



Lower FIB-4 threshold in patients with diabetes improves diagnostic accuracy of the test in a Hispanic population

Jasleen Singh¹, Brittney Ibrahim², Nicholas J. Jackson¹, Haydar Khalil², Julia Valenzuela², Beshoy Yanny¹, Sammy Saab^{1,2}

¹Department of Medicine, University of California at Los Angeles (UCLA), Los Angeles, CA, USA; ²Department of Surgery, Pflieger Liver Institute, University of California at Los Angeles (UCLA), Los Angeles, CA, USA

Contributions: (I) Conception and design: J Singh, B Ibrahim, S Saab; (II) Administrative support: S Saab; (III) Provision of study materials or patients: B Yanny, S Saab; (IV) Collection and assembly of data: B Ibrahim, H Khalil, J Valenzuela, B Yanny; (V) Data analysis and interpretation: NJ Jackson, J Singh, B Yanny, S Saab; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sammy Saab, MD, MPH, AGAF, FAASLD. Department of Medicine, University of California at Los Angeles (UCLA), Los Angeles, CA, USA; Department of Surgery, Pflieger Liver Institute, University of California at Los Angeles (UCLA), 100 Medical Plaza, Suite 700, Los Angeles, CA 90095, USA. Email: Ssaab@mednet.ucla.edu.

Background: Non-invasive tests (NITs) can be used to estimate the severity of fibrosis in patients with nonalcoholic fatty liver disease (NAFLD) but their diagnostic accuracy is variable. Hispanic patients are at increased risk of NAFLD and diabetes. We evaluate the diagnostic performance of the fibrosis index based on 4 factors (FIB-4) in a population of Hispanic patients who underwent vibration-controlled transient elastography (VCTE).

Methods: A total of 1,524 patients underwent VCTE at University of California, Los Angeles from July 18, 2019 to June 7, 2022. Ultimately 110 patients were identified as Hispanic, with confirmed NAFLD. Sensitivity, specificity, positive predictive value and negative predictive value of FIB-4 threshold ≥ 1.3 were calculated. Logistic regression models were used to determine updated thresholds for patients with and without diabetes based on Youden's index.

Results: Of the 110 patients, the majority (65%) were female. Prevalence of diabetes was higher in the group with clinically significant fibrosis (76% vs. 36%, $P < 0.001$). Using a FIB-4 threshold ≥ 1.3 to predict clinically significant fibrosis (F2–F4 on VCTE), area under the receiver operating characteristic (AUROC) was 0.74. By incorporating diabetes status, AUROC was 0.81 when employing a FIB-4 threshold of ≥ 1.0 in patients with diabetes and ≥ 1.5 in patients without diabetes.

Conclusions: Using a FIB-4 threshold of ≥ 1.0 in patients with diabetes and ≥ 1.5 in patients without diabetes improves the diagnostic performance of the test. The new FIB-4 including diabetes status will lead to improved screening in patients who are at risk of clinically significant fibrosis.

Keywords: Non-invasive tests (NITs); nonalcoholic fatty liver disease (NAFLD); liver fibrosis; transient elastography; screening

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Introduction

Staging of liver fibrosis is considered the most important predictor of liver-related morbidity and mortality in patients with nonalcoholic fatty liver disease (NAFLD) (1-5). Non-invasive tests (NITs) to determine fibrosis stage have

largely replaced liver biopsy in clinical practice, especially in patients with metabolic associated fatty liver disease (1,6). Imaging elastography and serum biomarkers are the two predominant types of NITs that are currently available (7-9). As NAFLD is increasing in prevalence, screening for the

disease in at-risk populations, such as those with metabolic comorbidities, is warranted in the primary care and endocrinology settings. In fact, the American Association of Clinical Endocrinology and newly published American Association for the Study of Liver Diseases (AASLD) practice guidelines propose an algorithm for screening NAFLD in the non-gastroenterology (GI)/hepatology setting using the fibrosis index based on 4 factors (FIB-4). If FIB-4 is <1.3 , the patient is considered low risk and FIB-4 can be monitored periodically. Whereas, if FIB-4 is >2.67 or if secondary risk assessment with elastography or enhanced liver fibrosis (ELF) indicates intermediate or high risk, the patient should be referred to GI/hepatology care (1,10). The widespread use of this NIT in clinical practice relies on its diagnostic abilities.

The diagnostic performance of scores such as FIB-4, NAFLD Fibrosis Score (NFS) and Aspartate aminotransferase-to-platelet ratio index (APRI) is variable and can vary across disease etiologies (11-15). The inconsistent results of NITs and variability between the different scores are certainly a limitation for providers to

consider when utilizing in clinical practice (16). Recent studies have demonstrated the poor performance of FIB-4, especially in patients with diabetes (17,18). In fact, one study found a 43% overall false negative rate of FIB-4 using elastography as the reference standard with a higher proportion of false negatives in patients with diabetes than in patients without diabetes (18). Another recent study evaluated the accuracy of FIB-4 in detecting elevated liver stiffness measurement (LSM) and found that diabetes was one variable in which there was a higher proportion of false negative FIB-4 scores (19). This may be due to the fact that patients with diabetes may not have elevated aminotransferases and have a more progressive clinical course than their non-diabetic counterparts (1,10,17,20).

Furthermore, the reliability of NITs is unknown in patients of Hispanic ethnicity and has not been validated in this population. Prevalence of both NAFLD and diabetes is higher in Hispanic patients (1,10,21). If NITs underperform in patients with comorbid conditions such as diabetes, then patients of Hispanic origin may be further disadvantaged by these noninvasive scores. Therefore, we aimed to evaluate diagnostic performance of FIB-4 in NAFLD using LSM as the comparative standard in patients of Hispanic origin and proposed a modified FIB-4 to include diabetes. We present this article in accordance with the STARD reporting checklist (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-62/rc>).

Highlight box

Key findings

- Authors provide a novel concept of modifying the fibrosis index based on 4 factors (FIB-4) threshold to ≥ 1.0 in patients with diabetes and ≥ 1.5 in patients without diabetes to improve the diagnostic performance of the test.

What is known and what is new?

- Non-invasive tests are commonly used to estimate severity of fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). Patients with diabetes are known to have a more progressive course of NAFLD and can have normal aminotransferases which could falsely lower the FIB-4 score. Per society guidelines, a FIB-4 threshold of <1.3 is often used to rule out advanced fibrosis.
- The new finding from the study included a modified FIB-4 threshold of ≥ 1.0 in patients with diabetes to improve the sensitivity of the test and thus, properly screen patients with diabetes who are at risk of significant or advanced fibrosis. Patients without diabetes can be appropriately risk stratified for significant or advanced fibrosis with a higher FIB-4 threshold of ≥ 1.5 .

What is the implication, and what should change now?

- By lowering the FIB-4 threshold, patients with diabetes, who are at a higher risk of fibrosis progression in NAFLD, will be more appropriately screened.
- Providers should consider modifying FIB-4 threshold in patients with diabetes, especially those with normal aminotransferases, so that fibrosis can be appropriately screened in this population.

Methods

Study population

We conducted a retrospective, single-center review of patients who underwent vibration-controlled transient elastography (VCTE) for suspected NAFLD at University of California, Los Angeles from July 18, 2019 to June 7, 2022. A total of 1,524 patients completed VCTE in this time period. Patients were then identified as “Hispanic” origin based on ethnicity/race in electronic medical record (EMR). Disease etiology was confirmed as NAFLD in this group of patients based on EMR and steatosis score on VCTE. Data on co-morbid conditions were identified via chart extraction. Ultimately, 110 patients were included in the study. A flow chart of patients included in the study is depicted in *Figure 1*. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was certified exempt from the Institutional Review Board (IRB) at UCLA per 45 CFR 46.104 category

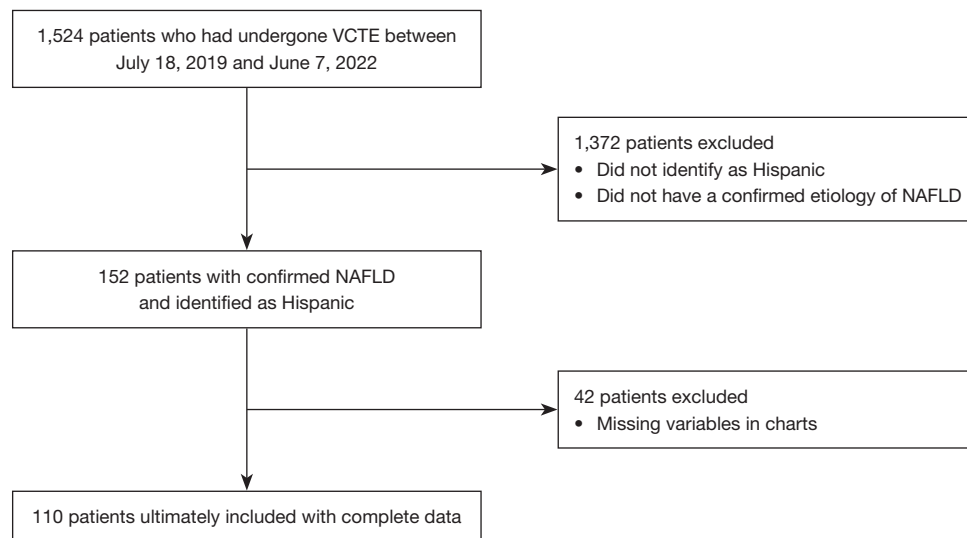


Figure 1 Patient inclusion flow chart. VCTE, vibration-controlled transient elastography; NAFLD, nonalcoholic fatty liver disease.

4(iii). Informed consent was waived due to the IRB exempt status of the study.

Data collection

Basic demographic information including age, sex, weight, height, body mass index (BMI), household income, insurance type, co-morbid conditions, lab values, VCTE scores and imaging results were obtained from the EMR. Laboratory values were collected within 1 year of the date of VCTE. FIB-4 was calculated based on the following equation: $[\text{age (years)} \times \text{AST (U/L)}] / [(\text{platelets (10}^9/\text{L)}) \times [\text{ALT (U/L)}]^{1/2}]$ (22). LSM values and steatosis scores were the average of 10 values that were obtained. Patients were designated into the F0–F1 fibrosis group and F2–F4 fibrosis group based on the LSMs. Values of LSM ranging from 1.5 kilopascals (kPa) to 8.2 kPa were categorized as F0–F1, 8.3–9.7 as F2, 9.8–13.6 as F3 and 13.6 and above as F4 (23).

Outcomes

We evaluated the sensitivity, specificity, positive predictive value and negative predictive value of FIB-4 in 110 patients of Hispanic origin. We defined a positive test using a threshold of ≥ 1.3 , which is based on the algorithm for fibrosis assessment developed by the AASLD (1). We also evaluated the performance of a score including both FIB-4 and presence or absence of diabetes. Using the enhanced

diagnostic accuracy of this new score, we proposed new thresholds for FIB-4 to predict significant fibrosis in patients with diabetes and without diabetes.

Statistical analysis

Differences in demographic and clinical characteristics between fibrosis groups (F0–F1 *vs.* F2–F4) were assessed using *t*-tests for continuous variables and exact tests for categorical. These tests were also used to assess for bivariate differences in imaging characteristics between those with FIB-4 values < 1.3 *vs.* ≥ 1.3 . Because diabetes is a known confounder of fibrosis, we attempted to identify diabetes status specific FIB-4 thresholds. Logistic regression models were used with quadratic terms for continuous FIB-4 in order to determine the discriminatory ability of FIB-4 to differentiate between fibrosis group membership within groups with diabetes.

Models were fit using clustered robust standard error for patient to account for the correlation within patients across repeated observations. Area under the receiver operating curve (AUROC) was computed as the primary measure of discriminatory ability and sensitivity, specificity, positive predictive value, and negative predictive value were computed at the various thresholds of FIB-4. Youden's index was used to select an optimal threshold for FIB-4 which maximized both sensitivity and specificity (24). Conducted in Stata version 17.0, StataCorp LLC (College Station, Texas, USA). Descriptive statistics were utilized.

Results

A total of 110 Hispanic patients were included in the study. Demographic characteristics comparing patients with F0–F1 fibrosis and F2–F4 fibrosis based on LSM are shown in *Table 1*. Sixty-five percent were female. Mean BMI in the cohort was 32.4 ± 5.9 kg/m² with a significantly higher mean BMI of 35.1 ± 6.0 kg/m² in the F2–F4 group compared to a mean BMI of 31.3 ± 5.5 kg/m² in the F0–F1 group ($P=0.003$). Household income was evenly distributed between the categories of <\$75,000, \$75,000–100,000 and \$100,000–150,000 with a minority in the >\$150,000 group and was similar between patients with F0–F1 and F2–F4 fibrosis ($P=0.380$). The majority of patients had private insurance. Almost half (48%) of patients had diabetes and there was a significantly higher incidence of diabetes in the group with F2–F4 fibrosis as compared to the group with F0–F1 fibrosis (76% vs. 36%, $P<0.001$). Many patients also had other comorbid conditions such as hypertension, dyslipidemia and obesity. Laboratory values were also collected and are included in *Table 1*. Notably, the mean ALT was elevated at 57.1 ± 37.7 but was not significantly different between patients with F0–F1 and F2–F4 fibrosis (55.1 ± 37.7 and 61.5 ± 38.0 respectively, $P=0.419$). Mean liver stiffness was 7.63 ± 6.30 kPa overall, with a mean LSM of 5.00 ± 1.17 kPa in the F0–F1 group and 13.77 ± 8.75 kPa in the F2–F4 group ($P<0.001$). The majority of patients overall had S3 steatosis (56%). Additional patient characteristics

are shown in *Table 1*. All patients had imaging with either computed tomography (CT), ultrasound or magnetic resonance imaging (MRI). Eighty-two percent of patients overall had steatosis on imaging, 29% with hepatomegaly, 7% with splenomegaly and 7% with a nodular contour.

We calculated the diagnostic accuracy of FIB-4, with LSM as the reference standard, using ≥ 1.3 as the threshold for a positive test. Sensitivity was 68.8% and specificity was calculated to be 67.1%. The positive and negative predictive value were 46.8% and 83.6% respectively. The odds ratio for predicting significant fibrosis (F2–F4 on LSM) was 4.49 [95% confidence interval (CI): 1.88–10.66; $P<0.001$] with an AUROC of 0.74, depicted in *Figure 2*.

Since diabetes was found to be a significant predictor of F2–F4 fibrosis, we opted to evaluate the diagnostic performance of FIB-4 by adding the presence or absence of diabetes. In patients with diabetes, Youden's index indicates a FIB-4 threshold of 1.247 to maximally optimize the sensitivity and specificity which would be 70.8% and 71.4% respectively. However, to enhance sensitivity, a FIB-4 threshold of 1.000 with a sensitivity of 87.5% and specificity 46.4% would optimally identify patients at risk of significant fibrosis without foregoing specificity (*Table 2*). In patients without diabetes, Youden's index for FIB-4 is 1.522 which corresponds to a sensitivity of 75% and specificity of 75% (*Table 3*). Clinically, the threshold of 1.522 also reflects the number that optimizes sensitivity in this population. Modifying FIB-4 to include the presence or absence of

Table 1 Patient characteristics by fibrosis stage on vibration-controlled transient elastography

Variable	Total (n=110)	F0–F1 (n=77)	F2–F4 (n=33)	P
Age (years)	53.2±13.5	51.0±13.8	59.3±11.4	0.005
Sex				0.189
Male	38 (35%)	30 (39%)	8 (24%)	
Female	72 (65%)	47 (61%)	25 (76%)	
Weight (kg)	87.2±17.5	84.7±16.5	92.9±18.7	0.035
Height (cm)	164±11	165±11	163±11	0.373
BMI (kg/m ²)	32.4±5.9	31.3±5.5	35.1±6.0	0.003
Household income				0.380
<\$75,000	30 (27%)	19 (25%)	11 (33%)	
\$75,000–100,000	29 (26%)	23 (30%)	6 (18%)	
\$100,000–150,000	36 (33%)	23 (30%)	13 (39%)	
>\$150,000	15 (14%)	12 (16%)	3 (9%)	

Table 1 (continued)

Table 1 (continued)

Variable	Total (n=110)	F0–F1 (n=77)	F2–F4 (n=33)	P
Insurance				0.584
Private	78 (71%)	55 (71%)	23 (70%)	
Public	29 (26%)	19 (25%)	10 (30%)	
Other	3 (3%)	3 (4%)	0	
Diabetes	53 (48%)	28 (36%)	25 (76%)	<0.001
Essential hypertension	51 (46%)	32 (42%)	19 (58%)	0.146
Dyslipidemia	53 (48%)	38 (49%)	15 (45%)	0.835
Obesity (BMI >30 kg/m ²)	71 (65%)	43 (56%)	28 (85%)	0.004
White blood cell count (×10 ⁹)	6.84±2.19	6.83±2.18	6.86±2.23	0.941
Hemoglobin (g/dL)	13.9±1.8	14.1±1.9	13.6±1.6	0.140
Platelet count (×10 ⁹)	251±65	258±64	235±68	0.111
Glucose (mg/dL)	116±39	110±34	128±47	0.049
AST (IU/L)	47.0±43.7	43.0±46.3	56.5±35.6	0.101
ALT (IU/L)	57.1±37.7	55.1±37.7	61.5±38.0	0.419
Elevated ALT*	83 (75%)	56 (73%)	27 (82%)	0.345
AST/ALT ratio	0.907±0.495	0.875±0.536	0.983±0.382	0.235
Alkaline phosphatase (IU/L)	92.7±31.6	89.3±31.9	100.6±29.9	0.081
Total bilirubin (mg/dL)	0.545±0.431	0.532±0.414	0.576±0.473	0.650
Albumin (g/dL)	4.43±0.39	4.50±0.40	4.29±0.30	0.005
Total cholesterol (mg/dL)	185±49	186±48	182±51	0.729
Hemoglobin A1c (%)	6.56±1.38	6.29±1.07	7.15±1.78	0.019
TSH (mIU/L)	2.52±3.96	2.70±4.63	2.10±1.31	0.347
CAP score	329±46	328±43	330±52	0.815
IQR CAP	29.3±14.5	30.8±15.3	25.8±11.9	0.072
Liver stiffness (kPa)	7.63±6.30	5.00±1.17	13.77±8.75	<0.001
IQR liver stiffness	0.871±0.920	0.506±0.279	1.721±1.277	<0.001
Steatosis				0.057
S1	20 (18%)	12 (16%)	8 (24%)	
S2	28 (25%)	16 (21%)	12 (36%)	
S3	62 (56%)	49 (64%)	13 (39%)	
FIB-4 >1.3				0.001
No	63 (57%)	52 (68%)	11 (33%)	
Yes	47 (43%)	25 (32%)	22 (67%)	
FIB-4, mean ± SD		1.29±1.29	1.99±1.31	0.013
FIB-4, median [IQR]		1.01 [0.70, 1.49]	1.57 [1.16, 2.77]	<0.001

Values, where applicable, reported as mean ± SD, n (%), or median [IQR]. *, defined as >33 IU/L for men and >25 IU/L for women. Equation: FIB-4 = age (years) × AST (U/L)/[PLT (10⁹/L) × ALT (U/L)^{1/2}]. BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; TSH, thyroid stimulating hormone; CAP, controlled attenuation parameter; IQR, interquartile range; FIB-4, fibrosis-4; SD, standard deviation; PLT, platelet count.

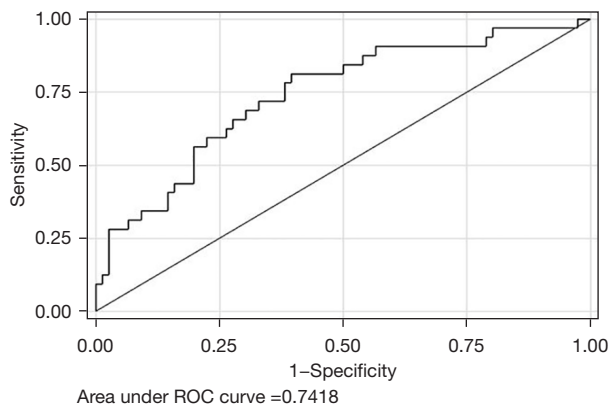


Figure 2 Area under the receiver operating characteristic 0.74 for fibrosis stage 2 to fibrosis stage 4 in model using quadratic fibrosis-4 predictor. ROC, receiver operating characteristic.

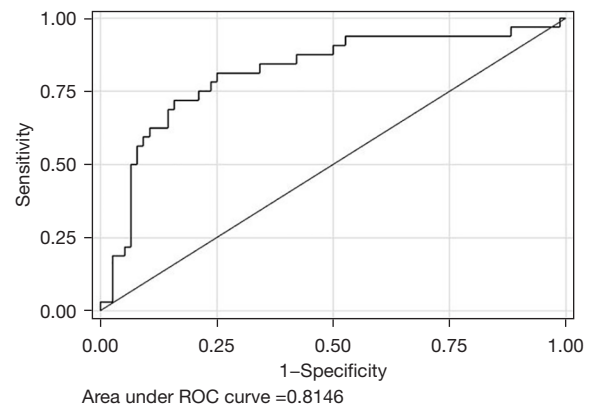


Figure 3 Area under the receiver operating characteristic 0.81 for fibrosis stage 2 to fibrosis stage 4 in model using quadratic fibrosis-4 predictor and adjusting for diabetes status. ROC, receiver operating characteristic.

Table 2 Fibrosis-4 thresholds and diagnostic performance in patients with diabetes

FIB-4 cutoff	Youden's index	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
0.887	–	95.8	28.6	53.5	88.9
1.000*	–	87.5	46.4	58.3	81.2
1.247	Yes	70.8	71.4	68.0	74.1

*, a threshold of 1.000 corresponds to the clinically significant value that optimizes sensitivity. FIB-4, fibrosis index based on 4 factors.

Table 3 Fibrosis-4 thresholds and diagnostic performance in patients without diabetes

FIB-4 cutoff	Youden's index	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
1.441	–	75.0	68.8	28.6	94.2
1.522*	Yes	75.0	75.0	33.3	94.7
1.739	–	50.0	87.5	40.0	91.3

*, a threshold of 1.522 corresponds to the clinically significant value that maximizes sensitivity and specificity. FIB-4, fibrosis index based on 4 factors.

diabetes increases the AUROC to 0.81, shown in *Figure 3*.

Discussion

In this study, we demonstrated the suboptimal sensitivity and specificity of a FIB-4 threshold of 1.3 to predict significant fibrosis in patients of Hispanic origin with NAFLD, with an AUROC 0.74. By including the presence or absence of diabetes, the AUROC improved to 0.81, using a threshold of 1.0 for patients with diabetes and a threshold of 1.5 for patients without diabetes to predict significant fibrosis. By modifying the thresholds using diabetes as a

factor in the FIB-4 model, we increase the sensitivity of the noninvasive test, thereby capturing more patients who are at risk of significant fibrosis.

Fibrosis is the single most important predictor of liver-related morbidity and mortality and thus, screening modalities to estimate fibrosis need to be accurate (1-5). Patients with diabetes are at higher risk of advanced fibrosis and the need to minimize false negatives in this population is critical (1,10,20). In fact, patients with diabetes and NAFLD with or without steatohepatitis can have normal aminotransferases and thus, a FIB-4 score of <1.3 may not appropriately capture patients at risk of fibrosis (25). The

prevalence of diabetes is also higher in certain minority groups, such as those of Hispanic origin, who would then be disadvantaged by the current FIB-4 model and thresholds (1,10,21).

Furthermore, patients of Hispanic origin have a higher prevalence of NAFLD, which is likely the result of a combination of genetic, environmental, socioeconomic and cultural factors (26). Metabolic disease and in particular diabetes are prevalent in Hispanic patients which is a known risk factor for progression of NAFLD. The I148M allele of the patatin-like phospholipase domain containing 3 (*PNPLA3*) gene is known to be associated with increased hepatic fat content and associated inflammation and is found more commonly in Hispanic patients than other ethnicities (27). Diet and cultural factors may also play a role in propagation of NAFLD within the Hispanic population. One study by Heredia *et al.* demonstrated that in a population of Hispanic/Latino adults, high diet quality based on the Healthy Eating Index and higher levels of physical activity were associated with a 40% lower risk of NAFLD (28). These data suggest that lifestyle can have an impact on NAFLD in the Hispanic population. The development of NAFLD in the Hispanic population is evidently multifactorial, contributing to the progressively fibrotic nature of the disease.

The relationship between diabetes and NAFLD in the Hispanic population is critical to understand in order to appropriately risk stratify patients who may have clinically significant fibrosis. As non-invasive testing is over taking liver biopsies for risk assessment, it is crucial to employ NITs with high sensitivity when used as a screening tool. Studies have shown limitations with FIB-4 and poor diagnostic performance in various populations and false negative rates as high as 43% (17,18). Although NFS incorporates diabetes into its algorithm, it also includes BMI which may not necessarily be reflective of metabolic syndrome (1). Thus, we suggest adding diabetes status to FIB-4, which is the most validated NIT in NAFLD. By proposing to lower the cutoff of FIB-4 in patients with diabetes, we will capture more patients with clinically significant fibrosis and even higher stages of fibrosis.

To our knowledge, this is the first study of its kind to evaluate the diagnostic performance of FIB-4 in Hispanic patients with NAFLD and propose a new FIB-4 cutoff by incorporating diabetic status to benefit this population which identifies patients at risk for significant fibrosis with enhanced accuracy. A limitation of this study is that it represents a small population at a single center, in patients

of Hispanic origin and may not be generalizable. However, the data is granular, demonstrating that diabetes is a significant factor in fibrosis and can impact the performance of FIB-4. Another limitation is that the reference standard was transient elastography and not liver biopsies. VCTE though is now widely used in lieu of liver biopsies so this study reflects real-world practice. Future studies with larger populations are warranted to investigate lower thresholds of FIB-4 in patients at risk of clinically significant fibrosis.

Conclusions

To optimize sensitivity and thereby minimizing false negatives in patients with diabetes, we propose a new FIB-4 threshold of 1 to identify this patient population that is at risk for significant fibrosis. On the converse, a higher FIB-4 cutoff of 1.5 may be employed in patients without diabetes who may not be as high risk as their diabetic counterparts. By incorporating diabetes into the FIB-4 model, we can better identify patients at higher risk of significant fibrosis and provide enhanced care to a disadvantaged population.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-62/rc>

Data Sharing Statement: Available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-62/dss>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-23-62/coif>). S.S. reports receiving consulting fee from Gilead, Madrigal, Mallinckrodt, and speakers bureaus from AbbVie, Gilead, Intercept, Salix, Eisai, Exelisis, Mallinckrodt, Takeda. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was certified exempt from the Institutional Review Board (IRB) at UCLA per 45 CFR 46.104 category 4(iii). Informed consent was waived due to the IRB exempt status of the study.

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