






ORIGINAL ARTICLE

Improved prognosis of hepatitis C-related hepatocellular carcinoma in the era of direct-acting antivirals

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Funding information

Japan Agency for Medical Research and Development (AMED): JP21fk0210113, JP22fk0210113, JP21fk0210066, and JP22fk0210066; The Health, Labour, and Welfare Policy Research Grants from the Ministry of Health, Labour, and Welfare of Japan: H30-Kansei-Shitei-003.

Abstract

The prognostic impact of direct-acting antivirals (DAAs) on patients with hepatitis C-related hepatocellular carcinoma (C-HCC) is still unclear. This study aimed to evaluate the prognosis of C-HCC in the DAA era. We enrolled 1237 consecutive patients with treatment-naive C-HCC who underwent radical radiofrequency ablation between 1999 and 2019. We also enrolled 350 patients with nonviral HCC as controls. We divided these patients into three groups according to the year of initial treatment: 1999–2005 (cohort 1), 2006–2013 (cohort 2), and 2014–2019 (cohort 3). The use of antiviral agents and their effect in patients with C-HCC was investigated. Overall survival was evaluated for each cohort using the Kaplan-Meier method and a multivariable Cox proportional hazards regression model. Sustained virologic response (SVR) was achieved in 52 (10%), 157 (26%), and 102 (74%) patients with C-HCC in cohorts 1–3, respectively. The 3- and 5-year survival rates of patients with C-HCC were 82% and 59% in cohort 1; 80% and 64% in cohort 2; and 86% and 78% in cohort 3, respectively ($p = 0.003$). Multivariable analysis adjusted for age, liver function, and tumor extension showed that the prognosis of C-HCC improved in cohort 3 compared to cohort 1 (adjusted hazard ratio [aHR], 0.49; 95% confidence interval [CI], 0.32–0.73; $p < 0.001$), whereas the prognosis of nonviral HCC did not improve significantly (aHR, 0.96; 95% CI, 0.59–1.57; $p = 0.88$). The prognosis of C-HCC drastically improved with the advent of DAAs.

Tsuyoshi Fukumoto and Tatsuya Minami contributed equally to this work.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading common cause of cancer-related death worldwide.^[1] HCC usually develops in patients with chronic liver diseases, mostly related to hepatitis C virus (HCV) infection in Western countries and Japan.^[1,2] In many cases, fibrosis progresses from chronic hepatitis C, leading to the development of HCC. Even after the treatment of HCC, chronic inflammation persists, resulting in a decrease in liver reserve. Therefore, the prognosis depends on both tumor burden and liver functional reserve.

In patients with chronic hepatitis C or cirrhosis, sustained virologic response (SVR) as a result of antiviral treatment has been reported in various studies to contribute to the suppression of hepatocarcinogenesis, preservation of liver function, and eventually improvement in overall survival.^[3–7] These beneficial effects of viral eradication could potentially apply to patients with a history of HCC. Some researchers reported that SVR due to interferon (IFN)-based therapies after treatment of HCC could reduce the risk of HCC recurrence and improve prognosis.^[8] However, most patients with HCC were not indicated for IFN-based therapies because of background cirrhosis; furthermore, even if they could have received the therapy, SVR rates were low. As a result, the prognosis of patients with curatively treated hepatitis C-related HCC (C-HCC) has improved only moderately in spite of recent advances in diagnostic and treatment modalities.^[9]

Since direct-acting antivirals (DAAs) became available, most patients, including those with a history of HCC, have been able to achieve SVR with favorable tolerability.^[10] Although some reported an accelerated recurrence after DAA therapy in patients with HCC,^[11,12] as data accumulate, it appears that DAA may not increase recurrence rates of HCC.^[13–15] However, whether the prognosis of patients with C-HCC has improved in the era of DAA has not been well documented. In this study, we evaluated the trends in the prognosis of patients with C-HCC following radical radiofrequency ablation (RFA) therapy over time during the past 2 decades.

METHODS

Study design and participants

This retrospective cohort study was approved by the University of Tokyo Medical Research Center Ethics Committee according to the comprehensive protocol for retrospective studies at the University of Tokyo Hospital, Department of Gastroenterology (approval number 2058). The study and its protocol complied with the ethical guidelines for epidemiological research by

the Japanese Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor, and Welfare. Written consent was obtained from all subjects for the RFA treatment and subsequent study on prognosis.

Using a prospectively collected computerized database, we identified patients with treatment-naive HCC admitted to the Department of Gastroenterology, the University of Tokyo Hospital, a tertiary center, from January 1999 to December 2019. We included patients who were successfully treated for initial HCC with RFA, positive for HCV antibody, and negative for hepatitis B surface antigen (HBsAg) (C-HCC group). We also included those who were negative for both HBsAg and HCV antibody (non-B, non-C HCC) as controls. We divided these patients into three groups according to the year of initial treatment for HCC: 1999–2005 (cohort 1), 2006–2013 (cohort 2), and 2014–2019 (cohort 3).

Data collection

We collected clinical data at the time of initial admission to our department for the treatment of HCC. These data included age, sex, anthropometric parameters, hepatitis infection status, daily alcohol consumption, presence of diabetes, tumor factors (such as maximum tumor diameter and the number of tumors), presence of ascites, symptom of hepatic encephalopathy, and laboratory data, including serum total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, prothrombin activity, alpha-fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and des-gamma-carboxy prothrombin (DCP). Body mass index and the albumin–bilirubin (ALBI) score were calculated using obtained data. The ALBI score was calculated by the following formula: $ALBI = 0.66 \times \log_{10} [\text{bilirubin (mg/dL)} \times 17.1] - 0.85 \times \text{albumin [g/dL]}$.^[16] ALBI was classified as grade 1 (≤ -2.60), grade 2a (> -2.60 to ≤ -2.27), grade 2b (> -2.27 to ≤ -1.39), grade 3 (> -1.39), according to the modified ALBI (mALBI) grade classification.^[17]

Diagnosis of HCC, treatment of HCC, and follow-up

HCC was diagnosed using dynamic computed tomography (CT) or magnetic resonance imaging (MRI) findings. Early enhancement in the arterial phase and washout in the delayed phase were considered to have diagnostic importance.^[18] If the diagnostic imaging tests could not help reach a definitive diagnosis of HCC, ultrasound-guided tumor biopsy was performed; pathological diagnosis was made based on the Edmondson-Steiner criteria.^[19]

In general, the indication for RFA was a single tumor ≤ 5 cm in diameter or three or fewer tumors ≤ 3 cm in diameter. RFA procedures were performed percutaneously under real-time ultrasound guidance using a monopolar electrode device (Cool-tip; Covidien, Boulder, CO, or Medtronic, Minneapolis, MN) (VIVARF; STARmed, Gyeonggi-do, Korea). For large tumors, we performed overlapping cauterizations to the tumors so that the treatment areas contained the entire tumor volumes. The precise techniques of RFA have been described elsewhere.^[20]

We monitored the recurrence of HCC using dynamic CT or MRI and measurement of serum AFP, AFP-L3, and DCP levels every 4 months. HCC recurrence was diagnosed using the same criteria used to diagnose HCC as described above. RFA was used for recurrent HCC as the principal treatment. If multiple intrahepatic recurrences were untreatable with RFA, transarterial chemoembolization was performed. If macrovascular invasion or extrahepatic metastasis occurred, intra-arterial infusion chemotherapy or molecular targeted drugs, such as sorafenib or lenvatinib, were used.

Antiviral therapy and definition of viral response

To confirm the absence of viable HCC nodules, we performed dynamic CT- or MRI-initiating antiviral therapies. After DAAs became available in Japan from September 2014, DAA therapy was the principal treatment for hepatitis C infection. Before the era of DAAs, patients were treated with IFN-based therapy. We defined SVR as undetectable HCV RNA at 24 weeks after the end of antiviral therapy.

Outcomes

The primary outcome was overall survival, defined as the interval between the day of first treatment with RFA and the day of death or the last visit. Observations were censored as of December 31, 2020. Patients who were lost to follow-up were censored. The secondary outcome was liver-related mortality, cumulative HCC recurrence, and change of liver reserve function after initial HCC treatment. For deceased patients, the causes of death were categorized according to the criteria of the Liver Cancer Study Group of Japan.^[21] In the current study, we further categorized the causes of death into groups. Liver-related death included liver cancer progression, liver failure (massive ascites, jaundice, hepatic encephalopathy, or a combination of these), gastrointestinal bleeding, gastroesophageal varices rupture, rupture of liver cancer, and HCC operative death. Liver-unrelated

death included death due to extrahepatic malignancy, cardiovascular or cerebrovascular disease, infectious disease, and unknown cause of death. Time to recurrence was defined as the interval between the initial HCC treatment and the detection of HCC recurrence. The change in the ALBI score 1 year after the initial HCC treatment was used to evaluate the chronological change of liver reserve function after the initial HCC treatment.

Statistical analysis

Data are presented as median with interquartile range (IQR) for quantitative variables and number and percentage to represent qualitative variables. When evaluating trends among cohorts, we used the Jonckheere-Terpstra test for continuous variables and the Cochran-Armitage trend test for categorical variables. Cumulative survival curves were plotted using the Kaplan-Meier method and were compared using the log-rank test. To analyze the prognostic relevance for the cohorts in each group, multivariable Cox proportional hazards regression models adjusted for baseline variables that exhibited significant association in the univariable analysis were used, considering multicollinearity of variables. A sensitivity analysis on overall survival was also conducted after excluding patients who achieved SVR before initial HCC treatment or with heavy alcohol consumption (≥ 60 g/day) in the C-HCC group. Another sensitivity analysis was conducted after censoring enrolled patients in the C-HCC group at 5 years after the initial treatment of HCC.

In the analysis of cause-specific mortality, cumulative incidences of liver-related and liver-unrelated mortality were evaluated using competing risk analysis with Gray's method.^[22] The relevance of cause-specific mortality for the cohorts was analyzed in each etiology group using Fine-Gray proportional subdistribution hazards models^[23] adjusted for baseline variables that exhibited significant association in the univariable analysis, considering multicollinearity of variables.

The competing risk model was also used in the analysis of recurrence after the initial treatment. In the analysis, HCC recurrence and death without recurrence were treated as competing risks. A multivariable proportional subdistribution hazards model was used for the adjustment with baseline variables that exhibited significant association in the univariable analysis.

The liner mixed model was used to evaluate the transition of ALBI score at baseline and 1 year after baseline. If data at 1 year after baseline were missing, the patient was excluded from this model.

Statistical analyses were performed using R 4.0.3 (<http://www.R-project.org>). All tests were two tailed, and $p < 0.05$ was considered to indicate a significant difference.

RESULTS

Patient profiles

A total of 3688 patients with HCC visited our department between January 1999 and December 2019 (Figure 1). Among them, 1803 patients were treated with RFA for

treatment-naïve HCC, and of the patients included, 1237 had C-HCC and 350 had non-B, non-C HCC. The enrolled patients were divided into three groups based on the year of initial treatment, and 503, 597, and 137 patients with C-HCC and 78, 162, and 110 patients with non-B, non-C HCC belonged to cohort 1 (1999–2005), cohort 2 (2006–2013), and cohort 3 (2014–2019), respectively.

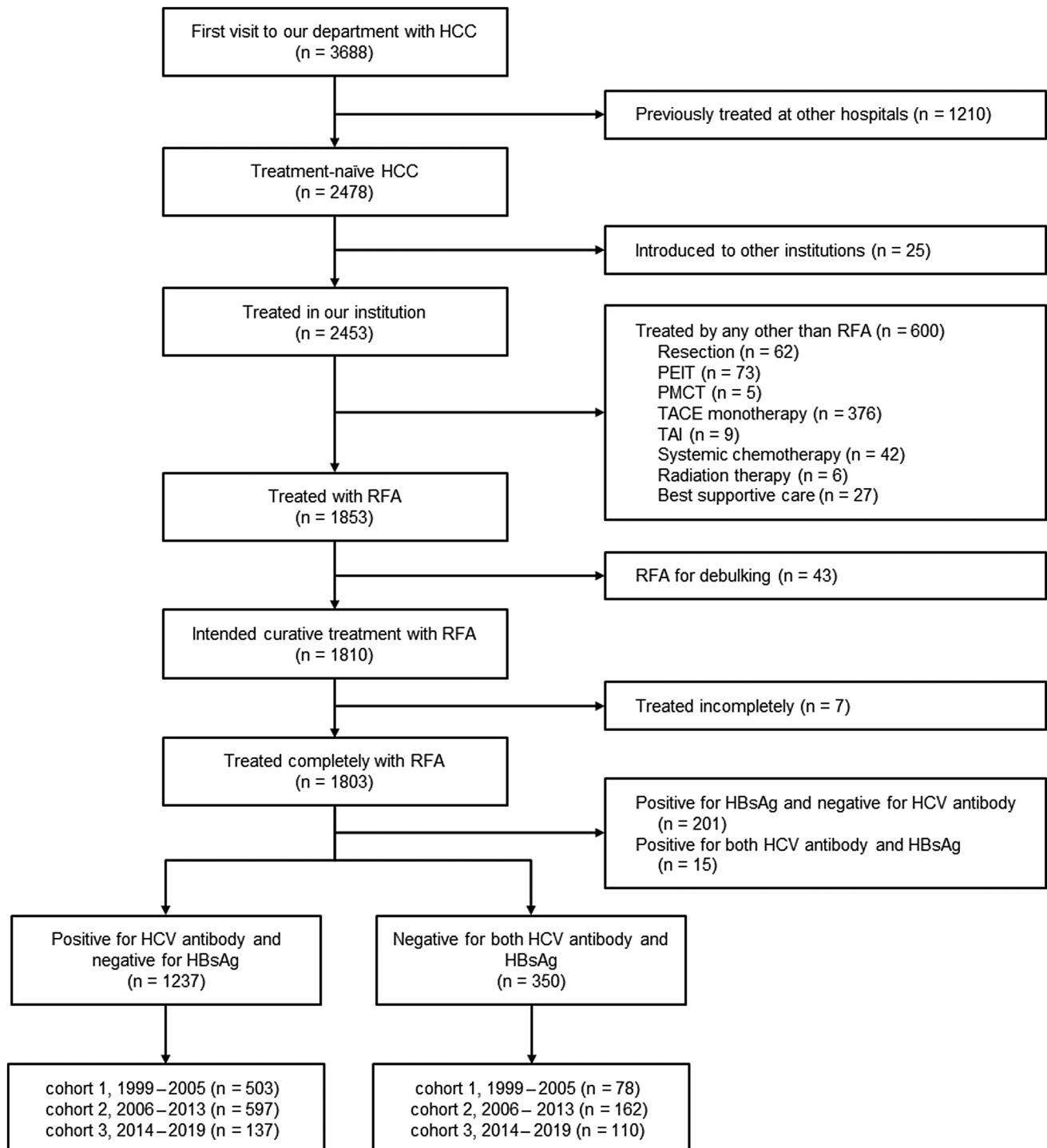


FIGURE 1 Patient flow diagram. HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PEIT, percutaneous ethanol injection therapy; PMCT, percutaneous microwave coagulation therapy; RFA, radiofrequency ablation; RT, radiation therapy; TACE, transarterial chemoembolization; TAI, transcatheter arterial infusion.

TABLE 1 Baseline characteristics

Variable	C-HCC (n = 1237)			p value	Non-B, non-C HCC (n = 350)			p value
	Cohort 1 (n = 503)	Cohort 2 (n = 597)	Cohort 3 (n = 137)		Cohort 1 (n = 78)	Cohort 2 (n = 162)	Cohort 3 (n = 110)	
Age (years)	69 (65–74)	72 (65–77)	76 (67–82)	<0.001	67 (62–74)	71 (64–76)	72 (66–77)	0.02
Male sex, n (%)	305 (61)	345 (58)	77 (56)	0.26	55 (71)	114 (70)	70 (64)	0.28
AST, IU/L	60 (46–81)	56 (40–75)	41 (30–68)	<0.001	37 (25–51)	40 (28–52)	35 (25–48)	0.33
ALT, IU/L	57 (37–81)	47 (32–70)	33 (20–56)	<0.001	29 (21–46)	29 (19–47)	27 (17–39)	0.15
PLT, × 10 ⁴ /μL	10.5 (7.8–14.1)	10.1 (7.5–13.3)	11.8 (8.5–15.7)	0.65	13.6 (9.8–18.9)	12.1 (7.7–17.0)	11.9 (9.5–19.5)	0.71
Liver cirrhosis, n (%) ^a	393 (78)	475 (80)	78 (57)	<0.001	47 (60)	121 (75)	61 (55)	0.28
Child-Pugh class				<0.001				0.24
A, n (%)	353 (70)	480 (80)	115 (84)		59 (76)	128 (79)	92 (84)	
B, n (%)	145 (29)	109 (18)	22 (16)		15 (19)	34 (21)	15 (14)	
C, n (%)	5 (1)	8 (1)	0 (0)		4 (5)	0 (0)	3 (3)	
mALBI grade				0.11				0.38
1, n (%)	132 (26)	158 (26)	48 (35)		35 (45)	59 (36)	40 (36)	
2a, n (%)	144 (29)	167 (28)	31 (23)		19 (24)	37 (23)	30 (27)	
2b, n (%)	215 (43)	248 (42)	56 (41)		22 (28)	60 (37)	36 (33)	
3, n (%)	12 (2)	24 (4)	2 (1)		2 (3)	6 (4)	4 (4)	
MELD score	9 (8–10)	7 (6–9)	7 (6–8)	<0.001	9 (8–11)	7 (6–9)	7 (6–9)	<0.001
AFP>100 ng/mL, n (%)	116 (23)	109 (18)	16 (12)	0.002	11 (14)	7 (4)	9 (8)	0.22
DCP>100 mAU/mL, n (%)	54 (11)	75 (13)	11 (8)	0.93	8 (10)	29 (18)	20 (18)	0.19
AFP-L3>15%, n (%)	65 (13)	70 (12)	15 (11)	0.46	12 (15)	16 (10)	15 (14)	0.83
Tumor size, mm	24 (18–30)	21 (17–27)	18 (15–25)	<0.001	26 (20–33)	23 (18–30)	21 (15–26)	<0.001
≤20mm	178 (35)	266 (45)	78 (57)		22 (28)	62 (38)	55 (50)	
>20mm, ≤30mm	207 (41)	241 (40)	49 (36)		28 (36)	63 (39)	44 (40)	
>30mm	118 (23)	90 (15)	10 (7)		28 (36)	37 (23)	11 (10)	
Tumor number				0.005				0.34
1, n (%)	293 (58)	388 (65)	102 (74)		49 (63)	95 (59)	78 (71)	
2–3, n (%)	174 (35)	182 (30)	34 (25)		24 (31)	62 (38)	30 (27)	
≥4, n (%)	36 (7)	27 (5)	1 (1)		5 (6)	5 (3)	2 (2)	
BMI, kg/m ²				0.06				0.19
<25 kg/m ² , n (%)	379 (75)	438 (73)	91 (66)		44 (56)	79 (49)	51 (46)	
≥25 kg/m ² , n (%)	124 (25)	159 (27)	46 (34)		34 (44)	83 (51)	59 (54)	
Diabetes mellitus, n (%)	91 (18)	142 (24)	35 (26)	0.01	28 (36)	80 (49)	56 (51)	0.06
Alcohol consumption, g/day				0.93				0.32
<20 g/day, n (%)	323 (64)	384 (64)	86 (63)		36 (46)	58 (36)	59 (54)	
≥20, and <60 g/day, n (%)	100 (20)	114 (19)	27 (20)		8 (10)	26 (16)	9 (8)	
≥60 g/day, n (%)	80 (16)	99 (17)	24 (18)		34 (39)	78 (48)	42 (38)	

Note: Values are medians (interquartile range) or numbers (percentages).

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AU, arbitrary unit; BMI, body mass index; C-HCC, hepatitis C-related hepatocellular carcinoma; DCP, des-gamma-carboxy prothrombin; HCC, hepatocellular carcinoma; mALBI, modified albumin–bilirubin; MELD, Model for End-Stage Liver Disease; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody; PLT, platelet count.

^aLiver cirrhosis was defined as cases with at least one of the following features: liver biopsy with F4, FibroScan value >15 kPa, platelet count <10 × 10⁴/μL, or the presence of gastroesophageal varix or splenomegaly.

Baseline characteristics of patients with C-HCC and non-B, non-C HCC stratified by cohorts are shown in Table 1. The median age increased in both C-HCC (69, 72, and 76 years old in cohorts 1–3, respectively, $p < 0.001$) and non-B, non-C HCC (67, 71, and 72 years old in cohorts 1–3, respectively, $p < 0.001$). AST and ALT levels decreased significantly in C-HCC ($p < 0.001$) but did not decrease in non-B, non-C HCC ($p = 0.33$). Tumor size decreased significantly in both C-HCC ($p < 0.001$) and non-B, non-C HCC ($p < 0.001$), and tumor number decreased significantly in C-HCC ($p = 0.005$).

After excluding patients who achieved SVR before initial HCC treatment or who had heavy alcohol consumption in the C-HCC group, baseline characteristics showed a similar trend among cohorts (Table S1).

Antiviral therapy

The proportion of patients with C-HCC who achieved SVR is shown in Figure 2. Antiviral therapy was started before the initial HCC treatment in 246 (49%), 214 (36%), and 69 (50%) patients in cohorts 1–3, respectively. Among them, SVR was achieved in eight (3.3%), 34 (16%), and 44 (64%) patients in cohorts 1–3, respectively ($p < 0.001$). All patients achieved SVR with IFN-based therapy in cohorts 1 and 2, whereas 14 patients achieved SVR with IFN-based therapy and 30 patients with DAA therapy in cohort 3.

After the initial HCC treatment, 79 (16%), 153 (26%), and 64 (47%) patients received antiviral therapy in cohorts 1–3, respectively, with SVR being achieved in 44 (56%), 123 (81%), and 58 (91%) patients ($p < 0.001$). SVR with IFN-based therapy was achieved in 29, 23,

and one of these patients, respectively, and 15, 100, and 57 patients achieved SVR with DAA therapy. The median (IQR) interval between initial HCC treatment and antiviral therapy initiation that led to SVR was 3.2 (1.4–11.1), 4.3 (2.3–5.7), and 0.4 (0.2–0.9) years in cohorts 1–3, respectively.

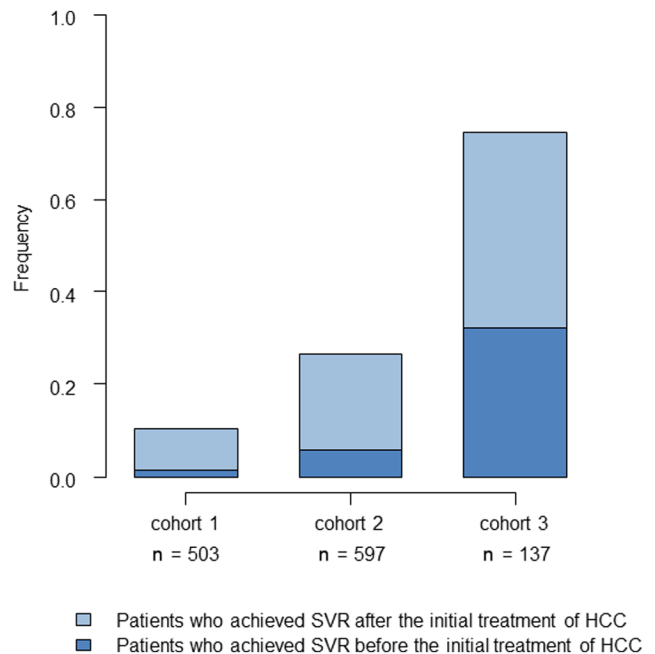


FIGURE 2 Proportion of patients who achieved SVR according to cohort. SVR was achieved in 52 (10%), 157 (26%), and 102 (74%) patients with hepatitis C-related hepatocellular carcinoma in cohorts 1–3, respectively. SVR was achieved in 8, 34, and 44 patients before initial treatment of HCC and 44, 123, and 58 patients after the initial treatment of HCC in cohorts 1–3, respectively. HCC, hepatocellular carcinoma; SVR, sustained virologic response.

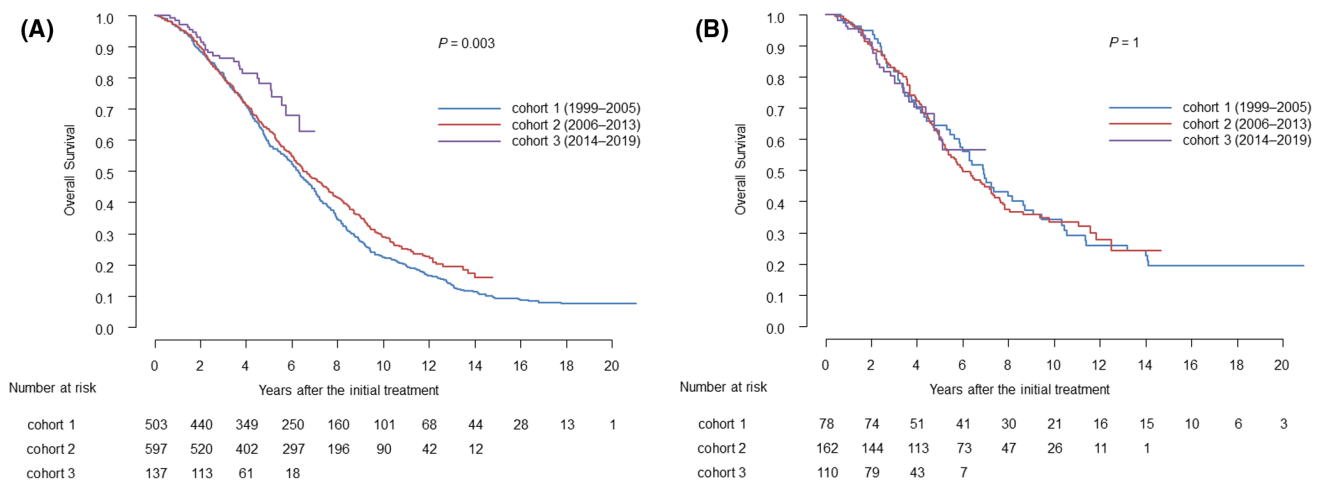


FIGURE 3 Overall survival according to cohort. (A) Patients with C-HCC. The 1-, 3-, and 5-year survival rates of patients with C-HCC were 97%, 82%, and 59% in cohort 1; 97%, 80%, and 64% in cohort 2; and 99%, 86%, and 78% in cohort 3, respectively ($p = 0.003$, by log-rank test). (B) Patients with non-B, non-C HCC. The 1-, 3-, and 5-year survival rates of patients with non-B, non-C HCC were 97%, 82%, and 64% in cohort 1; 98%, 83%, and 61% in cohort 2; and 96%, 80%, and 60% in cohort 3, respectively ($p = 1$, by log-rank test). C-HCC, hepatitis C-related hepatocellular carcinoma; HCC, hepatocellular carcinoma; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody.

TABLE 2 Cause of death

Cause of death	C-HCC			Non-B, non-C HCC		
	Cohort 1	Cohort 2	Cohort 3	Cohort 1	Cohort 2	Cohort 3
Total deaths, n	433	401	28	57	104	30
Liver related, n (%)	337 (78)	261 (65)	22 (79)	41 (72)	62 (60)	18 (60)
Tumor progression, n (%)	241 (56)	173 (43)	14 (50)	27 (47)	41 (39)	11 (37)
Liver failure, n (%)	96 (22)	88 (22)	8 (29)	14 (25)	21 (20)	7 (23)
Liver unrelated, n (%)	96 (22)	140 (35)	6 (21)	16 (28)	42 (40)	12 (40)
Other cancer, n (%)	16 (4)	26 (6)	1 (4)	3 (5)	11 (11)	2 (7)
Infectious disease, n (%)	24 (6)	17 (4)	2 (7)	3 (5)	3 (3)	3 (10)
Cerebrovascular disease, n (%)	9 (2)	4 (1)	0 (0)	1 (2)	3 (3)	3 (10)
Cardiovascular disease, n (%)	9 (2)	8 (2)	0 (0)	1 (2)	4 (4)	1 (3)
Other, n (%)	16 (4)	17 (4)	0 (0)	5 (9)	5 (5)	0 (0)
Unknown cause, n (%)	22 (5)	68 (17)	3 (11)	3 (5)	16 (15)	3 (10)

Note: Values are numbers (percentages).

Abbreviations: C-HCC, hepatitis C-related hepatocellular carcinoma; HCC, hepatocellular carcinoma; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody.

Survival and cause of death

Of the 1587 enrolled patients, 1053 (66%) patients died during the observation period and 168 (11%) patients were lost to follow-up. Mean follow-up time was 6.8, 6.2, and 3.8 years in cohorts 1–3 in C-HCC and 7.7, 6.2, and 3.4 years in cohorts 1–3 in non-B, non-C HCC. There was significant difference in the overall survival among cohorts in the C-HCC group ($p = 0.003$, by log-rank test). The 1-, 3-, and 5-year survival rates of patients with C-HCC were 97%, 82%, and 59% in cohort 1; 97%, 80%, and 64% in cohort 2; and 99%, 86%, and 78% in cohort 3, respectively (Figure 3A). Sensitivity analysis after excluding patients who achieved SVR before initial HCC treatment or with heavy alcohol consumption in the C-HCC group showed similar results with significant difference of overall survival among cohorts (Figure S1). Another sensitivity analysis after censoring enrolled patients in the C-HCC group at 5 years after the initial treatment of HCC showed similar results with significant differences of overall survival among cohorts (Figure S2). In contrast, there was no significant difference in overall survival among cohorts in the non-B, non-C HCC group ($p = 1$, by log-rank test). The 1-, 3-, and 5-year survival rates of patients with non-B, non-C HCC were 97%, 82%, and 64% in cohort 1; 98%, 83%, and 61% in cohort 2; and 96%, 80%, and 60% in cohort 3, respectively (Figure 3B).

Causes of death are shown in Table 2. The most common cause was liver-related death in both groups, of which tumor progression was the most common in each cohort.

Using competing risk analysis, there was a significant difference in both liver-related and liver-unrelated mortality among cohorts in the C-HCC group ($p < 0.001$, by Gray's test), as shown in Figure 4A,B. In contrast,

there was no significant difference in liver-related and liver-unrelated mortality among cohorts in the non-B, non-C HCC group ($p = 0.58$ and $p = 0.46$, respectively, by Gray's test), as shown in Figure 4C,D.

Predictors of overall survival and cause-specific mortality

Univariable analysis showed that the following factors were significantly associated with poorer prognosis: older age, higher AST level, lower platelet count, higher mALBI grade, higher AFP level, higher DCP level, higher AFP-L3 level, larger tumor size, larger number of tumor lesions in patients with C-HCC (Table 3); older age, higher AST level, lower platelet count, higher mALBI grade, larger tumor size, and larger number of tumor lesions in the non-B, non-C HCC group (Table 4). Multivariable analysis showed that the prognosis of C-HCC, adjusted for factors with significant association in the univariable analysis, improved with time (adjusted hazard ratio [aHR] of cohort 3 vs. cohort 1, 0.49; 95% confidence interval [CI], 0.32–0.73; $p < 0.001$), whereas the prognosis of non-B, non-C HCC did not significantly improve (aHR of cohort 3 vs. cohort 1, 0.96; 95% CI, 0.59–1.57; $p = 0.88$). Sensitivity analysis after excluding patients who achieved SVR before initial HCC treatment or with heavy alcohol consumption in the C-HCC group showed similar results, with improved prognosis in cohort 3 (aHR of cohort 3 vs. cohort 1, 0.40; 95% CI, 0.24–0.67; $p < 0.001$) (Table S2). Another sensitivity analysis after censoring enrolled patients in the C-HCC group at 5 years after the initial treatment of HCC showed similar results, with improved prognosis in cohort 3 (aHR of cohort 3 vs. cohort 1, 0.50; 95% CI, 0.31–0.79; $p = 0.003$) (Table S3).

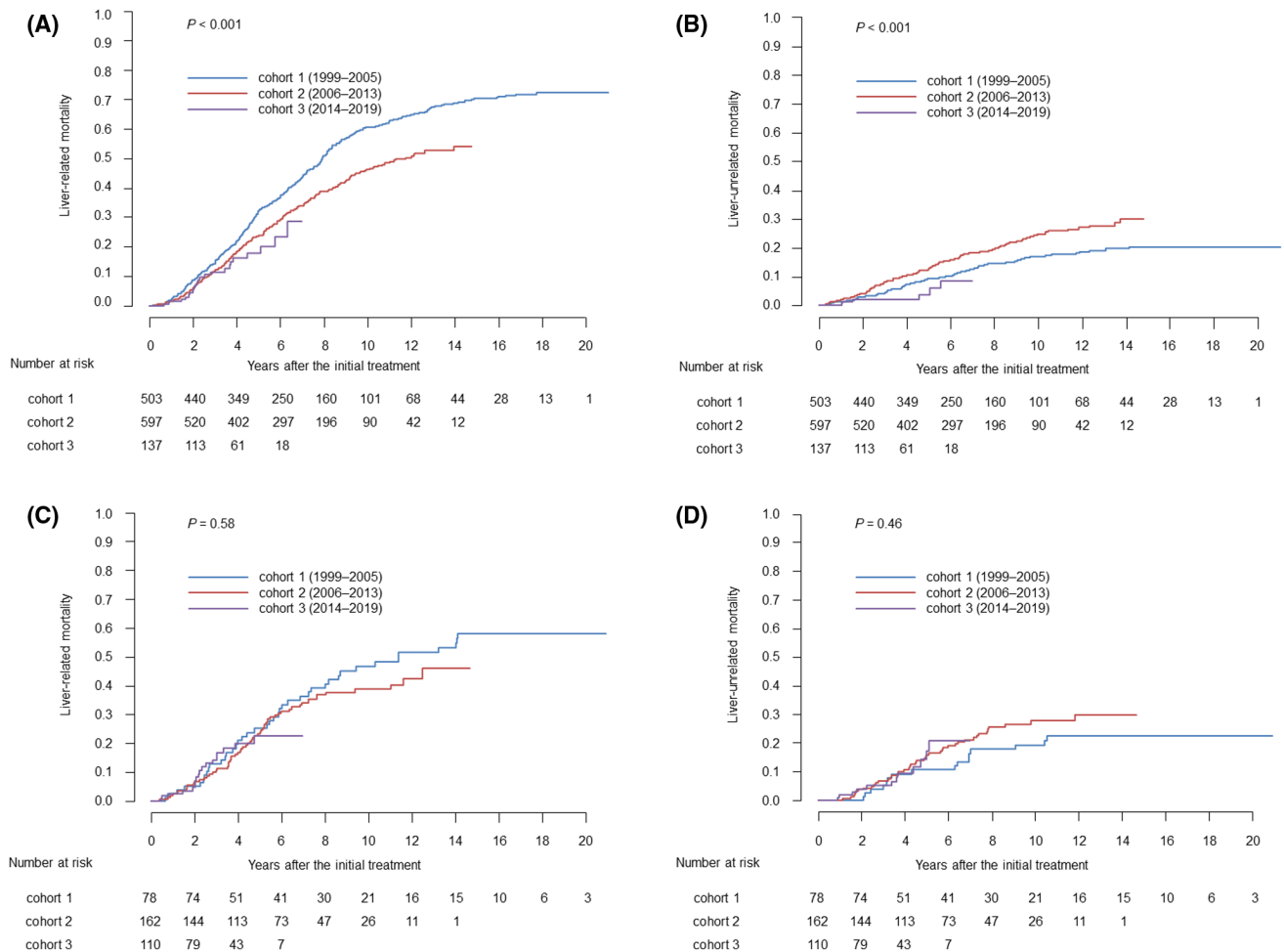


FIGURE 4 Cause-specific mortality according to cohort. (A) Liver-related mortality in patients with C-HCC. There was a significant difference among cohorts ($p < 0.001$, by Gray's test). (B) Liver-unrelated mortality in patients with C-HCC. There was a significant difference among cohorts ($p < 0.001$, by Gray's test). (C) Liver-related mortality in patients with non-B, non-C HCC. There was no significant difference in liver-related mortality among cohorts ($p = 0.58$, by Gray's test). (D) Liver-unrelated mortality in patients with non-B, non-C HCC. There was no significant difference in liver-unrelated mortality among cohorts ($p = 0.46$, by Gray's test). C-HCC, hepatitis C-related hepatocellular carcinoma; HCC, hepatocellular carcinoma; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody.

Fine-Gray proportional subdistribution hazard analysis showed that tumor burden and liver function were risk factors for liver-related death in both groups. In the C-HCC group, the risk of liver-related death was significantly lower in cohort 2 than in cohort 1 (aHR of cohort 2 vs. cohort 1, 0.68; 95% CI, 0.57–0.81; $p < 0.001$) and was much lower in cohort 3 (aHR of cohort 3 vs. cohort 1, 0.56; 95% CI, 0.35–0.91; $p = 0.02$). Older age was a risk factor for liver-unrelated death in both groups.

HCC recurrence

Cumulative HCC recurrence of C-HCC and non-B, non-C HCC is shown in Figure 5. There were significant differences among cohorts in the C-HCC group ($p < 0.001$), and there was no significant difference in the non-B, non-C HCC group ($p = 0.21$). In the C-HCC group, multivariable analysis showed that mALBI

grade 2a and 2b, higher AST level, larger tumor size, and larger number of tumor lesions were significantly related to higher HCC recurrence and that cohort 3 was significantly related to lower risk of HCC recurrence (aHR of cohort 3 vs. cohort 1, 0.74; 95% CI, 0.57–0.96; $p = 0.02$) (Table 5). In the non-B, non-C HCC group, multivariable analysis showed that lower platelet count and a larger number of tumor lesions were significantly related to higher HCC recurrence. In the non-B, non-C HCC group, there was no significant difference in the risk of HCC recurrence among cohorts (aHR of cohort 3 vs. cohort 1, 1.26; 95% CI, 0.85–1.89; $p = 0.25$) (Table 5).

Liver function

Liver function as evaluated by ALBI score significantly deteriorated at 1 year after the initial treatment

TABLE 3 Univariable and multivariable analysis of all-cause and cause-specific death in patients with C-HCC

Variable	All-cause death			Liver-related death			Liver-unrelated death					
	Univariable	Multivariable		Univariable	Multivariable		Univariable	Multivariable				
	HR (95% CI)	p value	HR (95% CI)	HR (95% CI)	p value	HR (95% CI)	HR (95% CI)	p value	HR (95% CI)	p value		
Age per 1 year	1.02 (1.02–1.03)	<0.001	1.03 (1.02–1.04)	<0.001	0.99 (0.98–1.00)	0.006	0.99 (0.98–1.01)	0.26	1.07 (1.05–1.09)	<0.001	1.07 (1.05–1.09)	<0.001
Male sex	0.96 (0.84–1.10)	0.56		0.91 (0.77–1.06)	0.22		1.15 (0.89–1.49)	0.29				
AST per 10 IU/L	1.03 (1.02–1.05)	<0.001	1.03 (1.01–1.05)	0.003	1.05 (1.03–1.06)	<0.001	1.03 (1.01–1.05)	0.0057	0.96 (0.92–1.00)	0.08		
ALT per 10 IU/L	0.99 (0.98–1.01)	0.50		1.02 (0.98–1.03)	0.03		0.95 (0.91–0.99)	0.01				
PLT per $1 \times 10^4/\mu\text{L}$	0.97 (0.96–0.99)	<0.001	0.99 (0.98–1.01)	0.46	0.97 (0.95–0.99)	0.007	1.00 (0.98–1.02)	0.74	1.00 (0.98–1.02)	0.97		
mALBI grade												
1	1		1			1			1			
2a	1.54 (1.27–1.87)	<0.001	1.41 (1.15–1.72)	<0.001	1.44 (1.16–1.78)	<0.001	1.36 (1.08–1.71)	0.008	1.18 (0.84–1.66)	0.34		
2b	2.50 (2.09–2.98)	<0.001	2.42 (1.99–2.93)	<0.001	2.10 (1.71–2.57)	<0.001	1.94 (1.54–2.44)	<0.001	1.26 (0.92–1.72)	0.15		
3	4.79 (3.26–7.04)	<0.001	4.51 (3.00–6.78)	<0.001	4.49 (2.63–7.69)	<0.001	4.10 (2.26–7.43)	<0.001	0.60 (0.22–1.68)	0.33		
AFP>100 ng/mL	1.26 (1.07–1.48)	0.006	0.92 (0.77–1.11)	0.40	1.54 (1.28–1.87)	<0.001	1.28 (1.04–1.57)	0.02	0.63 (0.44–0.89)	0.01	0.63 (0.44–0.90)	<0.001
DCP>100 mAU/ mL	1.57 (1.28–1.92)	<0.001	1.40 (1.13–1.73)	0.002	1.38 (1.09–1.75)	0.007	1.36 (1.06–1.74)	0.02	1.12 (0.77–1.63)	0.56		
AFP-L3>15%	1.36 (1.12–1.65)	0.002	1.35 (1.08–1.70)	0.01	1.21 (0.95–1.55)	0.13			1.12 (0.77–1.64)	0.55		
Tumor size												
≤20 mm	1		1			1			1			
>20 mm, ≤30 mm	1.30 (1.12–1.51)	<0.001	1.31 (1.12–1.52)	<0.001	1.32 (1.11–1.58)	0.002	1.27 (1.05–1.53)	0.01	0.96 (0.73–1.27)	0.78		
>30 mm	1.45 (1.21–1.74)	<0.001	1.31 (1.08–1.60)	0.006	1.66 (1.34–2.04)	<0.001	1.47 (1.18–1.84)	<0.001	0.81 (0.57–1.17)	0.26		
Tumor number												
1	1		1			1			1			

TABLE 3 (Continued)

Variable	All-cause death			Liver-related death			Liver-unrelated death		
	Univariable		Multivariable	Univariable		Multivariable	Univariable		Multivariable
	HR (95% CI)	p value	HR (95% CI)	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
2-3	1.25 (1.08-1.44)	0.003	1.22 (1.06-1.42)	1.26 (1.07-1.49)	0.006	1.19 (1.00-1.42)	0.046	0.96 (0.73-1.27)	0.78
≥4	1.52 (1.13-2.03)	0.006	1.47 (1.08-1.98)	1.57 (1.11-2.23)	0.01	1.33 (0.91-1.96)	0.14	0.86 (0.47-1.59)	0.64
BMI ≥25kg/m ²	1.05 (0.90-1.23)	0.52		1.21 (1.01-1.44)	0.03	1.08 (0.89-1.30)	0.44	0.74 (0.54-1.01)	0.06
Diabetes mellitus	1.03 (0.88-1.22)	0.72		0.99 (0.82-1.20)	0.94			1.01 (0.74-1.37)	0.97
Alcohol consumption									
<20 g/day	1			1				1	
≥20 and <60 g/day	0.95 (0.80-1.13)	0.55		0.86 (0.70-1.05)	0.13			1.21 (0.89-1.64)	0.23
≥60 g/day	0.93 (0.77-1.12)	0.42		0.93 (0.75-1.14)	0.47			1.01 (0.70-1.44)	0.97
cohort 1	1		1	1		1		1	
cohort 2	0.86 (0.75-0.99)	0.03	0.81 (0.71-0.94)	0.65 (0.55-0.76)	<0.001	0.68 (0.57-0.81)	<0.001	1.39 (1.08-1.80)	0.01
cohort 3	0.55 (0.38-0.81)	0.003	0.49 (0.32-0.73)	0.52 (0.33-0.81)	<0.001	0.56 (0.35-0.91)	0.02	0.45 (0.20-1.04)	0.06
								0.30 (0.13-0.68)	0.004

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AU, arbitrary unit; BMI, body mass index; C-HCC, hepatitis C-related hepatocellular carcinoma; CI, confidence interval; DCP, des-gamma-carboxy prothrombin; HR, hazard ratio; mALBI, modified albumin-bilirubin; PLT, platelet count.

TABLE 4 (Continued)

Variable	All-cause death			Liver-related death			Liver-unrelated death		
	Univariable		Multivariable	Univariable		Multivariable	Univariable		Multivariable
	HR (95% CI)	p value	HR (95% CI)	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
1	1		1	1		1		1	
2-3	1.28 (0.95-1.73)	0.11	1.05 (0.77-1.45)	1.13 (0.77-1.64)	0.74	1.32 (0.81-2.16)	0.54	1.32 (0.81-2.16)	0.73
≥4	2.62 (1.41-4.88)	0.002	2.90 (1.53-5.52)	2.48 (1.08-5.70)	0.001	1.25 (0.38-4.11)	0.03	1.25 (0.38-4.11)	0.07
BMI ≥25kg/m ²	1.03 (0.77-1.37)	0.85		1.24 (0.87-1.76)	0.24	0.71 (0.44-1.14)	0.24	0.71 (0.44-1.14)	0.16
Diabetes mellitus	1.09 (0.82-1.45)	0.55		1.21 (0.85-1.72)	0.29	0.92 (0.58-1.47)	0.29	0.92 (0.58-1.47)	0.73
Alcohol consumption									
<20g/day	1			1		1		1	
≥20, and <60g/day	1.07 (0.68-1.68)	0.78		0.65 (0.35-1.20)	0.17	1.94 (1.01-3.71)	0.045	1.94 (1.01-3.71)	0.045
≥60g/day	1.03 (0.76-1.40)	0.85		1.10 (0.76-1.60)	0.61	0.95 (0.57-1.59)	0.85	0.95 (0.57-1.59)	0.85
cohort 1	1		1	1		1		1	
cohort 2	1.02 (0.74-1.42)	0.89	0.90 (0.64-1.28)	0.77 (0.53-1.12)	0.57	1.36 (0.77-2.39)	0.17	1.36 (0.77-2.39)	0.07
cohort 3	1.01 (0.63-1.61)	0.97	0.96 (0.59-1.57)	0.65 (0.37-1.13)	0.88	1.13 (0.54-2.39)	0.12	1.13 (0.54-2.39)	0.12
							0.74		0.74
									1.00
									(0.47-2.13)

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; ALT, alanine aminotransferase; AU, arbitrary unit; BMI, body mass index; C-HCC, hepatitis C-related hepatocellular carcinoma; CI, confidence interval; DCP, des-gamma-carboxy prothrombin; HR, hazard ratio; mALBI, modified albumin-bilirubin; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody; PLT, platelet count.

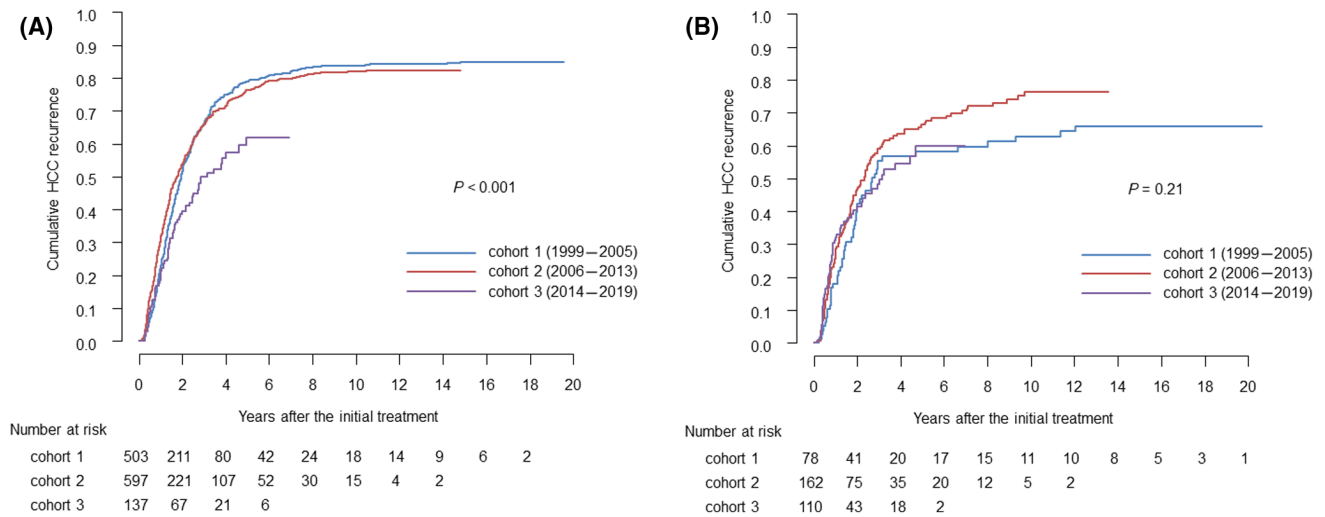


FIGURE 5 Cumulative HCC recurrence according to cohort. (A) patients with C-HCC. The 1-, 3-, and 5-year cumulative HCC recurrence rates of patients with C-HCC were 23%, 66%, and 79% in cohort 1; 31%, 66%, and 76% in cohort 2; and 20%, 50%, and 62% in cohort 3, respectively ($p < 0.001$, by Gray's test). (B) Patients with non-B, non-C HCC. The 1-, 3-, and 5-year cumulative HCC recurrence rates of patients with non-B, non-C HCC were 18%, 55%, and 58% in cohort 1; 27%, 59%, and 66% in cohort 2; and 31%, 48%, and 60% in cohort 3, respectively ($p = 0.21$, by Gray's test). C-HCC, hepatitis C-related hepatocellular carcinoma; HCC, hepatocellular carcinoma; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody.

of HCC in cohort 1 (0.12/year, $p < 0.001$) and cohort 2 (0.09/year, $p < 0.001$) and tended to improve in cohort 3 (-0.05 /year, $p = 0.07$) in the C-HCC group (Figure 6A). In the non-B, non-C HCC group, liver function tended to deteriorate in cohort 1 (0.08/year, $p = 0.08$) and cohort 2 (0.11/year, $p < 0.001$) but had no significant change in cohort 3 (0.007/year, $p = 0.81$) (Figure 6B).

DISCUSSION

This retrospective cohort study investigated the change of prognosis in patients with C-HCC over the past 2 decades compared to patients with non-B, non-C HCC, with adjustment for clinical baseline characteristics. The results showed that the prognosis of patients with C-HCC significantly improved with the advent of DAA, with a reduced risk of both liver-related and liver-unrelated death, whereas that of patients with non-B, non-C HCC did not improve over the same period.

Over the past 2 decades, there has been a change in patients' characteristics that could affect prognosis. First, patients with C-HCC have been aging over time. In Japan, most patients with chronic HCV infection acquired the virus in the 1950s and 1960s, and new cases of HCV infection have been rare since 1990.^[24] Therefore, patients in cohort 3 were of advanced age with a 7-year difference in median age compared to cohort 1. As for patients with non-B, non-C HCC, a 5-year difference was also observed, probably reflecting aging of the general population. Second, tumor size at initial diagnosis decreased; this is likely due to advances in

diagnostic imaging in both C-HCC and patients with non-B, non-C HCC.

In addition to the 32% of patients who achieved SVR before the initial diagnosis of HCC, 42% of patients in cohort 3 achieved SVR after RFA, which can be attributed to the feasibility of DAA therapy with a high antiviral effect. Achieving SVR even after HCC treatment could maintain liver function during the clinical course and could prevent the progression to hepatic decompensation.^[13] This could also enable repeated treatment for recurrent HCC, which could improve the prognosis. In this study, liver function was well preserved in cohort 3 in the C-HCC group, as shown by the transition of the ALBI score. It is likely that DAA therapy during the clinical course improved patient prognosis.

Unlike for patients with C-HCC, preserving liver function after curative treatment for patients with non-B, non-C HCC has not been established nor has a strategy for improving their prognosis.

Theoretically, improved liver function due to SVR should have affected liver-related death. In fact, cause-specific hazard regression analysis revealed improvement in liver-related mortality in cohort 3. However, contrary to our expectation, cohort 3 had a lower risk of non-liver-related death than cohort 1, with a hazard ratio of 0.30 (95% CI, 0.13–0.68) in multivariable cause-specific analysis. Achieving SVR was associated with a significant decrease in liver-unrelated death.^[7,25] Furthermore, there was a significantly lower risk of HCC recurrence in cohort 3 of the C-HCC group. The risk of HCC recurrence is reportedly reduced by achieving SVR with IFN-based therapy,^[8] and the risk is similar with DAA.^[13,14,26] In addition to the tumor burden or tumor marker, the reduction in the risk of HCC

TABLE 5 Univariable and multivariable analysis of HCC recurrence in patients with C-HCC and patients with non-B, non-C HCC

Variable	C-HCC				Non-B, non-C HCC			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age per 1 year	1.00 (0.99–1.00)	0.38			1.01 (1.00–1.02)	0.24		
Male sex	1.06 (0.93–1.21)	0.36			1.43 (1.07–1.91)	0.02	1.40 (0.94–2.08)	0.10
AST per 10 IU/L	1.04 (1.02–1.05)	<0.001	1.03 (1.01–1.05)	<0.001	1.03 (0.97–1.09)	0.38		
ALT per 10 IU/L	1.03 (1.02–1.04)	<0.001			1.01 (0.96–1.07)	0.75		
PLT per $1 \times 10^4/\mu\text{L}$	0.99 (0.98–1.00)	0.01	1.00 (0.99–1.01)	0.50	0.97 (0.95–0.99)	0.002	0.97 (0.94–0.99)	0.003
mALBI grade								
1	1		1		1			
2a	1.35 (1.15–1.59)	<0.001	1.25 (1.06–1.47)	0.01	1.13 (0.82–1.57)	0.44		
2b	1.36 (1.16–1.60)	<0.001	1.23 (1.04–1.46)	0.02	1.34 (0.98–1.83)	0.07		
3	1.07 (0.70–1.65)	0.75	0.89 (0.56–1.40)	0.60	0.96 (0.37–2.50)	0.94		
AFP >100 ng/mL	1.34 (1.13–1.58)	<0.001	1.13 (0.94–1.36)	0.18	0.91 (0.53–1.56)	0.73		
DCP >100 mAU/mL	1.19 (0.96–1.48)	0.11			1.42 (1.03–1.96)	0.03	1.26 (0.89–1.77)	0.20
AFP-L3 >15%	1.33 (1.07–1.65)	0.009	1.24 (0.98–1.57)	0.07	1.14 (0.74–1.76)	0.55		
Tumor size								
≤20 mm	1		1		1		1	
>20 mm, ≤30 mm	1.31 (1.14–1.50)	<0.001	1.26 (1.09–1.45)	0.003	1.63 (1.21–2.18)	0.001	1.37 (1.00–1.87)	0.053
>30 mm	1.39 (1.15–1.67)	<0.001	1.31 (1.09–1.58)	0.005	1.30 (0.90–1.88)	0.16	1.34 (0.90–1.99)	0.15
Tumor number								
1	1		1		1		1	
2–3	1.30 (1.14–1.49)	<0.001	1.27 (1.10–1.46)	<0.001	1.85 (1.41–2.43)	<0.001	1.71 (1.30–2.24)	<0.001
≥4	2.27 (1.73–2.97)	<0.001	2.11 (1.58–2.81)	<0.001	2.12 (0.92–4.88)	0.08	2.06 (0.89–4.75)	0.09
BMI ≥25 kg/m ²	1.06 (0.93–1.22)	0.38			1.07 (0.82–1.39)	0.62		
Diabetes mellitus	0.98 (0.84–1.14)	0.75			1.27 (0.98–1.64)	0.08		
Alcohol consumption								
<20 g/day	1				1		1	
≥20, and <60 g/day	1.12 (0.96–1.31)	0.16			1.01 (0.63–1.62)	0.97	0.82 (0.48–1.42)	0.48
≥60 g/day	1.00 (0.84–1.19)	0.99			1.33 (1.01–1.76)	0.04	1.06 (0.74–1.51)	0.75
cohort 1	1		1		1		1	
cohort 2	1.01 (0.89–1.15)	0.86	1.10 (0.96–1.26)	0.18	1.31 (0.95–1.80)	0.10	1.32 (0.95–1.84)	0.10
cohort 3	0.61 (0.47–0.79)	<0.001	0.74 (0.57–0.96)	0.02	1.06 (0.72–1.56)	0.78	1.26 (0.85–1.89)	0.25

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AU, arbitrary unit; BMI, body mass index; C-HCC, hepatitis C-related hepatocellular carcinoma; CI, confidence interval; DCP, des-gamma-carboxy prothrombin; HR, hazard ratio; mALBI, modified albumin–bilirubin; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody; PLT, platelet count.

recurrence observed in cohort 3 was probably due to the increased rate of SVR.

There are several limitations in this study. First, our study did not directly indicate, although it suggested, the effect of DAA therapy on the improved prognosis of patients with C-HCC. To prove the concept,

a randomized controlled trial, which is not feasible considering the high potency and infrequent adverse events in DAA therapy, is needed. Second, the observation period of cohort 3 was relatively short and the number of events was small; this could be associated with insufficient statistical precision. Third, this study

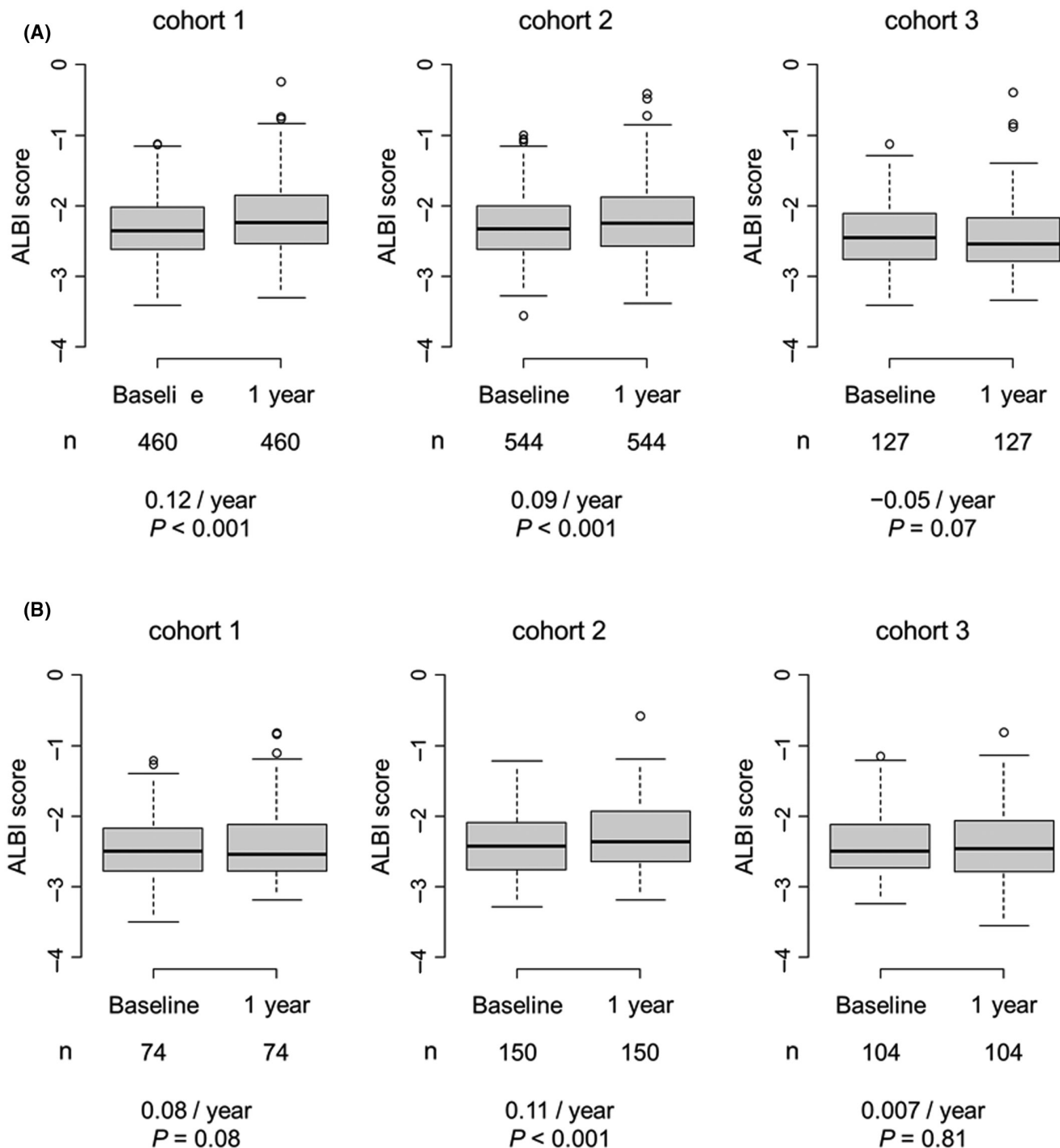


FIGURE 6 ALBI score at baseline and 1 year after initial treatment. (A) C-HCC. ALBI scores at baseline and 1 year after initial HCC treatment were -2.35 (-2.62 to -2.02) and -2.23 (-2.53 to -1.84) in cohort 1, -2.31 (-2.62 to -2.01) and -2.25 (-2.57 to -1.88) in cohort 2, and -2.45 (-2.75 to -2.11) and -2.53 (-2.79 to -2.18) in cohort 3. (B) Non-B, non-C HCC. ALBI scores at baseline and 1 year after initial HCC treatment were -2.48 (-2.77 to -2.19) and -2.53 (-2.77 to -2.13) in cohort 1, -2.42 (-2.76 to -2.09) and -2.36 (-2.64 to -1.93) in cohort 2, and -2.48 (-2.73 to -2.11) and -2.46 (-2.79 to -2.06) in cohort 3. In these box-and-whisker plots, lines within the boxes represent median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively; the upper and lower bars outside the boxes represent 1.5 times the interquartile range (IQR) above the 75th percentiles and 1.5 times the IQR below the 25th percentiles, respectively. The open circles indicate outliers. ALBI, albumin–bilirubin; C-HCC, hepatitis C-related hepatocellular carcinoma; HCC, hepatocellular carcinoma; non-B, negative for hepatitis B surface antigen; non-C, negative for hepatitis C virus antibody.

population consisted largely of patients with early stage HCC who could be treated with RFA. It is unclear whether DAA therapy is also beneficial in patients with more advanced HCC.

In conclusion, the prognosis of C-HCC has improved in the DAA era. A high proportion of patients with C-HCC have achieved SVR over time, which might have an impact on improved prognosis in these patients.

However, in patients with non-B, non-C HCC, no improvement was observed.

AUTHOR CONTRIBUTIONS

Conception and design: Tsuyoshi Fukumoto, Tatsuya Minami, Ryosuke Tateishi. *Acquisition of data:* Tsuyoshi Fukumoto, Tatsuya Minami, Ryosuke Tateishi, Makoto Moriyama, Tomoharu Yamada, Taijiro Wake, Mizuki Nishibatake Kinoshita, Naoto Fujiwara, Ryo Nakagomi, Takuma Nakatsuka, Masaya Sato, Kenichiro Enooku, Hayato Nakagawa, Shuichiro Shiina, Kazuhiko Koike. *Analysis and interpretation of data:* Tsuyoshi Fukumoto, Tatsuya Minami, Ryosuke Tateishi. *Drafting of the manuscript:* Tsuyoshi Fukumoto, Tatsuya Minami, Ryosuke Tateishi. *Statistical analysis:* Tsuyoshi Fukumoto, Tatsuya Minami, Ryosuke Tateishi. *Study supervision:* Ryosuke Tateishi, Mitsuhiro Fujishiro, Kazuhiko Koike. *Final approval and agreement to be accountable for all aspects of the work:* All authors.

ACKNOWLEDGMENT

This research was supported by the Research Program on Hepatitis from Japan Agency for Medical Research and Development (AMED) under Grant Number JP21fk0210113, JP22fk0210113, JP21fk0210066, and JP22fk0210066, and the Health, Labour, and Welfare Policy Research Grants from the Ministry of Health, Labour, and Welfare of Japan H30-Kansei-Shitei-003.

CONFLICT OF INTEREST

Tatsuya Minami has received lecture fees from Merck Sharp & Dohme, Gilead Sciences, and AbbVie GK. Hayato Nakagawa has received lecture fees from Merck Sharp & Dohme and Gilead Sciences. Mitsuhiro Fujishiro has received lecture fees from Takeda Pharmaceutical Company and research funding from AbbVie GK, Chugai Pharmaceutical Company, Eisai Company, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceutical Company. Shuichiro Shiina has received lecture fees from Bayer Pharmaceuticals Company, Chugai Pharmaceutical Company, AbbVie GK, Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Company, Sumitomo Dainippon Pharma Company, and Eisai Company. Kazuhiko Koike has received research funding from Merck Sharp & Dohme, Chugai Pharmaceutical Company, Bristol-Meyers Squibb, Gilead Sciences, AbbVie GK, Jansen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Eisai Company, Bayer Pharmaceuticals Company, Eli Lilly and Company, and Takeda Pharmaceutical Company. Ryosuke Tateishi has received lecture fees from Merck Sharp & Dohme, Chugai Pharmaceutical Company, Bristol-Meyers Squibb, Gilead Sciences, AbbVie GK, Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Company, Sumitomo Dainippon Pharma Company,

Eisai Company, and Bayer Pharmaceuticals Company. The other authors have nothing to report.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Fukumoto T, Minami T, Moriyama M, Yamada T, Wake T, Kinoshita MN, Improved prognosis of hepatitis C-related hepatocellular carcinoma in the era of direct-acting antivirals. *Hepatol Commun*. 2022;6: 2496–2512. <https://doi.org/10.1002/hep4.2010>