Associations of Hepatosteatosis With Cardiovascular Disease in HIV-Positive and HIV-Negative Patients: The Liverpool HIV–Heart Project

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Background: Hepatosteatosis (HS) has been associated with cardiovascular disorders in the general population. We sought to investigate whether HS is a marker of cardiovascular disease (CVD) risk in HIV-positive individuals, given that metabolic syndrome is implicated in the increasing CVD burden in this population.

Aims: To investigate the association of HS with CVD in HIV-positive and HIV-negative individuals.

Methods and results: We analyzed computed tomography (CT) images of 1306 subjects of whom 209 (16%) were HIV-positive and 1097 (84%) HIV-negative. CVD was quantified by the presence of coronary calcification from both dedicated cardiac CT and non-dedicated thorax CT. HS was diagnosed from CT data sets in those with noncontrast dedicated cardiac CT and those with venous phase liver CT using previously validated techniques. Previous liver ultrasound was also assessed for the presence of HS. The HIV-positive group had lower mean age ($P < 0.005$), higher proportions of male sex ($P < 0.005$), and more current smokers ($P < 0.005$). The HIV-negative group had higher proportions of hypertension ($P < 0.005$), type II diabetes ($P = 0.032$), dyslipidemia ($P < 0.005$), statin use ($P = 0.008$), and HS ($P = 0.018$). The prevalence of coronary calcification was not significantly different between the groups. Logistic regression (LR) demonstrated that in the HIV-positive group, increasing age [odds ratio (OR): 1.15, $P < 0.005$], male sex (OR 3.37, $P = 0.022$), and HS (OR 3.13, $P = 0.005$) were independently associated with CVD. In the HIV-negative group, increasing age (OR: 1.11, $P < 0.005$), male sex (OR 2.97, $P < 0.005$), current smoking (OR 1.96, $P < 0.005$), and dyslipidemia (OR 1.66, $P = 0.03$) were independently associated with CVD. Using a machine learning random forest algorithm to assess the variables of importance, the top 3 variables of importance in the HIV-positive group were age, HS, and male sex. In the HIV-negative group, the top 3 variables were age, hypertension and male sex. The LR models predicted CVD well, with the mean area under the receiver operator curve (AUC) for the HIV-positive and HIV-negative cohorts being 0.831 [95% confidence interval (CI): 0.713 to 0.928] and 0.786 (95% CI: 0.735 to 0.836), respectively. The random forest models outperformed LR models, with a mean AUC in HIV-positive and HIV-negative populations of 0.877 (95% CI: 0.775 to 0.959) and 0.828 (95% CI: 0.780 to 0.873) respectively, with differences between both methods being statistically significant.

Conclusion: In contrast to the general population, HS is a strong and independent predictor of CVD in HIV-positive individuals. This suggests that metabolic dysfunction may be attributable to the excess CVD risk seen with these patient groups. Assessment of HS may help accurate quantification of CVD risk in HIV-positive patients.

Key Words: HIV, cardiovascular disease, fatty liver, hepatosteatosis, random forest

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INTRODUCTION

Hepatosteatosis (HS) is the most common cause of liver disease in patients living with HIV (PLWHIV), affecting between 13% and 65%[1–3] of individuals. HS describes hepatic ectopic fat accumulation and is present when it affects >5% of the liver by weight. HS encompasses a spectrum of clinical entities, including nonalcoholic fatty liver disease (NAFLD). The prevalence of HS is underreported.

Histologically, progressive hepatic fat accumulation is associated with lipotoxicity and chronic inflammation, progressing in many cases to cirrhotic liver disease, and with a 3-

fold increase in mortality.[4] The relationship of obesity, insulin resistance, type II diabetes, and HS is well defined in non-HIV populations.[5] The estimated prevalence of NAFLD in the United States is predicted to reach 33% of the adult population by 2030.[6]

PLWHIV have unique risk factors for the development of HS compared with non-HIV populations. They have been shown to develop lean NAFLD, defined as NAFLD in BMI <25 kg/m^2, at increased rates compared with that in non-HIV populations.[7] The complex interplay of viral-related factors, antiretroviral medications, and chronic inflammation may cause PLWHIV to be more susceptible to the development of HS. Liver disease represents a huge source of morbidity and mortality in PLWHIV, with up to 13% of deaths in the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort study attributable to liver disease.[8] In both HIV-positive and HIV-negative populations, dyslipidemia, insulin resistance, and overt type II diabetes are strongly associated with the presence of HS.

HS has been shown to be associated with cardiovascular disease (CVD) in HIV-negative populations;[9–11] however, this is not universal.[12–14] Given the increasing burden of HS in HIV-positive populations, we sought to examine whether HS was independently associated with CVD in HIV-positive compared with that in HIV-negative populations.

METHODS

We conducted a real-world retrospective analysis to compare the associations of HS and CVD in both HIV-positive and HIV-negative patients. Data were collected from the Royal Liverpool University Hospital HIV clinical database and Computed Tomography Coronary Angiography (CTCA) clinical database. Both the HIV and CTCA databases exist for both clinical use and quality improvement purposes and are approved by the host institution's audit committee. All demographic and clinical variables present on the databases were cross-checked by the research team using the Trusts electronic patient record (clinical notes). The Royal Liverpool University Hospital audit committee approved this study. The HIV database includes all patients under follow-up with service. It contains clinical comorbidities, current and previous medications, anthropometric measurements, blood chemistry, and CVD risk.

The HIV database was cross-checked for patients who had received a thorax computed tomography (CT) within the past 10 years. The images were inspected by an independent imaging cardiologist for the presence of coronary calcification, which was recorded in a binary fashion (yes or no). HS was assessed using noncontrast CT scans or venous phase CT scans in those with liver parenchyma visible on the images. Both imaging techniques are established methods for quantifying liver fat content. Two regions of interest circles covering 100 mm^2 were drawn on the right lobe of the liver and one on the left lobe. The mean attenuation (Hounsfield unit) was recorded for liver parenchyma. Regions with nonuniform attenuation and hepatic vessels were avoided. A further 100-mm^2 region of interest was drawn on the spleen and the Hounsfield unit recorded. HS was confirmed if the liver to spleen ratio was less than 1 and/or the mean hepatic measurement was <40 HU in noncontrast scans.[15–18] Liver attenuation of 20 HU less than spleen attenuation was used for the venous phase imaging.[19] HS was also confirmed in patients who had a previous imaging (ultrasound) or biopsy-confirmed diagnosis of fatty liver. The HIV-positive group was taken exclusively from this database.

The CTCA database contains demographic and clinical variables for all patients referred for cardiac CT (either CAC scoring or CTCA) between January 2014 and November 2016. Most of the patients were referred for the investigation of atypical angina and were considered low to medium risk in line with guidelines from the National Institute for Clinical Excellence, which were established then.[20] The presence of HS had previously been calculated by 2 independent radiologists and added to the clinical database. This was performed using gated noncontrast studies from the CAC protocol. The methodology and criteria used to establish HS was the same as outlined with the HIV-positive cohort. Patients were labeled as having coronary calcification if the calcium score was >0.

Variables were collected by reviewing patients' case notes, including consultation letters, for previous and current diagnoses. Patients with previous diagnoses of CVD (including clinical diagnosis, imaging diagnosis of coronary plaque or coronary event, or intervention) were excluded. Patients were also excluded if quantification of coronary calcifications or quantification of HS was not possible.

Statistical Analysis

Summary statistics were calculated to compare the difference in clinical and demographic covariates between HIV-positive and HIV-negative groups. The prevalence of categorical variables was presented in absolute prevalence and percentages. All data were inspected using graphical representation for normality (histograms and Q–Q plots) and Shapiro–Wilk test. The proportions between categorical variables were compared using the χ^2 test. Continuous variables were presented as means and standard deviations where normally distributed. The means were compared using an independent t test. P values were considered statistically significant if <0.05. The data used were complete. Any case with missing values was excluded from the analysis.

A multiple logistic regression (LR) model was developed to ascertain the association between coronary calcifications and CVD risk covariates in HIV-positive and HIV-negative patient groups using odds ratio as a measure of association. In addition, we performed a sensitivity analysis using random forest (RF) to assess variables of importance in both HIV-positive and HIV-negative patients. Variables of importance were determined by Gini index. The Gini index is an established measure of accumulated nodal impurity for each variable in RF algorithms. A high mean decrease in Gini index indicates a high variable importance.[21]

For the development of the models, we performed bootstrapping, with 1000 repetitions (including replacements), each with the same size as the original data sets. This was performed to calculate the standard errors and

confidence intervals (CI). For the sensitivity analysis, we split the data sets into 70% training and 30% test in both groups of patients. The area under the receiver operator curve (AUC) for the test sets were calculated, and 95% CIs were estimated from the standard error. The statistical analysis and development of the machine learning models were performed using RStudio, version 1.3.1056.

RESULTS

The HIV database contains data on 1294 patients who are under follow-up. After removing those with previous documented CVD and those where assessment of coronary calcification or HS was not possible, there were 209 cases available for analysis. There were 1744 patients within the CTCA database. Again, after removing those with previous CVD, there were 1097 cases available for assessment. This left an overall total of 1306 cases (mean age 52.32; 46.6% male sex) to be included in the analysis.

The clinical and demographic covariates for the whole cohort and stratified by HIV status are displayed in Table 1. The groups differed regarding the proportion of clinical and demographic covariates. The mean age was lower in the HIV-positive group (49.9 versus 52.8, $P = 0.002$), and the proportion of male sex was higher (76.6% versus 40.9%, $P < 0.001$). The proportion of patients with hypertension, type II diabetes, and dyslipidemia were significantly higher in the HIV-negative group ($P < 0.05$ in all). The proportion of current smokers was higher in the HIV-positive group (28.7% versus 18.8%, $P < 0.005$).

The overall prevalence of HS was 44.6% and was significantly higher in the HIV-negative group (46% versus 36.8%, $P = 0.018$). The rate of coronary calcification was similar between the 2 groups (38.4% in HIV-negative group versus 32.5% in HIV-positive group, $P = 0.128$). Within the HIV-positive group, 91.9% had HS quantified by CT.

Multivariate Analysis

In the multivariate model, including all clinically relevant demographic and clinical risk factors, HS was significantly associated with CVD in HIV-positive patients (OR: 3.13, 95% CI: 1.51 to 6.63, $P = 0.005$). The only other significant covariates associated with CVD were increasing age (OR: 1.15, 95% CI: 1.10 to 1.20, $P < 0.005$) and male sex (OR: 3.77, 95% CI: 1.37 to 11.69, $P = 0.014$ (Table 2). The associations of clinical covariates with CVD differed in the HIV-negative group. Current smoking (OR: 1.96, 95% CI: 1.37 to 2.81, $P < 0.005$) and dyslipidemia (OR: 1.66, 95% CI: 1.24 to 2.22 $P < 0.005$) along with increasing age and male sex were significantly associated with CVD. HS was not significantly associated with CVD in this group (OR: 1.08, 95%CI: 0.81 to 1.44, $P = 0.60$) (Table 3). The AUC for the LR was 0.841 (95% CI: 0.785 to 0.897) for the HIV-positive model and 0.796 (95% CI: 0.770 to 0.822) for the HIV-negative model. On removing HS from the model, the AUC dropped to 0.819 (95% CI: 0.758 to 0.881) for the HIV-positive model and 0.796 (95% CI: 0.770 to 0.822) for the HIV-negative model (Fig. 1). There was no statistically significant difference between either AUC (HIV-positive: 0.619, HIV-negative: 0.993, Wilcoxon test).

Sensitivity Analysis

For the HIV-positive model, age, HS, and male sex were the top 3 variables of importance, according to the mean decrease in Gini index. In the HIV-negative group, the top 3 variables of importance were age, male sex, and hypertension (Fig. 2). The mean AUC for the HIV-positive and HIV-negative models were 0.877 (95% CI: 0.755 to 0.959) and 0.828 (95% CI: 0.780 to 0.873), respectively. The LR models and the RF models were significantly different for both cohorts ($P < 0.001$, Wilcoxon test) (see Supplemental Digital Content, http://links.lww.com/QAI/B666).

DISCUSSION

In this retrospective analysis, we sought to assess the differences in the association of HS with CVD between HIV-positive and HIV-negative patients. The principal finding from this study is that HS is independently associated with

TABLE 1. Summary Statistics of the Cohort and Stratified by HIV Serostatus

	Overall	HIV-Negative	HIV-Positive	
n	1306	1097	209	*P*
Age, yrs, mean (SD)	52.32 (±12.00)	52.77 (±12.26)	49.92 (±10.22)	<0.005
Male sex, n (%)	609 (46.6)	449 (40.9)	160 (76.6)	<0.005
Current smoker (%)	266 (20.4)	206 (18.8)	60 (28.7)	<0.005
HTN (%)	375 (28.7)	342 (31.2)	33 (15.8)	<0.005
DMII (%)	124 (9.5)	113 (10.3)	11 (5.3)	0.032
Dyslipidemia (%)	389 (29.8)	374 (34.1)	15 (7.2)	<0.005
Statin (%)	343 (26.3)	304 (27.7)	39 (18.7)	0.008
Coronary calcium (%)	489 (37.4)	421 (38.4)	68 (32.5)	0.128
HS (%)	582 (44.6)	505 (46.0)	77 (36.8)	0.018
Obesity (%)	135 (10.3)	72 (6.6)	66 (31.2)	<0.005

DMII, type II diabetes; HTN, hypertension; HS, hepatosteatosis.

TABLE 2. Multivariate Analysis in HIV-Positive Patients for the Association of Coronary Calcification

	Odds Ratio (95% CI)	*P*
Age	1.15 (1.10 to 1.20)	<0.005*
Male sex	3.77 (1.37 to 11.69)	0.014*
Current smoker	2.14 (0.93 to 5.06)	0.077
HTN	0.58(0.19 to 1.67)	0.317
DMII	0.75 (0.14 to 3.45)	0.718
Dyslipidemia	2.89 (0.84 to 10.73)	0.097
HS	3.13 (1.51 to 6.63)	0.005*
Obesity	1.58 (0.70 to 3.56)	0.269

*Denotes significant association.
DMII, type II diabetes; HTN, hypertension; HS, hepatosteatosis.

TABLE 3. Multivariate Analysis in HIV-Negative Patients for the Association of Coronary Calcification

	Odds Ratio (95% CI)	*P*
Age	1.11 (1.09 to 1.13)	<0.005*
Male sex	2.97 (2.19 to 4.05)	<0.005*
Current smoker	1.96 (1.37 to 2.81)	<0.005*
HTN	1.39 (1.02 to 1.90)	0.04
DMII	1.14 (0.72 to 1.82)	0.58
Dyslipidemia	1.66 (1.24 to 2.22)	<0.005
HS	1.08 (0.81 to 1.44)	0.60
Obesity	0.95 (0.54 to 1.65)	0.87

*Denotes significant association.
DMII, type II diabetes; HTN, hypertension; HS, hepatosteatosis.

CVD in HIV-positive patients, whereas there was no significant association in HIV-negative patients. To our knowledge, our study is the first to directly compare the effect of HS on CVD in both HIV-positive and HIV-negative patients. The finding that HS was independently associated with CVD in HIV-positive patients but not in HIV-negative patients was confirmed in our sensitivity analysis.

Despite a higher proportion of HS in the HIV-negative group ($P = 0.018$) and similar rates of coronary calcification ($P = 0.128$), we found HS to be independently associated with CVD in the HIV-positive group (Table 2) but not in the HIV-negative group (Table 3) after adjusting for CVD risk factors. We also observed a significant association of the traditional risk factors of age and male sex with subclinical CVD. The association of HS and CVD in HIV-positive patients was assessed in previous analyses. However, there are no studies comparing HS and CVD in HIV-positive and HIV-negative groups. Kaplan et al[22] compared 232 HIV-positive patients with and without NAFLD and found that NAFLD, as assessed by ICD-9 codes, was independently associated with CVD (OR: 3.08, 95% CI: 1.37 to 6.94). Our HIV-positive patients were similar in age and proportions of male sex. However, the definition of CVD differed from this study because they used a broad composite, which included coronary artery disease, heart failure, peripheral vascular disease, stroke, transient ischemic attack, myocardial infarction, and revascularization. In our analysis, we assessed the association with subclinical CVD found on CT rather than hard clinical outcomes.

In a separate analysis, using a mainly male HIV-positive cohort, Crum-Cianflone et al[23] found that HS diagnosed on noncontrast CT was significantly associated with coronary calcification (OR: 3.8, $P < 0.01$). In a further analysis, Guaraldi et al[24] assessed HIV-positive patients and found no significant association with NAFLD and coronary calcium.

Studies assessing the impact of HS as an independent CVD risk factor in HIV-negative groups demonstrate conflicting results. In their meta-analysis, Kapuria et al[13] concluded that NAFLD was associated with increased prevalence of subclinical atherosclerosis (based largely on CAC score). Vanwagner et al[12] analyzed the association of NAFLD from CT scans, defined as liver attenuation <40 HU, and found no significant association with coronary calcium after adjustment for obesity. In this study, we found that HS was not independently associated with CVD in the HIV-negative group (OR 1.08, 95% CI: 0.81 to 1.44).

Current smoking, hypertension, type II diabetes, and dyslipidemia are established risk factors of CVD in both HIV-positive and HIV-negative groups. The relatively low incidence of these risk factors within this study makes it difficult to interpret the magnitude of effect. In the case of dyslipidemia, only 7.2% (n = 15) of the HIV-positive group had this risk factor documented. This is reflected in the wide CI produced by the multivariate analysis (95% CI: 0.85 to 10.58). Although these results did not show an association between traditional risk factors and CVD, the study was underpowered to demonstrate any association. The purpose of this retrospective analysis was to compare the associations of HS with CVD in the HIV-positive and HIV-negative groups. It was not designed to determine the impact of traditional risk factors.

In the sensitivity analysis, we used a RF algorithm to investigate the variables of importance in both HIV-positive and HIV-negative groups (Fig. 2). The benefit of using this technique in a sensitivity analysis is that it is not constrained by the same assumptions as LR and offers an alternative methodology to examine the results. In both groups, age was the most important variable. In the HIV-positive group, HS was the second most important variable, followed by dyslipidemia. In the HIV-negative group, HS was the fifth most important variable. This further illustrates the difference in the impact of HS as an independent risk factor between the HIV-positive and HIV-negative groups.

The RF models demonstrated good discriminatory ability and were statistically significantly superior to LR performed on the same testing data (see Supplemental Digital Content, http://links.lww.com/QAI/B666). The performance of each model is summarized in the box plots in Supplemental Digital Content, http://links.lww.com/QAI/B666. Although the RF models demonstrated superior discriminatory ability compared with LR models, they demonstrated similar results. The use of this contemporary alternative analysis increases the robustness of the finding that HS is significantly

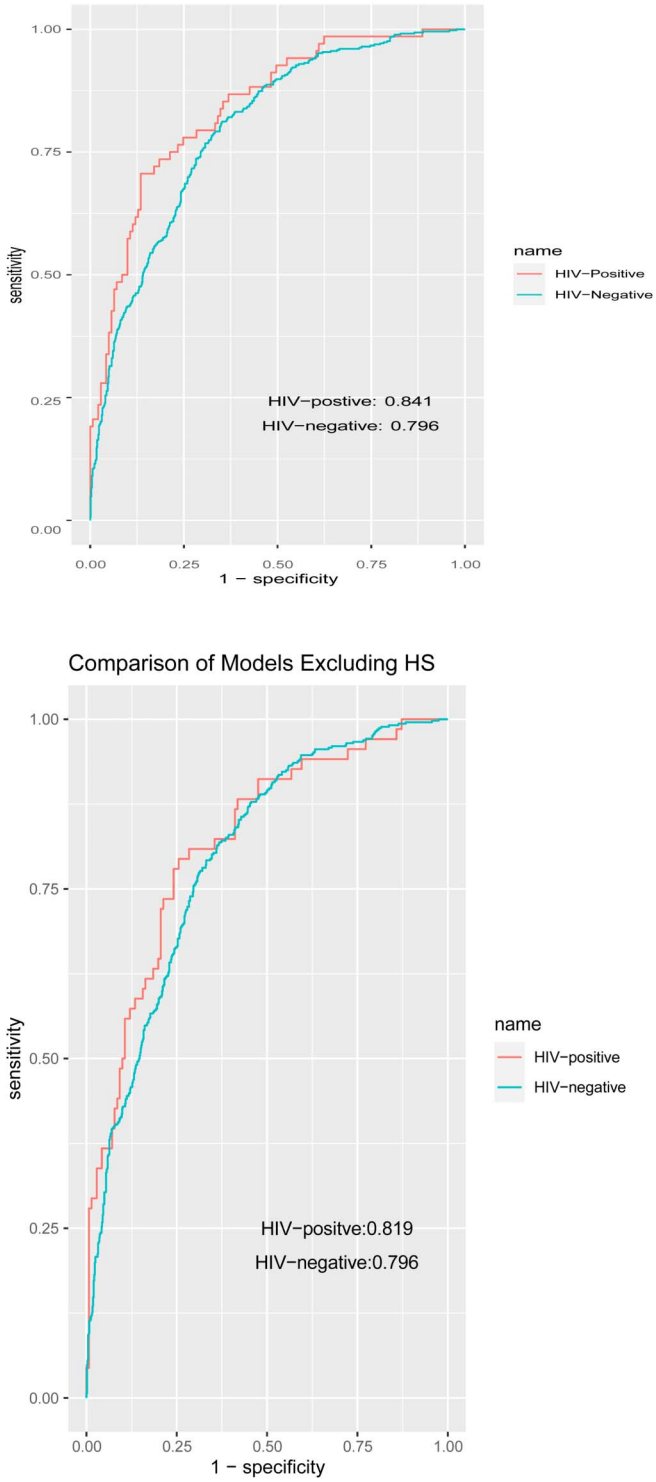

FIGURE 1. Comparison of HIV-positive and HIV-negative models including and excluding HS using receiver operator characteristic curves for the LR models. The first plot demonstrates the predictive ability between HIV-positive and HIV-negative groups. The second plot demonstrates the predictive ability of the models not including HS. full color online

associated with CVD in HIV-positive group and not associated in the HIV-negative group.

The association of HS as an independent risk factor may be attenuated by adjustment for other metabolic disease–related conditions such as diabetes, obesity, dyslipidemia, and hypertension. Our finding, showing that HS is an independent predictor of CVD in HIV-positive but not in HIV-negative group, suggests potential differences in the drivers of CVD between these 2 cohorts. HS that manifests in HIV-positive populations may represent a more severe adverse metabolic phenotype compared with that in non-HIV populations.

HS drives cardiovascular risk through increased atherogenic lipid profiles, inflammation, and insulin resistance. HIV-positive patients have been shown to have increased rates of lean adiposity compared with HIV-negative groups.[7] Ectopic fat deposition has also been shown to be associated with previous CVD events.[25] An individual's susceptibility to this process may also be derived from genetic factors.[26] The findings from this study further demonstrate the unique pathophysiological process underpinning the increased CVD risk seen in PLWHIV.

Limitations and Strengths

There were several limitations to our study. First, the way in which patients had coronary calcifications assessed in the HIV-positive group was based on, in some instances, the presence of a nondedicated CT scan. These CT scans had taken place historically for different indications. Although the assessment of coronary calcification using nondedicated thorax CT is recognized,[27] the assessment between groups was not homogenous. Second, by opportunistically selecting patients who had received thorax CT scans for alternative indications, we may have introduced selection bias into the study. Third, the HIV-negative group was a predefined group of patients with low to intermediate risk chest pain. This may affect the generalizability of this result. We did not adjust for HIV-related covariates, including antiretroviral medications. However, this study was designed to assess the differences between 2 different cohorts rather than determinants of CVD risk specific to HIV-positive patients. In addition, previous studies did not demonstrate any significant HIV-related associations with HS and CVD.[22]

Finally, we were not able to adjust for alcohol consumption or other secondary causes of HS (such as hepatitis C) in either group because of the retrospective design of the study. Although these influences are of significant interest, it is outside the scope of this retrospective study to assess their impact on the presence of HS. Crum-Cianflone et al performed a sensitivity analysis in which participants with significant alcohol consumption were excluded. This did not significantly alter their result.[23] Further prospective work is required to assess their impact on the presence of HS and CVD.

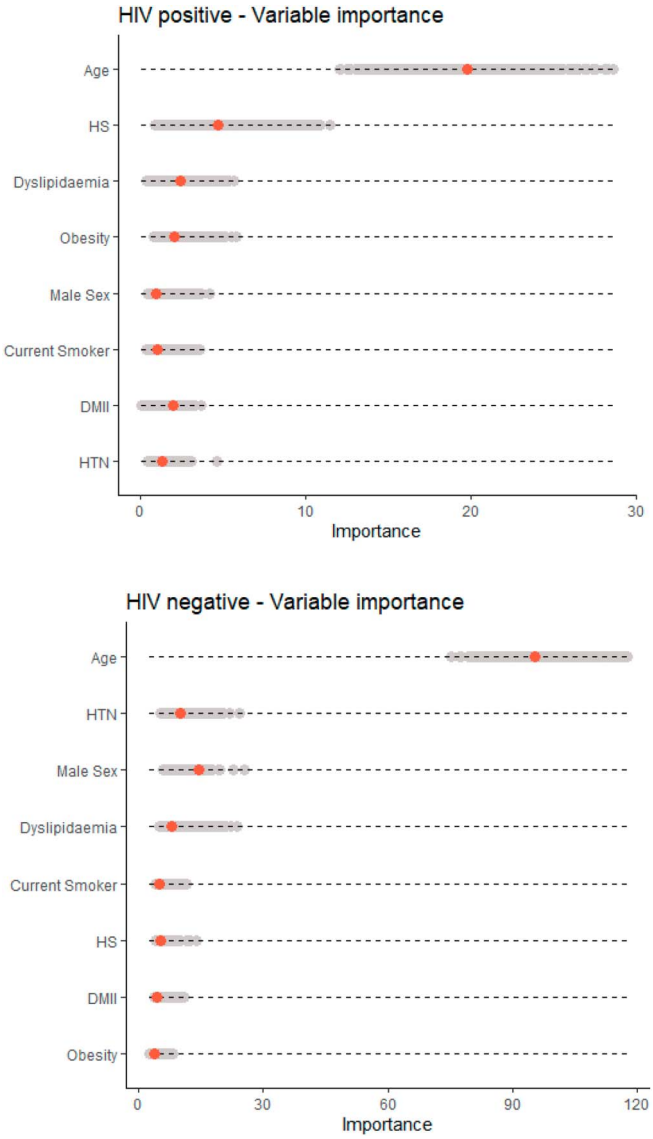

FIGURE 2. RF analysis of the variables of importance in HIV-positive and HIV-negative patients. Variables of importance given by mean decrease in Gini index. The shaded area (gray points) is the variable importance given by all models. The variables of importance of the model with the best AUC are highlighted in red. Variable abbreviations are the same as presented in Table 1. full color online

Despite these limitations, there were multiple strengths to our analysis. Both cohorts used in this comparison were extremely well characterized, and data used within this analysis were 100% complete. This study is also unique in the fact that it is the first to compare the impact of HS on CVD between HIV-positive and HIV-negative cohorts. We were able to confirm the validity of the result by using a RF algorithm in our sensitivity analysis. The broad agreement between LR models and RF models confirms the robustness of the result. This study was designed to be hypothesis generating rather than to show definitive causality. Future studies quantifying CVD risk, plaque burden, and homogenous assessment of HS and coronary calcium scores are required to further delineate this emerging field. These findings may have important clinical implications for the way in which CVD risk is quantified in HIV-positive patients.

In conclusion, in these well-characterized cohorts, we have demonstrated a significant difference in the impact of HS as an independent CVD predictor between the HIV-positive and HIV-negative groups. This may represent a unique metabolic process that drives the excess CVD risk seen in PLWHIV.

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