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REVIEW

Uncovering the NAFLD burden in people living with HIV from high- and middle-income nations: a meta-analysis with a data gap from Subsaharan Africa

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) has become a significant concern among people living with HIV (PLHIV), albeit its burden remains unclear. The primary objective of this systematic review (SR) and meta-analysis (MA) was to estimate the prevalence of NAFLD and significant fibrosis in PLHIV. The secondary objective was to determine the risk factors for NAFLD among PLHIV.

Methods: We searched MEDLINE and Scopus from inception to 30 December 2022 for peer-reviewed studies that included PLHIV and reported the prevalence of NAFLD. MA of proportions was used to estimate the pooled prevalence of NAFLD and significant fibrosis. MA of pre-calculated effect estimates examined risk factors for NAFLD in PLHIV.

Results: We included 24 articles published between 2009 and 2022, encompassing 6326 PLHIV. The pooled prevalence of NAFLD was 38% (95% CI: 31–45%) with high heterogeneity (I^2 = 96.3%). The pooled prevalence of significant fibrosis was 13% (95% CI: 8–18%) with high heterogeneity (I^2 = 92.09%). Subgroup analyses showed a NAFLD prevalence of 40% (95% CI: 24–57%) in the United States, 33% (95% CI: 31–36) in Asia, 42% (95% CI: 24–61%) in Europe and 33% (95% CI: 29–37) in South America. When stratifying by income level, NAFLD was 39% (95% CI: 31–48) prevalent in PLHIV from high-income economies and 34% in both upper-middle-income (95% CI: 31–37%) and lower-middle-income economies (95% CI: 28–41%). Higher body mass index (BMI) (OR = 1.32, 95% CI: 1.13–1.55; I^2 = 89.9%), increasing triglycerides (OR = 1.48, 95% CI: 1.22–2.79; I^2 = 27.2%) and dyslipidaemia (OR = 1.89, 95% CI: 1.32–2.71; I^2 = 15.5%) were all associated with higher risk-adjusted odds of NAFLD in PLHIV.

Discussion: The burden of NAFLD and significant fibrosis in PLHIV is significant. Therefore, targeted efforts to screen and diagnose NAFLD in this population are needed. Health services for PLHIV could include ways to target NAFLD risk factors, screen for liver disease and implement interventions to treat those with significant fibrosis or more advanced stages of liver disease. Taking no action to address NAFLD in PLHIV should not be an option.

Conclusions: This SR and MA found a 38% NAFLD and 13% significant fibrosis prevalence in PLHIV. Increasing triglyceride levels, higher BMI values and dyslipidaemia were associated with higher risk-adjusted odds of NAFLD among PLHIV.

Keywords: NAFLD; MAFLD; liver fibrosis; HIV; people living with HIV; HIV epidemiology

Additional information may be found under the Supporting Information tab of this article.

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1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become a major global public health issue affecting more than 30% of adults worldwide [1, 2]. It is the leading aetiology of chronic liver disease globally and will likely become the main cause of end-stage liver disease in the near future [3, 4]. Additionally, NAFLD progresses to non-alcoholic steatohepatitis (NASH) in about 20% of cases [5]. NASH is a major cause of progression to cirrhosis and hepatocellular carcinoma [6–8], with the latter being the second foremost driver of years of life lost among all cancers [9]. Furthermore, it has been determined

that NAFLD patients have a high burden of comorbidities and often experience reduced quality of life [10]. The high overall burden of the disease is associated with increasing socioeconomic costs [11].

Despite the high burden of NAFLD in the general population, the prevalence and predictors of NAFLD in specific patient populations, such as people living with HIV (PLHIV), remain unclear. Yet, evidence suggests that chronic liver disease is the second leading cause of non-HIV-related mortality in PLHIV and that NAFLD disproportionately affects this population [12]. Recently, an expert panel review examined current knowledge gaps regarding the comorbidity burden in PLHIV and highlighted NAFLD/NASH as a research priority, including determining their prevalence and exploring predictors of NAFLD in this population [13]. This is central to ensuring the long-term wellbeing of PLHIV through person-centric health [14–16], as set out by the World Health Organization in the Global Sector Strategy on HIV for the period 2022–2030 [17], which proposes a continuum of care prioritizing prevention, diagnosis, treatment and chronic care as the pillars to deliver health services to PLHIV [14]. Of particular interest is the integration of HIV services with services for comorbidities that PLHIV may present.

However, to prioritize those pillars and improve the integration of HIV care with other health services, it is paramount to measure the HIV-comorbidity burden to design and implement actions more efficiently. Measuring the burden of NAFLD in PLHIV will help us understand the potential threat metabolic-associated fatty liver disease puts on this population. So far, however, efforts to quantify the NAFLD burden in PLHIV have been based on a few multicentre studies or data from particular settings. In 2017, Maurice et al. [18] synthesized the available data on NAFLD in PLHIV from the literature and estimated a pooled NAFLD prevalence of 35%. However, this prevalence estimation was based on data from five studies. Since then, the literature on the subject has expanded, which has increased the stakeholders' awareness of NAFLD in priority populations such as PLHIV.

Synthesizing the growing body of literature can generate fresh insights and quantitative estimates of the burden of NAFLD in PLHIV. In this scenario, proportion meta-analysis (MA) methods [19, 20] provide a means of getting a reliable and precise estimate of disease frequency. Therefore, serving as a convenient tool to appraise the burden of NAFLD in PLHIV. Unlike traditional MAs, used to examine the effects of interventions or study associations and thus aimed to calculate pooled estimates of effect size (i.e. risk ratio (RR), odds ratio [OR], risk difference and mean difference), an MA of proportions allows for pooling prevalence estimates under the assumption that prevalence follows a binomial distribution (number of events in a sample) [19, 20]. These methods have suffered significant improvements in recent years [20] and are now widely used to obtain disease frequency estimates using data from different settings across various disciplines [21–23].

The primary objective of this systematic review (SR) and MA was to estimate the prevalence of NAFLD and significant fibrosis in PLHIV. The secondary objective was to determine the risk factors for NAFLD among PLHIV.

2 | METHODS

The present SR was conducted following the recommendations from the Cochrane Handbook of Systematic Reviews of interventions [24] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [25].

Although not registered in PROSPERO, a protocol prepared before the review kickoff was used as the guide to plan and carry out the SR.

2.1 | Inclusion and exclusion criteria

We included all peer-reviewed studies that included persons being positive for HIV and reported the proportion (prevalence) of patients with NAFLD. In addition, studies examining risk factors for NAFLD in PLHIV were also considered eligible for inclusion.

In cases of overlapping populations (i.e. studies conducted in the same hospital or during overlapping periods), the publication with the largest sample size or more appropriate for the objective of this SR was selected for inclusion.

We excluded studies that included patients with either evidence of hepatitis B or C co-infection or significant alcohol use. If studies did not specify these as exclusion criteria in the methodology section, we reviewed the results to know if patients with these characteristics were included. We also excluded case reports, reviews and comments/editorials/viewpoints.

2.2 | Outcomes

The prevalence (proportion) of NAFLD in PLHIV was the primary outcome of interest.

NAFLD was defined as the presence of significant steatosis demonstrated by a right upper quadrant ultrasound, computer tomographic (CT) scan, magnetic resonance imaging (MRI) techniques, vibration-controlled transient elastography (VCTE)-based controlled attenuation parameter (CAP) measurements or liver biopsy. If the studies reported the assessment of liver steatosis by any of the methods mentioned above, then the study was considered to inform the primary outcome.

Secondary outcomes included the prevalence (proportion) of significant fibrosis in PLHIV and risk factors of NAFLD in the study population.

Data about significant fibrosis were collected as reported in the included studies, and the cut-off values for it were defined in each study. Although current EASL guidelines [26] recommend a cut-off value of 8 kPa to define significant fibrosis on VCTE, the synthesis reported in SRs and MAs depends on the data reported in primary sources. Therefore, we had to base our quantitative synthesis on the data and definitions of NAFLD from the studies included in this SR. If available, we defined significant liver fibrosis as a VCTE cut-off value equal to or higher than 8 kPa as in the current EASL practice recommendation [26].

Reported measures relating to patient characteristics and comorbidities were extracted from the included articles to assess risk factors for NAFLD in PLHIV. The extracted risk

factors of NAFLD had to be the result of a multivariate logistic regression analysis reporting adjusted ORs and corresponding 95% confidence intervals (CIs). We did not prespecify particular risk factors; instead, we extracted those available in the included studies.

2.3 | Search methods

Following established recommendations [27–29], a computerized database search strategy of the available literature was performed. The literature search was performed in MEDLINE and Scopus from inception to 30th December 2022. The search strategy was developed with keywords and synonyms related to the population of interest (PLHIV) and the exposure/outcome of interest (NAFLD). We screened the references from the included studies and previous reviews on the same topic [18]. Complete electronic search strategies for each database are available in Supplementary File 1.

2.4 | Study selection

The results from the search strategies were imported into Rayyan [30]. Then, two authors (RM and ES) independently reviewed the titles and abstracts identified in the database searches and made an initial selection based on inclusion and exclusion criteria. Papers that appeared relevant for inclusion were retrieved as full texts and subsequently reviewed by two investigators (RMN and ES) who independently applied inclusion and exclusion criteria to full texts for final eligibility. As previously mentioned, we selected the publication with the largest sample size or more appropriate for the SR objectives in cases where papers were at risk of reporting results from overlapping populations.

2.5 | Data collection process

We created a data extraction form in which we collected the following information from the included studies: author, year of publication, study design, period of data collection, region where the study took place, hospital where the study was conducted, the total number of patients, number of patients with the outcomes of interest, patient demographic and clinical characteristics, comorbidity information and relevant labvalues. In addition, we collected the data on the outcomes of interest and, whenever available, the results from the multivariable logistic regression models examining NAFLD risk factors in PLHIV.

We also collected the inclusion and exclusion criteria reported in each study and synthesized this information in Table S1 available in Supplementary File 1.

2.6 | Risk of bias

Each study's quality and internal validity were assessed using the JBI's Critical Appraisal Tools (https://jbi.global/critical-appraisal-tools) [31, 32]. These tools assess the methodological quality of each study to determine the level to which research takes into account the potential for bias in its design and planning [31–33]. The procedures by which the JBI's tools assess the methodological quality and the risk of bias are described elsewhere [31–34].

The critical appraisal and quality assessment results and a full explanation of how it was carried out are available in Supplementary File 1 (Figures S1–S3).

We did not assess for publication bias because available methods (funnel plot) were developed for comparative MA and are unreliable for MA of proportions [35].

2.7 | Data synthesis and MA

The information and data used for this SR were extracted as reported in each study and summarized descriptively.

We undertook two different MAs: 1. To estimate the prevalence of NAFLD and significant fibrosis among PLHIV; we performed an MA of proportions with the "metaprop" command in Stata [20]. 2. To estimate the risk factors for NAFLD in PLHIV, we used reported effect estimates whenever available (adjusted ORs resulting from a multivariable regression analysis exploring the risk factors for NAFLD in each study) and combined these effect estimates in a random effect MA with the "metan" function in Stata [36].

2.7.1 | Prevalence of NAFLD among PLHIV: MA of proportions

The prevalence (proportion) of NAFLD and significant fibrosis were obtained by dividing the number of patients with the outcomes of interest (***n***) by the total number of patients (***N***) from each study. Then, these proportions were pooled in MAs of proportions using the "metaprop" command [20]. This command provides statistical methods for binomial data: ***n/N***, where ***n*** denotes the number of individuals with the characteristic/outcome of interest, and ***N*** refers to the total number of individuals. In our analysis, ***n*** corresponded to the number of patients with the outcome of interest (NAFLD, significant fibrosis) and ***N*** was the total number of PLHIV included in each study.

Study-specific proportions with 95% CIs were estimated. To this end, we enabled the variance-stabilizing transformation of the proportions suggested by Freeman and Tukey [37] and estimated study-specific CIs by computing score confidence intervals [20, 38, 39]. Then, based on the transformed values and their variance, a random-effects (Dersimonian and Laird) MA was used to compute the pooled estimates (pooled prevalence). For these pooled estimates, their respective confidence intervals were determined using the Wald method [20].

Subgroup analyses were performed for the pooled NAFLD prevalence on available study-level characteristics. Hence, we performed subgroup analyses stratified by region and country income level, NAFLD diagnostic method and study design. We also performed a subgroup analysis of the NAFLD prevalence in the studies that reported data on significant fibrosis. Income level was defined according to the <*World Bank Country and Lending Groups*> definitions, which classify countries by income levels as high-income, upper-middle-income, lower-middle-income and low-income economies.

2.7.2 | MA of risk factors

MAs of risk factors of NAFLD were performed using the "metan" command in Stata [20]. We reviewed the studies that assessed and reported the risk factors (reported in adjusted

ORs with 95% CIs) for NAFLD among PLHIV resulting from a multivariable regression analysis (Table 3). The adjusted ORs and its 95% CI (resulting from a multivariable regression analysis) were used as the effect statistics for the MAs. When at least three (≥3) studies captured the same risk factor and reported an adjusted OR for the same risk-factor variable, we combined these effect estimates in a random-effects (DerSimonian and Laird) MA to account for inevitable variations in settings, populations and adjusted covariates. We combined and meta-analysed adjusted ORs for similar variables intending to assess the strength of association between the reported risk factor and NAFLD in PLHIV. The results were reported in forest plots of the estimated effects of the included studies with a 95% CI. The Supplementary File (3.2 Commands for the meta-analysis of risk factors) provides a detailed explanation of pooling adjusted ORs.

In both MAs (proportion and precalculated effect estimates), heterogeneity was evaluated using the I^2 test. I^2 values corresponded to low (I^2<25%), medium (I^2 = 25–75%) and high (I^2>75%) heterogeneity.

All statistical analyses were performed in Stata statistical software version 14. The Stata commands employed to perform the MAs are available in the Supplementary File.

3 | RESULTS

We identified 1785 articles from the electronic database searches (time-period: inception–30 December 2022), of which 61 were considered eligible for inclusion in our SR. After applying all inclusion and exclusion criteria to the full texts, 22 peer-reviewed articles were included. In addition, we reviewed a seminal prior SR and MA by Maurice et al. [18] and included two additional references that fulfilled the review's inclusion/exclusion criteria. Twenty-four articles (n = 24) were finally included [40–63]. Table S2 in the Supplementary File lists a number of key articles that were excluded from the present SR (reasons for exclusion are provided in the Table).

Of the 24 articles, eight (n = 8) reported a multivariate regression analysis of the factors associated with NAFLD in PLHIV and were included in the MA of risk factors. Figure 1 shows the PRISMA diagram for the selection of the studies.

3.1 | Characteristics of included studies

The studies included in this SR were published between 2009 and 2022. As shown in Table 1, of the 24 included studies, six recruited participants in Asia and eight in Europe. Seven recruited patients in the United States. The two Latin-American studies were from South America (Brazil). One was a multicentre study recruiting patients from Europe and North America (Sebastiani 2022) [56].

More than half of the papers included (n = 18, 75%) presented a cross-sectional study design (Table 1). Four and two studies were case–control and cohort studies, respectively. Eight of the studies used data from cohorts registered in clinicaltrials.gov (Table 1).

The studies were comparable in terms of the populations included. All of them reported very similar inclusion and exclusion criteria, including PLHIV and excluding patients with known hepatitis B or C infection and significant/harmful alcohol use. Table S1, included in the Supplementary File, shows each study's objectives, inclusion, exclusion criteria, and relevant methodological characteristics.

3.2 | Characteristics of participants

An overview of patients' characteristics is shown in Table 2. We extracted and summarized data presented in each study from PLHIV.

The studies included in this SR recruited 6326 PLHIV with a PLHIV sample size ranging from 14 to 1749 (median, 153; interquartile range, 84–345). Of these, 1435 (22.6%%) were females, and, as shown in Table 2, they tended to be young as all the reported means and medians of age were below 55 years. The reported values of the cluster of differentiation-4 (CD4) lymphocyte count, BMI, lipid panel, hepatic enzymes, and the proportion of patients with diabetes and arterial hypertension are reported in Table 2.

3.3 | NAFLD assessment

The methods to assess and the definitions with cut-off values to diagnose NAFLD are detailed in Table 1.

VCTE was used in 10 (n = 10) studies. Hepatic steatosis was diagnosed with CAP values ≥248 dB/m in five of the studies and ≥238 dB/m in two. Michel (2022) and Arka De (2022) reported that hepatic steatosis was diagnosed using CAP values of 275 dB/m or higher and 251 dB/m or higher, respectively.

Five studies (n = 5) reported the use of MRI techniques (Table 1). In two of these studies, a liver fat content ≥5% in the MRI-derived proton density fat fraction (MRI-PDFF≥5%) was diagnostic of steatosis. In the other three (n = 3), steatosis was diagnosed by a liver fat content ≥5% in proton magnetic resonance spectroscopy (H-MRS≥5%).

Four studies diagnosed steatosis through liver ultrasound. Two studies used biopsy, two CT scan and another (a multicentre study) reported the use of either biopsy, CT scan, or ultrasound to define steatosis (Table 1).

Nine of the 24 studies (including 3280 patients) reported data on significant fibrosis. In these studies (n = 9), significant fibrosis was diagnosed using VCTE to estimate liver stiffness (cut-off values defining significant fibrosis are provided in Table 1). Among PLHIV, significant fibrosis was diagnosed in 459 (13.9%) of the 3280 participants from the nine studies reporting significant fibrosis data.

3.4 | Risk of bias

Overall, the methodological quality of the included studies was deemed appropriate, and the research workflow appeared consistent throughout each report, meaning that the research aims were relevant and adequately defined, and the methodology used was pertinent to the objectives proposed. We did not find major red flags or significant methodological flaws in the studies included in the SR (Figures S1–S3).

Table 1. Characteristics of included studies in the systematic review and meta-analysis

Author/year	Country	City	Did the data originate from a well-known-relevant cohort?	Study design/analysis	Recruitment period	NAFLD evaluation method	NAFLD definition	PLHIV (*N*)	NAFLD (*N*)	SF definition	SF (*N*)
Crum-Cianflone 2009	USA	San Diego, CA	No	Cross-sectional	2006–2007	LUS	"Steatosis described as diffusion in hepatic echogenicity"	216	67	NR	NR
Sterling 2013	USA	Richmond, VA	No	Cross-sectional	2007–2011	Biopsy	Biopsy >5%	14	9	NR	NR
Nishijima 2014	Japan	Tokyo	No	Cross-sectional	2004–2013	LUS	NR	435	135	NR	NR
G Lui 2016	China	Hong Kong	No	Case–control	NR	MRI	H-MRS ≥5%	80	23	LS≥7.0 kPa	11
Kardashian 2017	USA	Multicenter-1	Yes: WIHS (NCT00000797)	Case–control	1994–2015	MRI	H-MRS ≥5%	122	35	NR	NR
Lombardi 2017	UK	London	No	Cross-sectional	2014	LUS	NR	156	47	NR	NR
Price 2017	USA	Multicenter-2	Yes: MACS (NCT00046280)	Cross-sectional	2010–2013	CT	Liver/spleen attenuation ratio<1.0 on non-contrast CT	329	44	NR	NR
Aepfelbacher 2019	USA	Bethesda, MA	Yes: Clinical Outcomes of People Who Acquired HIV in Early Life (NCT01656564)	Case–control	2016–2018	VCTE	CAP> = 248 dB/m	46	15	LS≥7.1 kPa	3
Lallukka-Brück 2019	Finland	Helsinki	No	Retrospective cohort	2001–2019 (16 years follow-up)	MRI	H-MRS> = 5%	41	14	NR	NR
Vujanović 2019	Serbia	Novi Sad	No	Cross-sectional	2016–2018	LUS	Increased liver echogenicity when compared to the parenchyma of the right kidney	88	37	NR	NR
Ajmera 2020	USA	San Diego, CA	No	Cross-sectional	2016–2018	MRI	MRI-PDFF ≥5%	70	56	NR	NR

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Table 1. (Continued)

Author/year	Country	City	Did the data originate from a well-known-relevant cohort?	Study design/analysis	Recruitment period	NAFLD evaluation method	NAFLD definition	PLHIV (*N*)	NAFLD (*N*)	SF definition	SF (*N*)
Ferri Pezzini 2020	Brazil	Porto Alegre	No	Cross-sectional	2016–2017	VCTE	CAP ≥238 dB/m	98	31	LS≥7.1 kPa	7
Kaplan 2020	USA	Boston, MA	No	Cross-sectional	2010–2017	Biopsy or CT-scan or ultrasound	Biopsy >5% OR validated radiographic criteria for CT/LUS	232	97	NR	NR
Kirkegaard 2020	Denmark	Copenhagen	Yes: COCOMO (NCT02382822)	Case–control	2015–2016	CT	CT-liver attenuation <48 HUs	453	39	NR	NR
Rasoulinejad 2020	Iran	Tehran	No	Cross-sectional	2018–2019	VCTE	NR	100	35	NR	NR
Bischoff 2021	Germany	Bonn	No	Cohort study	2013–2018 (24 months follow-up)	VCTE	CAP ≥238 dB/m	319	109	NR	NR
Fonseca de Almeida 2021	Brazil	Rio de Janeiro	Yes: PROSPEC-HIV (NCT02542020)	Cross-sectional	2015–2019	VCTE	CAP ≥248 dB/m	451	152	LS≥7.1 kPa	72
Jongraksak 2021	Thailand	Bangkok	No	Cross-sectional	2017–2018	VCTE	CAP ≥248 dB/m	150	48	LS≥7.1 kPa	9
Liu Danping 2021	China	Shangai	No	Cross-sectional	2019–2020	VCTE	CAP ≥248 dB/m	361	136	LS≥10 kPa	30
Arka De 2022	India	Chandigarh	No	Cross-sectional	NR	VCTE	CAP ≥251 dB/m	100	34	LS≥7.0 kPa	47
Busca 2022	Spain	Madrid	No	Cross-sectional	2017–2018	Biopsy	Biopsy >5%	69	62	NR	NR
Lemoine 2022	Belgium, France and Germany	Paris, Bruxelles, Hambourg, Berlin, Düsseldorf and Hannover	Yes: ECHAM (NCT02093754)	Cross-sectional	2014–2015	MRI	MRI-PDFF> = 5%	402	257	NR	NR
Michel 2022	Germany	Mainz	Yes: FLASH (NCT04066608)	Cross-sectional	2018–2021	VCTE	CAP ≥275 dB/m	245	85	LS≥8.2 kPa	16
Sebastiani 2022	Italy and Canada	Modena, Italy/Montreal, Canada/Palermo and Italy	Yes: LIVEHIV (CTN326 Canadian), MHMC (NR) and LHIVPA (NR)	Cross-sectional	NR	VCTE	CAP ≥248 dB/m	1749	684	LS≥7.1 kPa	264

Abbreviations: CAP, controlled attenuation parameter; LS, liver stiffness; LUS, liver ultrasound; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NR, not reported; PLHIV, people living with HIV; SF, significant fibrosis; VCTE, vibration-controlled transient elastography.

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Table 2. Characteristics of participants (PLHIV' data from the studies included in the systematic review and meta-analysis)

Author/year	PLHIV (*N*)	Age $	Females (*N*) %	CD4 count $	BMI $	Tcho $	TG $	AST $	ALT $	T2DM $	AHT %
Crum-Cianflone 2009	216	39.6 (11.1)	12 (5.6)	535.2 (247.5)	26 (4.1)	185.9 (41.9)	172.1 (158.3)	NR	NR	11 (5.1)	49 (22.7)
Sterling 2013	14	45 (10)	4 (29)	614 (357)	29.9 (7.4)	172 (38)	235 (180)	76 (46)	94 (58)	3 (21)	NR
Nishijima 2014	435	40 (35–50)	29 (7)	349 (203–512)	22.1 (20.2–24.9)	175 (150–205)	162 (104–233)	25 (19–37)	26 (17–47)	22 (5)	86 (20)
G Lui 2016	80	54 (11)	6 (8)	503 (248)	23.6 (3.9)	185.6 (38.6)	159.29 (123.8–274.3)	26 (22–32)	86 (69–107)	39 (48.8)	33 (41.3)
Kardashian 2017	122	NR	58 (47.5)	NR	NR	NR	NR	NR	NR	NR	NR
Lombardi 2017	156	47.5 (8.5)	13 (8)	683 (4–1900)	NR	NR	NR	41 (22–299)	56 (29–372)	17 (11)	28 (18.2)
Price 2017	329	52 (47–57)	0 (0)	598 (438–776)	26 (23–29)	NR	130 (91–205)	24 (20–31)	25 (18–35)	39 (12)	152 (48)
Aepfelbacher 2019	46	27 (3.1)	28 (61)	605 (400)	27 (7)	165 (41)	109 (73)	25 (12)	23 (16)	NR	NR
Lallukka-Brück 2019	41	41.9 (1.3)	7 (17)	NR	23.1 (0.5)	NR	168.1 (141.59–292.04)	32 (28–44)	30 (23–50)	0 (0)	NR
Vujanović 2019	88	39.94 (9.91)	0 (0)	NR	24.76 (3.58)	NR	290.27 (364.6)	25.1 (12.3)	30.5 (22.8)	NR	NR
Ajmera 2020	70	48.6 (10.2)	7 (10)	791 (688)	26.9 (4.6)	193.5	116.5 (48)	24.5 (20)	30.5 (19)	11 (15.7)	NR
Ferri Pezzini 2020	98	49 (11)	45 (46)	657.5 (118–208)	25.45 (23.6–28.2)	188.6 (34)	156 (118–218)	21 (17–26)	22 (16–30)	35 (35.7)	27 (27.6)
Kaplan 2020	232	54 (9)	55 (23.7)	NR	NR	NR	NR	NR	NR	44 (18.9)	98 (42.2)
Kirkegaard 2020	453	52.4 (46.8–61)	65 (14.3)	690 (520–884)	24.7 (22.4–27.5)	189.2 (162.1–220)	159.3 (115–247.8)	NR	26 (20–34)	33 (7.3)	NR
Rasoulinejad 2020	100	39.9 (9.5)	51 (51)	610	NR	NR	NR	NR	NR	1 (1)	NR
Bischoff 2021	319	47.5 (11.5)	72 (22.5)	NR	24.9 (4.5)	197.6 (43.1)	187.6 (148.3)	24.5 (14.2)	35.4 (18.1)	19 (6)	65 (20.4)

(*Continued*)

Table 2. (Continued)

Author/year	PLHIV (N)	Age $	Females (N) %	CD4 count $	BMI $	Tcho $	TG $	AST $	ALT $	T2DM $	AHT %
Fonseca de Almeida 2021	451	45 (36–53)	272 (60.3)	665 (421–881)	25 (23–29)	185 (158–219)	124 (84–171)	25 (20–33)	29 (23–43)	46 (10.2)	100 (22.2)
Jongraksak 2021	150	45.83 (9.54)	67 (44.7)	562 (217.7)	22.77 (3.57)	202.23 (42.78)	149.23 (98.92)	31.36 (10.27)	37.97 (34.14)	10 (6.7)	NR
Liu danping 2021	361	38 (31–48)	17 (4.7)	459 (327–633.5)	22.64 (21.04–24.73)	180.57 (155.82–205.7)	143.36 (95.58–238.05)	NR	29 (20–51)	29 (8.03)	36 (9.9)
Arka De 2022	100	36.8 (10.4)	35 (35)	NR	22.9 (4.3)	NR	187.2 (60.7)	NR	NR	4 (4)	8 (8)
Busca 2022	69	50 (44–54)	13 (9)	740 (593–930)	27 (24–30)	182 (159–203)	147 (97–213)	36 (28–43)	50 (41–77)	63 (44)	57 (39)
Lemoine 2022	402	55 (50–61)	62 (15)	603 (510–832)	27 (23.6–28.7)	NR	141.6 (97.3–221.2)	29 (23–37)	34 (24–50)	NR	NR
Michel 2022	245	52 (42–58)	71 (29)	727 (516–901)	25 (22.4–28.5)	202 (177–229)	133 (90–191)	26 (23–31)	23 (18–32)	27 (11)	75 (30.6)
Sebastiani 2022	1749	50.2 (10.4)	446 (25.5)	NR	NR	NR	NR	NR	NR	595 (34)	NR

Abbreviations: AHT, arterial hypertension; Tcho, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.
– $: Data presented in means/medians (SD/IQR); %: data presented in frequencies and percentages.

3.5 | Quantitative synthesis (MA)

3.5.1 | *MA of NAFLD and significant fibrosis prevalence*

We found that the pooled prevalence of NAFLD was 38% (95% CI: 31–45%) with high heterogeneity (I^2 = 96.3%) (Figure 2). Regarding significant fibrosis, we found a pooled prevalence of 13% (95% CI: 8–18%) with high heterogeneity (I^2 = 92.09%) (Figure 3).

3.5.2 | *Subgroup analyses (MA of prevalence)*

Subgroup analyses by region and country income level. The subgroup analysis by region (Figure 4) showed that the pooled prevalence in Asia (data from six studies) and Europe (data from eight studies) was 33% (95% CI: 31–36%; I^2 = 0.0%) and 42% (95% CI: 24–61%; I^2 = 98.4%), respectively. The pooled prevalence in the United States (data from seven studies) was 40% (95% CI: 24–57; I^2 = 96.07%). Two studies reported data from South America with a pooled prevalence of 44% (95% CI: 29–59%; I^2 = not estimable).

The subgroup analysis according to the World Bank's country income groups is shown in Figure 5. The pooled prevalence of NAFLD in high-income countries was estimated in 39% (95% CI: 31–48%) with high heterogeneity (I^2 = 97.2%). In upper-middle-income and lower-middle-income countries, NAFLD was detected in 34% of PLHIV (Figure 5).

Subgroup analyses by NAFLD diagnostic method. We stratified the data by the NAFLD diagnostic method. The results from this analysis are shown in Figure 6. Ten studies reported the use of VCTE to detect/diagnose NAFLD. The pooled prevalence from these studies was 36% (95% CI: 34–38) with low heterogeneity (I^2 = 15.1%). The pooled prevalence from the studies (n = 4) using liver ultrasound was 32% (95% CI: 28–36) with medium heterogeneity (I^2 = 31.6%) (Figure 6). The pooled NAFLD prevalence from studies using MRI techniques (n = 5), CT-scan (n = 2) and biopsy (n = 2) was 47% (I^2 = 95.9%), 10% (I^2 = not estimable) and 87% (I^2 = not estimable), respectively (Figure 6).

Five studies reported a CAP threshold for detecting NAFLD of ≥248 dB/m. The pooled prevalence from these studies was 36% (95% CI: 33–39%) with medium heterogeneity (I^2 = 43.3%). The pooled prevalence from the two studies with a CAP threshold for NAFLD diagnosis of ≥238 dB/m was 34% (95% CI: 29–38%) (heterogeneity not estimable). One study used a CAP threshold of ≥251 dB/m, finding a NAFLD prevalence of 34% (95% CI: 25–44). Another one that defined NAFLD as a CAP≥275 dB/m found a 34% (95% CI: 25–44) NAFLD prevalence (heterogeneity not estimable).

Other subgroup analyses. We performed a subgroup analysis by the type of study design (Figure S4 available in the Supplementary File). The pooled prevalence from cross-sectional studies (n = 18 studies) was 41% (95% CI: 35–49) with high heterogeneity (I^2 = 95.5%). In case–control (n = 4) and cohort studies (n = 2), NAFLD was detected in 23% (95% CI: 10–40%; I^2 = 93.9%) and 34% (95% CI: 29–39%; I^2 = not estimable) of PLHIV, respectively.

A second subgroup analysis of the studies that reported patients with significant fibrosis was performed. This analysis included nine studies and found a pooled NAFLD prevalence

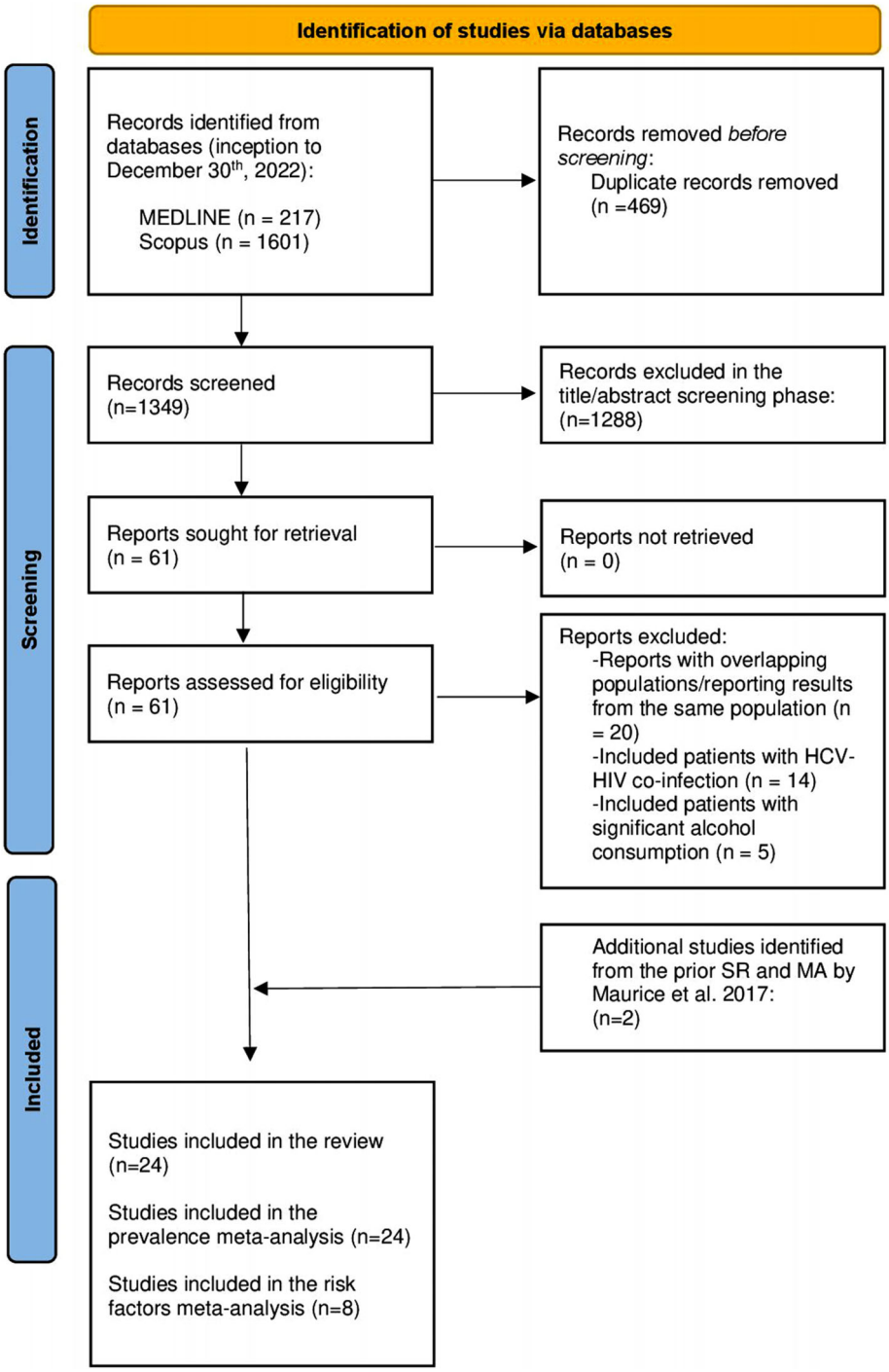

Figure 1. PRISMA diagram.

of 35% (95% CI: 33–38%) with medium heterogeneity (I^2 = 32.8%).

3.5.3 | *MA of risk factors*

We found eight (n = 8) studies reporting a multivariable regression analysis of the factors associated with NAFLD. These studies used logistic regression analysis, with NAFLD as the outcome variable and several independent variables (factors associated/predictors), to determine the risk factors for NAFLD among PLHIV. The ORs resulting from the analyses reported in each study are reported in Table 3.

Figure 7 contains the MAs of adjusted ORs showing that higher BMI (four studies: OR = 1.32, 95% CI: 1.13–1.55; I^2 = 89.9%), increasing triglycerides (four studies: OR = 1.48, 95% CI: 1.22–2.79; I^2 = 27.2%) and dyslipidaemia (four stud-

Table 3. Logistic regression models from each study reporting the factors associated with NAFLD

	Variable	Reported aOR (95% CI)
Crum-Cianflone 2009	Waist circumference, cm (per 10-cm increment)	2.1 (1.6–2.8)
	Triglycerides, mg/dl (per 100 mg/dl increment)	1.2 (1.0–1.5)
	Race: African American	0.4 (0.2–1.1)
	Race: Hispanics	1.4 (0.6–3.3)
	Race: others (Filipino, Pacific Islander, other Asian or mixed)	1.7 (0.4–6.8)
	HDL, mg/dl	0.7 (0.5–1.0)
	Dyslipidaemia (on lipid-lowering drugs)	1.3 (0.7–2.7)
	Years of HIV	1.1 (0.8–1.6)
	Staduvine history	0.9 (0.3–2.2)
Nishijima 2014	Male sex	1.95 (0.64–5.96)
	Age (per 1-year difference)	1.005 (0.98–1.02)
	BMI, kg/m^2 (per 1 kg/m^2 increment)	1.19 (1.11–1.29)
	Dyslipidaemia (on lipid-lowering drugs)	2.04 (1.18–3.53)
	ALT/AST ratio (per 1-unit increment)	3.55 (2.12–5.94)
	Hypertension	0.95 (0.51–1.80)
	CD4 count (per cell)	1.001 (0.999–1.0002)
Lui 2016[a]	Triglycerides, mmol/L	1.79 (1.12–2.86)
Jongraksak 2020	Age, years (per 1-year difference)	1.076 (1.017–1.907)
	BMI, kg/m^2 (per 1 kg/m^2 increment)	1.596 (1.336–1.907)
	Dyslipidaemia (triglycerides>150 mg/dl)	3.72 (1.508–9.187)
Kaplan 2020	BMI, kg/m^2 (per 1 kg/m^2 increment)	1.10 (1.04–1.17)
	Hypertension	1.36 (0.71–2.60)
	Obstructive sleep apnea	1.89 (0.59–6.02)
	Smoking	0.74 (0.30–1.78)
	Dyslipidaemia (LDL>160 mg/dl)	1.67 (0.89–3.14)
	Diabetes	1.13 (0.51–2.52)
	CD4 count <200	4.67 (1.82–12.02)
	Diagnosis of HIV in the last 10 years	1.00 (0.96–1.03)
	Cardiovascular disease	3.08 (1.37–6.94)
Kirkegaard 2020	Age (per decade)	1.09 (0.64–1.86)
	Sex (female)	0.08 (0.01–0.78)
	Non-Caucasian	1.08 (0.36–3.23)
	BMI, kg/m^2 (per 1 kg/m^2 difference/increment)	1.58 (1.35–1.85)
	Cholesterol (per 1 mM)	0.96 (0.58–1.57)
	Triglycerides (per 1 mM)	1.07 (0.80–1.44)
	Diabetes	3.43 (0.58–20.16)
	Plasma glucose (per 1 mM)	0.82 (0.58–1.16)
	ALT (per unit increment)	1.76 (1.31–2.37)
Liu Danping 2021	Age (per 1-year difference)	1.01 (0.983–1.037)
	ALT, U/L (per unit increment)	1.015 (1.002–1.028)
	GGT, U/L (per unit increment)	1.000 (0.991–1.009)
	Waist/hip ratio (per 0.01)	0.944 (0.869–1.027)
	Waist/height ratio (per 0.01)	1.359 (1.219–1.515)
	Uric acid, μmol/L (per unit increment)	1.005 (1.002–1.009)
	CD4 count, cells/μl (per cell increment)	1.000 (0.999–1.001)
	Total cholesterol, mmol/L (per unit increment)	1.44 (1.05–1.97)
	LSM, kPa (per unit increment)	1.082 (0.9.0–1.259)

(*Continued*)

Table 3. (Continued)

	Variable	Reported aOR (95% CI)
Lemoine 2022	ALT, U/L (per 5 units increment)	1.23 (1.16–1.31)
	CD4 cell count (per log2 unit)	4.04 (1.92–8.51)
	Ferritin, mmol/L (per unit increment)	1.05 (1.03–1.07)
	Triglycerides, mmol/L (per unit increment)	1.48 (1.18–1.84)
	Leptin ≥3.2 μg/L	2.12 (1.14–3.93)
	PNPLA3 rs738409 not C/C	1.84 (1.22–2.79)

Abbreviation: aOR, adjusted odds ratio.
[a]The study by G. Lui 2016 reported the OR only for triglycerides; however, it was an adjusted odds ratio.

ies: OR = 1.89, 95% CI: 1.32–2.71; I^2 = 15.5%) were all associated with significantly higher risk-adjusted odds of NAFLD in PLHIV.

Three studies reported the association between alanine transferase (ALT) levels and NAFLD in PLHIV. After pooling the data from these studies, we found that increasing ALT levels were significantly associated with NAFLD risk in PLHIV (Figure 8). Finally, in a random effect model pooling data from four studies, age was not associated with NAFLD (four studies: OR = 1.01; 95% CI: 0.99–1.02; I^2 = 0%) (Figure S5 in the Supplementary File).

4 | DISCUSSION

This SR and MA, pooling data from 24 studies published worldwide (n = 6326 patients), found a 38% NAFLD and 13% significant fibrosis prevalence in PLHIV. Further, we combined NAFLD risk factor estimates (ORs) and found that increasing

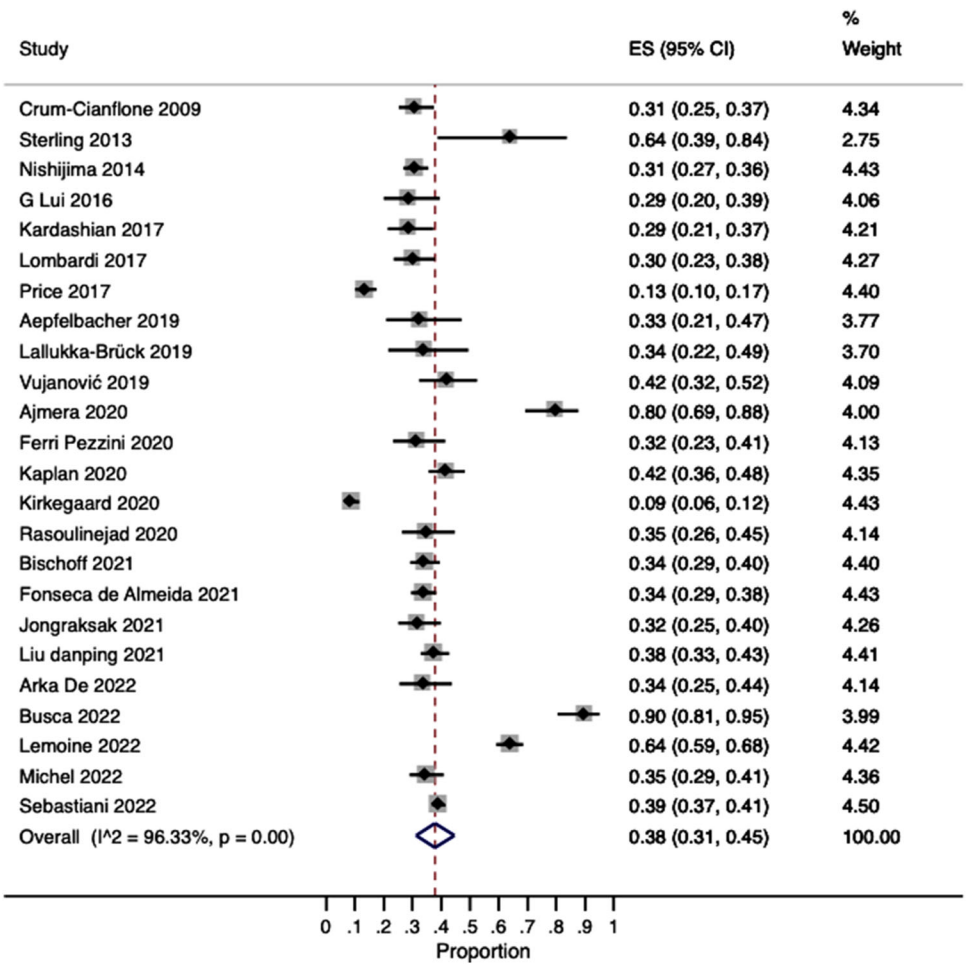

Figure 2. Pooled estimates of NAFLD prevalence.

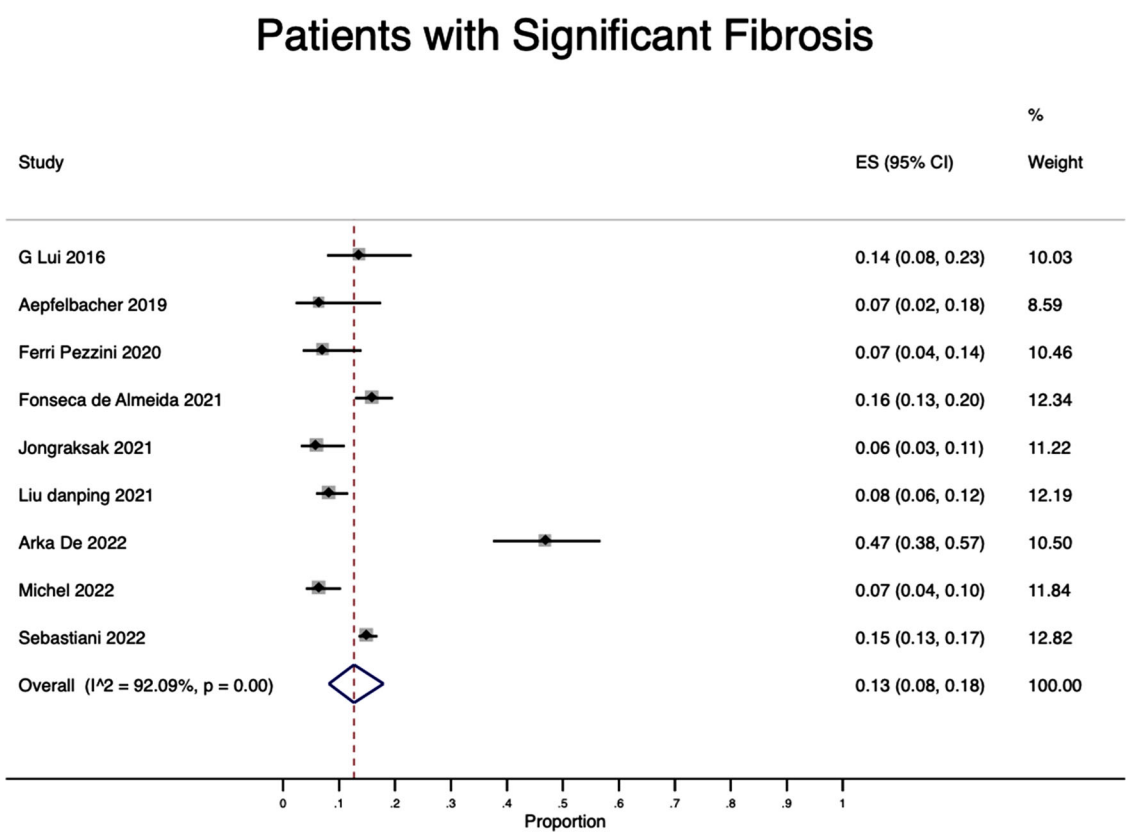

Figure 3. Pooled estimates of significant fibrosis prevalence.

triglyceride levels, higher BMI values and dyslipidaemia were associated with higher risk-adjusted odds of NAFLD among PLHIV.

The NAFLD prevalence estimations did not show clinically relevant/substantial variations in the subgroup analyses by region and income level (Figures 4 and 5); however, most studies were from high-income/upper-middle-income countries, with none from low-income economies. Of concern, Africa, the world's most affected region by the HIV epidemic [64, 65], was not represented in the MA, as we could not find articles from this continent that fulfilled our inclusion criteria. There is, therefore, an urgent need to address this knowledge gap in future investigations. Furthermore, stakeholders from regions with limited data should consider uniting efforts and resources to determine the NAFLD burden in PLHIV to enhance local patient care [66].

Similar to the prevalence estimates reported herein, a 2017 MA examining NAFLD in 1256 PLHIV found a pooled NAFLD prevalence of 35% with high heterogeneity (I^2 = 85.3%) [18]. This is similar to NAFLD prevalence in individuals aged 15–49 in the general population, estimated at 34% globally [67]. Although the overall prevalence reported herein (38%) was associated with high heterogeneity (I^2 = 96.3%), we found that heterogeneity dramatically decreased for VCTE and liver ultrasound when stratifying by diagnostic methods (Figure 6), which means that the high heterogeneity was likely explained (in part) by the variations in NAFLD diagnostic techniques across studies. Notwithstanding the subgroup analyses performed, statistical heterogeneity seems to be an unavoidable issue in MA [68] as true heterogeneity is expected when combining data obtained in different regions, settings and cultures with some degree of variations in clinical practice; however, if SR's inclusion and exclusion criteria apply to the included studies and there are not evident discrepancies between them, a high statistical heterogeneity (I^2) does not necessarily mean that studies are not combinable and data are inconsistent.

The high NAFLD prevalence in PLHIV is worrying as it depicts a scenario where these individuals are at higher risk of chronic liver disease, including NASH and cirrhosis. Thus, adding an issue to be addressed by the Global Health Sector Strategy on HIV proposed by the World Health Organization [14]. PLHIV stakeholders should undertake efforts to further advance the knowledge about the NAFLD burden in this population, where it is often overlooked. Targeted screening programmes and prevention strategies focusing on PLHIV are needed, as part of comprehensive care provision [16, 69, 70]. Clinical guidelines for PLHV should include fatty liver disease prevention and care, recognizing the importance of early diagnosis and the bidirectional relationship between NAFLD and other metabolic conditions such as diabetes.

We found that dyslipidaemia, increasing triglycerides levels and higher BMI values were associated with higher risk-adjusted odds of NAFLD in PLHIV and these results do indeed match those observed in earlier studies on the

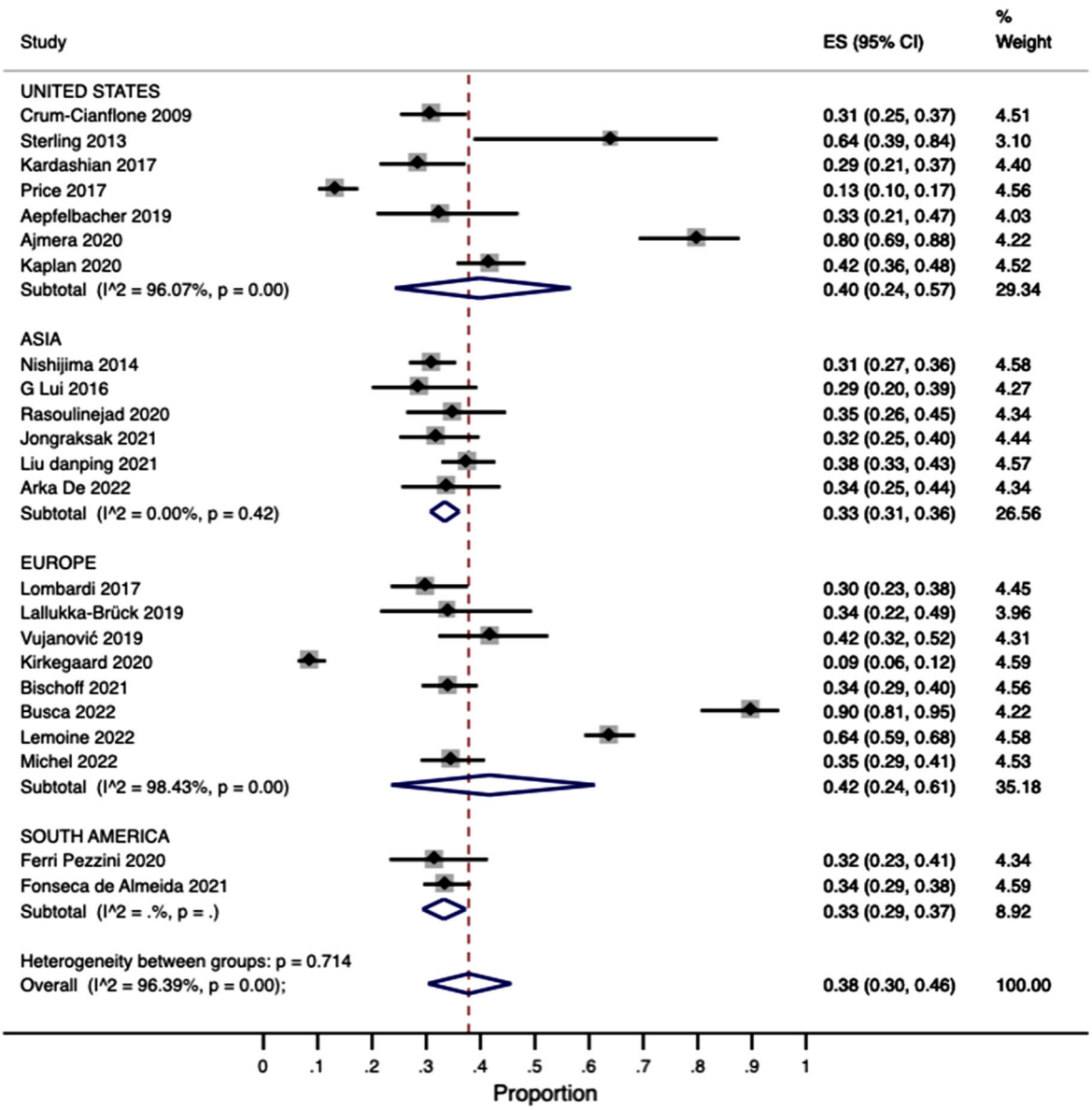

Figure 4. Subgroup analysis by region.

general population [67]. Well-established risk factors for NAFLD include waist circumference, high triglycerides, diabetes [71] and high BMI [67, 72]. Moreover, it is well-known that cardiovascular risk factors are highly prevalent in PLHIV [73]. Of particular concern is the clustering of some of these factors forming metabolic syndrome [74, 75], the single most predictive factor of NAFLD. Since BMI is the monitoring method used to track obesity (a hallmark feature of metabolic syndrome), practitioners caring for PLHIV should ensure that patients with a high BMI are supported in attaining a healthier lifestyle, as previous studies have demonstrated that NAFLD prevalence increases linearly with increasing BMI [76, 77], along with the other risks associated with it. For example, higher BMI values have been related to the risk of developing diabetes and a progressively increased risk of complications from diabetes [78].

On the other hand, in the case of dyslipidaemia and high triglyceride levels in PLHIV, its management should be based on their cardiovascular risk and adhere to current guideline recommendations, albeit bearing in mind that high untreated triglyceride levels increase the risk of NAFLD. In contrast, lipid-lowering agents (i.e. statins) have proven benefits on NAFLD incidence and the progression to hepatic fibrosis in cohorts of NAFLD-affected individuals [79].

This study also found a prevalence of significant fibrosis of 13% in PLHIV. Although the cut-off values to define this outcome were lower in the included studies than those proposed in current EASL guidelines [26], we consider this finding relevant for clinical practice as it provides a quantitative estimate of the proportion of "high-risk" individuals with established NAFLD who merit further medical interventions and closer follow-up. Previous research found that liver stiffness

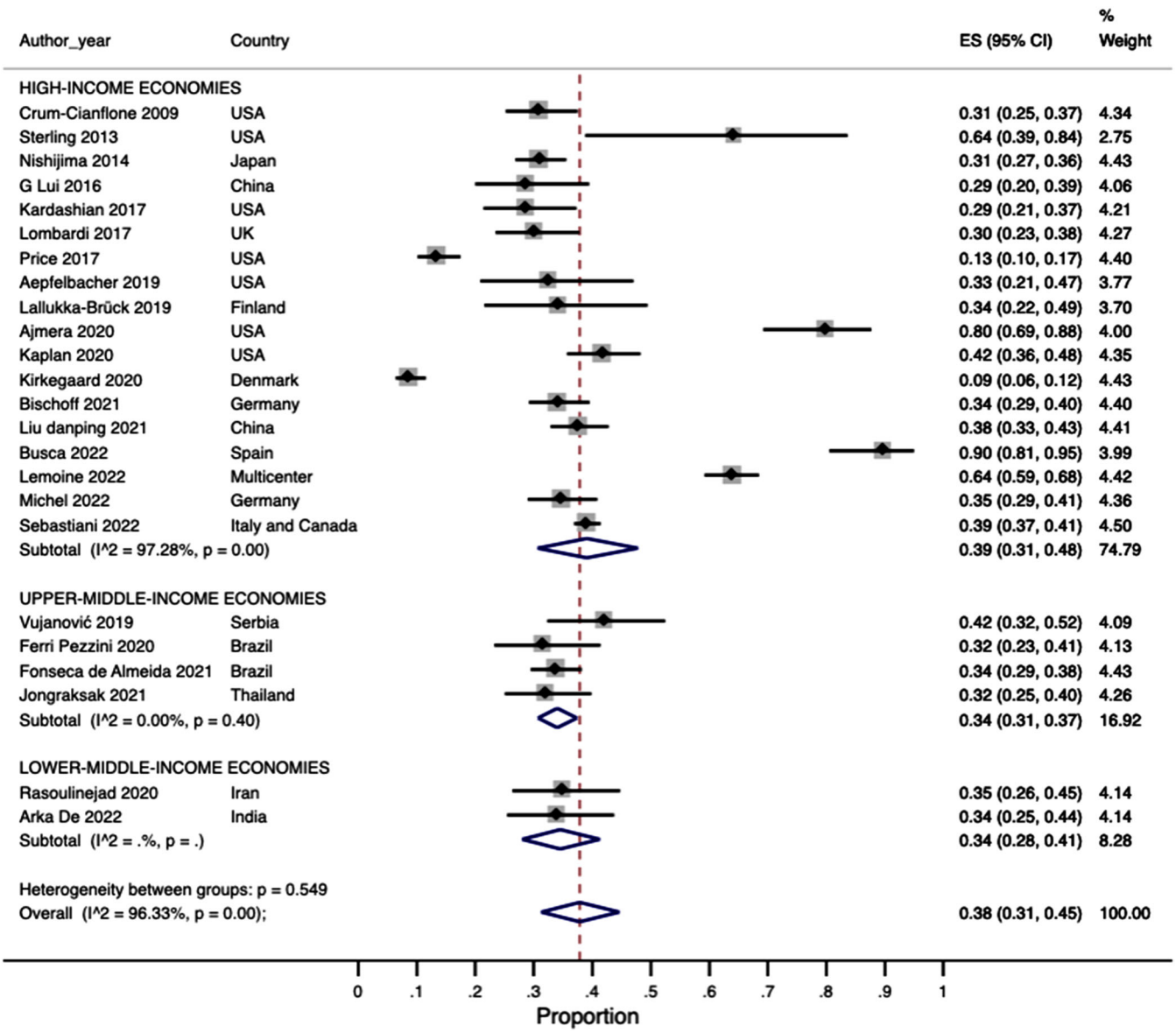

Figure 5. Subgroup analysis by country-income level.

is significantly higher in PLHIV compared to healthy controls; however, no prior studies comprehensively reported on the prevalence of significant fibrosis in PLHIV. Studies assessing the prevalence of significant liver fibrosis due to NAFLD in the general population are scarce and there is no agreement regarding the most suitable method to estimate the prevalence of fibrosis in the general population. Available data suggest that it is close to 5–6% according to studies from various settings. Using the FIB-4 score upper cut-off, the prevalence of advanced fibrosis in a population-based study in Germany was 1.1% [80]. Whereas in NAFLD patients from the general population, the better-known risk factor for fibrosis progression is diabetes and other metabolic comorbidities [81, 82], this has not been systematically assessed in most studies on NAFLD in PLHIV. Consequently, we could not analyse the risk factors of significant and/or advanced fibrosis in PLHIV.

The burden of NAFLD and its risk factors among PLHIV described in this review should nourish efforts to create and implement NAFLD screening programmes in this patient population. The fact that the prevalence of NAFLD reported herein was higher than the one reported for the general population is of particular concern.

Since many PLHIV have or will eventually have metabolic syndrome or its components [83], further research is required to uncover the particularities of NAFLD in PLHIV, especially the effect that the time living with the disease may have on the progression and outcomes of the co-existing hepatic metabolic comorbidity.

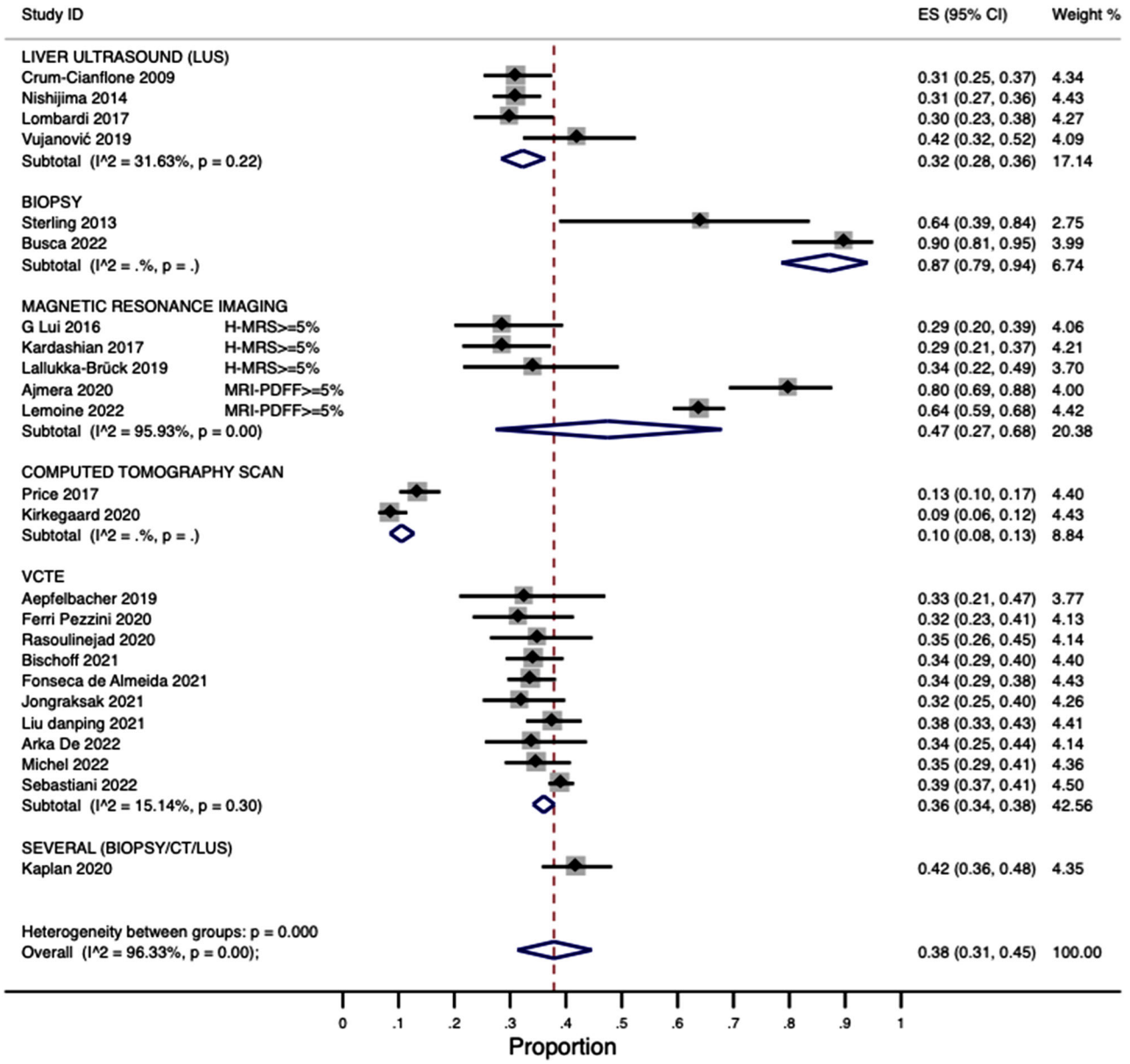

Figure 6. Subgroup analysis by diagnostic method.

4.1 | Limitations

This study has limitations and results should be interpreted in the context of the study design. First, the review was not registered in PROSPERO. Second, the main limitation of the present MA is the high heterogeneity found across studies, which could theoretically comprise the validity of the pooled estimates presented. Third, the used-cut-offs for CAP and liver stiffness have been redefined over time according to recent EASL guidelines [26] and this affects the outcomes of interest synthesized in this review. However, as the MAs were based on methodologically similar studies with analogous inclusion and exclusion criteria, one can infer that clinical and methodological heterogeneity levels were likely low. Moreover, previous simulation studies demonstrated that determining levels of heterogeneity is of little value at the extremes of it [84], such as in this study.

Fourth, the sources from which the pooled prevalence estimates were calculated are subjected to selection bias as they represent the setting where they were recruited, albeit not the whole PLHIV population. Thus, there is potential for meta-bias and overestimation because the meta-analytic pooled estimates may not accurately represent the true NAFLD prevalence in the whole PLHIV population in the society. Nevertheless, we consider the results from the present study reliable because meta-analytic methods may provide a more precise estimate of such measures than any individual study contributing to the pooled analysis (MA).

Fifth, due to a lack of data in the analysed studies, we could not establish the effect of the duration of HIV and

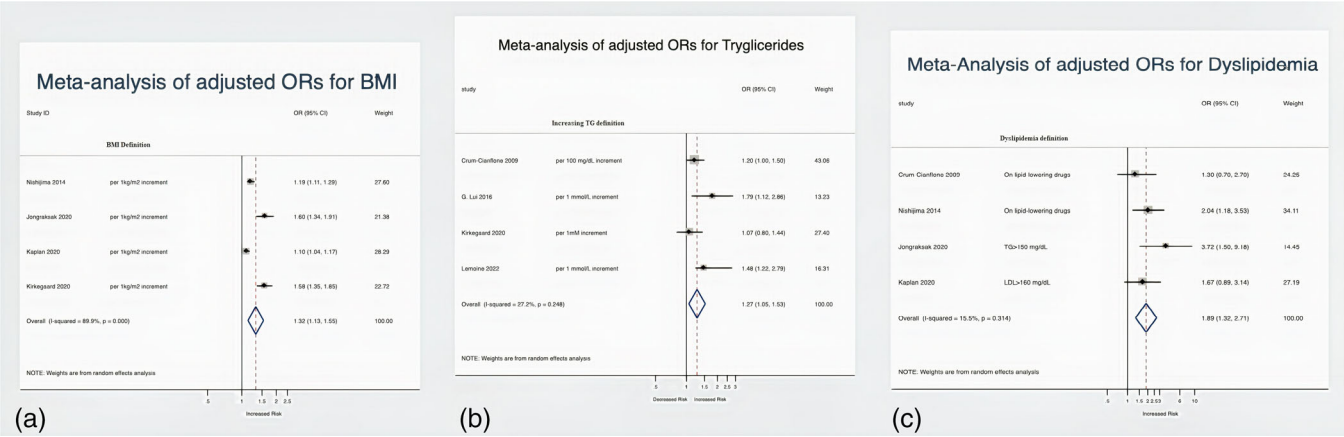

Figure 7. Meta-analysis of risk factors. (a) Forest plot for BMI. (b) Forest plot for triglycerides. (c) Forest plot for dyslipidemia.

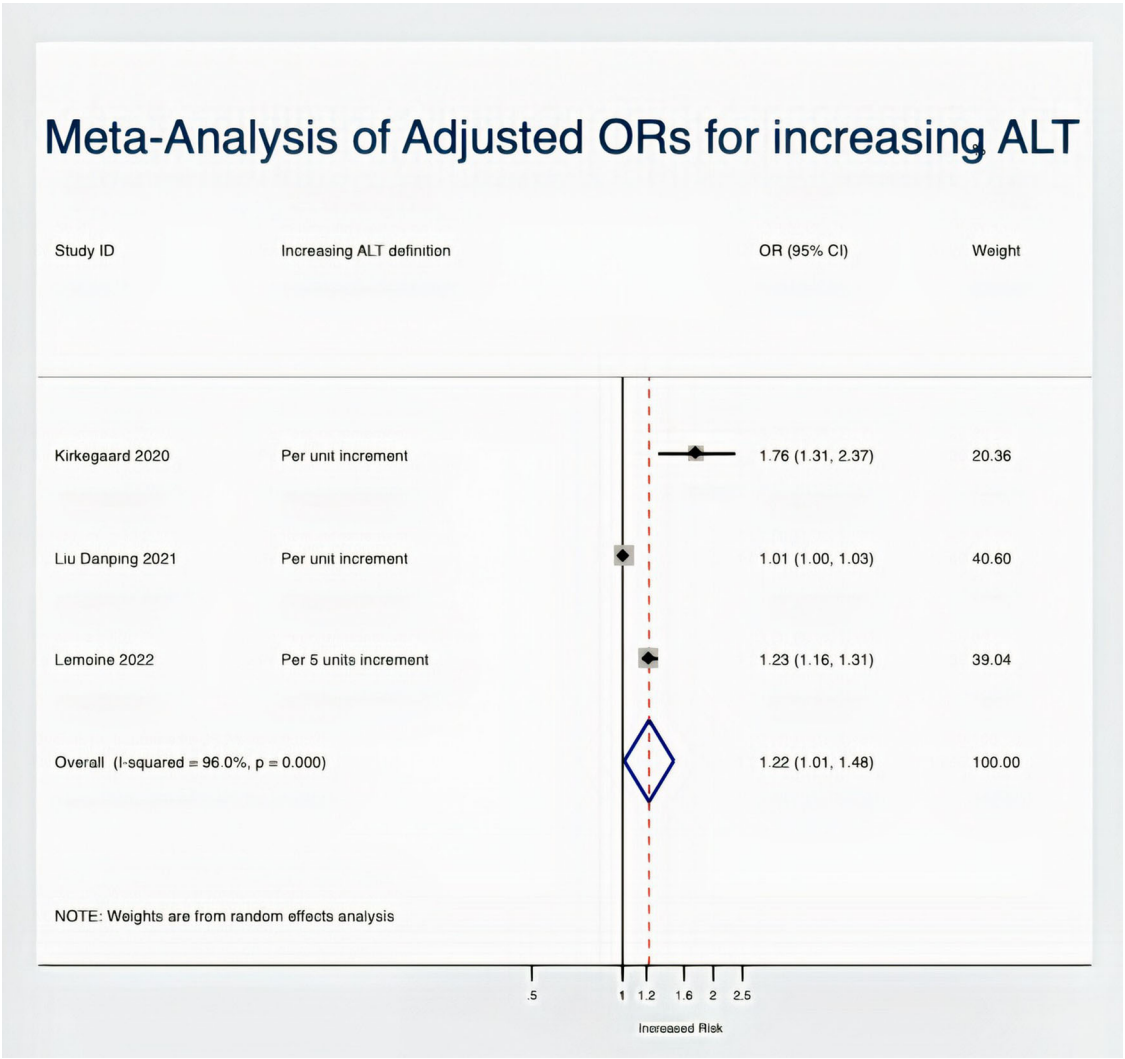

Figure 8. Meta-analysis of ALT as a risk factor for NAFLD.

antiretroviral therapy on NAFLD. Therefore, additional studies should address this and NAFLD's natural history and focus on the highly prevalent burden of comorbidities with particular attention to finding a differential effect of these factors in PLHIV compared to the general population.

Finally, the study was limited by the lack of information from low-income economies, making these findings not generalizable to a significant share of the world's population residing in these often-underserved regions.

5 | CONCLUSIONS

The burden of NAFLD and significant fibrosis in PLHIV is significant. Therefore, targeted efforts to screen and diagnose NAFLD in this population are needed. Health services for PLHIV could include ways to target NAFLD risk factors, screen for liver disease and implement interventions to treat those with significant fibrosis or more advanced stages of liver disease. Taking no action to screen for NAFLD in PLHIV and address this often-overlooked metabolic comorbidity should not be an option.

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AUTHORS' CONTRIBUTIONS

Conceptualization and design: JRE, RMN and JMP. Data collection: JRE, RMN and ES. Drafting of the first manuscript: RMN, JRE, ES and JMP. Data analyses: RMN. Data interpretation: JRE, RMN, JN, JVL, JMS, AC and JMP. Critical revision of the manuscript: JN, JVL, JMS and AC. Supervision: JMP. Access and verification of data: JMP. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

COMPETING INTERESTS

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DATA AVAILABILITY STATEMENT

The datasets and Stata commands generated and used to perform the present systematic review and meta-analysis can be available from the corresponding author at reasonable request.

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