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Noninvasive Fibrosis Screening in Fatty Liver Disease Among Vulnerable Populations: Impact of Diabetes and Obesity on FIB-4 Score Accuracy

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OBJECTIVE

Fatty liver disease (FLD) is prevalent in diabetes, and both disproportionately affect vulnerable populations. The FIB-4 index is recommended to screen for advanced liver fibrosis. Limited data have suggested that diabetes may impact FIB-4.

RESEARCH DESIGN AND METHODS

We evaluated FIB-4 accuracy for advanced fibrosis compared with liver biopsy in the presence of diabetes and obesity.

RESULTS

Among 363 FLD patients receiving care in San Francisco's safety net health care system from August 2009 to February 2020, characteristics were as follows: median age 51 years, 46% male, 59% Hispanic, 68% obese, 33% with diabetes, and 31% with advanced fibrosis on histology. Overall, the c-statistic for FIB-4 was 0.79, but was worse in patients with diabetes, 0.68, than without, 0.85 (P = 0.003). Accuracy also varied by weight, at 0.65, 0.85, and 0.75 for normal weight, overweight, and obese, respectively, although not significantly (P = 0.24).

CONCLUSIONS

The findings highlight limitations of FIB-4 in screening for advanced liver fibrosis, particularly in individuals with diabetes.

Fatty liver disease (FLD) (nonalcoholic [NAFLD], alcohol related [ALD], and both) is a leading cause of liver disease (1,2) that disproportionately affects individuals with diabetes (3) and results in advanced liver fibrosis, liver cancer (4,5), and increased mortality (6). Simple serologic noninvasive tests (NITs) of liver fibrosis are commonly used as an alternative to liver biopsy (7). FIB-4 score outperforms other NITs in detecting advanced liver fibrosis (8) and has been recommended as a screening tool in national guidelines (7,9). However, recently, results of limited studies have suggested that diabetes may impact the performance of FIB-4 (10,11). Vulnerable populations are disproportionately affected by both FLD and diabetes (12) and, considering barriers to specialty care engagement, will likely benefit from readily available FIB-4 that can be performed in any setting including primary care. Data on the performance of FIB-4 in this population are not available. Therefore, we aimed to assess the impact of diabetes, as well as BMI category, on the accuracy of

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FIB-4 to identify advanced fibrosis within a diverse vulnerable population with FLD on liver biopsy.

RESEARCH DESIGN AND METHODS

This is a single-center retrospective analysis of 363 adult patients (≥18 years old) with histologic evidence of FLD on liver biopsies performed for clinical care from August 2009 to February 2020 at Zuckerberg San Francisco General Hospital and Trauma Center, a hospital within the safety net health care system serving vulnerable populations of San Francisco. Clinical data were collected from electronic medical records at the time of the liver biopsy. The study was approved by the Institutional Review Board of the University of California, San Francisco, and San Francisco General Hospital.

Alcohol use was quantified using categories defined by the National Institute on Alcohol Abuse and Alcoholism (13). Race-based BMI categories were used: normal weight, <25 kg/m^2 (<23 kg/m^2 for Asians); overweight, 25–29 kg/m^2 (23–27.4 kg/m^2 for Asians); and obese, >30 kg/m^2 (≥27.5 kg/m^2 for Asians) (14). Type 2 diabetes (referred to as diabetes throughout) was defined on the basis of past medical history, use of current diabetes medication, or elevated hemoglobin A_{1c}. FIB-4 was calculated as (age × AST)/(platelets × $\sqrt{}$(ALT)) using laboratory values and age at the time of biopsy. FLD FIB-4 categories were defined as follows: advanced fibrosis excluded, <1.30; indeterminate, 1.30–2.67; and advanced fibrosis likely, >2.67 (15). The areas under the receiver operating characteristic (AUROC) curves of FIB-4 to detect advanced fibrosis (stage 3 or 4 on liver histology) were calculated overall and stratified by diabetes and BMI category.

RESULTS

Baseline characteristics for the population (N = 363) were median age 51 years, 46% men, 59% Hispanic, 29% Asian, 8% White, and 3% Black. Of the population, 7% were normal weight, 68% were obese, 11% had heavy alcohol use, 33% had diabetes, and approximately half had hypertension and dyslipidemia (Supplementary Table 1). Compared with those without diabetes (N = 243), those with diabetes (N = 119) had a higher prevalence (all $P < 0.05$) of hypertension (68% vs. 31%), dyslipidemia (61% vs. 42%), and obesity (77% vs. 63%). Steatohepatitis (inflammation associated with fat) and advanced fibrosis were more common among those with versus without diabetes: 89% vs. 75% with steatohepatitis and 46% vs. 23% with advanced fibrosis, respectively (all $P \leq 0.001$). With respect to BMI category, the only significant differences were presence of diabetes (32% vs. 21% vs. 38%, P = 0.04) and steatohepatitis (79% vs. 72% vs. 88%, P = 0.004) in normal weight (N = 19), overweight (N = 75), and obese (N = 197) groups. Rate of advanced fibrosis was higher in the obese versus overweight and normal weight groups (30% vs. 27% vs. 21%, P = 0.5).

Overall, the performance of FIB-4 was acceptable and comparable with that in prior studies, with an AUROC of 0.79; sensitivity, specificity, and likelihood ratios for the 1.30 and 2.67 cutoffs are shown in Table 1. When only including individuals with diabetes, the AUROC of FIB-4 for advanced fibrosis was 0.68 vs. 0.85 for individuals without diabetes (P = 0.003). With respect to misclassification, compared with those without diabetes, a higher proportion of individuals with diabetes and advanced fibrosis had low FIB-4 <1.3 (4% vs. 13%, respectively). With respect to FIB-4 performance across BMI categories, the AUROC varied from 0.65 for normal weight, 0.85 for overweight, and 0.75 for obese individuals; however, this was not statistically significant (P = 0.24). Specificity was high (≥94%) with use of the 2.67 cutoff among the overweight/obese participants but only at 60% in normal weight participants. On sensitivity analysis with use of age-adjusted FIB-4 cutoffs (>2.0 for individuals ≥65 years old), measures of sensitivity and specificity overall did not change >5% except for specificity for those with diabetes, which increased from 51 to 57%, and sensitivity for overweight individuals, which decreased from 81 to 71%.

As NAFLD and ALD can occur together, with the high prevalence of obesity in the general population, we performed our primary analysis with our entire

Table 1—Performance of FIB-4 for detection of advanced fibrosis in study population, by diabetes and BMI

Population	AUROC	95% CI	P	FIB-4 cutoff	Sensitivity (%)	95% CI	Specificity (%)	95% CI	LR +ve	LR −ve
Total (N = 363)	0.79	0.74–0.84	—	1.30	77	72–81	65	60–70	2.22	0.35
				2.67	40	35–45	93	90–95	5.88	0.65
Diabetes (N = 119)	0.68	0.58–0.77	0.003	1.30	70	61–78	51	42–61	1.43	0.58
				2.67	31	23–40	85	77–91	2.05	0.81
No diabetes (N = 243)	0.85	0.79–0.91		1.30	84	79–88	70	64–76	2.80	0.23
				2.67	47	41–53	96	93–98	12.59	0.55
Normal weight (N = 19)	0.65	0.31–0.99	0.24	1.30	75	49–91	40	20–67	1.25	0.63
				2.67	50	29–76	60	33–80	1.25	0.83
Overweight (N = 75)	0.85	0.75–0.95		1.30	81	71–89	80	69–88	3.97	0.24
				2.67	43	31–55	94	87–99	7.71	0.61
Obese (N = 197)	0.75	0.68–0.83		1.30	69	62–75	64	57–71	1.91	0.49
				2.67	30	24–37	96	92–98	6.69	0.74

LR +ve, positive likelihood ratio; LR −ve, negative likelihood ratio.

cohort irrespective of alcohol use. On sensitivity analysis, after exclusion of 37 individuals with heavy alcohol use, FIB-4 performance was similar across BMI categories and by diabetes status when compared with the full cohort, and sensitivity and specificity percentages did not change by >3% (data not shown). AUROC remained similar (0.67) in the presence of diabetes. For individuals without diabetes, AUROC was the same (0.85) after exclusion of those with heavy alcohol use and remained significantly higher in comparisons with individuals with diabetes ($P = 0.005$).

To further assess the difference in FIB-4 performance by diabetes status, we generated receiver operating characteristic (ROC) curves with adjustment for sex, race/ethnicity, hypertension, hyperlipidemia, and heavy alcohol use for those with diabetes versus without. Adjusted AUROCs increased to 0.87 and 0.79 for those without diabetes and those with diabetes, respectively. We also evaluated the ROC curve for each component of FIB-4 among those with diabetes versus those without. There was no significant difference (all P values $\geq$0.4) in the ROC area for age, platelets, and ALT; however, for AST we found a statistically significant difference in AUROC between the two groups: 0.59 with diabetes vs. 0.75 without diabetes ($P = 0.009$).

CONCLUSIONS

Overall FIB-4 performs well in this vulnerable population with biopsy-proven FLD. However, the accuracy of FIB-4 was significantly lower in the setting of diabetes. This finding is clinically relevant as FIB-4 is currently being incorporated into clinical decision-making and risk stratification. This has potential to negatively impact individuals with diabetes at increased risk of FLD with advanced fibrosis.

Limited studies have compared the performance of FIB-4 in the presence and absence of diabetes, and similar to results of our study, AUROC of FIB-4 was lower in individuals with diabetes (10,11). The results of our study add to the existing data in that our study population of vulnerable patients was unique and included a higher proportion of racial/ethnic minorities than prior studies (10). These populations have limited access to care and are at increased risk of experiencing FLD, obesity, and diabetes-related disparities (12). Uptake of reliable and easily accessible NITs for fibrosis screening and monitoring is thus critical for this population.

The comparison of FIB-4 performance across BMI categories in this study was limited by sample size due to a small group of normal weight individuals with FLD. FIB-4 performance in normal weight FLD thus requires further investigation. Nevertheless, we show that the accuracy of FIB-4 varied by BMI category and diabetes status. More importantly, before general use of FIB-4 in primary care is recommended, it is critical to further optimize noninvasive studies and screening algorithms to detect advanced fibrosis. This is of particular importance for individuals with diabetes due to an increased risk of poor liver-related and cardiovascular outcomes associated with FLD (9). Alternative NITs may need to be considered for individuals with diabetes.

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Author Contributions. R.G.K. designed the study, collected data, performed data analysis, and wrote the manuscript. J.D. collected data, reviewed the manuscript, and approved final submission. J.N.R. collected data, reviewed the manuscript, and approved final submission. J.P.G. contributed to study design, collected data, reviewed the manuscript, and approved final submission. M.K. contributed to study design, provided material support, reviewed statistical analyses, edited the manuscript, and approved final submission. M.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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