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## ORIGINAL ARTICLE

# Racial/ethnic differences in fibrosis prevalence and progression in biopsy-proven steatosis: A focus on the Asian American population

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## Abstract

Fatty liver disease (FLD) is a leading cause of chronic liver disease (CLD) globally, and vulnerable populations are disproportionately affected. Prior studies have suggested racial/ethnic differences in FLD prevalence and severity; however, these studies often excluded Asian Americans. This study aims to evaluate racial/ethnic differences in the prevalence of, and predictors associated with steatohepatitis, advanced fibrosis, and fibrosis progression over time within a diverse population. Using descriptive analyses and multivariable modeling, we performed a longitudinal evaluation of 648 patients with histologic evidence of FLD (steatosis or steatohepatitis) from August 2009 to February 2020 within San Francisco's safety-net health care system. Overall demographics were median age of 53 years, 54% male, and 38% Asian (40% Hispanic, 14% White). On histology, 61% had steatohepatitis and 30% had advanced fibrosis ( $\geq F3$ ). The comparison between steatosis and steatohepatitis groups showed differences in sex, race/ethnicity, metabolic risk factors, and co-existing CLD (predominantly viral hepatitis); patients with steatosis were more likely to be Asian (50%), and those with steatohepatitis were more likely to be Hispanic (51%). On multivariable modeling, while Asian race (vs. non-Asian) was not associated with steatohepatitis or advanced fibrosis when models included all relevant clinical predictors, Asian race was associated with higher relative risk of fibrosis progression as defined by change in Fibrosis-4 category over time (relative risk ratio = 1.9;  $p = 0.047$ ). **Conclusion:** In this vulnerable population with a large proportion of Asian Americans, Asian race was associated with progression of fibrosis. Given the relative paucity of data in this high-risk group, future studies should confirm these findings.

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## INTRODUCTION

Fatty liver disease (FLD) from nonalcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD) has rapidly become a leading cause of chronic liver disease (CLD),<sup>[1,2]</sup> and has been associated with increased risk of hepatocellular carcinoma<sup>[3,4]</sup> and mortality.<sup>[5,6]</sup> Although each have unique risk factors, NAFLD and ALD often co-exist<sup>[7]</sup> and are similar histologically.<sup>[8]</sup> Prior studies have also reported FLD concomitant with chronic viral hepatitis. Steatosis is common in patients with chronic hepatitis C (HCV) (30%–70%)<sup>[9,10]</sup> and among individuals with FLD, those with chronic HCV have more severe steatosis and fibrosis compared to those without.<sup>[11]</sup> The relationship between chronic hepatitis B virus (HBV) and steatosis from predominantly Asian studies remains controversial,<sup>[12,13]</sup> but FLD prevalence has ranged from 18%–40% FLD.<sup>[14–17]</sup> In a recent North American multiethnic cohort of participants within the National Institutes of Health–sponsored Hepatitis B Research Network, about 30% had FLD.<sup>[15]</sup> Moreover, presence of steatohepatitis was associated with increased risk of advanced fibrosis in the setting of chronic HBV.<sup>[15]</sup>

Importantly, prior studies have suggested racial/ethnic differences in FLD (ALD and NAFLD) prevalence and severity<sup>[18–22]</sup>; however, these have focused on White, Hispanic, and Black populations. Most studies examining the burden of FLD among Asians are from countries in Asia. ALD is prevalent in the Asia-Pacific region, accounting for 21% of cirrhosis-related deaths in 2015.<sup>[23]</sup> The prevalence of NAFLD in Asia is estimated to be about 25% (similar to Western countries), and NAFLD prevalence has been increasing over the last two decades,<sup>[24,25]</sup> tracking with the rise in the prevalence of obesity as well as sedentary lifestyle.<sup>[26,27]</sup> However, it has also been recognized that NAFLD is seen in those without obesity; in fact, about 20% of the global NAFLD population has lean NAFLD,<sup>[28]</sup> including an estimated 8%–19% in Asia,<sup>[24]</sup> and 13% in the United States.<sup>[29]</sup>

It is unclear whether these findings of FLD prevalence and risk factors in Asia are relevant to North America; FLD among Asian Americans has not been well studied. In one national cross-sectional study using National Health and Nutrition Examination Survey data, NAFLD prevalence among Asian Americans was 18% compared with 42% among Hispanic Americans, 28% among non-Hispanic Whites, and 17% among non-Hispanic Blacks.<sup>[30]</sup> Compared to non-Hispanic Whites with NAFLD, Asians with NAFLD tended to be younger, have a lower body mass index (BMI), and were less likely to have metabolic syndrome<sup>[30]</sup>; in addition, advanced fibrosis ranged between 12% and 14% and was not statistically different from non-Hispanic Whites with NAFLD. In another study of CLD in a multiethnic cohort, NAFLD prevalence based on International

Classification of Diseases codes was highest among Japanese Americans (4.4%), followed by Hispanic (3.1%), Native Hawaiians (2.3%), non-Hispanic Whites (1.7%), and African Americans (1.5%).<sup>[31]</sup> With respect to ALD, mortality related to ALD is increasing among Asians, similar to that observed in other racial groups (2007–2016).<sup>[32]</sup> Importantly, the presence of advanced fibrosis in FLD increases risk of liver-related complications and death.<sup>[33]</sup> However, few studies have explored FLD prevalence and risk factors among Asians in socioeconomically disadvantaged and vulnerable populations,<sup>[34]</sup> who are at risk of experiencing health disparities.

To explore racial/ethnic differences in FLD among underrepresented populations including Asian Americans, this longitudinal study aimed to evaluate the prevalence of steatohepatitis in a diverse, safety-net cohort with histologic evidence of FLD. In addition, we assessed predictors of advanced fibrosis on baseline biopsy and change in fibrosis-4 score (FIB-4) among racial/ethnic groups.

## METHODS

### Subjects

This is a retrospective longitudinal analysis of 648 adults ( $\geq 18$  years old) with histologic evidence of FLD (steatosis or steatohepatitis defined below) on clinically indicated liver biopsies performed from August 2009 to February 2020 at San Francisco General Hospital (SFGH), San Francisco's safety-net hospital.<sup>[35]</sup> Sociodemographic characteristics and clinical data were collected from electronic medical records (EMR) at the time of liver biopsy, and follow-up clinical data were collected from the most recent clinical visit at the time of analysis. This study was approved by the Institutional Review Board of the University of California, San Francisco, and SFGH.

### Measures

The primary outcomes were (1) presence of steatohepatitis, (2) presence of advanced fibrosis, and (3) change in FIB-4 category over time as a noninvasive measure of advanced fibrosis. Predictors of interest were identified *a priori* and included race/ethnicity, age, sex, metabolic measures (BMI, dyslipidemia, hypertension, diabetes mellitus [DM]), alcohol use, and presence of coexisting CLD. All predictors and outcomes are defined subsequently.

Data were collected and entered into standardized forms after manual review of the EMR by R.G.K, J.D, and J.N.R. Collected data included sociodemographic, anthropometric measures, medical

history, alcohol use, laboratory values, and histologic features.

## Clinical and laboratory data definitions

Race/ethnicity and sex were collected from the EMR. Alcohol use at the time of the baseline and follow-up visits was quantified using categories defined by the National Institute on Alcohol Abuse and Alcoholism.<sup>[36]</sup> Moderate alcohol use for women was defined as up to one drink per day and no more than 7 drinks per week, and for men, up to two drinks per day and no more than 14 drinks per week.<sup>[36]</sup> Heavy alcohol use was defined as more than moderate, which also includes binge drinking defined as 4+ drinks for women and 5+ drinks for men on the same occasion.<sup>[36]</sup> Race-based BMI categories used were “normal weight” <25 kg/m<sup>2</sup> (<23 kg/m<sup>2</sup> for Asians), “overweight” 25–29 kg/m<sup>2</sup> (23–27.4 kg/m<sup>2</sup> for Asians), and “obese” >30 kg/m<sup>2</sup> (≥27.5 kg/m<sup>2</sup> for Asians).<sup>[37]</sup>

Pertinent medical conditions including dyslipidemia, hypertension, and DM were entered after manual review of the EMR including participants' problem list, clinical notes, medications, and laboratory values (e.g., hemoglobin A1c). Medications were included based on participants' active prescriptions. Presence of co-existing viral hepatitis, autoimmune hepatitis, or other etiologies of CLD were identified based on laboratory and histologic data. Steatosis was graded as minimal (<5%), mild (5%–33%), moderate (34%–66%), and severe (≥67%).<sup>[38]</sup> Steatohepatitis was based on parenchymal inflammation, hepatocyte ballooning, and perisinusoidal fibrosis.<sup>[38]</sup> Finally, FIB-4 score was calculated as  $(\text{age} \times \text{aspartate aminotransferase [AST]}) / (\text{platelets} \times \sqrt{\text{alanine aminotransferase (ALT)}})$  using available laboratory values and age at (1) the time of biopsy and (2) most recent follow-up visit. FLD FIB-4 categories defined as “advanced fibrosis excluded” <1.3, “indeterminate” 1.3–2.67, and “advanced fibrosis likely” >2.67<sup>[39]</sup> (as well as age-adjusted categories for ≥65 years old: <2.0, 2.0–2.67, and >2.67<sup>[40]</sup>) were used for our primary analysis. HCV FIB-4 cutoffs defined as “fibrosis stage F0–F1” <1.45, “F2–F3” 1.45–3.25, and “F3–F4” >3.25 were used in our sensitivity analysis.<sup>[41]</sup>

## Statistical analysis

Descriptive statistics included median (interquartile range) and frequency (percentage). Patient characteristics were compared by baseline histology (steatosis vs. steatohepatitis) and race (Asian vs. non-Asian) using chi-squared or Fisher's exact tests where appropriate for categorical variables and Kruskal-Wallis tests for

continuous variables. Standardized mean differences were calculated using *stddiff*.<sup>[42]</sup> Our primary analysis used univariable and multivariable logistic regression models to assess the association of predictors with (1) steatohepatitis and (2) advanced fibrosis at baseline. For our primary predictor of interest, race/ethnicity, we performed minimally and fully adjusted multivariable models.

Change in FIB-4 category from baseline to follow-up was evaluated using multinomial logistic regression models with outcomes of (1) no change (reference outcome), (2) improvement (from higher FIB-4 category to lower), and (3) progression (from lower FIB-4 category to higher). On sensitivity analysis, we also assessed the comparison between no change (defined as change in FIB-4 score by ≤1 in either direction) versus improvement (decrease by >1) and progression (increase by >1).

Missing covariate values, including BMI (n = 462, 21% missingness) and alcohol use (n = 565, 13% missingness), were multiply imputed<sup>[43]</sup> using iterative chained equations. We used the *mi impute chained* command in Stata to create 20 imputation data sets. Imputed values were based on all pertinent predictor and outcome variables. We then used the Stata *mi estimate* to synthesize the results of fitting multivariable logistic regression models to the 20 imputed data sets, accounting for variability introduced by the imputation. All minimally adjusted models included age and sex, and final, fully adjusted models included all clinically relevant predictors. Multinomial logistic regression models estimating associations with change in FIB-4 category were adjusted for follow-up time, baseline FIB-4 score (natural log), baseline histology (steatosis vs. steatohepatitis), alcohol use (heavy vs. none/moderate), and coexisting CLD. All statistical analyses were performed using Stata statistical software package version 14 (Stata Corp LP).

## RESULTS

### Study population

Baseline sociodemographic characteristics for the total population (n = 648) were median age of 53 years, 54% were men, 40% Hispanic, 38% Asian (63% Chinese, 12% Filipino, 8% Vietnamese, 17% other), 14% White, and 57% obese; 10% had heavy alcohol use, 29% DM, 19% HBV, and 21% HCV. On histology, 4% (n = 27) had minimal steatosis, 63% (n = 405) mild, 23% (n = 149) moderate, and 10% (n = 67) had severe steatosis. Thirty-nine percent (n = 254) had steatosis alone, 61% (n = 394) had steatohepatitis, and 20%, 31%, 19%, 17%, and 13% had stage F0, F1, F2, F3, and F4 fibrosis, respectively.

## Baseline characteristics by histologic diagnosis

Among individuals with steatosis compared to those with steatohepatitis, there was a higher proportion of men (63% vs. 48%), Asians (50% vs. 31%), and normal weight (22% vs. 7%), and a lower proportion

were Hispanic (24% vs. 51%). DM, dyslipidemia, and obesity were less prevalent within the steatosis group, whereas hypertension was similar. Other coexisting CLDs were more common within the steatosis group, and ALT and AST levels and fibrosis stage were higher among those with steatohepatitis (Table 1).

**TABLE 1** Baseline sociodemographic and clinical characteristics by histologic diagnosis

Characteristic	Steatosis (n = 254) <sup>a</sup>	Steatohepatitis (n = 394) <sup>a</sup>	Standardized mean differences <sup>b</sup>
Age at biopsy (years), median (IQR)	53 (45–61)	53 (43–60)	0.08
Sex (male), n (%)	159 (62.6)	188 (47.7)	0.3
Race/ethnicity, n (%)			
White, non-Hispanic	44 (17.3)	45 (11.4)	0.17
Hispanic	61 (24.0)	201 (51.0)	
Asian, non-Hispanic	127 (50.0)	121 (30.7)	
Black, non-Hispanic	21 (8.3)	17 (4.3)	
Race-adjusted BMI category <sup>c</sup> , n (%)	(n = 135)	(n = 327)	
Normal	29 (21.5)	24 (7.3)	0.7
Overweight	61 (45.2)	85 (26.0)	
Obese	45 (33.3)	218 (66.7)	
Diabetes, n (%)	(n = 249)	(n = 394)	0.42
	45 (18.1)	143 (36.5)	
Hypertension, n (%)	(n = 249)	(n = 392)	0.02
	107 (43.0)	172 (43.9)	
Dyslipidemia, n (%)	(n = 249)	(n = 392)	0.3
	76 (30.5)	176 (44.9)	
Statin, n (%)	(n = 249)	(n = 391)	0.2
	42 (16.9)	97 (24.8)	
Current alcohol, n (%)	(n = 193)	(n = 372)	
None/low	154 (79.8)	281 (75.5)	0.13
Moderate	25 (13.0)	50 (13.4)	
Heavy	14 (7.3)	41 (11.0)	
ALT (U/L), median (IQR)		(n = 391)	0.38
	53 (14–315)	74 (46–128)	
AST (U/L), median (IQR)		(n = 391)	0.38
	39 (36–85)	59 (39–94)	
Stage of fibrosis, n (%)			
0, no fibrosis	94 (37.0)	33 (8.4)	0.71
1–2, mild to moderate	126 (49.6)	202 (51.3)	
3–4, advanced fibrosis	34 (13.4)	159 (40.4)	
Other etiology of liver disease, n (%)			
HBV	80 (31.5)	42 (10.7)	0.75
HCV	92 (36.2)	46 (11.7)	
Other	6 (2.4)	14 (3.6)	

Abbreviation: BMI, body mass index.

<sup>a</sup>Unless otherwise specified in the table.

<sup>b</sup>Standardized mean difference > 0.1 indicates meaningful difference.

<sup>c</sup>Race-based body mass index categories: normal weight < 25 kg/m<sup>2</sup> (< 23 kg/m<sup>2</sup> for Asian), overweight 25–29 kg/m<sup>2</sup> (23–27.4 kg/m<sup>2</sup> for Asian), and obese > 30 kg/m<sup>2</sup> (≥ 27.5 kg/m<sup>2</sup> for Asian).

**TABLE 2** Baseline sociodemographic and clinical characteristics by race: Asian versus non-Asian

Characteristic	Asian (n = 248) <sup>a</sup>	Non-Asian (n = 400) <sup>a</sup>	Standardized mean differences <sup>b</sup>
Age at biopsy (years), median (IQR)	56 (46–62)	51 (42–59)	0.28
Sex (male), n (%)	137 (55.2)	210 (52.5)	0.05
Race-adjusted BMI category <sup>c</sup> , n (%)	(n = 188)	(n = 274)	
Normal	28 (14.9)	25 (9.1)	0.43
Overweight	79 (42.0)	67 (24.5)	
Obese	81 (43.1)	182 (66.4)	
Diabetes, n (%)		(n = 393)	0.03
	71 (28.6)	117 (29.8)	
Hypertension, n (%)		(n = 393)	0.2
	123 (49.6)	156 (39.7)	
Dyslipidemia, n (%)		(n = 393)	0.21
	113 (45.6)	139 (35.4)	
Statin, n (%)		(n = 392)	0.18
	65 (26.2)	74 (18.9)	
Current alcohol, n (%)	(n = 216)	(n = 349)	
None/low	191 (88.4)	244 (69.9)	0.53
Moderate	21 (9.7)	54 (15.5)	
Heavy	4 (1.9)	51 (14.6)	
ALT (U/L), median (IQR)	(n = 246)	(n = 399)	0.34
	54 (37–84)	74 (45–122)	
AST (U/L), median (IQR)	(n = 246)	(n = 399)	0.57
	38 (29–61)	61 (40–103)	
Histologic diagnosis, n (%)			
Steatosis	127 (51.2)	127 (31.8)	0.4
Steatohepatitis	121 (48.8)	273 (68.3)	
Stage of fibrosis, n (%)			
0, no fibrosis	60 (24.2)	67 (16.8)	0.48
1–2, mild to moderate	139 (56.1)	189 (47.3)	
3–4, advanced fibrosis	49 (19.8)	144 (36.0)	
Other etiology of liver disease, n (%)			
HBV	106 (42.7)	16 (4.0)	0.69
HCV	28 (11.3)	110 (27.5)	
Other	7 (2.8)	13 (3.3)	

<sup>a</sup>Unless otherwise specified in the table.<sup>b</sup>Standardized mean difference >0.1 indicates meaningful difference.<sup>c</sup>Race-based BMI categories: normal weight <25 kg/m<sup>2</sup> (<23 kg/m<sup>2</sup> for Asian), overweight 25–29 kg/m<sup>2</sup> (23–27.4 kg/m<sup>2</sup> for Asian), and obese >30 kg/m<sup>2</sup> (≥27.5 kg/m<sup>2</sup> for Asian).

## Baseline characteristics by Asian race

Sociodemographic and clinical characteristics among Asian individuals compared with all other racial/ethnic groups are reported in Table 2. The Asian group was older (56 vs. 51 years) and had a higher proportion of normal weight individuals (15% vs. 9%). They had a higher prevalence of hypertension, dyslipidemia, and statin use; heavy alcohol use was rare (2%). Approximately half of Asian individuals had steatohepatitis on biopsy,

and 56% had stage F1–F2 fibrosis. HBV infection was more common, affecting 43%, compared with only 4% among non-Asian individuals.

## Presence of steatohepatitis

To estimate the overall association of race/ethnicity with presence of steatohepatitis, a minimally adjusted multivariable model that included age, sex, and race/

**TABLE 3** Univariable and multivariable logistic regression models for the association of race/ethnicity (Asian vs. non-Asian) with presence of steatohepatitis among patients with fatty liver disease on baseline biopsy (n = 648<sup>a</sup>)

	Univariable			Model 1 (minimally adjusted) (n = 648)			Model 2 (fully adjusted) (n = 638)		
	Odds ratio	95% CI	p-Value <sup>b</sup>	Odds ratio	95% CI	p-Value <sup>b</sup>	Odds ratio	95% CI	p-Value <sup>b</sup>
Age at biopsy, per decade	0.9	0.8–1.1	0.36	0.9	0.8–1.1	0.26	1.1	0.9–1.4	0.32
Sex, ref male	<b>1.8</b>	<b>1.3–2.5</b>	<b>&lt;0.001</b>	<b>1.9</b>	<b>1.4–2.7</b>	<b>&lt;0.001</b>	1.1	0.7–1.8	0.57
Race/ethnicity, ref non-Asian									
Asian	<b>0.4</b>	<b>0.3–0.6</b>	<b>&lt;0.001</b>	<b>0.5</b>	<b>0.3–0.6</b>	<b>&lt;0.001</b>	0.7	0.4–1.2	0.16
BMI <sup>c</sup> category; ref Normal				—	—	—			
Overweight	1.7	1.0–2.8	0.06				1.9	1.0–3.6	0.06
<b>Obese</b>	<b>4.8</b>	<b>2.8–8.3</b>	<b>&lt;0.001</b>				<b>4.3</b>	<b>2.2–8.2</b>	<b>&lt;0.001</b>
<b>Diabetes (n = 641)</b>	<b>2.6</b>	<b>1.8–3.8</b>	<b>&lt;0.001</b>	—	—	—	<b>2.2</b>	<b>1.4–3.7</b>	<b>0.002</b>
Hypertension (n = 641)	1	0.8–1.4	0.82	—	—	—	0.7	0.5–1.1	0.16
Dyslipidemia (n = 641)	<b>1.9</b>	<b>1.3–2.6</b>	<b>&lt;0.001</b>	—	—	—	1.3	0.7–2.3	0.36
Statin prescription	<b>1.6</b>	<b>1.1–2.4</b>	<b>0.017</b>	—	—	—	1	0.5–2.0	0.95
Alcohol, ref				—	—	—			
none/low	1	0.6–1.7	0.99				0.9	0.5–1.7	0.78
Moderate	<b>2</b>	<b>1.1–3.7</b>	<b>0.03</b>				1.1	0.5–2.6	0.76
Heavy									
ALT, log <sub>2</sub> U/L (n = 645)	<b>1.6</b>	<b>1.4–1.9</b>	<b>&lt;0.001</b>	—	—	—	1	0.6–1.4	0.77
<b>AST, log<sub>2</sub> U/L (n = 645)</b>	<b>1.8</b>	<b>1.5–2.2</b>	<b>&lt;0.001</b>	—	—	—	<b>2.3</b>	<b>1.5–3.7</b>	<b>&lt;0.001</b>
Other CLD, ref None				—	—	—			
<b>HBV</b>	<b>0.1</b>	<b>0.1–0.2</b>	<b>&lt;0.001</b>				<b>0.3</b>	<b>0.2–0.5</b>	<b>&lt;0.001</b>
<b>HCV</b>	<b>0.1</b>	<b>0.1–0.2</b>	<b>&lt;0.001</b>				<b>0.1</b>	<b>0.1–0.2</b>	<b>&lt;0.001</b>
Other	0.6	0.2–1.6	0.32				0.5	0.2–1.6	0.28

Abbreviation: CI, confidence interval.

<sup>a</sup>Unless otherwise specified in the table.<sup>b</sup>p value < 0.05 considered statistically significant, which are bolded.<sup>c</sup>Race-based BMI categories: normal weight < 25 kg/m<sup>2</sup> (< 23 kg/m<sup>2</sup> for Asian), overweight 25–29 kg/m<sup>2</sup> (23–27.4 kg/m<sup>2</sup> for Asian), and obese > 30 kg/m<sup>2</sup> (≥ 27.5 kg/m<sup>2</sup> for Asian).

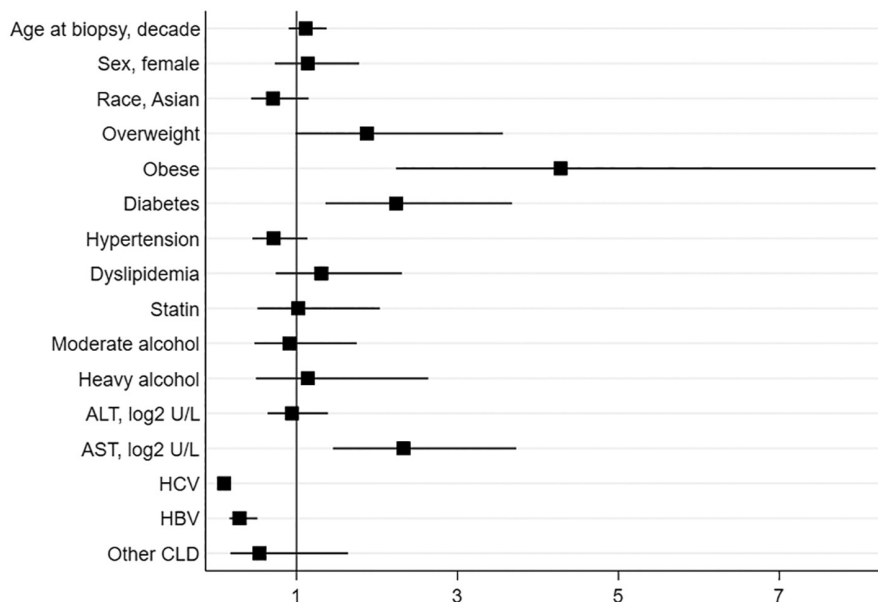
ethnicity was generated. Within the Asian versus non-Asian model, Asian race was associated with lower odds of steatohepatitis (vs. non-Asian; odds ratio [OR] = 0.5, 95% confidence interval [CI] 0.3–0.6), and women had higher odds of steatohepatitis (OR = 1.9, 95% CI 1.4–2.7) (Table 3). When all races/ethnicities were included separately, Hispanic ethnicity (reference Asian, OR = 3.3, 95% CI 2.2–4.9) and women (OR = 1.7, 95% CI 1.2–2.3) had higher odds of steatohepatitis (Table S1).

In the fully adjusted logistic regression model that included all clinically relevant predictors and race/ethnicity categorized as Asian versus non-Asian, Asian race was no longer associated with steatohepatitis. In addition, those who were obese, had DM, or higher AST level were more likely to have steatohepatitis (Table 3; Figure 1). Presence of HBV or HCV was associated with lower odds of steatohepatitis. Similarly, there was no association between race/ethnicity and steatohepatitis in the fully adjusted model with all races/ethnicities included separately (Table S1).

## Presence of advanced fibrosis

In the minimally adjusted model for the association of race/ethnicity with advanced fibrosis, Asian race (vs. non-Asian, OR = 0.4, 95% CI 0.3–0.6) and older age (OR = 1.3, 95% CI 1.1–1.5) were associated with advanced fibrosis (Table 4). When all races/ethnicities were included separately, older age (OR = 1.3, 95% CI 1.1–1.6), White race (reference Asian, OR = 3.3, 95% CI 1.9–5.7), and Hispanic ethnicity (reference Asian, OR = 2.5, 95% CI 1.6–3.7) were associated with advanced fibrosis (Table S2).

Using fully adjusted models for the associations of Asian race versus other groups both combined and separately, older age, DM, higher AST level, steatohepatitis, and HCV were associated with higher odds of advanced fibrosis; ALT level was associated with lower odds of advanced fibrosis (Table 4; Table S2). As observed with steatohepatitis, Asian race (vs. non-Asian) was not associated with advanced fibrosis once all clinical factors were included (Figure 2).



**FIGURE 1** Forest plot showing the results of the multivariable regression analysis for presence of steatohepatitis. Overweight and obese are based on race-adjusted body mass index categories. Squares indicate odds ratios and lines represent confidence intervals. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus.

Black race, however, was associated with lower odds of advanced fibrosis (reference Asian, OR = 0.2, 95% CI 0.1–0.7) with inclusion of additional predictors (Table S2).

## Change in FIB-4 category over time

FIB-4 values at baseline (time of biopsy) and at most recent follow-up laboratory data were calculated for all participants with available data. Baseline FIB-4 was calculated for 641 participants (99%), and follow-up FIB-4 was calculated for 575 participants (89%). Figure 3 shows the median FIB-4 score at baseline and follow-up for (a) non-Asian and Asian groups and (b) all race/ethnicity groups. Baseline FIB-4 for the Asian group was lowest, consistent with lower histologic fibrosis stage at baseline. However, the Asian group was the only one to have an increase in median FIB-4 over time, and notably this is across the cutoff of 1.3 from “advanced fibrosis excluded” to “indeterminate.”

Multinomial logistic regression modeling was used to estimate the association of race/ethnicity with change in FIB-4 category from baseline to follow-up. For the Asian group, median follow-up time was 3 years (interquartile range [IQR] 1.3–5.6) and 3.1 years (IQR 1.3–5.6) for the non-Asian group. The model was adjusted for follow-up time, baseline FIB-4, and baseline histology. Asian race (vs. non-Asian) was associated with increased risk of fibrosis progression as measured by increase in FIB-4 category (RRR = 1.9, 95% CI 1.0–3.5). Heavy alcohol use was also associated with fibrosis progression (Table 5).

Race/ethnicity was not associated with fibrosis improvement or progression when five categories of race/ethnicity were used; however, non-Hispanic White (vs. Asian) approached statistical significance for fibrosis progression with RRR = 0.4 (95% CI 0.2–1.1;  $p = 0.07$ ) (Table S3).

## Sensitivity analysis

When we used HCV FIB-4 cutoffs and age-adjusted FIB-4, no association of Asian race with fibrosis progression was observed (data not shown). When a change in the absolute value of the FIB-4 score was used to indicate improvement (decrease by >1) or progression (increase by >1) in fibrosis, we found weak evidence for an association of Asian race (vs. non-Asian) with lower odds of improvement (OR = 0.4, 95% CI 0.2–1.0;  $p = 0.052$ ).

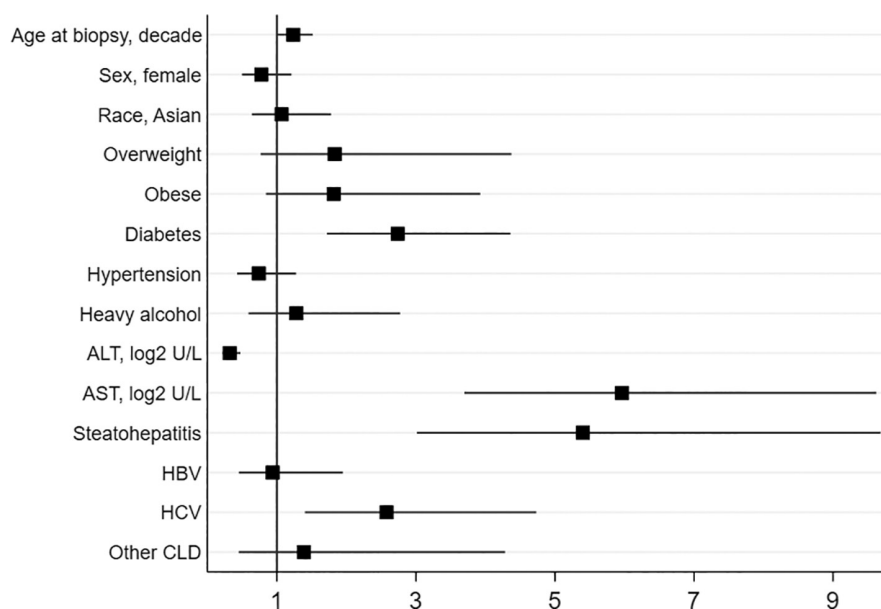
Finally, we repeated our multinomial logistic regression model while excluding individuals with concomitant liver disease and found that while Asian race remained positively associated with fibrosis progression, it was no longer statistically significant (data not shown). However, the significant reduction in the overall sample size by 66% (from 563 to 371) and the number of Asian patients by over 40% (from 248 to 107) likely affected the estimated effect size.

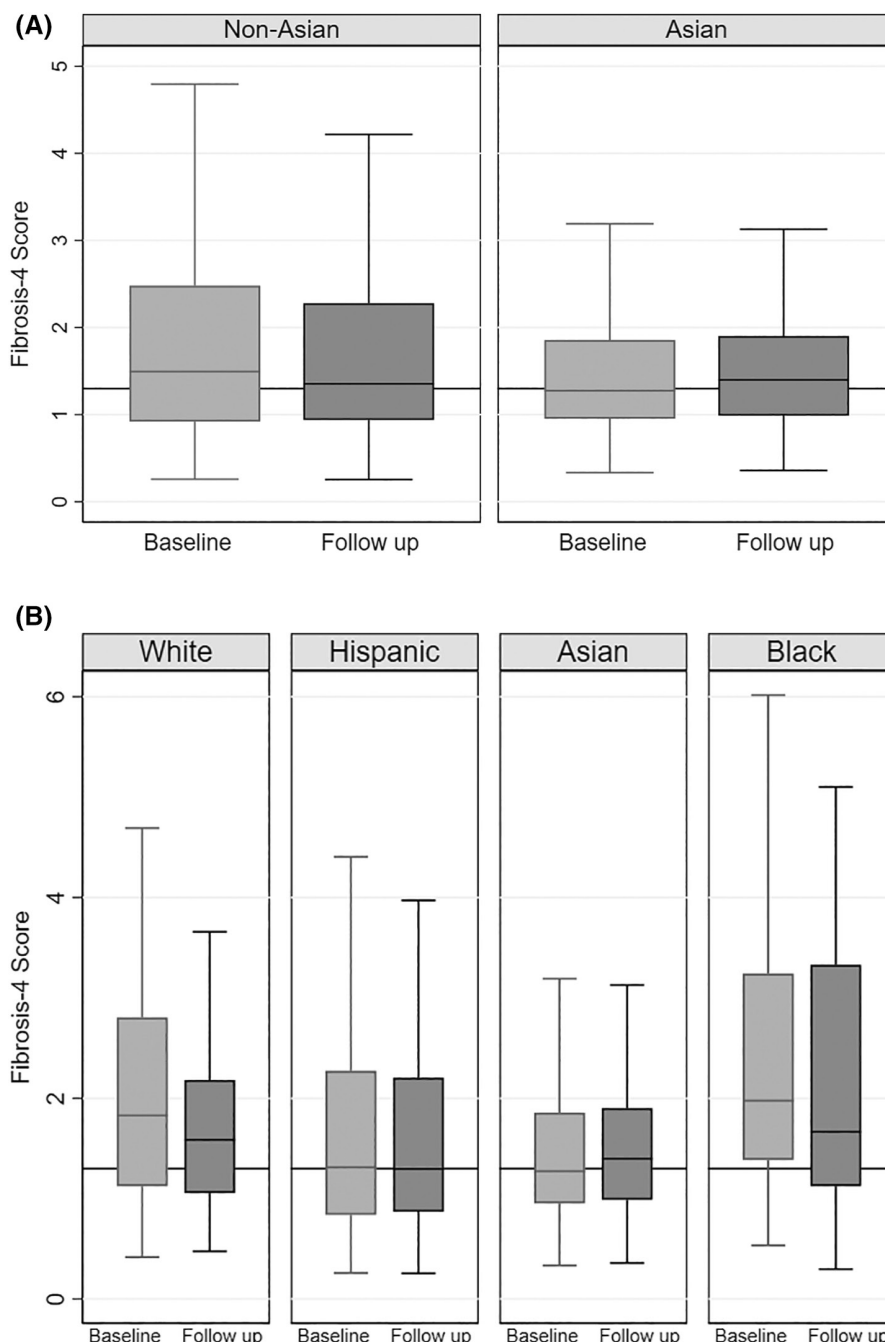
## DISCUSSION

In this longitudinal study of a diverse, safety-net cohort with histologic evidence of FLD, there were racial/ethnic differences in the distribution of steatohepatitis, with

**TABLE 4** Univariable and multivariable logistic regression models for the association of race/ethnicity (Asian vs. non-Asian) with presence of advanced fibrosis among patients with fatty liver disease on baseline biopsy (n = 648<sup>a</sup>)

	Univariable			Model 1 (minimally adjusted) (n = 648)			Model 2 (fully adjusted) (n = 638)		
	Odds ratio	95% CI	p-Value <sup>b</sup>	Odds ratio	95% CI	p-Value <sup>b</sup>	Odds ratio	95% CI	p-Value <sup>b</sup>
<b>Age at biopsy, per decade</b>	<b>1.3</b>	<b>1.1–1.5</b>	<b>0.003</b>	<b>1.3</b>	<b>1.1–1.5</b>	<b>0.001</b>	<b>1.2</b>	<b>1.0–1.5</b>	<b>0.04</b>
Sex, ref male	1.4	1.0–1.9	0.08	1.2	0.8–1.7	0.33	0.8	0.5–1.2	0.26
Race/ethnicity, ref non-Asian									
Asian	<b>0.4</b>	<b>0.3–0.6</b>	<b>&lt;0.001</b>	<b>0.4</b>	<b>0.3–0.6</b>	<b>&lt;0.001</b>	1.1	0.6–1.8	0.8
BMI <sup>c</sup> , category; ref Normal				—	—	—			
Overweight	1.1	0.6–2.2	0.69				1.8	0.8–4.4	0.18
Obese	1.4	0.8–2.5	0.25				1.8	0.8–3.9	0.13
<b>Diabetes (n = 641)</b>	<b>2.4</b>	<b>1.7–3.4</b>	<b>&lt;0.001</b>	—	—	—	<b>2.7</b>	<b>1.7–4.4</b>	<b>&lt;0.001</b>
Statin prescription	1	0.7–1.5	0.91	—	—	—	0.7	0.4–1.3	0.28
Heavy alcohol; ref None/Mod	<b>2.7</b>	<b>1.5–4.7</b>	<b>&lt;0.001</b>	—	—	—	1.3	0.6–2.8	0.53
<b>ALT, log<sub>2</sub> U/L (n = 645)</b>	<b>1.3</b>	<b>1.1–1.5</b>	<b>0.004</b>	—	—	—	<b>0.3</b>	<b>0.2–0.5</b>	<b>&lt;0.001</b>
<b>AST, log<sub>2</sub> U/L (n = 645)</b>	<b>2.4</b>	<b>2.0–3.0</b>	<b>&lt;0.001</b>	—	—	—	<b>6</b>	<b>3.7–9.6</b>	<b>&lt;0.001</b>
<b>Biopsy diagnosis; ref steatosis</b>				—	—	—			
<b>Steatohepatitis</b>	<b>4.4</b>	<b>2.9–6.6</b>	<b>&lt;0.001</b>				<b>5.4</b>	<b>3.0–9.7</b>	<b>&lt;0.001</b>
Other CLD, ref None				—	—	—			
HBV	<b>0.3</b>	<b>0.2–0.6</b>	<b>&lt;0.001</b>				0.9	0.5–1.9	0.87
<b>HCV</b>	<b>1.4</b>	<b>1.0–2.2</b>	<b>0.08</b>				<b>2.6</b>	<b>1.4–4.7</b>	<b>0.002</b>
Other	1.8	0.7–4.5	0.2				1.4	0.5–4.3	0.57

<sup>a</sup>Unless otherwise specified in the table.<sup>b</sup>p value < 0.05 considered statistically significant.<sup>c</sup>Race-based BMI categories: normal weight < 25 kg/m<sup>2</sup> (< 23 kg/m<sup>2</sup> for Asian), overweight 25–29 kg/m<sup>2</sup> (23–27.4 kg/m<sup>2</sup> for Asian), and obese > 30 kg/m<sup>2</sup> (≥ 27.5 kg/m<sup>2</sup> for Asian).**FIGURE 2** Forest plot showing the results of the multivariable regression analysis for presence of advanced fibrosis. Overweight and obese are based on race-adjusted body mass index categories. Heavy alcohol versus none/moderate. Steatohepatitis versus steatosis. Squares indicate odds ratios and lines represent confidence intervals.



**FIGURE 3** Median Fibrosis-4 (FIB-4) at baseline and follow-up by non-Asian versus Asian (A) and all race/ethnicity groups (B). Boxplots show the median FIB-4 at time of biopsy and at follow-up ([line], interquartile range [box outline], upper and lower adjacent values [ $1.5 \times \text{IQR}$ , whiskers], and outliers [not shown]). Baseline FIB-4 is lowest for the Asian group, which is consistent with the lower fibrosis stage at baseline. The Asian group is also the only one to have an increase in median FIB-4 over time, and notably this is across the cutoff of 1.3. (A) FIB-4 median (IQR) at baseline and follow-up for non-Asian (1.50 [0.92–2.48,  $n = 397$ ] to 1.35 [0.94–2.28,  $n = 361$ ]), and Asian (1.27 [0.95–1.86,  $n = 244$ ] to 1.40 [0.99–1.9,  $n = 214$ ]), respectively. (B) FIB-4 median (IQR) at baseline and follow-up for White individuals (1.83 [1.13–1.80,  $n = 88$ ] to 1.59 [1.06–2.18,  $n = 85$ ]), Hispanic (1.31 [0.84–2.27,  $n = 260$ ] to 1.30 [0.87–2.21,  $n = 232$ ]), Asian (1.27 [0.95–1.86,  $n = 244$ ] to 1.40 [0.99–1.9,  $n = 214$ ]), and Black individuals (1.98 [1.39–3.24,  $n = 38$ ] to 1.67 [1.13–3.33,  $n = 34$ ]). IQR, interquartile range.

steatosis more common among non-Hispanic individuals; steatohepatitis was more common among Hispanic individuals. Asians were older, more likely to be normal weight, and have coexisting HBV. While known risk factors including metabolic risks and alcohol were associated with steatohepatitis and advanced fibrosis, race/

ethnicity was not associated with these outcomes after adjustment. However, Asian race was associated with an increased risk of fibrosis progression based on increase in FIB-4 category.

Similar to prior studies, which found that among U.S. patients with NAFLD, 13.6% had lean NAFLD

**TABLE 5** Change in FIB-4 category from baseline to follow-up using a multinomial logistic regression model with no change as base outcome (n = 563)

Variable	Relative risk ratio	95% CI	p-Value <sup>a</sup>
<i>IMPROVEMENT, ref no change</i>			
Asian, ref non-Asian	0.9	0.5–1.5	0.61
Diabetes	1.6	0.9–2.6	0.08
Heavy alcohol use, ref none/moderate	0.8	0.4–1.9	0.66
Other CLD, ref none			
HBV	1.0	0.4–2.2	0.97
HCV	1.7	0.9–3.3	0.08
Other	1.2	0.4–4.0	0.78
<i>PROGRESSION, ref no change</i>			
<b>Asian, ref non-Asian</b>	<b>1.9</b>	<b>1.0–3.5</b>	<b>0.047</b>
Diabetes	1.3	0.7–2.4	0.39
<b>Heavy alcohol use, ref none/moderate</b>	<b>2.7</b>	<b>1.2–6.2</b>	<b>0.017</b>
Other CLD, ref none			
HBV	1.4	0.6–3.0	0.41
HCV	2.0	0.9–4.3	0.07
Other	2.0	0.5–7.8	0.33

Note: Model adjusted for follow-up time (months), baseline FIB-4 (natural log), and baseline histology (steatosis/steatohepatitis).

<sup>a</sup>p value < 0.05 considered statistically significant, which are bolded.

and 29.7% were nonobese,<sup>[29]</sup> a similar proportion of our participants had lean NAFLD (11.5%) and more were nonobese (43.1%), with a higher proportion of Asian Americans with normal weight or nonobese FLD compared with their non-Asian counterparts. Existing research on patients with nonobese and lean FLD have shown that metabolic comorbidities were more common, and they had a higher risk of advanced fibrosis.<sup>[29]</sup> Indeed, Asians in our study were more likely to have hypertension, dyslipidemia, and be on a statin. However, Asians were more likely to have mild to moderate fibrosis at baseline despite a high prevalence of other coexisting CLD, specifically HBV, compared with non-Asian counterparts, who had a higher proportion of advanced fibrosis. While other studies that did not use histologic evaluation have shown that Asians with FLD have rates of advanced fibrosis not statistically different from non-Hispanic Whites,<sup>[30]</sup> the prevalence of fibrosis in our study was similar to reports of histologic FLD within the context of HBV.<sup>[15]</sup>

It is possible that race/ethnicity is a proxy for socioeconomic factors; however, as our patient population is socioeconomically homogeneous (patients all come from a safety-net cohort), we may have not been able

to detect some racial/ethnic differences related to FLD observed in other studies. In our study, racial/ethnic differences were initially observed in minimally adjusted models, with Hispanic ethnicity associated with higher odds and Asian Americans with lower odds of steatohepatitis and advanced fibrosis on baseline biopsy. However, these associations were attenuated in multivariable models with inclusion of clinical predictors. On the other hand, non-Hispanic Black race was associated with lower odds of advanced fibrosis compared with non-Hispanic Asian individuals. While this is consistent with prior literature when non-Hispanic White race is used as the reference,<sup>[18]</sup> we interpret this result with caution given the relatively small number (n = 38) of Black patients in our cohort. Instead, our results highlight the role of metabolic risk factors on increased odds of steatohepatitis and fibrosis on biopsy, which has been consistently shown in prior literature.<sup>[20,25,44,45]</sup>

Asians had almost two times higher odds of progression compared with non-Asians, even after controlling for known metabolic risk factors, other etiologies of CLD, and heavy alcohol use. The San Francisco Bay Area has a particularly high prevalence of chronic HBV, with prevalence over 4 times that of the national rates.<sup>[46]</sup> Asian Americans/Pacific Islanders in San Francisco bear a disproportionate burden of chronic HBV infection, representing about 90% of cases but comprising only one-third of San Francisco's population.<sup>[47]</sup> As prior studies have shown that those with coexisting chronic HBV have a greater degree of steatosis or higher fibrosis stage,<sup>[48]</sup> the increased odds of progression among Asians may be related to high prevalence of chronic HBV in this population.

Our study has several limitations. First, the study was conducted at a single, urban location, which may limit the generalizability of our results in other settings. However, we prioritized this safety-net cohort given the relative lack of data on race/ethnicity and FLD in vulnerable populations. Additionally, our study included patients with concurrent FLD as well as alcohol use, HBV, or HCV, which may make it challenging to isolate the contribution of FLD on fibrosis progression despite adjusting for coexisting CLD in multivariable models. Finally, we used FIB-4 to determine progression of fibrosis in our study, which has not been adequately validated as a monitoring tool for measuring change in fibrosis. While liver biopsy is the gold standard,<sup>[49]</sup> noninvasive measures are regularly used and FIB-4 has been shown to outperform other noninvasive serologic measures of assessing progression of fibrosis.<sup>[50]</sup> The strength of our work includes a relatively large and diverse marginalized population at high risk of poor health outcomes from CLD as well as the use of biopsy for diagnosis of FLD.

## CONCLUSIONS

While we observed racial/ethnic differences in the distribution of steatohepatitis and advanced fibrosis among this safety-net cohort, these differences were explained predominantly by metabolic risk factors. However, Asian Americans had increased risk of progression of fibrosis, even after controlling for known risk factors. Given the relative paucity of data in this high-risk group for CLD, future studies should further explore factors that may contribute to this increased risk. Developing targeted interventions to address metabolic risk factors in the vulnerable population and further exploring contributors of differential disease progression and outcomes may help mitigate ongoing disparities in FLD.

## AUTHOR CONTRIBUTIONS

**Study design:** Rebecca G. Kim, Janet N. Chu, Eric Vittinghoff, James P. Grenert, and Mandana Khalili. **Data collection:** Rebecca G. Kim, Jasmine Deng, Jewel N. Reaso, and James P. Grenert. **Data analysis:** Rebecca G. Kim and Janet N. Chu. **Manuscript draft:** Rebecca G. Kim and Janet N. Chu. **Statistical analyses:** Eric Vittinghoff and Mandana Khalili. **Manuscript review:** Eric Vittinghoff, Jasmine Deng, Jewel N. Reaso, and James P. Grenert. **Approval of final submission:** Eric Vittinghoff, Jasmine Deng, Jewel N. Reaso, James P. Grenert, and Mandana Khalili. **Material support and manuscript editing:** Mandana Khalili.

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## CONFLICT OF INTEREST

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## SUPPORTING INFORMATION

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

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