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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Transarterial Chemoembolization of Hepatocellular Carcinoma: Propensity Score Matching Study Comparing Survival and Complications in Patients with Nonalcoholic Steatohepatitis Versus Other Causes Cirrhosis

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Abstract

Purpose To evaluate the oncologic outcomes and complication profile in nonalcoholic steatohepatitis (NASH)-induced cirrhosis leading to hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE).

Materials and Methods Two hundred and twenty patients who underwent treatment of 353 HCCs were retrospectively reviewed, including 30 NASH patients who received TACE for 46 HCCs. Patient charts were evaluated for time to progression (TTP), complications and overall survival (OS). The group was split into NASH and non-NASH cohorts for comparison and additional analyses were done using propensity score matching (PSM).

Results Patients in the NASH cohort presented with significantly larger lesions (4.9 ± 5.8 cm vs 3.1 ± 2.4 cm, $p = 0.05$). There was no significant difference in TTP overall [Median NASH 396 days (95% CI 308–526 days) vs non-NASH cohort 307 days (95% CI 272–364), $p = 0.25$) or after PSM [259 days non-NASH (95% CI 215–490) vs 396 days NASH (95% CI (349–not reached), $p = 0.43$]. There was a non-significant increased OS in the non-NASH [median 1078 days (95% CI 668–1594)] as compared to the NASH cohort [median 706 days (95% CI 314–not reached)] ($p = 0.08$) which decreased following PSM [853 days (95% CI 526–1511) non-NASH vs 706 days (95% CI 314–not reached) NASH, $p = 0.48$]. The number of complications did not differ significantly between the two groups ($p = 0.23$).

Conclusion The oncologic outcomes and complication profile of TACE for HCC induced by NASH cirrhosis appear to be similar to that of other etiologies of cirrhosis. NASH patients presented with larger tumors emphasizing the need for early surveillance.

Keywords Nonalcoholic fatty liver disease · Chemoembolization · Hepatocellular carcinoma

Introduction

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) continue to increase in prevalence with some putting the global incidence at 25% [1, 2]. This has driven an increase in the frequency with which NASH is identified as the underlying cause of cirrhosis in hepatocellular carcinoma (HCC) patients and the number of those awaiting liver transplantation secondary to this etiology of liver dysfunction [3, 4]. Because of the fundamentally different characteristics and underlying mechanism of cirrhosis induction in the NASH demographic, it is not clear whether treatment outcomes are equivalent in this cohort as compared to other etiologies of cirrhosis which induce HCC [5].

Previous authors have evaluated how treatment outcomes differ in patients with NASH in the setting of thermal ablation [5–7], surgical resection [5, 7, 8], and

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transplantation [5, 7, 9]. Many of these investigations have noted significant differences in outcomes in the NASH cohort as compared to other etiologies of cirrhosis leading to HCC [5–9]. While the data have focused on the curative treatments for HCC (thermal ablation, surgical resection, and transplantation), only approximately 25% of patients who present with HCC are eligible for these therapies [10]. When unable to undergo curative therapy, or when needing to be treated while waiting for transplantation, patients frequently undergo intra-arterial therapies. Perhaps the most commonly utilized intra-arterial therapy in this setting is transarterial chemoembolization (TACE).

However, despite the fact that TACE is a very frequent treatment method for HCC and NASH is an increasing cause of HCC [4], little data are available in this area. To date, only cursory mentions of TACE in the NASH population have been published [11–13]. To the authors knowledge, no data comparing complication rates and oncologic outcomes following TACE in patients with NASH-induced HCC as compared to other etiologies of HCC are available. This is a significant knowledge gap given the obesity epidemic, climbing rates of NAFLD/NASH, and increasing prevalence of NASH-induced HCC.

The goal of this single-center retrospective study was to evaluate the oncologic outcomes and complication profile of TACE when performed for HCC in patients with NASH-induced cirrhosis as compared to other etiologies.

Materials and Methods

After Institutional Review Board approval, all patients who underwent TACE for HCC between 1/1/2011 and 31/12/2016 at a single institution were reviewed. In total, 255 consecutive BCLC A or B patients received initial treatment with TACE of 404 HCCs. However, 35 patients who underwent treatment of 51 lesions were excluded because they were lost to follow-up (34 patients) or were under the age of 18 (1 patient). The remaining 220 patients who underwent treatment of 353 HCCs are the subject of this analysis; of the 353 treatments, 71 were performed with drug-eluting beads and 282 were performed with conventional TACE. Conventional TACE was performed utilizing 50 mg of Doxorubicin and 10 mg of mitomycin C mixed with lipiodol (Guerbet, Villepinte, France) at a 1:2 ratio and followed by spherical particle embolization. Drug-eluting bead TACE was performed utilizing up to two vials of beads (LC beads, BTG, London, United Kingdom) each loaded with 75 mg of Doxorubicin. The group included 30 patients who received TACE for 46 NASH-induced cirrhosis leading to HCC. The non-NASH cohort included 115 (60.5%) patients with hepatitis C and 23 (12.1%) with alcohol-induced cirrhosis. The average number of tumors per patient was 1.6 (range 1–6).

The electronic medical records were reviewed for demographic data, preprocedural laboratory values, model for end-stage liver disease (MELD), Child–Pugh, and Easter Cooperative Oncology Group (ECOG) performance status were collected. Tumoral factors were also evaluated including size of lesion, number of TACE treatments required, and alpha-fetoprotein (AFP).

The imaging was independently reviewed by one of the authors (TS) who has over 5 years of experience as a body radiology attending. If discrepancies between the reviewing radiologist and initial interpreting radiologist were found, they were resolved by discussion between the two interpreting body radiologists. Radiologic response was evaluated utilizing the European Association for the Study of the Liver (EASL) criteria [14]. The modality of follow-up imaging was contrast-enhanced magnetic resonance imaging (MRI) for 334 lesions and contrast-enhanced computed tomography (CT) for 19 lesions. Follow-up was performed at 1 and 3 months after TACE and then every 3–6 months until death or transplant. Overall survival (OS) was calculated and considered to be the survival from the date of first TACE until death and was censored for transplantation. Time to progression (TTP) was evaluated and considered to be time from first TACE to progression as defined by EASL criteria. Overall radiologic response (ORR) was considered to be positive if patients had a partial or complete response by EASL criteria. Radiologic response was evaluated after initial TACE as well as after maximal response following multiple TACE treatments when applicable. TACE was performed per the on demand model, and no patients had planned serial TACE procedures.

Complications were reviewed and recorded. Complication grades for non-laboratory events were defined per the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) reporting standards [15], laboratory value escalations at 1 day and 1 month were graded based on the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 [16]. To further determine complication profiles ratio of total bilirubin, AST, ALT, and albumin were calculated at 1 day and 1 month by dividing the values at these postprocedural time points by the pretreatment values. Change in total bilirubin, INR, AST, ALT, and albumin were also evaluated at 1 month by subtracting the pretreatment values from the 1 month posttreatment values.

Statistical Methods

For analyses, patients were divided into the NASH HCC and non-NASH HCC cohorts. As the non-NASH cohort represents a heterogenous group of patients, subanalyses of NASH HCC as compared to hepatitis C and alcohol related

HCC was also performed. Two-sample T Tests and Fisher exact tests were utilized as appropriate. Kaplan–Meier and the clustered competing risks regression model for sub-distribution were utilized for the time to progression [17]. The clustered competing risks model, generated using the "crrSC" package (V1.1) in R, takes into account the dependence from multiple TACE observations per subject, as well as the competing risks due to death. Because the survival probability is only considered on the subject level, overall survival analyses were analyzed using the Kaplan–Meier method and the log-rank test.

The above analyses were completed using a cohorts generated from propensity score matching (PSM). A 2:1 non-NASH:NASH ratio using "nearest neighbor" matching was conducted with the "MatchIt" package (V3.0.2) in R. Lesion size, MELD score, sex, and age were used as matching factors and selection was done without replacement. Propensity score matching becomes more difficult with the addition of more variables; these variables were felt to be the most influential on outcomes. Therefore, these 4 variables were felt to best balance creating an accurate model with not creating so stringent a model that a limited number of matches could be made. The R Version 3.5.1 was used for all analyses and a p value of ≤ 0.05 was considered significant.

Results

The demographic data for the NASH and non-NASH cohorts can be found in Table 1. Of note, there was a significant difference in the percentage of women in each cohort, with the NASH cohort having significantly more women [Women in non-Nash cohort 20% (38/190) vs

Table 1 Demographic data comparing Non-NASH and NASH cohorts

Variable	Non-NASH (N = 190)	NASH (N = 30)	*P value*
Gender			
Female	38 (20%)	16 (53.3%)	< 0.001
Male	152 (80%)	14 (46.7%)	
Age	60.5 ± 7.2 years	66.9 ± 7.9 years	< 0.001
BMI	28 ± 5	32.1 ± 4.9	< 0.001
Comorbities			
Smoking	136 (76%)	17 (63%)	0.15
HTN	103 (57.5%)	18 (66.7%)	0.37
DM	56 (31.3%)	15 (55.6%)	0.01
CHF	4 (2.2%)	1 (3.7%)	0.64
DL	17 (9.5%)	8 (29.6%)	0.003
Pack years of smoking[a]	23.8 (15.3) years	20.9 (17.0) years	0.65
Creatinine	1 ± 0.9 mg/dL	1.1 ± 0.6 mg/dL	0.53
INR	1.2 ± 0.2	1.2 ± 0.2	0.15
Total Bilirubin	1.3 ± 0.7 mg/dL	1.1 ± 0.8 mg/dL	0.06
Albumin	3.3 ± 0.6 g/dL	3.3 ± 0.7	0.68
MELD	10.3 ± 3.1	10.4 ± 3.3	0.87
Child.Pugh	6.4 ± 1.3	6.3 ± 1.1	0.47
Child.Pugh			0.66
A	107 (57.2%)	18 (60.0%)	
B	75 (40.1%)	12 (40.0%)	
C	5 (2.7%)	0 (0%)	
AFP[b]	54.4 (2.6-363,848) ug/L	18.2 (1.5-229,396) ug/L	0.56
ECOG	0.3 ± 0.5	0.4 ± 0.5	0.17
# of TACE Treatments	1.4 ± 0.7	1.6 ± 0.9	0.15
Lesion Size	3.1 ± 2.4 cm	4.9 ± 5.8 cm	0.05

MELD model for end stage, *HTN* hypertension, *DM* diabetes, *DL* dyslipidemia, *INR* international normalization ratio, *AFP* alphafeto protein. *BMI* body mass index, *# number TACE* Transarterial Chemoembolization

[a]Mean of those who had a history of smoking

[b]Median with range presented

46.7% (14/30) in the NASH cohort $p < 0.001$]. The NASH cohort was also older (66.9 ± 7.9 years vs 60.5 ± 7.2 years, $p < 0.001$) than the non-NASH cohort, and had a higher BMI (NASH 32.1 ± 4.9, non-NASH 28 ± 5, $p < 0.001$). As expected, the non-NASH cohort had a lower incidence of diabetes [31.3% (56/179) vs 55.6% (15/27), $p = 0.01$] and dyslipidemia [9.5% (17/179) vs 29.6% (8/27), $p = 0.003$]. Finally, the NASH cohort had larger lesions than the non-NASH cohort (4.9 ± 5.8 cm vs 3.1 ± 2.4 cm, $p = 0.05$). The baseline characteristics for the PSM groups can be found in Table 2, and no significant differences were found, other than BMI (27.9 ± 4.9 non-NASH vs 32.1 ± 4.9 NASH, $p = 0.001$) and diabetes [12 (21.1%) non-NASH vs 15 (55.6%) NASH, $p = 0.002$].

The median TTP for the NASH cohort was 396 days (95% CI 308–526 days), while the TTP of the non-NASH cohort was 307 days (95% CI 272–364 days). The Kaplan–Meier curve can be found in Fig. 1; however, the NASH and non-NASH cohort did not differ significantly in TTP ($p = 0.25$). The data were further analyzed utilizing the clustered competing risks regression model, and again the two groups did not significantly differ ($p = 0.11$). Next, TTP was compared between NASH and hepatitis C (HCV) patients and did not differ significantly by the Kaplan–Meier [NASH 396 days 95% CI (308–526) vs HCV 300 days 95% CI (259–367), $p = 0.44$] or clustered competing risk regression model ($p = 0.16$). Similarly, when compared to alcoholic cirrhosis (EtOH) patients, the NASH TTP did not differ significantly by the Kaplan–Meier [NASH 396 days 95% CI (308–526) vs EtOH 293 days 95% CI (233–631), $p = 0.72$] or clustered competing risk regression model ($p = 0.55$).

The radiologic response, both after initial treatment and maximal response, can be found in Table 3. The two groups did not differ significantly ($p = 0.28$) in their initial response to treatment. When evaluating maximal response, the non-NASH cohort had a complete response rate of 67%, compared to 54% of NASH patients ($p = 0.09$). The ORR did not differ significantly between the two groups after either the initial treatment (non-NASH 80% vs NASH

Table 2 Propensity score analysis

Variable	Non-NASH (N = 60)	NASH (N = 30)	*P* value
Gender			1
Male	28 (46.7%)	14 (46.7%)	
Female	32 (53.3%)	16 (53.3%	
Age	64 ± 8.4 years	66.9 ± 7.9 years	0.11
BMI	27.9 ± 4.9	32.1 ± 4.9	0.001
Comorbities			
Smoking	34 (59.6%)	17 (63%)	0.77
HTN	32 (56.1%)	18 (66.7%)	0.36
DM	12 (21.1%)	15 (55.6%)	0.002
CHF	3 (5.3%)	1 (3.7%)	0.75
DL	8 (14%)	8 (29.6%)	0.09
Pack years of smoking[a]	26.1 (18.5) years	20.9 (17.0) years	0.61
Creatinine	1 ± 1 mg/dL	1.1 ± 0.6 mg/dL	0.90
INR	1.2 ± 0.2	1.2 ± 0.2	0.29
Total bilirubin	1.3 ± 0.8 mg/dL	1.1 ± 0.8 mg/dL	0.11
Albumin	3.3 ± 0.6 g/dL	3.3 ± 0.7 g/dL	0.97
MELD	10.7 ± 3.5	10.4 ± 3.3	0.74
Child.Pugh	6.4 ± 1.3	6.3 ± 1.1	0.71
Child.Pugh			0.73
A	33 (55.0%)	18 (60.0%)	
B	26 (43.3%)	12 (40.0%)	
C	1 (1.7%)	0 (0%)	
AFP	6887.1 ± 48,151.7 ug/L	13,965.7 ± 48,331.2 ug/L	0.24
ECOG	0.3 ± 0.6	0.4 ± 0.5	0.73
# of TACEs	1.4 ± 0.9	1.6 ± 0.8	0.44
Lesion Size	3.9 ± 3.4 cm	5.8 ± 6.7 cm	0.16

MELD model for end stage, *INR* international normalization ratio, *AFP* alphafeto protein. *BMI* body mass index, *# number TACE* transarterial chemoembolization

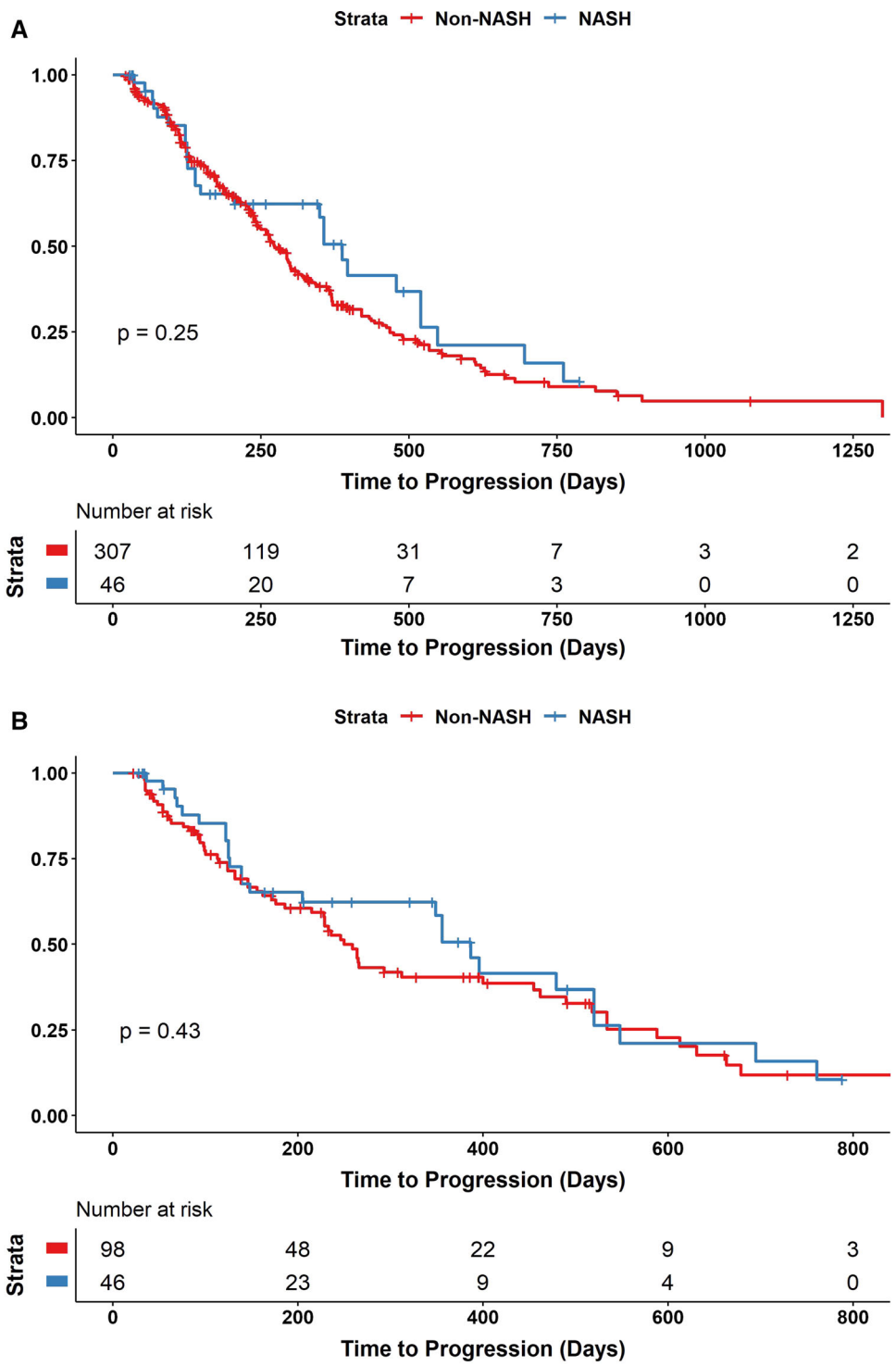

Fig. 1 **A** Kaplan–Meier curve of time to progression in nonalcoholic steatohepatitis (NASH) and non-NASH cohorts. **B** Kaplan–Meier curve of time to progression in nonalcoholic steatohepatitis (NASH) and non-NASH cohorts following propensity score matching

72%, $p = 0.16$) or after maximal response (non-Nash 88% vs NASH 80%, $p = 0.17$). Similarly, the ORR did not differ significantly when NASH was compared to HCV on initial (NASH 72% vs HCV 82%, $p = 0.12$) or maximal response (NASH 80% vs HCV 88%, $p = 0.21$). Nor did NASH differ from EtOH on initial (NASH 72% vs EtOH 78%, $p = 0.49$) or maximal response (NASH 80% vs EtOH 87%, $p = 0.46$).

Sixty-one patients were bridged to transplant and were censored at the time of transplant. The median overall survival for the NASH cohort was 706 days (95% CI 314-not reached days), while the median OS for the non-

Table 3 EASL responses after initial treatment and maximal achieved response by cohort

EASL criteria	Non-NASH	NASH
Initial response		
PD	7 (2%)	1 (2%)
SD	52 (17%)	12 (26%)
PR	75 (24%)	10 (22%)
CR	173 (56%)	23 (50%)
Maximal response		
PD	7 (2%)	1 (2%)
SD	30 (10%)	8 (17%)
PR	65 (21%)	12 (26%)
CR	205 (67%)	25 (54%)

PD progressive disease, *SD* stable disease, *PR* partial response, *CR* complete response, *EASL* European Association for the Study of the Liver, *NASH* nonalcoholic steatohepatitis

NASH cohort was 1078 days (95% CI 668–1594 days). The Kaplan–Meier curve for the NASH and non-NASH cohort can be found in Fig. 2. There was a non-significant increased overall survival in the non-NASH as compared to the NASH cohort ($p = 0.08$). The median OS was then compared between NASH and HCV patients (NASH 706 days 95% CI (314-not reached) vs HCV 1105 days 95% CI (739-not reached), $p = 0.05$) as well as EtOH patients [NASH 706 days 95% CI (314-not reached) vs EtOH 1078 days 95% CI (321–not reached), $p = 0.16$].

The complications in the NASH and non-NASH cohorts can be found in Table 4. The most common complication in the non-NASH cohort was pain requiring analgesics (16/303, 5.2%), while the most common complication of the NASH cohort was new onset ascites (4/46, 8.7%). The groups did not differ significantly in the number of complications which occurred ($p = 0.23$). The change in the INR, AST, ALT, and total bilirubin as well as the ratio of these values at 1 day and 1 month posttreatment can be found in Table 5. There was not a significant difference between the two groups in any of these categories.

A PSM was performed utilizing MELD, tumor size, sex, and age and successfully matched 30 NASH to 60 non-NASH patients. After PSM, there was no significant difference in complications ($p = 0.09$) or change in INR ($p = 0.61$), AST ($p = 0.76$), or ALT ($p = 0.26$) at 1 month (Table 5). The ORR was not significantly different between the two groups either initially [ORR non-NASH 78/98 (79.6%) vs NASH 33/46 (81.7%), $p = 0.30$] or after maximal response [ORR non-NASH 85/98 (86.7%) vs NASH 37/46 (80.4%), $p = 0.33$] after PSM.

PSM did not result in a significant difference in the median TTP for the Non-NASH and NASH cohorts by either the Kaplan–Meier [259 days Non-NASH (95% CI 215–490) vs 396 days NASH (95% CI (349-not reached), $p = 0.43$] (Fig. 1) or clustered competing risks regression model ($p = 0.18$). Similarly, the OS did not differ between the Non-NASH and NASH groups in either the Kaplan–Meier [853 days (95% CI 526–1511) Non-NASH vs 706 days (95% CI 314-not reached) NASH, $p = 0.48$] (Fig. 2). There were not enough patients to PSM NASH to EtOH; however, PSM was performed between NASH and HCV. After PSM, the TTP did not differ between HCV and NASH [HCV 319 days (95% CI (269-468)) vs 396 days NASH (95% CI 349-not reached), $p = 0.58$]. Similarly, after PSM OS did not differ between HCV and NASH [HCV 853 days (95% CI 560–NA) vs 706 days (95% CI 314-not reached) NASH, $p = 0.18$]

Discussion

This study found that while the non-NASH cohort had a longer OS as compared to the NASH cohort (NASH mean OS 396 days (95% CI 308–526) vs non-NASH cohort was 1078 days (95% CI 668–1594) $p = 0.08$), it did not quite achieve significance. The likelihood that there is a significant difference between the two cohorts is underlined by the fact that the 95% confidence intervals do not overlap on the OS analyses. However, when factors such as tumor size were controlled for in the propensity score matched analysis, these differences went away [853 days (95% CI 526–1511) non-NASH vs 706 days (95% CI 314-not reached) NASH, $p = 0.48$]. These findings were mirrored when NASH was compared to HCV with the OS differing initially [NASH 706 days 95% CI (314-not reached) vs HCV 1105 days 95% CI (739-not reached), $p = 0.05$], but not persisting after PSM was performed [HCV 853 days (95% CI 560 - NA) vs 706 days (95% CI 314-not reached) NASH, $p = 0.18$]. This seems to suggest that underlying factors, including tumor size played a large role in the differences between the two groups. The fact that the NASH cohort tumors were significantly larger than the non-NASH cohort at baseline may indicate a lack of identification of NASH patients and therefore a failure to introduce early HCC surveillance programs. However, other possible explanations include effects of factors such as hormones and comorbidities. Comorbidities were fairly well controlled in the PSM analyses, but NASH HCC patients remained heavier and more likely to have diabetes. Weinmann et al. [18] retrospectively reviewed 1119 patients with HCC, 45 of who had NASH-induced HCC. They found patients with HCC had a non-significant decreased overall survival, similar to this study, they postulate lack of screening and comorbidities may explain these differences.

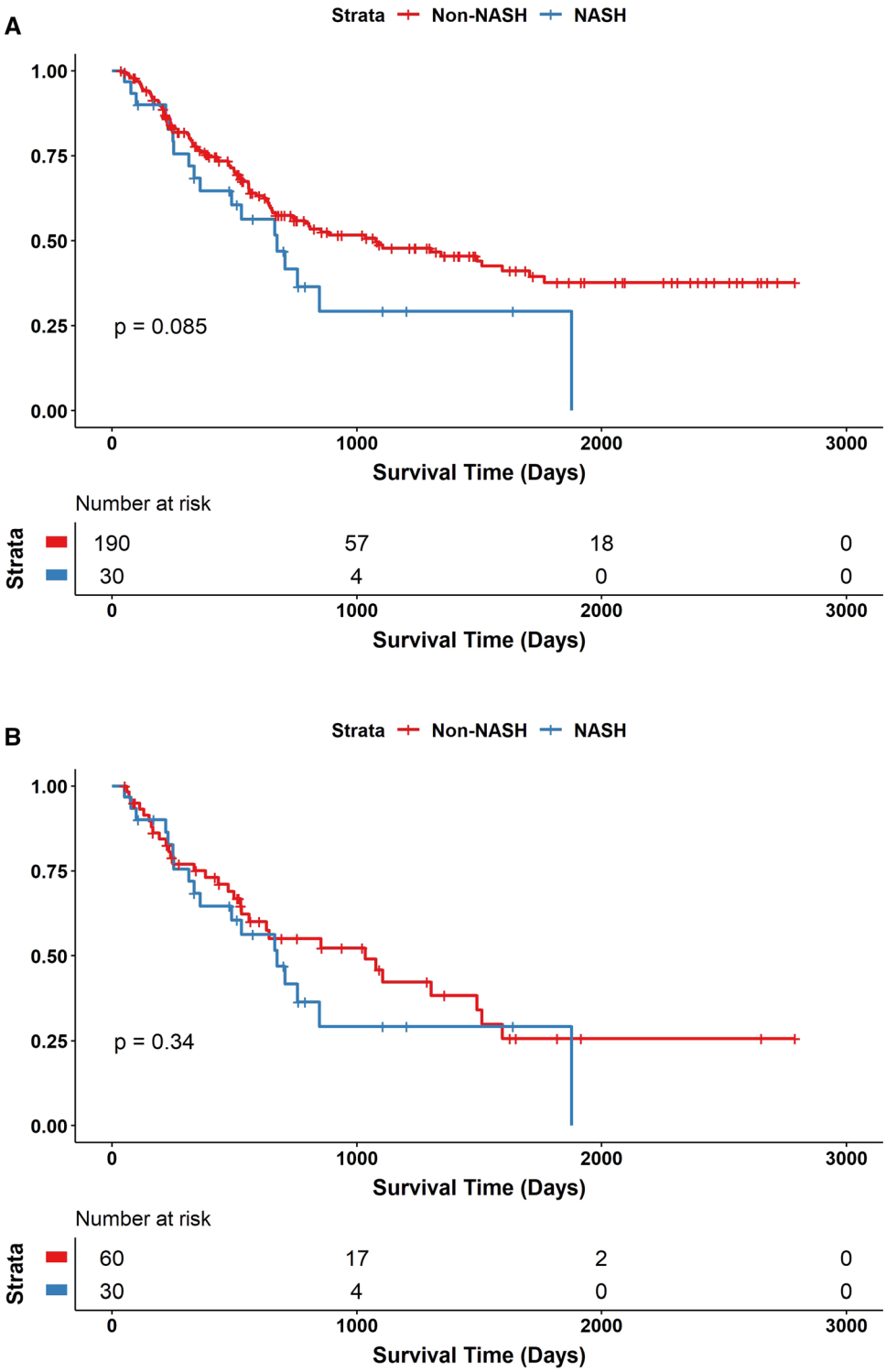

Fig. 2 **A** Kaplan–Meier curve of overall survival in nonalcoholic steatohepatitis (NASH) and non-NASH cohorts. **B** Kaplan–Meier curve of overall survival in nonalcoholic steatohepatitis (NASH) and non-NASH cohorts following propensity score matching

The TTP, which to the authors knowledge has not been previously studied, was not significantly different between the NASH and non-NASH cohorts ($p = 0.25$), and remained statistically equivalent on PSM analysis ($p = 0.43$). Furthermore, TTP did not differ significantly between NASH and EtOH or HCV patients. Similarly, the radiologic response initially ($p = 0.28$) was not significantly different; however, the maximal response appeared to favor the non-NASH cohort with a complete response rate of 67%, compared to 54% in the NASH cohort, but this did not reach significance ($p = 0.09$). This may again reflect the baseline differences between the two cohorts at

Table 4 Complications

Complications	Non-NASH	NASH	*p* value
Non-laboratory-based complications[a]			0.23
None	174 (56.7%)	25 (54.3%)	
Pain requiring analgesics	16 (5.2%)	1 (2.2%)	
Fatigue	33 (10.7%)	4 (8.7%)	
Fatigue and nausea	1 (0.3%)	0 (0%)	
Nausea	3 (1%)	0 (0%)	
Developed new ascites	11 (3.6%)	4 (8.7%)	
Gastritis	1 (0.3%)	0 (0%)	
FATIGUE pain and fever	3 (1%)	0 (0%)	
Cholecystitis	0 (0%)	2 (4.3%)	
Alopecia	5 (1.6%)	0 (0%)	
Pain and fatigue	2 (0.7%)	0 (0%)	
HE	4 (1.3%)	1 (2.2%)	
Jaundice	1 (0.3%)	0 (0%)	
Non-laboratory-based complications by grade[a]			0.17
None	67.9% (129/190)	76.7% (23/30)	
Grade 1	26.3% (50/190)	10% (3/30)	
Grade 2	6.3% (12/190)	10% (3/30)	
Grade 3	0.5% (1/190)	3.3% (1/30)	
Grade 4	0% (0/190)	0% (0/30)	
Grade 5	0% (0/190)	0% (0/30)	
Total bilirubin change at 1 day			0.07
None	97.4% (185/190)	96.7% (29/30)	
Grade 1	2.1% (4/190)	0% (0/30)	
Grade 2	0.5% (1/190)	0% (0/30)	
Grade 3	0% (0/190)	3.3% (1/30)	
Grade 4	0% (0/190)	0% (0/30)	
Total bilirubin change at 1 month[b]			0.90
None	94.7% (180/190)	100% (30/30)	
Grade 1	3.6% (7/190)	0% (0/30)	
Grade 2	1.1% (2/190)	0% (0/30)	
Grade 3	0.5% (1/190)	0% (0/30)	
Grade 4	0.5% (1/190)	0% (0/30)	
AST change at 1 day[b]			
None	57.4% (109/190)	53.3% (16/30)	0.10
Grade 1	14.7% (28/190)	16.7% (5/30)	
Grade 2	12.6% (24/190)	10% (3/30)	
Grade 3	17.4% (33/190)	20% (6/30)	
Grade 4	2.1% (4/190)	6.7% (2/30)	
AST change 1 month			0.90
None	92.1% (175/190)	93.3% (28/30)	
Grade 1	4.7% (9/190)	3.3% (1/30)	
Grade 2	2.1% (4/190)	3.3% (1/30)	
Grade 3	1.1% (2/190)	0% (0/30)	
Grade 4	0% (0/190)	0% (0/30)	
ALT change 1 day[b]			0.84
None	79.5% (151/190)	83.3% (25/30)	
Grade 1	7.9% (15/190)	6.7% (2/30)	

Table 4 continued

Complications	Non-NASH	NASH	*p* value
Grade 2	8.9% (17/190)	10% (3/30)	
Grade 3	5.3% (10/190)	0% (0/30)	
Grade 4	0% (0/190)	0% (0/30)	
ALT change 1 month			0.67
None	97.4% (185/190)	100% (30/30	
Grade 1	2.1% (4/190)	0% (0/30)	
Grade 2	0% (0/190)	0% (0/30)	
Grade 3	0.5% (1/190)	0% (0/30)	
Grade 4	0% (0/190)	0% (0/30)	

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *Alb* albumin

[a]Indicates performed on per treatment basis, all other on a per patient basis

[b]Indicates some patients had more than one complication during multiple treatments of their HCC

presentation. The ORR of both groups did compare favorably to some other studies, including the PRECISION V trail which had a ORR of 43.3% in their cTACE arm [19]. The discrepancy in these findings is unclear; however, the authors do focus on performing very subselective embolizations during their TACE procedures, which has been shown to positively influence outcomes [20]. The ORR is also in line with other studies which have focused on this technical aspect such as Bouvier et al. who found a 78.1% ORR in there selective cTACE cohort [20].

Table 5 Change in laboratory values

Variable	NASH	Non-NASH	*p* value
Entire study population			
Ratio TB at 1 day	1.1 ± 0.4	1.6 ± 3.5	0.34
Ratio AST at 1 day	4 ± 7.6	4.4 ± 5.6	0.23
Ratio ALT at 1 day	2.8 ± 5.2	2 ± 1.8	0.32
Ratio of Alb at 1 day	0.9 ± 0.1	0.9 ± 0.1	0.83
Ratio TB at 1 month	1.7 ± 10.1	1 ± 0.5	0.25
Ratio AST at 1 month	1.1 ± 1.2	1 ± 0.6	0.66
Ratio ALT at 1 month	1.1 ± 1.5	1 ± 0.4	0.71
Ratio of Alb at 1 month	1.0 ± 0.1	1.0 ± 0.2	0.87
Δ INR at 1 month	0.5 ± 7.8	0.1 ± 0.4	0.44
Δ AST at 1 month	− 5.5 ± 87.2	− 13.1 ± 104.9	0.67
Δ ALT at 1 month	− 4.6 ± 62.1	− 8.8 ± 42.9	0.59
Δ TB at 1 month	0.4 ± 5.1	0 ± 0.5	0.22
Δ Alb at 1 month	− 0.1 ± 0.6	− 0.2 ± 0.6	0.45
Propensity matched cohort			
Δ TB (1 day)	1.1 ± 0.4	1.9 ± 4.3	0.35
Δ AST (1 day)	4.4 ± 7.6	5 ± 5.9	0.73
Δ ALT (1 day)	2.8 ± 3.3	2.1 ± 1.8	0.20
Δ TB (1 month)	2.7 ± 1.3	1 ± 0.4	0.27
Δ AST (1 month)	1.2 ± 1.7	1 ± 0.6	0.47
Δ ALT (1 month)	1.2 ± 2.3	1 ± 0.3	0.41

Δ = Change, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TB* total bilirubin, *Alb* albumin. All ratios calculated by dividing the postprocedural time point value by the preprocedural value

Patients with cirrhosis are known to have hypertrophy of the peribiliary plexus, which can act as a portoarterial shunt and at least theoretically protect against negative ischemic effects from arterial embolization [21, 22]. This raises the question of whether more ischemic related complications would be present in the NASH cohort which was evaluated in two ways, through complication rates and changes in hepatic enzymes. Neither enzymatic change, which have been shown to be correlates to ischemic injuries [21], nor complication rates differed significantly between the NASH and non-NASH cohorts. These findings may in part be explained by the emphasis placed on subselective catheter positioning prior to embolization at the study center. Conversely, the findings may simply indicate that the background liver histologic differences do not factor into the complication rate significantly.

This study has a number of limitations, including its retrospective design. The number of NASH HCC patients is also limited, despite being one of the larger published cohorts to date, and this weakness is compounded by the fact that not all data points were available for every patient. Furthermore, two different techniques of TACE were utilized, drug-eluting bead and conventional, which may have differences in outcomes. Finally, the study was performed at a high volume tertiary/quaternary referral center and therefore the findings may not be translatable to all settings. This setting also means that some follow-up may be missed due to presentation at local facilities.

In conclusion, NASH-induced cirrhosis leading to HCC appears to have equivalent outcomes in terms of time to

progression, radiologic response, and complication profile, to other underlying causes of cirrhosis which result in HCC following TACE. Patients treated with TACE for HCC secondary to NASH-induced cirrhosis may have larger tumors emphasizing the need for early identification and surveillance in this emerging disease process.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed Consent This study has obtained IRB approval from the University of Minnesota and the need for informed consent was waive.

Consent for Publication For this type of study, consent for publication is not required.

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