Nonalcoholic Fatty Liver Disease Underdiagnosis in Primary Care: What Are We Missing?

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is underdiagnosed in primary care despite a high prevalence (>25%) and strong ties to metabolic syndrome.[1–3] Advanced liver fibrosis from NAFLD is associated with poor outcomes, and non-invasive tests including the Fibrosis-4 Index (FIB-4), NAFLD Fibrosis Score (NFS), and AST-to-Platelet Ratio Index (APRI) can predict advanced fibrosis risk.[1,4,5] We created a primary care NAFLD cohort from electronic health record (EHR) data to evaluate the proportion of patients with radiographic evidence of hepatic steatosis diagnosed with NAFLD and compare advanced fibrosis risk scores between diagnosed and undiagnosed patients.

METHODS

This retrospective study of patient-centered medical home (PCMH) EHR data from 2012 to 2018 included patients with radiographic reports of liver steatosis and no preceding liver disease diagnoses. Patients with abdominal ultrasound, computed tomography, or magnetic resonance imaging results were evaluated. Imaging report text was filtered, searched, and tabulated using natural language processing to identify "hepatic steatosis." Patients with hepatic steatosis and possessing aminotransferase (values < 500 U/L) and platelet count results within 1 year before imaging were included. Patients with non-NAFLD chronic liver disease diagnoses were excluded. We reviewed 706 patient charts to identify imaging indication; the location of steatosis notation on report; the status of viral hepatitis testing; alcohol use documentation; and gastroenterology referral within 1 year after imaging.

Diagnostic assignment of NAFLD or nonalcoholic steatohepatitis (NASH) any time after imaging was the primary outcome (ICD-9: 571.8; ICD-10: K75.81 or K76.0). Other variables included demographic, clinical, and chart review data. Aspartate (AST > 34 U/L) and alanine aminotransferase (ALT > 45 U/L) values were categorized as "elevated" based on thresholds at our institution to represent the "abnormal" signal provided by the EHR. Comorbidity data came from Elixhauser coding algorithms.[6] FIB-4, NFS, and APRI were calculated.[4,5]

Patient characteristics were reported overall and by NAFLD diagnostic assignment. Normally distributed continuous values were reported as means and compared with Student *t* tests; non-normal continuous variables were reported as medians and compared with Mann–Whitney *U* tests; and categorical variables were reported as proportions and compared with chi-square tests. Statistical analyses were performed using SAS version 9.4. The IRB at the Medical University of South Carolina approved this study.

RESULTS

The cohort included 652 patients after chart review excluded 6 for lacking steatosis affirmation and 48 for heavy alcohol use. Included patients had a median BMI of 32.4 kg/m^2, and 46%, 78%, and 68% of patients had diabetes, hypertension, and hyperlipidemia, respectively (Table 1). Overall, 38% had an elevated aminotransferase, 79% had steatosis noted in the radiographic report's "Impression," and 25% received a NAFLD diagnosis.

Univariate analyses demonstrated similar demographic and comorbidity variables between patients with and without a NAFLD diagnosis. Patients diagnosed with NAFLD had higher median AST and ALT values ($p < 0.001$), and a higher proportion of these patients had aminotransferase elevations (51%) compared to undiagnosed patients (33%, $p < 0.001$). Higher proportions of diagnosed patients had imaging for abnormal liver tests ($p < 0.001$) and negative viral hepatitis assessments ($p < 0.001$) compared to those without NAFLD assigned.

Comparing advanced fibrosis risk scores, median FIB-4 ($p = 0.087$) and NFS ($p = 0.243$) values were similar between groups, while APRI scores were higher for diagnosed patients ($p < 0.001$, Table 2). Diagnosed patients had higher proportions of high-risk FIB-4 ($p = 0.044$) and APRI ($p = 0.015$) scores. In undiagnosed patients, 9%, 10%, and 17% had high-risk APRI, FIB-4, and NFS scores, respectively.

DISCUSSION

Only 25% of this cohort received a NAFLD diagnosis and 9–17% of undiagnosed patients had high-risk advanced fibrosis scores. These findings emphasize the degree of NAFLD

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Table 1 Cohort Characteristics Overall and by Nonalcoholic Fatty Liver Disease (NAFLD) Diagnosis

		NAFLD diagnosis		*p* value
	Overall	**Yes**	**No**	
	n = 652	**n = 164**	**n = 488**	
Demographics				
Age, mean, years (SD)	54.7 (± 14.1)	53.8 (± 12.7)	55.0 (± 14.5)	0.346*
Gender, % (*n*)				0.248†
Male	35.9% (234)	39.6% (65)	34.6% (169)	
Female	64.1% (418)	60.4% (99)	65.4% (319)	
Race, % (*n*)				0.270†
Black	35.9% (234)	32.3% (53)	37.1% (181)	
Non-Black	64.1% (418)	67.8% (111)	62.9% (307)	
Married, % (*n*)	56.0% (365)	57.3% (94)	55.5% (271)	0.691†
Clinical variables, median (IQR)				
BMI, kg/m^2	32.4 (27.7, 37.6)	32.5 (28.2, 37.5)	32.4 (27.7, 37.6)	0.882‡
Bili, mg/dL	0.5 (0.4, 0.8)	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)	0.943‡
AST, U/L	26 (20, 39)	30 (23, 56)	25 (20, 35)	< 0.001‡
ALT, U/L	28 (19, 49)	37 (23, 70)	27 (19, 45)	< 0.001‡
ALP, U/L	82 (66, 105)	83 (65, 114)	82 (67, 102)	0.163‡
Platelets, $\times 10^9$/L	241 (200, 293)	246 (197, 296)	240 (200, 292)	0.684‡
Albumin, g/dL	3.7 (3.4, 4.0)	3.8 (3.5, 4.1)	3.7 (3.4, 4.0)	0.033‡
Liver chemistry abnormality, % (*n*)				
Elevated AST	31.9% (208)	44.5% (73)	27.7% (135)	< 0.001†
Elevated ALT	28.7% (187)	41.5% (68)	24.4% (119)	< 0.001†
Elevated AST or ALT	37.6% (245)	50.6% (83)	33.2% (162)	< 0.001†
Elevated AST and ALT	23.0% (150)	35.4% (58)	18.9% (92)	< 0.001†
Comorbidities, % (*n*)				
Diabetes	46.0% (300)	51.8% (85)	44.1% (215)	0.084†
Hypertension	77.8% (507)	79.9% (131)	77.1% (376)	0.451†
Hyperlipidemia	67.8% (442)	73.2% (120)	66.0% (322)	0.088†
Imaging indication, % (*n*)				< 0.001†
GI symptoms	53.1% (346)	45.7% (75)	55.5% (271)	
Abnormal liver tests	17.9% (117)	29.9% (49)	13.9% (68)	
Finding follow-up	11.5% (75)	6.7% (11)	13.1% (64)	
Other	17.5% (114)	17.7% (29)	17.4% (85)	
Where steatosis reported, % (*n*)				< 0.001†
Findings only	20.6% (134)	5.5% (9)	25.6% (125)	
Impression only	46.2% (301)	60.4% (99)	41.4% (202)	
Both	33.3% (217)	34.2% (56)	33.0% (161)	
Negative HCV testing, % (*n*)	46.2% (301)	57.9% (95)	42.2% (206)	< 0.001†
Negative HBV testing, % (*n*)	35.3% (230)	50.0% (82)	30.3% (148)	< 0.001†
Alcohol use history, % (*n*)				0.924†
Yes, below threshold§	37.9% (247)	36.6% (60)	38.3% (187)	
None	52.6% (343)	53.7% (88)	52.3% (255)	
Not recorded	9.5% (62)	9.8% (16)	9.4% (46)	
GI specialty referral, % (*n*)	19.6% (128)	23.8% (39)	18.2% (89)	0.122†

NAFLD nonalcoholic fatty liver disease, *SD* standard deviation, *IQR* interquartile range, *Bili* bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *GI* gastrointestinal, *HCV* viral hepatitis C, *HBV* viral hepatitis B

*Two-sample Student *t* test

†Chi-square test

‡Mann–Whitney *U* test

§ > 21 drinks per week in men, 14 drinks per week in women, or notation of alcohol abuse

Table 2 Non-invasive Serologic Advanced Fibrosis Risk Scores and the Proportion of Patients with High-Risk Assessments by NAFLD Diagnosis

Advanced fibrosis risk scores, median (IQR)*	Overall	NAFLD diagnosis		*p* value
		Yes	No	
	n = 652	n = 164	n = 488	
Fibrosis-4 Index	1.14 (0.76, 1.78)	1.25 (0.78, 1.88)	1.12 (0.75, 1.73)	0.087†
NAFLD Fibrosis Score	−0.74 (−1.91, 0.21)	−0.93 (−2.26, 0.16)	−0.72 (−1.83, 0.21)	0.243†
APRI	0.33 (0.23, 0.52)	0.41 (0.26, 0.73)	0.31 (0.22, 0.47)	< 0.001†
% with high-risk scores (*n*) ‡				
Fibrosis-4 Index	11.5% (75)	15.9% (26)	10.0% (49)	0.044§
NAFLD Fibrosis Score	17.9% (117)	19.5% (32)	17.4% (85)	0.545§
APRI	10.3% (67)	15.2% (25)	8.6% (42)	0.015§

NAFLD nonalcoholic fatty liver disease, *IQR* interquartile range, *APRI* AST-to-platelet ratio index, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

*Fibrosis-4 Index = [(age × AST)/(platelet × $\sqrt{}$ALT)]; NAFLD Fibrosis Score = −1.675 + (0.037 × age) + (0.094 × BMI) + (1.13 × diabetes [yes = 1, no = 0]) + (0.99 × [AST/ALT]) − (0.013 × platelet) − (0.66 × albumin); APRI = [(AST/34) × 100]/platelet

†Mann–Whitney *U* test

‡High-risk thresholds: Fibrosis-4 index > 2.67, NAFLD Fibrosis Score > 0.676, APRI > 1.0[4,5]

§Chi-square test

underdiagnosis in primary care and indicate that providers are missing advanced disease.[2,3] Significant differences in abnormal liver chemistries and imaging indications between groups suggest clinicians may intentionally pursue NAFLD diagnoses in response to abnormal aminotransferases. This approach may contribute to underdiagnosis due to varying "normal" aminotransferase thresholds between lab systems and the possibility of NAFLD despite normal liver chemistries. Also, where steatosis documentation appears in radiographic reports may matter, as a higher proportion of diagnosed patients had this finding in the report's "Impression." This data comes from a single PCMH that may possess resources not available to all primary care practices, which could threaten generalizability. These findings reinforce the need to improve NAFLD diagnosis in primary care, especially for patients at high risk for advanced fibrosis.

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Declarations

Ethics Approval The Institutional Review Board at the Medical University of South Carolina approved this study.

Conflict of Interest The authors declare that they do not have a conflict of interest.

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