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ORIGINAL ARTICLE

Liver Resection for Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease: a Multicenter Propensity Matching Analysis with HBV-HCC

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Abstract

Background The incidence of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) is increasing worldwide. Higher perioperative risks may be anticipated due to underlying steatohepatitis, while long-term outcomes after liver resection are unknown. We sought to investigate outcomes after liver resection for NAFLD-HCC versus hepatitis B virus (HBV)-HCC using propensity score matching (PSM).

Methods Consecutive patients who underwent liver resection for HCC between 2003 and 2014 were identified from a multicenter database. Patients with NAFLD-HCC were matched one-to-one to patients with HBV-HCC.

Results Among 1483 patients identified, 96 (6.5%) had NAFLD-HCC and 1387 (93.5%) had HBV-HCC. Patients with NAFLD-HCC were older (median age 57 vs. 50 years), more often overweight (50.0% vs. 37.5%), less often to have cirrhosis (30.2% vs. 72.5%) and liver dysfunction (Child-Pugh B: 4.2% vs. 10.7%), had larger tumor size (median 7.2 vs. 6.2 cm) yet had better tumor differentiation (27.1% vs. 17.6%) compared with patients with HBV-HCC (all $P < 0.05$). Perioperative mortality and morbidity were comparable between the two groups (1.0% vs. 1.4% and 20.8% vs. 23.2%, both $P > 0.05$). No differences were noted in median OS and RFS among patient with NAFLD-HCC versus HBV-HCC before or after PSM.

Conclusion While patients with NAFLD-HCC had different clinical characteristics than patients with HBV-HCC, liver resection resulted in similar perioperative outcomes and comparable OS and RFS among patients with NAFLD-HCC and HBV-HCC.

Keywords Hepatocellular carcinoma · Hepatectomy · Non-alcoholic fatty liver disease · Hepatitis B virus · Overall survival · Recurrence-free survival

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Abbreviations

HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
HEV	hepatitis E virus
BMI	body mass index
ASA	American Society of Anesthesiologists
AST	aspartate transaminase
ALT	alanine aminotransferase
AFP	alpha-fetoprotein
CT	computed tomography
MRI	magnetic resonance imaging
PSM	propensity score matching
OS	overall survival
RFS	recurrence-free survival
95% CI	95% confidence interval.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death worldwide.[1] In the United States and Europe, hepatitis C virus (HCV) infection is the main risk factor of HCC, followed by alcoholic liver disease.[2,3] In contrast, in most Asian and African countries, especially in China, HCC is predominantly associated with hepatitis B virus (HBV) infection.[4] Surgical resection is widely accepted as first-line curative treatment for HCC.

In recent years, non-alcoholic fatty liver disease (NAFLD) has become more common in developed countries, where obese or overweight adults make up a growing majority of the population.[5,6] NAFLD comprises a wide spectrum of diseases, ranging from steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis.[7–10] The impact of NAFLD in many developing countries has been increasingly recognized. In addition, the incidence of NAFLD-HCC is on the rise on a global scale and is expected to further increase in coming years. However, the clinical patterns, perioperative and long-term outcomes of patients with NAFLD-HCC, especially after curative liver resection, have not been well defined. Patients with NAFLD-HCC may be at higher operative risk due to the underlying steatosis or steatohepatitis. Recent studies from the West comparing curative-intent liver resection for NAFLD-HCC versus HCV/alcoholic liver disease-related HCC reported no differences in long-term surgical outcomes.[11–13] However, whether there are differences in short- and long-term outcomes after curative-intent liver resection for NAFLD-HCC versus HBV-HCC has not been well-studied.

Therefore, the objective of the current study was to assess short- and long-term surgical outcomes among patients with NAFLD-HCC versus HBV-HCC using the propensity matching analysis. Specifically, using a multi-center database, we sought to define possible differences in perioperative and long-term survival among HCC patients secondary to NAFLD versus HBV.

Patients and Methods

Patients

Data from a multi-institutional database of patients who underwent curative-intent liver resection for HCC between January 2003 and December 2014 at six hospitals were retrospectively analyzed (Eastern Hepatobiliary Surgery Hospital of Shanghai, Pu'er People's Hospital of Yunnan, Fourth Hospital of Harbin of Heilongjiang, Liuyang People's Hospital of Hunan, Ziyang First People's Hospital of Sichuan, and Mengchao Hepatobiliary Hospital of Fujian). The diagnosis of HCC was confirmed by histopathological examination of the resected specimens after operation. Patients with recurrent, ruptured, or combined HCC-cholangiocarcinoma were excluded. Curative resection was defined as R0 liver resection, which was defined as complete resection of all microscopic and macroscopic tumors. Patients who had microscopically positive (R1 resection), grossly positive (R2 resection), or unknown resection margins were excluded.

Patients were classified as having NAFLD by the presence of metabolic syndrome (overweight or obesity, type 2 diabetes mellitus, hypertension, and dyslipidemia), consistent ultrasonographic features of fatty liver, and/or past or present histological features of hepatic fatty infiltration with an alcohol intake < 30 g/day.[11–13] Patients with a history of alcohol abuse (defined as chronic alcohol intake exceeding 30 g/day) and chronic hepatitis infection [including HBV, HCV, and hepatitis E virus (HEV)] by serological and virological tests were excluded. Patients with drug-induced liver diseases (including herbal and dietary supplements), autoimmune liver diseases (autoimmune hepatitis, celiac disease, primary biliary cholangitis, and primary sclerosing cholangitis), and metabolic liver disorders (Wilson's disease, alpha-1-antitrypsin deficiency, primary hemochromatosis, and Pompe's syndrome) were also excluded.[5] The definition of diabetes, dyslipidemia, hypertension, and fatty liver disease was based on patients' medical history, examination at admission, and laboratory results. The control group consisted of patients with HCC related to chronic HBV infection, which was defined by either a diagnosis of viral hepatitis on histopathologic examination and/or a positive serology of HBsAg. Patients with co-infection of HCV or HEV were excluded. The period of enrollment in the control group was the same as that of the NAFLD-HCC group.

Informed consent for the data to be used for clinical research was obtained from all enrolled patients. The data were collected using a standardized form. Data were collected both in a prospective fashion and retrospective fashion, depending on the particular data field. The process of pre-operative work-up and evaluation in all these six hospitals was virtually identical. The selection criteria for liver resection for HCC were constant over the study period and included location and number of tumors, liver functional reserve, and volume of the future liver remnant, as reported previously.[14] The study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of all the six enrolled hospitals.

Clinicopathological Variables

Patient baseline characteristics including age, sex, diabetes mellitus, hypertension, dyslipidemia, body mass index (BMI), American Society of Anesthesiologists (ASA) score, clinical presentation, cirrhosis, portal hypertension, Child-Pugh grade, preoperative aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, preoperative alpha-fetoprotein (AFP) level, maximum tumor size, tumor number, macroscopic or microscopic vascular invasion, satellite nodules, and tumor differentiation were recorded. Overweight was defined as a BMI $\geq$ 25 kg/m^2 and obesity as a BMI $\geq$ 30 kg/m^2. Cirrhosis was diagnosed histopathologically. Portal hypertension was defined by the presence of either esophageal varices or splenomegaly with thrombocytopenia ($\leq 100 \times 10^9$/L). Operative variables included intraoperative blood loss, requirement of blood transfusion during operation, extent of liver resection (minor vs. major), and type of liver resection (anatomical vs. non-anatomical). Minor liver resection was defined as resection of fewer than three Couinaud liver segments, and major liver resection as resection of three or more liver segments. Non-anatomical liver resections included limited resection or wedge resection and anatomical resections were defined by the Brisbane 2000 system.[15] Perioperative outcomes included perioperative mortality and morbidity. Perioperative mortality was defined as death within 90 days after surgery or before discharge from hospital. Perioperative complications included the occurrence of postoperative hepatic failure, biliary complications, sepsis of any etiology, pulmonary, renal, cardiac and wound complications, which previously reported.[14,16,17] Perioperative morbidity was graded according to the Clavien-Dindo classification,[18] and major morbidity was defined as Clavien-Dindo grade $\geq$ 3.

Patient Follow-Up

Patients were regularly followed up at the outpatient clinics of each participating hospital. The postoperative surveillance strategy for recurrence were consistent in the six participating hospitals and consisted of physical examination, serum AFP level, ultrasonography or contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen at 2 or 3 monthly intervals for the first 6 months after liver resection, 3 or 4 monthly intervals for the next 18 months, and then 3 or 6 monthly thereafter. Tumor recurrence was defined as the new appearance of an intra- or extra-hepatic nodule(s), with or without a rise in serum AFP level, and these intrahepatic nodules had the typical imaging features consistent with the characteristics of HCC on enhanced CT or MRI imaging.

Propensity Score Matching

Patients with NAFLD-HCC were matched with patients who had HBV-HCC using the propensity score matching (PSM) method as described by Rubin and Rosenbaum.[19,20] Covariates entered into the propensity model included age, sex, diabetes mellitus, hypertension, dyslipidemia, overweight, obesity, clinical presentation, cirrhosis, portal hypertension, Child-Pugh grading, preoperative AST, ALT, and AFP levels, maximum tumor size, tumor number, macrovascular and microvascular invasion, satellite nodules, and tumor differentiation. This model was used to provide a one-to-one match between the two groups. The matching procedure has been described previously.[14,21]

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics version 25.0. Continuous variables were expressed as mean ± standard deviations or medians (range) and interquartile ranges as appropriate after testing for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were reported as numbers (n) and proportions (%). Continuous variables were compared using the Student's t test and categorical variables were compared using the Fisher's exact test or the χ^2 test, as appropriate. Overall survival (OS) was defined as the duration from the date of surgery to the date of the last clinical follow-up or death. Recurrence-free survival (RFS) was defined as the duration from the date of surgery to the date when HCC recurrence was first diagnosed for patients with recurrence, or from the date of surgery to the date of the last follow-up or death for patients without recurrence. The OS and RFS rates were compared using the Kaplan-Meier method and the log-rank test. All tests were two-tailed, with a significant P value defined as < 0.05.

Results

Among 1483 patients, there were 96 patients with NAFLD-HCC and 1387 patients with HBV-HCC. PSM created 89 pairs of patients with NAFLD-HCC or HBV-HCC.

Comparisons of Clinicopathological Variables and Perioperative Outcomes

Comparisons of the patient baseline characteristics, operative variables, and perioperative outcomes between patients with NAFLD-HCC and patients with HBV-HCC before and after PSM are noted in Table 1. In the entire cohort, compared with patients who had HBV-HCC, patients with NASH-HCC were older (median age 57 vs. 50 years), more often overweight (50.0% vs. 37.5%), and female (25.0% vs. 16.4%), as well as more often had diabetes mellitus (11.5% vs. 5.6%), dyslipidemia (20.8% vs. 12.7%), clinical symptoms (56.3% vs. 44.7%); in contrast, NAFLD-HCC patients less often had cirrhosis (30.2% vs. 72.5%) and portal hypertension (13.5% vs. 32.3%), yet more often had lower preoperative AST and ALT levels and favorable liver functions (Child-Pugh A: 95.8% vs. 89.3%) at HCC diagnosis (all $P < 0.05$). As for tumor characteristics, the NAFLD-HCC group more often had a large tumor size (median 7.2 vs. 6.2 cm), yet had less poor tumor differentiation (72.9% vs. 82.4%) at HCC diagnosis versus the HBV-HCC group (all $P < 0.05$). There were no differences in the incidences of multiple tumors, macrovascular and microvascular invasion, and satellite nodules between these two groups (all $P > 0.05$). Regarding operative variables, there were no differences in intraoperative blood loss, and in the incidences of intraoperative blood transfusion, major liver resection, and anatomical resection (all $P > 0.05$).

Among the entire cohort, the overall perioperative mortality and morbidity (1.0% vs. 1.4%, $P = 1.000$, and 22.9% vs. 24.0%, $P = 0.902$), and major and minor morbidity (14.6% vs. 13.9%, $P = 0.879$, and 9.4% vs. 10.1%, $P = 0.725$) were similar between the two groups of patients. After PSM, all the clinicopathological variables became balanced between the two groups of patients (all $P > 0.2$). Of note, there was no difference in the overall perioperative morbidity (including major and minor) between two groups in the PSM cohort (all $P > 0.05$).

Comparisons of Long-Term Surgical Outcomes

Comparison of the long-term surgical outcomes between the NAFLD-HCC and HBV-HCC groups of patients before and after PSM is noted in Table 2. In the entire cohort, after a median follow-up of 60 months, death and HCC recurrence were observed in 54.7% and 64.6% of patients with NAFLD-HCC versus 56.5% and 71.5% among patients with HBV-HCC, respectively. No differences were noted between the two groups (both $P > 0.05$). Before PSM, the median OS and RFS among patients with NAFLD-HCC were 73.9 and 43.9 months, which were comparable to outcomes among patients with HBV-HCC (77.5 and 35.3 months, $P = 0.929$ and 0.169, respectively). The OS and RFS among patients with NAFLD-HCC versus patients with HBV-HCC in the entire cohort are shown in Fig. 1 and Fig. 2.

After PSM, death and HCC recurrence were observed in 56.2% and 66.3% among patients with NAFLD-HCC versus 56.2% and 65.2% among patients with HBV-HCC, respectively. There were no differences between the two groups (both $P > 0.05$). After PSM, the median OS and RFS among patients with NAFLD-HCC were 70.4 and 43.9 months, which were also comparable to patients with HBV-HCC (75.2 and 39.3 months, $P = 0.960$ and 0.896, respectively). OS and RFS among patients with NAFLD-HCC versus patients with HBV-HCC in the PSM cohort are shown in Fig. 3 and Fig. 4.

Discussion

NAFLD has become a growing public health problem in recent years and the incidence of HCC in patients with NAFLD has dramatically increased worldwide.[22,23] However, the natural history of NAFLD-HCC is still not well-understood.[13] With improved global HBV vaccination coverage and effective treatment to control chronic HBV infection, the proportional burden of HBV-HCC in China and in most western countries is going down, while that of NAFLD-HCC is noticeably rising.[4,24–26] Comparison of the clinical patterns and prognosis after treatment among patients with NAFLD-HCC versus patients with HBV-HCC has not been well studied.

In this large multicenter study, we used comparatively strict and generally recognized definitions of NAFLD-HCC,[11–13,27–31] to characterize the clinical patterns, perioperative and long-term outcomes of patients who underwent curative-intent liver resection for NAFLD-HCC compared with patients who had HBV-HCC. In doing this, we demonstrated that patients with NAFLD-HCC had acceptable surgical outcomes. Specifically, the 5-year OS reached greater than 50% and the 5-year RFS was roughly 40%. Despite being older and having larger tumors than patients with HBV-HCC, patients with NAFLD-HCC had comparable short- and long-term outcomes to the patients with HBV-HCC when assessing both the entire cohort and the PSM cohort.

Previous studies had demonstrated that patients with hepatitis-related HCC and patients with NAFLD-HCC had different characteristics including older age, higher incidence of diabetes mellitus, hypertension, and dyslipidemia, preserved liver functions, and also larger tumors.[9,11,12,32,33] These characteristics were confirmed in the present study (median age 57 years, tumor size > 5 cm in more than half of the

Table 1 Comparisons of patients' baseline characteristics, operative variables, and perioperative outcomes between patients with NAFLD-HCC and HBV-HCC before and after propensity score matching (PSM)

N (%)	The entire cohort			The PSM cohort		
	NAFLD-HCC (*N* = 96)	HBV-HCC (*N* = 1387)	*P*	NAFLD-HCC (*N* = 89)	HBV-HCC (*N* = 89)	*P*
Age, years[a]	57.3 ± 12.5	50.0 ± 10.4	< 0.001	56.6 ± 12.4	55.5 ± 12.0	0.557
Sex						
Male	72 (75.0)	1240 (89.4)	< 0.001	70 (78.7)	73 (82.0)	0.706
Female	24 (25.0)	147 (10.6)		19 (21.3)	16 (18.0)	
Diabetes mellitus	11 (11.5)	77 (5.6)	0.025	8 (9.0)	6 (7.9)	0.782
Hypertension	14 (14.6)	120 (8.7)	0.063	12 (13.5)	10 (11.2)	0.820
Dyslipidemia	20 (20.8)	176 (12.7)	0.029	18 (20.2)	15 (16.9)	0.700
Overweight	52 (54.2)	607 (43.8)	0.047	44 (49.4)	39 (43.8)	0.548
Obesity	11 (11.5)	96 (6.9)	0.102	9 (10.1)	6 (6.7)	0.591
ASA score						
≤ 2	83 (86.5)	1237 (89.2)	0.399	78 (87.6)	80 (89.9)	0.813
> 2	13 (13.5)	150 (10.8)		11 (12.4)	9 (10.1)	
Clinical presentation						
Symptomatic	58 (60.4)	620 (44.7)	0.003	50 (56.2)	41 (46.1)	0.230
Subclinical	38 (39.6)	767 (55.3)		39 (43.8)	48 (53.9)	
Cirrhosis	29 (30.2)	1006 (72.5)	< 0.001	29 (32.6)	31 (34.8)	0.874
Portal hypertension	13 (13.5)	448 (32.3)	< 0.001	13 (14.6)	12 (13.5)	1.000
Child-Pugh grade						
A	92 (95.8)	1239 (89.3)	0.042	85 (95.5)	81 (91.0)	0.371
B	4 (4.2)	148 (10.7)		4 (4.5)	8 (9.0)	
Preoperative AST level, U/L						
≤ 40 U/L	62 (64.6)	661 (47.7)	0.001	55 (61.8)	49 (55.1)	0.362
> 40 U/L	34 (35.4)	726 (52.3)		34 (38.2)	40 (44.9)	
Preoperative ALT level, U/L						
≤ 40 U/L	58 (60.4)	599 (43.2)	0.001	51 (57.3)	45 (50.6)	0.452
> 40 U/L	38 (39.6)	788 (56.8)		38 (42.7)	44 (49.4)	
Preoperative AFP level						
≤ 400 μg/L	78 (81.3)	842 (60.7)	< 0.001	71 (79.8)	71 (79.8)	1.000
> 400 μg/L	18 (18.8)	545 (39.3)		18 (20.2)	18 (20.2)	
Maximum tumor size, cm[a]	7.2 ± 3.7	6.2 ± 4.2	0.022	7.2 ± 3.8	7.4 ± 4.3	0.673
Tumor number						
Solitary	72 (75.0)	1021 (73.6)	0.812	65 (73.0)	71 (79.8)	0.378
Multiple	24 (25.0)	366 (26.4)		24 (27.0)	18 (20.2)	
Macrovascular invasion	10 (10.4)	195 (14.1)	0.362	10 (11.2)	17 (19.1)	0.209
Microvascular invasion	51 (53.1)	772 (55.7)	0.671	48 (53.9)	46 (51.7)	0.881
Satellite nodules	27 (28.1)	393 (28.3)	1.000	25 (28.1)	25 (28.1)	1.000
Tumor differentiation						
Well or moderately	26 (27.1)	244 (17.6)	0.028	22 (24.7)	21 (23.6)	1.000
Poorly	70 (72.9)	1143 (82.4)		67 (75.3)	68 (76.4)	
Intraoperative blood loss						
≤ 400 ml	53 (55.2)	758 (54.7)	1.000	48 (53.9)	45 (50.6)	0.764
> 400 ml	43 (44.8)	629 (45.3)		41 (46.1)	44 (49.4)	
Intraoperative blood transfusion	22 (22.9)	320 (23.1)	1.000	18 (20.2)	23 (25.8)	0.477
Extent of liver resection						
Major liver resection	35 (36.5)	392 (28.3)	0.102	32 (36.0)	27 (30.3)	0.524
Minor liver resection	61 (63.5)	995 (71.7)		57 (64.0)	62 (69.7)	

Table 1 (continued)

N (%)	The entire cohort			The PSM cohort		
	NAFLD-HCC (*N* = 96)	HBV-HCC (*N* = 1387)	*P*	NAFLD-HCC (*N* = 89)	HBV-HCC (*N* = 89)	*P*
Type of liver resection						
Anatomical	34 (35.4)	419 (30.2)	0.303	34 (38.2)	32 (36.0)	0.877
Non-anatomical	62 (64.6)	968 (69.8)		55 (61.8)	57 (64.0)	
Perioperative mortality	1 (1.0)	19 (1.4)	1.000	0 (0)	0 (0)	NS
Perioperative morbidity	22 (22.9)	333 (24.0)	0.902	19 (21.3)	20 (22.4)	1.000
Minor morbidity (Clavein-Dindo grade I-II)	14 (14.6)	193 (13.9)	0.879	12 (13.5)	12 (13.5)	1.000
Major morbidity (Clavein-Dindo grade III-V)	8 (9.4)	140 (10.1)	0.725	7 (7.9)	8 (9.0)	1.000

[a] Values are mean ± standard deviation or median (range) unless otherwise indicated

AFP alpha-fetoprotein, *ASA* American Society of Anesthesiologists, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CI* confidence interval, *NAFLD* nonalcoholic fatty liver disease, *HBV* hepatitis B virus, *PSM* propensity score matching

patients). Regarding the age difference among patients with NAFLD-HCC and HBV-HCC, several studies have indicated that the occurrence of NAFLD-HCC is related to the progress and severity of NAFLD, being more common among elderly patients.[1,27,34] Unlike NAFLD-HCC, HBV-HCC more frequently occurred among relatively younger patients. In China, a large proportion of HBV infection is induced by vertical transmission in uterus from their mothers. As a result, most patients with HBV-HCC have a long history of hepatitis B infection for several decades, and quite a few young patients have had cirrhosis for a period of time.[23] In addition, tumor pathogenesis definitely differed among various types of HCC due to the various etiological factors. Therefore, it is possible that differences of age and gender may exist between NAFLD-HCC and HBV-HCC.

Of note, another major difference between patients with NAFLD-HCC versus patients with hepatitis-related HCC was in the non-tumoral liver parenchyma. Specifically, NAFLD-HCC are more likely to originate in the absence of cirrhosis or severe fibrosis, while most hepatitis-related HCCs

Table 2 Comparisons of long-term surgical outcomes between patients with NAFLD-HCC and HBV-HCC before and after propensity score matching (PSM)

N (%)	The entire cohort[b]			The PSM cohort		
	NAFLD-HCC (*N* = 95)	HBV-HCC (*N* = 1368)	*P*	NAFLD-HCC (*N* = 89)	HBV-HCC (*N* = 89)	*P*
Period of follow-up, months[a]	59.5 ± 47.7	61.0 ± 45.5	0.757	59.3 ± 48.7	60.3 ± 45.6	0.895
Recurrence during the follow-up	62 (64.6)	978 (71.5)	0.199	59 (66.3)	58 (65.2)	1.000
Early recurrence (within 2 years)	38 (40.0)	586 (42.8)	0.668	36 (40.4)	40 (44.9)	0.650
Late recurrence (beyond 2 years)	24 (3\25.3)	392 (28.7)	0.557	23 (25.8)	18 (20.2)	0.477
Death during the follow-up	52 (54.7)	773 (56.5)	0.749	50 (56.2)	50 (56.2)	1.000
Median OS	73.9 ± 22.1	77.5 ± 3.8	0.929	70.4 ± 20.8	75.2 ± 12.2	0.960
1-year OS rate	85.3	86.2		85.4	89.9	
3-year OS rate	65.2	67.7		63.9	70.7	
5-year OS rate	52.3	56.5		51.4	55.3	
Median RFS	43.9 ± 8.4	35.3 ± 2.4	0.169	43.9 ± 6.4	39.3 ± 18.8	0.896
1-year RFS rate	72.6	69.0		71.9	73.0	
3-year RFS rate	57.8	49.3		57.2	51.6	
5-year RFS rate	39.2	37.9		38.8	43.3	

[a] Values are mean ± standard deviation

[b] Remove the cases of operative death (*n* = 20)

NAFLD nonalcoholic fatty liver disease, *HBV* hepatitis B virus, *OS* overall survival, *PSM* propensity score matching, *RFS* recurrence-free survival

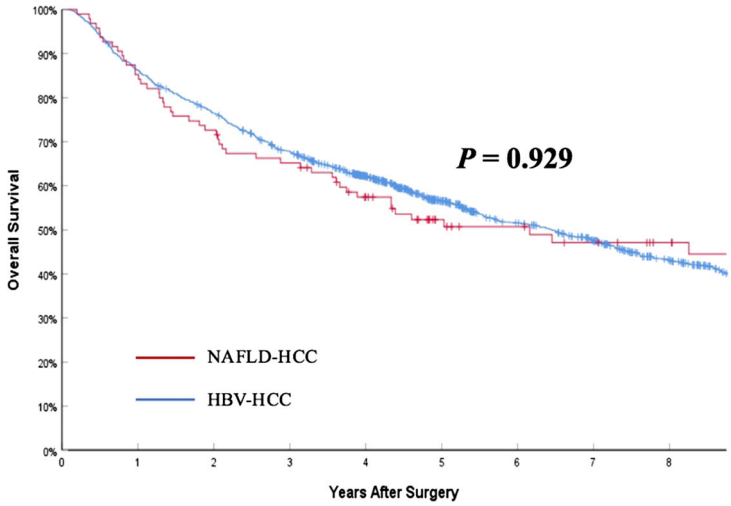

Fig. 1 Cumulative incidence of overall survival curve comparisons between patients with NAFLD-HCC and HBV-HCC in the entire cohort

Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs
NAFLD-HCC	95	81	69	61	48	33	29	25	20
HBV-HCC	1368	1178	1041	909	754	546	441	381	299

had a background of liver fibrosis or even cirrhosis.[11–13,35,36] Consistent with previous reports, we noted that cirrhosis was present in only 30.2% of patients with NAFLD-HCC. This incidence was much less than the incidence noted in patients with HBV-HCC (72.5%). Moderate to severe steatosis or NASH was invariably identified in patients with NAFLD-HCC, which theoretically could lead to more complications like bleeding during parenchyma transection, increased rates of bile leak, and acute hepatic dysfunction after resection. In the present study, liver resection for NAFLD-HCC did not, however, lead to increased mortality and morbidity compared with HBV-HCC patients.

Regarding long-term outcomes of NAFLD-HCC, Reddy et al.[11] retrospectively compared clinicopathologic data and long-term outcomes among 52 patients with NAFLD-HCC and 162 patients with HCV and/or alcoholic liver disease-related HCC who underwent curative treatment (including liver transplantation, hepatic resection, or radiofrequency ablation). These authors concluded that patients with NAFLD-HCC had less severe liver dysfunction at the time when HCC

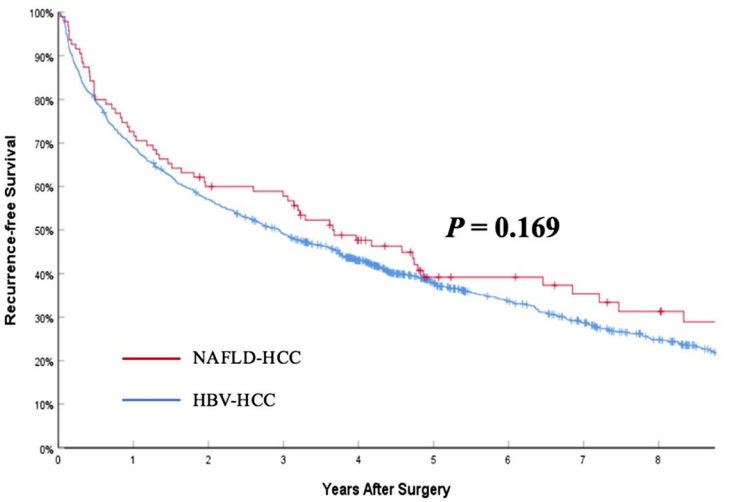

Fig. 2 Cumulative incidence of recurrence-free survival curve comparisons between patients with NAFLD-HCC and HBV-HCC in the entire cohort

Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs
NAFLD-HCC	95	69	56	53	38	24	22	18	15
HBV-HCC	1368	942	776	658	514	354	274	219	162

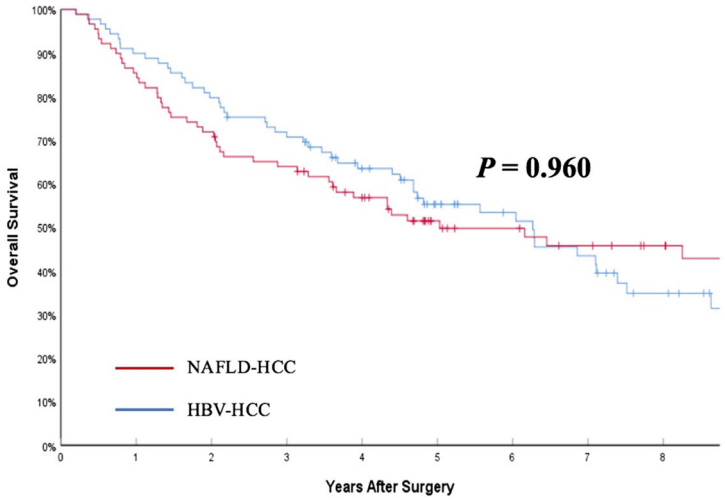

Fig. 3 Cumulative incidence of overall survival curve comparisons between patients with NAFLD-HCC and HBV-HCC in the propensity score matching cohort

Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs
NAFLD-HCC	89	76	64	56	45	30	26	22	18
HBV-HCC	89	80	71	62	49	35	27	22	14

was diagnosed and had better OS after curative-intent treatment compared with patients who had HCV and/or alcoholic liver disease-related HCC. In a separate study, Wakai et al.[32] compared the clinicopathological characteristics and surgical outcomes among three groups of patients: NAFLD-HCC group ($n = 17$), HCV-HCC group ($n = 147$), and HBV-HCC group ($n = 61$). Despite a small sample size, this study indicated that patients with NAFLD-HCC had better disease-free survival than patients with HCV-HCC or HBV-HCC after liver resection. The authors postulated that postoperative late recurrence caused by multicentric carcinogenesis was less common in patients with NAFLD-HCC versus patients with hepatitis-related HCC. The results of the present study were similar to the results of the study by Pais et al.[12] in that the clinical characteristics and long-term outcomes after liver resection among patients with NAFLD-HCC ($n = 39$) and patients with non-NAFLD-HCC ($n = 284$) were similar. While patients with NAFLD-HCC were older and had larger tumors, long-term survival and recurrence rates were comparable to patients with non-NAFLD-HCC. Unlike the study by Pais

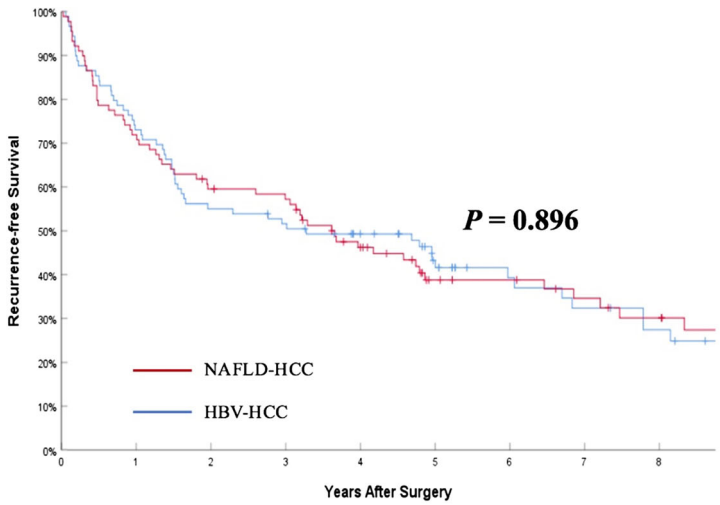

Fig. 4 Cumulative incidence of recurrence-free survival curve comparisons between patients with NAFLD-HCC and HBV-HCC in the propensity score matching cohort

Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs
NAFLD-HCC	89	64	52	49	35	22	20	16	13
HBV-HCC	89	65	49	45	37	26	17	14	11

et al., PSM was used in the present study—which provided a better means to balance in the baseline characteristics among patients with NAFLD-HCC and HBV-HCC.

In the current study, patients with NAFLD-HCC had larger tumors than patients with HBV-HCC (median 7.2 vs. 6.2 cm, $P = 0.022$) at the time of HCC diagnosis. A possible explanation may be the delay in diagnosis of NAFLD-HCC. Patients with chronic hepatitis B or C are more likely to undergo routine surveillance for HCC, while poor surveillance is a constant problem among patients with NAFLD.[36,37] In the current study, the percentage of symptomatic presentation among patients with NAFLD-HCC in the entire cohort was also much higher versus patients with HBV-HCC (60.4% vs. 44.7%, $P = 0.003$). In an Italian multicenter prospective study,[13] which included 756 patients with HCC related either to NAFLD or HCV, 52% of patients with NAFLD-HCC were not diagnosed by regular surveillance compared with 7% of patients with HCV-HCC ($P < 0.001$). In a national US cohort study,[28] the diagnosis of HCC among 1500 patients was made by surveillance in only 40% of patients with NAFLD versus 80% of patients with hepatitis C. Inadequate knowledge on the mechanisms leading to HCC carcinogenesis in NAFLD also hampers development of biomarkers to target this high-risk population and impedes effective care of patients with NAFLD-HCC.[13,36] In addition, it is possible that specific oncogenic mechanisms may be activated in a non-fibrotic and steatotic liver leading to a particular phenotype characteristic of large tumors. Current guidelines recommend HCC screening only in patients with chronic hepatitis B or C, and in patients with cirrhosis.[38,39] As non-cirrhotic HCC represents a sizeable proportion of HCC in NAFLD, many such patients may present with intermediate or advanced tumors with less chance to undergo curative treatments. Unfortunately, attempts to define a group that is at a high risk of developing non-cirrhotic HCC have not been identified.

The current study had several limitations. Firstly, there were no unified diagnostic criteria for NAFLD-HCC. As such, NAFLD-HCC may have been underdiagnosed. Since all enrolled patients in this study had resectable tumors with compensated liver function, the data cannot be generalized to all patients with NAFLD-HCC. Secondly, although PSM analysis was used, the relatively small number of patients with NAFLD-HCC ($n = 96$) limited the statistical power of the present study. However, to our knowledge, this remains one of the largest series comparing surgical outcomes among patients with NAFLD-HCC and patients with hepatitis-related HCC. Thirdly, detailed histological analysis of the non-tumoral liver was not available. As such, this precluded the distinction between steatosis and steatohepatitis and, therefore, whether these entities carried a different risk for development of HCC could not be investigated. Fourthly, the number of NAFLD-HCC cases varied at each hospital. Given the low over incidence, comparison of outcomes among the various centers was not feasible. Finally, similar to previous studies on surgery for NAFLD-HCC,[11–13,32,33] this study also lacked external validation. Future studies will need to validate our findings in external cohorts of both Eastern and Western patients.

In conclusion, the results of the current study demonstrated that patients with NAFLD-HCC had larger tumor and most patients with NAFLD-HCC had no evidence of cirrhosis. Liver resection was safe in patients with NAFLD-HCC. Compared with patients who had HBV-HCC, patients with NAFLD-HCC had similar perioperative outcomes, as well as long-term OS and RFS after curative-intent liver resection.

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Compliance with Ethical Standards

The study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of all the six enrolled hospitals.

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