Liver Resection for Nonalcoholic Fatty Liver Disease-Associated Hepatocellular Carcinoma

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BACKGROUND: Nonalcoholic fatty liver disease (NAFLD)-related hepatocellular carcinoma (HCC) is on the rise worldwide, but data on long-term outcomes after curative operations are limited. The primary aim of this study was to characterize the perioperative and long-term outcomes after liver resection. The secondary aim was to investigate the influence of the histologic severity of nonalcoholic steatohepatitis and its impact on perioperative outcomes and long-term survival.

METHODS: A total of 996 patients who underwent liver resection for HCC in our institution were analyzed. Patients were categorized into subgroups of NAFLD vs non-NAFLD HCC based on histologic evidence of hepatic steatosis. Comparisons of patients' demographic, clinical, and surgical characteristics; postoperative complications; and survival outcomes were performed.

RESULTS: Eight hundred and forty-four patients had non-NAFLD HCC and 152 patients had NAFLD HCC. Comorbidities were significantly more common in the NAFLD group ($p < 0.0001$). In the non-NAFLD group, larger median tumor size, higher liver cirrhosis, and lower median neutrophil to lymphocyte ratio were observed ($p < 0.0001$). The NAFLD group had a greater amount of intraoperative blood loss, more postoperative complications, and longer length of stay. Five-year overall survival was significantly better in the NAFLD group ($p = 0.0355$). Significant factors that contribute to poorer survival outcomes include age, congestive cardiac failure, Child-Pugh's class B, cirrhosis, tumor size, multinodularity, and R1 resection. For NAFLD group, patients with abnormal parenchyma showed poorer survival and 5-year overall survival rates (64.8% vs 75.6%; $p = 0.2291$).

CONCLUSIONS: Nonalcoholic fatty liver disease-related HCC is associated with greater surgical morbidity and post-hepatectomy liver failure. Despite this, long-term survival outcomes are favorable compared with non-NAFLD etiologies. (J Am Coll Surg 2019;229:467–478. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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The increasing prominence of nonalcoholic fatty liver disease (NAFLD)-related hepatocellular carcinoma (HCC) is a worldwide phenomenon due to the rise of related diseases, such as metabolic syndrome, obesity, and diabetes mellitus.[1,2] In the past 2 decades, the prevalence of metabolic syndrome rose from 25% to 33% and contributed to a 9% annual rise in NAFLD-related HCC in the US.[3] Several other studies in the West have also reported a rising trend in NAFLD-related HCC, accounting for >30% of all HCCs in recent years.[3-5] Similarly in Asia, the prevalence rates of NAFLD have been reported to reach >40% and have been predicted to rise even higher.[6] A South Korean study showed that the proportion of

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Abbreviations and Acronyms

HCC = hepatocellular carcinoma
NAFLD = nonalcoholic fatty liver disease
NASH = nonalcoholic steatohepatitis
OS = overall survival
PHLF = post-hepatectomy liver failure

patients with NAFLD-related HCC had increased from 3.8% in 2005 to 12.2% in 2010.[7] In a Japanese cohort study of nonalcoholic steatohepatitis (NASH) cirrhosis patients, the incidence rate of HCC was 11.3% in the recent years, comparable with that of the predominant hepatitis C-related cirrhosis.[8]

In general, NAFLD-related HCCs have been reported to have worse survival outcomes compared with HCCs from other causes.[3] However, long-term outcomes after curative procedures for NAFLD-related HCCs are nonconclusive. Reddy and colleagues[5] reported improved overall survival after curative treatment for NASH-related HCCs, and others reported poorer overall survival.[9] Determining the true survival benefit is crucial when recommending curative treatment, especially when significant perioperative morbidity of >50% and mortality of >10% have been reported after liver resection for NAFLD-related HCC.[10] In addition, there is a pressing need for Asian data that report surgical outcomes for NAFLD-related HCC to inform therapeutic decisions in view of the rising trend of NAFLD in this region.[6,8,11]

The current studies describing surgical outcomes for NALFD-related HCCs are limited by their sample sizes and noncontrolled study design.[5,9,10] Inverse probability weighting has the ability to overcome this limitation and is especially useful when randomized controlled trials are difficult to perform.

The primary aim of this study was to characterize the perioperative and long-term outcomes after liver resection in patients with NAFLD-related HCC using inverse probability weighting. The secondary aim was to investigate the influence of the histologic severity of NASH and its impact on perioperative outcomes and long-term survival.

METHODS

Study design and population

We extracted information based on a prospectively collected database of all patients who underwent liver resection for HCC by the combined Hepatopancreatobiliary Surgery service of the SingHealth Healthcare Cluster, Singapore General Hospital, and National Cancer Centre Singapore between 2000 and 2015. The IRB of SingHealth approved this study.

Data collection

Patients demographic, clinical, biochemical, and radiologic variables were collected retrospectively from a prospectively maintained electronic clinical database (Sunrise Clinical Manager, version 5.8; Eclipsys Corporation).

Assessment of resectability was based on radiologic findings from CT or MRI scans. Preoperative liver function status was assessed by Child-Pugh's class and liver biochemistry status and 3-dimensional CT reconstruction and volumetry, where needed.

Information about the presence of cirrhosis, size, nodularity, major vascular invasion, microvascular invasion, and margins were determined based on histopathology reports. Major liver resection was defined as resection of 3 or more segments. Postoperative complications were categorized according to the Clavien-Dindo classification.[12] Operative records were reviewed for operation time, inflow occlusion duration (Pringle's duration), blood loss, and hospital stay. Postoperative complications were reviewed and liver failure was classified according to the International Study Group of Liver Surgery definition of post-hepatectomy liver failure (PHLF).[13] Operative mortality was recorded up to 90 days after operation.

Histologic analysis

Dedicated liver pathologists reviewed the histologic slides in all resected specimens. The diagnosis of NAFLD is based on histologic evidence of hepatic steatosis. For the 152 patients with NAFLD, liver parenchyma was assessed based on the NASH Clinical Research Network criteria.[14] Stage of fibrosis ranged from 0 to 4 with stage 3 and 4 fibrosis representing advanced fibrosis. The NAFLD activity score was graded from 0 to 8, consisting of steatosis (0 to 3), lobular inflammation (0 to 3), and hepatocellular ballooning (0 to 2). The diagnosis of NASH was made in patients with an NAFLD activity score of 4 or more.[10]

Survival outcomes

All patients were followed up at 3 monthly intervals postoperation, and disease recurrence was detected based on α-fetoprotein levels and radiologic imaging (CT or MRI). Overall survival was defined as time from

Table 1. Patient, Disease, and Surgical Characteristics of Nonalcoholic Fatty Liver Disease vs Non-Nonalcoholic Fatty Liver Disease Hepatocellular Carcinoma

Characteristic	Non-NAFLD HCC (n = 844)	NAFLD HCC (n = 152)	p Value*	p Value†
Patient characteristic				
Age, y, median (IQR)	63 (56–70)	69 (62–73)	<0.0001	0.0948
Male, n (%)	663 (78.6)	111 (73.0)	0.1317	0.1500
BMI, kg/m^2, mean (SD)	25.0 (3.8)	25.4 (4.5)	0.3047	0.1600
Diabetes mellitus, n/N (%)	310/841 (36.9)	95/152 (62.5)	<0.0001	0.5410
Hypertension, n/N (%)	420 (49.9)	111/152 (73.0)	<0.0001	0.0860
Hyperlipidemia, n/N (%)	235/840 (28.0)	78/152 (51.3)	<0.0001	0.2450
Ischemic heart disease, n (%)	110 (13.0)	33/152 (21.1)	0.0092	0.1723
Congestive cardiac failure, n (%)	4 (0.5)	6 (4.0)	<0.0001	0.9923
Chronic kidney disease, n (%)	40 (4.7)	10 (6.5)	0.3580	0.3542
Child-Pugh class, n/N (%)			0.0652	0.8758
A	780/842 (92.6)	147/152 (96.7)		
B	62/842 (7.4)	5/152 (3.3)		
Disease characteristic				
Tumor size, mm, median (IQR)	40 (25–70)	7 (3.8–14)	<0.0001	0.4242
Hepatitis B/C, n (%)	536 (63.5)	0 (0.0)	NA	NA
Cirrhosis, n/N (%)	429/840 (51.1)	52/152 (34.2)	0.0001	0.5595
Multinodular, n/N (%)	136/843 (16.1)	26/152 (17.1)	0.7650	0.8816
High-grade, n (%)	313/818 (38.3)	60/152 (39.5)	0.7527	0.5055
Microvascular invasion, n/N (%)	212/832 (25.5)	31/152 (20.5)	0.1945	0.4920
Fibrosis, n/N (%)				
F0	NA	78/151 (51.7)	NA	NA
F1	NA	10/151 (6.6)		
F2	NA	45/151 (29.8)		
F3	NA	9/151 (6.0)		
F4	NA	9/151 (6.0)		
Steatosis, n (%)				
S1	NA	30/151 (19.9)	NA	NA
S2	NA	107/151 (70.9)		
S3	NA	14/151 (9.3)		
Lobular inflammation, n (%)				
0	NA	69/152 (46.1)	NA	NA
1	NA	57/152 (37.5)		
2	NA	25/152 (16.6)		
Hepatocellular ballooning, n (%)				
0	NA	142/152 (93.4)	NA	NA
1	NA	8/152 (5.3)		
2	NA	2/152 (1.3)		
NAFLD score, n (%)				
≤2	NA	83/152 (54.6)	NA	NA
3	NA	35/152 (23.0)		
≥4	NA	34/152 (22.4)		
α-Fetoprotein, n (%)			0.0646	0.3233
<200 ng/mL	583 (69.1)	119 (78.3)		
200-400 ng/mL	24 (2.8)	4 (2.6)		
>400 ng/mL	237 (28.1)	29 (19.1)		

(Continued)

Table 1. Continued

Characteristic	Non-NAFLD HCC (n = 844)	NAFLD HCC (n = 152)	p Value*	p Value†
Neutrophil to lymphocyte ratio, median (IQR)	2.2 (1.6–3.1)	2.8 (1.9–5.0)	<0.0001	0.2211
Platelet to lymphocyte ratio, median (IQR)	100 (66–147)	125 (92–209)	0.0002	0.2431
Surgical characteristic				
Major resection, n/N (%)	238/843 (28.2)	21/152 (13.8)	0.0002	0.1300
R1 resection, n/N (%)	44/832 (5.3)	6/152 (4.0)	0.4888	0.4664

*Unadjusted p value from univariable comparisons.
†Adjusted p value from inverse probability-weighted comparisons ($p > 0.05$ indicates that distributions conditioned on the propensity score are balanced).
HCC, hepatocellular carcinoma; IQR, interquartile range; NA, not applicable; NAFLD, nonalcoholic fatty liver disease.

operation to death (all causes). Recurrence-free survival was defined as time from operation to first recorded evidence of recurrence on imaging, or death. Patients without these outcomes were censored at their last follow-up.

Statistical analysis

Comparisons of treatment outcomes between NAFLD and non-NAFLD patients were conditioned using inverse probability of exposure weights to minimize confounding biases arising from imbalances in baseline patient characteristics, clinical, biochemical, and histopathologic characteristics that might have influenced prognosis on the different group of patients. Inverse probability of exposure weights was calculated based on a propensity score model that included the following variables: BMI, age, ischemic heart disease, hyperlipidemia, hypertension, diabetes mellitus, congestive cardiac failure, cirrhosis, tumor size, multinodularity, major vs minor resection, positive margins, hepatitis B or C seropositivity, microvascular invasion, and Child-Pugh class. Although NAFLD is diagnosed before operation and/or the diagnosis of HCC in many cases, it is a common misconception that a propensity score model can only be established using covariates obtained before an exposure (ie before a diagnosis of NAFLD HCC). Theoretical arguments by Rubin and Thomas,[15] as well as empirical simulation studies by Brookhart and colleagues,[16] have shown that variables that are unrelated to the exposure but related to outcome(s) of interest (eg margin positivity, extent of resection) should always be included in a propensity score model. The inclusion of variables that are not necessarily related to the exposure improves precision without increasing the bias of the estimated exposure effect.[16] This propensity score model exhibited excellent discrimination and calibration statistics (eFigs. 1 and 2). Continuous variables were analyzed using quantile regression, except for BMI, which was analyzed using linear regression. Categorical and time-to-event outcomes were compared using chi-square tests and Cox proportional hazards regression, respectively. A sensitivity analysis was also conducted using multivariable Cox proportional hazards regression, adjusting for variables that were imbalanced or were associated with overall survival in univariable analyses, to ascertain the prognostic effect of NAFLD.

Comparisons of baseline characteristics and treatment outcomes between NAFLD HCC patients with normal vs abnormal parenchyma were performed using Mood's median test, Pearson's chi-square test, and Cox regression were used for continuous, categorical, and time-to-event variables, respectively. Statistical analyses were conducted in STATA software, version 13.0 (Stata Corp), and 2-sided nominal $p < 0.05$ were considered to indicate statistical significance.

RESULTS

A total of 996 consecutive patients underwent curative liver resection for HCC in our institution during the study period. Of these patients, 536 tested positive for hepatitis B or hepatitis C. One hundred and fifty-two patients were diagnosed with NAFLD HCC. The diagnosis of NAFLD HCC was defined by histologic confirmation of NAFLD or NASH, in the absence of viral hepatitis B/C infection, autoimmune, or alcoholic liver disease.

Baseline characteristics, tumor characteristics, and surgical outcomes of NAFLD HCC and non-NAFLD HCC are summarized in Table 1. A total of 844 patients had non-NAFLD HCC, and 152 patients had NAFLD HCC. Relative to the patients in the non-NAFLD group, patients with

Table 2. Unadjusted and Inverse Probability-Weighted Comparison of Perioperative, Postoperative, and Survival Outcomes Between Nonalcoholic Fatty Liver Disease vs Non-Nonalcoholic Fatty Liver Disease Hepatocellular Carcinoma

Outcome	Non-NAFLD HCC (n = 844)	NAFLD HCC (n = 152)	p Value*	p Value†
Perioperative outcome				
Operation time, min, median (IQR)	185 (135–255)	200 (145–260)	0.1319	0.0674
Inflow occlusion performed, n (%)	351 (41.6)	58 (38.2)	0.3624	0.3221
Inflow occlusion, min, median (IQR)‡	35 (20–55)	31 (20–45)	0.5478	0.0572
Blood loss, mL, median (IQR)	400 (200–800)	500 (250–1,000)	0.0252	0.6368
Transfusion, n (%)	232 (28.0)	57 (37.8)	0.0208	0.2431
Transfusion volume, mL, median (IQR)§	500 (350–750)	500 (400–900)	1.0000	0.6886
Postoperative outcome, n (%)				
All complications	260 (30.8)	84 (54.6)	<0.0001	0.0115
Minor complication	204 (24.2)	61 (41.2)	<0.0001	0.0003
Major complication	68 (8.1)	24 (16.2)	<0.0001	0.0432
Post-hepatectomy liver failure, n/N (%)			<0.0001	0.0008
Grade A	80/843 (9.5)	44/149 (29.5)		
Grade B/C	61/843 (7.2)	30/151 (20.1)		
Ascites, n (%)	14 (1.7)	3 (2.0)	0.7826	0.9820
Bile leak, n (%)	2 (0.2)	0 (0.0)	0.5480	0.1730
Bleeding, n (%)	15 (1.8)	5 (3.3)	0.2211	0.9461
Infective complication, n (%)	75 (8.9)	17 (11.2)	0.3677	0.2224
Pulmonary embolism, n (%)	3 (0.4)	3 (2.0)	0.0176	0.0219
Cardiorespiratory complication, n (%)	57 (6.8)	18 (11.8)	0.0286	0.8766
ICU stay, d, median (IQR)	0 (0-0)	0 (0-1)	<0.0001‖	0.1056
Total hospital stay, d, median (IQR)	6 (5-9)	8 (6-13)	<0.0001	<0.0001
Survival outcome				
OS			0.0355	0.0411
90-d mortality, %	2.46	1.99		
Median (IQR), mo	91.3 (34.8–180.7)	108.0 (51.0–NR)		
1-y OS, %	90.1	94.0		
3-y OS, %	73.4	82.5		
5-y OS, %	60.9	70.1		
10-y OS, %	41.0	49.6		
RFS			0.0552	0.0931
Median (IQR), mo	38.6 (12–NR)	54 (16–NR)		
1-y RFS, %	74.5	78.0		
3-y RFS, %	51.2	60.9		
5-y RFS, %	40.8	45.4		
10-y RFS, %	32.2	40.2		

*Unadjusted p value from univariable comparisons.
†Adjusted p value from inverse probability-weighted comparisons ($p < 0.05$ indicates inequality of distributions conditioned on the propensity score).
‡Among patients who had inflow occlusion.
§Among patients who received blood transfusion.
‖From Mood's median test instead of quantile regression due to nonconvergence of the latter.
HCC, hepatocellular carcinoma; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; NR, not reached; OS, overall survival; RFS, recurrence-free survival.

NAFLD HCC were older at time of diagnosis (63 vs 69 years; $p < 0.0001$). Male preponderance was comparable between both groups (78.6% vs 73%; $p = 0.131$). Comorbidities such as diabetes mellitus (62.5% vs 36.9%; $p < 0.0001$), hypertension (73% vs 49.9%; $p < 0.0001$), hyperlipidemia (51.3% vs 28%; $p < 0.0001$), ischemic heart disease (21.1% vs 13%; $p = 0.0092$), and congestive cardiac failure (4% vs 0.5%; $p < 0.0001$) were more

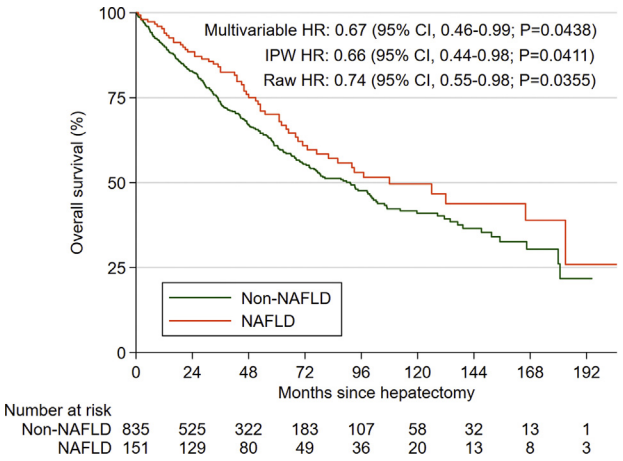

Figure 1. Overall survival in nonalcoholic fatty liver disease (NAFLD) vs non-NAFLD-associated hepatocellular carcinoma. HR, hazard ratio; IPW, inverse probability-weighted.

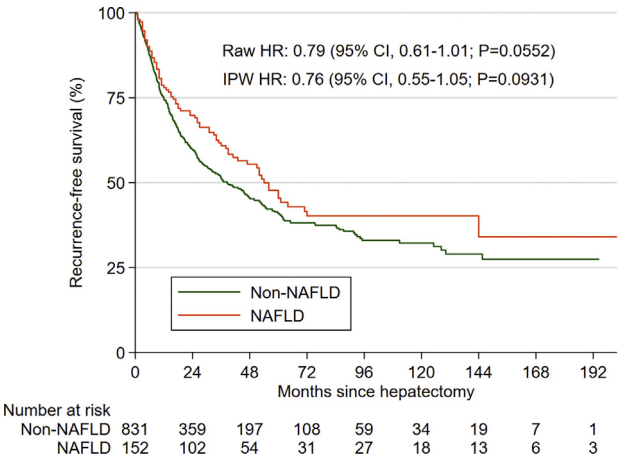

Figure 2. Recurrence-free survival in nonalcoholic fatty liver disease (NAFLD) vs non-NAFLD-associated hepatocellular carcinoma. HR, hazard ratio; IPW, inverse probability-weighted.

significantly and more commonly seen in the NAFLD group. In the non-NAFLD group, larger median tumor size (40 mm vs 7 mm; $p < 0.0001$), higher proportion of liver cirrhosis (51.1% vs 34.2%; $p < 0.0001$), lower median neutrophil to lymphocyte ratio (2.2 vs 2.8; $p < 0.0001$), and lower median platelet to lymphocyte ratio (100 vs 125) were observed. In addition, more patients in the non-NAFLD group underwent major resection (28.2% vs 13.8%; $p = 0.0002$). The histologic descriptions of the NAFLD specimens are illustrated in Table 1. The majority of the patients had mild fibrosis, with 12% of patients having F3/4 fibrosis. There were 22.4% of the patients with NAFLD score of ≥ 4, and determined to have NASH.

Table 2 describes the comparisons of the perioperative, postoperative, and survival outcomes between the 2 groups. Despite the lower proportion of patients who underwent major resections, the NAFLD group had a greater amount of median intraoperative blood loss (500 mL vs 400 mL; $p = 0.0252$) and more patients need intraoperative transfusions (37.8% vs 28%; $p = 0.0208$). In addition, there were more minor (41.2% vs 24.2%; $p < 0.0001$) and major (16.2% vs 8.1%; $p < 0.0001$) complications in the NAFLD group. Liver failure of all grades was higher in the NAFLD group (29.5% vs 9.5% grade A liver failure, and 20.1% vs 7.2% grade B/C; $p < 0.0001$). Cardiorespiratory complications (11.8% vs 6.8%; $p = 0.0286$) and pulmonary embolism (2% vs 0.4%; $p = 0.0176$) were also higher in the NAFLD group. Consequently, total hospital stay was longer in the NAFLD group (median hospital stay 8 days vs 6 days; $p < 0.0001$). After the perioperative period, long-term outcomes were significantly better in the NAFLD group in terms of overall survival (OS), with 5-year OS rates of 70.1% vs 60.9% ($p = 0.0355$), although the groups were not equally distributed on propensity score ($p = 0.0411$) (see Figs. 1 and 2).

Table 3 describes the sensitivity analysis of the prognostic effect of various factors on OS. On multivariate analysis, the significant factors that contribute to poorer survival outcomes include age, congestive cardiac failure, Child-Pugh's class B, cirrhosis, tumor size, multinodularity, and R1 resection. On the other hand, NALFD was associated with an adjusted hazard ratio of 0.673 ($p = 0.0438$).

Subgroup analysis for patient and disease characteristics of NAFLD HCC is presented in Table 4. There were more R1 resections in the normal parenchyma group compared with the abnormal parenchyma group (7.8% vs 0%; $p = 0.0136$), but there were no significant differences in patient or disease characteristics. Table 5 shows that there were more overall complications in the normal parenchyma group vs the abnormal parenchyma group (61% vs 46.7%; $p = 0.0755$), although this did not reach statistical significance. The OS trended toward poorer survival of the abnormal parenchyma group (median 82 months vs 126 months) and worse 5-year OS rates (64.8% vs 75.6%; $p = 0.2291$) (see Figs. 3 and 4). This was likely contributed to, in part, by a greater percentage of secondary cancers in the abnormal parenchyma

Table 3. Sensitivity Analysis of the Prognostic Effect of Nonalcoholic Fatty Liver Disease on Overall Survival Using Multivariable Cox Proportional Hazards Regression

	Univariable analysis			Multivariable analysis*		
Characteristic	**Unadjusted HR**	**95% CI**	**p Value**	**Adjusted HR**	**95% CI**	**p Value**
Patient characteristic						
Age, y	1.022	1.011−1.031	<0.0001	1.026	1.014−1.038	<0.0001
BMI, kg/m^2	0.992	0.975−1.010	0.3941	0.999	0.997−1.002	0.7069
Diabetes mellitus	1.215	0.988−1.494	0.0644	1.213	0.945−1.558	0.1289
Hypertension	1.058	0.861−1.302	0.5906	0.817	0.620−1.076	0.1496
Hyperlipidemia	1.011	0.812−1.258	0.9228	0.903	0.695−1.175	0.4484
Ischemic heart disease	1.057	0.801−1.394	0.6966	0.964	0.705−1.319	0.8184
Congestive cardiac failure	1.462	0.723−2.955	0.2903	2.758	1.273−5.974	0.0101
Chronic kidney disease	0.925	0.595−1.438	0.7297	—	—	—
Child-Pugh class B	1.723	1.231−2.412	0.0015	1.590	1.103−2.293	0.0130
Disease characteristic						
Tumor size, cm	1.046	1.022−1.070	0.0001	1.044	1.014−1.074	0.0037
Hepatitis B/C	0.912	0.743−1.120	0.3799	NE	NE	NE
Cirrhosis	1.377	1.121−1.692	0.0023	1.387	1.087−1.769	0.0085
Multinodular	1.704	1.318−2.204	<0.0001	1.646	1.244−2.178	0.0005
High-grade	1.069	0.864−1.323	0.5390	—	—	—
Microvascular invasion	1.694	1.353−2.121	<0.0001	1.539	1.197−1.979	0.0008
NAFLD	0.737	0.555−0.979	0.0355	0.673	0.457−0.989	0.0438
α-Fetoprotein, n (%)						
<200 ng/mL	Reference	Reference	1.0000	—	—	—
200−400 ng/mL	0.777	0.396−1.510	0.4561	—	—	—
>400 ng/mL	1.024	0.804−1.303	0.8487	—	—	—
Neutrophil to lymphocyte ratio	1.001	0.998−1.004	0.4570	1.030	0.995−1.067	0.0965
Platelet to lymphocyte ratio	1.001	1.000−1.002	0.2720	1.000	0.999−1.001	0.8744
Surgical characteristic						
Major resection	1.181	0.939−1.486	0.1558	1.210	0.945−1.551	0.1310
R1 resection	1.836	1.199−2.811	0.0052	1.936	1.213−3.091	0.0056

*Adjusted HRs were computed from a multivariable model that included covariates that were significantly imbalanced between NAFLD and non-NAFLD patients, as well as covariates that were associated with overall survival in univariable analyses.
HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NE, not estimable due to small sample numbers.

group vs the normal parenchyma group (34.7% vs 19.5%; p = 0.0349), with colorectal and genitourinary cancers forming the majority.

DISCUSSION

Our current study provides interesting findings that characterize a serious complication of a burgeoning disease entity, which can help to inform and guide approaches to surgical management of NAFLD-related HCC. Nonalcoholic fatty liver disease consists of a spectrum of steatotic changes to the liver parenchyma, ranging from simple steatosis, steatohepatitis, cirrhosis, and even HCC in the absence of apparent cirrhosis.[2,17-19] It is currently the most prevalent liver disease in the developed world and has brought about an increase in NAFLD and NASH-associated HCCs.[3,10,19] Although curative resection for NAFLD-associated HCC has been described in the Western literature, there is a lack of Asian data examining the surgical outcomes after resection.[5,10] This is currently the largest single-center study examining outcomes of surgically resected NAFLD HCC.

In the literature, smaller case series described NAFLD-associated HCCs to be larger in size, more likely to be multifocal, and more likely to require a major hepatectomy.[5,10,18] Our data were not affirming of the existing

Table 4. Comparison of Patient, Disease, and Surgical Characteristics of Nonalcoholic Fatty Liver Disease Based on Histologic Severity

Characteristic	Normal parenchyma (NAS <3 and F <3) (n = 77)	Abnormal parenchyma (n = 75)	p Value*
Patient characteristic			
Age, y, median (IQR)	71 (61–74)	66.5 (62–72)	0.0594
Male, n (%)	60 (77.9)	51 (68.0)	0.1682
BMI, kg/m^2, mean (SD)	24.7 (3.9)	26.2 (5.1)	0.0647
Diabetes mellitus, n (%)	49 (63.6)	45 (60.0)	0.6445
Hypertension, n (%)	54 (70.1)	57 (76.0)	0.4149
Hyperlipidemia, n (%)	40 (52.0)	37 (49.3)	0.7472
Ischemic heart disease, n (%)	17 (22.1)	15 (20.0)	0.7533
Congestive cardiac failure, n (%)	1 (1.3)	5 (6.8)	0.0893
Chronic renal failure, n (%)	3 (3.9)	7 (9.3)	0.1764
Child-Pugh class, n (%)			0.6279
A	75 (97.4)	72 (96.0)	
B	2 (2.6)	3 (4.0)	
Disease characteristic			
Tumor size, mm, median (IQR)	7 (3–11)	6.2 (4–15)	0.7456
Cirrhosis, n (%)	19 (24.7)	34 (45.3)	0.0075
Multinodular, n (%)	11 (14.3)	16 (21.3)	0.2557
High-grade, n (%)	29 (37.7)	31 (41.3)	0.6434
Microvascular invasion, n (%)	15 (19.5)	17 (22.7)	0.6596
α-Fetoprotein, n (%)			0.7811
<200 ng/mL	62 (80.5)	57 (76.0)	
200–400 ng/mL	2 (2.6)	2 (2.7)	
>400 ng/mL	13 (16.9)	16 (21.3)	
Neutrophil to lymphocyte ratio, median (IQR)	2.7 (1.8–3.9)	2.9 (1.9–5.7)	0.3303
Platelet to lymphocyte ratio, median (IQR)	123 (94–209)	125 (91–193)	0.8711
Surgical characteristic			
Major resection, n (%)	10 (13.0)	11 (14.7)	0.7642
R1 resection, n (%)	6 (7.8)	0 (0.0)	0.0136

*Mood's median test and Pearson's chi-square test were used for continuous and categorical variables, respectively.
F, fibrosis; IQR, interquartile range; NAS, nonalcoholic fatty liver disease activity score.

literature (refer to Table 1). Our results indicate that the recurrent disease and survival rates tended to be better when compared with inverse probability-weighted non-NAFLD HCC cohorts. In addition, overall median survival of NAFLD HCC was higher than non-NAFLD HCC (108 months vs 91.3 months; p = 0.0355). (refer to Table 2). Contrary to other studies that suggest that NASH-related HCCs are associated with poorer prognosis and outcomes, our findings suggest that patients with NAFLD HCC that were eligible for surgical treatment would have optimal outcomes. Therefore, surgical options should be considered preferentially, whenever possible.

Among all of the patients with HCCs who underwent curative resection, 152 patients were NAFLD-related HCC representing >15% of our entire cohort of HCC patients, which was consistent with the literature-reported rates.[17,18] From our series, only 18 (12%) patients had severe fibrosis (F3/F4) and the majority had only moderate or no fibrosis. This is a single series reporting the highest number of noncirrhotic HCCs due to NAFLD, adding to the growing body of evidence that suggests that NAFLD causes HCC independent of cirrhosis.[20] This represents an area where more information is urgently needed. Current society guidelines do not recommend any HCC screening or surveillance programs for NAFLD patients unless there is associated cirrhosis.[21] However, increasing evidence suggests possible development of NASH-related HCC in the absence of cirrhosis[18,19] and is reiterated in our

Table 5. Comparison of Perioperative, Postoperative, and Survival Outcomes, and Incidence of Secondary Cancers According to Severity of Nonalcoholic Fatty Liver Disease

Outcome	Normal parenchyma (NAS <2 and F <3) (n = 77)	Abnormal parenchyma (n = 75)	p Value*
Perioperative outcome			
Operation time, min, median (IQR)	190 (125–250)	215 (155–265)	0.0349
Inflow occlusion performed, n (%)	—	—	—
Inflow occlusion, min, median (IQR)†	26.5 (20–55)	35 (20–45)	0.3567
Blood loss, mL, median (IQR)	500 (300–1,000)	500 (250–1,000)	0.7559
Transfusion, n (%)	26 (33.8)	30 (40.0)	—
Transfusion volume, mL, median (IQR)‡	500 (380–600)	625 (400–1,050)	0.2174
Postoperative outcome			
All complications, n (%)	47 (61.0)	35 (46.7)	0.0755
Minor complication, n (%)	37 (48.1)	23 (32.4)	0.0526
Major complication, n (%)	13 (16.9)	11 (14.5)	0.8187
Post hepatectomy liver failure, n (%)			0.0391
Grade A	29 (37.7)	14 (19.4)	
Grade B/C	12 (15.6)	18 (25.0)	
Ascites, n (%)	1 (1.3)	2 (2.7)	0.5444
Bile leak, n (%)	0 (0.0)	0 (0.0)	NE
Bleeding, n (%)	4 (5.2)	1 (1.3)	0.1821
Infective complication, n (%)	9 (11.7)	8 (10.7)	0.8416
Pulmonary embolism, n (%)	2 (2.6)	1 (1.3)	0.5754
Cardiorespiratory complication, n (%)	9 (11.7)	9 (12.0)	0.9526
ICU stay, d, median (IQR)	0 (0–0)	0 (0–1)	0.3929
Total hospital stay, d, median (IQR)	8 (6–13)	7 (6–12)	0.7755
Survival outcome			
Overall survival			
90-day mortality	0	4.1	0.2291
Median, months, median (IQR)	126 (61–NR)	82 (46–183)	
1-y OS, %	94.7	93.2	
3-y OS, %	86.2	78.1	
5-y OS, %	75.6	64.8	
10-y OS, %	52.7	47.1	
RFS			
Median, months, median (IQR)	60 (25–NR)	53 (11–NR)	0.3225
1-y RFS, %	84.2	70.8	
3-y RFS, %	66.1	55.6	
5-y RFS, %	47.6	45.2	
10-y RFS, %	40.6	42.0	
Secondary cancer, n (%)			
Colon	6 (7.8)	11 (14.7)	0.1788
Urological	4 (5.2)	7 (9.3)	0.3248
Gynecologic	0 (0.0)	1 (1.3)	0.3093
Breast	1 (1.3)	4 (5.3)	0.1632
Gastric	1 (1.3)	2 (2.7)	0.5444
Head and neck cancer	1 (1.3)	1 (1.3)	0.9851
Skin	2 (2.6)	0 (0.0)	0.1600
Any site	15 (19.5)	26 (34.7)	0.0349

*Mood's median test, Pearson's chi-square test, and Cox regression were used for continuous, categorical, and time-to-event variables, respectively.
†Among patients who had inflow occlusion.
‡Among patients who received blood transfusion.
IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival; RFS, recurrence-free survival.

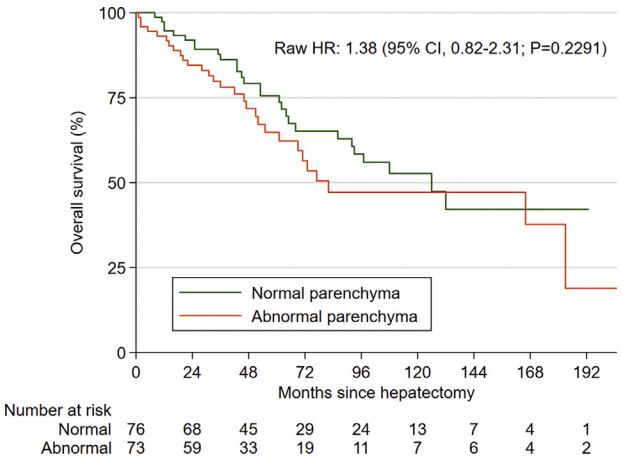

Figure 3. Overall survival in nonalcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma based on histologic severity. HR, hazard ratio.

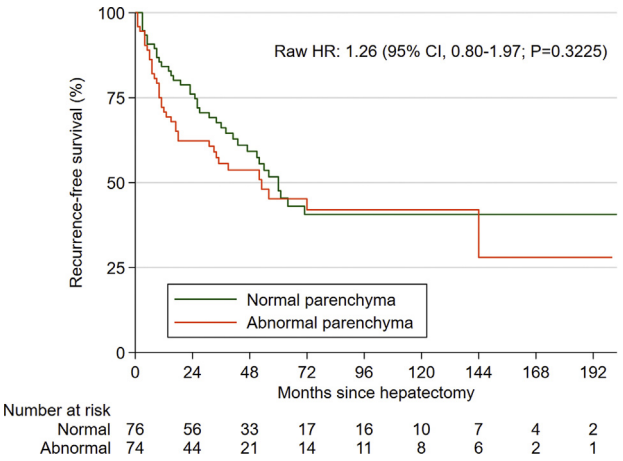

Figure 4. Recurrence-free survival in nonalcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma based on histologic severity. HR, hazard ratio.

current study. This highlights the need for increased awareness of this phenomenon, and also begs the question of how high-risk patients would be identified for screening. Additional research is required to provide guidance in this aspect.

With improvements in surgical techniques and postoperative care, mortality after hepatectomy has decreased remarkably from 58% to 10% and overall morbidity similarly decreased.[10] However, these advances have not been translated wholly into improved care for the specific group of patients with NAFLD-related HCC. In our study, overall morbidity for NAFLD-related HCC post-hepatectomy was >50%. The most common postoperative complication was liver failure (49.6%), followed by cardiorespiratory complications (11.8%) and pulmonary embolism (2%). We recently published our PHLF results in patients who had major hepatectomy (right and extended right hepatectomy) and reported that the PHLF rate was 41% based on International Study Group of Liver Surgery criteria.[22] This was still lower than the overall PHLF rate in NAFLD HCC, where PHLF (all grades) occurred in 49.6% of all post-hepatectomy patients, despite a lower proportion of NAFLD patients undergoing major hepatectomy. This could be related to the underlying hepatocellular dysfunction due to steatosis and the pro-inflammatory state, where a significantly higher neutrophil to lymphocyte ratio was seen in the NAFLD HCC cohort.[23] Perioperatively, the higher complication rates in NAFLD HCCs resulted in longer inpatient stay, but lower 90-day mortality rates (NAFLD HCC 1.99% vs non-NAFLD HCC 2.46%; $p = 0.0355$). To achieve better perioperative risk stratification, preoperative diagnosis of NAFLD by percutaneous biopsy could enhance preoperative counseling.

Currently, elevated inflammatory indices, including neutrophil to lymphocyte ratios, have been investigated with respect to survival outcomes in HCC.[24,25] Interestingly, an elevated neutrophil to lymphocyte ratio in the setting of NAFLD HCCs was not associated with poorer overall survival, this was contrary to reports of other HCC causes. Additional studies are needed to determine the effect of inflammatory indices on perioperative and survival outcomes.

Subgroup analyses based on normal or abnormal hepatic parenchyma showed no significant differences in patient, disease, and surgical characteristics or perioperative and postoperative outcomes. However, 5-year OS rate tended to be better in the normal parenchyma group compared with the abnormal parenchyma group (75.6% vs 64.8%; $p = 0.2291$). This is likely due to the higher proportion of secondary cancers seen in the abnormal parenchyma group (34.7% vs 19.5%; $p = 0.0349$).

This study has several limitations. Firstly, its retrospective nature renders it susceptible to inherent biases. To minimize this effect, we performed an inverse probability-weighted analysis to derive better estimates of the "average treatment effect." Ideally, a randomized controlled trial would be preferred. However, it would be a significant challenge, given that NAFLD HCC is

usually confirmed only on postoperative histology. Secondly, because NAFLD was not a well-recognized disease entity in the early years, some cases might be misclassified as cryptogenic HCC and excluded in our data. Nevertheless, this study represents the largest series of surgically resected NAFLD HCCs. The approach with adequate balance of baseline confounders between NAFLD and non-NAFLD causes provides strong evidence for the intrinsic differences in disease characteristics, survival outcomes, and perioperative morbidity.

CONCLUSIONS

Nonalcoholic fatty liver disease is a well-recognized chronic liver disease in Asia and an increasingly important cause of HCC. The majority of NAFLD-associated HCCs can occur without significant fibrosis. Nonalcoholic fatty liver disease-associated HCC is associated with greater surgical morbidity and PHLF. Despite this, the long-term survival outcomes are favorable compared with non-NAFLD etiologies.

Author Contributions

Study conception and design: Koh, Tan, Chan
Acquisition of data: Koh, Tan
Analysis and interpretation of data: Liew, Syn
Drafting of manuscript: Koh, Tan
Critical revision: Teo, Lee, BKP Goh, GBB Goh, Chan

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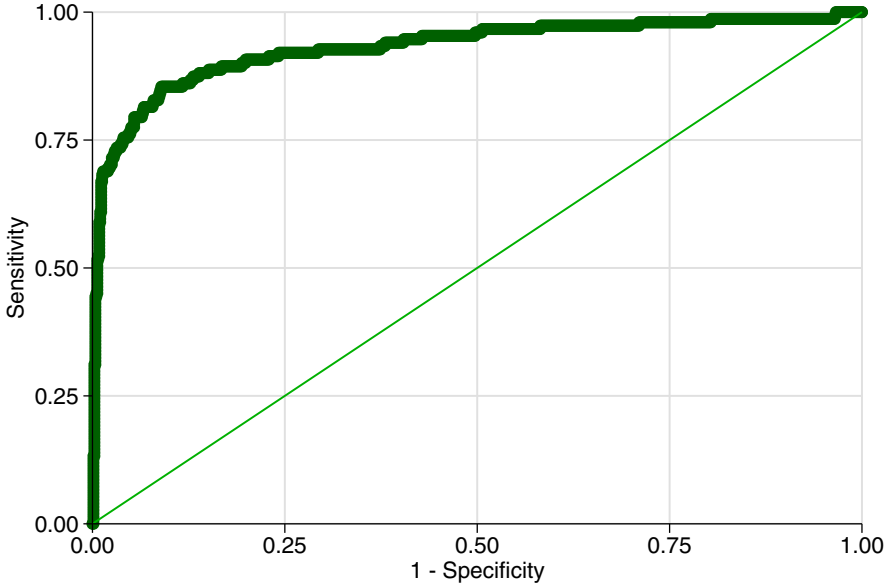
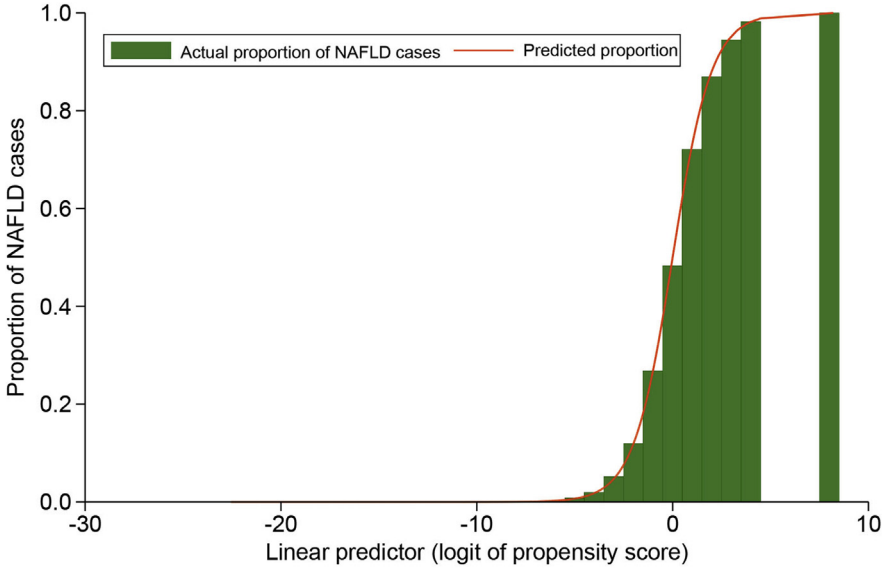


eFigure 1. Discrimination.



eFigure 2. Calibration. NAFLD, nonalcoholic fatty liver disease.