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MAJOR ARTICLE

Prevalence and Risk Factors of Liver Fibrosis Among People With HIV and Metabolic Dysfunction–Associated Steatotic Liver Disease

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Background. We aimed to investigate the prevalence of liver fibrosis and identify the associated risk factors among people with HIV (PWH) and metabolic dysfunction–associated steatotic liver disease (MASLD).

Methods. Abdominal ultrasonography and transient elastography were performed to assess liver fibrosis and steatosis. Lean MASLD was defined as MASLD occurring in PWH with a body mass index (BMI) < 24 kg/m^2. A cutoff of liver stiffness measurement ≥ 7.1 kPa was set for significant liver fibrosis. The prevalence, correlation factors, and risk factors were evaluated.

Results. Among 361 PWH, 250 (69.25%) had a BMI < 24 kg/m^2, and 141 (39.06%) were diagnosed with MASLD. The 141 PWH with MASLD were classified as 2 groups based on BMI: 58 (41.13%) as lean MASLD and 83 (58.87%) as overweight MASLD. Significant fibrosis was observed in 121 of the 361 PWH, including 75 of the 141 with MASLD, 28 of the 58 with lean MASLD, and 47 of the 83 with overweight MASLD. Among PWH with MASLD, independent risk factors for significant liver fibrosis included higher alanine aminotransferase levels and the presence of type 2 diabetes. Among PWH with lean MASLD, independent risk factors for significant liver fibrosis included elevated aspartate aminotransferase levels and the administration of non-nucleoside reverse transcriptase inhibitors.

Conclusions. Significant liver fibrosis is highly prevalent among PWH and MASLD. Multiple risk factors are associated with significant liver fibrosis among PWH. These findings underscore the importance of early identification and management of liver fibrosis in PWH.

Clinical Trials Registration. NCT04215926.

Keywords. HIV; liver fibrosis; metabolic dysfunction–associated steatohepatitis; metabolic dysfunction–associated steatotic liver disease.

HIV infection remains a substantial public health problem worldwide. Despite the lack of a radical cure for HIV, antiretroviral therapy (ART) induces durable suppression of plasma viremia and prolongs the life span of patients [1]. Liver diseases account for a disproportionately large share of non–AIDS-related deaths [2]. As the most prevalent chronic liver disease globally, metabolic dysfunction–associated steatotic liver disease (MASLD) refers to metabolic hepatic damage induced by overnutrition and insulin resistance in individuals who are predisposed [3]. It was previously referred to as nonalcoholic fatty liver disease (NAFLD) until 2020 when an international panel renamed it metabolic-associated fatty liver disease [4]. However, in 2023, a multisociety Delphi consensus statement led by the American Association for the Study of Liver Diseases suggested the name and acronym MASLD to replace NAFLD [5]. The Chinese Society of Hepatology, the Asian Pacific Association for the Study of the Liver, and the American Association for the Study of Liver Diseases have each recently proposed more explicit diagnosis and treatment protocols for metabolic-associated fatty liver disease or MASLD [1, 6, 7]. People with HIV (PWH) are at higher risk of MASLD as compared with the general population, as a result of complex pathogenetic factors, including HIV itself, chronic HIV-related inflammation, several ART drugs, and insulin resistance induced by ongoing immune activation [8]. The prevalence of NAFLD among PWH has been reported to range from 35% to 40% [9]. In recent years, research on the occurrence of NAFLD in lean individuals has garnered increasing attention [10]. Notably, the body mass index (BMI) distribution among PWH differs significantly from that of

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the general population [11]. Nevertheless, the prevalence and risk factors of MASLD in PWH remain underexplored in existing literature.

Chronic liver injury induced by diverse factors may result in liver fibrosis. This phenomenon is particularly complex among PWH. First, several antiretrovirals may be associated with liver injury [12]. Second, HIV may have a direct toxic effect on the liver [13]. Additionally, chronic HIV-related immune activation and inflammation lead to the production of inflammatory cytokines and may contribute to liver fibrosis [14]. Finally, another important factor is the combination of liver diseases (viral hepatitis, alcoholic liver disease, MASLD, etc). MASLD is frequently asymptomatic until patients develop hepatic decompensation, which leads to significant morbidity and mortality [2]. Patients with significant liver fibrosis, a precursor to cirrhosis, face an increased risk of decompensation and hepatocellular carcinoma [1, 3]. Early identification of significant liver fibrosis and metabolic dysfunction–associated steatohepatitis (MASH) with fibrosis among PWH is of paramount importance. Liver biopsy has long been regarded as the gold standard for fibrosis staging; however, this invasive method is not widely used [15]. Transient elastography has been validated as a noninvasive method to assess liver fibrosis by liver stiffness measurement (LSM) [15] and steatosis by controlled attenuation parameter [16]. More recently, the FibroScan–aspartate aminotransferase (FAST) score has been introduced to identify patients with MASH with significant liver fibrosis (F2–F4) [17]. The FAST score has been validated in global clinical trials of MASH-targeted therapies [18].

Currently, there is a striking paucity of data on liver fibrosis among PWH in China, particularly among lean individuals. Building on the preceding analysis, our objectives were to (1) evaluate the prevalence of significant fibrosis, (2) assess the prevalence of MASH with fibrosis, (3) identify independent risk factors associated with significant fibrosis, and (4) determine independent risk factors for MASLD among lean PWH.

METHODS

Study Design

We performed a cross-sectional study in the outpatient clinic of the infection and immunity department at the Shanghai Public Health Clinical Center of Fudan University. Participants included consecutive patients aged 18 to 70 years with confirmed HIV infection. Exclusion criteria were as follows: excessive alcohol consumption (>210 g/wk in men and >140 g/wk in women); coinfection with hepatitis B virus or hepatitis C virus; drug-induced fatty liver (eg, use of amiodarone and tamoxifen); severe cardiac, pulmonary, or other systemic diseases; autoimmune diseases; decompensated liver disease, hepatocellular carcinoma, or a history of liver transplantation; and pregnant or lactating women. All participants provided informed consent.

Ethical Considerations

Written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki. The ethics committee of the Shanghai Public Health Clinical Center approved the study protocol, including any relevant details.

Clinical and Biological Parameters

Routine blood examinations were performed with an automated blood cell analyzer (XN-1000; Sysmex). The biochemical parameters were measured by a biochemistry analyzer (Accelerator a3600; Abbott). In addition, the following were detected: hepatitis-related indicators, HIV antibodies, HIV RNA, fasting glucose, lipid profiles, fasting insulin, hemoglobin A_{1c}, and CD4+ and CD8+ lymphocyte counts. Demographic information, medical history, duration of HIV, and ART regimens were extracted from the patients' medical records. The aspartate aminotransferase to platelet ratio index, fibrosis-4 index, and FAST score were also calculated [17, 18].

Transient Elastography (FibroScan) and Fibrosis Biomarkers

Controlled attenuation parameter and LSM were obtained via transient elastography (FibroScan; Echosens). Hepatic steatosis was diagnosed as either controlled attenuation parameter ≥ 248 dB/m or the presence of a fatty liver as determined by abdominal ultrasound [16]. A cutoff of LSM ≥ 7.1 kPa was set for significant liver fibrosis (F2–F4) [15]. FAST > 0.35 was used to diagnose MASH with fibrosis [17, 18].

Diagnosis of MASLD

A diagnosis of MASLD was based on the presence of hepatic steatosis, at least 1 component of metabolic syndrome (MetS), and the exclusion of significant alcohol consumption, as well as any other specific causes of fatty liver diseases [1, 6]. MetS components [6] were as follows:

- BMI ≥ 24.0 kg/m^2, waist circumference ≥ 90 cm (male) and ≥ 85 cm (female), or excessive body fat content and percentage
- Blood pressure ≥ 130/85 mmHg or undergoing antihypertensive medication therapy
- Fasting plasma glucose ≥ 6.1 mmol/L, 2-hour postprandial plasma glucose ≥ 7.8 mmol/L, hemoglobin A_{1c} ≥ 5.7%, history of type 2 diabetes, or homeostasis model assessment of insulin resistance ≥ 2.5
- Plasma triglycerides ≥ 1.70 mmol/L or undergoing lipid-lowering medication therapy
- Plasma high-density lipoprotein cholesterol ≤ 1.0 mmol/L (male) and 1.3 mmol/L (female) or undergoing lipid-lowering medication therapy

Lean MASLD was defined as MASLD occurring in patients with a BMI < 24 kg/m^2.

Outcome Measures

The primary study outcome was the prevalence of significant liver fibrosis. Secondary outcomes were the prevalence of MASH with fibrosis, risk factors associated with significant fibrosis, and risk factors of MASLD among lean PWH.

Statistical Methods

Quantitative variables following a normal distribution are expressed as mean (SD); those not following a normal distribution are expressed as median (IQR). Categorical variables are expressed as number (percentage). Differences between the groups were evaluated by *t* tests for normally distributed continuous variables, Mann-Whitney *U* tests for nonnormally distributed continuous variables, and χ^2 tests for categorical variables.

All statistical analyses were conducted in SPSS version 23.0 (IBM) and Prism version 8.0 (GraphPad Software). OriginPro 2025 (Learning edition) was used for generation of the correlation heat map and construction of the forest plot.

RESULTS

Demographic and Clinical Characteristics

In this study, 400 PWH were initially eligible. However, 3 cases were excluded due to hepatitis B virus or hepatitis C virus coinfection, 5 cases due to excessive alcohol consumption, and 31 cases due to unsuccessful transient elastography examination or unreliable measurements (Figure 1). Finally, a cohort of 361 individuals with HIV was enrolled, of whom 141 (39.05%) were diagnosed with MASLD. Among the patients with MASLD, 75 (53.19%) exhibited significant liver fibrosis. The clinical characteristics of those with MASLD stratified by fibrosis status are presented in Table 1.

Among the 361 PWH, 250 (69.25%) had a BMI < 24 kg/m^2 (classified as lean). Among the 250 lean PWH, 58 (23.20%) were diagnosed with MASLD (ie, lean MASLD), while 192 (76.80%) were classified as non-MASLD (ie, lean non-MASLD; Supplementary Table 1).

Prevalence of Hepatic Fibrosis in PWH Stratified by BMI

Among the 361 PWH, 121 had LSM values ≥ 7.1 kPa, resulting in a prevalence of 33.52% (Figure 2*A*), while 47 had FAST scores > 0.35, corresponding to a prevalence of 13.02% (Figure 2*B*). Among the 141 patients with MASLD, 75 (53.20%) had LSM ≥ 7.1 kPa and 47 (33.30%) had FAST > 0.35. In the lean subgroup with MASLD (n = 58), 28 (48.28%) had LSM ≥ 7.1 kPa and 17 (29.31%) had FAST > 0.35. In the overweight subgroup with MASLD (n = 83), 47 (56.63%) had LSM ≥ 7.1 kPa and 30 (36.14%) had FAST > 0.35.

Clinical Predictors of Significant Fibrosis in PWH Stratified by BMI

Among the 141 patients with MASLD, significant fibrosis showed significant correlation with waist circumference, alanine aminotransaminase, aspartate aminotransferase, alanine aminotransferase/aspartate aminotransferase ratio, fasting insulin, fasting blood glucose, homeostasis model assessment of insulin resistance, MetS, systolic blood pressure, and controlled attenuation parameter. The detailed data are presented in Figure 3*A*. As shown in Figure 3*B*, among lean PWH, the prevalence of MASLD showed significant correlation with age, liver function (alanine aminotransaminase, aspartate aminotransferase, γ-glutamyl transpeptidase, total cholesterol, triglycerides, and high-density lipoprotein), metabolic conditions (BMI, MetS, number of MetS components, uric acid, fasting insulin, fasting plasma glucose, hemoglobin A_{1c}, homeostasis model assessment of insulin resistance), as well as HIV-related factors (time since HIV diagnosis, duration of treatment, past exposure to zidovudine).

Figure 4 shows the results of the multivariable analysis of cofactors associated with significant fibrosis among patients with MASLD. As shown in Figure 4*A*, among the 141 patients with MASLD, type 2 diabetes (odds ratio [OR], 5.45; 95% CI, 1.33–22.36; *P* = .018) and elevated alanine aminotransaminase levels (OR, 1.03; 95% CI, 1.02–1.05; *P* < .001) were independently associated with significant fibrosis. As shown in Figure 4*B*, in the overweight subgroup consisting of 83 PWH with MASLD, type 2 diabetes (OR, 6.52; 95% CI, 1.14–37.14; *P* = .035) and elevated alanine aminotransaminase levels (OR, 1.04; 95% CI, 1.02–1.07; *P* = .001) were similarly found to be independently associated with significant fibrosis. As shown in Figure 4*C*, in the subgroup of 58 lean PWH with MASLD, elevated aspartate aminotransferase levels (OR, 1.22; 95% CI, 1.07–1.38; *P* = .002) and the administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs; OR, 7.53; 95% CI, 1.49–37.98; *P* = .017) were also independently associated with significant fibrosis.

Clinical Predictors of MASLD in Lean PWH

As shown in Supplementary Figure 1, the following were independently associated with MASLD in lean PWH: past exposure to zidovudine (OR, 1.63; 95% CI, 1.08–6.40; *P* = .033), the number of MetS components (OR, 1.79; 95% CI, 1.21–2.64; *P* = .004), elevated alanine aminotransaminase levels (OR, 1.03; 95% CI, 1.01–1.05; *P* < .001), higher BMI (OR, 1.56; 95% CI, 1.14–2.13; *P* = .006), and older age (OR, 1.04; 95% CI, 1.00–1.08; *P* = .037).

DISCUSSION

Our study found that significant liver fibrosis, as detected by LSM, affected 33.52% of PWH in China, while MASH with significant fibrosis, as identified by FAST score, affected 13.02% of PWH. Additionally, we identified cofactors associated with

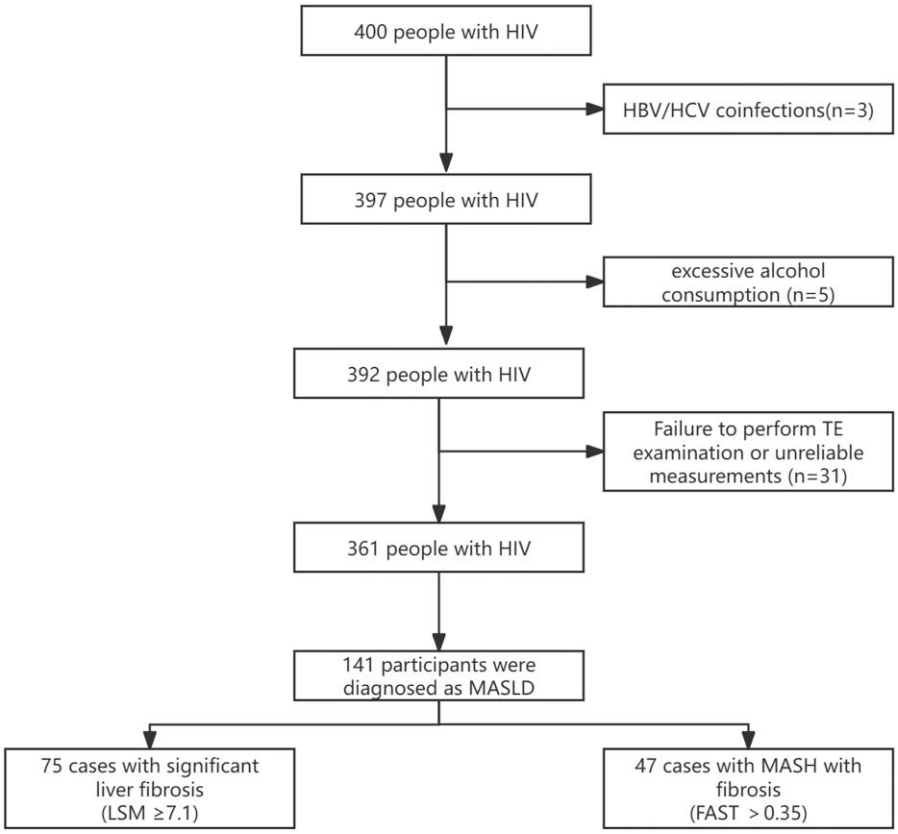


Figure 1. Flowchart displays the selection of study participants. FAST, FibroScan–aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; LSM, liver stiffness measurement; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; TE, transient elastography.

significant fibrosis and assessed the prevalence and associated cofactors of MASLD among lean PWH. This study enhances the understanding of liver fibrosis in PWH, providing valuable insights into its prevalence and associated risk factors.

Hepatic fibrosis is a pathologic physiologic response during the liver's injury repair process, characterized by an imbalance between the synthesis and degradation of extracellular matrix. Under the continuous influence of various pathogenic factors, this imbalance may lead to the further progression of fibrosis to liver cirrhosis and its severe complications. Steatosis is a key mechanism in the occurrence of liver fibrosis among individuals with MASLD. However, the pathogenesis appears to be more complex in PWH. First, HIV directly exerts its effects on hepatocytes and nonparenchymal cells, thereby inducing liver injury [13]. Second, HIV can indirectly cause liver problems mainly through ongoing inflammation and immune reactions. These processes trigger the release of numerous proinflammatory substances, ultimately leading to liver damage and fibrosis [19]. Finally, several ARTs may be associated with liver injury [20].

We found that the proportion of significant liver fibrosis among PWH and MASLD was as high as 53.19%, while the prevalence of significant liver fibrosis due to MASH among PWH reached 13.02%. The data suggest that the occurrence of liver fibrosis in PWH is not only related to steatosis but also involves other complex factors. In contrast, within the general population, the prevalence of significant liver fibrosis among patients with MASLD is approximately 33% [21], while that of MASH with significant liver fibrosis is estimated at 1% to 3% [22]. This discovery highlights a relatively high incidence of liver fibrosis among PWH, particularly that caused by MASH, underscoring the intricate nature of the etiologic factors contributing to liver fibrosis in this population. Michel et al [23] incorporated 282 PWH and discovered that 6.7% had LSM $\geq$ 8.2% and 12.3% had a FAST $>$ 0.35. Sebastiani et al [24] reported that 8% of the 1472 PWH included had a FAST $>$ 0.35. Lemoine et al [15] reported that among 402 PWH, 140 (34.8%) were suspected of having significant fibrosis (FibroScan $\geq$ 7.1 kPa and/or FibroTest $\geq$ 0.49). Different cutoff value settings of LSM will have a significant impact on the research findings. The positive predictive value of LSM to rule

Table 1. Clinical Characteristics of Patients With Metabolic Dysfunction–Associated Steatotic Liver Disease Stratified by Fibrosis

Characteristic	Fibrosis, No. (%) or Median (IQR)		*P* Value
	Significant (n = 75)	Non-significant (n = 66)	
Male	71 (94.67)	65 (98.48)	.443
Age, y	38 (31–52)	44 (36.75–52)	.114
Body mass index, kg/m^2	25.39 (23.36–27.44)	24.47 (22.66–26.32)	.088
Overweight, ≥24 kg/m^2	47 (62.67)	36 (54.55)	.328
Visceral adiposity index	3.26 (2.21–5.27)	3.08 (1.81–5.13)	.464
Mean ± SD			
Waist circumference, cm	94.13 ± 8.7	90.39 ± 7.87	.009
Waist-hip ratio	0.93 ± 0.05	0.91 ± 0.05	.0507
ALT, IU/L	64 (38–97)	29 (22.75–43.25)	<.001
AST, IU/L	36 (28-48)	23 (19–30.25)	<.0001
ALT/AST ratio	1.68 (1.29–2)	1.27 (1.06–1.73)	.0004
GGT, IU/L	69 (38–114)	39.50 (27–54.50)	<.0001
Total cholesterol, mmol/L, mean ± SD	5.14 ± 0.99	4.94 ± 0.92	.2026
Triglyceride, mmol/L	2.35 (1.70–3.61)	2.33 (1.38–3.54)	.548
HDL, mmol/L	1.01 (0.88–1.15)	1.02 (0.89–1.11)	.914
Urid acid, μmol/L	380.10 (333–483.80)	372.30 (328.70–428.50)	.407
Fasting insulin, μU/mL	16.05 (11.45–25.03)	12.30 (7.85–17.80)	.011
FPG, mmol/L	5.68 (5.31–6.02)	5.40 (5.02–5.73)	.002
Hemoglobin A_{1c}, %	5.40 (5.10–5.83)	5.20 (5–5.70)	.042
Type 2 diabetes	14 (18.67)	3 (4.55)	.010
HOMA-IR	4.26 (2.74–6.70)	3.01 (1.90–4.32)	.003
Metabolic syndrome	59 (78.67)	37 (56.06)	.004
Components	3 (3–4)	3 (2–4)	.0015
SBP, mm Hg	129 (120–135)	122 (115–132)	.0080
Hypertension	14 (18.67)	8 (12.12)	.285
CAP, dB/m	277 (261–291)	263.50 (252–274)	.0002
Time since HIV diagnosis, mo	52.5 (20.75–89.75)	64 (35–93)	.2171
Duration of treatment, mo	45 (17–85.50)	61 (28–81)	.3302
Undetectable HIV RNA	65 (86.67)	59 (89.39)	.620
Current antiretroviral regimen			
NNRTI	54 (72)	45 (68.18)	.621
NRTI	65 (86.67)	62 (93.94)	.150
Protease inhibitor	4 (5.33)	9 (13.64)	.089
Integrase inhibitor	7 (9.33)	8 (12.12)	.592
Zidovudine	17 (22.67)	24 (36.36)	.075
Tenofovir disoproxil	40 (53.33)	33 (50)	.693
CD4+ count, cells/μL	218 (144–312)	256.5 (166–312.80)	.3373
Fibrosis-4 index	0.89 (0.47–1.23)	0.73 (0.54–1.17)	.4091
APRI	0.43 (0.27–0.64)	0.26 (0.19–0.35)	<.0001

Abbreviations: ALT, alanine aminotransaminase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; SBP, systolic blood pressure.

in significant fibrosis greatly depends on the disease prevalence in the population. Future research should focus on conducting prospective studies to determine the optimal cutoff value for significant liver fibrosis, as validated by pathology, among Chinese PWH.

Type 2 diabetes, a key driver of disease progression in patients with NAFLD, has been reported to be associated with fibrosis due to MASH [25]. Higher alanine aminotransaminase levels were identified as having the highest predictive value for MASH as defined by the FAST score [23]. Similarly, our study demonstrated that among all patients with MASLD, there was a significant association between type 2 diabetes and significant liver fibrosis, with an OR of 5.45. In the overweight subgroup of patients with MASLD, this association exhibited an even higher OR of 6.52, indicating a stronger correlation. However, multivariable regression analysis showed that among lean PWH with MASLD, type 2 diabetes was not a significant risk factor for liver fibrosis, whereas NNRTIs were independently associated with fibrosis. Upon stratification based on BMI, the independent risk factors for significant fibrosis differed, and the potential reasons may include the following aspects. First, this divergence may stem from metabolic

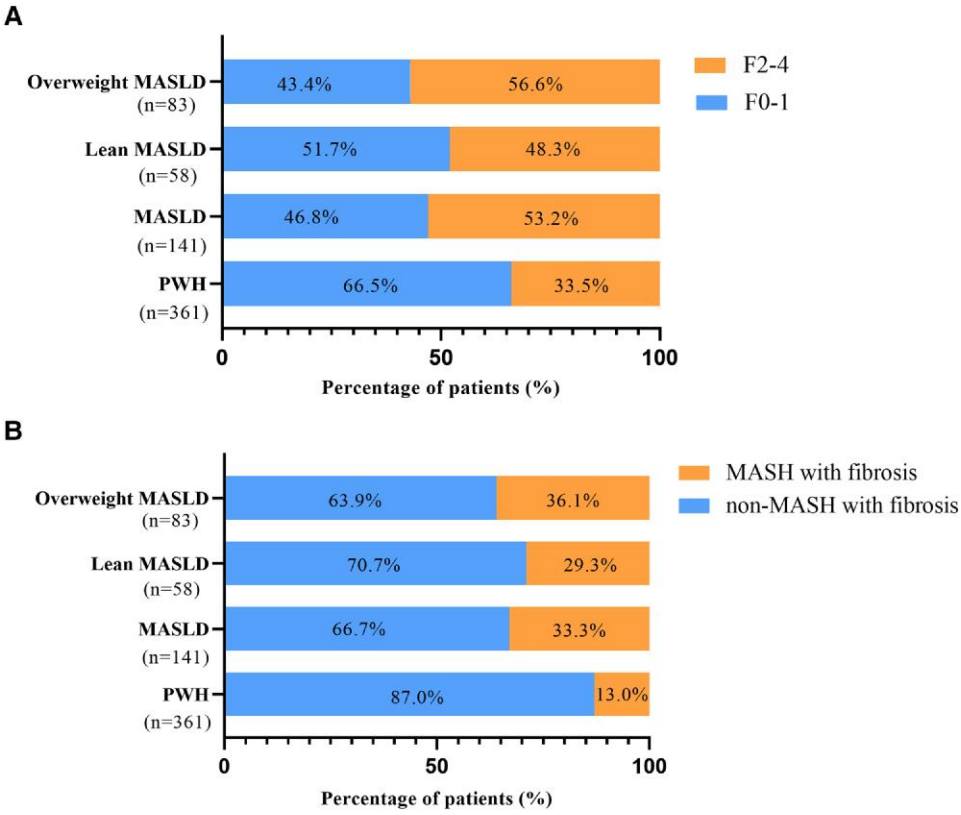
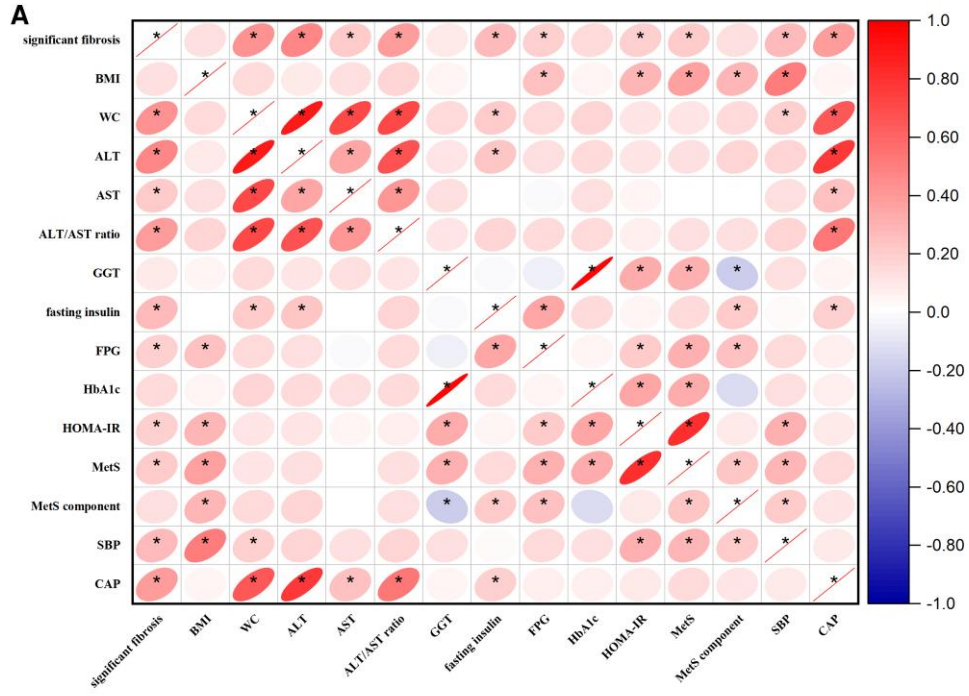


Figure 2. *A*, Distribution of liver fibrosis stages in prevalence of significant fibrosis (liver stiffness measurement ≥ 7.1 kPa). *B*, Prevalence of MASH with significant fibrosis (FibroScan–aspartate aminotransferase > 0.35). Overweight, BMI ≥ 24 kg/m^2; lean, BMI, < 24 kg/m^2. BMI, body mass index; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; PWH, people with HIV.

heterogeneity. PWH who are overweight frequently present with multiple MetS components [9]. Nakamuta et al [26] demonstrated significant differences in fatty acid metabolism between obese and nonobese patients with MASLD. Moreover, establishing appropriate cutoff values of LSM for diagnosing significant liver fibrosis in different BMI populations requires further exploration. Lemoine et al [15] established 7.1 kPa as the cutoff value for diagnosing significant liver fibrosis among PWH, a criterion later adopted in the investigation by Sebastiani et al [24]. On this basis, we set the diagnostic threshold for significant liver fibrosis at 7.1 kPa. Currently, there is a lack of large-sample studies that can accurately determine the threshold value of LSM for diagnosing significant liver fibrosis in populations with different BMIs.

Almomani et al found that patients with lean NAFLD were at higher risk of future severe liver disease than those who were overweight [27]. Sebastiani et al recently reported that PWH who have NAFLD and/or significant liver fibrosis, even if they are of normal weight and young, exhibit an elevated risk for cardiovascular disease [28]. Given the adverse outcomes of lean MASLD and the distribution characteristics of BMI in PWH, we also conducted a multivariable regression analysis of MASLD in the lean PWH subgroup. Cofactors associated with MASLD mainly included age (OR, 1.04), alanine aminotransaminase (OR, 1.03), MetS components (OR, 1.79), BMI (OR, 1.56), as well as past exposure to zidovudine (OR, 1.63). This finding underscores the complexity of MASLD among PWH and confirms the role of ARTs in its occurrence. Notably, among lean PWH, BMI remains an independent risk factor for MASLD, suggesting that for PWH with normal BMI, weight control is still necessary. Previous studies [10, 29] have shown that the occurrence of lean MASLD is closely related to factors such as abdominal obesity and sarcopenia. In our experience, indicators representing abdominal obesity, such as waist circumference and visceral adiposity index, are not associated with the occurrence of lean MASLD, suggesting that MASLD in lean PWH may have a limited relationship with abdominal obesity. Reports showed high sarcopenia rates among PWH [2]. Unfortunately, our study lacks body composition data. More research is needed to address this gap.

Although the primary objective of this study was not to elucidate the role of ART in the pathogenesis of MASLD and liver fibrosis among PWH, based on the findings of this study and the data in the literature, ART may serve as a factor contributing to MASLD and liver fibrosis, warranting further discussion. Contemporary ART regimens based on the use of integrase



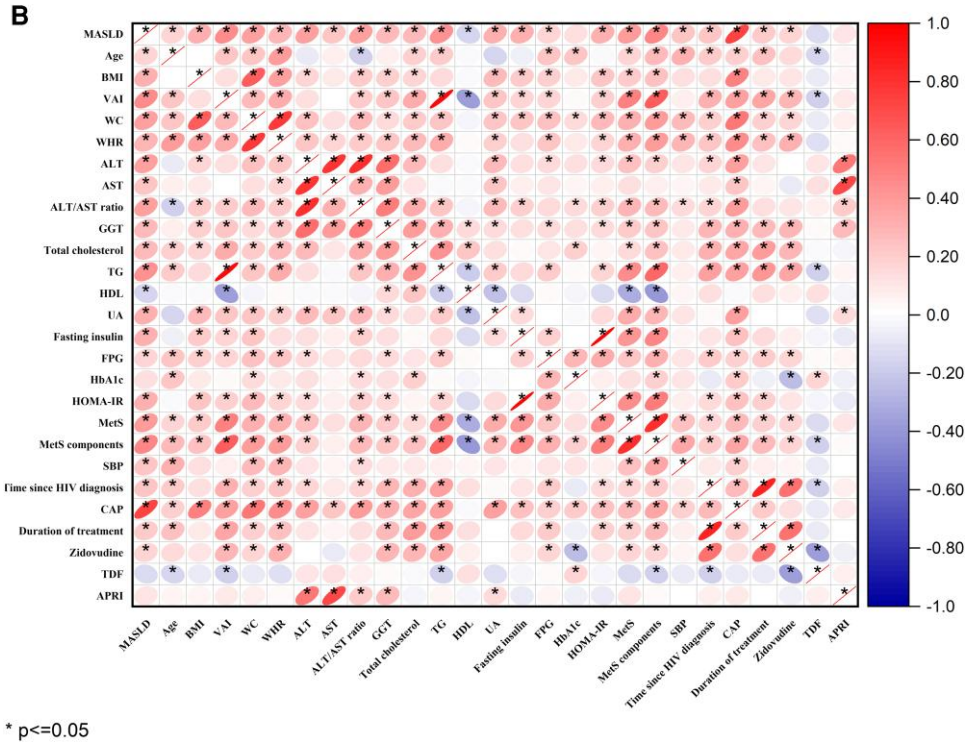


Figure 3. Correlation matrix between indicators and (*A*) significant liver fibrosis in the total MASLD group and (*B*) prevalence of MASLD among lean PWH (BMI < 24 kg/m^2). The circle color represents the Spearman coefficient value: red, positive correlation; blue, negative correlation. ALT, alanine aminotransaminase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MASLD, metabolic dysfunction–associated steatotic liver disease; MetS, metabolic syndrome; SBP, systolic blood pressure; TDF, tenofovir disoproxil; TG, triglyceride; UA, urid acid; VAI, visceral adiposity index; WC, waist circumference; WHR, waist-hip ratio.

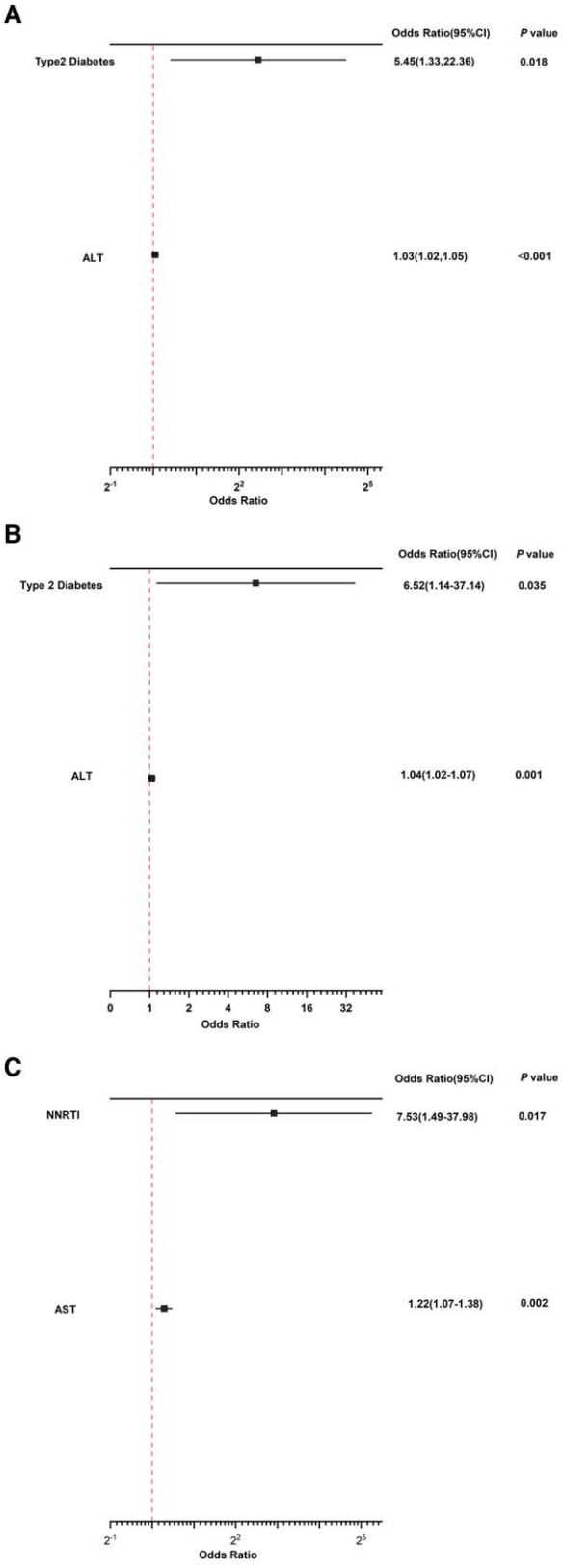


Figure 4. Forest plots of multivariable regression analyses for significant liver fibrosis among patients with MASLD: *A*, total group; *B*, overweight group; *C*, lean group. ALT, alanine aminotransaminase; AST, aspartate aminotransferase; MASLD, metabolic dysfunction–associated steatotic liver disease; NNRTI, non-nucleoside reverse transcriptase inhibitor.

strand transfer inhibitors (INSTIs) have been associated with greater weight gain. The most extensively studied mechanisms included the inhibition of the melanocortin 4 receptor, alterations in thermogenesis and mitochondrial function, as well as modifications in adipose tissue functionality [30]. Interestingly, the impact of INSTIs and weight gain on metabolic outcomes remains uncertain. Bischoff et al found that weight gain and development or progression of hepatic steatosis are linked and that INSTIs, along with tenofovir alafenamide, might significantly affect this progression [31]. Debroy et al found that PWH switching to INSTIs experienced an increase in subcutaneous and visceral adipose tissue area, as assessed by computed tomography scan [32]. However, some studies reported favorable effects of INSTIs on lipid parameters. A multicenter trial showed that PWH switching to INSTI-based regimens had significant reductions in proatherogenic lipids over 48 weeks [33]. Milic et al showed that switching to INSTI in PWH without metabolic alterations is not associated with higher diabetes risk as compared with non-INSTI regimens [34]. Conversely, switching to INSTIs may counterbalance the negative effects of weight gain on insulin resistance incidence, confirming INSTI regimens as metabolically satisfactory options.

Regarding NNRTIs, the first-generation drug efavirenz (EFV) increases the risk of lipid metabolism disorders. EFV is known to damage mitochondria, leading to liver cell death and reactive oxygen species production; it also activates pregnane X receptor, resulting in changes in the expression of genes related to liver lipogenesis [35]. At present, most international guidelines no longer recommend EFV as a first-line treatment drug. Our study found that a high proportion of participants had NNRTI-based regimens, with the majority using EFV. The primary reason for this limitation was the use of retrospective cross-sectional data in the study. Notably, we found that in patients with lean MASLD, the use of NNRTI was an independent predictor of significant liver fibrosis. It is unclear if this finding relates to hepatic steatosis or mitochondrial function. Further studies in diverse BMI populations are needed to explore how NNRTIs cause significant fibrosis.

Regarding their impact on metabolism, nucleoside reverse transcriptase inhibitors are another class of drugs receiving widespread attention. Zidovudine, one of the earliest drugs employed for HIV treatment, may trigger lipoatrophy, osteonecrosis, and lipid accumulation due to elevated oxidative stress and endoplasmic reticulum stress [36]. Our research indicates that in lean PWH, past exposure to zidovudine is an independent predictor of MASLD. Future research should focus on stratifying ART regimens and conducting in-depth analyses of the metabolic and hepatotoxic effects of individual drugs, which will provide a more comprehensive understanding of the complex relationship among ART, metabolism, and liver disease in PWH.

This study has several limitations that should be acknowledged. First, the sample sizes were relatively small, necessitating long-term follow-up and prospective data for further validation. Second, the cohort primarily consisted of men with low BMI, potentially limiting the generalizability of the findings to other populations. Last, the study enrolled patients from a single center, which might introduce selection bias and affect the external validity of the results.

In conclusion, PWH demonstrate a high prevalence of significant liver fibrosis and MASH with fibrosis. Importantly, multiple risk factors are associated with significant liver fibrosis in PWH. Furthermore, in lean PWH, the occurrence of MASLD is closely related to BMI, suggesting that individuals with normal weight should also practice adequate weight management to minimize the risk of MASLD.

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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Consent for publication. All authors read and approved the manuscript.

Data availability. We declare that materials described in this article, including all relevant raw data, will be freely available to any scientist wishing to use them for noncommercial purposes, without breaching participant confidentiality.

Patient consent statement. Written informed consents were obtained from all patients. This study was performed in accordance with the Declaration of Helsinki. The ethics committee of the Shanghai Public Health Clinical Center approved the study protocol, including any relevant details (No. 2019-S040-02). This study was registered with the US National Library of Medicine's ClinicalTrials.gov platform under the identifier NCT04215926 on 29 December 2019.

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