

NAFLD with significant fibrosis in people living with HIV inform the natural history of cardiovascular disease

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Background

Non-alcoholic fatty liver disease (NAFLD) is associated with hepatic and extrahepatic manifestations such as cardiovascular diseases (CVD), leading to an increased morbidity and mortality. We hypothesized that the natural history of CVD and NAFLD are parallel. We postulated that NAFLD with/without significant fibrosis was independently associated with various stages of CVD in people living with HIV (PLWH).

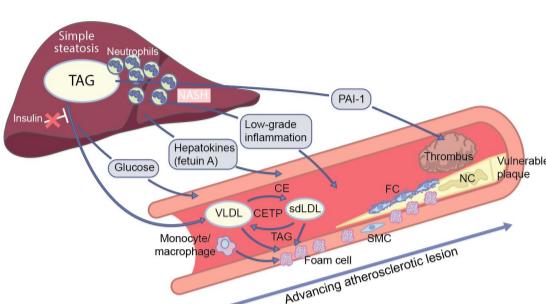


Figure 1. Biologically plausible mechanisms that link NAFLD to the pathogenesis of an atherosclerotic lesion, adapted from Brouwers et al (2020) Diabetologia, 63:253-260

The aim of the study was to compare the performance of transient elastography as a measure of NAFLD and significant fibrosis with ASCVD algorithm in the prediction of subclinical cardiovascular disease (CVD) and major adverse CVD event (MACE) in people living with HIV (PLWH).

Methods

This was a cross-sectional study including consecutive PLWH attending Modena HIV Metabolic Clinic (MHMC) from June 2018 to October 2019. We included ART-experienced PLWH who were evaluated for NAFLD, subclinical and clinical CVD.

NAFLD assessment

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).



Liver fibrosis was diagnosed by LSM as follows:

- F0-F1 (mild fibrosis, LSM<7.1 kPa)
- F2-F3 (significant fibrosis, 7.1>LSM<13 kPa)
- F4 (cirrhosis, LSM>13 kPa).

NAFLD with fibrosis was defined as the contemporary presence of liver steatosis (CAP≥248 dB/m) and significant liver fibrosis or cirrhosis (stage F2).

Study outcomes

The study outcomes were:

1) cardiovascular risk, assessed by ASCVD risk score; a 10-year risk for CVD was categorised as low (<7.5%) and high (≥7.5%);

2) subclinical CVD, assessed by:

- ultrasound carotid intima-media thickness - IMT (plaque was defined as a focal structure invading the lumen with an IMT ≥1.5 mm; the presence of subclinical carotid atherosclerosis was identified as IMT ≥0.7 mm, presence of plaque, or both.)
- pulse wave velocity – PWV (a PWV >10 m/s was considered an estimate of significant alterations of arterial stiffness)
- coronary calcium score (CAC) by computed tomography (presence of subclinical atherosclerosis was defined by CAC score >100).

3) MACE including myocardial infarction, coronary artery disease, peripheral vascular disease, stroke, and angina pectoris.

Statistical analysis

Receiver operating characteristic curve (ROC) analysis was conducted to assess the performance of NAFLD and NAFLD with significant fibrosis in the prediction of CVD compared to ASCVD algorithm.

Results

We analysed 616 PLWH. Mean age was 56 (± 7.8) years, 79.2% were males. Mean body mass index (BMI) was 24.6 (± 3.8) kg/m², median CD4 was 708 μ L (IQR=550-903), HIV RNA viral load was undetectable in 98.6% of cases. Low ASCVD, high ASCVD, subclinical CVD and MACE were present in 209 (33.9%), 123 (20%), 216 (35.1%), 68 (11%) respectively. NAFLD and NAFLD with significant fibrosis were present in 443 (39.7%) and 92 (8.2%), respectively.

Table 1. Characteristics of study population according to ASCVD score, subclinical CVD disease and CVD.

	Low ASCVD (N=209)	High ASCVD (N=123)	Subclinical disease (N=216)	CVD (N=68)	p
Age, years, mean (SD)	50.4 (6.2)	57.5 (5.2)	59.1 (7.5)	60.1 (7.4)	<0.001
Sex, males, %	148 (70.8%)	99 (80.5%)	178 (82.4%)	63 (92.7%)	<0.001
Body mass index, kg/m ² , mean (SD)	24.5 (3.6)	24.2 (3.8)	24.7 (3.8)	25.2 (3.8)	0.33
Obesity, %	18 (8.6%)	6 (4.9%)	22 (10.3%)	7 (10.3%)	0.37
Nadir CD4, c/microL, median (IQR)	235 (120- 353)	200 (110- 282)	200 (78-288.5)	222 (91-300)	0.01
HIV duration, months, median (IQR)	232 (136- 315)	317 (249.5- 385.5)	303.5 (234- 345.5)	309.5 (260.75-355)	<0.001
CD4/CD8 ratio, mean (SD)	1.03 (0.46)	0.99 (0.5)	1.02 (0.55)	1.05 (0.64)	0.62
Current CD4, c/microL, median (IQR)	712 (545- 923)	681.5 (497- 882)	719 (529-907)	745 (595- 937)	0.35
Multimorbidity, %	69 (33.5%)	89 (73.6%)	135 (64.6%)	63 (94%)	<0.001
Polypharmacy, %	8 (5.4%)	16 (19.8%)	24 (19.8%)	32 (68.1%)	<0.001
Use of statins, %	26 (23.6%)	22 (31.4%)	60 (45.1%)	19 (76%)	<0.001

Figure 2

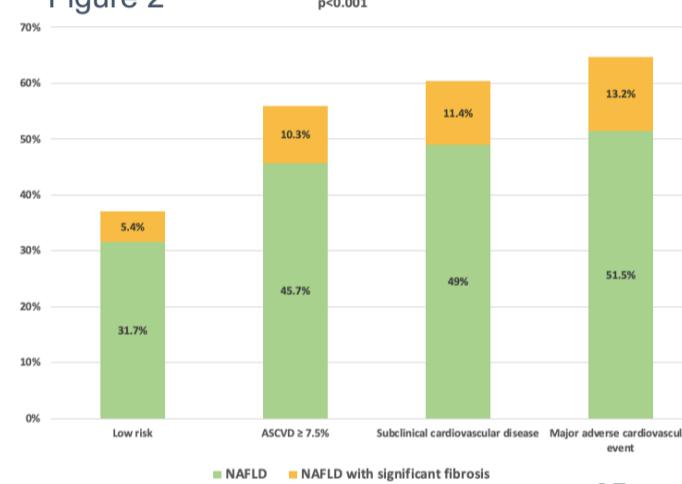
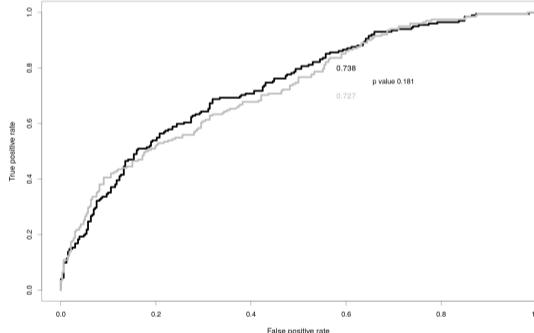


Figure 2. Prevalence of NAFLD and NAFLD with significant fibrosis across natural history of CVD. It can be observed that two thirds of PLWH with CVD have also NAFLD with/without fibrosis.

3A



3B

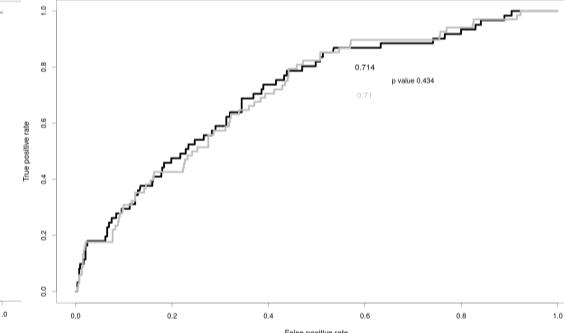
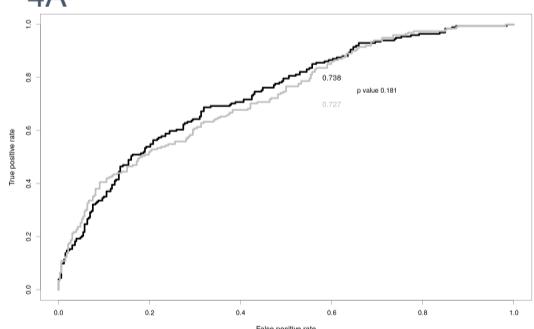


Figure 3. Subclinical CVD (panel A, grey) and MACE (panel B, grey) are well predicted by NAFLD in comparison to ASCVD (black).

4A



4B

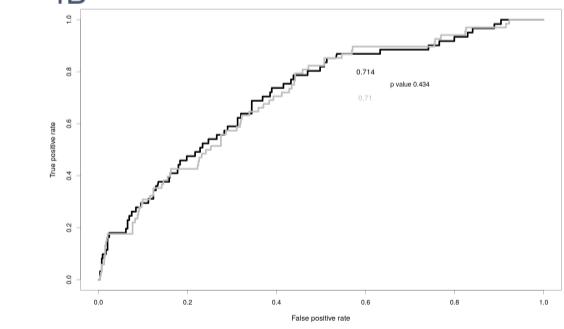


Figure 4. Subclinical CVD (panel A) and MACE (panel B) are excellently predicted by NAFLD with fibrosis in comparison to ASCVD.

Conclusions

- This is the first study to explore the relationship between NAFLD and CVD in PLWH.
- NAFLD and NAFLD with fibrosis have similar performance in prediction of CVD as ASCVD risk algorithm.
- NAFLD and NAFLD with fibrosis may be used as biomarkers of metabolic age in the prediction of CVD.