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BRIEF COMMUNICATION

Validation of Noninvasive Methods for Detecting Hepatic Steatosis in Patients With Human Immunodeficiency Virus Infection

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Nonalcoholic fatty liver disease (NAFLD) is common among patients with human immunodeficiency virus (HIV) infection; a reliable noninvasive method of detection is needed. We aimed to validate noninvasive means of identifying steatosis in HIV-positive patients. We performed a single-center retrospective study to validate the abilities of the liver fat score (LFS) and the lipid accumulation product (LAP) to detect hepatic steatosis in HIV-positive patients, compared with HIV-negative individuals (controls); NAFLD was confirmed by histology, and findings were compared with those from ultrasonography. These models then were validated in HIV-positive patients with NAFLD vs patients co-infected with HIV and hepatitis C virus (HCV) infection, without hepatic steatosis. LFS identified hepatic steatosis in HIV-positive subjects, compared with controls, with an area under the receiver operating curve value of 0.971 ± 0.027 (95% confidence interval, 0.91–1.000). At a cut-off value of -0.945, the LFS identified patients with steatosis with 100% sensitivity and 84% specificity. At a cut-off of value of -0.234, the LFS differentiated between HIV-positive subjects with NAFLD and patients co-infected with HIV and HCV with 100% sensitivity and 74% specificity. LAP scores ≥38 identified HIV-positive patients with steatosis with 89% sensitivity and 83% specificity. LAP scores ≥42 differentiated between HIV-positive subjects with steatosis and patients co-infected with HIV and HCV with 89% specificity and 70% sensitivity. We validated the accuracy of LFS and LAP in detecting hepatic steatosis in HIV-positive patients.

Keywords: Liver Disease; Diagnosis; Prognostic Factor; Test.

Human immunodeficiency virus (HIV) infection affects 34 million globally. Improvements in highly active antiretroviral therapy (HAART) has shifted the mortality related to acquired immune deficiency syndrome to liver-related diseases,[1] which have become a leading cause of hospitalization and death in HIV-infected patients.[2] Nonalcoholic fatty liver disease (NAFLD) is emerging as an important cause of chronic liver disease in HIV patients.[3] NAFLD is associated closely with metabolic syndrome, particularly insulin resistance,[4] and insulin resistance associated with HAART often can predispose HIV patients to NAFLD.[5] The estimated prevalence of NAFLD in HIV patients has been reported to be even greater than in the general population,[3,6] and a significant proportion of those with NAFLD had nonalcoholic steatohepatitis associated with advanced fibrosis, highlighting the importance of identifying these individuals early in their disease course.[7]

The gold standard for diagnosing NAFLD is a liver biopsy. Although many noninvasive models to identify fibrosis in those with viral hepatitis have been developed,[8] few have focused on NAFLD.[9] Noninvasive assessment of steatosis using radiographic imaging is costly and might not be as accurate in individuals with less than 30% steatosis. The liver fat score (LFS) and the lipid accumulation product (LAP) are noninvasive models that use readily available clinical parameters to predict steatosis, but have not been validated in patients with HIV.[10,11] Therefore, the aim of the current study was to validate LFS and LAP histologically in HIV patients with NAFLD.

Materials and Methods

This was a single-center retrospective study that validated the use of LFS and LAP in predicting the presence of hepatic steatosis in HIV-positive patients. The study populations included HIV-positive patients who either had steatosis or were co-infected with HCV. The first cohort consisted of HIV-positive patients without HCV with at least 5% steatosis on a liver biopsy.[12] The second cohort consisted of HIV–HCV patients. The choice of this cohort as a control group was based primarily on the following: (1) HIV subjects on HAART therapy may develop mild steatosis that can be missed on liver ultrasound and therefore a histologic assessment would improve the robustness of the model, and (2) patients with HIV may have competing etiologies of increased liver

Abbreviations used in this paper: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LAP, lipid accumulation product; LFS, liver fat score; NAFLD, nonalcoholic fatty liver disease; ROC, receiver-operating curve.

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enzyme levels (ie, HCV) and therefore it is important for the model to be able to distinguish between NAFLD and other causes of increased liver enzyme levels. The second cohort was subdivided further into patients with or without concurrent steatosis (>5% liver fat content). Finally, the HIV-negative control group consisted of subjects with no known liver disease, normal serum alanine aminotransferase levels,[13] and absence of steatosis on ultrasound. Hepatic steatosis was modeled noninvasively using LFS and LAP as described previously.[10,11] We validated these models in an HIV-positive cohort in the following 3 stages. In the first stage, the receiver-operating curve (ROC) of the LFS and LAP was used to identify optimal cut-off points for predicting steatosis using the Youden Index in the HIV-positive cohort with NAFLD compared with HIV-negative controls. Because the models rely on parameters that can be abnormal in patients with any liver disease (ie, serum aminotransferase levels), these models subsequently were used in stage 2 to determine if they could be used to differentiate between HIV-positive patients with NAFLD and HIV–HCV patients without steatosis. The ROC and Youden Index were used to redefine the optimal cut-off level. Finally, in stage 3 we determined if these models could be used to identify the presence of steatosis in a larger cohort of HIV–HCV patients.

Results

The 4 cohorts consisted of HIV-negative controls (n = 19), HIV-positive patients with NAFLD (n = 9), HIV–HCV patients with no steatosis (n = 53), and HIV–HCV patients with at least 5% hepatic steatosis on a liver biopsy (n = 18). The clinical characteristics of the cohorts are summarized in Table 1. Genotype 3 was more common in HIV–HCV patients with steatosis than in those without steatosis (13% vs 2%; $P < .001$).

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In stage 1, the ROC was 0.971 ± 0.027 (95% confidence interval [CI], 91.8–1.000) for LFS in predicting >5% steatosis (Figure 1). The optimal cut-off point was determined to be -0.945. A value greater than -0.945 predicted underlying steatosis in HIV-positive patients with 100% sensitivity and 84% specificity. The cut-off value of -0.945 then was applied to see how well the LFS could predict NAFLD in HIV-positive compared with HIV–HCV patients without steatosis. Although the sensitivity remained 100%, the specificity decreased from 84% to 53%.

To improve the accuracy of the LFS in identifying HIV-positive patients with NAFLD compared with HIV–HCV patients, the Youden index was reapplied to determine the optimal cut-off level between HIV-positive subjects with underlying steatosis and those with HIV–HCV but no histologic evidence of steatosis (stage 2). The ROC was 0.923 ± 0.038 (95% CI, 0.848–0.998), and the optimal cut-off value was determined to be -0.234 (Figure 2). An LFS of greater than -0.234 had 100% sensitivity and 74% specificity in predicting NAFLD in HIV patients compared with HIV–HCV patients. Reapplying the new cut-off value of -0.234, the LFS was 100% sensitive and 84% specific in identifying HIV patients with NAFLD compared with controls. Therefore,

Table 1. Baseline Clinical Characteristics in the 4 Cohorts

	Controls	HIV with steatosis	HIV HCV	HIV HCV with steatosis
N	19	9	53	18
Age, *y*	33.1 ± 12.6	46.8 ± 9.5	48.7 ± 8.5	47 ± 8.5
Body mass index	25.6 ± 4.0	31.1 ± 8.7	24.7 ± 7.0	28.0 ± 3.5
Sex, % male	58	77	76	78
Ethnicity, % cohort				
White	58	67	9.4	39
Black	5	33	91	61
Other	37	–	–	–
ALT level, *IU/L*	18 ± 13	109 ± 51	49 ± 19	75 ± 22
AST level, *IU/L*	20 ± 12	87 ± 49	52 ± 24	77 ± 32
HCV genotype, % cohort				
1	–	–	92	88
2	–	–	6	0
3	–	–	2	13
HIV viral load, % cohort				
<400	–	100	78	80
>400	–	0	22	20
CD4	–	605 ± 408	460 ± 337	621 ± 379
CD4, %	–	26.3 ± 14.4	24.7 ± 10.9	30.5 ± 13.5
CD8	–	815 ± 164	812 ± 431	783 ± 503
CD8, %	–	50 ± 24.6	44.5 ± 14.6	40.1 ± 16.7