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Undiagnosed abnormal alanine transaminase levels in vulnerable populations: Impact of sex, race/ethnicity, and body mass

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Abstract

Background: Liver disease is a leading cause of death in the United States and is often initially detected incidentally on lab tests ordered by general practitioners. Alanine transaminase (ALT), a marker of liver inflammation, is commonly ordered and may be abnormal in the setting of elevated body mass index, diabetes and dyslipidemia. Data regarding ALT testing within vulnerable populations are limited. Therefore, the prevalence of ALT testing and abnormal ALT in the absence of known chronic liver disease (CLD) among a safety-net population were assessed and factors associated with these outcomes were identified.

Methods: In this retrospective longitudinal study of 92,997 patients seen between 01/2017–01/2019 within San Francisco's Safety-Net Healthcare System, electronic medical records were used to abstract data back to 04/1997. Descriptive analyses and multivariable modeling were performed.

Results: Overall, 59,323 (69%) without known CLD received an ALT test. Age, Black race, Latinx ethnicity, and metabolic factors were associated with higher odds of ALT testing, ($p < 0.01$). Among those with an abnormal ALT (44%) without known CLD: median age 53 years, 41% male, 19% White, 11% Black, 40% Latinx, 29% Asian/Pacific Islander (API), and 84% overweight/obese. On multivariable analysis, female sex (OR 2.7), Latinx ethnicity (OR 2.6), API race (OR 1.3), overweight/obesity (OR 1.8, OR 2.6), and dyslipidemia (OR 1.3) were associated with abnormal ALT, ($p \leq 0.001$).

Conclusions: In the absence of known CLD, women, Latinx, API and persons with excess body weight were associated with greater odds of abnormal ALT. Future longitudinal studies are needed to confirm these differences and to determine if adequate work up for CLD is performed for abnormal ALT levels among at-risk populations.

KEYWORDS
abnormal liver tests, health disparities, NAFLD, undiagnosed liver disease

1 | INTRODUCTION

Chronic liver disease (CLD) is a leading cause of morbidity and mortality in the United States and disproportionately impacts racial/ethnic minorities and populations of low socioeconomic status.[1] CLD is often detected incidentally by primary care providers due to the variety of indications for ordering liver enzymes.[2–4] These tests, particularly alanine transaminase (ALT) reflect hepatic injury, and when abnormal, require further work up as outlined in societal guidelines.[5] Despite frequent testing[3,4,6] and accessible recommendations for work up,[5,7,8] CLD may remain undiagnosed,[9] and those disproportionately affected by socioeconomic barriers are at greatest risk.[10,11]

Abnormal ALT levels are relatively common and are estimated to range from 10% to 22% in the general population with variation due to different cut-off levels, or by sex, race/ethnicity and prevalence of elevated body mass index (BMI).[12] Within an academic primary care clinic, the prevalence of abnormal ALT was as high as 39%.[6] Metabolic risk factors including obesity, hyperglycemia and dyslipidemia can lead to higher ALT levels.[12–15] In the presence of these metabolic risk factors, particularly when viral hepatitis and heavy alcohol use have been excluded, the most likely etiology of an abnormal ALT is underlying non-alcoholic fatty liver disease (NAFLD).[15] NAFLD has become the leading cause of CLD worldwide.[16] It remains underdiagnosed in the real-world setting.[17,18] Therefore, when ALT is abnormal, a work-up for highly prevalent NAFLD should be pursued.

Normal ALT levels defined by clinical laboratories are based on the distribution among the general population, specifically the mean ± 2 standard deviations.[14,19] However, with the increasing prevalence of metabolic syndrome and possible underlying NAFLD,[20] these "normal" ALT ranges have continued to rise. More conservative, standardized, sex-based cut-offs for abnormal ALT were proposed in 2002,[21] and are recommended for use by gastroenterology and hepatology societies.[5,22] These lower normal ALT cut-offs improve the sensitivity for detecting liver injury.

There are only limited data on prevalence of abnormal ALT levels using lower sex-based cut-offs among vulnerable populations disproportionately affected by CLD.[23] This study aimed to assess demographic and metabolic risk factors associated with (1) receipt of an ALT test and (2) abnormal ALT among a large, diverse vulnerable population without known CLD. It was hypothesized that racial/ethnic minorities and those with metabolic risk factors would have a higher likelihood of an abnormal ALT test in the absence of a known CLD diagnosis.

2 | METHODS

2.1 | Participants

This is a retrospective longitudinal analysis of a primary care registry[24] that included 92,997 patients who had at least one primary care visit in the San Francisco Safety-Net Healthcare System between 1/2017–1/2019. Available data were captured retrospectively back through 4/1997. Electronic medical records (EMR) were used to abstract data for demographic, clinical and laboratory values.

Patients with a diagnosis of CLD were identified by either an ICD-9/ICD-10 code (571.0, 571.2, 571.5, 571.8, 571.9, 70.0, 76.0, 76.9, 74.60, 74.69) for cirrhosis or CLD, diagnostic laboratory testing (hepatitis C [HCV] antibodies, detectable HCV RNA, hepatitis B [HBV] surface antigen), use of anti-HCV or anti-HBV medications, or through documentation of a liver biopsy. The study was approved by the Institutional Review Board of the University of California, San Francisco and Zuckerberg San Francisco General.

2.2 | Measures

Predictors of interest were identified a priori and included sex, race/ethnicity, and metabolic measures (BMI, dyslipidemia, hypertension, and diabetes).

Variables were defined using EMR-extracted data for demographic information (age, sex, race/ethnicity, and BMI). As weight and height (for use of BMI calculation) were entered manually into the EMR, to reduce the impact of errors due to data entry, BMI was verified by a second value. If BMI values were missing for participants, manual review of the EMR was performed when possible, for calculation of a BMI. Diagnoses of dyslipidemia and diabetes were captured from the primary care registry. Hypertension was defined by the presence of a past or current prescription for an antihypertensive. Statin prescription was included as a possible explanation for liver enzyme testing and an indicator of increased metabolic risk. Human Immunodeficiency Virus (HIV) status was based on HIV antibody testing and was included as an indication for ALT monitoring.

Race-based BMI categories were used: "normal weight" <25 kg/m^2 (<23 kg/m^2 for Asian/Pacific Islander [API]), "overweight" 25–29 kg/m^2 (23–27.4 kg/m^2 for API), and "obese" >30 kg/m^2 (≥27.5 kg/m^2 for API).[25]

An assessment of available potential serologic work up for abnormal ALT in the absence of known CLD using HBV surface antigen, HCV antibody or HCV RNA was performed.

2.3 | Outcomes assessment

Primary outcomes were: (1) receipt of an ALT test and (2) an abnormal ALT value in the absence of CLD (vs. CLD group). Receipt of an ALT test was defined as the presence of an ALT result at any time in the study period. ALT value (normal vs. abnormal) was assessed using the most recent ALT value available for each participant. An abnormal ALT value was defined as >19U/L for women and >30U/L for men.[21] In addition, several other ALT cut-off values were also considered for sensitivity analysis (see Statistical Analysis). The secondary outcome was the available serologic work up of viral hepatitis conducted for the presence of an abnormal ALT in the absence of known CLD.

2.4 | Statistical analysis

Descriptive analyses included median (range and interquartile range [IQR]) and frequency (percentage). Comparative analyses were performed using Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and chi-squared test for categorical variables. Univariable and multivariable logistic regression models were used to assess the association of the predictors with the outcomes of (1) receipt of an ALT test and (2) abnormal ALT in the absence of CLD (vs. CLD group). For our primary analyses, sex-based cut-offs of >19U/L for women and >30U/L for men were used to define abnormal ALT based on guidelines.[5,22] To assess the relationships between age, sex, race/ethnicity and BMI, interaction terms were created (e.g., sex × age, race_ethnicity × age, sex × bmi, etc.) and included in the final multivariable model. Recently, a normal range of 19–25U/L for women and 30–33U/L for men was proposed.[5] Although the most conservative cut-off was selected for the primary analyses, models were repeated using the upper range of normal cut-off for men (>33U/L) and women (>25U/L) to define abnormal ALT in a sensitivity analysis. Finally, an additional sensitivity analysis was performed based on the laboratory's upper limit of normal of 35U/L to define abnormal ALT. All statistical analyses were performed using STATA statistical software package version 14, STATA Corp LP, College Station, TX.

3 | RESULTS

3.1 | Study population

Among the total study population (n = 92,997), the median age was 51 years (IQR 37–62), 50% were male, and nearly 80% were persons of color. More than half were persons with excess body weight, and medical comorbidities varied from 28% with hypertension to 7% with dyslipidemia, 4% with diabetes and 1% with HIV (Table 1). With regards to CLD work up and diagnosis, 60% received an HBV surface antigen test, 49% received an HCV antibody test, and 7% had a liver biopsy or a documented diagnosis of CLD. Overall, 6795 were found to have a CLD diagnosis or received a liver biopsy indicating full work up of abnormal liver tests (Figure 1). The most common causes of CLD were viral hepatitis with HCV (59%) and HBV (26%). Only 1.4% were documented to have NAFLD, 0.2% had a diagnosis of alcohol-associated liver disease and 4% had cirrhosis. Among those without a diagnosis of CLD (n = 86,202), 69% (n = 59,323) received an ALT test, and among whom 44% (n = 26,009) had an abnormal ALT (Figure 1).

3.2 | Receipt of an ALT test

Those with (vs. without) an ALT test were older, median age of 53 years (vs. 43), and there were racial/ethnic differences most notably among Black and API racial groups, 15% and 29% with ALT versus 9% and 35% without, respectively. Those with an ALT test were more likely to be persons with excess body weight, have metabolic risk factors, and HIV (Table 1).

On multivariable analysis while excluding those with known CLD, age, Black race, Latinx ethnicity, and excess body weight were all associated with 1.1- to 1.6-times odds of ALT testing, all $p \leq 0.005$ (Table 2). Metabolic risk factors were also associated with increased odds of ALT testing (all $p < 0.001$)—hypertension (OR 2.4, 95% CI 2.2–2.6); diabetes (OR 4.3, 95% CI 2.7–6.9); and dyslipidemia (OR 6.9, 95% CI 4.8–10.1). Interestingly, API race was associated with lower odds (OR 0.6, 95% CI 0.6–0.7, $p < 0.001$) of receiving an ALT test (Table 2).

3.3 | Abnormal ALT in the absence of diagnosed CLD

Baseline characteristics for those with a normal ALT compared to those with an abnormal ALT in the absence of CLD are shown in Table 3. Abnormal ALT occurred more frequently among women, Latinx persons, and persons with excess body weight. The proportions of individuals with no ALT test versus normal ALT versus abnormal ALT by sociodemographic and clinical characteristics are shown in Figure 2.

When comparing those with abnormal ALT in the absence of CLD to those with known CLD, the abnormal ALT group was younger (median age 53 years vs. 58), fewer were men (41% vs. 63%), non-Hispanic White (19% vs. 30%) or Black (11% vs. 23%), and significantly more were Latinx (40% vs. 17%) and persons with excess body weight (84% vs. 60%) (Figure 3). Moreover, a lower proportion with an abnormal ALT had hypertension (36% vs. 49%) or HIV (1.1% vs. 4.3%). The prevalence of dyslipidemia and statin prescription were similar across groups (data not shown).

3.3.1 | Sex-based ALT cutoff

Logistic regression was performed using predictors described above. Results using sex-based abnormal ALT cut-offs are shown in Table 4. On univariate analysis, female sex, Latinx ethnicity, API race, excess body weight, dyslipidemia, and statin prescription were all associated with increased odds of abnormal ALT. On multivariable analysis with all variables included in the model, female sex, Latinx ethnicity, and API were all associated with increased odds of abnormal ALT in the absence of CLD, (OR 2.7, 95% CI 2.5–2.9; OR 2.6, 95% CI 2.3–2.8; OR 1.3, 95% CI 1.2–1.4, respectively), all $p < 0.001$. Increased BMI was also associated with abnormal ALT; 1.8-times higher odds for overweight range (95% CI 1.6–1.9) and 2.6-times higher odds for obese category (95% CI 2.4–2.8). Dyslipidemia diagnosis and statin prescription were also associated with higher odds of abnormal ALT without CLD, while diabetes, hypertension, and HIV were associated with lower odds (Table 4). Of note, with use of a higher sex-based cut-off for abnormal ALT defined as >25U/L for women and >33U/L for men,[5] the OR for female sex decreased to 1.8 (95% CI 1.6–1.9, $p < 0.001$), (data not shown).

TABLE 1 Baseline characteristics of individuals without a chronic liver disease diagnosis by receipt of alanine aminotransferase test

Characteristic	Total population (*N* = 92,997)[a]	ALT test without CLD diagnosis (*N* = 59,323)[a]	No ALT test without CLD diagnosis (*N* = 26,879)[a]	CLD diagnosis or biopsy (*N* = 6795)[a]
Age, (median, IQR), years	51 (37–62)	53 (40–63)	43 (31–58)	58 (50–65)
Sex, male [*N* (%)]	46,441 (49.9)	29,002 (48.9)	13,195 (49.0)	4244 (62.5)
Race/ethnicity, [*N* (%)]	(*N* = 90,286)	(*N* = 57,741)	(*N* = 25,857)	(*N* = 6688)
White, non-Hispanic	19,660 (21.8)	12,384 (21.5)	5285 (20.4)	1991 (29.8)
Black, non-Hispanic	12,322 (13.7)	8446 (14.6)	2331 (9.0)	1545 (23.1)
Latinx	28,757 (31.9)	19,190 (33.2)	8466 (32.7)	1101 (16.5)
API	27,736 (30.7)	16,716 (29.0)	9127 (35.3)	1893 (28.3)
Other	1811 (2.0)	1005 (1.7)	648 (2.5)	158 (2.4)
BMI, (median, IQR) kg/m^2	(*N* = 63,007)	(*N* = 47,824)	(*N* = 9229)	(*N* = 5954)
	26.7 (23.4–31.0)	27.1 (23.7–31.5)	25.3 (22.4–29.1)	25.5 (22.6–29.2)
Race-based BMI category[b] [*N* (%)]	(*N* = 63,007)	(*N* = 47,824)	(*N* = 9229)	(*N* = 5954)
Normal	23,519 (37.3)	13,500 (28.2)	3832 (41.5)	2378 (39.9)
Overweight	20,863 (33.1)	17,161 (35.9)	3204 (34.7)	2111 (35.5)
Obese	18,625 (29.6)	17,163 (35.9)	2193 (23.8)	1465 (24.6)
Hypertension [*N* (%)]	26,106 (28.1)	21,652 (36.5)	1145 (4.3)	3309 (48.7)
Diabetes [*N* (%)]	3588 (3.9)	3168 (5.3)	38 (0.1)	382 (5.6)
Dyslipidemia [*N* (%)]	6008 (6.5)	5428 (9.2)	39 (0.2)	541 (8.0)
HIV [*N* (%)]	1108 (1.2)	806 (1.4)	7 (0.03)	295 (4.3)
ALT, (median, IQR), U/L	(*N* = 66,031)		--	(*N* = 6708)
	22 (16–32)	22 (16–32)		25 (17–40)
Statin [*N* (%)]	17,846 (19.2)	15,669 (26.4)	510 (1.9)	1667 (24.5)

Abbreviations: ALT, alanine aminotransferase; API, Asian/Pacific Islander; BMI, body mass index; CLD, chronic liver disease; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Unless otherwise specified in the table.

[b]Race-based BMI categories: normal weight <25 kg/m^2 (<23 kg/m^2 for API), overweight 25–29 kg/m^2 (23–27.4 kg/m^2 for API), and obese >30 kg/m^2 (≥27.5 kg/m^2 for API).

When evaluating for interactions between predictors of interest included in the final multivariable model, statistically significant interactions were identified between sex and age, sex and BMI, race/ethnicity and age, and race/ethnicity and BMI. There were lower odds of abnormal ALT (all $p < 0.001$) for both women (OR 0.8, 95% CI 0.8–0.9) and men (OR 0.6, 95% CI 0.6–0.7) with each decade of increase in age (from median age). Moreover, as age increased by decade, the lower odds of abnormal ALT varied by race/ethnicity—non-Hispanic White (OR 0.8, 95% CI 0.7–0.8), Black (OR 0.5, 95% CI 0.5–0.6), Latinx (OR 0.7, 95% CI 0.6–0.7), and API (OR 0.9, 95% CI 0.9–1.0). As BMI increased by 5 kg/m^2 (from median BMI), there were higher odds of having an abnormal ALT for women (OR 1.3, 95% CI 1.2–1.3) and for men (OR 1.5, 95% CI 1.5–1.6). Further, as BMI increased by 5 kg/m^2, the higher odds of abnormal ALT in the absence of CLD, varied by race/ethnicity - non-Hispanic White (OR 1.5, 95% CI 1.4–1.6), Black (OR 1.3, 95% CI 1.3–1.4), Latinx (OR 1.3, 95% CI 1.2–1.4), and API (OR 1.4, 95% CI 1.3–1.5).

3.3.2 | Lab-based ALT cutoff

Logistic regression modeling was repeated using the Zuckerberg San Francisco General lab range for ALT with a cut-off of >35U/L considered as abnormal (Table S1). All the same predictors were used within the multivariable model. With this higher cut-off, female sex was associated with lower odds of undiagnosed abnormal ALT, (OR 0.8, 95% CI 0.7–0.9). The ORs of the other variables remained similar.

3.3.3 | Additional work up of Abnormal ALT

Among those with an abnormal ALT without a CLD diagnosis using lab-based cut-offs, 66% had a negative HCV antibody test and 76% had a negative HBV surface antigen. On multivariable analysis with inclusion of all predictors, Latinx ethnicity, API race, hypertension, HIV, and statin prescription were all associated with increased odds of viral hepatitis testing. Female sex was associated with 0.8-times

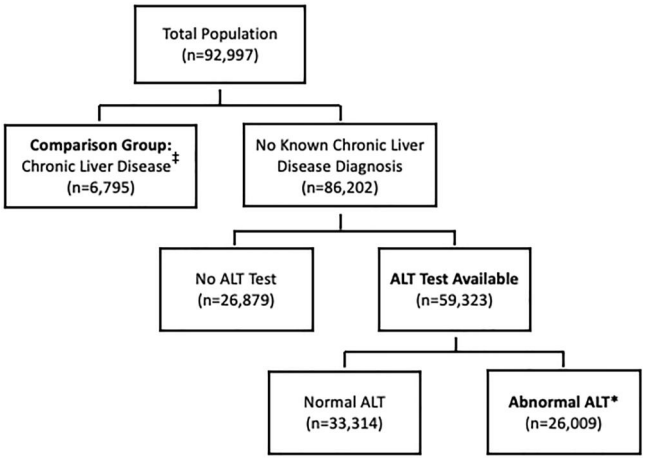

FIGURE 1 Patient flow chart by CLD diagnosis‡, ALT testing and abnormal alt using sex-based cut-offs*. ‡ Individuals with either a known CLD diagnosis or a liver biopsy indicating full work up of abnormal liver tests. * Sex-based ALT cut-offs of >19U/L for women and >30U/L for men. ALT, alanine transaminase; CLD, chronic liver disease

odds of viral hepatitis testing using either sex-based or lab-based ALT cut-offs (OR 0.8, 95% CI 0.7–0.8; OR 0.8, 95% CI 0.8–0.9, respectively) (data not shown).

4 | DISCUSSION

Overall, ALT testing in the absence of CLD was common in this study population, varied based on race/ethnicity, BMI, and presence of medical comorbidities. Moreover, 44% of individuals without CLD who received an ALT test, had at least one abnormal ALT, majority of whom, no specific diagnosis was documented. Additionally, these findings suggested differences in abnormal ALT without CLD across sexes, racial/ethnic groups, and BMI categories. While differences in abnormal ALT prevalence across these groups may represent biological variation across subpopulations, these data may also suggest disparate work up of abnormal liver tests among women, Latinx, API and persons with excess body weight receiving care in the safety-net setting.

Receipt of an ALT test was common in this study population, and risk factors for underlying NAFLD were associated with increased

TABLE 2 Univariate and multivariable analysis of factors associated with receipt of an alanine aminotransferase test among those without a CLD diagnosis; *N* = 86,202[a]

	Univariate analysis			Multivariable analysis (*N* = 55,260)		
Predictor variable	**Odds ratio**	**95% CI**	***p*-value[b]**	**Odds ratio**	**95% CI**	***p*-value[b]**
Age, per decade	**1.4**	**1.3–1.4**	**<0.001**	**1.6**	**1.6–1.7**	**<0.001**
Sex (male, ref)	1.0	1.0–1.0	0.58	1.0	0.9–1.0	0.54
Race/ethnicity (*N* = 83,598)						
White, non-Hispanic	Ref			Ref		
Black, non-Hispanic	**1.5**	**1.5–1.6**	**<0.001**	**1.3**	**1.2–1.4**	**<0.001**
Latinx	1.0	0.9–1.0	0.11	**1.1**	**1.0–1.2**	**0.005**
API	**0.8**	**0.8–0.8**	**<0.001**	**0.6**	**0.6–0.7**	**<0.001**
Other	**0.7**	**0.6–0.7**	**<0.001**	1.1	0.9–1.4	0.29
Race-based BMI category[c] (*N* = 57,053)						
Normal	Ref			Ref		
Overweight	**1.5**	**1.4–1.6**	**<0.001**	**1.2**	**1.1–1.2**	**<0.001**
Obese	**2.2**	**2.1–2.4**	**<0.001**	**1.6**	**1.5–1.7**	**<0.001**
Hypertension	**12.9**	**12.1–13.7**	**<0.001**	**2.4**	**2.2–2.6**	**<0.001**
Diabetes	**39.8**	**28.9–54.9**	**<0.001**	**4.3**	**2.7–6.9**	**<0.001**
Dyslipidemia	**69.3**	**50.6–95.0**	**<0.001**	**6.9**	**4.8–10.1**	**<0.001**
HIV	**52.9**	**25.1–111.3**	**<0.001**	**85.3**	**21.3–342.4**	**<0.001**
Statin	**18.6**	**17.0–20.3**	**<0.001**	**2.2**	**1.9–2.5**	**<0.001**

Abbreviations: ALT, alanine aminotransferase; API, Asian/Pacific Islander; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; ref, reference.

[a]Unless otherwise specified.

[b]*p*-value < 0.05 considered statistically significant, which are bolded in the table.

[c]Race-based BMI categories: normal weight <25 kg/m^2 (<23 kg/m^2 for API), overweight 25–29 kg/m^2 (23–27.4 kg/m^2 for API), and obese >30 kg/m^2 (≥27.5 kg/m^2 for API).

TABLE 3 Baseline characteristics of individuals without a CLD diagnosis and alanine aminotransferase (ALT) level using sex-based cut-offs

Characteristic	Normal ALT without CLD (*N* = 33,314)[a]	Undiagnosed abnormal[b] ALT (*N* = 26,009)[a]	*p*-value[c]
Age, (median, IQR), years	54 (40–64)	53 (41–62)	<0.001
Sex, male [*N* (%)]	18,442 (55.4)	10,560 (40.6)	<0.001
Race/ethnicity, [*N* (%)]	(*N* = 32,436)	(*N* = 25,305)	<0.001
White, non-Hispanic	7617 (23.5)	4767 (18.8)	
Black, non-Hispanic	5722 (17.6)	2724 (10.8)	
Latinx	9206 (28.4)	9984 (39.5)	
API	9333 (28.8)	7383 (29.2)	
Other	558 (1.7)	447 (1.8)	
BMI, (median, IQR) kg/m^2	(*N* = 27,076)	(*N* = 20,713)	<0.001
	26.3 (23.1–30.4)	28.4 (24.8–32.9)	
Race-based BMI category[d] [*N* (%)]	(*N* = 27,076)	(*N* = 20,748)	<0.001
Normal	9306 (34.4)	4194 (20.2)	
Overweight	9715 (35.9)	7446 (35.9)	
Obese	8055 (29.8)	9108 (43.9)	
Hypertension [*N* (%)]	12,179 (36.6)	9473 (36.4)	0.73
Diabetes [*N* (%)]	1749 (5.3)	1419 (5.5)	0.27
Dyslipidemia [*N* (%)]	2959 (8.9)	2469 (9.5)	0.01
HIV [*N* (%)]	512 (1.5)	294 (1.1)	<0.001
ALT, (median, IQR), U/L	17 (14–21)	34 (25–45)	<0.001
AST, (median, IQR), U/L	(*N* = 29,068)	(*N* = 23,687)	<0.001
	20 (17–24)	28 (23–36)	
Statin [*N* (%)]	8571 (25.7)	7098 (27.3)	<0.001

Abbreviations: ALT, alanine aminotransferase; API, Asian/Pacific Islander; AST, aspartate aminotransferase; BMI, body mass index; CLD, chronic liver disease; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Unless otherwise specified in the table.

[b]Sex-based cut-off for abnormal ALT, >19U/L for women, >30U/L for men.

[c]*p*-value < 0.05 considered statistically significant.

[d]Race-based BMI categories: normal weight <25 kg/m^2 (<23 kg/m^2 for API), overweight 25–29 kg/m^2 (23–27.4 kg/m^2 for API), and obese >30 kg/m^2 (≥27.5 kg/m^2 for API).

odds of receipt of an ALT test, including age, excess body weight, metabolic factors, and statin prescription. While Black and Latinx groups, persons with excess body weight and diabetes, were more likely to receive an ALT test, API individuals had lower odds of ALT testing. These findings suggest that metabolic risk factors may play a role in the decision to order an ALT test. However, as API individuals more commonly experience NAFLD at a non-obese BMI,[26] a suspicion for NAFLD in the presence of metabolic risk factors irrespective of BMI is critical to identify undiagnosed NAFLD in this group.

Looking more closely at those with abnormal ALT in the absence of known CLD compared to the group with CLD, age, sex, race/ethnicity, metabolic risk factors, HIV diagnosis and statin use were all significantly associated with an abnormal ALT irrespective of the ALT cut-off used. However, a reverse association was observed with female sex such that when using the sex-based ALT cut-offs, female sex was associated with 2.7-times higher odds of an abnormal ALT compared to 0.8-times lower odds with use of the lab-based cut-off. This suggests that ordering providers may be most often using the lab-based cut-offs to initiate work up of abnormal ALT, which is suboptimal. The lower ALT cut-offs were proposed to increase the sensitivity of an abnormal ALT test in identifying CLD and were developed based on the population at lowest risk for CLD including normal BMI, absence of metabolic risk factors and absence of medication use.[21] Use of the lower ALT cut-offs have been shown to predict meaningful liver-related outcomes when compared to higher cut-offs.[27] Additionally, increasing the sensitivity of ALT is crucial as elevated ALT has been associated with increased all-cause mortality among older adults in various populations,[28,29] as well as increased risk of cardiovascular disease in the United States, an association that was more prominent in women.[30] Importantly, although both men

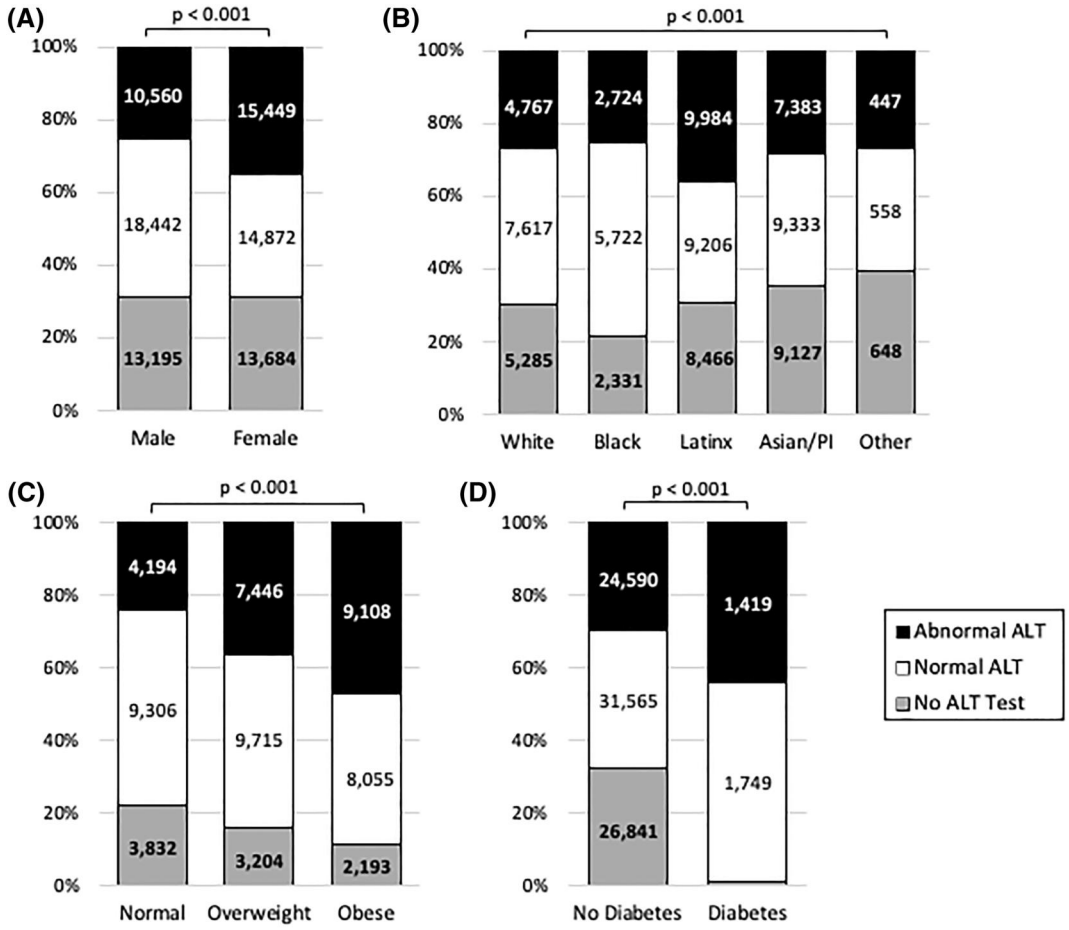

FIGURE 2 Proportions of those with an ALT Test, Normal ALT, and Abnormal ALT* without known CLD, by Sociodemographic and Clinical Categories. Percent and number of those without an ALT test (gray), with a normal ALT (white) and with an abnormal ALT (black) without known CLD by (A) sex, (B) race/ethnicity, (C) race-based BMI category, and (D) diabetes diagnosis shown on the *y*-axis and in the text box, respectively. Chi-squared tests used for comparative analyses and *p*-values as included above. * Sex-based ALT cut-offs of >19U/L for women and >30U/L for men. ALT, alanine transaminase; API, Asian/Pacific Islander; BMI, body mass index; CLD, chronic liver disease

and women had lower odds of an abnormal ALT with increasing age, (which may have been due to closer follow up and more thorough diagnostic evaluations among older adults), there was a 40% decrease in abnormal ALT with each increase in decade of age for men, while women only saw a 20% decrease suggesting a potential gender disparity in abnormal ALT work-up.

Potential racial disparities were observed in abnormal ALT prevalence particularly among Latinx and API groups. With known increasing prevalence of NAFLD among Latinx individuals,[31] and NAFLD occurring at lower BMIs among Asian individuals,[26] these groups are at greater risk of having undiagnosed NAFLD compared to the non-Hispanic White population. Increased awareness of risk factors, knowledge and application of updated abnormal ALT cut-offs, as well as clinical suspicion and diligence by general practitioners are critical to enhancing equity in diagnostic work up for underlying CLD in the setting of abnormal ALT across racial/ethnic minority groups.

Irrespective of which ALT cut-offs were used, diabetes and hypertension were associated with lower odds of an abnormal ALT. In this study, the reason for this inverse relationship could not be evaluated. On the other hand, dyslipidemia and elevated body weight were associated with increased odds of abnormal ALT. Regarding dyslipidemia, as statin prescription was also associated with increased odds of abnormal ALT in the absence of CLD, it is possible that for patients with dyslipidemia and a statin prescription, an abnormal ALT was attributed to statin use and no additional work up was initiated by the provider. Further studies are needed to explore these findings.

The study has several limitations. Data were collected within a single healthcare system that provides care for vulnerable populations limiting the study's generalizability. The chronicity of abnormal ALT levels is unknown as only the most recent ALT value was collected. It is possible that not all ICD-9/ICD-10 codes were extracted from the EMR, resulting in subjects misclassified as having no CLD. Additionally, reliance on ICD-9/ICD-10 codes to identify individuals with hypertension, diabetes and dyslipidemia, may have resulted in incompleteness of data or variable accuracy of coding for the proportion identified with these conditions in this study. Lastly, due to the inability to collect data regarding imaging studies, it is not

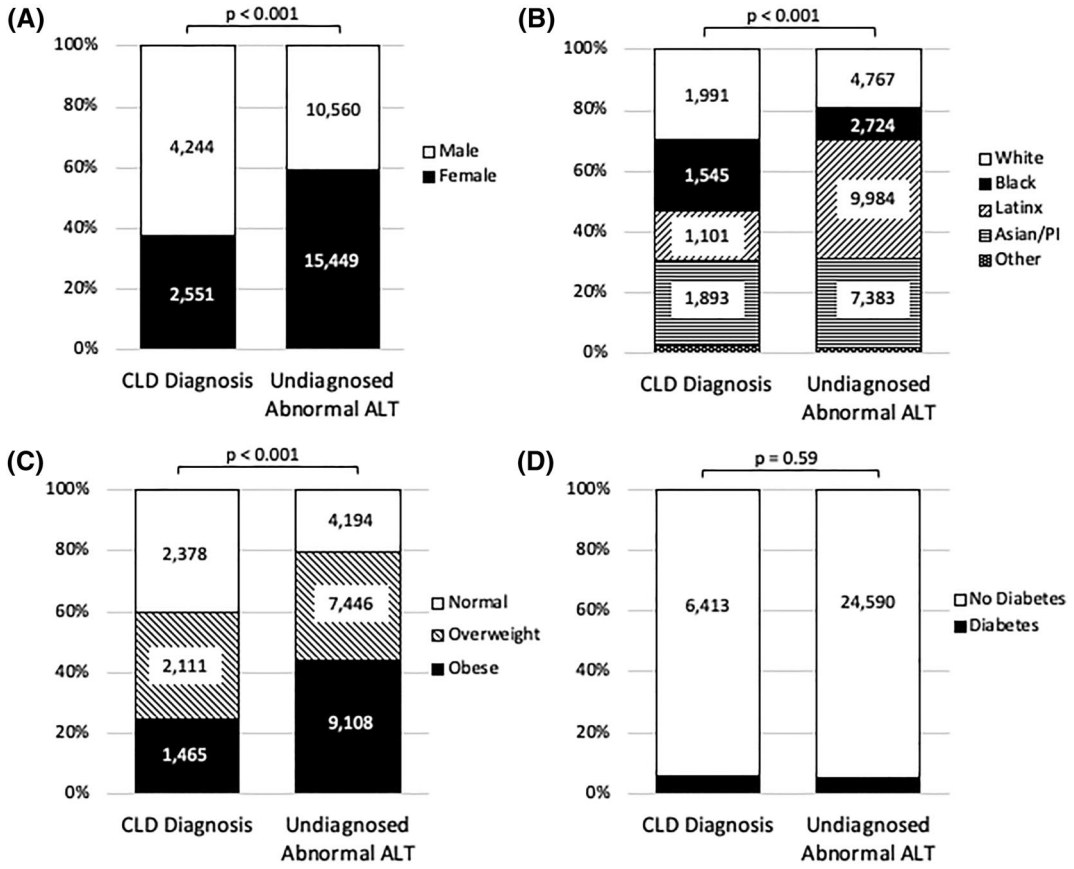

FIGURE 3 Proportions of Individuals within Sociodemographic and Clinical Categories Among our CLD and Undiagnosed ALT* Groups. Percent and number of those within each sociodemographic or clinical diagnosis group included within the CLD diagnosis group and the undiagnosed abnormal ALT group by (A) sex, (B) race/ethnicity, (C) race-based BMI category, and (D) diabetes diagnosis. Chi-squared tests used for comparative analyses and *p*-values as included above. *Sex-based ALT cut-offs of >19U/L for women and >30U/L for men. ALT, alanine transaminase; API, Asian/Pacific Islander; BMI, body mass index; CLD, chronic liver disease

known if patients received an abdominal ultrasound or cross-sectional study—a key component in the work up of abnormal ALT. Even with these limitations, the findings are important and highlight the high prevalence of abnormal ALT in the absence of CLD among this vulnerable population as well as the association of the outcomes with various clinical and sociodemographic characteristics. Strengths of the study include the large and diverse sample size and the use of a safety-net population that is underrepresented in research. Additionally, these data were collected over an extended period that captured work up completed longitudinally.

5 | CONCLUSION

In summary, ALT testing was common in this vulnerable population, and among individuals without CLD with an ALT test, nearly half had an abnormal ALT. When using the guideline recommended sex-based ALT cut-off, odds of an abnormal ALT in the absence of CLD was significantly greater for women, certain racial/ethnic groups, and persons with excess body weight. Based on these results, awareness of sex-based ALT cut-offs must be improved. Moreover, future studies to confirm these observations and to evaluate the work up performed for abnormal ALT levels among vulnerable populations are critical.

AUTHOR CONTRIBUTIONS

Rebecca G. Kim contributed to study design, performed data analysis, wrote the manuscript, and approved the final submission. Mandana Khalili contributed to study design, data collection, provided material support, reviewed statistical analysis, edited the manuscript, and approved the final submission. All authors had access to the data.

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CONFLICT OF INTEREST

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TABLE 4 Univariate and multivariable analysis for individuals with undiagnosed abnormal alanine aminotransferase (ALT) versus CLD—sex-based ALT cut-offs[b]; *N* = 32,804[a]

	Univariate analysis			Multivariable analysis (*N* = 25,997)		
Variable	**Odds ratio**	**95% CI**	***p*-value[c]**	**Odds ratio**	**95% CI**	***p*-value[c]**
Age, per decade	**0.8**	**0.8–0.8**	**<0.001**	**0.7**	**0.7–0.8**	**<0.001**
Sex (male, ref)	**2.4**	**2.3–2.6**	**<0.001**	**2.7**	**2.5–2.9**	**<0.001**
Race/ethnicity (*N* = 31,993)						
White, non-Hispanic	Ref			Ref		
Black, non-Hispanic	**0.7**	**0.7–0.8**	**<0.001**	**0.7**	**0.7–0.8**	**<0.001**
Latinx	**3.8**	**3.5–4.1**	**<0.001**	**2.6**	**2.3–2.8**	**<0.001**
API	**1.6**	**1.5–1.8**	**<0.001**	**1.3**	**1.2–1.4**	**<0.001**
Other	1.2	1.0–1.4	0.083	0.9	0.7–1.2	0.58
Race-based BMI category[d] (*N* = 26,702)						
Normal	Ref			Ref		
Overweight	**2.0**	**1.9–2.1**	**<0.001**	**1.8**	**1.6–1.9**	**<0.001**
Obese	**3.5**	**3.3–3.8**	**<0.001**	**2.6**	**2.4–2.8**	**<0.001**
Hypertension	**0.6**	**0.6–0.6**	**<0.001**	**0.7**	**0.6–0.8**	**<0.001**
Diabetes	1.0	0.9–1.1	0.59	**0.8**	**0.7–0.9**	**0.001**
Dyslipidemia	**1.2**	**1.1–1.3**	**<0.001**	**1.3**	**1.1–1.4**	**<0.001**
HIV	**0.3**	**0.2–0.3**	**<0.001**	**0.4**	**0.3–0.5**	**<0.001**
Statin	**1.2**	**1.1–1.2**	**<0.001**	**2.1**	**1.9–2.3**	**<0.001**

Abbreviations: ALT, alanine aminotransferase; API, Asian/Pacific Islander; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; ref, reference.

[a]Unless otherwise specified in the table.

[b]Sex-based cut-off for abnormal ALT, >19U/L for women, >30U/L for men.

[c]*p*-value < 0.05 considered statistically significant, which are bolded in the table.

[d]Race-based BMI categories: normal weight <25 kg/m^2 (<23 kg/m^2 for API), overweight 25–29 kg/m^2 (23–27.4 kg/m^2 for API), and obese >30 kg/m^2 (≥27.5 kg/m^2 for API).

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