Prevalence and factors associated with liver fibrosis among first-degree relatives of Mexican Americans with hepatocellular carcinoma

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Summary

Background and Aims: Whether hepatocellular carcinoma (HCC) increases the familial risk for hepatic fibrosis has not been thoroughly explored, particularly in Mexican Americans who are disproportionately affected by obesity and metabolic syndrome. We evaluated the risk of significant hepatic fibrosis in first-degree relatives of Mexican American adults with HCC.

Methods: We performed a cross-sectional analysis of a prospective cohort of Mexican American probands with HCC and first-degree relatives enrolled in the Hispanic Liver Cancer Cohort study. We evaluated the prevalence of hepatic fibrosis in first-degree relatives, defined by liver stiffness measurement (LSM)>= 7.0 kPa with transient elastography (TE). Secondary outcomes included

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the prevalence of definite hepatic steatosis, defined by controlled attenuation parameter >=288 dB/m.

Results: We identified 70 probands diagnosed with HCC; 47% were female and the mean age was 62 years (±13 years). Among 112 first-degree relatives with a mean age of 43 years (±14 years), 19 (17%) had significant fibrosis and 47 (42%) had definite hepatic steatosis, respectively. The prevalence of significant fibrosis was 20% in first-degree relatives 40 years of age or older. Regression analysis revealed that diabetes (OR 3.2, 95% CI: 1.1–9.2, $p = 0.03$) and aspartate aminotransferase >=30 units/L (OR 4.0, 95% CI: 1.4–11.7, $p = 0.01$) were predictors of significant fibrosis in first-degree relatives.

Conclusions: Using a well-phenotyped familial cohort, we found that the prevalence of significant fibrosis and definite hepatic steatosis are high in first-degree relatives of Mexican Americans with HCC, particularly those with diabetes, suggesting that this population may benefit from screening for liver disease.

1 | INTRODUCTION

The Hispanic population is the largest ethnic group within the United States with a growing population estimated to be around 110 million by the year 2060,[1] necessitating the need to accurately evaluate health disparities that affect this population. Hispanic Americans have a higher incidence rate of nonalcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC).[2–7] More specifically, Mexican Americans living in the southern region of Texas have one of the highest prevalence rates of NAFLD as well as the highest age-adjusted HCC incidence rate of any ethnic group in the United States,[8] representing a public health concern.[1]

Hepatic fibrosis is a primary risk factor for liver-related events and HCC. Previous studies have shown that both hepatic steatosis and hepatic fibrosis are heritable.[9] A recent study revealed increased incidences of fibrosis in first-degree relatives of patients with NAFLD cirrhosis, suggesting advanced fibrosis screening could be considered in first-degree relatives of patients with NAFLD cirrhosis.[10] However, to our knowledge there are no prospective data examining the prevalence of advanced fibrosis and hepatic steatosis in first-degree relatives of Mexican Americans with HCC. As such, there is currently insufficient insight into whether family members should be screened for NAFLD and hepatic fibrosis. As screening for fibrosis becomes more accessible with non-invasive imaging modalities, this discussion becomes more relevant and essential in this understudied patient population.[11–13]

To address this knowledge gap, we evaluated the prevalence of hepatic fibrosis and definite hepatic steatosis in first-degree relatives of Mexican Americans with HCC in a population-based cohort in South Texas and examined clinical factors associated with hepatic fibrosis and steatosis.

2 | MATERIALS AND METHODS

2.1 | Study population and design

This is a cross-sectional analysis of a prospective cohort study which included 70 adult probands with HCC enrolled in the Hispanic Liver Cancer Cohort (HLCC), a randomly ascertained, community-based cohort study of Mexican Americans, developed as an ancillary cohort to the Cameron County Hispanic Cohort and using the same protocols.[14,15] Briefly, individuals were recruited from border communities on the Texas-Mexico border. All probands included were diagnosed with HCC by a board-certified gastroenterologist either based on cross-sectional imaging (using the OPTN/LIRADs staging system) or histology of a targeted biopsy.

Detailed contact information for up to 10 first-degree relatives of each study participant with HCC was obtained. Study team members then attempted to contact the first-degree relatives: first by phone, then by up to five home visits at varying days and times. Each first-degree family member completed the standard Cameron County Hispanic Cohort examination described previously which includes a detailed physical examination, anthropometric measurements, fasting blood draw, urinalysis, personal medical history and vibration-controlled transient elastography (VCTE).[14,16] Diabetes (i.e. type 2 diabetes mellitus) was defined using (1) physician diagnosis, (2) HbA1c level (6.5%), (3) fasting blood glucose (126 mg/dl) or (4) anti-diabetic medication status according to American Diabetes Association diagnostic criteria.[17]

VCTE was performed using FibroScan® 502 Touch model (Echosens) by a trained technician, according to previously described methods.[18] VCTE liver stiffness measurement was obtained in the supine position during a 10-s breath hold. Participants were provided standardised instructions to fast for at least 3 hours and avoid alcohol use prior to VCTE. The procedure included a minimum of 10 measurements to determine the median valid liver stiffness measurements in kilopascals (kPa) and the IQR. According to the manufacturer protocol, all patients were first scanned using the M probe (3.5 MHz) and when indicated by the equipment upon initial assessment, patients were re-scanned using the XL probe (2.5 MHz). The controlled attenuation parameter (CAP) value in dB/m was simultaneously measured for the assessment of liver steatosis measurements, co-localised to the valid liver stiffness measurements. Technical failure was defined as inability to obtain 10 valid measurements.[19] Liver stiffness measurement (LSM) was considered unreliable when the interquartile range (IQR)/median was >0.30 in patients with a median 7.1 kPa.[20] Patients with a technical failure and/or unreliable exam were excluded from analyses. Patients with chronic viral hepatitis and significant alcohol use (defined by >=7 drinks per week in women or >=14 drinks per week in men) were excluded from our analyses to minimise confounding factors that may influence LSM.

2.2 | Primary and secondary outcomes

The primary outcome was the prevalence of significant hepatic fibrosis in first-degree relatives, defined by LSM >=7.0 kPa with VCTE.[21] Secondary outcomes included definite

hepatic steatosis and suspected cirrhosis. Hepatic steatosis was defined by CAP >= 288 dB/m.[22] Suspected cirrhosis was defined by either LSM >= 12 kPa or FIB-4>= 2.67.[21]

We subsequently performed sensitivity analyses to examine the prevalence of significant fibrosis, suspected cirrhosis and steatosis at other validated LSM (>9.7 and >13.6 kPa, respectively) and CAP (>274) cut-off points (Table S1).[23]

2.3 | Statistical analysis

Descriptive characteristics of data are presented as mean (SD), median (IQR) or number (%). Categorical data were compared using the chi-square and Fisher's exact tests. Differences between groups were analysed using a two-independent-sample t test or Wilcoxon–Mann–Whitney test. Univariable and multivariable logistic regression models were used to examine clinical factors associated with significant fibrosis and hepatic steatosis in first-degree relatives. Covariates in adjusted analyses were selected based on biologic plausibility to act as confounders as well as $p < 0.20$ in unadjusted analyses. Covariates that were not statistically significant ($p < 0.05$) in the multivariable models were sequentially omitted with backward stepwise regression. Sensitivity analyses were performed in the subset of the cohort with family membership data. Odds ratios were derived from generalised estimation equations (PROC GENMOD) to account for correlation within family members.

All analyses were performed using SAS 9.4 (SAS Institute). A two-tailed p 0.05 was considered statistically significant for all analyses.

2.4 | Study approval

All study participants provided informed consent. The study protocol was approved by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston. All authors had access to the study data and reviewed and approved the final manuscript.

3 | RESULTS

3.1 | Characteristics of Mexican American probands with hepatocellular carcinoma

Clinical characteristics of the 70 probands with HCC are detailed in Table S2. Probands had a mean age of 63 years (SD 13 years) and 53% were male. The mean body mass index (BMI) was 31.9 kg/m^2 (SD 8.9 kg/m^2) and 56% had type 2 diabetes mellitus. 90% of the proband cohort reported no alcohol use. Mean serum aspartate aminotransferase (AST) was 49 IU/L (SD 27 IU/L), and total bilirubin was 1.0 mg/dl (SD 0.7 mg/dl).

3.2 | Prevalence and factors associated with hepatic fibrosis in first-degree relatives

We identified 112 first-degree relatives, among which the mean age was 43 years (SD 14 years) with 58% (65/112) relatives that were age 40 or older (Table 1). 65% of first-degree relatives were female. The mean LSM among the first-degree relative cohort was 5.8 kPa (SD 5.4 kPa). The prevalence of hepatic fibrosis was 17% (19/112) in the overall cohort and 20% when limiting analyses to first-degree relatives aged 40 and older (Table 1 and

Figure 1). Among first-degree relatives 40 years or older, 5% met the criteria for suspected cirrhosis.

Comparisons between first-degree relatives with and without fibrosis are shown in Table 3. First-degree relatives with fibrosis had significantly higher BMI (34.1 vs. 30.9 kg/m^2, $p = 0.05$) and were more likely to have type 2 diabetes (42% vs. 19%, $p = 0.04$). AST was significantly higher in first-degree relatives with significant fibrosis. There were no significant differences in age, sex, hypertension, hypercholesterolemia, alcohol use or tobacco use between first-degree relatives with and without significant fibrosis (Table 2). Among first-degree relatives with hepatic fibrosis, 58% had serum AST < 30 IU/L and 32% were non-obese (BMI < 30 kg/m^2).

In logistic regression analyses, type 2 diabetes mellitus (OR 3.21, $p = 0.03$) and serum AST >= 30 IU/L (OR 4.0, $p = 0.01$) were factors significantly associated with hepatic fibrosis among first-degree relatives (Table 3). Serum AST >= 30 IU/L (OR 4.76, 95% CI: 1.57–14.5, $p = 0.006$) and serum albumin <3.5 g/dl (OR 8.3, 95% CI: 1.04–66.6, $p = 0.05$) were factors significantly associated with fibrosis in multivariable analyses. A sensitivity analysis performed in 102 first-degree relatives with family membership data revealed type 2 diabetes mellitus (OR 3.8, $p = 0.01$), serum AST >= 30 IU/L (OR 4.3, $p = 0.01$) and BMI >= 30 kg/m^2 (OR 2.7, $p = 0.02$) as factors most associated with fibrosis (Table S3).

3.3 | Prevalence and factors associated with hepatic steatosis in first-degree relatives

The prevalence of definite hepatic steatosis (defined by CAP   288 dB/m) in first-degree relatives was 42% with a mean CAP of 273.5 dB/m (SD 62 dB/m; Table 1 and Figure 1). Comparisons between first-degree relatives with and without definite hepatic steatosis are shown in Table 4. Mean age was similar among first-degree relatives with and without definite hepatic steatosis. BMI (35.2 vs. 28.8 kg/m^2, $p =< 0.001$) and serum alanine aminotransferase (ALT) level (46 vs. 33 IU/L, $p = 0.001$) were significantly higher in first-degree relatives with hepatic steatosis. First-degree relatives with definite hepatic steatosis were more likely to have type 2 diabetes (30% vs. 17%, $p = 0.04$).

Univariable logistic regression analysis revealed that BMI >= 30 kg/m^2 (OR 12.7, $p < 0.001$), serum ALT >= 30 IU/L (OR 3.5, $p = 0.002$) and serum triglycerides (every 10 unit increase, OR 1.08, $p = 0.004$) were significantly associated with hepatic steatosis in first-degree relatives (Table 5). BMI >= 30 kg/m^2 (OR 13.6, 95% CI: 4.65–39.75, $p < 0.001$) and serum triglycerides (OR 1.08, 95% CI: 1.02–1.14, $p = 0.008$) were factors significantly associated with hepatic steatosis in multivariable analysis. A sensitivity analysis that included 102 first-degree relatives with family membership revealed that BMI >= 30 kg/m^2 (OR 8.55, $p < 0.001$), serum ALT >= 30 IU/L (OR 2.94, $p = 0.007$) and serum triglycerides (OR 1.01, $p = 0.05$) were the strongest clinical factors associated with hepatic steatosis (Table S4).

4 | DISCUSSION

In this prospective, community-based cohort study, which included 70 Mexican American adults with HCC and 112 of their first-degree relatives, we found that hepatic fibrosis

was highly prevalent in first-degree relatives. Specifically, 17% of first-degree relatives had hepatic fibrosis (VCTE >= 7 kPa). The prevalence of fibrosis was 20% in first-degree relatives aged 40 years and older and 5% met the criteria for cirrhosis. Compared with first-degree relatives without fibrosis, those with fibrosis had significantly higher BMI and serum AST and were more likely to have type 2 diabetes. Regression analysis revealed that type 2 diabetes (OR 3.2) and AST >= 30 IU/L (OR 4.0) were independent risk factors for hepatic fibrosis in first-degree relatives. Our finding that diabetes was associated with a threefold increased risk of fibrosis in first-degree relatives corroborates prior findings that elevated HbA1c is associated with liver fibrosis in Mexican Americans.[16]

We also found a high prevalence of definite hepatic steatosis in first-degree relatives, as 42% had CAP >= 288 dB/m. Notably, we used a high cut-off for CAP to define hepatic steatosis. With a CAP cut-off of >250 dB/m, which has been shown to correlate with grade 1 steatosis in several prior studies,[24] the prevalence of hepatic steatosis in first-degree relatives was 66%. Obesity (OR 12.7), ALT >= 30 (OR 3.5) and triglycerides (every 10 unit increase, OR 1.1) were clinical factors most significantly associated with hepatic steatosis in first-degree relatives.

Altogether, these findings highlight the high prevalence of clinically significant liver disease in first-degree relatives of Mexican Americans with HCC and suggest that screening should be considered, to facilitate early identification of those at risk of subsequent liver-related morbidity. Previous studies have shown that hepatocyte ballooning and formation of Mallory bodies develop more rapidly in Hispanics, potentially underscoring the pathophysiology of why hepatic steatosis and fibrosis are increasing at an alarming rate in Mexican Americans living in the United States.[25] The majority of first-degree relatives had no evidence of viral hepatitis or history of alcohol consumption, and we suspect that liver disease is predominantly related to nonalcoholic fatty liver. Over the past decade, screening for hepatic fibrosis has become more accessible with non-invasive modalities such as VCTE (e.g. FibroScan), magnetic resonance elastography and risk stratification systems (e.g. FIB-4 index).[11–13] Early identification of liver disease in the Mexican American population could yield improved outcomes. Further studies to predict the risk of liver disease in first-degree relatives of Mexican Americans with HCC and to delineate clinical factors associated with liver disease in this population are needed.

Mexican American probands with HCC in our cohort had a high prevalence of obesity, diabetes, hypertension and hypercholesterolemia, which corroborates previous studies characterising Hispanic Americans with HCC.[2,4,26–28] Several population-based studies have indicated that there may a hereditary component of hepatic steatosis and fibrosis.[29–32] Our group has also previously demonstrated an increased incidence of hepatic fibrosis in the first-degree relatives of patients with cirrhosis secondary to nonalcoholic fatty liver disease (NAFLD).[10] Over the past few decades, there has been a significant leap in the discovery of possible pathophysiologic mechanisms that may explain the hereditary predisposition of hepatic fibrosis.[33] In genome-wide association studies, a number of genetic polymorphisms have been associated with increased risk for NAFLD and HCC via diverse mechanisms including lipid metabolism, oxidative stress and hepatic lipid compartmentalization.[26,33–37] Of these identified variants, the PNPLA3 rs73849 (I148M) variant has the strongest

association with hepatic steatosis, fibrosis progression and risk of HCC development.[26,38,39] Additional genome-wide studies have shown that the PNPLA3 I148M variant occurs twice as frequently in Hispanic populations than in non-Hispanics.[40–43]

There is a paucity of data on the prevalence of hepatic fibrosis and hepatic steatosis in first-degree relatives of Mexican American probands with HCC. To our knowledge, our study is the first to evaluate the prevalence of both hepatic steatosis and fibrosis as well as risk factors for these in this patient population. We used a well-characterised cohort of Mexican American adults with HCC and first-degree relatives ($n = 112$) with extensive data collection on co-morbidities as well as non-invasive assessment for hepatic steatosis and fibrosis with VCTE. Our study does have limitations. The sample size is small which limited multivariable analyses (particularly for factors associated with fibrosis); however, to our knowledge this is the largest study examining the risk of liver disease in first-degree relatives of Mexican Americans with HCC. Non-invasive assessment with VCTE was used to identify hepatic steatosis and fibrosis in first-degree relatives. While liver biopsy remains the gold standard for diagnosing hepatic steatosis and fibrosis, VCTE has been shown to reliably estimate hepatic fibrosis and steatosis,[11,24,44] although the interpretation of VCTE must take into account laboratory results and clinical parameters.[11,24,44,45] The LSM cut-off used in our study could have resulted in misclassification; therefore, we also performed sensitivity analyses to examine the prevalence at different cut-points with higher specificity for advanced fibrosis.[23] Our study comprised Mexican Americans living in Texas, a population previously shown to have one of the highest prevalence of hepatic steatosis and incidences of HCC in the United States, but whether these results are reflective of liver disease incidence in all Mexican Americans in the United States is not known. We excluded patients with significant alcohol use history from our analyses; however, we note the limitations of self-reported alcohol use and that alcohol intake may be underestimated, especially in a cohort of individuals previously shown to be at higher risk for alcohol use and related disorders.[46] Finally, while the primary focus of our study was to examine the prevalence of fibrosis and steatosis in first-degree relatives of Mexican Americans with HCC, future studies in the same geographic area with appropriate controls and long-term outcomes are warranted to examine whether the risk of fibrosis is significantly increased in this cohort compared with the general population. Nevertheless, our study has revealed the prevalence and risk factors associated with hepatic steatosis and advanced hepatic fibrosis in first-degree relatives of Mexican Americans with HCC, which provides valuable information for future research and has implications on patient care.

In summary, hepatic fibrosis and steatosis are common in Mexican American adults with a first-degree family history of HCC, particularly in those with type 2 diabetes and obesity, which should prompt consideration of screening for liver disease in this patient population.

Supplementary Material

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CONFLICT OF INTEREST

RL serves as a consultant for Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Inipharm, Intercept, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Sagimet, 89 Bio and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Pfizer and Siemens. He is also a co-founder of Liponexus, Inc. All other authors have no conflicts of interest to disclose.

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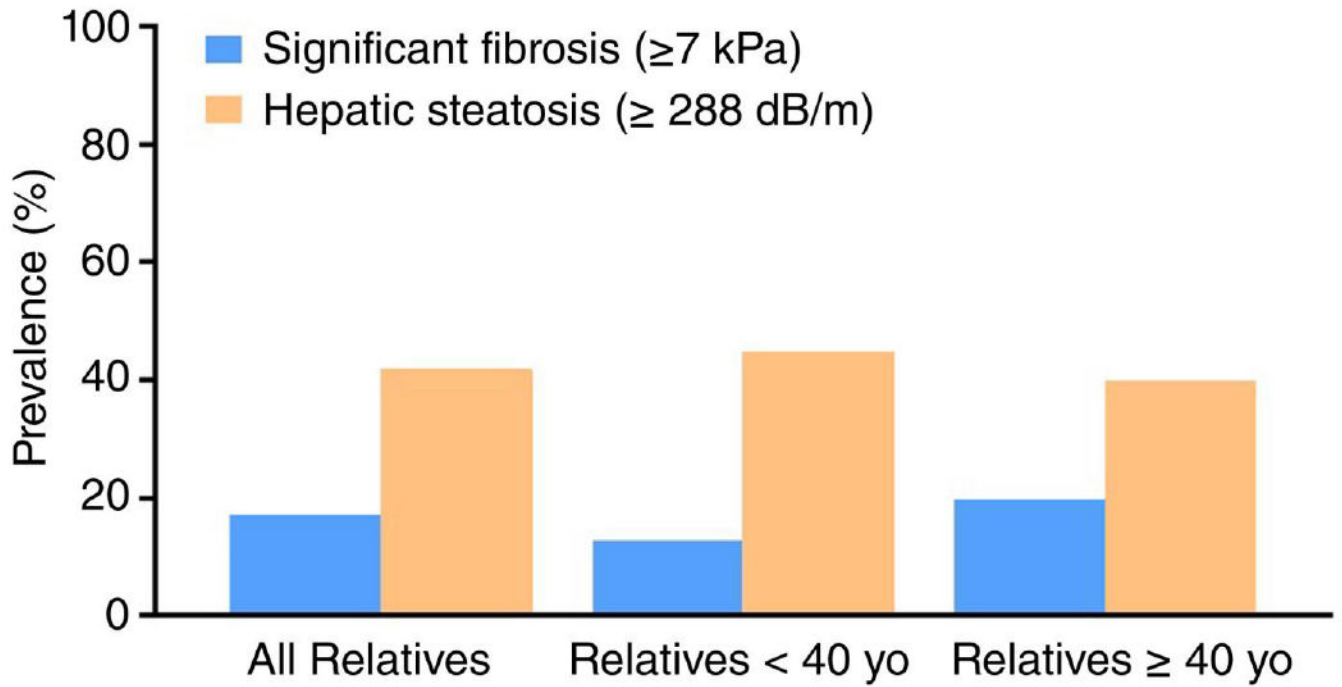
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FIGURE 1.

Prevalence of significant fibrosis and steatosis (with or without fibrosis) in first-degree relatives of Mexican Americans with hepatocellular carcinoma.

TABLE 1:

Characteristics of first-degree relatives of probands with hepatocellular carcinoma

Characteristic	All relatives ($n = 112$)	Relatives 40 years old ($n = 65$)
Age (years)[a]	42.8 (14.4)	52.9 (9.1)
Female, n (%)	73 (65.2%)	43 (66.2%)
Controlled attenuation parameter (CAP)		
CAP (dB/m)[a]	273.5 (62.0)	274.6 (60.2)
CAP 250 dB/m, n (%)	74 (66.1%)	46 (70.8%)
CAP 288 dB/m, n (%)	47 (42.0%)	26 (40.0%)
Liver stiffness with VCTE		
VCTE (kPa)[a]	5.8 (5.4)	6.3 (6.9)
VCTE (kPa) 7 kPa	19 (17.0%)	13 (20.0%)
VCTE (kPa) 12 kPa	4 (3.6%)	3 (4.6%)
FIB-4 index[a]	0.7 (0.4)	0.9 (0.4)
FIB-4 index 2.67, n (%)	1 (0.9%)	1 (1.7%)
VCTE (kPa) 12 kPa and/or FIB-4 2.67	4 (3.6%)	3 (4.6%)

Abbreviations: CAP, controlled attenuation parameter; HbA1c, glycated haemoglobin; VCTE, vibration-controlled transient elastography.

[a]Mean (SD).

TABLE 2

Characteristics of first-degree relatives of Mexican Americans with hepatocellular carcinoma by the presence of liver fibrosis

	First-degree relatives with fibrosis (N = 19)	First-degree relatives without fibrosis (N = 93)	p-value[*]
Age (years)[a]	45.3 (13.4)	42.3 (14.6)	0.42
BMI (kg/m^2), n (%)	34.1 (7.2)	30.9 (6.1)	**0.05**
Female, n (%)	13 (68.4%)	60 (64.5%)	0.74
Medical co-morbidities, n (%)			
Hypertension	7 (36.8%)	28 (30.1%)	0.56
Hypercholesterolemia	7 (36.8%)	27 (29.0%)	0.50
Type 2 diabetes	8 (42.1%)	17 (18.5%)	**0.04**
Alcohol use (drinks/week), n (%)			
None	17 (89.5%)	79 (85.0%)	1.00
1–7	1 (5.3%)	6 (6.4%)	
7	1 (5.3%)	8 (8.6%)	
Tobacco use, n (%)	2 (10.5%)	14 (15.1%)	1.00
Biochemical data[a]			
AST (IU/L)	36.1 (28.2)	22.3 (12.4)	**0.04**
ALT (IU/L)	46.6 (32.4)	36.4 (26.9)	0.085
Bilirubin (mg/dl)	0.5 (0.2)	0.5 (0.3)	0.59
Albumin (g/dl)	3.8 (0.3)	4.1 (0.3)	**0.002**
Total cholesterol (mg/dl)	188.4 (32.7)	177.4 (39.3)	0.24
HDL (mg/dl)	49.1 (8.8)	49.0 (11.4)	0.86
LDL (mg/dl)	107.9 (32.6)	97.5 (34.1)	0.29
TG (mg/dl)	156.5 (63.4)	145.7 (93.6)	0.16
Platelet count (10^9/L)	252.5 (65.1)	265.0 (61.9)	0.36
HbA1c (%)	6.6 (1.5)	6.1 (1.5)	0.069
FIB-4[a]	1.0 (0.6)	0.7 (0.4)	**0.02**
FIB4　2.67, n (%)	1 (5.3%)	0	0.18

Note: Bold values represent the significance of p-value ($p < 0.05$).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HbA1c, glycated haemoglobin; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

[a]Mean (SD).

[*]p-values for biochemical data from Wilcoxon two-sample test, otherwise from the t test, chi-square or Fisher's as appropriate.

TABLE 3

Factors associated with liver fibrosis (liver stiffness measurement ≥ 7 kPa) in first-degree relatives of Mexican American probands with hepatocellular carcinoma

	OR (95% CI)[a]	*p*-value
Age (1-year increase)	1.02 (0.98–1.05)	0.41
Male gender	0.83 (0.29–2.38)	0.72
Body mass index ≥ 30kg/m²	1.90 (0.67–5.44)	0.23
Type 2 diabetes	3.21 (1.12–9.19)	**0.03**
Hypercholesterolemia	1.40 (0.50–3.95)	0.52
Hypertension	1.40 (0.50–3.95)	0.52
Tobacco use	0.66 (0.14–3.16)	0.60
Any alcohol use	0.66 (0.14–3.16)	0.60
AST ≥ 30 IU/L	4.00 (1.37–11.71)	**0.01**
Albumin < 3.5 g/dl	5.24 (0.67–39.76)	0.11

Note: Bold values represent the significance of *p*-value ($p < 0.05$). Abbreviation: AST, aspartate aminotransferase.

[a]Results from univariable analysis are shown.

TABLE 4

Characteristics of first-degree relatives with definite hepatic steatosis

	First-degree relatives with hepatic steatosis (n = 47)	First-degree relatives without hepatic steatosis (N = 65)	p-value[*]
Age (years)[a]	43.5 (13.1)	42.4 (15.3)	0.69
BMI (kg/m^2)[a]	35.2 (6.1)	28.8 (5.2)	**<0.0001**
Female, n (%)	32 (68.1%)	41 (63.1%)	0.58
Medical co-morbidities, n (%)			
Hypertension	19 (40.4%)	16 (24.6%)	0.07
Hypercholesterolemia	15 (31.9%)	19 (29.2%)	0.76
Type 2 diabetes	14 (29.8%)	11 (17.2%)	**0.042**
Alcohol use (drinks/week)			
None	41 (87.2%)	55 (84.6%)	0.84
1–7	2 (4.3%)	5 (7.7%)	
7	4 (8.5%)	5 (7.7%)	
Tobacco use, n (%)	8 (17.0%)	8 (12.3%)	0.48
Biochemical data[a]			
AST (IU/L)	27.7 (19.9)	22.6 (14.2)	0.06
ALT (IU/L)	45.5 (30.7)	32.9 (24.9)	**0.0007**
Bilirubin (mg/dl)	0.5 (0.2)	0.5 (0.3)	0.96
Albumin (g/dl)	4.0 (0.3)	4.0 (0.3)	0.25
Total cholesterol (mg/dl)	186.1 (39.8)	174.4 (36.7)	0.17
HDL (mg/dl)	45.2 (9.6)	51.8 (11.1)	**0.003**
LDL (mg/dl)	105.2 (36.5)	95.3 (31.7)	0.25
TG (mg/dl)	178.6 (91.2)	125.3 (80.8)	**0.0003**
Platelet count (10^9/L)	253.1 (67.0)	269.6 (58.5)	0.094
HbA1c (%)	6.4 (1.5)	6.1 (1.5)	**0.01**
FIB-4 index[a]	0.8 (0.4)	0.7 (0.4)	0.24
FIB-4 À 2.67, n (%)	0	1 (1.6%)	1.00

Note: Bold values represent the significance of p-value ($p < 0.05$).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HbA1c, glycated haemoglobin; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

[a] Mean (SD).

[*] p-values for biochemical data from Wilcoxon two-sample test, otherwise from the t test, chi-square or Fisher's as appropriate.

TABLE 5

Factors associated with definite hepatic steatosis in first-degree relatives of Mexican Americans with hepatocellular Carcinoma

	OR (95% CI)[a]	p-value
Age (1-year increase)	1.01 (0.98–1.03)	0.66
Male gender	0.78 (0.35–1.73)	0.54
Body mass index 30 kg/m^2	12.73 (4.68–34.64)	**<0.0001**
Type 2 diabetes	2.04 (0.83–5.04)	0.12
Hypercholesterolemia	1.11 (0.49–2.51)	0.80
Any alcohol use	0.79 (0.27–2.35)	0.67
ALT >= 30 IU/L	3.49 (1.58–7.73)	**0.002**
AST >= 30 IU/L	1.91 (0.74–4.89)	0.18
TG (10 unit increase, mg/dl)	1.08 (1.02–1.14)	**0.004**

Note: Bold values represent the significance of *p*-value ($p < 0.05$).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglycerides.

[a]Results from univariable analysis shown.