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MAJOR ARTICLE

Risk Stratification of Advanced Fibrosis in Patients With Human Immunodeficiency Virus and Hepatic Steatosis Using the Fibrosis-4, Nonalcoholic Fatty Liver Disease Fibrosis, and BARD Scores

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Background. Nonalcoholic fatty liver disease (NAFLD) and subsequent progression to fibrosis is increasingly prevalent in people with HIV (PWH). We used noninvasive methods to stratify risk and identify associated factors of advanced fibrosis in PWH with NAFLD.

Methods. We conducted a retrospective study of PWH in our clinic from 2005 to 2022. We used liver imaging or biopsy reports to identify cases of hepatic steatosis after excluding specified etiologies. We used the Fibrosis-4 (FIB-4), NAFLD Fibrosis (NFS), and body mass index, aspartate transaminase/alanine transaminase ratio, and diabetes score scores to stratify fibrosis. We used logistic regression to identify factors associated with advanced fibrosis.

Results. Among 3959 PWH in care, 1201 had available imaging or liver biopsies. After exclusions, 114 of 783 PWH had evidence of hepatic steatosis (14.6%). Most were male (71.1%), with a median age of 47 years, and median body mass index of 30.1 kg/m^2. Approximately 24% had lean NAFLD (ie, body mass index < 25 kg/m^2). Based on the FIB-4 and NFS, 34 (29.8%) and 36 (31.6%) had advanced fibrosis, whereas 1 in 4 had low risk of fibrosis based on FIB-4, NFS, and BARD scores. In adjusted analysis using FIB-4, advanced fibrosis was associated with age > 45 years (adjusted odds ratio, 6.29; 95% confidence interval, 1.93–20.50) and hypoalbuminemia (adjusted odds ratio, 9.45; 95% confidence interval, 2.45–32.52) in addition to elevated transaminases and thrombocytopenia, whereas using the NFS did not identify associations with advanced fibrosis.

Conclusions. We found 14.6% of PWH had NAFLD, with 1 in 3 having advanced fibrosis. Our study provides practical insights into fibrosis risk stratification in HIV primary care settings.

Keywords. fibrosis; HIV; liver; NAFLD; steatosis.

Nonalcoholic fatty liver disease (NAFLD) is a growing global health problem. NAFLD results from the accumulation of fat in hepatocytes (steatosis) in the absence of a specified etiology such as alcohol use disorder, hepatitis B (HBV) or C (HCV), autoimmune hepatitis, Wilson disease, and hereditary metabolic disorders [1]. Clinically, 2 main phenotypes are recognized: nonalcoholic fatty liver, which is characterized by the accumulation of fat in hepatocytes with minimal inflammation/damage; and nonalcoholic steatohepatitis (NASH), in which significant hepatocellular damage and/or fibrosis has occurred [1]. According to recent estimates, NALFD affects approximately 37.8% of the general population worldwide, a dramatic rise from a prevalence of 25.5% before 2005 [2]. The growing problem of NALFD/NASH closely parallels rising trends in the global burden of classic risk factors such as obesity, type 2 diabetes mellitus, and the metabolic syndrome [1]. The presence of the NASH phenotype is associated with a higher risk of cirrhosis and hepatocellular carcinoma [3]. Consequently, NAFLD/NASH has now surpassed HCV as the leading indication for liver transplantation in developed countries [4].

NAFLD is a frequent, yet underappreciated cause of chronic liver disease among people with human immunodeficiency virus (HIV) (PWH), and prevalence estimates may vary widely depending on the diagnostic method used. A systematic review and meta-analysis of 10 studies published in 2017 estimated an NALFD prevalence of 35% among HIV monoinfected individuals [5],

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which is comparable to NAFLD rates reported in the general population [2]. However, in addition to established risk factors for NAFLD [1], PWH are susceptible to multiple pathophysiologic mechanisms of hepatocellular injury that may further increase their risk of NAFLD. Specifically, HIV-associated inflammation and immune activation accompanying HIV replication in Kupfer and hepatic stellate cells induces mitochondrial toxicity and promotes a profibrogenic microenvironment within the liver parenchyma [6–8]. Additional HIV-specific mechanisms that have been implicated in the development of NAFLD include HIV-induced enteropathy and alterations in the gut microbiome [7, 9, 10] and toxicities associated with antiretroviral treatment (ART) regimens such as older generation nucleos(t)ide reverse transcriptase inhibitors, protease inhibitors (PIs), and the newer generation integrase strand inhibitors (INSTI) [11–13].

Because the life expectancy of PWH has dramatically increased in the era of combination ART, it is anticipated that PWH will remain at increased risk of NAFLD and other noncommunicable diseases associated with aging [14, 15]. Unfortunately, current management strategies for NAFLD, such as lifestyle modifications and pharmacologic therapy, have limited efficacy in advanced disease, which often requires more extreme interventions, including bariatric surgery or liver transplantation [14, 15]. It is therefore essential that NAFLD is identified early for appropriate counseling, risk stratification, and management. However, diagnosing NAFLD can be challenging even in well-resourced settings. Liver biopsy, which is the gold standard for diagnosis and staging, is invasive and carries inherent risks. Noninvasive imaging methods such as transient elastography (TE) have been validated in PWH and provide accurate and reliable measurements of liver fibrosis [16–18]; however, they are costly and not always available in primary care clinics. Consequently, several predictive noninvasive scores have been developed such as the Fibrosis-4 (FIB-4) [19], NAFLD fibrosis (NFS) [20], and body mass index, aspartate transaminase/alanine transaminase ratio, and diabetes score (BARD) scores [21]. These scores use routine laboratory tests and anthropometric measures and have demonstrated acceptable diagnostic performance, especially for risk stratification of advanced fibrosis in NAFLD, which has led to their increased use as diagnostic tools in both the general population and PWH [19–22]. In particular, the American Association of Clinical Endocrinologists/American Association for the Study of Liver Diseases (AACE/AASLD) and the European AIDS Clinical Society (EACS) have endorsed the use of the FIB-4 and NFS in primary care and specialty clinic settings, respectively [23, 24].

In this study from a university hospital–based primary care HIV clinic in Northeast Ohio in the United States, we aimed to estimate the prevalence of NAFLD and stratify the risk of advanced fibrosis using the FIB-4, NFS, and BARD scores. Furthermore, we sought to identify risk factors associated with advanced fibrosis in the HIV primary care setting to aid decision-making for referral to specialty hepatology care for further assessment.

METHODS

Study Design, Setting and Cohort

We conducted a retrospective cross-sectional study by reviewing the medical records of patients with HIV who received routine care at the Special Immunology Unit (SIU) at the University Hospitals Cleveland Medical Center in Cleveland, Ohio, United States, from 2005 to 2022. The SIU was established in 1985 to provide comprehensive clinical care to PWH or those at risk of acquiring HIV infection, including HIV testing, counseling and support services, ART, preexposure prophylaxis, and clinical trials. To date, the SIU has provided clinical care to more than 4000 PWH, with 1214 patients actively in care in 2022.

Data Extraction and Study Definitions

The study inclusion criteria were age ≥ 18 years with at least 1 visit to the SIU between 2005 and 2022, documented evidence of HIV infection (ie, antibody/antigen testing, polymerase chain reaction, or Western blot), and evidence of hepatic steatosis based on characteristic findings on ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), TE, or liver biopsy report. Exclusion criteria were documented alcoholic fatty liver disease, HBV or HCV infection, autoimmune hepatitis, Wilson disease, hemochromatosis, or cryptogenic liver disease (see Supplementary material for International Classification of Diseases, 10th Edition codes).

We extracted demographic, clinical, and laboratory data from the medical records of patients who met the study inclusion criteria. We collected data on age, sex, race/ethnicity, body mass index (BMI), alcohol use, smoking history, drug history, comorbidities (ie, hypertension, prediabetes, diabetes, obesity, and dyslipidemia), angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), statins, antidiabetic agents (ie, insulin and metformin), and ART history and HIV indices (ie, CD4 count and viral load). Additional laboratory data collected included platelet count, hemoglobin A1c, serum aspartate transaminase (AST), alanine transaminase (ALT), bilirubin (total and direct), albumin, and lipid panel (total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), and triglycerides. All laboratory data extracted and medications were within 6 months of diagnosis of hepatic steatosis.

We calculated the BMI using the formula mass (kg)/height^2 (m^2) and classified participants as underweight (ie, BMI < 18.5 kg/m^2), normal (ie, BMI 18.5–24.9 kg/m^2), overweight (ie, BMI 25–29.9 kg/m^2), obese (ie, BMI 30–34.9 kg/m^2), and morbidly

obese (ie, BMI ≥ 35 kg/m^2) [25]. We defined prediabetes as an hemoglobin A1c of 5.7% to 6.4%, and diabetes as any of the following: (1) documented history of diabetes; (2) prescribed medication for treating diabetes; and (3) HgA1c ≥ 6.5 [26]. We defined hypertension as documented blood pressure ≥ 140/90 mm Hg or being on antihypertensive treatment [27]. We used the harmonized criteria for the metabolic syndrome to define dyslipidemia thresholds as follows: hypertriglyceridemia (triglycerides ≥ 150 mg/dL), low HDL-C (ie, HDL-C < 40 mg/dL for males or < 50 mg/dL for females), high LDL-C (ie, LDL-C > 100 mg/dL), and hypercholesterolemia (ie, total cholesterol ≥ 200 mg/dL) [28].

Noninvasive Assessments of Liver Fibrosis

We used 3 validated noninvasive scoring systems to estimate the degree of liver fibrosis. We calculated the FIB-4 Score using the formula:

FIB-4 = [age (years) × AST (IU/L)]/[platelet count (10^9/L) × [ALT (IU/L)]$^{1/2}$] [29].

We used the thresholds recommended by the AACE/AASLD and EACS guidelines for stratification of risk of fibrosis, with a FIB-4 Score < 1.3 classified as low risk, a FIB-4 Score of 1.3 to 2.67 as indeterminate risk, and a FIB-4 Score > 2.67 as high risk of fibrosis [23, 24].

We calculated the NFS using the formula:

NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, No = 0) + 0.99 × AST/ALT—0.013 × platelet count (×10^9/L)—0.66 × albumin (g/dL) [19], where IFG represents the presence of impaired fasting glucose. We used the thresholds provided by the EACS guidelines, with the risk of fibrosis was categorized as follows: NFS < −1.45 as low risk of fibrosis, NFS ≥ −1.45 to < 0.67 for mild/moderate fibrosis, and NFS ≥ 0.67 for high probability of advanced fibrosis [19, 24].

Last, we calculated the BARD Score using the BMI, AST/ALT ratio, and the presence or absence of type 2 diabetes mellitus to predict advanced fibrosis in NAFLD as originally described by Harrison et al [20]. The maximum possible BARD score is 4, with BMI > 28 kg/m^2 scored as 1, AST/ALT > 0.8 scored as 2, and diabetes mellitus scored as 1. A BARD score of 0–1 indicates a low probability of fibrosis and can rule out the need for a liver biopsy, whereas a score of 2–4 indicates an odds for advanced fibrosis of 17 (95% confidence interval [CI], 9.2–31.9), with a negative predictive value of 96% [20].

We reviewed the available liver imaging reports to confirm the diagnosis of hepatic steatosis as reported by a radiologist. For US, CT, and MRI reports, we scrutinized key phrases such as "diffuse hyperechogenicity consistent with hepatic steatosis" or "increased echogenicity of the liver parenchyma, consistent with hepatic steatosis," or "diffusely hyperechoic consistent with hepatic steatosis" to identify subjects for inclusion into the study.

For the minority of cases in which TE or biopsy reports were available, we corroborated the US, CT, and MRI findings for the presence of hepatic steatosis and fibrosis. We scrutinized TE reports for degree of hepatic steatosis commonly categorized as follows: controlled attenuation parameter > 238 dB/m for presence of hepatic steatosis [17, 24]. We used the thresholds liver stiffness measurement (LSM) ≤ 7 kPa for low, LSM 8–12 kPa as indeterminate, and LSM ≥ 12 kPa as high [23, 24]. Finally, we scrutinized liver biopsy reports for degrees of fibrosis, classified as F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis).

Statistical Analyses

We performed statistical analyses using SPSS Version 29.0 (Armonk, NY; IBM Corp). We reported categorical variables as frequencies (percentages) and assessed associations using Pearson χ^2 or Fisher exact tests. We presented continuous variables as medians (interquartile range [IQR]) and assessed associations using the nonparametric Mann-Whitney *U* test. We constructed a multivariate logistic regression model to identify factors associated with advanced fibrosis based on both the FIB-4 and NFS, respectively. For both scores, we retained a priori known sociodemographic factors associated with fibrosis (ie, age, gender, race, and BMI). Additionally, we also retained comorbidities and medications known to be associated with development of NAFLD or subsequent fibrosis (eg, class of ART) or potential modifiers of liver disease (eg, insulin, metformin, ACE-I/ARB use). However, for each of the invasive scores, we excluded laboratory parameters used to calculate each respective score for improved regression model fitness. For example, for the regression analysis using FIB-4, we excluded AST, ALT, and platelet count but retained total/direct bilirubin, albumin, and the lipid panel. Similarly, for the regression analysis using NFS, we excluded AST, ALT, platelet count, and albumin. Only covariates that attained a *P* value < .20 in the univariate analysis were included in the multivariate regression model. We reported associations as crude and adjusted odds ratios (AOR) with 95% CIs. In all analyses, *P* < .05 was considered statistically significant.

Patient Consent Statement

The study was approved by the Institution Board Review committee at Case Western Reserve University/University Hospitals Cleveland Medical Center. Written informed consent from patients was not required for this retrospective study because it involved use of deidentified data only.

RESULTS

Prevalence of NAFLD

Among 3959 PWH who received care at our clinic between 2005 and 2022, 1201 had available imaging or liver biopsy

reports. A further 418 PWH with known etiologies for liver disease were excluded. Of the remaining 783, 114 (14.6%) had imaging or biopsy evidence of hepatic steatosis (Figure 1). Of the 114 patients assessed, all (100%) underwent US, 25 had CT imaging, 12 had MRI, and 7 had TE. Furthermore, only 6 patients had undergone liver biopsy.

General Characteristics and Classification of NAFLD

Table 1 describes the characteristics of the study population. Of the 114 PWH with NAFLD, 81 (71.1%) were male. The median age was 47 years (IQR 39–54) and the majority (59, 51.8%) were Black. The median BMI was 30.1 kg/m^2 (IQR 25.4–36.0). Interestingly, 24 (21.1%) were normal/underweight

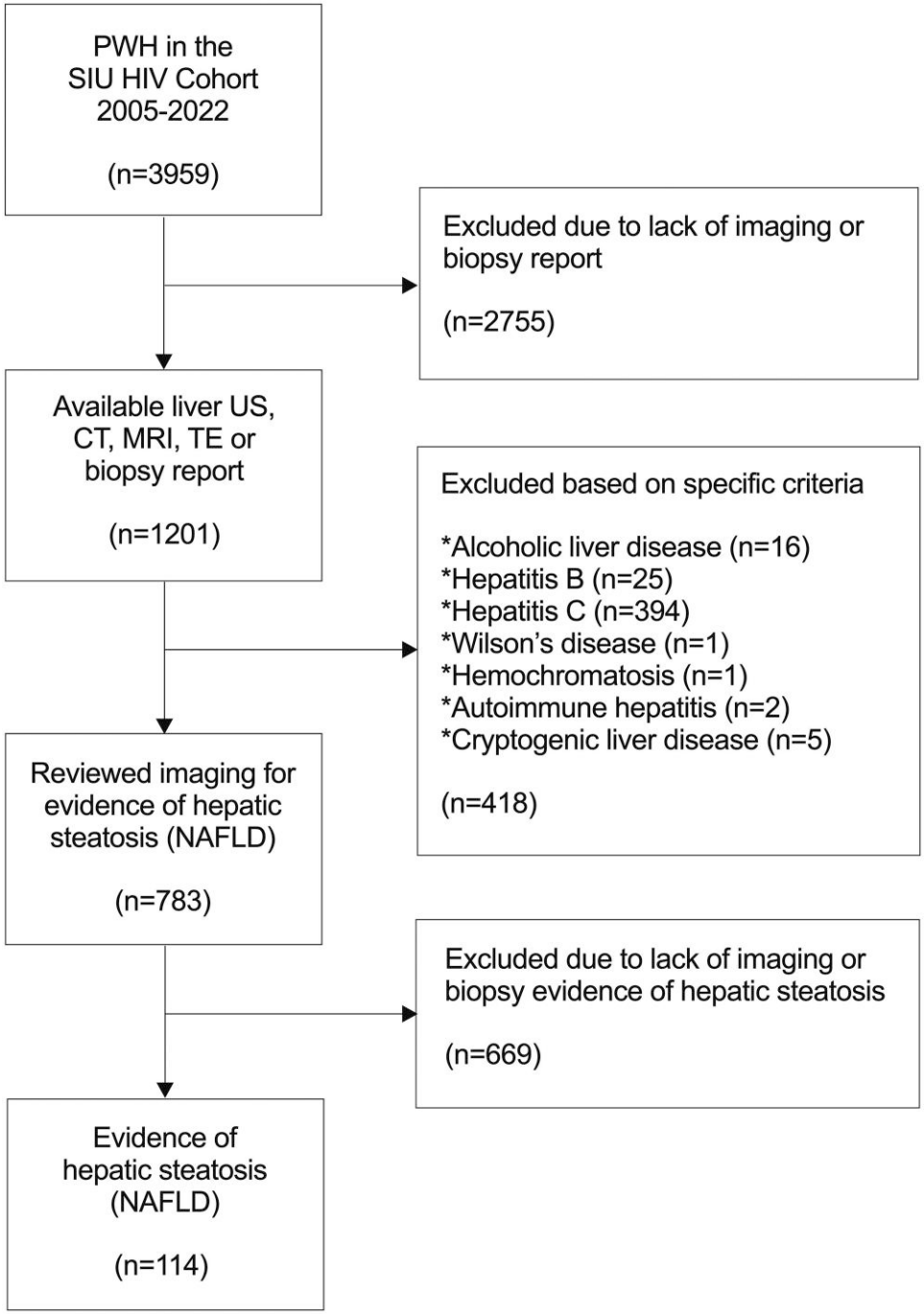

Figure 1. Flow chart demonstrating inclusion and exclusion of study participants. CT, computed tomography; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; PWH, people with HIV; SIU, Special Immunology Unit; TE, transient elastography. *Cases are not necessarily mutually exclusive to other conditions.

Table 1. Baseline Demographic and Clinical Characteristics of PWH With NAFLD

Characteristics	N (%)
Male	81 (71.1)
Age (y)	
Median (IQR)	47 (39–54)
≤ 34	19 (16.7)
35–44	25 (21.9)
45–54	44 (38.6)
≥ 55	26 (22.8)
Race/ethnicity	
Black	59 (51.8)
White	51 (44.7)
Hispanic	3 (2.6)
Asian	1 (0.9)
Body mass index (kg/m^2)	
Median (IQR)	30.1 (25.4–36.0)
< 18.5 (underweight)	3 (2.6)
18.5–24.9 (normal)	21 (18.4)
25.0–29.9 (preobesity)	32 (28.1)
30.0–34.9 (obesity)	23 (20.2)
≥ 35.0 (morbid obesity)	35 (30.7)
Life-style associated risk factors	
Smoking	73 (64.0)
Drug use	36 (31.6)
Comorbidities	
Hypertension	65 (57.0)
Dyslipidemia	25 (21.9)
Diabetes	54 (47.4)
CD4 count (cells/mm^3)	
Median (IQR)	491 (242–841)
≥ 200	94 (82.5)
HIV RNA < 20 copies/mL	107 (93.9)
ART regimen	
Tenofovir-based	96 (84.2)
INSTI-based	55 (48.2)
PI-based	33 (28.9)
NNRTI-based	26 (22.8)
Antihypertensives	
ACE-I or ARB	41 (36.0)
Others	24 (21.1)
Lipid-lowering agents	
Statin	47 (41.2)
Others	6 (5.3)
Antidiabetic treatment	
Insulin plus other(s)	16 (14.0)
Insulin alone	8 (7.0)
Metformin	12 (10.5)
FIB-4 Score	
Median (IQR)	1.89 (1.01–4.15)
< 1.3	31 (27.2)
1.3–2.67 (indeterminate risk)	49 (43.0)
> 2.67 (high risk)	34 (29.8)
NAFLD Score (NFS)	
Median (IQR)	0.27 (−1.17 to 1.29)
< −1.3 (low risk)	28 (24.6)
−1.45 to 0.67 (indeterminate risk)	50 (43.9)
≥ 0.67 (high risk)	36 (31.6)
BARD Score	
Median (IQR)	2 (2–3)
0–1 (low risk)	27 (23.7)
2–4 (indeterminate-to-high risk)	87 (76.3)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; APRI, aspartate aminotransferase to platelet ratio index; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; AST, aspartate aminotransferase; BARD score, body mass index, AST/alanine transaminase ratio, and diabetes score; FIB-4, fibrosis index based on 4 factors; HDL-C, high-density lipoprotein; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; LDL-C, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NNRTI, nonnucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

(BMI < 25 kg/m^2), a classification known as lean NAFLD, whereas 35 (30.7%) were morbidly obese (BMI > 35 kg/m^2). The majority were current or past smokers (73, 64.0%) and about one-third (36, 31.6%) had a history of drug use. The majority had hypertension (65, 57.0%), 54 (47.4%) had diabetes, and 25 (21.9%) had dyslipidemia. The median CD4 count was 491 cells/mm^3 (IQR 242–841) and 107 (93.9%) were virologically suppressed. All were on ART, with 96 (84.2%) on a tenofovir-based regimen, 55 (48.2%) on INSTIs, 33 (28.9%) on PIs, and 26 (22.8%) on NNRTIs.

The median FIB-4 score was 1.89 (IQR 1.01–4.15), with patients categorized into low (31, 27.2%), indeterminate (43.0%), and high risk of fibrosis (29.8%). The NFS showed a median of 0.27 (IQR −1.17 to 1.29), with patients classified into low (24.6%), indeterminate (43.9%), and high risk of fibrosis (31.6%). The BARD score demonstrated a median of 2 (IQR 2–3), stratifying patients into low (23.7%) and intermediate-to-high risk of fibrosis (76.3%).

Comparison of Characteristics of Lean NAFLD Versus non-lean NAFLD

We compared the 24 subjects (21.1%) who had lean NAFLD with the 90 (78.9%) with non-lean NAFLD (Table 2). PWH with lean NAFLD were more likely to have lower CD4 counts (330 cells/mm^3 vs 556 cells/mm^3, $P < .039$), lower platelet counts (170 vs 225 $\times 10^9$/L, $P < .001$), lower albumin (3.2 g/dL vs 4.0 g/dL, $P = .012$), and higher total bilirubin (0.9 mg/dL vs 0.6 mg/dL, $P = .036$). They were also more likely to be on PI-based ART (50.0% vs 23.3%, $P = .01$) but less likely to have diabetes (20.8% vs 54.4%, $P = .003$). There was no difference in the likelihood of fibrosis between those with lean NAFLD and non-lean NAFLD.

Comparison of Characteristics of Mild/Moderate and Advanced Fibrosis

Table 3 presents a comparison between patients with advanced versus those with mild/moderate fibrosis. Based on the FIB-4, patients with advanced fibrosis were significantly more likely to have a lower median CD4 count (353 vs 550 cells/mm^3,

Table 2. Comparison of Characteristics of Lean NAFLD Versus non-lean NAFLD

Characteristics	Lean NAFLD (n = 24)	Non-lean NAFLD (n = 90)	*P* Value
Age (y)[a]	49 (42–54)	47 (38–54)	.603
Male sex, n (%)	18 (75.0)	63 (70.0)	.631
Black race, n (%)	13 (54.2)	46 (51.1)	.790
Smoking, n (%)	17 (70.8)	56 (62.2)	.435
Drug use, n (%)	11 (45.8)	25 (27.8)	.091
Hypertension, n (%)	17 (70.8)	48 (53.3)	.124
Diabetes, n (%)	5 (20.8)	49 (54.4)	.003
Tenofovir-based ART, n (%)	22 (91.7)	73 (81.1)	.218
NNRI-based ART, n (%)	2 (8.3)	24 (26.7)	.061
PI-based ART, n (%)	12 (50.0)	21 (23.3)	.010
INSTI-based ART, n (%)	10 (41.7)	45 (50.0)	.468
ACE-I or ARB use, n (%)	7 (29.2)	34 (37.8)	.435
Statin use, n (%)	7 (29.2)	40 (44.4)	.177
Insulin use, n (%)	1 (4.2)	15 (16.7)	.186
Metformin use, n (%)	2 (8.3)	18 (10.0)	.237
CD4 count (cells/mm^3)[a]	330 (178–568)	556 (286–883)	.039
HIV RNA < 20 copies/mL, n (%)	2 (8.3)	5 (5.6)	.627
Platelet count (x10^9/L)[a]	170 (90–209)	225 (184–271)	<.001
AST (IU/L)[a]	71 (32–122)	54 (23–119)	.108
ALT (IU/L)[a]	46 (28–96)	46 (22–104)	.819
Total bilirubin (mg/dL)[a]	0.9 (0.5–2.1)	0.6 (0.5–1.2)	.036
Direct bilirubin (mg/dL)[a]	0.3 (0.2–0.6)	0.2 (0.1–0.5)	.603
Albumin (g/dL)[a]	3.2 (2.8–3.9)	4.0 (3.5–4.4)	0.012
Total cholesterol (mg/dL)[a]	170 (130–196)	185 (155–218)	.251
HDL-C (mg/dL)[a]	59 (40–90)	42 (31–53)	.491
LDL-C (mg/dL)[a]	78 (43–103)	101 (70–141)	.253
Triglycerides (mg/dL)[a]	139 (112–309)	219 (119–322)	.108
FIB-4[a]	2.58 (1.49–8.25)	1.52 (0.75–2.74)	.108
NFS[a]	0.36 (–1.01 to 1.06)	0.23 (–1.19 to 1.55)	.818

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; APRI, aspartate aminotransferase (AST) to platelet ratio index; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; BARD score, body mass index, AST/alanine transaminase (ALT) ratio, and diabetes score; FIB-4, fibrosis index based on 4 factors; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NNRTI, nonnucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

[a]Median (interquartile range).

P = .010), lower platelet count (145 vs 227 ×10^9/L, *P* < .001), higher AST (139 vs 32 IU/L, *P* < .001) and ALT (57 vs 40 IU/L, *P* = .137) levels, higher total bilirubin (0.9 vs 0.6 mg/dL, *P* < .001) and direct bilirubin (0.3 vs 0.2 mg/dL, *P* = .006) and lower albumin (3.2 vs 4.0 g/dL, *P* = .003).

Based on the NFS, PWH with high risk of advanced fibrosis were less likely to be male (58.3% vs 76.9%, *P* = .042) and less likely to be on a statin (27.8% vs 47.4%, *P* = .047) but were more likely to have lower platelet counts (171 vs 225 ×109/L, *P* < .001), elevated AST (88 vs 37 IU/L, *P* < .001), higher total bilirubin (0.9 vs 0.6 mg/dL, *P* = .026) and direct bilirubin (0.3 vs 0.2 mg/dL, *P* = .010), and with lower albumin (3.0 vs 4.1 g/dL, *P* < .001). There was no difference between the groups in terms of other sociodemographic factors, comorbidities, HIV viremia, class of ART, serum lipid profile, or potential modifiers of liver fibrosis such as antihypertensives, antidiabetics, and statins. There was no difference between the groups in terms of other sociodemographic factors, comorbidities, HIV viremia, class of ART, serum lipid profile, or potential modifiers of liver fibrosis such as antihypertensives and antidiabetics.

Predictors of Advanced Fibrosis

In adjusted multiple logistic regression analysis based on the FIB-4, advanced fibrosis was significantly associated with age > 45 years (AOR 6.29, 95% CI [1.93–20.50]; *P* = .002) and hypoalbuminemia (AOR 9.45, 95% CI [2.45–32.52]; *P* .001) (Table 4). The logistic regression analysis using NFS did not identify any independent predictors of advanced fibrosis.

DISCUSSION

In this study, we estimated an NAFLD prevalence of 14.6% among those with available imaging or biopsy reports in our HIV cohort, of which approximately 1 in 3 had advanced fibrosis using noninvasive scores. Comparatively, HIV cohort studies from North America and Europe have reported higher NAFLD prevalence rates ranging from 25% to 75% [30–34]. Several factors could account for the underdiagnosis of NAFLD among PWH. First, many studies such as ours primarily rely on liver ultrasonography, a readily available but less sensitive diagnostic method compared with liver biopsy and TE. Second, classic NAFLD symptoms may be absent, subclinical, or overlap with more frequently encountered presentations such as ART-related toxicities, metabolic disorders, and coinfections with HBV or HCV. Additionally, healthcare providers may have limited awareness about NAFLD in the context of HIV; this may result in delayed diagnosis, risk stratification, and management of NAFLD.

Our study had a few findings worthy of further discussion. First, despite the well-known association between high BMI and NAFLD, a significant proportion (24%) of our patients with NAFLD had normal BMI or were underweight, a condition referred to as lean NAFLD. We found that individuals with lean NAFLD were more likely to have lower CD4 counts, lower platelet count, lower albumin, and higher total bilirubin, and more likely to be on PI-based ART but less likely to have diabetes. Crucially, there was no difference in rates of advanced fibrosis between PWH with lean NAFLD versus non-lean NAFLD. Studies have reported that between 7% and 20% of people diagnosed with NAFLD fall into this category [35–38], highlighting the complex relationship between body weight and liver health. The underlying pathophysiologic mechanisms of lean NAFLD have not been elucidated; however, the emerging evidence points

Table 3. Comparison of Mild/Moderate and Advanced Fibrosis Using the FIB-4 and NAFLD Fibrosis Scores

Characteristics	FIB-4			NFS		
	Advanced fibrosis (n = 34)	Mild/moderate fibrosis (n = 80)	*P*-Value	Advanced fibrosis (n = 36)	Mild/moderate fibrosis (n = 78)	*P*-Value
Age (y)[a]	50 (43–54)	46 (36–54)	.122	47 (38–54)	47 (40–54)	.971
Sex, n (%)	…	…		…	…	
Male	24 (70.6)	57 (71.3)	.943	21 (58.3)	60 (76.9)	.042
Female	10 (29.4)	23 (28.7)		15 (41.7)	18 (23.1)	
Race/ethnicity, n (%)	…	…		…	…	
Black	20 (58.8)	39 (48.8)	.667	18 (50.0)	41 (52.6)	.716
White	14 (41.2)	37 (46.3)		18 (50.0)	33 (42.30	
Hispanic	…	3 (3.8)		…	…	
Asian	…	1 (1.3)		…	…	
Body mass index (kg/m^2)[a]	30.6 (26.8–35.8)	27.4 (23.7–39.6)	.376	33.4 (25.3–44.8)	29.5 (25.6–35.0)	.118
Smoking, n (%)	23 (67.6)	50 (62.5)	.600	22 (61.1)	51 (65.4)	.659
Drug use, n (%)	8 (23.5)	28 (35.0)	.228	9 (25.0)	27 (34.6)	.305
Hypertension, n (%)	17 (50.0)	48 (60.0)	.324	16 (44.6)	49 (62.8)	.065
Diabetes, n (%)	12 (35.3)	42 (52.5)	.092	15 (41.7)	39 (50.0)	.407
Tenofovir-based ART, n (%)	27 (70.4)	68 (85.0)	.464	30 (83.3)	65 (83.3)	1.000
NNRI-based ART, n (%)	8 (23.5)	18 (22.5)	.905	9 (25.0)	17 (21.8)	.705
PI-based ART, n (%)	9 (26.5)	24 (30.0)	.704	10 (27.8)	23 (29.5)	.852
INSTI-based ART, n (%)	17 (50.0)	38 (47.5)	.807	17 (47.2)	38 (48.7)	.882
ACE-I or ARB use, n (%)	15 (44.10	26 (32.5)	.237	15 (41.7)	26 (33.3)	.389
Statin use, n (%)	10 (29.4)	37 (46.3)	.095	10 (27.8)	37 (47.4)	.047
Insulin, n (%)	3 (8.8)	13 (16.3)	.386	4 (11.1)	12 (15.4)	.541
Metformin, n (%)	3 (8.8)	17 (21.3)	.177	3 (8.3)	17 (21.8)	.112
CD4 count (cells/mm^3)[a]	353 (181–617)	550 (317–886)	.010	389 (166–692)	501 (307–853)	.068
HIV RNA < 20 copies/mL, n (%)	31 (91.2)	76 (95.0)	.424	34 (94.4)	73 (93.6)	.860
Hemoglobin A1c	5.1 (4.6–6.1)	5.8 (4.3–7.4)	.123	5.4 (4.6–6.7)	5.7 (4.3–7.2)	.466
Platelets (×10^9/L)[a]	145 (84–223)	227 (190–276)	<.001	171 (106–245)	225 (189–277)	<.001
AST (IU/L)[a]	139 (80–258)	32 (21–76)	<.001	88 (53–210)	37 (22–91)	<.001
ALT (IU/L)[a]	57 (30–115)	40 (22–94)	.137	39 (21–81)	52 (26–116)	.164
Total bilirubin (mg/dL)[a]	0.9 (0.7–2.2)	0.6 (0.4–1.1)	<.001	0.9 (0.6–1.9)	0.6 (0.4–1.1)	.026
Direct bilirubin (mg/dL)[a]	0.3 (0.2–1.0)	0.2 (0.1–0.4)	.006	0.3 (0.2–1.0)	0.2 (0.1–0.4)	.010
Albumin (g/dL)[a]	3.2 (2.7–4.1)	4.0 (3.6–4.4)	.003	3.0 (2.4–3.8)	4.1 (3.6–4.5)	<.001
Total cholesterol (mg/dL)[a]	172 (142–197)	189 (155–218)	.052	173 (144–199)	189 (155–217)	.124
HDL-C (mg/dL)[a]	41 (33–64)	42 (31–50)	.459	42 (32–63)	42 (32–49)	.512
LDL-C (mg/dL)[a]	92 (56–133)	98 (71–131)	.550	83 (59–128)	99 (77–132)	.310
Triglycerides (mg/dL)	193 (93–272)	203 (129–346)	.297	244 (127–302)	182 (115–324)	.316
BARD score[a]	3 (2–4)	2 (2–3)	<.001	3 (2–4)	2 (1–3)	<.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; APRI, aspartate aminotransferase (AST) to platelet ratio index; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; BARD score, body mass index, AST/alanine transaminase (ALT) ratio and diabetes score; FIB-4, fibrosis index based on 4 factors; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; RNA, ribonucleic acid.

[a]Median (interquartile range).

to distinct mechanisms contributing to NAFLD in the absence of central visceral adiposity. These include impaired glucose metabolism, dysfunctional adipose tissue, and genetic factors such as carriage of the PNPLA3 minor allele [36–38]. Furthermore, recent genome-wide investigations have revealed a potential association between NAFLD susceptibility and specific human leukocyte antigen alleles, such as human leukocyte antigen-B*54:01, suggesting a potential influence of gut microbiota alterations [39]. These findings highlight the need for further research to better understand the pathophysiologic mechanisms of lean NAFLD. Moreover, clinicians should be vigilant in considering the possibility of NAFLD in nonobese patients presenting with liver-related symptoms, unexplained derangements in liver function tests, or other relevant risk factors.

Second, both the FIB-4 and NFS demonstrated agreement in stratifying liver fibrosis, with the NFS slightly overestimating the number of PWH with advanced fibrosis (ie, 36) compared with the FIB-4 (ie, 34). This aligns with previous studies that have suggested that the FIB-4 outperforms the NFS in estimating the risk of fibrosis (area under the receiver operating characteristic, 0.80 vs 0.78, respectively) [40]. Consequently, the AACE/AASLD recommends the routine clinical use of FIB-4 [23], whereas the EACS endorses both the FIB-4 and NFS, particularly in specialty hepatology clinic settings [23, 24]. Of note,

Table 4. Logistic Regression of Factors Associated With Advanced Fibrosis in PWH Using the FIB-4 and NAFLD Fibrosis Scores

	FIB-4				NFS			
Characteristics	Crude Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratio (95% CI)	*P* Value	Crude Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratio (95% CI)	*P* Value
Age > 45 y	2.28 (.97–5.38)	.056	6.29 (1.93–20.50)	.002	.92 (.41–2.02)	.830	…	
Male	.97 (.40–2.34)	.943	…		.39 (.16–.92)	.29	.49 (.19–1.29)	.149
Black race	1.50 (.67–3.38)	.325	…		1.08 (.48–2.45)	.855	…	
Body mass index ≥ 35 kg/m^2	1.12 (.47–2.65)	.803	…		2.48 (1.08–5.73)	.31	2.10 (.84–5.22)	.110
Smoking	1.25 (.54–2.93)	.600			1.10 (.47–2.59)	.825	…	
Drug use	.57 (.23–1.430	.228			.80 (.32–1.96)	.620	…	
Hypertension	.67 (.30–1.49)	.324			.56 (.25–1.29)	.172	.56 (.23–1.34)	.110
Diabetes	.49 (.22–1.13)	.092	.66 (.20–2.10)	.477	.71 (.32–1.59)	.407	…	
CD4 > 200 cells/mm^3	.44 (.16–1.19)	.102	.84 (.22–3.13)	.798	.31 (.11–.83)	.016	.45 (.16–1.30)	.141
HIV RNA < 20 copies/mL	.54 (.11–2.57)	.437			.97 (.18–5.30)	.976		
Tenofovir-based ART	.68 (.24–1.91)	.464			.82 (.28–2.37)	.709		
NNRI-based ART	1.06 (.41–2.74)	.905			1.19 (.46–3.08)	.727		
PI-based ART	.84 (.34–2.07)	.704			.95 (.38–2.34)	.904		
INSTI-based ART	1.11 (.50–2.47)	.807			.93 (.41–2.10)	.855		
ACE-I or ARB use	1.64 (.72–3.73)	.237			1.58 (.69–3.66)	.279		
Statin use	.48 (.21–1.14)	.095	.67 (.20–2.20)	.509	.37 (.15–.91)	.028	.83 (.30–2.33)	.724
Insulin use	.50 (.13–1.88)	.296			.83 (.25–2.80)	.768		
Metformin use	.36 (.10–1.320	.177	.70 (.14–3.62)	.675	.40 (.11–1.46)	.152	.34 (.07–1.56)	.164
Total bilirubin > 1.2 mg/dL	2.29 (.96–5.50)	.060	1.05 (.30–3.70)	.933	1.74 (.71–4.24)	.222		
Direct bilirubin > .3 mg/dL	2.48 (1.09–5.64)	.029	2.16 (.71–6.57)	.174	2.04 (.89–4.68)	.091	1.95 (.81–4.67)	.135
Albumin < 3.5 g/dL	6.19 (2.56–14.99)	<.001	9.45 (2.45–32.52)	<.001				
Total cholesterol > 200 mg/dL	.57 (.23–1.43)	.228			.64 (.26–1.62)	.345		
HDL-C < 40 mg/dL	.80 (.36–1.81)	.593			.69 (.30–1.57)	.375		
LDL-C > 100 mg/dL	.87 (.39–1.96)	.740			.60 (.26–1.38)	.229		
Triglycerides > 150 mg/dL	.65 (.28–1.47)	.294			1.41 (.59–3.36)	.439		

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; APRI, aspartate aminotransferase (AST) to platelet ratio index; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; BARD score, body mass index, AST/alanine transaminase ratio and diabetes score; FIB-4, fibrosis index based on 4 factors; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV.

the FIB-4, NFS, and BARD scores were in agreement in estimating that approximately 1 in 4 (ie, 23.6%–27.2%) of PWH in our study had a low probability of fibrosis, effectively ruling out the necessity for a liver biopsy. The BARD Score in particular merits further discussion in that it offers some advantages over the FIB-4 and the NFS in estimating the risk of fibrosis. The BARD Score uses easily obtainable clinical parameters (ie, BMI, AST/ALT ratio, and the presence of diabetes), making it convenient for routine clinical practice [20]. In comparison, the FIB-4 and NFS require more complex calculations or additional laboratory values. Furthermore, the BARD Score, like the NFS, incorporates the presence of diabetes, a key component of the metabolic syndrome and a major predictor of cardiovascular disease and NAFLD risk [28]. This additional parameter enhances the predictive ability of the BARD Score in ruling out the need for liver fibrosis testing. Moreover, extensive studies and validations [41, 42] have shown that the BARD score, as demonstrated by Harrison et al [20] in the original study, reliably eliminates the need for liver biopsy. Taken together, the noninvasive scores offer accurate risk stratification, reduce invasive procedures, and provide cost-effective monitoring for patients with NAFLD.

Third, we observed that older age (>45 years) and low albumin, in addition to other well-established markers of chronic liver disease such as elevated AST/ALT and thrombocytopenia, may help predict individuals with advanced fibrosis. These markers have also been recognized as indicators of advanced disease in NAFLD [43–49]. Furthermore, chronological changes in these indices may also have prognostic significance. For instance, a study by Kawaguchi et al [49] showed that a decline in serum albumin of 0.21 g/dL/year was significantly associated with a higher incidence of serious events in advanced NAFLD patients such as hepatocellular carcinoma, gastroesophageal varices, and cardiovascular events [49]. Thus, these readily obtainable indices can provide a practical means of alerting clinicians to NAFLD progression and aid in risk stratification.

Contrarily, we did not observe any significant effects of statins, antihypertensives, or antidiabetic treatment on the development of advanced fibrosis in NAFLD. This finding aligns with the current conflicting evidence regarding the impact of pharmacological agents on NAFLD and fibrosis. For example, a 2013 Cochrane review by Eslami et al [50] reported improvements in mortality, histological features, and biochemical profiles of patients with

NAFLD with statin use. However, the review included only 2 clinical trials with a small number of participants and a high risk of bias [51, 52]. Similarly, some studies have reported improvements in the biochemical profile, histological features, and liver-related events in patients with NAFLD treated with ACE-Is/ARBs [53], insulin [54], and metformin [55], but not resolution of NAFLD. However, recent studies have provided evidence supporting the favorable impact of semaglutide, a potent glucagon-like peptide-1 receptor agonist commonly used for the treatment of diabetes and obesity, on improving liver histology, liver function, and lipid profile, mostly in diabetic patients with NAFLD [56, 57], whereas other studies have produced contrary findings [58, 59]. Further studies are required, especially in PWH, to evaluate the efficacy of these pharmacological interventions in the management of NAFLD and related fibrosis.

Last, we did not observe significant associations between the class of ART and the degree of fibrosis, likely because of the small sample size of our study. Although ART has significantly prolonged the lifespan of PWH, it is associated with various side effects, including lipodystrophy and NAFLD [11–13, 60]. The risk of developing NAFLD is influenced by several factors including the specific type and duration of the ART regimen, with older generation NRTIs and ritonavir-boosted PIs in particular, and newer INSTIs being associated with a higher risk [60]. Oxidative stress resulting from ART-associated mitochondrial toxicity and insulin resistance appears to be the primary mechanisms contributing to the development of NAFLD and subsequent fibrosis [61, 62]. Despite this, the occurrence of ART-related NAFLD and subsequent fibrosis is relatively rare [60].

We acknowledge limitations that are inherent to our study design. These include limited generalizability resulting from the small sample size and restriction to a single health center. With a larger sample size, we could have potentially identified significant associations that were not apparent in our study. Furthermore, our reliance on noninvasive scores and US liver imaging may have introduced limitations and potential biases compared with more accurate diagnostic methods such as liver biopsy or TE. Despite these limitations, the study provides practical insights into diagnosing and managing advanced fibrosis in PWH with NAFLD, which is often challenging even in well-resourced settings.

CONCLUSIONS

In summary, we estimated an overall NAFLD prevalence of 14.6% in an Ohio-based HIV cohort using liver US imaging criteria. Of these, we estimated that approximately 1 in 3 had advanced fibrosis using noninvasive scores, whereas approximately 1 in 4 were stratified as low risk for liver fibrosis, reducing the need for liver biopsy. Factors associated with advanced fibrosis included older age and hypoalbuminemia in the presence of other established associations such as elevated AST/ALT and thrombocythemia. Our findings provide practical insights into risk stratification of PWH with NAFLD and may aid decision-making for referral to hepatology specialty care.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. G. A. Y. and J .M J. conceptualized and designed the study. G. A. Y. collected the data and conducted the statistical analysis. A. K. contributed important intellectual content. G. A. Y. and A. K. drafted the initial manuscript version. All authors critically revised and approved of the final version. G. A. Y. is the guarantor of this manuscript.

Data Availability Statement. The data presented in this study are available on request from the corresponding author upon reasonable request.

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