	0.801			

HR, hazard ratio; CI, confidence interval; NS, not significant; ALBI, Albumin-Bilirubin. [*]Fifty-eight patients who achieved SVR within the first two years after surgery were excluded from the analysis of early recurrence. Thirty-six patients who achieved SVR after two years of surgery were classified as untreated in the analysis of early recurrence. Eligible patients for SVR analysis: n=225.

years of surgery were excluded from the analysis of late recurrence.

BCLC stage, SVR by IFN-based therapy, tumor size, tumor number, AFP, GGT and microvascular invasion were factors associated with early recurrence in univariate analysis (**Table 2**). In multivariate analysis, BCLC stage B-C (hazard ratio (HR=2.862, P<0.001) and tumor size >5 cm (HR=2.694, P<0.001)) were independent predictors of early recurrence.

One hundred and twenty-four patients were included in the late recurrence analysis. In univariate analysis, FIB-4 score, platelet counts, serum albumin, GGT, creatinine and AFP levels were factors related to late recurrence (**Table 3**). By multivariate analysis, platelet counts >120×10^9/L (HR=0.530, P=0.024) and GGT

>70 U/L (HR=1.890, P=0.037) were the independent predictors of late recurrence.

Predictors of overall survival (OS)

One-hundred and two (35.8%) patients died during the follow-up period. In univariate analysis, BCLC stage, Child-Pugh score, ALBI grade, SVR by either IFN-based or DAA therapy, tumor size, albumin, FIB-4 score, microvascular invasion and Ishak inflammation score were associated with OS (**Table 4**). Multivariate analysis showed BCLC stage B-C (HR=2.005, P=0.015), the achievement of SVR (by IFN-based therapy: HR=0.304, P<0.001; by DAA: HR=0.205, P<0.001, **Figure 2A**), FIB-4 score >3.25 (HR=1.709, P=0.011) and microvascular invasion (HR=1.631, P=0.040) were independent predictors of OS.

Table 3. Univariate and multivariate analyses of factors associated with late recurrence after 2 years of surgery

		Univariate			Multivariate		
		HR	95% CI	P	HR	95% CI	P
Age (years)	>60 vs ≤60	1.353	0.738-2.479	0.328			
Sex	Male vs female	0.659	0.369-1.175	0.158			
BMI (kg/m^2)	>27 vs ≤27	0.868	0.458-1.648	0.666			
BCLC stage	B-C vs A	0.519	0.162-1.663	0.270			
Child-Pugh score	>5 vs 5	1.493	0.809-2.753	0.199			
ALBI grade	2-3 vs 1	1.297	0.761-2.212	0.339			
HCV RNA (IU/mL)	>8×10^5 vs ≤8×10^5	1.436	0.665-3.102	0.357			
Achieving SVR*	Non-SVR or untreated	1		0.503			
	Interferon-based	0.734	0.381-1.413	0.354			
	DAA	0.522	0.120-2.260	0.384			
Tumor size (cm)	>5 vs ≤5	0.848	0.362-1.986	0.704			
Tumor number	>1 vs 1	1.024	0.494-2.121	0.950			
AFP (ng/mL)	>7 vs ≤7	1.696	0.913-3.152	0.094			NS
Bilirubin (mg/dL)	>1.2 vs ≤1.2	0.708	0.252-1.987	0.511			
Albumin (g/dL)	>3.7 vs ≤3.7	0.536	0.313-0.920	0.024			NS
Creatinine (mg/dL)	>1.2 vs ≤1.2	0.360	0.112-1.155	0.086			NS
Platelet count (10^9/L)	>120 vs ≤120	0.507	0.293-0.878	0.015	0.530	0.305-0.921	0.024
ALT (U/L)	>80 vs ≤80	0.744	0.400-1.386	0.352			
AST (U/L)	>80 vs ≤80	0.780	0.393-1.546	0.476			
GGT (U/L)	>70 vs ≤70	1.998	1.103-3.619	0.022	1.890	1.040-3.434	0.037
FIB-4 score	>3.25 vs ≤3.25	1.618	0.960-2.727	0.071			NS
Histological grade	>1 vs 1	0.933	0.451-1.929	0.851			
Microvascular invasion	Presence vs absence	1.306	0.761-2.241	0.332			
Steatosis	Presence vs absence	1.214	0.679-2.170	0.513			
Ishak inflammation score	>6 vs ≤6	1.050	0.527-2.089	0.890			
Ishak fibrosis grade	5-6 vs ≤4	1.090	0.647-1.838	0.745			

HR, hazard ratio; CI, confidence interval; NS, not significant; ALBI, Albumin-Bilirubin. *Twenty-three patients who achieved SVR after two years of surgery were excluded from analysis of late recurrence. Eligible patients for SVR analysis: n=124.

To address the immortal time bias caused by the varied antiviral-surgery interval in the cohort, we repeated the Cox regression analysis using the adjusted OS, which was calculated from the date of antiviral therapy to death. Multivariate analysis using an adjusted OS showed that BCLC stage B-C (HR=1.914, P=0.024), the achievement of SVR (by IFN-based therapy: HR=0.321, P<0.001; by DAA: HR=0.396, P=0.011, **Figure 2B**), FIB-4 score >3.25 (HR=1.664, P=0.016) and microvascular invasion (HR=1.603, P=0.048) remained significant predictors of survival (**Table 4**). The 5-year OS rates before and after adjustment were 48.0%, 81.9%, 83.1% (**Figure 2A**) and 51.4%, 81.9%, 83.9% (**Figure 2B**), respectively in patients with non-SVR, SVR by IFN-based therapy and SVR by DAA therapy. Notably, there was no significant difference of OS between patients with SVR by IFN-based or DAA

therapy. Furthermore, patients achieving SVR before and after surgery had comparable OS, and both had significantly better OS than patients without antiviral therapy or without achieving SVR.

In subgroup patients with cirrhosis, the 5-year adjusted OS rates were 34.6%, 77.5%, 85.2%, respectively in patients with non-SVR, SVR by IFN-based therapy and SVR by DAA therapy (P<0.001, **Figure 2C**), whereas in subgroup patients without cirrhosis, the corresponding OS rates were 58.8%, 86.6%, 81.0%, respectively (P=0.007, **Figure 2D**). Similarly, in subgroup patients who developed tumor recurrence, the 5-year adjusted OS rates were 45.6%, 75.6%, 79.1%, respectively in patients with non-SVR, SVR by IFN-based therapy and SVR by DAA therapy (P<0.001, **Figure 2E**), whereas in subgroup patients without recur-

Table 4. Univariate and multivariate analyses of factors associated with overall survival

	Unadjusted overall survival						Adjusted overall survival†					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age >60 years	1.265	0.789-2.029	0.329				1.294	0.806-2.077	0.285			
Male	0.839	0.556-1.267	0.405				0.938	0.621-1.418	0.763			
BMI >27 kg/m^2	0.951	0.597-1.514	0.832				0.921	0.578-1.468	0.730			
BCLC stage B/C	1.795	1.078-2.988	0.025	2.005	1.142-3.519	0.015	1.685	1.012-2.804	0.045	1.914	1.090-3.361	0.024
Child-Pugh score >5	2.046	1.356-3.088	0.001			NS	1.981	1.312-2.990	0.001			NS
ALBI grade >1	1.804	1.214-2.679	0.003			NS	1.838	1.237-2.732	0.003			NS
HCV RNA >8×10^8 IU/mL	0.830	0.426-1.616	0.584				0.879	0.451-1.714	0.705			
SVR status												
Non-SVR or untreated	1		<0.001	1		<0.001	1		<0.001	1		<0.001
Interferon-based	0.263	0.157-0.442	<0.001	0.304	0.179-0.517	<0.001	0.276	0.164-0.463	<0.001	0.321	0.189-0.545	<0.001
DAA	0.195	0.098-0.390	<0.001	0.205	0.101-0.416	<0.001	0.381	0.188-0.770	0.007	0.396	0.193-0.810	0.011
Timing of SVR												
Non-SVR or untreated	1		<0.001			NS	1		<0.001			NS
SVR before surgery	0.266	0.133-0.532	<0.001			NS	0.264	0.132-0.527	<0.001			NS
SVR after surgery	0.223	0.133-0.374	<0.001			NS	0.329	0.197-0.550	<0.001			NS
SVR before vs after surgery	1.178	0.528-2.629	0.689				0.829	0.371-1.849	0.647			
Tumor size >5 cm	1.880	1.215-2.908	0.005			NS	1.829	1.183-2.830	0.007			NS
Tumor number >1	0.801	0.476-1.349	0.404				0.872	0.355-2.142	0.376			
AFP >7 ng/mL	1.502	0.921-2.450	0.103				1.523	0.934-2.484	0.092			NS
Bilirubin >1.2 mg/dL	0.699	0.306-1.596	0.395				0.675	0.296-1.541	0.351			
Albumin >3.7 g/dL	0.531	0.360-0.785	0.001			NS	0.504	0.341-0.746	0.001			NS
Creatinine >1.2 mg/dL	1.430	0.837-2.443	0.190				1.351	0.792-2.305	0.270			
Platelet count >120×10^9/L	0.844	0.550-1.295	0.437				0.788	0.512-1.213	0.279			
ALT >80 U/L	1.037	0.682-1.577	0.864				1.018	0.670-1.549	0.932			
AST >80 U/L	1.201	0.856-2.455	0.427				1.177	0.749-1.850	0.479			
GGT >70 U/L	1.325	0.865-2.029	0.196				1.312	0.857-2.009	0.212			
FIB-4 score >3.25	1.681	1.132-2.495	0.010	1.709	1.129-2.587	0.011	1.783	1.199-2.652	0.004	1.664	1.098-2.521	0.016
Histological grade >1	1.992	0.966-4.107	0.062			NS	1.905	0.924-3.929	0.081			NS
Microvascular invasion	2.006	1.283-3.136	0.002	1.631	1.022-2.603	0.040	1.766	1.128-2.763	0.013	1.603	1.005-2.557	0.048
Steatosis (vs absence)	0.808	0.525-1.244	0.333				0.749	0.486-1.155	0.191			
Ishak inflammation score >6	1.784	1.139-2.795	0.011			NS	1.780	1.136-2.788	0.012			NS
Ishak fibrosis grade >4	1.342	0.909-1.982	0.139				1.345	0.911-1.987	0.136			

†The adjusted overall survival is calculated from the date of antiviral therapy to death.
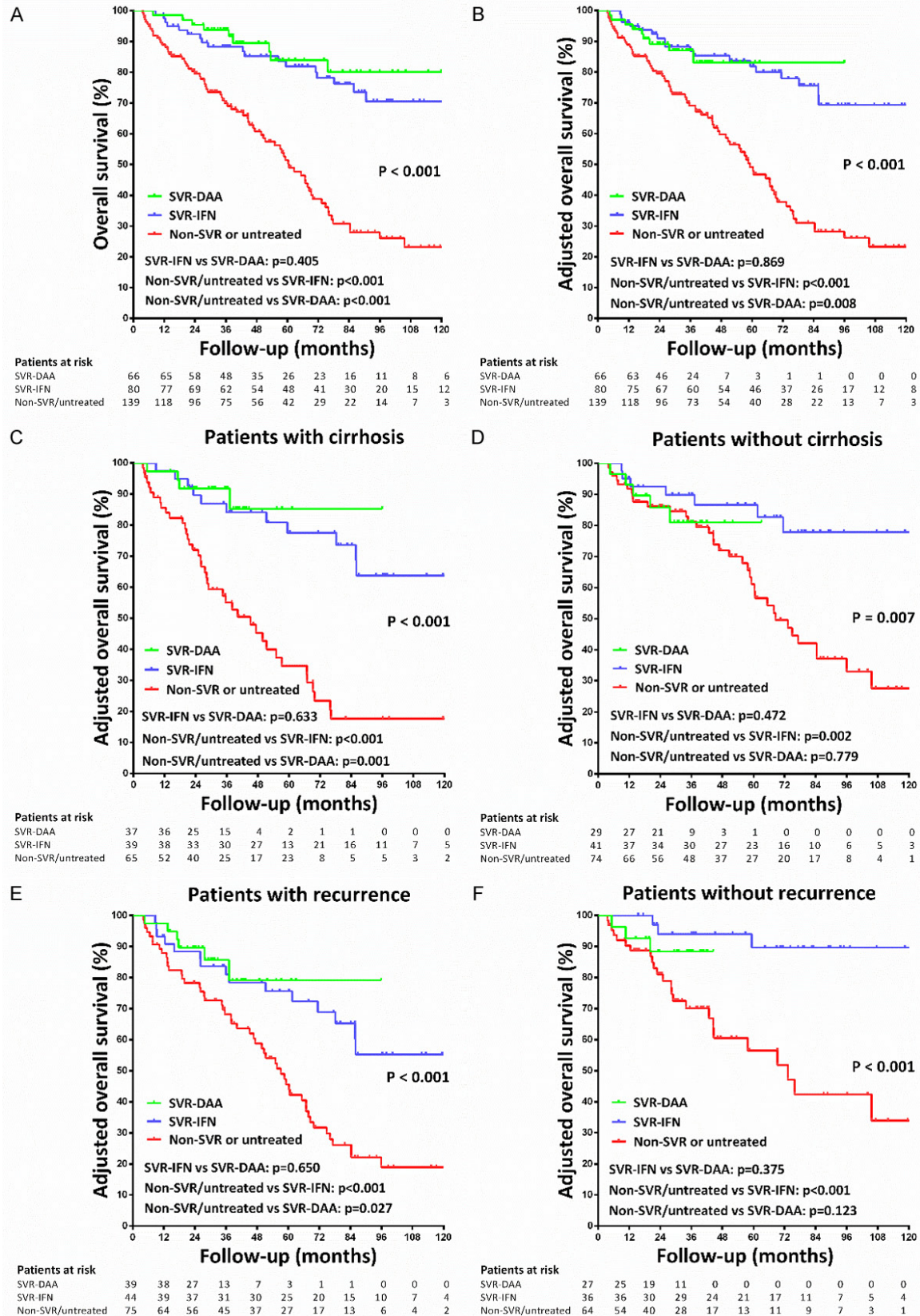
Figure 2. Kaplan-Meier curves of overall survival (OS) stratified by sustained virological response (SVR) after interferon (IFN)-based or direct-acting antiviral agent (DAA) in patients with HCV-related HCC receiving surgical resection. A. Unadjusted OS. B. Adjusted OS. C. Adjusted OS in patients with cirrhosis. D. Adjusted OS in patients without cirrhosis. E. Adjusted OS in patients with tumor recurrence. F. Adjusted OS in patients without tumor recurrence.

rence, the 3-year OS rates were 70.1%, 93.9%, 88.4%, respectively (P<0.001, **Figure 2F**).

Predictors of decompensation-free survival

Sixty-three (24.0%) patients developed hepatic decompensation during the follow-up period. In univariate analysis, BCLC stage, Child-Pugh score, ALBI grade, SVR by either IFN-based or DAA therapy, tumor size, albumin, GGT, FIB-4 score, microvascular invasion and Ishak inflammation score (**Table 5**) were associated with decompensation-free survival. Multivariate analysis showed that BCLC stage B-C (HR=3.042, P=0.001), the achievement of SVR (by IFN-based therapy: HR=0.275, P<0.001; by DAA: HR=0.112, P<0.001, **Figure 3A**), GGT >70 U/L (HR=2.019, P=0.009) and cirrhosis (HR=2.064, P=0.006) were independent predictors of decompensation-free survival. Further multivariate analysis using an adjusted decompensation-free survival showed that BCLC stage B-C (HR=2.975, P=0.001), the achievement of SVR (by IFN-based therapy: HR=0.295, P<0.001; by DAA: HR=0.193, P=0.002, **Figure 3B**), GGT >70 U/L (HR=1.931, P=0.015) and cirrhosis (HR=2.035, P=0.007) remained independently associated with decompensation-free survival (**Table 5**). Similarly, patients achieving SVR before and after surgery had comparable decompensation-free survival, and both had significantly better decompensation-free survival than patients without antiviral therapy or without achieving SVR.

The 5-year decompensation-free survival rates with and without adjustment were 59.7%, 86.5%, 92.0% (**Figure 3A**) and 61.1%, 86.3%, 90.9% (**Figure 3B**), respectively in patients with non-SVR, SVR by IFN-based therapy and SVR by DAA therapy. There was no significant difference of decompensation-free survival between patients with SVR by IFN-based or DAA therapy.

In subgroup patients with cirrhosis, the 5-year adjusted decompensation-free survival rates were 44.0%, 86.5%, 92.4%, respectively in patients with non-SVR, SVR by IFN-based therapy and SVR by DAA therapy (P<0.001, **Figure 3C**), whereas in subgroup patients without cirrhosis, the corresponding decompensation-free survival rates were 70.7%, 86.7%, 91.8%, respectively (P=0.049, **Figure 3D**). Similarly, in

subgroup patients who developed tumor recurrence, the 5-year adjusted decompensation-free survival rates were 53.4%, 78.6%, 88.7%, respectively in patients with non-SVR, SVR by IFN-based therapy and SVR by DAA therapy (P=0.005, **Figure 3E**), whereas in subgroup patients without recurrence, the 3-year decompensation-free survival rates were 77.8%, 96.6, 95.5, respectively (P=0.029, **Figure 3F**).

Discussion

Previous studies have reported that IFN-based therapy may reduce the incidence of recurrence and improve overall survival in HCC patients undergoing resection [8-11], whereas DAA therapy had neutral effect on HCC recurrence [11], but improved overall survival could still be observed after DAA therapy for patients undergoing resection [16-18]. Currently there was no data comparing the effect of DAA and IFN-based therapy in reducing mortality and hepatic decompensation after surgical resection. In this study, we demonstrated that tumor factors were associated with early recurrence and surrogate markers of hepatic fibrosis were related to late recurrence after surgical resection for HCV-related HCC. Although HCV eradication had neutral effect on HCC recurrence, patients achieving SVR by DAA and IFN-based therapy had significantly improved OS and reduced hepatic decompensation. Furthermore, this is the first study to show the comparable benefits in reducing mortality and hepatic decompensation between patients who achieved SVR by DAA and IFN-based therapy.

The IFN-based therapy had poorer tolerability and was limited to younger patients with better liver function reserve. As a result, we observed that HCC patients who received IFN-based therapy were significantly younger and had better liver function profile. In contrast, patients treated with DAA were older and had significantly higher HCV viral load and poorer liver function reserve. Nevertheless, a high SVR rate of 95.7% was observed in patient who mainly received DAA after surgical resection, which was concordant with previous observation of comparable high SVR rate in patients with inactive HCC and patients without HCC [25]. Since DAA therapy was only available in recent few years, we observed that about one third of patients received DAA therapy more

Table 5. Univariate and multivariate analyses of factors associated with decompensation-free survival

	Unadjusted overall survival						Adjusted overall survival†					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age >60 years	0.896	0.518-1.549	0.694				0.919	0.531-1.589	0.762			
Male	0.629	0.364-1.087	0.097			NS	0.681	0.394-1.177	0.169			
BMI >27 kg/m^2	1.239	0.701-2.191	0.461				1.190	0.673-2.103	0.550			
BCLC stage B/C	2.254	1.223-4.154	0.009	3.042	1.600-5.784	0.001	2.219	1.204-4.089	0.011	2.975	1.567-5.648	0.001
Child-Pugh score >5	2.361	1.414-3.943	0.001			NS	2.339	1.399-3.912	0.001			NS
ALBI grade >1	2.221	1.331-3.706	0.002			NS	2.254	1.351-3.760	0.002			NS
HCV RNA >8×10^8 IU/mL	0.900	0.431-1.881	0.779				0.973	0.464-2.037	0.941			
SVR status												
Non-SVR or untreated	1		<0.001	1		<0.001	1		<0.001	1		<0.001
Interferon-based	0.323	0.176-0.593	<0.001	0.275	0.148-0.511	<0.001	0.345	0.189-0.631	0.001	0.295	0.159-0.546	<0.001
DAA	0.140	0.050-0.389	<0.001	0.112	0.040-0.313	<0.001	0.234	0.083-0.658	0.006	0.193	0.068-0.542	0.002
Timing of SVR												
Non-SVR or untreated	1		<0.001			NS	1		<0.001			NS
SVR before surgery	0.219	0.086-0.553	0.001			NS	0.218	0.086-0.552	0.001			NS
SVR after surgery	0.310	0.174-0.555	<0.001			NS	0.441	0.248-0.785	0.005			NS
SVR before vs after surgery	0.710	0.259-1.941	0.504				0.485	0.177-1.330	0.160			
Tumor size >5 cm	1.791	1.013-3.166	0.045			NS	1.785	1.010-3.156	0.046			NS
Tumor number >1	0.859	0.448-1.648	0.648				0.884	0.461-1.696	0.712			
AFP >7 ng/mL	1.106	0.619-1.979	0.733				1.121	0.627-2.006	0.700			
Bilirubin >1.2 mg/dL	1.378	0.626-3.030	0.426				1.358	0.618-2.984	0.446			
Albumin >3.7 g/dL	0.473	0.288-0.777	0.003			NS	0.453	0.276-0.745	0.002			NS
Creatinine >1.2 mg/dL	0.767	0.330-1.781	0.537				0.725	0.312-1.682	0.454			
Platelet count >120×10^9/L	0.843	0.491-1.448	0.536				0.805	0.467-1.387	0.434			
ALT >80 U/L	1.556	0.938-2.581	0.087			NS	1.582	0.954-2.622	0.075			NS
AST >80 U/L	1.427	0.818-2.490	0.211				1.443	0.827-2.517	0.197			
GGT >70 U/L	1.705	1.015-2.863	0.044	2.019	1.188-3.431	0.009	1.668	0.993-2.800	0.053	1.931	1.139-3.273	0.015
FIB-4 score >3.25	1.483	0.900-2.442	0.122				1.584	0.958-2.617	0.073			NS
Histological grade >1	1.311	0.595-2.891	0.502				1.193	0.542-2.625	0.661			
Microvascular invasion	1.641	0.965-2.790	0.068			NS	1.533	0901-2.609	0.115			
Steatosis (vs absence)	0.772	0.447-1.336	0.356				0.715	0.412-1.241	0.233			
Ishak inflammation score >6	1.829	1.035-3.233	0.038			NS	1.771	1.001-3.132	0.049			NS
Ishak fibrosis grade >4	1.533	0.930-2.526	0.094	2.064	1.234-3.450	0.006	1.541	0.935-2.541	0.090	2.035	1.218-3.401	0.007

†The adjusted decompensation-free survival is calculated from the date of antiviral therapy to hepatic decompensation.
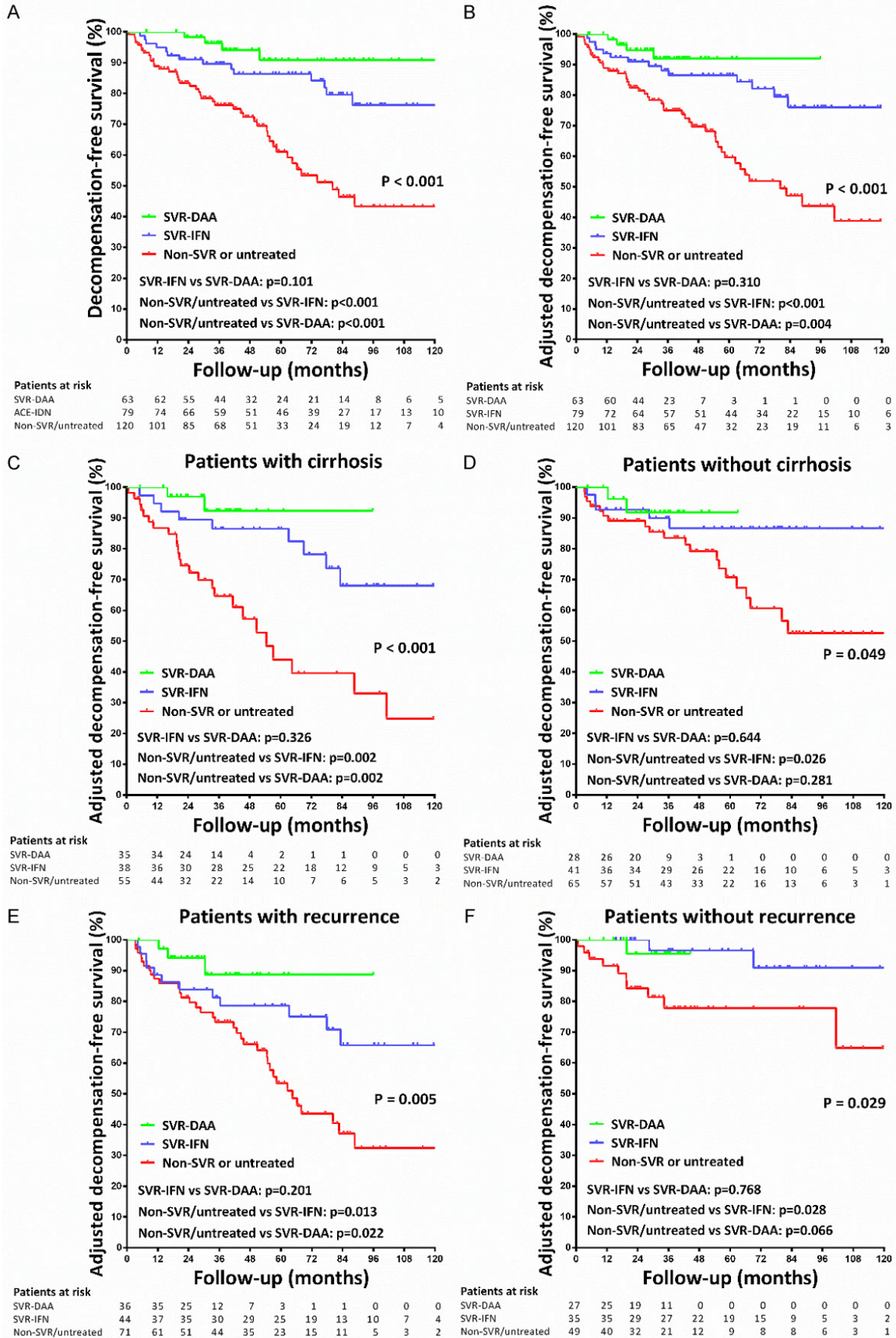
Figure 3. Kaplan-Meier curves of decompensation-free survival stratified by sustained virological response (SVR) after interferon (IFN)-based or direct-acting antiviral agent (DAA). A. Unadjusted decompensation-free survival. B. Adjusted decompensation-free survival. C. Adjusted decompensation-free survival in patients with cirrhosis. D. Adjusted decompensation-free survival in patients without cirrhosis. E. Adjusted decompensation-free survival in patients with tumor recurrence. F. Adjusted decompensation-free survival in patients without tumor recurrence.

than 2 years after surgery. Since DAA therapy is now widely available, early initiation of DAA after curative treatment of HCC is suggested as SVR after DAA therapy may result in improved liver function and facilitate additional HCC-directed therapy.

By multivariate analysis, BCLC stage and tumor size were shown as independent predictors of early recurrence, while platelet count and GGT levels were predictors of late recurrence, which were consistent with previous studies that tumor factors were the main determinants of early recurrence and hepatic fibrosis and inflammation were main predictors of late recurrence [20, 26]. The elevation of GGT accounts in part for the adaption and over-compensation of oxidative stress in the liver, and was shown to be associated with fibrosis progression in patients with chronic hepatitis C [27, 28]. Serum GGT level has also been shown to predict the occurrence of HCC in patients with HCV infection [29, 30]. Our results indicate that GGT could be a novel predictive biomarker for late recurrence of HCV-related HCC. High HCV viral load has been shown to be associated with higher risk of HCC development [31]. In this study, we did not observe a significant association between baseline HCV viral load and the outcomes of HCC after resection. Since HCV clearance by either IFN-based or DAA therapy would eradicate the long-term effect of HCV viremia, baseline HCV viral load might no longer be a significant factor of HCC recurrence or survival after SVR, which was similar to our previous observations that baseline HBV viral load was not associated with recurrence in patients with HBV-related HCC under antiviral therapy [32, 33]. The impact of SVR by DAA on HCC recurrence was a controversial issue [34]. Although some studies showed that SVR by antiviral therapy was associated with lower recurrence rate of HCV-related HCC [8, 35], our data did not show a significant correlation between SVR and HCC recurrence. The benefit of SVR on HCC recurrence needs to be confirmed by further long-term follow-up studies.

We identified BCLC stage, FIB-4 score, microvascular invasion and achieving SVR as independent predictors of OS. Tumor stage and liver fibrosis score are well known factors associated with OS in HCC patients [36]. Previous studies showed that SVR by IFN or DAA therapy may improve the survival of patients with HCC after surgical resection [11, 16-18]. Consistent with previous reports, we showed that patients with SVR had significantly better OS, and the survival benefit was comparable between patients treated with DAA and IFN-based therapy. Among our patients with SVR, both DAA and IFN-based therapy appears to exert a 70% risk reduction in all-cause mortality than those without SVR, despite the fact that the hepatic reserve at baseline was notably less favorable in patients receiving DAA therapy than IFN-based therapy. Besides, patients achieving SVR before and after surgery had comparable survival outcomes after surgery. The survival benefit of achieving SVR was consistently observed in cirrhotic and non-cirrhotic patients, and in patients with and without HCC recurrence. Comparable to previous publication regarding patients with surgically-treated HCV-related HCC, the 5-year survival in our patients without SVR was around 50% [6], whereas patients achieving SVR may have a 5-year OS rate of higher than 80%. Of note, the 5-year mortality rate was still higher than 40% in untreated patients without tumor recurrence, suggesting that hepatic decompensation still contribute to mortality in significant proportion of untreated patients even with HCC cure (**Figure 2F**).

Hepatic decompensation was considered to be an important survival factor after surgical resection of HCC. Currently, only few studies addressed the impact of SVR on hepatic decompensation after surgical resection [16]. In this study, we showed that BCLC stage, GGT levels, cirrhosis status and achieving SVR were independent predictors of hepatic decompensation after resection. Tumor stage was associated with tumor recurrence after surgery, which might lead to hepatic decompensation

due to tumor progression. Cirrhosis is also a well-known predictor of hepatic decompensation over the long-term, even in patients achieving SVR [37]. We observed that baseline GGT level, which was a surrogate marker of fibrosis progression in CHC, not only correlated with late recurrence, but also predict hepatic decompensation after surgical resection for HCV-related HCC. Importantly, achieving SVR by either DAA or IFN-based therapy could reduce the risk hepatic decompensation more than 70% after surgery, and the benefit was also comparable between patients treated with DAA and IFN-based therapy. The benefit of maintaining liver function reserve after SVR was consistently observed in cirrhotic and non-cirrhotic patients, and in patients with and without HCC recurrence. Our data suggest that SVR by either DAA or IFN-based therapy provide comparable and significant benefit in reducing hepatic decompensation after surgical resection of HCV-related HCC. The well-preserved liver function leads to long-term survival in patients without tumor recurrence, and provides a better chance of receiving rescue therapy for patients with recurrence.

Despite the comparable benefits of the DAA or IFN-based therapy in terms of reducing mortality and hepatic decompensation, DAA therapy had significantly higher SVR rate, shorter treatment duration and fewer side effects, and was more tolerable in patients with cirrhosis and hepatic decompensation. With accumulating evidences showing the benefit of DAA therapy for HCC patients undergoing resection, DAA therapy should be encouraged for all HCC patients with HCV viremia after surgery.

This study has some limitations. First, this is a retrospective study in a single medical center in Taiwan. Second, since DAA therapy was introduced only in recent 5 years, whereas IFN-based therapy has been used for more than 10 years, the follow-up time of DAA therapy group was shorter than the IFN-based therapy group. However, the median follow-up time of DAA therapy group was still longer than 4 years in this study. Besides, as DAA was only available in recent years, most patients received DAA later after surgical resection, which might result in immortal time bias. Nevertheless, we used adjusted OS and decompensation-free survival to minimize immortal time bias, and the survival analysis of OS and decompensa-tion-free survival before and after adjustment consistently showed significant reduction of mortality and decompensation by achieving SVR. Third, the case number in the DAA group is relatively small. Further long-term follow-up studies with larger case number are needed to prove the long-term benefit of DAA therapy. Fourth, HCV viral load data were not available in majority of the untreated patients, and certain proportion of these patients may have undetectable HCV RNA. Since patient with spontaneous HCV clearance may have better outcomes than viremic cases without treatment [31], the disparity of OS and decompensation-free survival between patients with and without SVR would be higher after excluding untreated patients with undetectable HCV RNA.

In conclusion, achieving SVR by either DAA or IFN-based therapy provides comparable and significant reduction of mortality and hepatic decompensation after surgical resection of HCV-related HCC. The well-maintained liver function reserve may provide long-term survival for patients without recurrence, and may offer the opportunity of receiving rescue therapy for patients with recurrence. The SVR rate of DAA for patients with HCV-related HCC after surgical resection remains higher than 95%. DAA therapy should be initiated early for all HCC patients after curative surgical resection.

Disclosure of conflict of interest

None.

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