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Changes in patient background and prognosis after hepatectomy for hepatocellular carcinoma by hepatitis virus infection status: New trends in Japan

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Abstract

Aim: Hepatitis C virus (HCV) infection is a major cause of hepatocellular carcinoma (HCC) in Japan. However, the cause and prognosis of HCC may be dramatically changed by direct acting antiviral agents (DAAs). Although the 2015 nationwide survey used a large cohort, its findings may be outdated. The present study therefore aimed to show the latest outcomes by patients' hepatitis virus infection status.

Methods: We included 552 patients who underwent hepatectomy for primary HCC between 2002 and 2018 and compared clinical factors between those treated before 2014 (n = 380) and after 2014 (n = 172), when DAAs became available.

Results: Distribution of hepatitis virus infection status between the two groups differed significantly ($P < 0.001$). In the earlier group, 46% of the patients had HCC with HCV infection (C-HCC), whereas the rate of C-HCC decreased (31%) and 54% of the patients had HCC with no hepatitis virus infection (NBNC-HCC) in the latter group. The proportion of HCC with hepatitis B virus infection (B-HCC) and the prognosis of B-HCC did not significantly change between the two groups. Among patients with C-HCC, the latter patients had significantly longer relapse-free survival (RFS) than the earlier patients ($P = 0.033$). However, RFS did not significantly differ between the earlier and latter patients with NBNC-HCC.

Conclusion: Postoperative prognosis has changed according to patients' hepatitis virus infection status. The proportion of patients with NBNC-HCC has increased, but their prognosis has not been improved. Treatment strategies for NBNC-HCC should be established.

KEYWORDS

direct acting antiviral agents, hepatitis virus infection status, hepatocellular carcinoma, prognosis

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer-related death in Japan.[1] Hepatitis C virus (HCV) infection was a major cause of HCC, and accounted for approximately 70% of all cases in Japan.[2,3] However, the percentage of HCC patients who tested negative for both hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb)—so-called "NBNC-HCC"—is rapidly increasing,[4,5] and the Japanese nationwide survey published in 2015 found that NBNC-HCC had a significantly lower risk of recurrence than $HBsAg^+$ HCC (B-HCC) or $HCVAb^+$ HCC (C-HCC).[6] However, overall survival (OS) of patients with NBNC-HCC is reported to be significantly worse than for patients with C-HCC.[7]

Treatment of chronic HCV with interferon-based regimens led to a cure in approximately 50% of treated patients in past decades. The recent introduction of direct acting antiviral agents (DAA) has resulted in sustained virologic response (SVR) rates of nearly 100% in treated patients, irrespective of the stage of liver fibrosis, with an excellent safety profile.[8] We previously reported that the postoperative prognosis for C-HCC has improved in recent years because of higher SVR rates.[9] Although the nationwide survey uses a large cohort, the detailed data take a long time to publish. For example, the Japanese nationwide survey published in 2015 revealed the outcomes and background of patients with HCC who were registered for treatment from 2000 to 2005.[6] As the results of this nationwide survey may be outdated, we aimed to find the latest patient background and postoperative prognosis by hepatitis virus infection status using single-institution data from a high-volume center for HCC in Japan.

2 | METHODS

2.1 | Patients

A total of 552 primary HCC patients underwent hepatectomy with curative intent between September 2002 and March 2018 at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center Hospital, which is a high-volume center for HCC in Japan. We retrospectively reviewed their hospital records until November 2020. We divided the study period into before and after 2014 because DAAs began to be covered under the national health insurance in Japan from 2014. We compared patients' characteristics and prognoses between the two periods, and then compared prognoses between the two periods by patients' hepatitis virus infection status.

This retrospective study was approved by the Institutional Review Board (IRB) of Shizuoka Cancer Center (number: 29-J11-30-2-3) and conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. Written informed consent for surgery and use of patients' clinical data was obtained as required by the IRB. We applied opt-out recruitment according to the policy of the Japanese government because we conducted clinical research using only retrospective clinical data without intervention.

2.2 | Preoperative examination

All patients included in this study had undergone preoperative diagnostic imaging examinations, such as abdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging. All patients underwent preoperative blood examinations such as viral serological testing, assessment of tumor markers (alpha-fetoprotein and des-gamma-carboxy prothrombin), and laboratory assessment of liver function before surgery. Liver function was assessed using the Child–Pugh classification[10] and liver damage criteria,[11] including the indocyanine green retention rate at 15 minutes ($ICGR_{15}$). All patients presented with a confirmed diagnosis of HCC after surgical pathology. Tumors were staged based on the seventh edition of the Union Internationale Contra le Cancer classification.[12]

2.3 | Surgical procedure

Surgical procedure and extent of hepatectomy for each patient were decided at a weekly surgical conference. Details of the surgical strategies and procedures have been reported previously.[13] The types of hepatectomies were defined in accordance with the Brisbane 2000 terminology as either minor (two liver segments or fewer) or major (three liver segments or more).[14] In the present study, patients who underwent procedures in addition to segmentectomy and partial resection for multiple HCCs were excluded from anatomical resection.

2.4 | Postoperative follow-up

The patients underwent physical examinations and blood tests every 3 months after surgery. Serial CT or liver ultrasonography was performed on each patient every 3 to 6 months. When recurrence of HCC was found, the most appropriate therapy, such as repeat hepatectomy, transcatheter arterial chemoembolization (TACE), radiofrequency ablation, molecular target drug such as sorafenib or lenvatinib, or other therapy, was applied, after considering the patient's liver function and tumor factors.

The management of hepatitis B virus (HBV) infection was performed according to the Japan Society of Hepatology guideline.[15] Postoperative antiviral therapy for HCV infection was introduced in principle after confirming absence of recurrence at postoperative month 3. An SVR was defined as a serum HCV-RNA titer below the detection sensitivity limit at 6 months after terminating antiviral therapy.

2.5 | Statistical analysis

Continuous variables are presented as median and range and were compared using the Mann-Whitney *U* test. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. The survival period was defined as the time between

TABLE 1 Clinicopathological characteristics

Variables	2002-2013 (N = 380)	2014-2018 (N = 172)	*P*
Patient characteristics			
Age (years)[a]	69 (30-87)	71 (35-87)	***0.004***
Sex (men/women)	309/71	135/37	0.487
Etiology of liver disease			
Non hepatitis virus infection	133 (35.0)	91 (52.9)	***0.001***
HBsAg-positive (%)	69 (18.2)	27 (15.7)	
Anti-HCV Ab-positive (%)	175 (46.1)	54 (31.4)	
Both HBsAg-positive and anti-HCV Ab-positive (%)	3 (0.8)	0	
Alcohol intake history (80 g/day over)	40 (10.6)	29 (16.9)	0.051
Child-Pugh grade (B)	10 (2.6)	5 (2.9)	0.786
Liver damage (B)	93 (24.5)	27 (15.7)	***0.026***
ASA-PS (1/2/3)	28/285/67	6/149/17	***0.008***
Hypertension (present)	218 (57.4)	102 (56.0)	0.131
Hyperlipidemia (present)	34 (8.9)	32 (18.6)	***0.002***
Diabetes mellitus (present)	124 (32.6)	59 (34.3)	0.697
Body mass index (kg/m^2) [a]	22.5 (14.5-38.2)	23.6 (16.2-35.9)	***<0.001***
Preoperative blood examinations			
Albumin (g/dL) [a]	41 (23-51)	41 (28-53)	0.231
PT (%) [a]	87 (53-130)	87 (55-125)	0.615
Total serum bilirubin (mg/dL) [a]	0.6 (0.2-2.3)	0.7 (0.3-1.8)	0.258
Platelet count (×10^4/μL) [a]	15.2 (4.8-42.9)	17.3 (6.1-39.4)	***0.019***
AST (U/L) [a]	39 (16-211)	34 (15-125)	***0.009***
ALT (U/L) [a]	39 (5-281)	28 (11-138)	***<0.001***
$ICGR_{15}$ (%)[a]	16.0 (2.6-37.0)	9.8 (1.4-44.5)	***<0.001***
AFP (ng/mL)[a]	16.6 (1.5-343,400)	8.7 (1.2-253,460)	***0.003***
DCP (mAL/mL)[a]	180 (1-345,000)	307 (11-446,000)	0.274
Operation procedures			
Major resection (present)	112 (29.5)	50 (29.1)	1.000
Anatomical resection (present)	224 (58.9)	107 (62.2)	0.512
Type of hepatectomy			
Partial hepatectomy	129 (33.9)	61 (35.5)	0.996
Segmentectomy	46 (12.1)	20 (11.6)	
Sectionectomy	96 (25.3)	44 (25.6)	
Hemihepatectomy	97 (25.5)	42 (24.4)	
Trisectionectomy	12 (3.2)	5 (2.9)	
Pathological findings			
Tumor diameter (mm)[a]	36 (6-180)	40 (10-180)	0.117
Tumor number (multiple)	90 (23.7)	53 (30.8)	0.093
Tumor differentiation (Well/Moderately/Poorly)	60/303/16	22/134/16	***0.048***
Vp (present)	65 (17.2)	52 (30.2)	***0.001***
Vv (present)	27 (7.1)	31 (18.0)	***<0.001***
Im (present)	50 (13.2)	35 (20.3)	***0.041***
Cirrhosis (present)	111 (29.2)	34 (19.8)	***0.013***

(Continues)

TABLE 1 (Continued)

Variables	2002-2013 (N = 380)	2014-2018 (N = 172)	*P*
Tumor stage (I/II/III/IV)	228/101/42/9	90/57/22/3	0.319
Treatment for recurrence			
Surgical resection	41 of 264 (15.5)	20 of 89 (22.5)	0.056
Radiofrequency ablation	62 of 264 (23.5)	19 of 89 (21.3)	
TACE	114 of 264 (43.2)	30 of 89 (33.7)	
Molecular target drugs	5 of 264 (1.9)	6 of 89 (6.7)	
Other therapies	18 of 264 (6.8)	2 of 89 (2.2)	
Best supportive care	7 of 264 (2.7)	4 of 89 (4.5)	
Unknown	17 of 264 (6.4)	8 of 89 (9.0)	

Note: Values in parentheses are percentages unless indicated otherwise.

Abbreviations: Ab, antibody; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA-PS, American Society of Anesthesiologists Performance Status; AST, aspartate aminotransferase; DCP, des-gamma-carboxy prothrombin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; $ICGR_{15}$, indocyanine green retention15; Im, intrahepatic metastasis; PT, prothrombin time; TACE, Transcatheter arterial chemoembolization; Vp, portal vein thrombosis; Vv, venous vein thrombosis.

Bold and italics show significant.

[a]Value is expressed as the median (range).

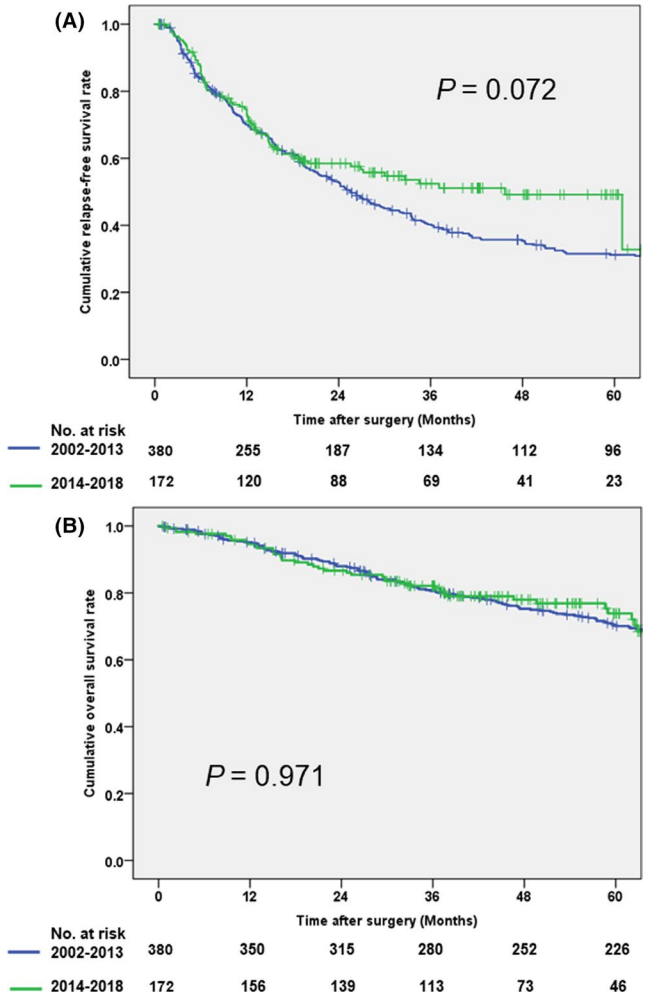

FIGURE 1 Relapse-free survival curve (A) and overall survival curve (B) for the earlier period (2002-2013) and the latter period (2014-2018)

the day of surgery and the event date (all-cause death for OS, and recurrence for recurrence-free survival [RFS]). The remaining patients were censored at the last follow-up visit during November 2020. The cumulative RFS and OS curves were analyzed using the Kaplan-Meier method, and were compared using the log-rank test. All statistical analyses were performed using SPSS 24.0 software (SPSS, Inc, Chicago, IL, USA). $P \leq 0.05$ (two-tailed) was considered significant.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are shown in Table 1. Among the 552 HCC patients, 380 patients underwent hepatectomy between 2002 and 2013 (earlier group) and 172 patients underwent hepatectomy between 2014 and 2018 (latter group). The median follow-up period in the earlier and latter groups was 72.6 months and 42.3 months, respectively. Median patient age at the surgery was significantly higher in the latter group (71 years) than in the earlier group (69 years; $P = 0.004$). Liver disease etiology was also significantly different between the earlier and latter groups (Table 1, $P < 0.001$). Although the proportion of B-HCC did not significantly change between the two groups, the latter group was more than 50% NBNC-HCC; the proportion of C-HCC has decreased as the proportion of NBNC-HCC has increased in the latter group. The numbers of different types of surgical procedures were not significantly different between the two groups ($P = 0.996$). The procedure for treating recurrence tended to differ between the two groups ($P = 0.056$). Specifically, the rate of surgical resection or treatment using molecularly targeted drugs administered to the latter group tended to be higher, whereas the rate of TACE in the latter group tended to be lower in comparison.

TABLE 2 Comparisons of clinical characteristics, operation procedure, and pathological findings according to the hepatitis virus infection status in 2002-2013

Variables	NBNC-HCC N = 133	B-HCC N = 69	P^a	C-HCC N = 175	P^b	P^c
Patient characteristics						
Age (years)[d]	71 (30-83)	62 (39-80)	***0.001***	71 (43-87)	0.293	***<0.001***
Gender (men/women)	113/20	48/21	***0.016***	145/30	0.643	***0.036***
Alcohol intake history (80 g/day over)	18 (13.5%)	4 (5.8%)	0.150	20 (11.4%)	0.603	0.237
Child-Pugh grade (B)	3 (2.3%)	0 (0%)	0.552	7 (4.0%)	0.604	0.196
Liver damage (B)	28 (21.1%)	13 (18.8%)	0.854	50 (28.6%)	0.147	0.144
ASA-PS (1/2/3)	11/93/29	9/51/9	0.223	6/141/28	0.057	***0.018***
Hypertension (present)	81 (60.9%)	24 (34.8%)	***0.001***	112 (64.0%)	0.382	***<0.001***
Hyperlipidemia (present)	23 (17.3%)	4 (5.8%)	***0.028***	7 (4.0%)	***<0.001***	0.511
Diabetes mellitus (present)	69 (51.9%)	11 (15.9%)	***<0.001***	44 (25.1%)	***<0.001***	0.130
Body mass index (kg/m^2)[d]	22.9 (15.9-38.2)	22.4 (18.0-31.4)	0.196	22.0 (14.5-32.9)	***0.002***	0.190
Preoperative blood examinations						
Albumin (g/dL)[d]	4.2 (2.3-4.9)	4.3 (3.1-5.0)	0.568	4.0 (2.7-5.1)	***0.001***	***0.001***
PT (%)[d]	89 (53-130)	86 (64-113)	0.080	86 (55-117)	***0.028***	0.922
Total serum bilirubin (mg/dL)[d]	0.6 (0.2-2.3)	0.7 (0.3-1.8)	0.076	0.6 (0.2-1.9)	0.777	0.100
Platelet count ($\times 10^4/\mu L$)[d]	17.9 (7.9-38.8)	15.2 (7.9-40.8)	***0.003***	14.0 (4.8-42.9)	***<0.001***	***0.024***
AST (U/L)[d]	30 (16-211)	33 (16-135)	0.063	47 (17-143)	***<0.001***	***<0.001***
ALT (U/L)[d]	31 (7-185)	35 (5-136)	0.148	45 (9-281)	***<0.001***	***<0.001***
$ICGR_{15}$ (%)[d]	16.0 (4.6-37.0)	13.0 (3.0-27.0)	***0.048***	17.0 (5.0-36.0)	***0.014***	***<0.001***
AFP (ng/mL)[d]	8.7 (1.4-343,400)	75.2 (2.1-239,100)	***<0.001***	20.3 (1.5-106,100)	***0.013***	***0.003***
DCP (mAL/mL)[d]	378 (11-198,000)	147 (10-345,000)	0.106	100 (1-124,000)	***<0.001***	0.133
Operation procedures						
Major resection (present)	52 (39.1)	20 (29.0%)	0.167	39 (22.3)	***0.002***	0.319
Anatomical resection (present)	100 (75.2)	42 (60.9%)	0.051	80 (45.7)	***<0.001***	***0.046***
Type of hepatectomy						
Partial hepatectomy	27 (20.3)	22 (20.3)	0.288	79 (45.1)	***<0.001***	0.115
Segmentectomy	16 (12.0)	9 (12.0)		21 (12.0)		
Sectionectomy	39 (29.3)	19 (29.3)		37 (21.1)		
Hemihepatectomy	45 (33.9)	15 (33.9)		36 (20.6)		
Trisectionectomy	6 (4.5)	4 (4.5)		2 (1.2)		
Pathological findings						
Tumor diameter (mm)[d]	50 (9-175)	35 (10-180)	***0.012***	31 (6-175)	***<0.001***	0.256
Tumor number (multiple)	21 (15.8%)	16 (23.2%)	0.250	53 (30.3%)	***0.003***	0.344
Tumor differentiation (Well/Moderately/Poorly)	22/106/4	5/59/5	0.085	33/136/6	0.860	***0.044***
Vp (present)	19 (14.3%)	13 (18.8%)	0.423	31 (17.7%)	0.533	0.854
Vv (present)	9 (6.8%)	5 (7.2%)	1.000	13 (7.4%)	1.000	1.000
Im (present)	23 (17.3%)	8 (11.6%)	0.313	19 (10.9%)	0.131	0.825
Cirrhosis (present)	21 (15.8%)	27 (39.1%)	***<0.001***	63 (36.0%)	***<0.001***	0.769
Tumor stage (I/II/III/IV)	91/27/10/5	39/18/10/2	0.260	97/54/22/2	***0.024***	0.377
Treatment for recurrence						
Surgical resection	14 of 86 (16.3)	10 of 50 (20.0)	0.647	17 of 127 (13.4)	0.545	0.601
Radiofrequency ablation	16 of 86 (18.6)	13 of 50 (26.0)		33 of 127 (30.0)		
TACE	38 of 86 (44.2)	18 of 50 (36.0)		58 of 127 (45.7)		

(Continues)

TABLE 2 (Continued)

Variables	NBNC-HCC N = 133	B-HCC N = 69	P^a	C-HCC N = 175	P^b	P^c
Molecular target drugs	2 of 86 (2.3)	0		3 of 127 (2.4)		
Other therapies	5 of 86 (5.8)	5 of 50 (10.0)		7 of 127 (5.5)		
Best supportive care	2 of 86 (2.3)	1 of 50 (2.0)		4 of 127 (3.1)		
Unknown	9 of 86 (10.5)	3 of 50 (6.0)		5 of 127 (3.9)		

Note: Values in parentheses are percentages unless indicated otherwise.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA-PS, American Society of Anesthesiologists Performance Status; AST, aspartate aminotransferase; B-HCC, hepatocellular carcinoma with positive for hepatitis B surface antigen; C-HCC, hepatocellular carcinoma with positive for hepatitis C antibody; DCP, des-gamma-carboxy prothrombin; $ICGR_{15}$, indocyanine green retention15; Im, intrahepatic metastasis; NBNC-HCC, hepatocellular carcinoma with negative for hepatitis B surface antigen and hepatitis C antibody; PT, prothrombin time; TACE, Transcatheter arterial chemoembolization; Vp, portal vein thrombosis; Vv, venous vein thrombosis.

Bold and italics show significant.

[a]*P*-value NBNC-HCC vs B-HCC.

[b]*P*-value NBNC-HCC vs C-HCC.

[c]*P*-value B-HCC vs C-HCC.

[d]Value is expressed as the median (range).

The 5-year RFS rate (42.6%) of the latter group tended to be longer compared with that of the earlier (30.7%, $P = 0.072$, Figure 1A). The 5-year OS rate did not significantly differ between the earlier group (70.1%) and latter group (73.8%, $P = 0.971$, Figure 1B).

3.2 | Patient characteristics and prognosis by hepatitis virus infection status in 2002-2013

Of 380 patients in the earlier group, three patients with both HBsAg-positive and HCVAb-positive were excluded from the analyses. They do not greatly differ from those in our previous study, which also compared patients by hepatitis virus infection status.[16] Briefly, the median age at surgery was significantly lower in patients with B-HCC; blood examinations related to liver function were significantly poorer and the rate of cirrhosis was significantly higher in the C-HCC group; and tumor diameter was significantly larger in patients with NBNC-HCC (Table 2).

The 5-year RFS rate of patients with C-HCC (22.4%), which was significantly shorter compared with that of patients with NBNC-HCC (36.8%, $P = 0.037$), tended to be shorter than that of patients with B-HCC (38.6%, $P = 0.095$). In contrast, there were no significant difference in the 5-year RFS between patients with NBNC-HCC patients or B-HCC ($P = 0.844$). The 5-year OS rate of patients with B-HCC (78.9%) was significantly longer compared with that of patients with C-HCC (67.3%, $P = 0.008$) and tended to be longer compared with that of patients with NBNC-HCC (68.9%, $P = 0.076$). In contrast, there was no significant difference in the 5-year OS of patients with NBNC-HCC compared with that of those with C-HCC ($P = 0.318$).

3.3 | Patient characteristics and prognosis according to hepatitis virus infection status in 2014-2018

Clinicopathological factors of the latter-treated patients are shown in Table 3. Although the age at surgery was significantly lower in patients with B-HCC, and tumor diameter was significantly larger in patients with NBNC-HCC, the clinicopathological factors in the latter group tended to be homogenous compared with those of the earlier group regardless of hepatitis virus infection status.

In the latter-treated group, 5-year RFS rates were: NBNC-HCC, 41.4%; B-HCC, 36.0%; and C-HCC, 44.6%. Their 5-year RFS rates did not significantly differ according to the hepatitis virus infection status. Their 5-year OS rates were: NBNC-HCC, 71.2%; B-HCC, 60.3%; and C-HCC, 82.7%. Five-year OS rate for patients with C-HCC tended to be longer than for patients with NBNC-HCC or B-HCC, but not significantly so ($P = 0.102$ and $P = 0.173$, respectively).

3.4 | Comparisons of patients with NBNC-HCC between the earlier and latter groups

Age at surgery and body mass index (BMI) in the latter-treated group were significantly higher than those in the earlier group ($P = 0.030$ and $P = 0.049$, respectively) and the rate of good performance status was significantly lower in the latter group ($P = 0.018$; Table 4). Tumor differentiation in the latter group was significantly deteriorated compared with the earlier group ($P = 0.004$), with higher rates of portal vein thrombosis and venous vein thrombosis in the latter group than in the earlier group (Table 4). Five-year RFS and OS rates did not significantly differ between the two groups ($P = 0.415$, Figure 2A; $P = 0.241$, Figure 2B, respectively).

3.5 | Comparison of patients with B-HCC between the earlier and latter groups

The BMI in the latter group was significantly higher than that in the earlier group ($P = 0.024$, Table 5). Although serum aspartate aminotransferase (AST) level and $ICGR_{15}$ in the latter group were significantly better than those in the earlier group ($P = 0.015$ and

TABLE 3 Comparisons of clinical characteristics, operation procedure, and pathological findings according to the hepatitis virus infection status in 2014-2018

Variables	NBNC-HCC N = 91	B-HCC N = 27	P^a	C-HCC N = 54	P^b	P^c
Patient characteristics						
Age (years)[d]	73 (42-87)	65 (35-79)	***<0.001***	70 (42-86)	0.101	***0.010***
Gender (men/women)	74/17	24/3	0.559	37/17	0.104	0.057
Alcohol intake history (80 g/day over)	20 (22.0)	1 (3.7)	***0.042***	8 (14.8)	0.385	0.259
Child-Pugh grade (B)	5 (5.5)	0	0.588	0	0.157	
Liver damage (B)	16 (17.6)	3 (11.1)	0.558	8 (14.8)	0.818	0.744
ASA-PS (1/2/3)	2/78/11	3/20/4	0.113	1/51/2	0.227	***0.031***
Hypertension (present)	57 (62.6)	12 (44.4)	0.120	33 (61.4)	0.861	0.165
Hyperlipidemia (present)	24 (26.4)	2 (7.4)	***0.038***	6 (11.1)	***0.034***	0.712
Diabetes mellitus (present)	36 (39.6)	9 (33.3)	0.655	14 (25.9)	0.107	0.602
Body mass index (kg/m^2)[d]	23.7 (16.2-35.9)	24.3 (18.2-33.8)	0.805	23.2 (16.6-30.9)	0.113	0.189
Preoperative blood examinations						
Albumin (g/dL)[d]	4.1 (2.8-5.3)	4.2 (2.9-4.8)	0.088	4.0 (3.1-5.6)	0.630	0.358
PT (%)[d]	86 (55-124)	90 (55-125)	0.708	89 (67-110)	0.239	0.722
Total serum bilirubin (mg/dL)[d]	0.6 (0.3-1.8)	0.7 (0.4-1.5)	0.472	0.7 (0.3-1.2)	0.571	0.799
Platelet count ($\times10^4/\mu L$)[d]	18.5 (6.2-41.1)	18.1 (9.5-38.4)	0.440	12.9 (6.1-25.3)	***<0.001***	***0.005***
AST (U/L)[d]	34 (15-125)	28 (17-90)	***0.027***	37 (17-113)	0.231	***0.002***
ALT (U/L)[d]	26 (13-120)	28 (8-76)	0.969	32 (11-119)	0.071	0.118
$ICGR_{15}$ (%)[d]	9.9 (1.4-44.5)	8.0 (1.6-17.9)	0.148	11.3 (2.2-26.2)	0.595	0.054
AFP (ng/mL)[d]	6.8 (1.2-253,500)	10.7 (1.7-36,700)	0.911	11.1 (1.4-168,900)	0.250	0.518
DCP (mAL/mL)[d]	385 (11-446,000)	198 (14-113,000)	0.385	115 (12-134,000)	***0.016***	0.357
Operation procedures						
Major resection (present)	32 (35.2)	8 (29.6)	0.505	10 (19.2)	0.056	0.582
Anatomical resection (present)	61 (67.0)	18 (62.1)	0.657	28 (53.8)	0.151	0.815
Type of hepatectomy						
Partial hepatectomy	29 (31.8)	9 (31.0)	0.634	23 (44.2)	0.120	0.577
Segmentectomy	8 (8.8)	4 (13.8)		8 (15.4)		
Sectionectomy	22 (24.2)	9 (31.0)		13 (25.0)		
Hemihepatectomy	28 (30.8)	7 (24.1)		7 (13.5)		
Trisectionectomy	4 (4.4)	0		1 (1.9)		
Pathological findings						
Tumor diameter (mm)[d]	55 (11-160)	40 (10-130)	***0.025***	30 (11-180)	***<0.001***	0.196
Tumor number (multiple)	16 (17.6)	10 (37.0)	0.640	15 (27.8)	0.851	0.449
Tumor differentiation (Well/Moderately/Poorly)	5/76/10	5/19/3	0.100	12/39/3	***0.008***	0.645
Vp (present)	29 (31.9)	10 (37.0)	0.646	13 (24.1)	0.349	0.296
Vv (present)	15 (16.5)	5 (18.5)	0.776	11 (20.4)	0.655	1.000
Im (present)	17 (18.7)	5 (18.5)	1.000	12 (22.2)	0.832	0.779
Cirrhosis (present)	20 (22.0)	5 (18.5)	0.794	9 (16.7)	0.523	1.000
Tumor stage (I/II/III/IV)	48/28/14/1	14/11/2/0	0.593	28/18/6/2	0.651	0.676
Treatment for recurrence						
Surgical resection	11 of 49 (22.4)	2 of 15 (13.3)	0.081	7 of 25 (28.0)	0.167	0.592
Radiofrequency ablation	14 of 49 (28.6)	2 of 15 (13.3)		3 of 25 (12.0)		
TACE	15 of 49 (30.6)	7 of 15 (46.7)		8 of 25 (32.0)		

(Continues)

TABLE 3 (Continued)

Variables	NBNC-HCC N = 91	B-HCC N = 27	P^a	C-HCC N = 54	P^b	P^c
Molecular target drugs	5 of 49 (10.2)	0		1 of 25 (4.0)		
Other therapies	1 of 49 (2.1)	1 of 15 (6.7)		0		
Best supportive care	0	2 of 15 (13.3)		2 of 25 (8.0)		
Unknown	3 of 49 (6.1)	1 of 15 (6.7)		4 of 25 (16.0)		

Note: Values in parentheses are percentages unless indicated otherwise.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA-PS, American Society of Anesthesiologists Performance Status; AST, aspartate aminotransferase; B-HCC, hepatocellular carcinoma with positive for hepatitis B surface antigen; C-HCC, hepatocellular carcinoma with positive for hepatitis C antibody; DCP, des-gamma-carboxy prothrombin; $ICGR_{15}$, indocyanine green retention15; Im, intrahepatic metastasis; NBNC-HCC, hepatocellular carcinoma with negative for hepatitis B surface antigen and hepatitis C antibody; PT, prothrombin time; TACE, Transcatheter arterial chemoembolization; Vp, portal vein thrombosis; Vv, venous vein thrombosis.

Bold and italics show significant.

[a]*P*-value NBNC-HCC vs B-HCC.

[b]*P*-value NBNC-HCC vs C-HCC.

[c]*P*-value B-HCC vs C-HCC.

[d]Value is expressed as the median (range).

$P < 0.001$, respectively), tumor factors between the two groups did not significantly differ (Table 5). Five-year RFS and OS did not significantly differ between the two groups ($P = 0.389$, Figure 2C and $P = 0.440$, Figure 2D, respectively).

3.6 | Comparison of patients with C-HCC between the earlier and latter groups

The percentage of patients in the latter group who were treated for hepatitis C virus as well as their SVR rates and DAA introduced rates were significantly higher compared those in the earlier group (both $P < 0.001$) (Table 6). Consequently, serum AST and alanine aminotransferase levels in the latter group were significantly lower than those in the earlier group (both $P = 0.001$, Table 6) and the cirrhosis rate was significantly lower in the latter group ($P = 0.007$, Table 6). Five-year RFS in the latter group was significantly longer than that in the earlier group ($P = 0.032$, Figure 2E), but 5-year OS was not significantly different ($P = 0.784$, Figure 2F). The treatment procedure for recurrence was significantly different between the two periods ($P = 0.037$). The rate of surgical resection in the latter group (28.0%) was twice that of the earlier group (13.4%), and the rate of TACE in the latter group (32.0%) tended to be lower compared with that of the earlier group (45.7%).

4 | DISCUSSION

The present study shows recent trends in the background and prognosis for patients who undergo hepatectomy for HCC in Japan. Briefly, compared with patients treated before 2014, the etiology of liver diseases that cause HCC has shifted from $HCV\text{-}Ab^+$ HCC to non-hepatitis virus infection; age at surgery and BMI are significantly higher, and liver-related factors are significantly better in the latter group, as recently reported in the nationwide survey.[17] Moreover, clinicopathological factors of latter-treated patients among hepatitis virus infection status tend to be homogeneous compared with those of earlier-treated patients.

The present study shows that the RFS of patients in the latter group tended to be longer compared with those in the earlier group, although OS was not significantly different. These results may be explained by the availability of multiple options for treating HCC recurrence.[18,19]

Although the prognosis of HCC dramatically improved from 1978 to 2005 in Japan, due to improved surgical procedure, diagnostic imaging, and more treatment options,[20,21] our results suggest that the prognosis of HCC patients who undergo hepatectomy has not improved for the last two decades, unlike other kinds of cancer. The concept of adjuvant chemotherapy was introduced and has improved postoperative prognosis in other cancer types, such as gastric cancer,[22] lung cancer,[23] breast cancer,[24] and pancreatic cancer,[25] since around 2000. However, adjuvant therapy treatment for HCC has not been established,[26] which is considered to be a major cause of lagging prognosis.

The SVR rate was 100% in the patients treated with DAA in the present study. Unlike adjuvant therapy, the postoperative use of DAA may be considered an alternative therapy for patients with C-HCC, to prevent recurrence. As we have previously reported, prognosis is significantly better in patients who obtain SVR, even after hepatectomy.[9] Postoperative anti-virus therapy for C-HCC had been difficult before the development of DAA due to adverse events of interferon therapy, and patients with C-HCC had a significantly higher rate of multi-centric recurrence than did patients with B-HCC or those with NBNC-HCC, as the RFS curve continued to decline at the approximately same angle even after 2 postoperative years. Conversely, the decline of the RFS curve for patients with B-HCC or NBNC-HCC flattened after 2 postoperative years. These facts can be confirmed in the Japanese nationwide survey[6] and our current and previous study.[9] However, the RFS curve of latter-treated patients with C-HCC has been close in shape to that of patients with B-HCC

TABLE 4 Clinicopathological characteristics of NBNC-HCC patients

Variables	2002-2013 (N = 133)	2014-2018 (N = 91)	*P*
Patient characteristics			
Age (years)[a]	71 (30-83)	73 (42-87)	***0.030***
Sex (men/women)	113/20	74/17	0.471
Etiology of liver disease			
HBcAb-positive (%)	43/112 (38.4)	28/88 (31.8)	0.373
Alcohol intake history (80 g/day over)	17 (12.8)	20 (22.0)	0.098
Child-Pugh grade (B)	3 (2.3)	5 (5.5)	0.275
Liver damage (B)	28 (21.0)	16 (17.6)	0.608
ASA-PS (1/2/3)	11/93/29	2/78/11	***0.018***
Hypertension (present)	81 (60.9)	57 (62.6)	0.677
Hyperlipidemia (present)	23 (17.3)	24 (26.4)	0.132
Diabetes mellitus (present)	69 (45.1)	36 (39.6)	0.077
Body mass index (kg/m^2)[a]	22.9 (15.9-38.2)	23.7 (16.2-35.9)	***0.049***
Preoperative blood examinations			
Albumin (g/dL)[a]	4.2 (2.3-4.9)	4.1 (2.8-5.3)	***0.010***
PT (%)[a]	89 (53-130)	86 (55-124)	0.059
Total serum bilirubin (mg/dL)[a]	0.6 (0.2-2.3)	0.6 (0.3-1.8)	0.490
Platelet count ($\times 10^4/\mu L$)[a]	17.9 (7.9-38.8)	18.5 (6.2-41.1)	0.323
AST (U/L)[a]	30 (16-211)	34 (15-125)	0.085
ALT (U/L)[a]	31 (7-185)	26 (13-138)	0.478
$ICGR_{15}$ (%)[a]	16.0 (4.6-37.0)	9.9 (1.4-44.5)	***<0.001***
AFP (ng/mL)[a]	8.7 (1.4-343,400)	6.8 (1.2-253,460)	0.429
DCP (mAL/mL)[a]	378 (11-198,000)	385 (11-446,000)	0.947
Operation procedures			
Major resection (present)	52 (39.1)	32 (35.2)	0.577
Anatomical resection (present)	100 (75.2)	61 (67.0)	0.226
Type of hepatectomy			
Partial hepatectomy	27 (20.3)	29 (31.8)	0.392
Segmentectomy	16 (12.0)	8 (8.8)	
Sectionectomy	39 (29.3)	22 (24.2)	
Hemihepatectomy	45 (33.9)	28 (30.8)	
Trisectionectomy	6 (4.5)	4 (4.4)	
Pathological findings			
Tumor diameter (mm)[a]	50 (9-175)	55 (11-160)	0.480
Tumor number (multiple)	21 (15.8)	16 (17.6)	0.718
Tumor differentiation (Well/Moderately/Poorly)	22/106/4	5/78/10	***0.004***
Vp (present)	19 (14.2)	29 (31.9)	***0.003***
Vv (present)	9 (6.8)	15 (16.5)	***0.028***
Im (present)	23 (17.3)	17 (18.7)	0.860
Cirrhosis (present)	21 (15.8)	20 (22.0)	0.297
Tumor stage (I/II/III/IV)	90/28/14/1	41/29/21/0	***0.004***
Treatment for recurrence			
Surgical resection	14 of 86 (16.3)	11 of 49 (22.4)	0.123
Radiofrequency ablation	16 of 86 (18.6)	14 of 49 (28.6)	
TACE	38 of 86 (44.2)	15 of 49 (30.6)	
Molecular target drugs	2 of 86 (2.3)	5 of 49 (10.2)	
Other therapies	5 of 86 (5.8)	1 of 49 (2.1)	
Best supportive care	2 of 86 (2.3)	0	
Unknown	9 of 86 (10.5)	3 of 49 (6.1)	

Note: Values in parentheses are percentages unless indicated otherwise.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA-PS, American Society of Anesthesiologists Performance Status; AST, aspartate aminotransferase; DCP, des-gamma-carboxy prothrombin; HBcAb, hepatitis B core antibody; $ICGR_{15}$, indocyanine green retention15; Im, intrahepatic metastasis; NBNC-HCC, hepatocellular carcinoma with negative for hepatitis B surface antigen and hepatitis C antibody; PT, prothrombin time; TACE, Transcatheter arterial chemoembolization; Vp, portal vein thrombosis; Vv, venous vein thrombosis.

Bold and italics show significant.

[a]Value is expressed as the median (range).

or NBNC-HCC, which suggests that achieving SVR decreases the rate of multi-centric recurrence in patients with C-HCC. Although we show here that only the RFS of the latter-treated patients with C-HCC was significantly longer, we believe a longer follow-up period will reveal that there is significant difference between the early and latter groups.

Results for the latter-treated group suggest that treatment strategies should change for patients with C-HCC who have not achieved SVR. Selecting aggressive treatment for patients with C-HCC with

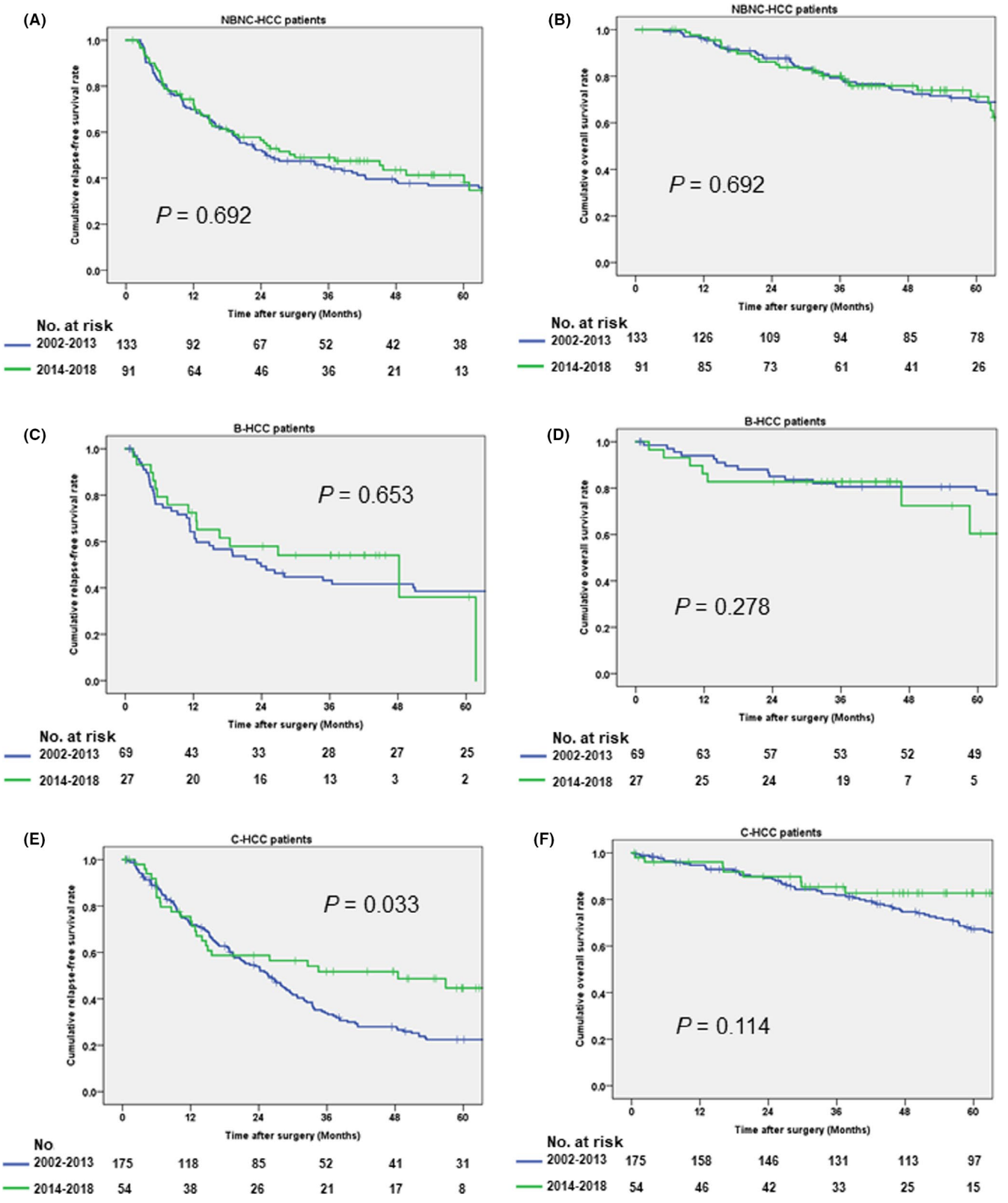

FIGURE 2 Relapse-free survival curves (A, C, and E) and overall survival curves (B, D, and F) for patients with NBNC-HCC, B-HCC, or C-HCC, who underwent hepatectomy during the earlier period (2002-2013) or the latter period (2014-2018)

poor liver function is difficult because the possibility of cure is low despite its high risk. However, curative treatment should be considered when accepting certain risk for such patients because anti-virus therapy is not recommended unless the patient is cancer-free. When preventative measures against HCV infection are established, we should have few patients with C-HCC in the near future. Thus

TABLE 5 Comparisons of clinicopathological characteristics of B-HCC patients

Variables	2002-2013 (N = 69)	2014-2018 (N = 27)	*P*
Patient characteristics			
Age (years)[a]	62 (39-80)	65 (35-79)	0.168
Sex (men/women)	48/21	24/3	0.066
Alcohol intake history (80 g/day over)	4 (5.8)	1 (3.7)	1.000
Child-Pugh grade (B)	0	0	
Liver damage (B)	13 (18.8)	3 (11.1)	0.544
ASA-PS (1/2/3)	9/51/9	3/20/4	0.950
Hypertension (present)	24 (34.8)	12 (44.4)	0.380
Hyperlipidemia (present)	4 (5.8)	2 (7.4)	1.000
Diabetes mellitus (present)	11 (15.9)	9 (33.3)	0.091
Body mass index (kg/m^2)[a]	22.4 (18.0-31.4)	24.3 (18.2-33.8)	***0.024***
Preoperative blood examinations			
Albumin (g/dL)[a]	4.3 (3.1-5.0)	4.2 (2.9-4.8)	0.632
PT (%)[a]	86 (64-113)	90 (55-125)	0.909
Total serum bilirubin (mg/dL)[a]	0.7 (0.3-1.8)	0.7 (0.4-1.5)	0.980
Platelet count ($\times 10^4/\mu L$)[a]	15.2 (7.9-40.8)	18.1 (9.5-38.4)	0.128
AST (U/L)[a]	33 (16-135)	28 (17-90)	***0.015***
ALT (U/L)[a]	35 (5-136)	28 (8-76)	0.064
$ICGR_{15}$ (%)[a]	13.0 (3.0-27.0)	8.0 (1.6-17.9)	***<0.001***
AFP (ng/mL)[a]	75.2 (2.1-231,100)	10.7 (1.7-36,710)	***0.012***
DCP (mAL/mL)[a]	147 (10-345,000)	198 (14-113,000)	0.935
Operation procedures			
Major resection (present)	20 (29.0)	8 (29.6)	1.000
Anatomical resection (present)	42 (60.9)	17 (63.0)	1.000
Type of hepatectomy			
Partial hepatectomy	22 (20.3)	9 (33.3)	0.766
Segmentectomy	9 (12.0)	4 (14.8)	
Sectionectomy	19 (29.3)	8 (29.6)	
Hemihepatectomy	15 (33.9)	6 (22.3)	
Trisectionectomy	4 (4.5)	0	
Pathological findings			
Tumor diameter (mm)[a]	35 (10-180)	40 (10-130)	0.785
Tumor number (multiple)	16 (23.2)	10 (37.0)	0.205
Tumor differentiation (Well/Moderately/Poorly)	5/59/5	5/19/3	0.196
Vp (present)	13 (18.8)	10 (37.0)	0.069
Vv (present)	5 (7.2)	5 (18.5)	0.138
Im (present)	8 (11.6)	5 (18.5)	0.507
Cirrhosis (present)	27 (39.1)	5 (18.5)	0.059
Tumor stage (I/II/III/IV)	39/18/10/2	14/11/2/0	0.389
Treatment for recurrence			
Surgical resection	10 of 50 (20.0)	2 of 15 (13.3)	0.443
Radiofrequency ablation	13 of 50 (26.0)	2 of 15 (13.3)	
TACE	18 of 50 (36.0)	7 of 15 (46.7)	
Molecular target drugs	0	0	
Other therapies	5 of 50 (10.0)	1 of 15 (6.7)	
Best supportive care	1 of 50 (2.0)	2 of 15 (13.3)	
Unknown	3 of 50 (6.0)	1 of 15 (6.7)	

Note: Values in parentheses are percentages unless indicated otherwise.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA-PS, American Society of Anesthesiologists Performance Status; AST, aspartate aminotransferase; B-HCC, hepatocellular carcinoma with positive for hepatitis B surface antigen; DCP, des-gamma-carboxy prothrombin; $ICGR_{15}$, indocyanine green retention15; Im, intrahepatic metastasis; PT, prothrombin time; TACE, Transcatheter arterial chemoembolization; Vp, portal vein thrombosis; Vv, venous vein thrombosis.

Bold and italics show significant.

[a]Value is expressed as the median (range).

C-HCC, which has been difficult to cure, could be considered to be almost overcome in Japan.

Conversely, B-HCC prognosis has not been much improved and its incidence among all patients with HCC is about same (15%-20%) despite the availability of anti-virus treatment. Although HBV viral load can be controlled by introducing anti-HBV therapy, the most important current issue in patients with B-HCC is that HBV cannot be completely eradicated, unlike HCV. The median age at surgery for the patients with B-HCC was significantly younger than for patients with NBNC-HCC or C-HCC for both periods. This implies that life expectancy after hepatectomy for B-HCC could be prolonged if it were possible to eradicate HBV completely, as with HCV. Implementation of infant HBV immunization programs in Japan is expected to lower B-HCC in Japan in the near future, and finally lead to almost zero

TABLE 6 Comparison of clinicopathological characteristics in patients with C-HCC

Variables	2002-2013 (N = 175)	2014-2018 (N = 54)	*P*
Patient characteristics			
Age (years)[a]	71 (43-87)	70 (42-86)	0.530
Sex (men/women)	145/30	37/17	***0.033***
Treated for hepatitis C virus (present)	41 (23.4)	40 (74.1)	***<0.001***
Treated for hepatitis C virus before surgery (present)	25 (14.3)	25 (46.3)	***<0.001***
DAA introduced (present)	0	5 (9.3)	***<0.001***
Treated for hepatitis C virus after surgery (present)	16 (9.1)	15 (27.8)	***<0.001***
DAA introduced (present)	6 (3.4)	15 (27.8)	***<0.001***
SVR (%)	22 (12.6)	33 (61.1)	***<0.001***
SVR before surgery (present)	13 (7.4)	17 (31.5)	***<0.001***
DAA introduced (present)	0	5 (9.3)	***<0.001***
SVR after surgery (present)	9 (5.1)	16 (29.6)	***<0.001***
DAA introduced (present)	6 (3.4)	15 (27.8)	***<0.001***
Alcohol intake history (80 g/day over)	19 (10.9)	8 (14.8)	0.470
Child-Pugh grade (B)	7 (3.9)	0	0.203
Liver damage (B)	50 (28.6)	8 (14.8)	***0.049***
ASA-PS (1/2/3)	6/141/28	1/51/2	***0.049***
Hypertension (present)	112 (64.0)	33 (61.1)	0.441
Hyperlipidemia (present)	7 (3.9)	6 (11.1)	0.084
Diabetes mellitus (present)	44 (24.7)	14 (25.9)	0.848
Body mass index (kg/m^2)[a]	22.0 (14.5-32.9)	22.9 (16.6-29.4)	0.063
Preoperative blood examinations			
Albumin (g/dL)[a]	4.0 (2.7-5.1)	4.0 (3.1-5.6)	0.735
PT (%)[a]	86 (55-117)	89 (67-110)	0.622
Total serum bilirubin (mg/dL)[a]	0.6 (0.2-1.9)	0.7 (0.3-1.2)	0.075
Platelet count (×10^4/μL)[a]	14.0 (4.8-42.9)	12.9 (6.1-25.3)	0.964
AST (U/L)[a]	47 (17-143)	37 (17-113)	***0.001***
ALT (U/L)[a]	45 (9-281)	31 (11-119)	***0.001***
$ICGR_{15}$ (%)[a]	17.0 (5.0-36.0)	10.7 (2.2-26.2)	***<0.001***
AFP (ng/mL)[a]	20.3 (1.5-106,100)	12.9 (1.4-168,900)	0.336
DCP (mAL/mL)[a]	100 (1-124,000)	115 (12-134,000)	0.771
Operation procedures			
Major resection (present)	39 (22.3)	10 (18.5)	0.705
Anatomical resection (present)	80 (45.7)	28 (51.9)	0.344
Type of hepatectomy			
Partial hepatectomy	79 (45.1)	25 (46.3)	0.756
Segmentectomy	21 (12.0)	8 (14.8)	
Sectionectomy	37 (21.1)	13 (24.1)	
Hemihepatectomy	36 (20.6)	7 (13.0)	
Trisectionectomy	2 (1.2)	1 (1.8)	
Pathological findings			
Tumor diameter (mm)[a]	31 (6-175)	30 (11-180)	0.536
Tumor number (multiple)	53 (29.8)	15 (27.8)	0.865
Tumor differentiation (Well/Moderately/Poorly)	33/136/6	12/39/3	0.645

(Continues)

TABLE 6 (Continued)

Variables	2002-2013 (N = 175)	2014-2018 (N = 54)	*P*
Vp (present)	31 (17.7)	13 (24.1)	0.325
Vv (present)	13 (7.4)	11 (20.4)	***0.011***
Im (present)	19 (10.9)	12 (22.2)	***0.041***
Cirrhosis (present)	63 (36.8)	9 (16.7)	***0.007***
Tumor stage (I/II/III/IV)	97/54/22/2	28/18/6/2	0.615
Treatment for recurrence			
Surgical resection	17 of 127 (13.4)	7 of 25 (28.0)	***0.037***
Radiofrequency ablation	33 of 127 (30.0)	3 of 25 (12.0)	
TACE	58 of 127 (45.7)	8 of 25 (32.0)	
Molecular target drugs	3 of 127 (2.4)	1 of 25 (4.0)	
Other therapies	7 of 127 (5.5)	0	
Best supportive care	4 of 127 (3.1)	2 of 25 (8.0)	
Unknown	5 of 127 (3.9)	4 of 25 (16.0)	

Note: Values in parentheses are percentages unless indicated otherwise.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA-PS, American Society of Anesthesiologists Performance Status; AST, aspartate aminotransferase; C-HCC, hepatocellular carcinoma with positive for hepatitis C antibody; DAA, direct acting antiviral agents; DCP, des-gamma-carboxy prothrombin; $ICGR_{15}$, indocyanine green retention15; Im, intrahepatic metastasis; PT, prothrombin time; SVR, sustained virological response; TACE, Transcatheter arterial chemoembolization; Vp, portal vein thrombosis; Vv, venous vein thrombosis.

Bold and italics show significant.

[a]Value is expressed as the median (range).

patients with B-HCC and C-HCC. However, HBV remains the leading cause of HCC cases and deaths worldwide.[27]

Of the three HCC types addressed here, NBNC-HCC is the most concerning because its incidence is increasing, but its prognosis has not improved much. Thus, more effective NBNC-HCC treatment would lead to more favorable survival rates for all HCCs.

One reason that outcomes for NBNC-HCC are not improving is that identifying patients without HBV or HCV who are at high risk for HCC is difficult. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have been shown to contribute to HCC development.[28] Type 2 diabetes, obesity, hyperlipidemia, and alcohol abuse are known risk factors for NBNC-HCC; patients with obesity and/or diabetes account for 37% of HCC cases in the United States.[29] We previously reported that the fibrosis-4 (FIB-4) index, which was calculated using Sterling's formula [age (years) × AST(IU/L) / platelet count ($\times 10^9$/L) × alanine aminotransferase (ALT)$^{1/2}$ (IU/L)], was a useful non-invasive marker of NAFLD.[30] Patients with many risk factors for NAFLD should be candidates for surveillance.

Another reason for lagging NBNC-HCC is that liver fibrosis in patients with NBNC-HCC with NAFLD or NASH is difficult to treat. Several epidemiological studies have addressed the topic of HCC prevention. Coffee consumption, aspirin use, and metformin treatment have consistently been shown to reduce HCC incidence in patients with diabetes.[31–33] Implementation of these findings may decrease the number of patients with NBNC-HCC with NAFLD or NASH.

The present study had several limitations. First, it was a retrospective, single-center study, which may have led to biased results. Moreover, the differences in the distributions of tumor differentiation and rates of vascular invasion between the early and latter groups may be explained by the replacement (approximately between 2013-2014) of the pathologist mainly responsible for diagnosing HCC. Second, the follow-up period for the latter-treated group was significantly shorter than for the earlier group. Prospective multi-institutional and longitudinal studies are needed to validate our findings. Another limitation is that we divided the treatment periods at 2014; results might differ if we had used a different cut-off year. However, the present study may predict the nationwide survey results that are expected to be published in the near future because the survival curves of the earlier group in the present study are similar to those in the Japanese nationwide survey.[6]

In conclusion, our findings indicate that postoperative prognosis has changed according to hepatitis virus infection. Although the proportion of patients with NBNC-HCC has increased, their prognosis has not improved. Better treatment strategies for NBNC-HCC patients are urgently needed.

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DISCLOSURE

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