Nonalcoholic steatohepatitis (NASH) or high probability of fibrosis based on noninvasive marker panels (APRI, FIB-4, NFS) at disease presentation is associated with increase all-cause mortality in patients with nonalcoholic fatty liver disease (NAFLD)

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OBJECTIVE

Our aim is to examine disease presentation and natural history of nonalcoholic fatty liver disease (NAFLD) in an ethnically diverse patient cohort.

BACKGROUND

- NAFLD is recognized as the most common liver disease in developed countries with an estimated prevalence of 20-30%.
- NAFLD represents a spectrum of disease ranging from simple steatosis of the liver to progressive inflammation and fibrosis, resulting in nonalcoholic steatohepatitis (NASH), which can progress to chronic liver disease, cirrhosis, and/or hepatocellular carcinoma (HCC).
- NASH-related cirrhosis is projected to become the leading indication for liver transplantation in the next 10-20 years.
- The natural history and incidence of disease sequelae from simple steatosis in patients with NAFLD has not been well studied, especially in regards to ethnic influences.

METHODS

- Retrospective cohort study of 872 consecutive NAFLD patients (246 Asians, 436 Caucasians, and 190 Hispanics) seen at a university medical center between 01/1999 and 12/2009.
- NAFLD was diagnosed by radiologic imaging and/or histological evaluation.
- Patients were included if they had no known viral infection, heavy alcohol consumption, toxic/drug-induced hepatitis, or inflammatory/genetic liver disease.
- Study endpoints were development of NASH, cirrhosis, decompensation, HCC, and death.
- Noninvasive fibrosis scoring systems
  - AST to Platelet Ratio Index (APRI): AST, PLT
  - Fibrosis-4 (FIB-4): age, ALT, AST, PLT
  - NAFLD Fibrosis Score (NFS): age, BMI, impaired fasting glucose/diabetes, albumin, ALT, AST, PLT

RESULTS

A. Baseline patient characteristics

- Asians were more likely to be male with a lower mean BMI, and less likely to be classified as extremely obese (Table 1).
- Comorbidities were similar among the three groups except hyperlipidemia and hypercholesterolemia, which were more prevalent among Asians (Table 1).

Table 1. Baseline patient characteristics

	Asian n = 246	Caucasian n = 436	Hispanic n = 190	*p*-value
Age (year)	46 ± 15	50 ± 14	42 ± 14	<0.001
Sex (male)	129 (52)	204 (47)	59 (31)	<0.001
Body mass index (kg/m^2)	28.2 ± 5.2	33.4 ± 7.8	33.8 ± 8.5	<0.001
BMI classification				0.004
Normal weight	27 (12)	46 (11)	16 (10)	
Overweight	41 (19)	107 (26)	42 (27)	
Obese class I	84 (38)	104 (25)	43 (28)	
Obese class II	48 (22)	78 (19)	24 (16)	
Obese class III	20 (9)	74 (18)	29 (19)	
Comorbidities				
Hypertension	133 (54)	262 (60)	114 (60)	0.06
Diabetes mellitus	78 (32)	132 (30)	76 (40)	0.053
Hypercholesterolemia	72 (29)	108 (25)	35 (18)	0.03
Hyperlipidemia	135 (55)	221 (51)	76 (40)	0.01
Coronary artery disease	27 (11)	61 (14)	24 (13)	0.53

- All three groups had similar low, intermediate, and high probability of fibrosis using the APRI and FIB-4 score. Asians were less likely to have a high probability of fibrosis based on the NFS (5%) compared to Caucasians (12%) and Hispanics (19%), respectively (p<0.001) (Table 2).

Table 2. Non-invasive marker panel for fibrosis

	Asian n = 246	Caucasian n = 436	Hispanic n = 190	*p*-value
AST to platelet ratio (APRI)				0.39
Low probability	158 (72)	280 (72)	111 (66)	
Intermediate probability	51 (23)	85 (22)	41 (24)	
High probability	12 (5)	26 (7)	17 (10)	
Fibrosis-4 (FIB-4)				0.27
Low probability	162 (73)	259 (67)	120 (72)	
Intermediate probability	46 (21)	96 (25)	31 (19)	
High probability	13 (6)	33 (9)	16 (10)	
NAFLD fibrosis score (NFS)				<0.001
Low probability	136 (71)	185 (51)	68 (50)	
Intermediate probability	47 (24)	134 (37)	42 (31)	
High probability	10 (5)	44 (12)	25 (19)	

- Multivariate analysis demonstrated that older age, higher BMI, diabetes, and Hispanic ethnicity were significantly associated with NASH and/or high probability of fibrosis at baseline (Table 3).

Table 3. Predictors of NASH and/or high probability of fibrosis at disease presentation

	Univariate analysis			Mutivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.03	1.02-1.05	<0.001	1.04	1.02-1.05	<0.001
Sex (male)	0.73	0.51-1.06	0.1	0.97	0.63-1.48	0.88
BMI	1.06	1.04-1.08	<0.001	1.06	0.53-1.60	<0.001
Ethnicity						
Caucasian	Referent		-	Referent		-
Asian	0.61	0.38-0.98	0.04	0.92	0.53-1.60	0.76
Hispanic	1.51	0.99-2.31	0.06	1.75	1.05-2.91	0.03
Diabetes	3.52	2.43-5.11	<0.001	2.73	1.81-4.14	<0.001

B. Natural disease outcomes

- Median follow-up was 85 (6-274) months.
- All three groups had similar 12-year cumulative incidence rates of NASH (5-8%, p=0.11), cirrhosis (3-8%, p=0.99), decompensation (3-7%, p=0.41), and all-cause mortality (4-9%, p=0.39) (Figures 1-4).

Figure 1. Cumulative incidence rates of nonalcoholic steatohepatitis among all patients

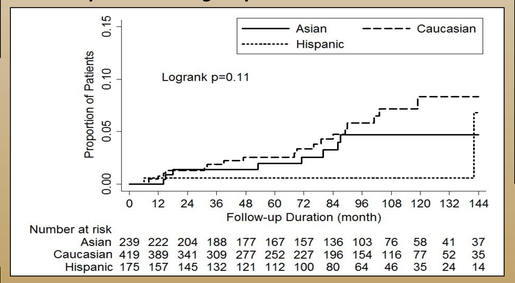


Figure 2. Cumulative incidence rates of cirrhosis among all patients

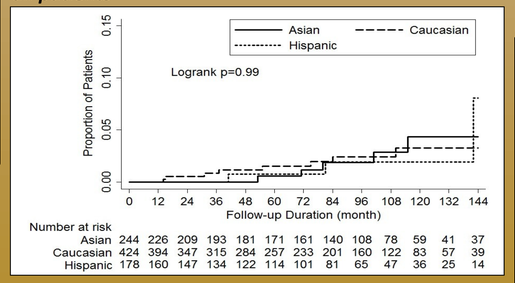


Figure 3. Cumulative incidence rates of decompensated cirrhosis among all patients

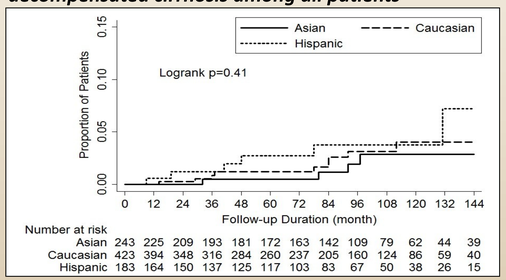
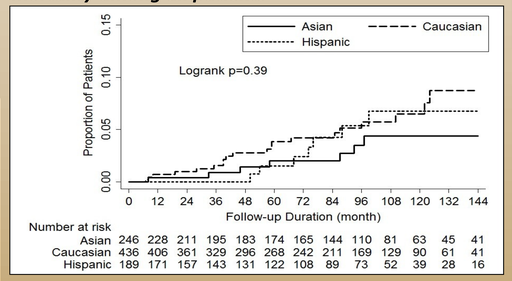
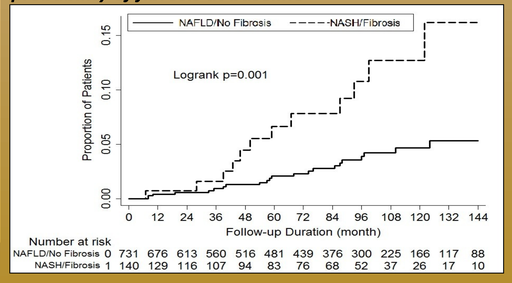


Figure 4. Cumulative incidence rates of all-cause mortality among all patients



- 12-year cumulative incidence rates of all-cause mortality was higher among patients with NASH and/or high probability of fibrosis at baseline (16.2% vs. 5.3%) (Figure 5).

Figure 5. Cumulative incidence rates of all-cause mortality among patients with NASH and/or high probability of fibrosis at baseline



C. Predictors of cirrhosis and all-cause mortality

In multivariate Cox proportional hazard models also inclusive of age, sex, BMI, diabetes, and ethnicity, NASH/high probability of fibrosis at baseline was significantly associated with development of cirrhosis (HR=4.27, 95% CI=1.35-13.51, p=0.01) (Table 4) and all-cause mortality (HR=2.72, 95% CI=1.19-6.22, p=0.02) (Table 5).

Table 4. Predictors of cirrhosis

	Univariate analysis			Mutivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.02	0.99-1.06	0.20	1.01	0.97-1.05	0.70
Sex (male)	0.89	0.33-2.40	0.82	0.84	0.28-2.48	0.75
BMI	1.06	1.00-1.12	0.047	1.03	0.96-1.10	0.39
Ethnicity						
Caucasian	Referent		-	Referent		-
Asian	0.94	0.31-2.88	0.92	1.53	0.44-5.34	0.51
Hispanic	0.91	0.24-3.41	0.88	0.69	0.15-3.04	0.62
Diabetes	4.03	1.40-11.61	0.01	3.04	0.88-10.43	0.08
NASH/high probability of fibrosis	7.56	2.82-20.24	<0.001	4.27	1.35-13.51	0.01

Table 5. Predictors of all-cause mortality

	Univariate analysis			Mutivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.04	1.02-1.07	<0.001	1.03	1.01-1.06	0.01
Sex (male)	0.66	0.33-1.34	0.25	0.80	0.37-1.71	0.57
BMI	1.02	0.98-1.07	0.36	1.02	0.97-1.07	0.53
Ethnicity						
Caucasian	Referent		-	Referent		-
Asian	0.55	0.23-1.31	0.18	0.93	0.45-2.96	0.89
Hispanic	0.80	0.34-1.90	0.61	1.16	0.45-2.96	0.76
Diabetes	0.84	0.41-1.73	0.64	0.57	0.25-1.27	0.17
NASH/high probability of fibrosis	3.03	1.50-6.13	0.002	2.72	1.19-6.22	0.02

CONCLUSIONS

- Despite differences in disease presentation, disease sequelae from nonalcoholic fatty liver disease to nonalcoholic steatohepatitis, cirrhosis, hepatic decompensation, and all-cause mortality was similar among Asians, Caucasians, and Hispanics.
- Patients with nonalcoholic steatohepatitis and/or high probability of fibrosis at disease presentation may benefit from closer disease monitoring to reduce mortality.

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