Differentiation of clinical patterns and survival outcomes of hepatocellular carcinoma on hepatitis B and nonalcoholic fatty liver disease

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Abstract

Background: The main etiologies of hepatocellular carcinoma (HCC) were often hepatitis B virus (HBV) or C and alcohol, rarely autoimmune and biliary diseases. Nonalcoholic fatty liver disease (NAFLD) has been an emerging role that could lead to chronic liver disease, nonalcoholic steatohepatitis, cirrhosis, and eventually HCC in recent years. The aim of our study is to investigate and compare the clinical features of HCC in patients with NAFLD and HBV, including age, gender, cirrhosis, liver function tests, largest tumor size, and cancer stage at the time of diagnosis. The survival outcome was compared between the two groups and the significant predictors of mortality were also analyzed in all patients with HCC.

Methods: Most patients with HCC were recruited from the database of Cancer Registries in Taipei City Hospital, Ren-Ai Branch, from 2011 to 2017; and the other patients consecutively from the HCC multidisciplinary conference between January 2018 and December 2019. NAFLD was defined as nonviral hepatitis B (negative HBsAg and either positive anti-HBs or negative anti-HBc), nonviral hepatitis C (negative antihepatitis C virus [HCV]), nonalcoholic (alcohol consumption of <30 g/d for men and <20 g/d for women) liver disease, or present or past histological or ultrasonographic evidence of fatty liver. Totally, 23 NAFLD-related and 156 HBV-related HCC patients were enrolled in our study for further analysis.

Results: NAFLD-related HCC patients were significantly older (median age: 70.0 [61.0–79.0] years vs. 63.0 [56.0–72.0] years, p = 0.012) and heavier (median body mass index [BMI]: 26.6 [24.2–30] kg/m^2 vs. 24.8 [22.0–27.1] kg/m^2, p = 0.044) than those with HBV-related HCC. They were also more susceptible to diabetes mellitus (DM), and 60.9% (14 of 23) of them had this comorbidity compared with 29.5% (46 of 156) of those with HBV-related HCC (p = 0.003). Only 34.8% (8 of 23) and 71.2% (111 of 156) of patients with NAFLD- and HBV-related HCC were cirrhotic, respectively (p = 0.001). However, gender, tobacco use, international normalized ratio, albumin, creatinine, and cholesterol levels were not significantly different between the two groups. Tumor characteristics such as the Barcelona clinic liver cancer stage, largest tumor size, tumor number, extrahepatic metastasis, and treatment modalities had no significant difference between such groups.

According to the Kaplan–Meier method analysis, the overall survival was not significantly different between these two patient groups (log-rank test, p = 0.101). To evaluate which patient group would lead to poor prognosis, we analyzed the survival of all patients through multivariate Cox proportional hazard regression after controlling other factors that may influence the hazard ratio. The analysis revealed that NAFLD and HBV infection as the cause of HCC are not risk factors of poor prognosis.

Conclusion: In conclusion, our study showed NAFLD-related HCC patients were older, heavier, and more had DM than HBV-related. In addition, more NAFLD-related HCC patients were noncirrhotic than HBV-related. The survival rate was similar between NAFLD and HBV-related HCC patients.

Keywords Fatty liver; Hepatitis B virus (HBV); Hepatocellular carcinoma (HCC); Nonalcoholic fatty liver disease (NAFLD)

1. INTRODUCTION

Hepatocellular carcinoma (HCC) has been the second leading cause of cancer death in Taiwan and the third worldwide. In 2018, it ranked sixth in the most common causes of cancer.[1] HCC generally occurs with liver cirrhosis, and the risk factors include chronic hepatitis B, chronic hepatitis C, alcoholism, aflatoxin, autoimmune hepatitis, hereditary hemochromatosis, and most recently, fatty liver.[2–4] The prevalence of obesity and diabetes mellitus (DM) increased with time, and people diagnosed as having fatty liver, which is also known as nonalcoholic fatty liver disease (NAFLD), are increasing in number.[5] It ranged from

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simple steatosis, steatohepatitis, liver fibrosis, and cirrhosis to liver cancer ultimately.[6]

Large population-based surveys in China, Japan, and Korea indicated that NAFLD is currently prevalent by 12% to 24%,[7] mainly because of the rapid change in lifestyle and urbanization. A recent meta-analysis on 237 studies in Asia revealed that the annual incidence of HCC was 1.8 cases per 1000 person-years in patients with NAFLD,[5] and another retrospective study in Japan indicated that the annual incidence rate of HCC among patients with NAFLD was only 0.043%.[8] Despite the relatively low-incidence rate of HCC in patients with NAFLD, the considerable number of fatty liver cases has made NAFLD an increasingly important disease that leads to HCC. According to a global epidemiologic study of NAFLD, the HCC in patients with nonalcoholic steatohepatitis (NASH) had a considerably higher incidence rate, reaching 5.29 per 1000 person-years, than that in patients with NAFLD with 0.44 per 1000 person-years.[9] The annual cumulative incidence of HCC caused by NASH cirrhosis ranged from 0.46% to 2.6%,[10–12] indicating that NASH has a high risk of developing into HCC.

Several previous studies reported that nearly half of the patients with NAFLD-related HCC were noncirrhotic, and the percentage was 46.2% in Italy, 37% in Switzerland, 34.6% in the United States, and 38.5% in Brazil.[13–16] Another study in Japan revealed that 33.7% of patients with NAFLD developed HCC without late-stage liver fibrosis or cirrhosis.[17] In all patients with HCC, NAFLD had a higher rate of noncirrhosis than other etiologies. In Sweden, patients with noncirrhotic HCC were older and had a larger tumor size than those with cirrhotic HCC, although the prognosis showed no difference between the two groups.[14] Similarly, in Japan, patients with noncirrhotic HCC were older and had a better differentiation of tumor cells than those with cirrhotic HCC, but no significant difference was found in the prognosis between these two groups.[17] In Italy, patients with NAFLD-related HCC were more likely to be noncirrhotic and be at an advanced stage during diagnosis than those with HCC related to chronic hepatitis C, but no significant difference was found in the prognosis between the two groups after a propensity score analysis.[13] To date, although hepatitis B is highly prevalent in Asia, the clinical features and survival outcomes of HCC on NAFLD and a comparison with HCC on hepatitis B have remained insufficiently known.

Hence, this study aimed to assess and compare the clinical features, such as patient age, gender, liver function, cirrhosis, largest tumor size, and cancer staging during diagnosis, between patients with NAFLD-related HCC and those with hepatitis B virus (HBV)-related HCC in Taiwan. Second, we intended to discover the difference in survival outcomes between these two patient groups.

2. METHODS

2.1. Patients

This study retrospectively analyzed most patients with HCC who were recruited from the database of Cancer Registries in Taipei City Hospital, Ren-Ai Branch, from 2011 to 2017 and those patients, especially with NAFLD-related HCC, who consecutively attended the HCC multidisciplinary conference between January 2018 and December 2019. Each case was registered either the time when HCC was first diagnosed or the first visit to our hospital at any time during the disease course. After the data collection, patients with alcohol-related HCC were excluded first, and then HBV-related and NAFLD-related cases were selected from the remaining population. Overall, 156 patients with HBV-related HCC and 23 patients with NAFLD-related HCC were enrolled for further comparison. This epidemiologic study was approved by the Institutional Review Board of Taipei City Hospital.

2.2. Diagnosis

Patients were diagnosed, as having HCC, according to the latest international guidelines in connection with the time of patient registration by dynamic computed tomography (CT), dynamic magnetic resonance imaging (MRI), or pathology. Patients with positive hepatitis B surface antigen (HBsAg) were defined as having either acute or chronic HBV infection. NAFLD was defined as nonviral hepatitis B (negative HBsAg and either positive anti-HBs or negative anti-HBc), nonviral hepatitis C (negative antihepatitis C virus [HCV]), nonalcoholic (alcohol consumption of <30 g/d for men and <20 g/d for women) liver disease, or present or past histologic or ultrasonographic evidence of fatty liver. Fatty liver was diagnosed on the basis of the presence of >5% steatosis by pathology or fulfilling one of the sonographic features of fatty liver by ultrasound, along with a higher parenchymal echogenicity than the renal cortex, intrahepatic vascular blurring, and far attenuation. In the NAFLD group, 15 of the 23 patients were anti-HBc positive; however, all of them had positive anti-HBs, indicating that they had recovered from a previous HBV infection and had gained immunity. That is, occult hepatitis B had been excluded from our patients with NAFLD. We enrolled these recovered patients into our study and classified them as having NAFLD-related HCC. Meanwhile, patients with concurrent active non-HCC, either primary or metastatic, were excluded. Cirrhosis was diagnosed based either on histology or on ultrasound, endoscopic, laboratory, and clinical evidence. Noninvasive serum markers such as Fibrosis-4 index (FIB-4) and aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) were also used to aid the diagnosis of advanced fibrosis and cirrhosis.

2.3. Treatment

Curative therapy in the form of hepatic resection or radiofrequency ablation was provided to available patients in both groups unless they refused. There were 56.5% (13 of 23) of NAFLD-related HCC patients and 56.4% (88 of 156) of HBV-related HCC patients who received curative treatment; no statistically significant difference was observed between the two groups of patients (p = 0.992). Transarterial chemoembolization (TACE) and targeted therapy were applied for advanced HCC. Complete supportive care was given for terminal cases. Most patients were treated according to the 2018 European Association for the Study of the Liver clinical practice guidelines. Antiviral therapy was offered to patients with active HBV infection or decompensated liver, as approved and reimbursed by the National Health Insurance in Taiwan. There were 52.6% (82 of 156) of HBV-related HCC patients who received antiviral therapy during the follow-up period. Diabetic patients were treated according to the usual clinical practice; no difference was observed between the two patient groups.

2.4. Data collection

The patients with HCC were registered to the database of Cancer Registries in Taipei City Hospital by clinical members during their diagnosis. Data on characteristics such as age, gender, body height, body weight, DM, tobacco use, etiology of underlying liver disease, daily alcohol consumption, and fatty liver by image study or pathology were collected. Clinical members also documented the laboratory data and liver function score as AST, alanine aminotransferase (ALT), total bilirubin, international normalized ratio (INR), albumin, platelet count, creatinine, cholesterol, cirrhosis, albumin-bilirubin (ALBI) score, FIB-4, APRI, and Child-Pugh score to the medical records. Furthermore,

tumor characteristics such as the largest tumor size, tumor number, major vascular invasion, extrahepatic metastasis, alpha-fetoprotein (AFP), and Barcelona clinic liver cancer (BCLC) stage were obtained and recorded to the Cancer Registries. The treatment modalities were reviewed and recorded in our study.

Patient survival status and survival time were also registered, and the cases were recruited from January 1, 2011 to December 31, 2019. The definition of survival status and the measurement of survival time were mentioned subsequently.

2.5. Statistical analysis

Data for continuous variables are expressed as medians with interquartile range (IQR), whereas categorical variables are presented as the number of cases and proportions. The continuous and categorical variables were analyzed using the Mann–Whitney U test and chi-square test, as appropriate. Child–Pugh classification has been widely accepted for evaluating liver function, especially those with liver cirrhosis; hence, it was applied in our study. The BCLC stage was used for cancer staging and evaluation of disease severity.

Moreover, survival time was measured as the interval between the day of the first diagnosis and the last follow-up visit or death until December 31, 2019. Survival status was defined as alive, dead, or lost to follow-up. Cumulative survival curves were built and compared using the Kaplan–Meier method and log-rank test, respectively. The hazard ratios of selected factors in the survival outcome were assessed by univariate and multivariate Cox proportional hazard regression analysis. The subgroup analysis was performed to compare the outcomes between NAFLD-related HCC and HBV-related HCC stratified by treatment modalities, age, gender, liver functional reserve, status of cirrhosis, and tumor factors such as BCLC stage and tumor number.

Missing values were extremely rare and were replaced by means or median values. All tests were two-tailed, and $p < 0.05$ was considered statistically significant. The IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA) was used for all data analyses.

3. RESULTS

The demographic characteristics, biochemistry, and liver function reserve of the study population are presented in Table 1. Patients with NAFLD-related HCC were significantly older (median age, 70.0 [61.0–79.0] years vs. 63.0 [56.0–72.0] years; $p = 0.012$) and heavier (median body mass index [BMI], 26.6 [24.2–30] kg/m^2 vs. 24.8 [22.0–27.1] kg/m^2; $p = 0.044$) than those with HBV-related HCC. They were also more susceptible to DM, and 60.9% (14 of 23) of them had this comorbidity compared with 29.5% (46 of 156) of those with HBV-related HCC ($p = 0.003$). Only 34.8% (8 of 23) and 71.2% (111 of 156) of patients with NAFLD- and HBV-related HCC were cirrhotic, respectively ($p = 0.001$). Furthermore, Child–Pugh classification A was in 95.7% (22 of 23) of patients with NAFLD-related HCC and in 77.6% (121 of 156) of those with HBV-related HCC ($p = 0.16$). Meanwhile, patients with HBV-related HCC had significantly higher AST, ALT, total bilirubin, and AFP levels and significantly lower platelet count than those with NAFLD-related HCC. However, gender, tobacco use, INR, albumin, creatinine, and cholesterol levels were not significantly different between the two groups. The ALBI score was a new evidence-based model to assess liver function and survival outcomes in patients with HCC,[18–20] and the FIB-4 and APRI score were developed to predict the risk of liver fibrosis and cirrhosis noninvasively.[21–23] These tools were applied in our study to evaluate the basic liver function and outcomes of the study populations. The outcomes subsequently demonstrated that HBV-related HCC patients tend to have worse liver function, more severe fibrosis, or even worse outcome than NAFLD-related HCC patients. Tumor characteristics such as the BCLC stage, largest tumor size, tumor number, and extrahepatic metastasis had no significant difference between such groups. The treatment modalities between the two patient groups also revealed no significant difference (Table 2). The survival curve and survival outcome are shown in Fig. 1. The median follow-up period was 20.7 (7.1–27.2) months and 26.9 (3.6–55.1) months in NAFLD-related HCC and HBV-related HCC patients, respectively. No difference was found in patients receiving curative treatments between the two patient groups, and the overall survival rate and recurrence-free survival rate for those who underwent curative treatments were not different between these two patient groups. The number of patients at risk at each time point in the NAFLD-HCC group and in the HBV-HCC group is presented in Fig. 1. The survival rates at 1 and 3 years were 90.2% and 72.9% in patients with NAFLD-related HCC and 67.4% and 63.0% in patients with HBV-related HCC. According to the Kaplan–Meier method analysis, the overall survival was not significantly different between these two patient groups (log-rank test, $p = 0.101$). However, a potentially better survival curve was observed in patients with NAFLD-related HCC; this inconclusive result might be related to the lack of long-term follow-up in these patients and because none of them were diagnosed until May 2013.

Table 1

Demographic and Clinical Features of the Study Population

	HCC on NAFLD (N = 23)	HCC on HBV (N = 156)	*p*
Demographic characteristics			
Age (y, median, IQR)	70 (61 to 79)	63 (56 to 72)	0.012*
Male gender [n (%)]	17 (73.9%)	113 (72.4%)	0.882
Body mass index (kg/m^2, median, IQR)	26.6 (24.2 to 30.0)	24.8 (22.0 to 27.1)	0.044*
Diabetes mellitus [n (%)]	14 (60.9%)	46 (29.5%)	0.003*
Tobacco [n (%)]	4 (17.4%)	34 (22.1%)	0.788[a]
Biochemistry tests			
AST (U/L)	30 (20 to 46)	44 (31 to 81)	0.002*
ALT (U/L)	27 (18 to 48)	40 (25 to 58)	0.008*
Bilirubin total (mg/dL)	0.73 (0.4 to 1.0)	1.0 (0.7 to 1.7)	0.001*
International normalized ratio	1.0 (0.97 to 1.04)	1.0 (1.0 to 1.1)	0.118
Albumin (g/dl)	4.2 (4.0 to 4.3)	4.0 (3.4 to 4.4)	0.129
Platelet (×10^3/μl)	190 (136 to 260)	140.5 (103.5 to 185.0)	0.003*
Creatinine (mg/dl)	1.0 (0.7 to 1.2)	0.9 (0.7 to 1.1)	0.312
Cholesterol (mg/dl)	163.5 (130.8 to 187.8)	163 (140 to 185)	0.752
Liver function			
Cirrhosis [n (%)]	8 (34.8%)	111 (71.2%)	0.001*
Albumin–Bilirubin Score (ALBI)	−2.94 (−3.05 to −2.62)	−2.71 (−2.95 to −2.00)	0.017*
Fibrosis-4 Index (FIB-4)	2.21 (1.52 to 4.28)	3.65 (2.15 to 6.18)	0.007*
AST to Platelet Ratio Index (APRI)	0.42 (0.21 to 0.74)	0.87 (0.55 to 1.90)	<0.001*
Child–Pugh score			0.160[a]
A [n (%)]	22 (95.7%)	121 (77.6%)	
B [n (%)]	1 (4.3%)	20 (12.8%)	
C [n (%)]	0 (0%)	15 (9.6%)	

Patients with NAFLD-related HCC were older, had higher body mass indices, were more predisposed to diabetes mellitus, and had a higher number of noncirrhotic cases than patients with HBV-related HCC. Liver function tests were significantly better in patients with NAFLD-related HCC.

*p value < 0.05.

HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease; HBV = hepatitis B virus; IQR = interquartile range.

[a]Fisher's exact test.

Table 2

Tumor Characteristics and Treatment Modalities of the Study Population

	HCC on NAFLD (N = 23)	HCC on HBV (N = 156)	*p*
Tumor characteristics			
Barcelona clinic liver cancer			0.056[a]
0 [n (%)]	3 (13.0%)	10 (6.4%)	
A [n (%)]	11 (47.8%)	66 (42.3%)	
B [n (%)]	7 (30.4%)	25 (16.0%)	
C [n (%)]	1 (4.4%)	37 (23.7%)	
D [n (%)]	1 (4.4%)	18 (11.6%)	
Largest tumor size(cm)	4.2 (2.2–6.3)	3.1 (2.0–7.5)	0.954
Tumor number			0.164
single	18 (78.3%)	99 (63.5%)	
multiple	5 (21.7%)	57 (36.5%)	
Major vascular invasion	1 (4.3%)	42 (26.9%)	0.018*
Extrahepatic metastasis [n (%)]	0 (0%)	8 (5.1%)	0.599[a]
Alpha-fetoprotein (ng/mL)	6.08 (1.8–11.0)	16.1 (4.0–354.9)	0.007*
Treatment modalities			
Curative treatment [n (%)]	13 (56.5%)	88 (56.4%)	0.992
Noncurative treatment [n (%)]	10 (43.5%)	68 (43.6%)	
Transarterial chemoembolization [n (%)]	10 (43.5%)	29 (18.6%)	
Target therapy [n (%)]	0 (0%)	11 (7.1%)	
Complete supportive care [n (%)]	0 (0%)	28 (17.9%)	
Antiviral therapy after HCC diagnosis	0 (0%)	82 (52.6%)	

Tumor characteristics such as BCLC stage, largest tumor size, tumor number, major vascular invasion, extrahepatic metastasis, and AFP are listed in this table. Treatment modalities such as curative treatment, TACE, target therapy, and supportive care are also presented.

*p value < 0.05.

HBV = hepatitis B virus; HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease.

[a]Fisher's exact test.

To evaluate which patient group would lead to poor prognosis, we analyzed the survival of all patients through multivariate Cox proportional hazard regression after controlling other factors that may influence the hazard ratio (Table 3). These factors included age, gender, BMI, DM, AST, ALT, total bilirubin, INR, albumin, platelet, AFP, cirrhosis, Child-Pugh score, and BCLC stage. Age, gender, cirrhosis, and significant risk factors observed in univariate analysis were further analyzed by multivariate analysis. The analysis revealed that NAFLD and HBV infection as the cause of HCC are not risk factors of poor prognosis.

The result of the subgroup analysis is presented in Table 4. The survival outcomes were significantly better in patients who received noncurative treatment in NAFLD-related HCC than in HBV-related HCC (44.4 [23.6–65.3] months vs. 22.0 [14.5–29.5] months, p = 0.011). Patients with HBV-related HCC had better survival outcomes when diagnosed as having an earlier BCLC stage than patients with NAFLD-related HCC (90.0 [82.2–97.9] months vs. 31.4 [23.0–39.8] months, p = 0.024). In contrast, NAFLD-related HCC had better outcomes than HBV-related HCC when diagnosed as having an advanced BCLC stage (56.4 [44.4–68.5] months vs. 27.7 [19.7–35.7] months, p = 0.010). The outcomes were not different between these two groups of patients when stratified by age, gender, liver function reserve, status of cirrhosis, and tumor number.

4. DISCUSSION

According to our observation, patients with NAFLD-related HCC had significantly higher BMI values and were more susceptible to DM than those with HBV-related HCC, consistent with the result of a previous study wherein overweight individuals were at an increased risk of developing DM and closely related to NAFLD by systemic reviews.[24–27] NAFLD represents the hepatic manifestation of metabolic syndrome and may evolve into HCC. In addition to liver cancer, NAFLD is associated with extrahepatic diseases such as cardiovascular disease, type II DM, and chronic kidney disease, which is also related to metabolic syndrome and obesity.[28–30] These diseases seemingly share common risk factors and influence each other by specific mechanisms. Patients with metabolic syndrome reportedly have increased risks of developing HCC and potential worsened cancer outcomes.[31] A possible explanation is that obesity and insulin resistance can trigger an inflammatory response, increase the release of tumor necrosis factor-α, and reduce adiponectin synthesis, leading to the increased exposure of hepatocytes to free fatty acids.[32] In a different study, obesity and insulin resistance

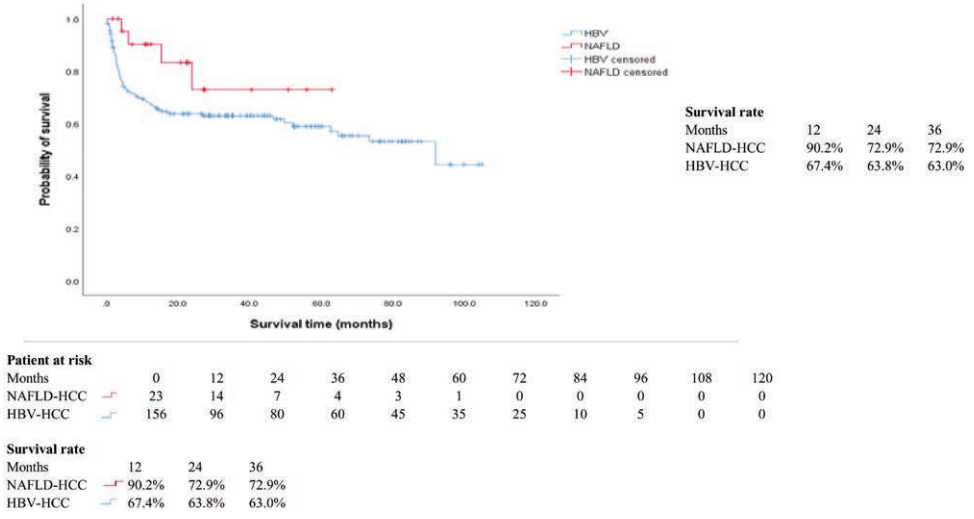

Fig. 1 No significant difference was observed in the survival between these two patient groups according to the Kaplan–Meier method analysis (log-rank test, p = 0.101). However, potentially better survival curve and survival rate were observed in patients with NAFLD-related HCC; this inconclusive result might be related to the lack of long-term follow-up in these patients and because none of them were diagnosed until May 2013. HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease.

Table 3

Multivariate Cox Proportional Hazard Regression Analysis of Survival

		Univariate			Multivariate		
Factor	**Category**	**Hazard ratio**	**95% CI**	***p***	**Hazard ratio**	**95% CI**	***p***
Demographic data							
Group	HBV	1			1		
	NAFLD	0.439	0.159–1.209	0.111	1.914	0.549–6.667	0.308
Age		1.013	0.99–1.036	0.276	1.023	0.988–1.059	0.198
Gender	Male	1			1		
	Female	0.862	0.491–1.513	0.604	0.677	0.299–1.532	0.350
Body mass index		0.919	0.862–0.98	0.010*	0.975	0.892–1.066	0.578
Diabetes mellitus	No	1					
	Yes	0.597	0.34–1.049	0.073			
Liver function tests and tumor characters							
AST		1.008	1.005–1.01	<0.001*	1.003	0.999–1.006	0.129
ALT		1.003	1.000–1.006	0.082			
Bilirubin total		1.182	1.134–1.231	<0.001*	1.068	0.985–1.158	0.110
International normalized ratio		31.288	12.809–76.423	<0.001*	1.749	0.331–9.233	0.510
Albumin		0.247	0.164–0.373	<0.001*	0.536	0.269–1.068	0.760
Platelet		1.000	0.996–1.005	0.9			
Cirrhosis	No	1			1		
	Yes	1.104	0.653–1.868	0.712	1.165	0.476–2.847	0.738
Child-Pugh score	Child A	1			1		
	Child B	6.241	3.409–11.423	<0.001*	1.758	0.628–4.922	0.283
	Child C	31.38	14.991–65.683	<0.001*	6.526	1.51–28.199	0.012*
BCLC stage	Stage 0 or A	1			1		
	Stage B,C or D	7.38	3.982–13.680	<0.001*	3.08	1.385–6.850	0.006*
Alpha-fetoprotein	<20 (ng/mL)	1			1		
	>20 (ng/mL)	5.61	3.028–10.392	<0.001*	1.875	0.856–4.107	0.116

Survival analyses of all patients were done through multivariate Cox proportional hazard regression after controlling other factors that may influence the hazard ratio. It revealed that NAFLD and HBV infection as the cause of HCC are not risk factors that led to poor prognosis.

*p value < 0.05.

CI = confidence interval.

Table 4

Subgroup Analysis for Comparison of the Outcomes Between NAFLD-related HCC and HBV-related HCC

	HCC on NAFLD (N = 23)	**HCC on HBV (N = 156)**	***p* (Log Rank test)**
Treatment modalities			
Patients receiving curative treatment (OS, mo)	47.4 [36.8 to 58.1] (n = 13)	87.3 [79.4 to 95.3] (n = 88)	0.679
Patients receiving noncurative treatment (OS, mo)	44.4 [23.6 to 65.3] (n = 10)	22.0 [14.5 to 29.5] (n = 68)	0.011*
Age			
Age < 65 y (OS, mo)	49.1 [37.0 to 61.3] (n = 7)	62.1 [51.2 to 72.9] (n = 84)	0.234
Age ≥ 65 y (OS, mo)	46.5 [29.8 to 63.2] (n = 16)	62.0 [50.4 to 73.6] (n = 72)	0.276
Gender			
Male (OS, mo)	45.2 [30.5 to 59.9] (n = 17)	62.4 [53.1 to 71.7] (n = 113)	0.283
Female (OS, mo)	(n = 6)[a]	(n = 43)[a]	0.145
Liver function reserve			
Child A (OS, mo)	52.2 [41.3 to 63.2] (n = 22)	75.6 [67.3 to 83.8] (n = 121)	0.483
Child B or C (OS, mo)	4.1 (n = 1)	14.5 [3.8 to 25.1] (n = 34)	0.776
Status of cirrhosis			
With no cirrhosis (OS, mo)	47.2 [36.4 to 58.1] (n = 15)	58.9 [44.4 to 73.3] (n = 45)	0.069
With cirrhosis (OS, mo)	44.6 [23.7 to 65.5] (n = 8)	61.4 [51.8 to 71.0] (n = 111)	0.595
BCLC stage			
BCLC stage 0 or A (OS, mo)	31.4 [23.0 to 39.8] (n = 14)	90.0 [82.2 to 97.9] (n = 76)	0.024*
BCLC stage B or C or D (OS, mo)	56.4 [44.4 to 68.5] (n = 9)	27.7 [19.7 to 35.7] (n = 80)	0.010*
Tumor number			
Single (OS, mo)	45.7 [35.5 to 55.9] (n = 18)	77.4 [68.4 to 86.4] (n = 99)	0.540
Multiple (OS, mo)	48.7 [24.6 to 72.9] (n = 5)	30.3 [21.3 to 39.4] (n = 57)	0.162

Subgroup analysis was performed to compare the outcomes between NAFLD-related HCC and HBV-related HCC stratified by treatment modalities, age, gender, liver functional reserve, status of cirrhosis, and tumor factors such as BCLC stage and tumor number.

[a]Overall survival could not be estimated because of no observed event.

*p value < 0.05.

BCLC = Barcelona clinic liver cancer; CI = confidence interval; HCC = hepatocellular carcinoma; HCC = hepatocellular carcinoma; NAFLD = nonalcoholic fatty liver disease; HBV = hepatitis B virus; OS = estimated overall survival, 95% CI.

could inhibit the oxidation of fatty acids in liver cells, resulting in oxidative stress exposure to DNA.[33] Compared with other malignancies, HCC development is strongly affected by obesity in males.[34] Obesity could also make the ultrasound screening of HCC technically challenging in patients with NAFLD, thereby increasing the misdiagnosis rate.[35] Moreover, weight control might be an issue of concern in treating patients with NAFLD by lifestyle modification, medication, or bariatric surgery in a selected population.[36–38]

A cross-sectional multicenter study in Japan revealed that almost 50% of histologically proven NASH cases developed into HCC in the absence of cirrhosis, more predominantly in men.[39] Kawada et al. reported that a significant proportion of NASH cases (75 %) evolved into HCC with mild-to-moderate fibrosis (F2–F3) but without evident cirrhosis.[40] Paradis et al. demonstrated that patients with HCC are associated with metabolic syndrome, and given that this syndrome was the only risk factor, were more often free of significant fibrosis than those with HCC with other overt causes of chronic liver disease (65% vs. 28%); the possible mechanism might be the malignant transformation of a preexisting liver adenoma.[41] A study by Degasperi et al. also supported a different carcinogenesis pathway in patients with NAFLD other than traditional fibrosis–cirrhosis–HCC sequence.[42] In our study, 15 of the 23 patients (65.2%) with NAFLD-related HCC and 45 of the 156 patients (28.8%) with HBV-related HCC were noncirrhotic. The proportion was similar to that in previous studies. Apparently, NAFLD could develop into HCC without cirrhotic change, raising concerns in clinical practice, especially in the Asian population. The current study is the first to investigate the difference in cirrhotic rate between NAFLD- and HBV-related HCC cases in Taiwan. Although no definite guidelines have been established for NAFLD and NASH surveillance, noninvasive cost-effective methods should be considered for monitoring disease progression and detecting early HCC.[43–45] A large prospective series from Japan highlighted the importance of early HCC detection by ultrasound screening in high-risk patients, including DM.[46] Patients with high NAFLD risk, including those with older age, advanced stage of liver fibrosis, low platelet count, and elevated AFP should be regularly followed up by ultrasound.[25]

The survival outcomes between patients with NAFLD-related HCC and those with other causes of HCC were compared, revealing inconsistent results.[47] Patients with NAFLD-related HCC also reportedly had a worse prognosis because of an advanced stage during cancer diagnosis and failure to receive curative therapy; however, survival difference disappeared in the Italian study by Piscaglia et al. after the propensity score matching.[13,48] Reddy et al. declared that patients with NASH-related HCC had better overall survival after the curative treatment than those with HCV and alcoholic liver disease, considering that the former had a significantly better liver function during a cancer diagnosis.[49] European cohort studies by Weinmann et al. and Dyson et al. reported similar survival outcomes between patients with NAFLD-related HCC and those with other etiologies and no difference in cancer staging at diagnosis and receipt of curative therapy was observed.[29,30] In contrast, Xue et al. reported that the overall survival rate of non-HBV non-HCV HCC (NBNC-HCC) is significantly better than that of HBV-HCC.[50] Utsunomiya et al. reported that patients with NBNC-HCC had a significantly lower risk of HCC recurrence than those with HBV-HCC and HCV-HCC.[51] In our study, the survival outcome between NAFLD-related HCC and HBV-related HCC showed no significant difference. Multivariate analysis using several influential factors did not reveal the NAFLD and HBV infection as the cause of HCC leading to poor prognosis. In subgroup analysis, the survival outcomes were significantly better in patients who received noncurative treatments in NAFLD-related HCC, compared with HBV-related HCC. This might be the reason that a potentially better survival curve was observed in NAFLD-related HCC patients.

Globally, HBV and HCV infections are the leading causes of HCC;[52] however, their incidence is decreasing, most likely because of effective immunization, health education, and treatment. Conversely, the incidence of NAFLD-induced cirrhosis and HCC has increased over the past few decades.[53] The same trend was also observed in our study, and roughly half of the NAFLD-HCC group was recruited in the recent 2 years, resulting in a shortened follow-up period. Despite that patients with NAFLD-related HCC seemed to have better survival outcomes than those with HBV-related HCC, no statistical difference was observed according to the Kaplan–Meier method analysis. It may be caused by the insufficient follow-up time of patients with NAFLD-related HCC and by the fact that only half of them were recruited recently.

Child–Pugh score is useful in evaluating the liver function, whereas the BCLC stage is the most accepted system for liver cancer staging and guide for the treatment plan; both are important prognostic factors for patients with HCC.[54,55] AFP can be used in combination with the BCLC stage to provide prognostic information.[56] We controlled these prognostic factors and age, gender, BMI, liver function tests, AFP, and cirrhosis to compare the survival outcome of patients with HBV and NAFLD. The prognosis between HCV- and NAFLD-induced HCC was previously compared extensively,[13] but the difference between HBV-related and NAFLD-related HCC was poorly investigated. Our study provided the updated data and indicated no significant difference in the survival outcome between patients with HBV-related and NAFLD-related HCC.

NAFLD has different disease progression rates and different clinical manifestations among individuals. Most patients with NAFLD are asymptomatic during their lifetime, but some can progress rapidly, leading to liver cancer.[57] In this retrospective study, few patients with NAFLD-related HCC were symptomatic, and most of them were diagnosed as having HCC by routine health examination or incidental image finding; this finding should raise concerns on regular ultrasound and laboratory follow-up in patients with fatty liver disease.

In conclusion, patients with NAFLD-related HCC were older, heavier, and more susceptible to DM than those with HBV-related HCC. The former also had more noncirrhotic cases than the latter. However, the survival between these two patient groups was not significantly different, and NAFLD and HBV were not risk factors related to poor prognosis after controlling for other influential factors.

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