Predictors of Significant Fibrosis Among People Living with HIV with Metabolic Dysfunction-Associated Steatotic Liver Disease

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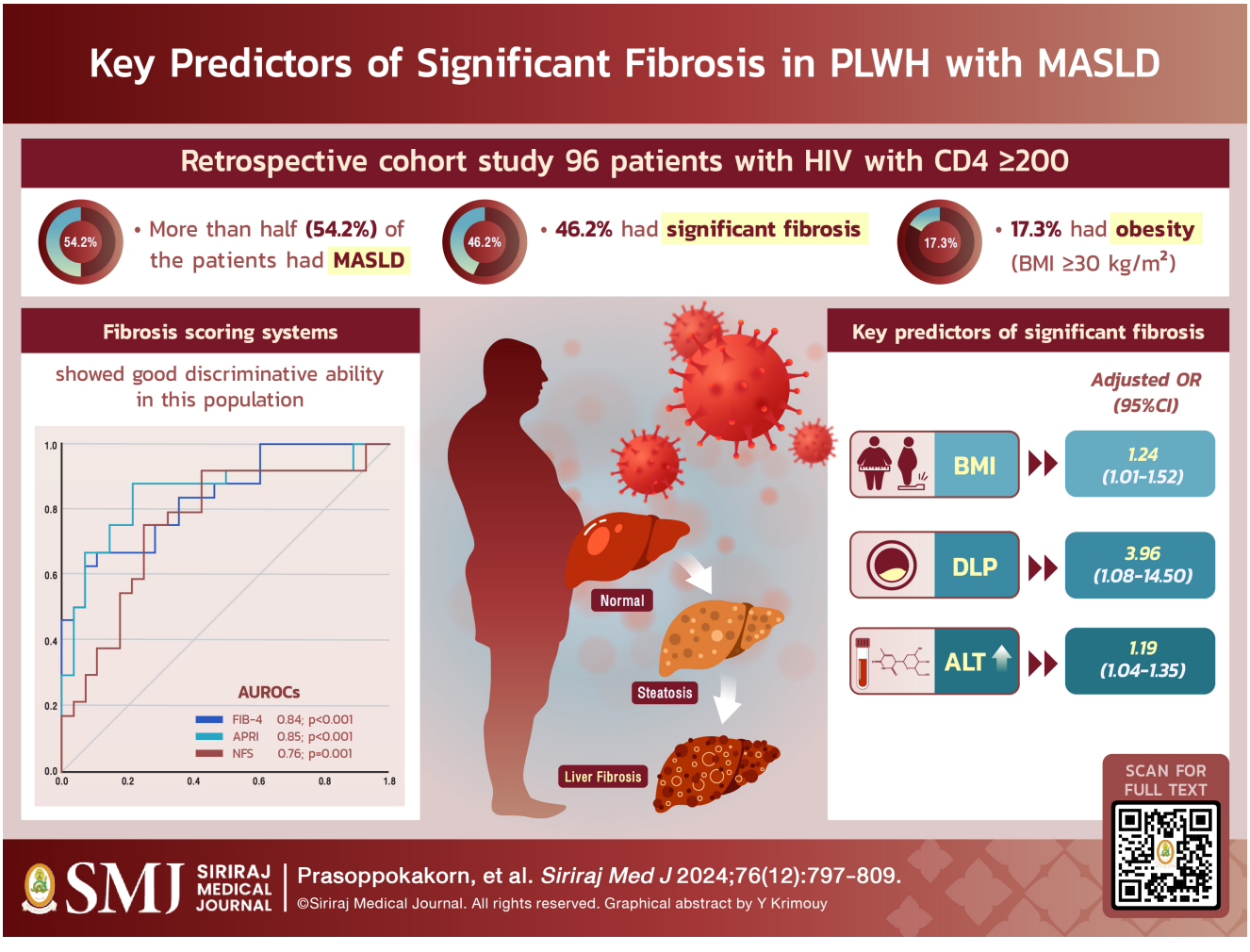

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ABSTRACT

Objective: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent among people living with HIV (PLWH) due to comorbidities and factors related to HIV infection. This study aimed to identify clinical predictors of significant fibrosis among PLWH with MASLD.

Materials and Methods: A retrospective cohort study was conducted with PLWH having CD4 counts ≥200, enrolled between April and October 2023 at two tertiary hospitals. The primary outcome was identifying the clinical predictors of significant fibrosis (F≥2) defined by TE≥8 kPa. Secondary outcomes included MASLD prevalence and characteristics.

Results: Among 96 PLWH, 52 (54.2%) had MASLD. The mean age was 49.7±8.0 years, 63.5% were male, and the mean BMI was 25.8±4.1 kg/m^2. Obesity, diabetes, and dyslipidemia were present in 17.3%, 19.2%, and 46.2% of participants, respectively. The mean CAP and TE were 285±36 dB/m and 8.7±7.8 kPa, respectively. Significant fibrosis was present in 24 patients (46.2%). Fibrosis scoring systems (FIB-4, APRI, NFS) demonstrated good accuracy (AUROCs: 0.84, 0.85, 0.76, respectively). Multivariate analysis identified predictors of significant fibrosis: higher BMI (aOR 1.24, p=0.042), dyslipidemia (aOR 3.96, p=0.038), and higher AST (aOR 1.19, p=0.011). The AGA pathway using two steps (FIB-4 and TE) improved reclassification of significant fibrosis risk, reducing the number of individuals at indeterminate risk, 12 out of 52 in the first step to 7 out of 52 in the second step.

Conclusion: MASLD is highly prevalent in PLWH, with about half experiencing significant fibrosis. Predictors of significant fibrosis include dyslipidemia, higher BMI, and elevated AST levels. Fibrosis scoring systems accurately predict significant fibrosis.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease; steatotic liver disease; metabolic syndrome; HIV infection; People Living with HIV (Siriraj Med J 2024; 76: 797-809)

INTRODUCTION

People living with HIV (PLWH) in Thailand nowadays experience extended lifespans comparable to those of the general population due to advances in antiretroviral therapy (ART).[1,2] However, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) in PLWH is rising globally, with estimates ranging between 30-50%.[3-5] This association is attributed to factors such as an aging population, a high prevalence of metabolic risk factors, comorbidities, and HIV-related infection.[6-9] Additionally, ART has been associated with negative metabolic side effects, such as weight gain and hepatic steatosis, further elevating the risk of MASLD.[10-12]

MASLD in PLWH is concerning due to its association with advanced fibrosis, cirrhosis, hepatocellular carcinoma, and reduced survival.[13-15] Early detection of MASLD can inform clinical management, allowing for lifestyle modification or therapeutic intervention to mitigate potential complications. While the reference standard for assessing prognosis and disease monitoring involves the histologic examination of liver biopsy specimens, this invasive procedure may not be the preferred approach in patients with HIV and MASLD. In such case, the utilization of non-invasive scoring systems is valuable for facilitating risk stratification and longitudinal assessment of disease progression.[16-18]

Several non-invasive scoring systems, including the fibrosis-4 (FIB-4) score, aspartate aminotransferase to platelet ratio index (APRI), and non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS), are commonly used for detecting liver fibrosis in this population.[19] These scoring systems are generally safer and more acceptable for patients, making them well-suited for serial monitoring of disease progression or response to treatment.

The identification of advanced liver fibrosis serves as a crucial prognostic marker for unfavorable outcomes in individuals with MASLD. Currently, imaging-based biomarkers play a significant role, offering rapid and outpatient-compatible procedures. Among the ultrasound-based techniques, vibration-controlled transient elastography (VCTE), commercially available as FibroScan® (Echosens, Paris, France), was the first to be introduced and is currently the most extensively validated.[20-21] This non-invasive imaging technique provides a dual advantage for screening, offering simultaneously information on both liver stiffness measurement (LSM) and the degree of hepatic steatosis, estimated through the controlled attenuation parameter (CAP).

It is important to note that the diagnostic performance of these tests can vary based on the specific population studies, the prevalence of liver fibrosis in that population,

and the reference standard used for comparison.[22-24] The diverse influences of ethnicity, race, socioeconomic status, and varying lifestyles contribute to the impact of liver fibrosis in people living with HIV. However, there is limited data about the importance of liver fibrosis and fatty liver in PLWH, particularly among Asian population.[25-26] Therefore, this study aims to identify clinical predictors of significant fibrosis in PLWH with MASLD in Thailand.

MATERIALS AND METHODS

Study design and participants

We conducted a retrospective cohort study, enrolling patients from two tertiary hospitals between April and October 2023. The inclusion criteria were patients aged ≥18 years who visited outpatient liver and infectious disease clinics with HIV infection, had been treated with standard antiretroviral therapy for ≥6 months, and had an HIV RNA count ≤200 copies/mL. Our study included patients with hepatitis B and C coinfections, as well as those who consumed alcohol. There were no exclusion criteria. Baseline patient characteristics such as age, gender, body weight, body mass index (BMI), waist and hip circumference, and underlying comorbidities including type 2 diabetes mellitus, dyslipidemia, and hypertension were recorded. Personal history information on smoking and alcohol consumption was also retrieved. Laboratory tests included liver function tests, metabolic profiles (fasting blood sugar, HbA1C, lipid profile), CD4 counts, and HBV and HCV status. The laboratory tests were conducted within six months of the hepatic steatosis and fibrosis assessment.

Steatosis and fibrosis assessment: All PLWH underwent a FibroScan® study conducted by dedicated operators after fasting for less than 3 hours. Two parameters derived from this vibration-controlled transient elastography (VCTE) were the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), which reflected steatosis (in decibels per meter or dB/m) and fibrosis (in kilopascals or kPa), respectively. The cut-off values to define steatosis were: no signs of steatosis (S0) < 238 dB/m, beginning steatosis (S1): 238-259 dB/m, advanced steatosis (S2): 260-291 dB/m, and severe steatosis (S3) > 292 dB/m. A TE cut-off value of at least 6.5 kPa indicated liver fibrosis (F1), and 8.0 kPa indicated significant fibrosis (F2). For more advanced stages, a TE value of ≥9.5 kPa was used to define advanced fibrosis (F3), while a TE value of ≥12.5 kPa indicated cirrhosis (F4).[28]

Fibrosis scoring systems were also calculated. The fibrosis-4 score (FIB-4 score) was determined using the formula [Age (years)×AST (U/L)/[platelet (10^9/L)×ALT$^{1/2}$ (U/L)],[29] the AST to platelet ratio index (APRI) was computed as [AST (IU/L)/AST upper limit of normal (IU/L)/platelets (10^9/L) x 100],[30] and the NAFLD fibrosis score (NFS) was derived from the formula [-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × platelet count (x10^9/L) - 0.66 × albumin (g/dL).[31]

Individual consent for retrospective analysis was exempted. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No.903/63), and adhered to the principles outlined in the Helsinki Declaration of 1983.

Definition of MASLD and dyslipidemia

According to a recently published international consensus statement,[32] a diagnosis of MASLD required the presence of hepatic steatosis, as defined by a CAP of ≥ 238 dB/m. Apart from the identification of hepatic steatosis detected by imaging or biopsy, at least one of the following five criteria had to be evident: 1) overweight/obesity (BMI > 23 kg/m^2) or waist circumference > 90 cm in men, > 80 cm in women, 2) fasting serum glucose levels > 100 mg/dL or 2-hour post-load glucose level > 140 mg/dL or HbA1c > 5.7%, or specific drug treatment, 3) blood pressure > 130/85 mmHg or specific drug treatment, 4) plasma TG levels > 150 mg/dL or specific drug treatment, 5) plasma HDL-C levels below 40 mg/dL for men and 50 mg/dL for women or specific drug treatment. Dyslipidemia was defined as elevated levels of serum TC, LDL-C, TG, or a reduced serum HDL-C concentration.

Outcomes

The primary outcome was identifying clinical predictors of significant fibrosis (F ≥2), defined as TE ≥ 8 kPa in PLWH with MASLD. Secondary outcomes included: 1) the prevalence and clinical characteristics of MASLD, defined as CAP ≥ 238 dB/m in those meeting cardiometabolic criteria; 2) the performance of non-invasive fibrosis scoring systems among these patients; and 3) the clinical applicability of the two-step non-invasive testing recommended by the American Gastroenterological Association (AGA) pathway, using the FIB-4 score and VCTE.

Statistical analysis

Continuous variables were reported as mean ± standard deviation and analyzed using unpaired t-tests for normally distributed data. Skewed variables were expressed as median with interquartile range and assessed

for differences using the Mann-Whitney U test. Categorical variables were expressed as numbers (percentages) and compared using Fisher's exact test or Chi-square test as appropriate. Factors associated with significant fibrosis were determined using a logistic regression model. Age, sex, and other factors with a p-value of < 0.05 in the univariate model were included in the multivariate model. Statistical analyses were performed using SPSS version 22.0.0 (SPSS Inc., Chicago, Illinois, USA). A p-value of < 0.05 was considered statistically significant.

Ethical Statement

The study protocol received approval from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB number 903/63).

RESULTS

Baseline patient characteristics

A total of 96 participants with HIV infections were enrolled at two tertiary hospitals. Of these, 52 (54.2%) were diagnosed with MASLD. Table 1 demonstrates the baseline characteristics between the MASLD and non-MASLD groups. Patients with MASLD had significantly higher body weight (70.9 ± 11.9 kg vs. 61.1 ± 8.8 kg, p < 0.001), BMI (25.8 ± 4.1 kg/m² vs. 21.6 ± 3.0 kg/m², p < 0.001), waist circumference (WC) (35.8 ± 3.5 inches vs. 31.4 ± 3.2 inches, p < 0.001), and hip circumference (HC) (39.4 ± 3.6 inches vs. 35.7 ± 3.2 inches, p < 0.001) compared to those without MASLD. Additionally, 100% of the MASLD group had a BMI ≥30, while none of the non-MASLD group did (p < 0.001). Comorbidities such as impaired fasting glucose (IFG), diabetes (DM), dyslipidemia (DLP), and hypertension (HT) showed a trend towards higher incidence in the MASLD group compared to the non-MASLD group, although these differences did not reach statistical significance (IFG: 44.2% vs. 27.3%, p = 0.083; DM: 19.2% vs. 6.8%, p = 0.068; DLP: 46.2% vs. 36.4%, p = 0.331; HT: 34.6% vs. 20.5%, p = 0.121).

Regarding laboratory values, fasting blood sugar (FBS) was significantly higher in the MASLD group compared to the non-MASLD group (103.8 ± 25.5 mg/dL vs. 96.5 ± 9.4 mg/dL, p = 0.029). Triglyceride (TG) levels were also significantly higher in the MASLD group (158.7 ± 82.9 mg/dL vs. 121.3 ± 72.6 mg/dL, p = 0.010), and LDL cholesterol was significantly elevated in the MASLD group as well (118.8 ± 36.7 mg/dL vs. 107.0 ± 28.9 mg/dL, p = 0.041). However, there were no significant differences in AST, ALT, or HDL cholesterol between the two groups. Liver stiffness, as measured by transient elastography (TE), was significantly higher in the MASLD group (8.7 ± 7.8 kPa vs. 7.5 ± 8.6 kPa, p = 0.014). Additionally, the CAP score, indicating hepatic steatosis, was also significantly higher in the MASLD group (285 ± 36 dB/m vs. 195 ± 28 dB/m, p < 0.001).

Among the MASLD patients, the mean age was 49.7 ± 8.0 years, and 33 (63.5%) were male. The mean BMI was 25.8 ± 4.1 kg/m². Obesity, defined by WHO criteria for the Asia-Pacific region (BMI ≥ 30.0 kg/m²), was present in 9 (17.3%) patients. Dyslipidemia was the most common comorbidity, affecting 24 (46.2%) patients, followed by diabetes in 10 (19.2%) patients and hypertension in 18 (34.6%) patients. Regarding hepatitis virus coinfection, 5 (9.6%) patients had HBV and 7 (13.5%) had HCV. Additionally, two-thirds of the patients (67.3%) had a history of alcohol consumption. Baseline characteristics of the total cohort are shown in Table 2.

Regarding steatosis, the mean CAP was 285 ± 36 dB/m, and the median CAP was 276 (255, 303) dB/m. Among the patients, 16 (30.8%) had steatosis grade 1, 17 (32.7%) had grade 2, and 19 (36.5%) had grade 3. For liver fibrosis, the mean TE was 8.7 ± 7.8 kPa, and the median TE was 6.1 (5.2, 8.8) kPa. Significant fibrosis (F ≥2) was found in 24 patients (46.2%), advanced fibrosis (F ≥3) in 8 patients (15.4%), and cirrhosis (F ≥4) in 4 patients (7.7%).

Comparison of Patient Characteristics Between Fibrosis Grades 0-1 and ≥2

Patients with significant fibrosis (≥ F2) compared to those with fibrosis stage 0-1 had significantly higher BMI (27.1 ± 4.6 vs 24.7 ± 3.3 kg/m², p = 0.016), higher waist circumference (37.1 ± 3.4 vs 34.6 ± 3.3 inches, p = 0.004), and higher hip circumference (40.7 ± 3.7 vs 38.3 ± 3.2 inches, p = 0.008). These patients also had a higher prevalence of dyslipidemia (62.5% vs 32.1%, p = 0.029) and HCV co-infection (29.2% vs 0%, p = 0.002). Additionally, they exhibited higher AST levels (53.5 vs 28.2 U/L, p < 0.001), ALT levels (72.1 vs 37.9 U/L, p = 0.002), and globulin levels (3.5 ± 0.6 vs 3.3 ± 0.3 g/dL, p = 0.035). Furthermore, they had a lower platelet count (221 ± 88 vs 290 ± 84, p = 0.003) and lower HDL-cholesterol (41.4 ± 11.4 vs 48.3 ± 8.6 mg/dL, p = 0.008) (Table 2). However, no association was found between CAP grades and the degrees of liver fibrosis (p = 0.893).

Performance of Non-Invasive Tests in Predicting Significant Fibrosis

Patients with significant fibrosis had significantly higher levels of all non-invasive fibrosis tests, including the FIB-4 score (2.54 ± 3.89 vs 0.86 ± 0.32, p < 0.001), APRI

TABLE 1. Baseline characteristics of the entire cohort compared between MASLD and non- MASLD (n=96).

Variables	Total (n=96)	MASLD (n=52)	Non-MASLD (n=44)	p-value
Age (yr), mean ±SD	48.9±9.9	49.7±8.0	48.1±11.8	0.213
Sex Male, n(%)	68 (70.8%)	33(63.5%)	35 (79.5%)	0.081
BW (kg)	66.4±11.6	70.9±11.9	61.1±8.8	<0.001
BMI (kg/m^2)	23.9±4.2	25.8±4.1	21.6±3.0	<0.001
BMI ≥30, n(%)	9 (9.4%)	9 (100%)	0 (0%)	<0.001
WC (inch)	33.8±4.0	35.8±3.5	31.4±3.2	<0.001
HC (inch)	37.7±3.8	39.4±3.6	35.7±3.0	<0.001
IFG, n(%)	35 (36.5%)	23 (44.2%)	12 (27.3%)	0.083
T2DM, n(%)	13 (13.5%)	10 (19.2%)	3 (6.8%)	0.068
DLP, n(%)	40 (41.7%)	24 (46.2%)	16 (36.4%)	0.331
HT, n(%)	27 (28.1%)	18 (34.6%)	9 (20.5%)	0.121
HBV, n(%)	6 (6.3%)	5 (9.6%)	1 (2.3%)	0.120
HCV, n(%)	18 (18.8%)	7 (13.5%)	11 (25%)	0.149
Alcohol, n(%)	69 (71.9%)	35 (67.3%)	34 (77.3%)	0.521
Smoking, n(%)	37 (38.5%)	22 (42.3%)	15 (34.1%)	0.585
AST (U/L)	38.9±23.5	39.9±25.4	37.8±21.3	0.329
ALT (U/L)	49.6±42.5	53.7±43.2	44.8±41.7	0.155
ALP (U/L)	87.7±30.3	89.1±26.0	86.1±34.9	0.634
Albumin (g/dL)	4.3±0.4	4.3±0.3	4.2±0.4	0.638
Globulin (g/dL)	3.4±0.5	3.4±0.5	3.4±0.5	0.788
Hb (g/dL)	14.9±13.1	13.3±1.9	16.8±19.3	0.246
WBC (cell/µL)	6829±1957	7087±2264	6525±1487	0.149
Platelet (x10^9/µL)	251±85	258±92	243±77	0.387
Creatinine (mg/dL)	1.0±0.3	1.0±0.2	1.0±0.3	0.867
FBS (mg/dL)	100.5±20.1	103.8±25.5	96.5±9.4	0.029
TC (mg/dL)	183.0±37.8	188.9±40.9	176.0±32.9	0.045
TG (mg/dL)	141.5±80.2	158.7±82.9	121.3±72.6	0.010
HDL-chol (mg/dL)	45.7±10.4	45.1±10.5	46.3±10.3	0.581
LDL-chol (mg/dL)	113.4±33.7	118.8±36.7	107.0±28.9	0.041
CD4 (cell count)	640±269	679±269	595±264	0.125
ARV used, n(%)	96 (100%)	52 (100%)	44 (100%)	NA
CAP (dB/m)				
Mean ±SD	244±55	285±36	195±28	<0.001
Median (IQR)	246 (200,285)			
TE (kPa)				
Mean ±SD	8.1±8.2	8.7±7.8	7.5±8.6	0.014
Median (IQR)	5.8 (4.5,8.7)			

TABLE 2. Baseline characteristics compared between Fibrosis stage 0-1 and Fibrosis stage ≥2 of MASLD in PWLH (n=52).

Variables	Total (n=52)	Fibrosis stage F0-1 (n=28)	Fibrosis stage ≥2 (n=24)	p-value
Age (yr), mean ±SD	49.7±8.0	48.3±9.1	51.3±6.4	0.085
Male, n (%)	33 (63.5%)	17 (60.7%)	16 (66.7%)	0.775
BW (kg)	70.9±11.9	68.4±9.7	73.7±13.8	0.058
BMI (kg/m^2)	25.8±4.1	24.7±3.3	27.1±4.6	0.016
BMI ≥30, n (%)	9 (17.3%)	3 (10.7%)	6 (25.0%)	0.175
WC (inch)	35.8±3.5	34.6±3.3	37.1±3.4	0.004
HC (inch)	39.4±3.6	38.3±3.2	40.7±3.7	0.008
IFG, n (%)	23 (44.2%)	12 (42.9%)	11 (45.8%)	0.829
T2DM, n (%)	10 (19.2%)	7 (25.0%)	3 (12.5%)	0.254
DLP, n (%)	24 (46.2%)	9 (32.1%)	15 (62.5%)	0.029
HT, n (%)	18 (34.6%)	8 (28.6%)	10 (41.7%)	0.322
HBV, n (%)	5 (9.6%)	4 (14.3%)	1 (4.2%)	0.217
HCV, n (%)	7 (13.5%)	0 (0.0%)	7 (29.2%)	0.002
Alcohol, n (%)	35 (67.3%)	19 (67.9%)	16 (66.7%)	0.838
Smoking, n (%)	22 (42.3%)	15 (53.6%)	7 (29.2%)	0.184
Laboratory tests				
AST (U/L)	39.9±25.4	28.2±11.4	53.5±6.2	<0.001
ALT (U/L)	53.7±43.2	37.9±27.8	72.1±50.7	0.002
ALP (U/L)	89.1±26.0	88.6±25.1	89.7±27.6	0.445
Albumin (g/dL)	4.3±0.3	4.3±0.2	4.3±0.4	0.387
Globulin (g/dL)	3.4±0.4	3.3±0.3	3.5±0.6	0.035
Hb (g/dL)	13.3±1.9	13.6±2.1	13.1±1.6	0.152
WBC (cell/µL)	7087±2264	7496±2243	6608±2239	0.080
Platelet (x10^9/µL)	258±92	290±84	221±88	0.003
Creatinine (mg/dL)	1.02±0.24	1.0±0.2	1.1±0.3	0.056
FBS (mg/dL)	103.8±25.5	102.7±21.6	105.1±29.8	0.376
TC (mg/dL)	188.9±40.9	193.9±43.1	183.0±38.3	0.171
TG (mg/dL)	158.7±82.9	151.7±87.4	166.9±78.3	0.257
HDL-chol (mg/dL)	45.1±10.5	48.3±8.6	41.4±11.4	0.008
LDL-chol (mg/dL)	118.8±36.7	123.2±38.3	113.6±34.9	0.177

TABLE 2. Baseline characteristics compared between Fibrosis stage 0-1 and Fibrosis stage ≥2 of MASLD in PWLH (n=52). (Continue)

Variables	Total (n=52)	Fibrosis stage F0-1 (n=28)	Fibrosis stage ≥2 (n=24)	p-value
HIV parameters				
CD4 (cell count)	679±269	697±265	658±279	0.304
ARV used, n (%)	52 (100%)	28 (100%)	24 (100%)	NA
FibroScan® study				
CAP grade, n (%)				
1	16 (30.8%)	8 (28.6%)	8 (33.3%)	0.893
2	17 (32.7%)	9 (32.1%)	8 (33.3%)	
3	19 (36.5%)	11 (39.3%)	8 (33.3%)	
CAP (dB/m)				
Mean ±SD	285±36	291.9±41.5	276.5±25.5	0.054
Median (IQR)	276 (255,303)			
TE (kPa)				
Mean ±SD	8.7±7.8	5.1±0.8	12.8±10.1	<0.001
Median (IQR)	6.1 (5.2,8.8)			
Non-invasive fibrosis testing				
FIB-4 score				
Mean ±SD	1.64±2.75	0.86±0.32	2.54±3.89	<0.001
Median (IQR)	1.06 (0.71,1.58)			
APRI score				
Mean ±SD	0.54±0.68	0.27±0.15	0.87±0.89	<0.001
Median (IQR)	0.32 (0.20,0.63)			
NFS score				
Mean ±SD	-2.17±1.63	-2.78±1.24	-1.46±1.76	0.001
Median (IQR)	-2.30 (-3.30,-1.41)			

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; ARV, antiretroviral; BMI, body mass index; BW, body weight; CAP, controlled attenuation parameter; CD-4, cluster of differentiation 4; FBS, fasting blood sugar; DLP, dyslipidemia; FIB-4 score, fibrosis index based on 4 factors; IFG, impaired fasting glucose; IQR, interquartile range; Hb, hemoglobin; NFS, HBV, hepatitis B virus; HC, hip circumference; HCV, hepatitis C virus; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; NAFLD fibrosis score; SD, standard deviation; T2 DM, type 2 diabetes mellitus; TC, total cholesterol; TE, transient elastography; TG, triglyceride; WBC, white blood cell; WC, waist circumference.

score (0.87 ± 0.89 vs 0.27 ± 0.15, p < 0.001), and NFS score (-1.46 ± 1.76 vs -2.78 ± 1.24, p = 0.001), compared to those with fibrosis stage 0-1. Using transient elastography as the reference diagnostic test, we assessed the efficacy of different non-invasive tests. The areas under the receiver operating characteristic curves (AUROCs) for FIB-4, APRI, and NFS were 0.84, 0.85, and 0.76, respectively (Fig 1). Both FIB-4 and APRI demonstrated comparable and superior performance to NFS in predicting liver fibrosis among adults at risk, particularly in PLWH and those susceptible to MASLD.

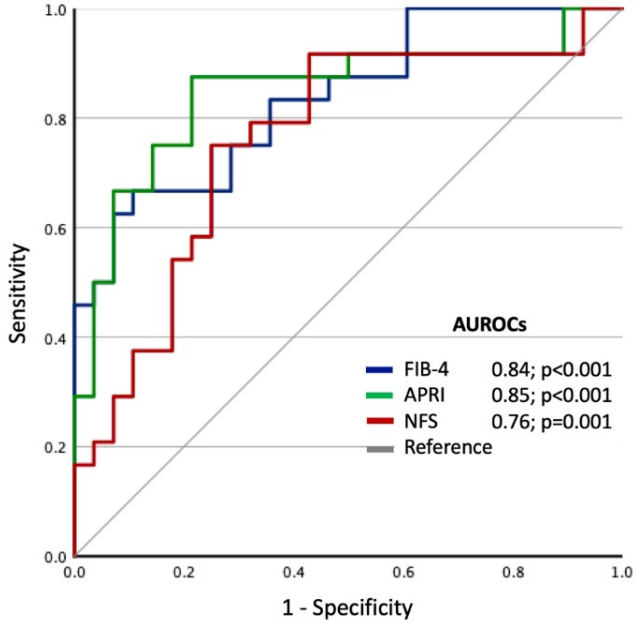

Fig 1. The AUROCs of the FIB-4 score, APRI score, and NFS score for predicting significant fibrosis (F≥2) in MASLD Patients with PLWH

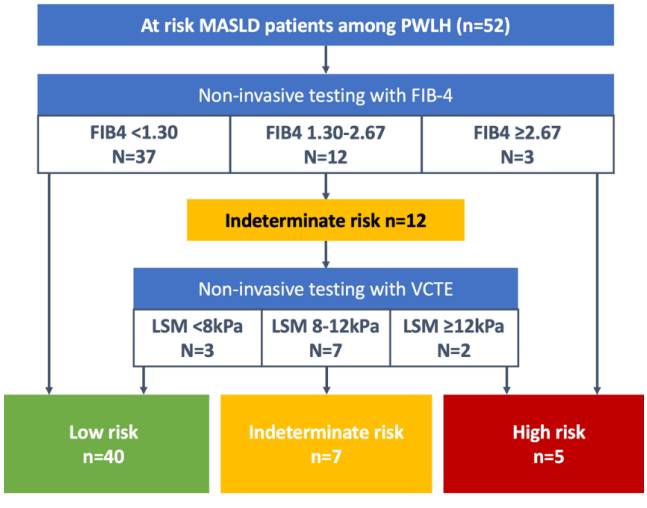

Fig 2. Implementation of a two-step approach involving non-invasive testing with FIB-4 and VCTE, as recommended by the American Gastroenterological Association (AGA) for MASLD in PLWH (n = 52).

Factors associated with significant fibrosis among MASLD with PLWH

Univariate analysis revealed several factors significantly associated with significant liver fibrosis: BMI (OR 1.17, p = 0.039), waist circumference (OR 1.28, p = 0.016), hip circumference (OR 1.24, p = 0.026), presence of dyslipidemia (OR 3.52, p = 0.031), AST levels (OR 1.08, p = 0.001), ALT levels (OR 1.03, p = 0.011), platelet count (OR 0.98, p = 0.017), and HDL-cholesterol level (OR 0.92, p = 0.024). After adjusting for age and sex in the multivariate analysis, higher BMI (aOR 1.24, p = 0.042), presence of dyslipidemia (aOR 3.96, p = 0.038), and elevated AST levels (aOR 1.19, p = 0.011) were independently associated with significant fibrosis (Table 3).

Two-Step Non-invasive Testing with FIB-4 Score and VCTE

To further enhance the accuracy of prediction, we analyzed the implementation of a two-step pathway using the FIB-4 score followed by TE, as recommended by the American Gastroenterological Association (AGA)[33], among PLWH with MASLD (n = 52). This approach improved risk reclassification for significant liver fibrosis, reducing the number of individuals at indeterminate risk from 12 out of 52 after the first step (FIB-4) to 7 out of 12 after the second step (VCTE), as illustrated in Fig 2. Consequently, among PLWH at risk for MASLD, patients were categorized into a low-risk group (40 patients, 76.9%), an indeterminate-risk group (7 patients, 13.5%), and a high-risk group (5 patients, 9.6%). This resulted in a reduced number of individuals in the indeterminate risk group, thereby minimizing the need for unnecessary liver biopsies.

DISCUSSION

In this analysis, the prevalence of MASLD among PLWH is notably high at 54.2%, comparable to rates observed in in Western countries.[3,4,8,9] Additionally, approximately half of these patients are experiencing significant fibrosis. With the improvement of healthcare in Thailand and the availability of ART, the burden of MASLD and significant fibrosis in this population is anticipated to become increasingly significant in the future. Therefore, targeted efforts to screen and diagnose MASLD in population are imperative.

Our study found that the MASLD group had significantly higher anthropometric measures (body weight, BMI, waist circumference, and hip circumference) and higher levels of triglycerides and LDL cholesterol, along with higher liver stiffness and hepatic steatosis,

TABLE 3. Univariate and multivariate logistic regression analysis of factors associated with significant fibrosis (F≥2) in MASLD among PLWH.

Variable	Univariate		Multivariate	
	OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Age (years)	1.05 (0.98-1.13)	0.172		
Male gender	1.29 (0.42-4.04)	0.657		
BMI (kg/m^2)	1.17 (1.01-1.36)	0.039	1.24 (1.01-1.52)	0.042
BMI ≥30	2.78 (0.61-12.61)	0.186		
WC (inch)	1.28 (1.05-1.57)	0.016		
HC (inch)	1.24 (1.03-1.50)	0.026		
Presence of DM	1.13 (0.38-3.38)	0.829		
Presence of DLP	3.52 (1.12-11.06)	0.031	3.96 (1.08-14.50)	0.038
Presence of HT	1.79 (0.56-5.66)	0.325		
AST (U/L)	1.08 (1.03-1.14)	0.001	1.19 (1.04-1.35)	0.011
ALT (U/L)	1.03 (1.01-1.04)	0.011		
Globulin (g/dL)	3.83 (0.78-18.73)	0.098		
Platelet (x109/μL)	0.98 (0.98-0.99)	0.017		
Triglyceride (mg/dL)	1.00 (0.99-1.01)	0.509		
HDL-chol (mg/dL)	0.92 (0.87-0.99)	0.024		
LDL-chol (mg/dL)	0.99 (0.97-1.00)	0.350		
CAP (dB/m)	0.99 (0.97-1.01)	0.987		

compared to the non-MASLD group. Although trends in metabolic comorbidities such as IFG, DM, DLP, and HT were higher in the MASLD group, they did not reach statistical significance. These findings highlight the metabolic profile associated with MASLD and emphasize the importance of managing these metabolic risk factors to prevent disease progression.

As acknowledged, the reported prevalence is influenced by the chosen cut-off of CAP, and notably, the optimal cut-off in PLWH is not yet to be determined. While studies in this population suggest using a CAP of 248 dB/m as a cut-off for hepatic steatosis,[34,35] current practice guidelines for non-invasive tests recommend a cut-off of 275 dB/m, irrespective of HIV status.[34,36] However, our study employed an even lower cut-off of 238 dB/m, likely resulting in an overestimation of MASLD prevalence. Given the limited data for the Asian population, we opted for a lower cut-off CAP for use as a screening test to facilitate early detection, modification of risk factors, and adjustment of ART regimen to prevent liver complications.

In our study, we observed a lack of correlation between CAP and liver fibrosis. Several reasons contribute to this absence of direct correlation: 1) distinct pathological processes, as steatosis and fibrosis are separate yet often parallel occurrences; 2) variable progression rate, with liver diseases advancing at different rates in different individuals; 3) multiple factors influencing fibrosis, including inflammation, oxidative stress, and immune response, which may not be adequately captured by a marker primarily designed for fat content assessment; and 4) the heterogeneity of liver disease (e.g., non-alcoholic fatty liver disease, viral hepatitis, alcoholic liver disease, HIV infection), each potentially having

unique relationships between steatosis and fibrosis. While CAP may not predict liver fibrosis, it can serve as a valuable screening test, signaling the need for risk factor modification to prevent MASLD.

Characterizing PLWH based on MASLD, and liver fibrosis risk factors is crucial for identifying those at particular risk of developing advanced liver disease. In our study, significant MASLD and fibrosis were associated with high BMI, dyslipidemia, and a high level of AST, but not with HIV-related factors. These findings suggest that metabolic risk factors play a more substantial role in fibrosis development in PLWH, and targeted interventions such as weight management, diet modification, and exercise are crucial in preventing disease progression.

Overweight and obesity, as measured by BMI, is the main risk predictors for PLWH to develop fibrosis.[37] In contrast to the past, where HIV patients were often cachectic due to opportunistic infections and ineffective ART, today, with effective ART and increased treatment accessibility, people living with HIV can lead longer and healthier lives. The causes of weight gain are similar to metabolic syndrome population, and certain ART regimens, such as tenofovir-alafenamid and integrase strand transfer inhibitors, can contribute to weight gain.[10,38,39] Switching to tenofovir disoproxil fumarate has been independently associated with a lower risk of clinically significant weight gain, potentially slowing the development and progression of steatosis.[10] Therefore, it is crucial for HIV patients to focus on diet control, limit alcohol consumption, and engage in exercise to manage body weight. While metabolic factors such as BMI, dyslipidemia, and AST levels were found to be significant predictors of fibrosis in our study, we cannot overlook the potential influence of HIV-specific factors, such as viral load, CD4+ T-cell count, and the duration of HIV infection. These factors, which were not significant in our analysis, may still play a crucial role in liver disease progression among PLWH, and future studies should explore their impact further.

Dyslipidemia is a common concern in PLWH, attributed to specific antiretroviral medications, chronic inflammation, and immune activation associated with HIV infection.[40] Certain antiretroviral medications, especially protease inhibitors and some nucleoside reverse transcriptase inhibitors have been associated with increased level of TG and cholesterol.[41] Effective management of dyslipidemia in HIV population is important to reduce cardiovascular risk but presents multiple challenges due to interactions between ART agents and lipid-lowering medications. Optimal medical therapy, including lipid-lowering therapy and changing ART regimens, is vital for managing dyslipidemia and mitigating liver and cardiovascular risks.

While elevated AST levels were associated with hepatic steatosis and fibrosis in our study, it is important to recognize the limitations of using AST as a marker, as it lacks specificity for fibrosis. AST can be influenced by various factors, including ART-related mitochondrial injury, which could lead to overestimation of fibrosis severity.

Additionally, HIV and HBV or HCV coinfection or alcoholic consumption are additional predictors that warrant attention. HIV and viral hepatic coinfection promote hepatic injuries during MASLD through several mechanisms triggered by their persistent replication, enhanced inflammatory response and metabolic interference.[42] Although not proven as predictors of significant liver fibrosis in our study due to the small sample size, HIV patients are strongly encouraged to manage viral hepatitis coinfections and limit alcohol consumption to reduce liver damage. We included patients with hepatitis B and C in this study because these are common comorbidities in PLWH, reflecting real-world clinical practice. Excluding them could have compromised the statistical power of the study. Similarly, we examined the impact of alcohol consumption, which showed no significant association with fibrosis development in our cohort. However, this may be due to the limited sample size, and the influence of alcohol should still be carefully considered when managing MASLD in PLWH.

Early detection and prompt treatment are crucial to slowing progressions and preventing liver fibrosis and hepatic complications. Out study confirms the benefit of non-invasive fibrosis markers, particularly the FIB-4 score and APRI, which exhibited the highest AUROCs. These markers can serve as screening tests to alert HIV patients to the risk of liver fibrosis and prompt treatment. Combining different non-invasive assessments, such as FIB-4 or APRI score and VCTE, according to the AGA pathway of a two-step approach,[33] improves reclassification in the indeterminate group and reduces the need for unnecessary liver biopsy. It is essential to acknowledge that while liver biopsy remains the gold standard for assessing both steatosis and fibrosis, non-invasive methods are increasingly utilized due to their lower risk and greater patient acceptance. Although the AGA pathway is intended for advanced fibrosis, we adapted it for significant fibrosis due to the limited number of advanced fibrosis cases in our cohort. This adaptation allowed us to better capture the full spectrum of fibrosis in this population, but it will be acknowledged as a limitation. In addition to early detection, specific

clinical recommendations are essential. HIV patients should be counseled on lifestyle interventions such as diet modification, exercise, and alcohol reduction. Moreover, certain ART regimens associated with weight gain and dyslipidemia, such as integrase strand transfer inhibitors and tenofovir-alafenamide, should be re-evaluated. Switching to alternative regimens, such as tenofovir disoproxil fumarate, could mitigate some of the metabolic complications associated with MASLD progression.

This study has some limitations to acknowledge. First, the absence of liver biopsy data for correlation with TE findings is noteworthy. However, TE has demonstrated reasonable accuracy in estimating liver fibrosis and steatosis.[27,28] Second, the cross-sectional nature of this study, lacking a longitudinal design, prevent the provision of data on cumulative exposure to specific ART regimens, which could potentially influence the development of hepatic steatosis and fibrosis over time. Third, variations in the defined cut-offs for significant fibrosis and hepatic steatosis have a determining impact on overall results and observed associations. Our utilization of cut-offs at 238 dB/m, in contrast to the recommended 275 dB/m by the European Association for the Study of the Liver (EASL) guideline[36] for non-invasive tests, may have included patients with lesser degree of steatosis. Consequently, our results might not be directly comparable with other studies. Lastly, this study may not have comprehensively accounted for all confounding variables, such as herbs, medicines, and antioxidant supplements, as well as boarder factors like socioeconomic and concomitant treatment. Despite these limitations, our study underscores the importance of early detection and targeted interventions for MASLD in PLWH, especially in the context of rising metabolic comorbidities. Future studies should consider a prospective design, more stringent exclusion criteria, and a larger sample size to further validate these findings.

CONCLUSION

The prevalence of MASLD and significant fibrosis is notably high among PLWH. The predictors of significant fibrosis include higher BMI, dyslipidemia, and elevated AST levels. Additionally, fibrosis scoring systems exhibit good accuracy for fibrosis prediction. The integration of two-step approach involving a fibrosis scoring system and liver stiffness measurement has further improved the accuracy of prediction. To ascertain the effectiveness of this approach, future prospective longitudinal studies are warranted to identify early interventions and novel therapies within this population.

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DECLARATION

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Conflict of Interest

All authors declare no conflicts of interest.

Author Contributions

T.P., S.T. - Conceptual design of the work; T.P., V.L., S.S., P.P., T.S., K.S., P.A., K.T., C.S., S.T. - Data collection and data acquisition; T.P. - Data analysis and interpretation; V.L., T.P. - Drafting the manuscript; S.T. - Critical revision of the manuscript; All authors - Final approval of the version to be published.

Use of Artificial Intelligence

No artificial intelligence tools or technologies were used in the writing, analysis, or development of this research.

Abbreviations

AGA: American Gastroenterological Association
ALT: Alanine aminotransferase
aOR: adjusted odd ratio
APRI: Aspartate aminotransferase to platelet ratio index
ART: Antiretroviral therapy
AST: Aspartate aminotransferase
AUROC: Areas under the receiver operating characteristic curves
BMI: Body mass index
CAP: Controlled attenuation parameter
F: Fibrosis
FIB-4: Fibrosis-4 score
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
LSM: Liver stiffness measurement
MASLD: Metabolic dysfunction-associated steatotic liver disease
NFS: Non-alcoholic fatty liver disease (NAFLD) fibrosis score

OR: odd ratio
PLWH: People living with HIV
S: Steatosis
VCTE: Vibration-controlled transient elastography

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