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Liver steatosis and non-alcoholic fatty liver disease with fibrosis are predictors of frailty in people living with HIV / Milic, J., Menozzi, V., Schepis, F., Malagoli, A., Besutti, G., Franconi, I., Raimondi, A., Carli, F., Mussini, C., Sebastiani, G., Guaraldi, G.. - In: AIDS. - ISSN 0269-9370. - 34:13(2020), pp. 1915-1921. [10.1097/QAD.0000000000002650]

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13/09/2026 01:33

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AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000002650

Liver steatosis and non-alcoholic fatty liver disease with fibrosis are predictors of frailty in people living with HIV

Jovana Milic[1,2], Valentina Menozzi[3], Filippo Schepis[4], Andrea Malagoli[1], Giulia Besutti[2], Iacopo Franconi[1], Alessandro Raimondi[1], Federica Carli[1], Cristina Mussini[1], Giada Sebastiani[5], Giovanni Guaraldi[1]

[1] Modena HIV Metabolic Clinic, University of Modena and Reggio Emilia, Italy

[2] Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy

[3] University of Modena and Reggio Emilia, Modena, Italy

[4] Department of Gastroenterology, University of Modena and Reggio Emilia, Italy

[5] Department of Medicine, Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Canada

Correspondence:

Jovana Milic, MD

Modena HIV Metabolic Clinic

Clinical and Experimental Medicine PhD Program

University of Modena and Reggio Emilia

Largo del Pozzo, 71

41124 Modena, Italy

M: +39 324 953 2500

Email: jovana.milic@gmail.com

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ABSTRACT

Objective

The aim was to investigate the contribution of liver steatosis and significant fibrosis alone and in association (NAFLD with fibrosis) to frailty as a measure of biological age in people living with HIV (PLWH).

Design

This was a cross-sectional study of consecutive patients attending Modena HIV Metabolic Clinic in 2018-2019.

Methods

Patients with hazardous alcohol intake and viral hepatitis co-infection were excluded. Liver steatosis was diagnosed by controlled attenuation parameter (CAP), while liver fibrosis was diagnosed by liver stiffness measurement (LSM). NAFLD was defined as presence of liver steatosis (CAP≥248), while significant liver fibrosis or cirrhosis (stage ≥F2) as LSM≥7.1 kPa. Frailty was assessed using a 36-Item frailty index (FI). Logistic regression was used to explore predictors of frailty using steatosis and fibrosis as covariates.

Results

We analyzed 707 PLWH (mean age 53.5 years, 76.2% males, median CD4 700 μL, 98.7% with undetectable HIV RNA). NAFLD with fibrosis was present in 10.2%; 18.9% and 3.9% of patients were classified as frail and most-frail, respectively. Univariate analysis demonstrated that neurocognitive impairment (OR=5.1, 1.6-15), vitamin D insufficiency (OR=1.94, 1.2-3.2), obesity (OR=8.1, 4.4-14.6), diabetes (OR=3.2, 1.9-5.6) and osteoporosis (OR=0.37, 0.16-0.76) were significantly associated with NAFLD with fibrosis. Predictors of FI included : steatosis (OR=2.1, 1.3-3.5), fibrosis (OR=2, 1-3.7), NAFLD with fibrosis (OR=9.2, 5.2-16.8), diabetes (OR=1.7, 1-2.7) and multimorbidity (OR=2.5, 1.5-4).

Conclusion

Liver steatosis and NAFLD with fibrosis were associated with frailty. NAFLD with fibrosis exceeded multimorbidity in the prediction of frailty, suggesting the former as an indicator of metabolic age in PLWH.

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Background

Non-alcoholic fatty liver disease (NAFLD) has become an emerging condition in general aging population and the most common cause of chronic liver disease [1]. The predictions show that NAFLD prevalence will increase by 21%, from 83.1 million in 2015 to 101 million in 2030 in the United States [2]. NAFLD is defined as fat accumulation in >5% hepatocytes not attributable to consumption of alcohol and may be associated to fibrosis. Both steatosis and fibrosis could be diagnosed by non-invasive diagnostic tools, such as transient elastography (TE) with controlled attenuation parameter (CAP). On the other side, the diagnosis of non-alcoholic steatohepatitis (NASH) is based on liver biopsy that combines liver steatosis with hepatocyte ballooning and lobular inflammation, that potentially leads to progressive liver fibrosis and hepatic failure [1].

Recent studies confirm the increasing burden of NAFLD in people living with HIV (PLWH), as viral hepatitis prevalence and associated mortality decline [3]. Moreover, liver disease is a leading cause of non-AIDS related deaths in PLWH [4].

Nevertheless, NAFLD should not be considered as a liver condition only, but rather as a multisystemic state involving other organs [5]. Indeed, NAFLD has been linked to increased risk of type 2 diabetes mellitus, cardiovascular disease, and chronic kidney disease in the general population. In this scenario, NAFLD is not only seen as a risk factor, but can play an important role in the complex pathogenesis of non-infectious co-morbidities (NICMs) [5]. This relationship remains unexplored in PLWH, despite metabolic syndrome and its components are frequent and consistently reported as risk factors for NAFLD in this population [6].

Accumulation of NICMs described by multimorbidity, is a typical feature in people reaching geriatric age, nevertheless this construct fails to describe the clinical complexity of aging. For this reason, geriatric medicine has conceptualized the construct of frailty to identify individuals more vulnerable to adverse health outcomes and to provide suitable clinical interventions.

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So far, it has been shown that frailty represents a more accurate measure of an individual's biological age that may replace the traditional metric of chronological age, which does not necessarily correspond [7]. Frailty is defined as a condition characterized by the reduction of homeostatic reserves exposing the individual to a greater risk of negative outcomes such as multimorbidity, falls, disability, nursing home placement and death [8].

In the clinical setting, how to measure frailty is still a matter of debate. At the organ level, sarcopenia assessment has been proposed as an equivalent of frailty, while for a more profound and holistic approach, frailty phenotype and frailty index had been used [9]. In fact, while sarcopenia is an important component of frailty, it may be seen as a one-dimensional approach, while the aging in an individual is a complex process where multiple factors play a role. The association of NAFLD and sarcopenia has been investigated both in HIV and the general population [10–12]. Our group has recently reported that sarcopenia assessed by grip strength increased the risk of NAFLD [13], while the data regarding association between NAFLD and frailty remains scarce (Supplementary figure 1).

We hypothesized that NAFLD could be a significant determinant of frailty, in the context of a multisystemic nature of both these conditions. Therefore, the objective of the study was to investigate the correlation between liver steatosis and significant fibrosis alone and in association (NAFLD with fibrosis) and frailty, as a measure of biological age, in PLWH.

Material and methods

Study design

This was a cross-sectional study that included consecutive PLWH attending Modena HIV Metabolic Clinic (MHMC) from June 2018 to May 2019. MHMC is a tertiary level referral center established in 2004 where PLWH are screened for NICMs and immuno-metabolic disorders including NAFLD, geriatric syndromes and frailty to better describe their aging trajectory.

Inclusion and exclusion criteria

We included ART-experienced PLWH who were evaluated for liver steatosis and fibrosis by transient elastography at MHMC. Patients with hepatitis B (HBV), hepatitis C (HCV) co-infection and hazardous alcohol intake were excluded from the study. HBV and HCV co-

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infection diagnosis were based on serology, while the alcohol intake was evaluated through an AUDIT questionnaire that collects self-reported information, using as cut-offs 30g/day for men and 20g/day for women [14].

Assessment of steatosis and fibrosis

Liver stiffness measurement (LSM) and associated CAP were evaluated using TE with M probe. Liver steatosis was diagnosed by CAP as follows: S0 (no steatosis; CAP<248 dB/m), S1 (mild steatosis; 248≥ CAP <268 dB/m), S2 (moderate steatosis; 269≥ CAP<280 dB/m), S3 (severe steatosis; CAP≥ 280 dB/m) [15]. All measurements >248 dB/m were considered as NAFLD. Liver fibrosis was diagnosed by LSM as follows: stage F0-F1 (mild fibrosis, LSM<7.1 kPa), F2-F3 (significant fibrosis, 7.1≥LSM<13 kPa), F4 (cirrhosis, LSM≥13 kPa) [16].

NAFLD with fibrosis was defined as the contemporary presence of liver steatosis (CAP≥248) and significant liver fibrosis or cirrhosis (stage ≥F2). In the unavailability of liver biopsy, we considered NAFLD with fibrosis as a proxy of NASH .

Covariates

Demographic, anthropometric, HIV-related and immune-metabolic variables were collected on the same day of the visit at MHMC. Co-morbidities were defined using the European AIDS Clinical Society (EACS) guidelines [17]. Hypertension was defined as two consecutive measurements of blood pressure >140/90 mmHg. T2DM was defined as fasting serum glucose levels >126 mg/dL or HbA1C >6.5%. Diagnoses of hypertension and T2DM were also identified based on the current use of antihypertensive or antidiabetic drugs. Obesity was diagnosed as body mass index (BMI) > 30 kg/m^2. Dyslipidemia was defined as elevated total or low density lipoprotein (LDL) cholesterol or low high density lipoprotein (HDL) cholesterol above laboratory limits. Chronic kidney disease (CKD) as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m2 calculated using the CKD-Epi equation. Laboratory values for the diagnosis of CKD and dyslipidemia were confirmed in two consecutive measurements. Metabolic syndrome was defined using MetS ATPIII classification [18], including three or more of the following five criteria: waist circumference

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over 102 cm (men) or 88 cm (women), blood pressure over 130/85 mmHg, fasting triglyceride level over 150 mg/dl, fasting HDL cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women), and fasting blood glucose over 100 mg/dl [18]. Cardiovascular disease included myocardial infarction, coronary artery disease, peripheral vascular disease, stroke, and angina pectoris, as well as coronary artery bypass grafting and angioplasty, based on diagnoses recorded in patient files. Chronic obstructive pulmonary disease was defined as post-bronchodilator FEV1/FVC <0.70 with spirometry. Vitamin D insufficiency was defined as < 20 ng/mL (< 50 nmol/L). Osteoporosis in postmenopausal women and men aged ≥50 years was defined as a bone mass index (BMD) T-score ≤-2.5 and in premenopausal women and men aged <50 years as a BMD Z-score ≤-2 and fragility fracture. The presence of a cancer was considered if a diagnosis was reported in the patient's medical history. Depression was evaluated using the CES-D questionnaire. Neurocognitive impairment was evaluated using CogState battery that comprises six tasks, one for each cognitive domain [19]. Multi-morbidity was defined as ≥2 comorbidities in the same individual.

Frailty assessment

Frailty was determined using 36-Item frailty index (FI) generated by a standardized comprehensive geriatric assessment, previously validated at MHMC and constructed from health variables collected at the same study visit (Supplementary table 1). Each variable included in the FI was coded with a value of 1 when a deficit was present, and 0 when it was absent. Missing values were removed from both the numerator and the denominator of the FI [20]. The FI for each patient visit was calculated as the ratio between the number of deficits present and the total number of deficits assessed. Missing values were removed from both the numerator and denominator of the FI ($FI = \frac{\sum Deficit}{(36-\sum Missingvalues)}$). Each FI was computed when a minimum of 80% of valid data for the health variables was available. We categorized PLWH according to FI score as fit (<0.25), frail (0.25-0.4), most frail (>0.4) [21]. Of note, NAFLD, selected as a covariate of interest for this study, was excluded from the computation of the FI.

Statistical analysis

Results were expressed as mean and standard deviation (± SD), or median and interquartile range (IQR) for continuous variables based on the normality of distribution, and as

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frequencies and percentages for categorical variables. Student's t-test and ANOVA were applied to identify statistical difference for the continuous variables with normal distribution, while the Mann-Whitney and Walls-Kruskal test was used for those without normal distribution. The $\chi 2$ test was performed to assess the frequency of the categorical variables. Logistic regression models were built to explore the contribution of liver steatosis and significant fibrosis alone and in association (NAFLD with fibrosis) to frailty along with age, gender, diabetes mellitus and multi-morbidity. Multivariate regression models included covariates with a p-value<0.05 in univariable analysis or covariates that were determined *a priori* to be clinically important, based on previous literature.

Subgroups of PLWH with liver steatosis, significant fibrosis and NAFLD with fibrosis were mutually exclusive. The missing data was removed from denominator and was not considered in the calculations. The numbers between square brackets [N°] refer to number of people in which the given variable was available. The significance of the tests was set to 0.05. The statistical program R, v. 3.6.0 in GNU Linux environment was used to analyze the data.

This study was approved by the University of Modena and Reggio Emilia ethics committee according to the Helsinki declaration.

Results

We analyzed 707 PLWH. Mean age was 53.5 (±8.2) years, 76.2% were males, mean BMI was 24.6 (±4.2), 18.3% had T2DM, median CD4 was 700 μL (IQR=540-889), HIV RNA viral load was undetectable in 98.7% of cases. Prevalence of NAFLD was 39.7%, while NAFLD with fibrosis was present in 10.2%, frail and most-frail in 18.9% and 3.9%, respectively. Study population characteristics according to frailty index categories is provided in Supplementary table 2. Detailed description of liver steatosis and fibrosis is provided in Supplementary table 3.

Supplementary figure 2 depicts trends of prevalence of steatosis, fibrosis and NAFLD with fibrosis across different chronological age categories (<45, 46-50, 51-55, 56-60, 61-65, >65 years). The highest peaks for all three conditions are observed in PLWH at the age of 51-55

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(43.4%, 21.4% and 15.1% respectively) and at the age 65+, which is defined as geriatric age (46.2%, 25.6% and 15.4% respectively).

With regards to a biological age, assessed by FI, prevalence of frailty increased with higher levels of liver steatosis and fibrosis, and NAFLD with fibrosis (Figure 1). Frailty was present in 41.2% and 52.3% in PLWH with mild/moderate and severe liver steatosis respectively (Figure 1A, $p<0.001$). A similar pattern is observed for liver fibrosis, i.e. FI scores >0.25 were found in 54.8% and 70% PLWH with significant fibrosis and cirrhosis, respectively (Figure 1B, $p<0.001$). In PLWH with NAFLD with fibrosis, frailty was identified in 69% (Figure 1C, $p<0.001$).

NAFLD with fibrosis group showed a higher prevalence of obesity (36% vs. 6%) ($p<0.001$) (Table 1). With regards to HIV variables, PLWH with NAFLD with fibrosis presented a longer mean HIV duration and lower CD4 nadir. The use of NNRTI was observed in 24% of PLWH with more than two times higher use in people without NAFLD with fibrosis. This observation was accompanied by higher HDL cholesterol levels, while LDL and total cholesterol levels were lower (Table 1).

Univariate analysis demonstrated that neurocognitive impairment (OR=5.08, 1.61-14.96), vitamin D insufficiency (OR=1.94, 1.18-3.24), obesity (OR=8.06, 4.44-14.55), diabetes mellitus (OR=3.24, 1.91-5.59) and osteoporosis (OR=0.37, 0.16-0.76) were associated with NAFLD with fibrosis (Table 2).

To better explore this association, a multivariate logistic model was built. Independent positive predictors for FI were steatosis (OR=2.12, 1.3-3.45) and fibrosis (OR=1.95, 1.03-3.66) alone and in association – NAFLD with fibrosis (OR=9.19, 5.17-16.79), diabetes mellitus (OR=1.65, 1-2.74) and multimorbidity (OR=2.46, 1.53-4.01) (Figure 2).

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Discussion

The relationship between liver steatosis and significant fibrosis alone and in association (NAFLD with fibrosis) and frailty is not a widely investigated topic in PLWH and general population.

This study explored in detail liver steatosis and fibrosis in relation to chronological age and frailty as a proxy of biological age. With regards to chronological age, steatosis and NAFLD with fibrosis follow the same trend of prevalence across age groups in our study. The curves have an initial increase until the age of 50, followed by a plateau that occurs between 50-65. The prevalence of NAFLD across age remains controversial. Most studies showed that NAFLD prevalence increases with advancing age [22]. However, the cross-sectional nature of the study and a small subset of patients older than 65 years do not permit us to make strong conclusions about prevalence of liver steatosis and NAFLD with fibrosis in geriatric PLWH.

It remains unclear if NAFLD with fibrosis is regulated by age or is a regulator of biological age itself. According to the second scenario, NAFLD with fibrosis would reflect better biological age (frailty) of the individual, consistent with our initial hypothesis and the main finding. NAFLD with fibrosis and frailty showed almost a linear association. In our multivariate analysis, NAFLD with fibrosis was associated with frailty, 3-fold more than multimorbidity, suggesting that NAFLD with fibrosis as a multisystemic construct [5] exceeds the construct of multimorbidity, defined as a simple sum of single NICMs. Given this strong association with frailty as a measure of biological age, we may suggest NAFLD with fibrosis as an indicator to assess the metabolic age of an individual. From the present study emerges lack of association between chronological age and frailty index, both in univariate and multivariate analysis. This is not consistent with previous studies from our group and to what was shown in general population [21]. Such finding could be justified by different of cut-offs to identify frail individuals or choice not to use FI as a continuous variable, as in the previously quoted study [21].

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Our multivariate analysis showed that male gender is protective against frailty, which is in line with observations in general population [23]. In HIV setting were identified different variables associated with frailty in males (VACS index, C-reactive protein and falls) and females (CRP, AIDS, and menopause) [24]. These observations imply that choice of variables that entered in the frailty index used in our study might have played a role in the gender difference. However, further studies are needed to investigate patterns of frailty with the regards to gender.

As expected, obesity, BMI, waist circumference, higher aminotransferase, GT and triglycerides and lower HDL levels were strongly associated with NAFLD with fibrosis suggesting that PLWH share common metabolic patterns occurring in the general population [25]. Similar findings were obtained in a large cohort study that comprised PLWH with and without metabolic syndrome in which obesity and insulin resistance were key factors associated with liver fibrosis independently of the HIV duration and exposure to ART [26]. However, the pathogenesis of NAFLD in PLWH has some additional features [27], expressed by viro-immunological parameters, depicted by low nadir and longer HIV duration or other factors that may contribute to immune activation in PLWH. This suggests that also an "immunological scar" that might be depicted by higher levels of sCD163 is associated with metabolic harm and hepatic inflammation, captured by NAFLD with fibrosis [26].

We arbitrary chose a definition of NAFLD with fibrosis based on the European Association for the Study of the Liver (EASL) definitions of liver steatosis and fibrosis singularly evaluated with TE [16]. This combined definition was used in order to offer a proxy measurement of NASH. Liver fibrosis, as the most important histological determinant of NASH, is associated with long-term negative outcomes in the general population and PLWH [28,29].

We found that not only NAFLD with fibrosis, but also liver steatosis was associated with frailty, implying that health care interventions that are proven to be effective, such as weight loss and other lifestyle changes [30,31], should be reinforced and promoted in order to decrease the burden of frailty, as well as the burden of NAFLD with fibrosis in PLWH.

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In patients in which lifestyle changes are not sufficient to treat NAFLD/NASH, some other therapeutic options are considered, such as pharmacologic treatment or liver transplantation [32,33]. In the last few years, an increased number of clinical trials for treatment of NAFLD/NASH are noted [34,35], recognizing this condition as one of the major challenges in contemporary and future health care. We observed that 69% of PLWH with NAFLD with fibrosis were frail in our study. The only validated test to prove NASH is liver biopsy [1,16]. NASH diagnosis is rarely made because of the unavailability and invasiveness of liver biopsy, implying that the selection of the affected patients for pharmacologic treatment will also be an issue. Frailty assessment could serve as an additional criterion in decision making, as it is more feasible in the routine clinical practice.

This study has a number of limitations. Some of these are intrinsic to the cross-sectional nature of the study, which cannot reveal a causative association between NAFLD with fibrosis and frailty. The absence of a control group does not allow us to show whether demographic, anthropometric, HIV variables and comorbidities associated both with NAFLD with fibrosis and frailty represent a different pattern of PLWH when compared to the general population.

In conclusion, liver steatosis and fibrosis alone and in association were associated with frailty. NAFLD with fibrosis exceeded multimorbidity in the prediction of frailty, suggesting the former as an indicator of metabolic age in PLWH.

Conflict of interest

GS has acted as speaker for Merck, BMS, Gilead, Abbvie, ViiV, served as an advisory board member for Merck, BMS and Novartis has received research funding from Merck and Echosens. GG received research grant and speaker honorarium from Gilead, ViiV, MERCK and Jansen. GG attended advisory boards of Gilead, ViiV and MERCK. Other authors reported no conflict of interest.

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Authors contributions

JM, FS, AM, GS and GG conceptualized and designed the study. JM, VM and GG wrote the manuscript. JM, GS and GG did the supervision of the final version of the manuscript. All the authors contributed to discussion and revision of the manuscript.

Funding

This study was not funded.

Academic presentations

The results of this study were presented at 17th EACS (6-9 November 2019, Basel, Switzerland) as an oral presentation and at 21st International Workshop on Co-Morbidities and Adverse Drug Reactions in HIV (5-6 November 2019, Basel, Switzerland) as a poster.

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Figure 1 shows the association between frailty index divided into three groups (fit (<0.25), frail (0.25-0.4), most frail (>0.4)) and liver steatosis (1A), liver fibrosis (1B) and NAFLD with fibrosis (1C). **Abbreviations:** F0-F1 – mild fibrosis; F2-F3 – significant fibrosis; F4 – cirrhosis; S0 – without steatosis; S1-S2 – mild-moderate steatosis; S3 – severe steatosis.

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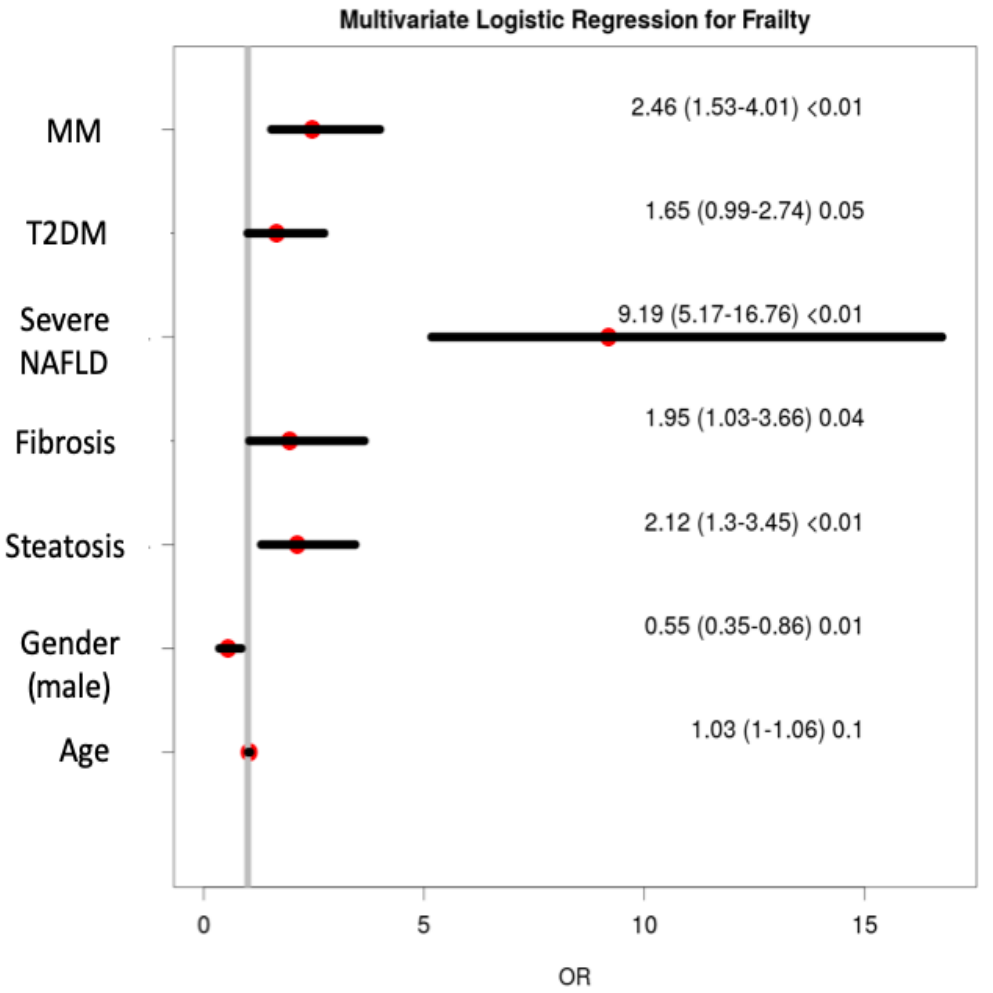
Figure 2 depicts a multivariate logistic model that identified independent predictors for FI were liver steatosis and fibrosis alone and in association (NAFLD with fibrosis), diabetes and multi-morbidity. **Abbreviations:** MM – multimorbidity; T2DM – type 2 diabetes mellitus.



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Variable	NAFLD without fibrosis	NAFLD with fibrosis	p
N	635 (89.8%)	72 (10.2%)	
Sex, male (%)	479 (75.4%)	60 (83.3%)	0.20
Age, years, mean (±SD), [N°]	53.2 (8.1) [635]	55.8 (8.2) [72]	0.02
BMI, kg/m^2, mean (±SD), [N°]	24.2 (4) [633]	28.7 (4.2) [72]	<0.001
Waist circumference, cm, mean (±SD), [N°]	90.8 (34.4) [595]	104.9 (11.2) [67]	<0.001
Obesity (%)	38 (6%)	26 (36.1%)	<0.001
Mild/moderate physical activity (%)	292 (46%)	18 (25%)	0.001
HIV duration, months, median (IQR), [N°]	275 (165.5-338) [615]	322 (229-372) [71]	0.007
Nadir CD4, median, c/µL, median (IQR) [N°]	224 (100-328.8) [606]	180 (67-287) [68]	0.03
Current CD4, median, c/µL, median (IQR) [N°]	700 (542.3-884.8) [622]	689 (436-891) [69]	0.39
Current CD8, median, c/µL, median (IQR) [N°]	778.5 (581.8-1038) [620]	823 (550-1054) [69]	0.92
CD4/CD8 ratio, mean (±SD), [N°]	1 (0.5) [620]	0.98 (0.5) [69]	0.65
Undetectable viral load (%)	627 (98.7%)	71 (98.6%)	0.99
Type 2 diabetes (%)	99 (15.6%)	30 (41.7%)	<0.001
Polypharmacy (%)	81 (12.8%)	17 (23.6%)	0.02
Current exposure to NNRTI (%)	160 (28.1%)	9 (13.6%)	0.02
FIB-4. mean (±SD), [N°]	1.5 (0.9) [285]	1.6 (0.6) [37]	0.02
AST, U/l, mean (±SD), [N°]	24.1 (12.5) [605]	30.2 (14.9) [65]	<0.001
γGT, U/L, mean (±SD), [N°]	29 (28.9) [600]	48.1 (36) [65]	<0.001
Total cholesterol, mg/dl, mean (±SD), [N°]	180.9 (35.6) [603]	166.9 (41.9) [65]	0.003
LDL cholesterol, mg/dl, mean (±SD), [N°]	117.8 (32.7) [600]	106.1 (38.7) [64]	0.004
HDL cholesterol, mg/dl, mean (±SD), [N°]	51.6 (15) [600]	43.8 (10.6) [65]	<0.001
Triglycerides, mg/dl, mean (±SD), [N°]	133.5 (90) [603]	169.8 (108.2) [64]	0.002
Metabolic syndrome (%)	176 (27.7%)	49 (68.1%)	<0.001
Grip strength, kg, mean, (±SD), [N°]	36 (9.6) [573]	37.3 (8.3) [68]	0.46
4m walk speed test, seconds, mean, (±SD) [N°]	3.6 (0.6) [588]	3.8 (0.6) [66]	0.005
30s chair-stand test, mean (±SD) [N°]	8.1 (2.8) [603]	8.6 (2.8) [67]	0.12

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Table 1 describes demographic, anthropometric HIV and clinical characteristics in PLWH with and without severe NAFLD.

Abbreviations: AST - aspartate aminotransferase; BMI – body mass index; HDL – high density lipoprotein; HIV – human immunodeficiency virus; IQR – interquartile range; LDL – low density lipoprotein; [N°] – number of people in which the given variable was available; NAFLD – non-alcoholic fatty liver disease; NNRTI – non-nucleoside reverse transcriptase inhibitors; SD – standard deviation

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Table 2. Univariate analysis demonstrates that neurocognitive impairment, vitamin D insufficiency, obesity, T2DM and osteoporosis are associated with NAFLD with fibrosis.

	NAFLD with fibrosis		
	OR	**IQR**	**P**
Depression	1.78	0.93-3.31	0.07
NC impairment	5.08	1.61-14.96	<0.01
Vitamin D insufficiency	1.94	1.18-3.24	0.01
Obesity	8.06	4.44-14.55	<0.01
Hypertension	1.59	0.95-2.7	0.08
Type 2 diabetes	3.28	1.91-5.59	<0.01
CVD	0.85	0.25-2.29	0.78
CKD	0.71	0.35-1.35	0.32
COPD	1.32	0.38-3.57	0.62
Osteoporosis	0.37	0.16-0.76	0.01
Dyslipidemia	0.92	0.47-1.92	0.8
Cancer	1.36	0.70-2.50	0.34
Metabolic syndrome	2.41	1.47-3.95	<0.01

Abbreviations: CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; CVD – cardiovascular disease; IQR – interquartile range; NAFLD – non-alcoholic fatty liver disease; NC – neurocognitive, OR – odds ratio.

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