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Metabolic factors affecting hepatocellular carcinoma in steatohepatitis

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Abstract

Background & Aims: With the rising prevalence of alcoholism, obesity and metabolic syndrome, steatohepatitis will become the leading cause of end-stage liver disease and hepatocellular carcinoma in the United States by 2025. Patients with non-alcoholic steatohepatitis and alcoholic liver disease have similar clinical and histopathological presentations, whether these similarities persist in non-alcoholic steatohepatitis and alcoholic liver disease patients with hepatocellular carcinoma remains unknown.

Methods: A retrospective analysis of the clinical features of adult patients from a large transplant center who underwent liver transplantation for steatohepatitis due to non-alcoholic steatohepatitis and alcoholic causes (alcoholic liver disease) between 1/1/02 and 1/1/12 was performed. Clinical features, explant histopathology, and clinical outcomes were compared.

Results: Hepatocellular carcinoma was present in 80 of 317 patients, who underwent liver transplantation for steatohepatitis with equivalent distribution in non-alcoholic steatohepatitis and alcoholic liver disease patients (24% vs 26%; $P=0.8$). On multivariate analysis, significant predictors of hepatocellular carcinoma included age, ethnicity (Hispanic), and diabetes, but not BMI, hypertension or smoking. A lower risk of hepatocellular carcinoma was associated with a clinical history of hyperlipidemia. Clinical parameters were similar between patients with alcoholic liver disease-hepatocellular carcinoma and non-alcoholic steatohepatitis-hepatocellular carcinoma, except sex and presence of metabolic syndrome. non-alcoholic steatohepatitis-hepatocellular carcinoma livers retained histopathological features of non-alcoholic steatohepatitis such as ballooning and Mallory bodies, while alcoholic liver disease-hepatocellular carcinoma

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

CONFLICT OF INTEREST

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livers did not. There were no significant differences in hepatocellular carcinoma recurrence rates or post-transplant overall survival.

Conclusions: We report the largest single-center study evaluating clinical, histopathological and outcome measures of patients undergoing liver transplantation for steatohepatitis. Older patients, diabetics, and Hispanics may warrant more frequent cancer screening due to increased risk of hepatocellular carcinoma.

Keywords

alcoholic liver disease; fatty liver disease; liver cancer; liver transplantation

1 | INTRODUCTION

The global increase in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome have been accompanied by an increase in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) related cirrhosis.¹ Indeed NASH has over-taken alcoholic liver disease (ALD) as the second most common aetiology of liver disease among patients on the liver transplant waitlist and appears on pace to become the most common aetiology soon.^{2,3} This is despite the fact that ALD is itself increasing in prevalence.²

While the prevailing theory is that hepatocarcinogenesis is potentiated by cycles of hepatocellular death and regeneration in cirrhosis, there is also increasing evidence that steatosis, T2DM, and metabolic syndrome also directly promote carcinogenesis.^{4,5} Both T2DM and obesity have been established as independent risk factors for the development of a number of cancers, including HCC.^{6,7} What is not clear, however, is whether the aetiology of the fatty liver disease (NAFLD or ALD) can independently affect the pathology of HCC and its outcomes. It should be noted that histological features of NASH are difficult to distinguish from those of ALD.^{8–10} The distinction between the two is usually based on patient history and clinical presentation, especially the inherently unreliable history of alcohol consumption. Even the definition of significant alcohol consumption has not been agreed upon; it ranges from 30 to 60 g per day.¹¹ Given this overlap, we performed a detailed analysis of the clinical and histopathologic features of patients with both alcoholic and non-alcoholic steatohepatitis to identify variables that predispose these patients to HCC.

2 | METHODS

2.1 | Patient selection

We performed a retrospective analysis of adult patients who under-went liver transplantation (LT) for steatohepatitis due to non-alcoholic (NASH) and alcoholic causes (ALD) at a large urban transplant center between 1/1/02 and 1/1/12. As previously described,¹² rigorous clinical and laboratory evaluations were undertaken to identify patients meeting diagnostic criteria for NASH or ALD and to exclude other aetiologies of liver disease. Diagnoses were based both on histopathologic criteria (hepatic steatosis, hepatocyte injury, lobular inflammation, and/or pericellular fibrosis) and clinical history. Morbidly obese patients were not routinely excluded. Center policy dictates that all patients abstain from alcohol before and after liver transplantation. This study was approved by the UCLA Institutional Review

Board. Informed consent was not required. Patient clinical features, liver explant pathology and outcomes were compared.

2.2 | Clinical variables

Variables collected for analysis included donor and recipient age and sex, recipient ethnicity, Model for End-Stage Liver Disease (MELD) score at time of transplantation, BMI, clinical diagnosis of T2DM, hypertension, and hyperlipidemia, history of smoking, medications at time of transplant, hospitalization status, creatinine, bilirubin, international normalized ratio, and need for preoperative mechanical ventilation, vasopressors, and haemodialysis. Outcome measures included 90-day, 1-year, and 5-year patient survival, overall graft and patient survival, and retransplantation. The explant pathology of HCC patients was re-reviewed in a blinded fashion by a single expert liver pathologist (BN).

2.3 | Statistical analyses

Descriptive statistics were reported for the cohorts. Categorical variables were summarized as numbers and percentages. Continuous variables were summarized as means $\pm$ standard deviations. Comparisons between groups were performed using Chi-square or Fisher's Exact test for categorical variables and Kruskal-Wallis or Student *t*-test for continuous variables. All continuous variables were dichotomized at a single cut-off point using receiver-operating characteristic analysis to maximize both sensitivity and specificity. Correlation between the dichotomized variables and outcomes were fitted in a logistic regression model.

Patient survival rates were estimated using Kaplan-Meier method. Multivariable analysis with backward logistic regression was performed to identify recipient factors that would contribute to the presence of HCC in the explant. The alpha-level for inclusion of risk factors in the multivariable regression analysis was set at $P < 0.2$. Only variables with known values in $>60\%$ of subjects were used. All analyses were performed using JMP Pro 13.1 (SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

3.1 | Study population and characteristics associated with HCC in liver explant

During the study period 317 patients underwent primary LT for NASH ($n = 135$) or ALD ($n = 182$) associated steatohepatitis. HCC was present in 80 of the 317 explants. To investigate, if specific clinical characteristics were associated with HCC in the explant, we evaluated patient demographic data and prevalence of metabolic risk factors. Differences between patients who underwent LT for steatohepatitis with and without HCC are presented in Tables 1, 2. Of the 80 patients with HCC, 33 (41.2%) were diagnosed with NASH and 47 (58.8%) were diagnosed with ALD. Patients with HCC were significantly older (mean age 61.3 ± 6.5 years vs 54.6 ± 9.4 years; $P < 0.0001$). While the majority of all patients undergoing LT for steatohepatitis were male, HCC patients tended to have an even higher male preponderance; that difference, however, did not reach statistical significance (73.8% vs 63.7%; $P = 0.13$). Evaluation of patient race/ethnicity showed that Hispanic patients were overrepresented in the HCC group (58.8% of HCC patients vs 37.6% of non-HCC patients) in comparison to non-Hispanic blacks (1.3% HCC vs 2.5% non-HCC), non-Hispanic whites (31.3% HCC vs

51.9% non-HCC), and other races (8.8% HCC vs 8% non-HCC). Of all Hispanic patients transplanted with steatohepatitis, 34.6% had HCC, compared to 14.3% of black patients, 16.9% of white patients, and 26.9% of patients of other races/ethnicities.

Risk factors associated with metabolic syndrome, such as BMI > 35 kg/m² and hypertension, were not different between the HCC and non-HCC groups. However, a clinical history of hyperlipidemia was more common in patients without HCC compared to patients with HCC (15.6% vs 6.3%; $P = 0.04$). Evaluation of lipid laboratory values at time of transplantation found differences between HCC and non-HCC groups in mean values of high-density lipoprotein (HDL) and total cholesterol, but not in triglycerides and low-density lipoprotein (LDL) (Tables 1, 2). In contrast to the clinical hyperlipidemia finding, patients with HCC were more likely to have HDL > 23 mg/dL and total cholesterol > 111 mg/dL (Table 2). Finally, patients with HCC were more likely to have T2DM compared to those without HCC (56.3% vs 37.1%; $P = 0.004$). This was accompanied by higher HbA1c levels in HCC patients ($5.7\% \pm 1.7\%$ vs $5.2\% \pm 0.9\%$; $P = 0.02$).

Multivariate analysis of these clinical characteristics found age ≥ 60 , total serum cholesterol level > 111 mg/dL, Hispanic ethnicity, male sex, and T2DM to be risk factors for the presence of HCC. Conversely, having a clinical history of hyperlipidemia was statistically associated with lower risk of HCC in the explant (Table 3). An examination of the medical record for each patient's medication history at the time of transplantation was undertaken, looking specifically for anti-diabetic, lipid-lowering, steroid, or antiplatelet drugs. No correlation was found between any of the medications and the presence of HCC in the explant.

3.2 | ALD-HCC vs NASH-HCC clinical characteristics

To investigate whether HCC risk factors vary depending on steatohepatitis etiologies, we compared clinical characteristics of NASH-HCC and ALD-HCC patients undergoing LT (Tables 4, S1). Mean age at LT of the 33 NASH-HCC and 47 ALD-HCC patients were 62 and 61 years, respectively. ALD-HCC patients were more likely to be male (96% vs 42%; $P < 0.0001$). The incidence of HCC according to race/ethnicity was similar between NASH-HCC and ALD-HCC groups with the majority of patients in both groups being Hispanic (55% and 62%). Metabolic syndrome was more common in NASH-HCC patients than in ALD-HCC patients (70% vs 38%; $P = 0.01$). There was a trend towards increased prevalence of hypertension and BMI > 35 in the NASH-HCC group, and smoking in the ALD-HCC group. The NASH-HCC group had a higher prevalence of a clinical diagnosis of T2DM (70% vs 47%; $P = 0.07$) but there was no statistical difference between groups in HbA1c (5.8 vs 5.7; $P = 0.86$), at the time of LT. The average physiologic MELD scores at the time of LT were similar between ALD-HCC and NASH-HCC groups (23.3 vs 25.7; $P = 0.43$). Accordingly, serum markers of hepatic function (INR and bilirubin), and kidney function (creatinine and haemodialysis requirement) were not statistically different.

Including the aetiology of liver disease in the multivariate analysis did not reveal it to be significant. Limiting the analysis to either only ALD patients or NASH patients limited the power of the analysis and decreased the number of significant variables: sex, age, Hispanic

ethnicity, and total cholesterol in ALD; age and total cholesterol in NASH; it did not add any other factors as significant (Tables S2, S3).

3.3 | Histopathology of cirrhotic liver explants and tumours from NASH-HCC and ALD-HCC

3.3.1 | Histological comparison of cirrhotic liver explants—Histological features of liver explants from NASH-HCC and ALD-HCC patients are described in Table 5. The majority of NASH-HCC livers, while cirrhotic, still retained histopathological features of NASH including: steatosis, steatohepatitis, ballooning, Mallory bodies, and pericellular fibrosis. Furthermore, these histopathological characteristics were significantly more prevalent in NASH-HCC vs ALD-HCC. Percentages of NASH-HCC vs ALD-HCC liver explants with these characteristics are as follows: mild-severe steatosis (93% vs 65%; $P = 0.0047$), steatohepatitis (96% vs 49%; $P < 0.0001$), ballooning (100% vs 62.5%; $P < 0.0001$), Mallory bodies (91% vs 50%; $P = 0.0003$), and moderate-severe pericellular fibrosis (47% vs 22%; $P = 0.002$). No differences were observed in the degree of inflammation and grades of fibrosis. Moderate to severe iron deposition was more common in ALD-HCC than NASH-HCC livers (56% vs 31%; $P = 0.03$).

3.3.2 | Histological comparison of tumours—To be eligible for LT, patients had to have tumours within Milan criteria. As a result, we expected tumour number and size to be similar between the two groups. Consistent with this prediction, analysis of NASH and ALD liver explants harbouring HCC found no statistical differences between the number of tumours (2.6 vs 2.7; $P = 0.73$), total tumour diameter (3.91 cm vs 4.07 cm; $P = 1$), largest tumour diameter (2.95 cm vs 2.93 cm; $P = 0.74$), and multifocality (39% vs 47%; $P = 1$) (Table 6). There were no differences in histological features associated with tumour aggressiveness. The majority of tumours in the NASH group (73%) and in the ALD group (75%) were classified as moderately differentiated. Only 22% of NASH-HCC tumours and 32% of ALD-HCC tumours had lymphovascular invasion. While NASH explants had a significantly higher percentage of steatosis, we found no statistical difference in prevalence and degree of steatosis in the HCCs from NASH and ALD patients.

3.4 | Clinical outcomes of NASH-HCC and ALD-HCC patients undergoing LT

There was no statistically significant difference in 90-day survival of NASH-HCC patients compared to ALD-HCC patients (85% vs 96%). The long-term survival was almost identical. Sixty-two per cent of NASH-HCC and 64% of ALD-HCC patients were alive after 5 years ($P = 0.36$). The recurrence-free survival of both groups post-LT were also similar (ALD-HCC 48% vs NASH-HCC 50%, $P = 0.49$) (Figure S1).

4 | DISCUSSION

Steatohepatitis variants ALD and NASH have similar clinical characteristics and histopathological features. In fact, the most significant feature distinguishing them is the quantity of alcohol consumption, an unreliable and not yet standardized factor. Studies comparing NASH and ALD are small and do not evaluate characteristics of patients with end-stage liver disease (ESLD) and HCC. Hence, it is unclear if ALD and NASH patients

with ESLD and HCC retain overlapping clinical and histopathological features. Identifying similarities and differences between ALD-HCC and NASH-HCC patients may provide insight into risk factors driving HCC in patients with steatohepatitis.

The majority of clinical parameters were similar between ALD-HCC and NASH-HCC patients undergoing LT. Patients had similar ethnicity, age, BMI, and laboratory values. Only two clinical parameters separated the steatohepatitis variants: sex and metabolic syndrome. The ALD-HCC group was 96% male vs 42% in the NASH-HCC group. This finding is possibly due to the fact ALD is predominately diagnosed in men.^{13–16} It is also possible that sex-specific factors, such as hormones, play a role in the high incidence of HCC in men with ALD.¹⁷

Metabolic syndrome was diagnosed in 70% of NASH-HCC patients compared to 38% of ALD-HCC patients, likely because metabolic syndrome contributes to the pathogenesis of NASH.¹⁸ In contrast to metabolic syndrome, the prevalence of individual metabolic syndrome risk factors, such as T2DM, hypertension, and BMI > 35, were not significantly different between ALD and NASH groups. In fact, the high percentage of ALD-HCC patients having these risk factors is note-worthy. We found 38% of ALD-HCC patients had BMI > 35, 43% had HTN, and 47% had T2DM. Another study evaluated the same factors in ALD patients without HCC undergoing LT and found only 16% had HTN, and only 11% had T2DM.^{14,15} In our cohort, the rates of HTN and T2DM in non-HCC patients are approximately double those. It is possible that metabolic syndrome risk factors are associated with increased risk of HCC in ALD patients, or alternatively that there is an overlap of NASH and ALD in a large fraction of patients.

The histology of NASH livers are difficult to distinguish from ALD.⁸ Though not blinded to clinical diagnosis, we did observe differences in histopathological features of liver explants removed from NASH-HCC and ALD-HCC patients. Liver explants from NASH-HCC patients were more likely to have moderate to severe steatosis, steatohepatitis, ballooning, Mallory bodies, and pericellular fibrosis compared to ALD-HCC. Hemosiderosis, while not statistically significant, was more common in ALD-HCC explants. Hence, it is possible that histological differences between ALD and NASH livers are more pronounced in the setting of cirrhosis. Similarly, previous comparisons of ALD-HCC and NASH-HCC livers of which ~90% were cirrhotic found statistically significant differences in the degree of steatosis, Mallory bodies, and hemosiderosis.¹⁶

While we observed differences in cirrhotic liver explants, gross pathology and histology of HCC tumours from NASH and ALD patients were similar. There were no differences in indicators of tumour aggressiveness (differentiation and lymphovascular invasion). In both groups, ~50% of tumours had moderate to severe steatosis, and Mallory bodies were detected in ~70% of tumours. These histopathological features are similar to the recently described HCC histological subtype termed steatohepatitic hepatocellular carcinoma (SH-HCC).¹⁹ The authors found SH-HCC in ~35% of patients with steatohepatitis associated HCC. They also reported no correlation between the amount of steatosis in the non-neoplastic liver and in SH-HCC tumours.¹⁹ This may explain our surprising finding that moderate to severe steatosis was much more prevalent in ALD-HCC tumours compared to

the ALD liver explants (53% vs 11%). Other questions raised by our findings include why NASH livers fail with features of steatohepatitis, while ALD livers seem to burn out the fat component. Whether this is due to the requirement that ALD patients abstain from alcohol before LT, whereas NASH patients continue to have metabolic disease, or other biological differences remains to be answered.

Overall, our study suggests that ALD and NASH patients with ESLD and HCC have more similarities than differences in histopathological and clinical features. These data support the idea that biological mechanisms and risk factors contributing to hepatocarcinogenesis in these two steatohepatitis variants are similar. In particular we found that age, Hispanic ethnicity, T2DM, and not being diagnosed with hyperlipidemia were associated with presence of HCC.^{13,20,21} While the precise age may vary, increased screening for HCC in patients with NASH and ALD starting at 60 years of age may be warranted.

Multiple epidemiological studies have shown that in the United States NAFLD is most prevalent in patients of Hispanic ethnicity.^{9,22} Likewise, Hispanics have increased susceptibility to ALD and metabolic risk factors such as T2DM.^{23,24} In addition, Hispanic ethnicity is also an independent risk factor for HCC. Genetic factors likely contribute to this increased risk. For example, Hispanics are the most prevalent carriers of the rs738409 single nucleotide polymorphism (SNP) in the gene encoding patatin-like phospholipase A3 (PNPLA3).²⁵ The PNPLA3 SNP has been shown to be an independent risk factor of NAFLD, ALD, and more recently, HCC.²⁶ We did not evaluate the PNPLA3 variant in our study, but this SNP may be a useful tool to identify at risk patients. Hispanic ethnicity has also been found to be a strong risk factor for rapid HCC progression.²⁷

Numerous studies have also found T2DM to be a risk factor for HCC regardless of liver disease aetiology.^{28–31} While the role of T2DM in hepatocarcinogenesis is still unclear, evidence suggest that T2DM may contribute to HCC risk by promoting fibrosis.^{28,30} Insulin resistance increases ROS production and free fatty acid accumulation in the liver and upregulates pro-inflammatory mediators thus inducing hepatocyte injury and stellate cell activation.^{32,33} T2DM only appears to be associated with HCC in patients with cirrhosis. A recent study of HCC in patients with NASH without cirrhosis found no association with HCC and T2DM.³⁴ Since fibrosis is an established risk factor for HCC, multiple groups have proposed that treatment of T2DM with metformin, peroxisome proliferator-activated receptor γ inhibitors, or sulfonylureas may decrease the risk of HCC.^{35–37} We found no association between use of anti-diabetic agents and HCC. This could be explained by the fact that all our patients already had cirrhosis, and this population likely did not, or would not, respond to the potential anti-fibrotic effects of anti-diabetic agents. It is also possible that the medication history of these patients was inadequate and incomplete, thus making such a finding difficult.

We also found that hyperlipidemia was previously diagnosed more in patients without HCC than those with HCC. Hashimoto et al have described a low prevalence of hyperlipidemia in NASH-HCC (25%) and ALD-HCC (10%) patients but they did not compare patients without HCC.¹⁶ Paradoxically, while a diagnosis of hyperlipidemia was anti-correlated with HCC, patients with HCC had elevated total cholesterol levels. It can be hypothesized that

diagnosis of hypercholesterolemia led to its treatment and thus to subsequent lowering of lipids. Our review of medication records failed to reveal a correlation between HCC and lipid lower agents. The clinical data were not complete enough to make an accurate determination.

Due to the association of NASH and metabolic syndrome, patients with NASH are more likely to have hyperlipidemia.²¹ Previous studies have not associated hyperlipidemia with HCC.^{20,21} About 10% of patients with HBV-and HCV-associated HCC have hypercholesterolemia, but the lipid abnormality is considered a paraneoplastic syndrome and not involved in carcinogenesis.³⁸ Case-controlled and observational studies have reported that statins lower the risk and recurrence of HCC.^{39,40} Other lipid-lowering agents have not been reported to lower risk of HCC.⁴¹ Biological studies indicate that statins may in fact directly target HCC cells by inhibiting post-translational modifications of oncogenic G-proteins.⁴¹

There are several limitations in our study. Since all patients had cirrhosis and were undergoing LT, our findings are not necessarily generalizable. In particular, 20%–40% of NASH patients who develop HCC do not have cirrhosis and may have different risk factors for developing HCC than patients with cirrhosis.⁴² Also, we only evaluated patients with tumours within Milan criteria. Therefore, it is possible that our findings are not applicable to patients with more extensive HCC. BMI was used to quantitate obesity and was not corrected for ascites. This may explain why obesity was not a risk factor for HCC in our study. Due to lack of detailed clinical histories, we could not to determine if chronic T2DM was more strongly correlated with HCC than new onset T2DM. Also, while we found an association between hyperlipidemia and HCC, lipid values were collected close to or at the time of LT. These values only reflect one time point and cannot describe the lipid homeostasis at the early stages of HCC development. Additionally we were unable to obtain lipid panel chemistries for approximately a quarter of the patients, since our routine evaluation of liver transplant candidates does not include lipid profiles.

5 | CONCLUSION

We report the largest study evaluating clinical, histopathological, and outcome measures of patients undergoing LT for NASH and ALD-associated HCCs. Our study is consistent with the prevailing notion that NASH and ALD are similar diseases, and we show that in the setting of ESLD and HCC, the majority of clinical and histopathological features of these groups are similar. We also found that metabolic factors including T2DM and hyperlipidemia appear to play roles in promoting hepatocarcinogenesis in the background of steatosis. Specific demographic groups (Hispanics, males, and older patients) also seem to be at an elevated risk of developing NASH-or ALD-associated HCC. Further studies include evaluating screening measures for HCC in these high-risk groups and investigating, how metabolic factors contribute mechanistically to HCC development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ALD	alcoholic liver disease
BMI	body mass index
HCC	hepatocellular carcinoma
HDL	high-density lipoprotein
HgbA1c	haemoglobin A1c
LDL	low-density lipoprotein
LT	liver transplantation
NASH	non-alcoholic steatohepatitis
TG	triglyceride

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Key points

- We report the largest single-center study evaluating clinical, histopathological, and outcome measures of patients undergoing liver transplantation for steatohepatitis.
- On multivariate analysis, significant predictors of hepatocellular carcinoma included age, ethnicity (Hispanic), and diabetes, but not BMI, hypertension, or smoking.
- A lower risk of hepatocellular carcinoma was associated with a clinical diagnosis of hyperlipidemia.
- While there were histopathological differences in the background liver between NASH-HCC and ALD-HCC, no differences were found in tumor histopathology.

Clinical features of patients undergoing OLT with non-alcoholic steatohepatitis (NASH) compared with alcoholic liver disease (ALD) (with or without hepatocellular carcinoma [HCC])

TABLE 1

Clinical feature	NASH/HCC (n = 33)	NASH/No HCC (n = 102)	P value	ALD/HCC (n = 47)	ALD/No HCC (n = 135)	P value
Male	14 (42%)	48 (47%)	0.69	45 (96%)	103 (76%)	0.002
Race/ethnicity						
Black	0 (0%)	6 (6%)	0.13	1 (2%)	0 (0%)	0.0005
Hispanic	18 (55%)	40 (39%)		30 (64%)	49 (36%)	
White	13 (39%)	44 (43%)		12 (26%)	79 (59%)	
Other	2 (6%)	12 (12%)		4 (9%)	7 (5%)	
BMI > 35 kg/m ²	8 (24%)	35 (35%)	0.29	5 (11%)	23 (17%)	0.35
T2DM diagnosis	23 (70%)	52 (51%)	0.07	22 (47%)	36 (27%)	0.02
Hypertension diagnosis	21 (64%)	48 (47%)	0.11	20 (43%)	47 (35%)	0.38
Hyperlipidemia diagnosis	3 (9%)	20 (20%)	0.19	2 (4%)	17 (13%)	0.16
Smoking history	11 (33%)	38 (37%)	0.84	24 (51%)	72 (53%)	0.87
Metabolic syndrome	23 (70%)	58 (57%)	0.22	18 (38%)	40 (30%)	0.28
Hemodialysis	12 (38%)	42 (48%)	0.41	6 (17.1%)	64 (56%)	<0.0001
Age (years)	62 ± 7.3	56 ± 10.1	0.003	61 ± 5.9	54 ± 8.7	<0.0001
MELD -physiologic	25.7 ± 11.5	32.0 ± 8.4	0.10	23.3 ± 11.7	31.8 ± 8.7	<0.0001
BMI (kg/m ²)	30.9 ± 5.8	32.5 ± 6.8	0.25	28.9 ± 5.4	28.4 ± 5.9	0.61
Serum total bilirubin (mg/dL)	12.5 ± 16.6	19.8 ± 15.4	0.03	12.0 ± 14.0	19.9 ± 16.0	0.01
INR	1.65 ± 0.53	2.1 ± 0.81	0.01	1.67 ± 0.58	1.9 ± 0.53	0.08
Serum creatinine (mg/dL)	2.40 ± 1.45	2.72 ± 1.4	0.12	1.80 ± 1.4	2.98 ± 1.36	0.05
HgbA1c (%)	5.79 ± 0.95	5.18 ± 0.77	0.01	5.70 ± 2.1	5.20 ± 0.92	0.16

Bold indicates *P*value < .05

TABLE 2
Clinical features associated with hepatocellular carcinoma (HCC) in patients undergoing OLT for steatohepatitis

Clinical feature	No HCC	HCC	P value
Age 60 y	79/237(33.3%)	51/80(63.8%)	<0.0001
Male	151/237 (63.7%)	59/80(73.8%)	0.13
Etiology of steatohepatitis			
NASH	102/237 (43.0%)	33/80(41.2%)	0.80
ALD	135/237 (57.0%)	47/80(58.8%)	
Race/ethnicity			
Black	6/237(2.5%)	1/80(1.3%)	0.005
Hispanic	89/237(37.6%)	48/80(58.8%)	
White	123/237 (51.9%)	25/80(31.3%)	
Other	19/237(8.0%)	6/80(8.8%)	
BMI > 35 kg/m ²	58/233(24.9%)	13/79(16.5%)	0.16
Weight > 105 kg	43/232(18.5%)	7/79(8.9%)	0.051
Height > 173 cm	92/232(39.7%)	19/79(24.1%)	0.01
Hypertension diagnosis	95/237(40.1%)	41/80(51.3%)	0.09
Hyperlipidemia diagnosis	37/237(15.6%)	5/80(6.3%)	0.04
Total cholesterol > 111 mg/dL	118/225 (52.4%)	57/78(73.1%)	0.001
HDL > 23 mg/dL	50/114(43.9%)	29/44(65.9%)	0.02
T2DM diagnosis	88/237(37.1%)	45/80(56.3%)	0.004
HgbA1c > 5.9%	14/125(11.2%)	11/42(26.2%)	0.02
Smoking history	110/237 (46.4%)	35/80(43.8%)	0.70

Bold indicates *P* value < .05

ALD, alcoholic liver disease; BMI, body mass index; HDL, high-density lipoprotein; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; HgbA1c, hemoglobin A1c

TABLE 3

Predictors of presence of hepatocellular carcinoma (HCC) in patients undergoing OLT for steatohepatitis

Clinical feature	OR (95% CI)	P value
Age ≥ 60 y	3.87 (2.16–7.09)	<0.0001
Total cholesterol > 111 mg/dL	2.41 (1.32–4.54)	0.0041
Hispanic	2.34 (1.32–4.20)	0.0035
Male	1.91 (1.01–3.73)	0.045
T2DM diagnosis	1.83 (1.02–3.29)	0.041
Hyperlipidemia diagnosis	0.35 (0.11–0.94)	0.036

TABLE 4

Clinical features of patients undergoing OLT with non-alcoholic steatohepatitis (NASH)-hepatocellular carcinoma (HCC) compared with alcoholic liver disease (ALD)-HCC

Clinical feature	NASH-HCC	ALD-HCC	<i>P</i> value
Male	14/33 (42%)	45/47 (96%)	<0.0001
Incidental	12/33 (36%)	17/47 (36%)	1.0
Race/ethnicity			
Black	0/33 (0%)	1/47 (2%)	0.51
Hispanic	18/33 (55%)	30/47 (64%)	
White	13/33 (39%)	12/47 (26%)	
Other	2/33 (6%)	4/47 (9%)	
BMI > 35 kg/m ²	8/33 (24%)	5/46 (11%)	0.13
T2DM diagnosis	23/33 (70%)	22/47 (47%)	0.07
Hypertension	21/33 (64%)	20/47 (43%)	0.07
diagnosis			
Hyperlipidemia	3/33 (9%)	2/47 (4%)	0.64
diagnosis			
Smoking history	11/33 (33%)	24/47 (51%)	0.17
Metabolic syndrome	23/33 (70%)	18/47 (38%)	0.01
diagnosis			
Hemodialysis	12/32 (37.5%)	6/35 (17.1%)	0.10
Age (years)	62 ± 7.3	61 ± 5.9	0.54
MELD – physiologic	25.7 ± 11.5	23.3 ± 11.7	0.43
BMI (kg/m ²)	30.9 ± 5.8	28.9 ± 5.4	0.12
Serum total bilirubin	12.5 ± 16.6	12.0 ± 14.0	0.9
(mg/dL)			
INR	1.65 ± 0.53	1.67 ± 0.58	0.9
Serum creatinine	2.40 ± 1.45	1.80 ± 1.40	0.11
(mg/dL)			
HgbA1c (%)	5.8 ± 0.9	5.7 ± 2.1	0.86

Bold indicates *P* value < .05

TABLE 5

Pathological features of background liver in patients undergoing OLT with non-alcoholic steatohepatitis (NASH)-hepatocellular carcinoma (HCC) compared with alcoholic liver disease (ALD)-HCC

Pathological feature	NASH-HCC	ALD-HCC	P value
Steatosis			
None (<5%)	2	16	0.0047
Mild (5%-33%)	21	25	
Moderate (33%-66%)	7	5	
Severe (>66%)	2	0	
Steatohepatitis	26/27 (96%)	17/35(49%)	<0.0001
Ballooning	31/31 (100%)	25/40(62.5%)	<0.0001
Mallory body	91%(29/32)	50%(21/42)	0.0003
Inflammation			
None	0(0%)	3(7%)	NS
Mild	24(77%)	27(63%)	
Moderate	5(16%)	8(19%)	
Severe	2(6%)	5(12%)	
Pericentral fibrosis			
None	3(17%)	18(53%)	0.002
Mild	0(0%)	6(18%)	
Moderate	10(56%)	7(21%)	
Severe	5(28%)	3(9%)	
Fibrosis			
1	0	0	1
2	0	0	
3	1(3%)	1(2%)	
4	31(97%)	44(98%)	
Iron in parenchyma			
None	15(54%)	16(36%)	0.03
Minimal	3(11%)	3(7%)	
Mild	7(25%)	9(20%)	
Moderate	0(0%)	11(24%)	

Bold indicates *P* value < .05

Pathological feature	NASH-HCC	ALD-HCC	<i>P</i> value
Severe	3(11%)	6(13%)	

TABLE 6

Pathological features of tumor in patients undergoing OLT with non-alcoholic steatohepatitis (NASH)-hepatocellular carcinoma (HCC) compared with alcoholic liver disease (ALD)-HCC

Pathological feature	NASH-HCC	ALD-HCC	<i>P</i> value
Largest tumor diameter (cm)	2.95 ± 1.60	2.93 ± 1.84	0.95
Tumor number	2.6 ± 2.5	2.7 ± 2.5	0.92
Total tumor diameter (cm)	3.91 ± 2.90	4.07 ± 2.97	0.81
Multifocal	13/33 (40%)	22/47 (47%)	0.64
Differentiation			
Well	7 (23%)	9 (20%)	0.90
Moderate	22 (73%)	33 (75%)	
Poor	1 (3%)	2 (5%)	
Lymphovascular invasion	7/32 (22%)	15/47 (32%)	0.44
Steatosis			
None (<5%)	9 (35%)	15 (39%)	0.20
Mild (5%–33%)	4 (15%)	3 (8%)	
Moderate (33%–66%)	5 (19%)	2 (5%)	
Severe (>66%)	8 (31%)	18 (47%)	
Mallory bodies			
0	8 (30%)	11 (28%)	0.40
1	6 (22%)	4 (10%)	
2	13 (48%)	24 (62%)	