Fibroblast growth factor 21 is independently associated with severe hepatic steatosis in non-obese HIV-infected patients

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Title: Fibroblast Growth Factor 21 is independently associated with severe hepatic steatosis in non-obese HIV-infected patients

Short title: FGF-21 and hepatic steatosis in HIV

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Abbreviations:

FGF-21, fibroblast growth factor 21; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; YGT, γ-glutamyl transferase; HIV, human deficiency virus; INR, international normalized ratio; MELD, model for end-stage liver disease; c-index, concordance index; CAP, controlled attenuation parameter; AUC, area under the curve; ROC, receiver operating characteristics; HCV, hepatitis C virus; HBV, hepatitis B virus.

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Author contributions:

MP, ND: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis

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RM, RS, JB, LD, AP: acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis

CSZ, JCW, CB, JKR: interpretation of data, critical revision of the manuscript regarding important intellectual content

JT: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript regarding important intellectual content, funding recipient, administrative, technical and material support, study supervision

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ABSTRACT

BACKGROUND: Severe hepatic steatosis shows a high prevalence and contributes to morbidity and mortality in human immunodeficiency virus (HIV) infected patients. Known risk factors include obesity, dyslipidemia and features of metabolic syndrome. Fibroblast growth factor 21 (FGF-21) is involved with hepatic glucose and lipid metabolism. This study aimed to evaluate FGF-21 as a biomarker for severe hepatic steatosis in non-obese HIV-infected patients.

METHODS: This is a prospective, cross-sectional, monocentric study including HIV-infected out-patients. Hepatic steatosis was measured via controlled attenuation parameter (CAP) using FibroScan 502 touch (ECHOSENS, France). Severe hepatic steatosis was defined at CAP ≥253 dB/m. Peripheral blood samples were collected and plasma was analysed for FGF-21. Demographic and clinical characteristics were collected from patient’s health records.

RESULTS: In total, 73 non-obese HIV-monoinfected patients were included in this study. Prevalence of severe hepatic steatosis was 41%. Patients with severe hepatic steatosis showed significantly higher levels of FGF-21. Univariate analysis revealed
FGF-21, BMI, hyperlipidemia, ALT levels and arterial hypertension as significant, while multivariate analysis showed only FGF-21, arterial hypertension and ALT levels as significant independent risk factors for severe hepatic steatosis.

CONCLUSION: This study presents FGF-21 as an independent and stronger predictor of severe hepatic steatosis than blood lipids in HIV-infected patients. Moreover, arterial hypertension and ALT levels predict severe steatosis even in non-obese HIV-monoinfected patients. Furthermore, this study supports existing metabolic risk factors and expands them to non-obese HIV-infected patients.

LAY SUMMARY: Fatty liver disease occurs frequently in patients with HIV infection. This study shows that Fibroblast Growth Factor 21 (FGF-21) is an independent and stronger predictor of severe fatty liver than blood lipids in HIV-infected patients.

Key words: HIV, FGF-21, liver, steatosis, BMI, dyslipidemia, hyperlipidemia, fibroscan, CAP, NAFLD, NASH

INTRODUCTION

Patients with human immunodeficiency virus (HIV) infection nowadays can be treated effectively with combined antiretroviral therapy (cART), which can efficiently suppress virus replication and improve survival. However, hepatic steatosis is a growing health care burden not only in the general population, but especially in the high prevalence risk group of HIV-infected patients. In some patients, hepatic steatosis can progress to non-alcoholic steatohepatitis (NASH), a condition including inflammation and fibrosis, contributing to morbidity and mortality. In a recent meta-analysis prevalence of non-alcoholic fatty liver disease (NAFLD) in HIV-infected patients was 35%, while prevalence of NASH was 42%. Up to 22% of hepatocellular carcinoma (HCC) as life-threatening complication are now attributed to NASH.

HIV infection itself is implicated in the development of metabolic disorders. The degree of HIV viremia has been associated with hypertriglyceridemia, dyslipidemia, and insulin resistance in patients with untreated HIV and HIV-associated
mitochondrial damage has been implicated in systemic immune activation in the pathogenesis of diabetes. Moreover, HIV promotes hepatic steatosis by interacting with sterol regulatory element-binding-protein 1 and peroxisome proliferator-activated receptor γ, which are key regulators of lipogenesis and insulin signaling. Finally, in a study of 222 patients with HIV–HCV co-infection, which involved the assessment of paired liver biopsy samples to identify risk factors for steatosis progression, cumulative exposure to ART between biopsy samples and high CD4+ T-cell counts were associated with reduced progression of steatosis. Interestingly, metabolic disorders such as obesity, dyslipidemia and diabetes mellitus have been published as independent risk factors for hepatic steatosis in HIV-infected patients, while HIV-related factors (except for co-infection with certain hepatitis C virus (HCV) genotypes) were not. However, metabolic disorders and dyslipidemia are risk factors for hepatic steatosis in the general population as well. Therefore, identifying biomarkers for hepatic steatosis in HIV-infected patients independent of metabolic disorders is an unmet need.

Fibroblast growth factor 21 (FGF-21) is an important regulator of hepatic lipid and glucose metabolism. In a large multi-ethnic cohort, elevated FGF-21 levels have been associated with metabolic syndrome. In animal models, FGF-21 has been shown to beneficially influence hepatic lipogenesis and fatty acid oxidation in hepatocytes. In fact, it is currently investigated as a therapeutic target in non-HIV patients. Besides that, FGF-21 serum levels are regarded as marker of mitochondrial dysfunction and have been used as a biomarker in extrahepatic diseases. In patients with advanced liver cirrhosis FGF-21 has been reported as a predictor of acute-on-chronic liver failure (ACLF), while in HIV-1-infected patients, it has been associated with lipodystrophy.

In this study, we aimed to evaluate FGF-21 as a biomarker for hepatic steatosis in non-obese patients with HIV-infection.
MATERIALS AND METHODS

For this cross-sectional prospective study HIV-infected patients from the Infectious Diseases out-patient clinic at University of Bonn were identified. Patients with confirmed HIV infection, self reported alcohol intake of 30g/day (male) or 20g/day (female) or less were included. Exclusion criteria were absence of serum samples to analyze FGF-21, unreliable controlled attenuation parameter (CAP) measurements, body-mass-index (BMI) ≥ 30 and co-infection with HCV (detected by anti-HCV antibody or viremia) and/or HBV (detected by HBs antigen or viremia). To study the association of FGF-21 in HIV-positive patients without obesity as a well-established confounder, those with BMI ≥ 30 were excluded from analysis.

Data acquisition

Biochemical blood analyses were performed using standard tests including serum cholesterol, low-density and high-density lipoprotein (LDL, HDL), triglycerides, aminotransferases, bilirubin and creatinine. Demographic and clinical characteristics were collected from patient’s health records at our institution. Diagnosis of hyperlipidemia, diabetes mellitus and arterial hypertension was made according to medical history, medication use and/or laboratory assessment at time of inclusion. The local ethics committee of the University of Bonn approved the study (279/14), and all patients agreed and signed an informed consent in accordance with the Helsinki Declaration for the procedures they underwent.

Hepatic steatosis measurement

CAP measurements were performed using FibroScan 502 touch (ECHOSENS, France) by experienced and trained operators. Included patients had to be in fasting condition at least 3 hours from the last meal. According to standard operating protocol, examinations with at least ten valid measurements, interquartile range (IQR/M) lower than 30% of the median value and successful acquisition rate of more than 60% were approved for analysis. Patients with less than ten valid measurements were excluded. Since in this study only non-obese patients were included, skin-capsula distance was <2.5 cm. Therefore, all patients were studied with the M probe.
Hepatic steatosis was defined by CAP as follows: no steatosis (S0) CAP ≤ 215 dB/m, mild (S1) steatosis CAP 216 – 252 dB/m, sever hepatic steatosis was defined by CAP 253 – 296 dB/m (S2) and CAP > 296 dB/m (S3).

Measurement of fibroblast growth factor 21 (FGF-21)

On the day of inclusion, a sample of peripheral blood was collected (in fasting condition) in tubes containing ethylene diamine tetraacetic acid, which was immediately centrifuged; the obtained supernatant was stored at –80°C. Levels of FGF-21 were analyzed in the Laboratory for Liver Fibrosis and Portal Hypertension at the University Hospital Bonn using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's guidelines (R&D Systems Inc., Minneapolis, MN). All tests were run in duplicate.

Statistical Analysis

Demographic, clinical, and laboratory characteristics stratified by severity of HS were compared. Differences in continuous variables, expressed as median (range) using nonparametric Mann–Whitney test. Categorical variables, expressed as absolute frequencies and percentages, were compared using Pearson chi squared test. Area under the receiver operating characteristic curves (AUROCs) were constructed to obtain cutoffs. Uni- and multivariable analyses were performed using logistic regression models. P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS 24 (IBM, Armonk, New York, USA). Data was plotted using GraphPad Prism v.6 (Graph Pad Software, La Jolla, CA, USA).

RESULTS

Patient characteristics

A total of 246 patients with HIV-infection fulfilling inclusion criteria were identified. In 118 patients no serum samples were available, 14 patients had BMI > 30, 25 patients had co-infection (13 HCV, 11 HBV and 1 HBV/HCV co-infection), in 14 patients CAP measurements did not fulfill protocol criteria described above, 2
patients were excluded for decompensation (ascites). After exclusion, a total of 73 patients were included in the analysis (figure 1a).

The patient cohort included 64 men, median age was 49 (24-74) years with a median BMI of 24 (18-30). As a criteria of metabolic syndrome diabetes mellitus was present in 4 (5%), arterial hypertension in 16 (22%) patients. 25 patients (34%) were smokers.

Fibroscan showed that most patients (65, 89%) did not have liver fibrosis with a median E 5.3 kPa (2.0-9.5). 43 patients (59%) had no or mild hepatic steatosis, the remaining 30 (41%) patients showed severe hepatic steatosis.

Ultrasound data was collected for 42 patients. In total, 64% of patients had sonographic signs of hepatic steatosis. Less than half (46%) of the patients with S0-1 steatosis and the majority (89%) of patients with S2-3 showed sonographic signs of hepatic steatosis (table 1).

HIV-related general characteristics such as viral load, CD4-positive cell count and percentage of patients under cART were not significantly different between no/mild and severe steatosis patients (table 1).

Laboratory work up showed slightly elevated median cholesterol (202 mg/dl (72-291)) and triglyceride (192 mg/dl (28-5501)).

The general characteristics of the study population are summarized in table 1.

**Fibroblast Growth Factor 21 and general characteristics in hepatic steatosis**

The median levels of FGF-21 were 49.3 pg/ml in the whole cohort. Importantly, patients with severe hepatic steatosis showed significantly higher levels of FGF-21 compared to patients with no/mild steatosis (figure 1b). Moreover, patients with severe hepatic steatosis displayed significantly higher BMI, weight and serum cholesterol as well as ALT levels (table 1).

**Fibroblast Growth Factor 21 and prediction of severe hepatic steatosis**

To determine a cut-off for FGF-21 to predict severe hepatic steatosis we performed AUROC analysis, which revealed 51 pg/ml as the optimal cut-off (AUC 0.649, p=0.031, 95%-CI 0.517-0.782) (figure 1c). Next, we grouped the patients according
to the determined cut-off for FGF-21. Using this stratification, we could predict severe hepatic steatosis with a sensitivity of 67%, specificity of 63%, positive predictive value of 56%, negative predictive value of 73%, resulting in a diagnostic accuracy of 64% (c-index 0.649) (table 2).

We used logistic regression model to assess significant confounders to severe hepatic steatosis. In univariate analysis FGF-21, cholesterol, BMI, arterial hypertension and alanine aminotransferase (ALT) were predictors of severe hepatic steatosis. Including all variables with p<0.1 in multivariate analysis showed only FGF-21, arterial hypertension and ALT as independent predictors of severe hepatic steatosis (table 3).

**DISCUSSION**

This study demonstrates, that FGF-21 is independently associated with severe hepatic steatosis in non-obese HIV-infected patients.

In our cohort, we can confirm a high prevalence of severe hepatic steatosis of 41% in HIV patients compared to the general population, where NAFLD affects 25% of the population. This is in line with many previous studies and underlines the robustness of our data.

Importantly, risk factors for hepatic steatosis are similar in HIV-infected patients and general population, namely obesity, dyslipidemia and features of metabolic syndrome. However, co-infection with certain genotypes of HCV are reported to cause hepatic steatosis. In this study, we minimized potential general, not HIV-related confounders by exclusion of obese and co-infected patients to analyse only the effect of HIV on hepatic steatosis.

In this cohort, metabolic factors such as BMI, arterial hypertension and hypercholesterinemia were significantly associated with severe hepatic steatosis. Additionally, ALT levels have also been shown to be associated with CAP measurement. These results further support previously reported cohorts. Although dyslipidemia as a well-known risk factor is significantly associated with severe hepatic steatosis in our cohort, only FGF-21, arterial hypertension and ALT levels were independent predictors in multivariate analysis. This major original
finding suggests, that circulating FGF-21 is a stronger risk factor compared to dyslipidemia. This result seems reliable as FGF-21 has been shown to be associated with liver injury independent of the etiology and has even been positively associated with liver fat in HIV patients\textsuperscript{26,36}. Interestingly, in non-HIV patients FGF-21 has been shown to be protective for NASH and recombinant FGF-21 is being studied therapeutically\textsuperscript{21}. However, our study supports existing reports, that in HIV patients higher levels of FGF-21 are associated with impaired lipid metabolism\textsuperscript{27}. These results suggest, that in HIV patients FGF-21 plays a different pathophysiological role, which should be studied in future studies.

Transient elastography as a non-invasive method is influenced by a number of factors such as hepatic congestion in patients with heart failure and cholestasis, both conditions which were not reported in this cohort\textsuperscript{37,38}. Moreover, transient elastography is influenced by hepatic inflammation and given the association with FGF-21 in our study underlying hepatic inflammation is possibly involved\textsuperscript{39,40}.

This study has several limitations, mainly its cross-sectional design, which limits the ability to evaluate the dynamics of FGF-21 and other risk factors of severe hepatic steatosis over a period of time. Moreover, this study represents a real-world patient cohort without randomization. Homeostasis model assessment index to quantify insulin resistance and dual-energy X-ray absorptiometry or magnetic resonance tomography imaging to quantify body composition\textsuperscript{41} were not available. Liver biopsy as the gold standard for the assessment of hepatic steatosis was not performed. However, the acceptability and potential risks of biopsy make its application difficult for a large study population.

Alcohol consumption as well as anabolic use was self-reported by the patients, for example, binge drinking behavior may have been underestimated. PNPLA3 genotype as a major determinant for NAFLD as well as other genetic disorders (e.g. hemochromatosis, alpha1-antitrypsin deficiency) were not assessed in this study, which is a limitation of our study. Finally, the lack of a validation cohort limits this study’s generalizability.
CONCLUSION

In conclusion, this study presents FGF-21, arterial hypertension and ALT as independent predictors of severe hepatic steatosis in a cohort non-obese HIV-monoinfected patients. The results of this study suggest circulating FGF-21 as a stronger biomarker than blood lipids. Moreover, this study supports existing metabolic risk factors and expands them to non-obese HIV-infected patients.

Literature


**Figure legends**

**Figure 1:**

(A) shows patient selection and exclusion according to the study’s exclusion criteria. (B) shows levels of circulating FGF-21 stratified for severe hepatic steatosis (mean ± SEM). Patients with severe hepatic steatosis showed significantly higher levels compared to patients with no/mild hepatic steatosis. (C) shows AUROC analysis for FGF-21 with sever hepatic steatosis as endpoint. Figure detail shows area under curve (AUC), significance level (p) and 95%-confidence interval (95%-CI). *p < 0.05.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>No/Mild Steatosis (S0/1)</th>
<th>Severe Steatosis (S2/3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=73</td>
<td>n=43</td>
<td>n=30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49(24-74)</td>
<td>49(24-74)</td>
<td>49(25-74)</td>
</tr>
<tr>
<td>Sex male / female</td>
<td>64/9 (88/12%)</td>
<td>35/8 (81/19%)</td>
<td>29/1 (97/3%)</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>178(158-200)</td>
<td>178(158-200)</td>
<td>178(167-198)</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>78(51-99)</td>
<td>74(51-99)</td>
<td>83(57-98)**</td>
</tr>
<tr>
<td>BMI</td>
<td>24(18-30)</td>
<td>23(18-30)</td>
<td>25(19-30)**</td>
</tr>
<tr>
<td>FGF-21</td>
<td>49.3(1.1-545.3)</td>
<td>35.1(1.1-343.4)</td>
<td>75.5(1.3-545.3)**</td>
</tr>
<tr>
<td><strong>FGF-21</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (5%)</td>
<td>1 (2%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>16 (22%)</td>
<td>4 (9%)</td>
<td>12 (40%)**</td>
</tr>
<tr>
<td>Smoking</td>
<td>25 (34%)</td>
<td>15 (35%)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Statins Medication</td>
<td>4 (5%)</td>
<td>3 (7%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>E [kPa]</td>
<td>5.3(2.0-9.5)</td>
<td>4.8(2.0-9.5)</td>
<td>5.4(3.5-9.3)</td>
</tr>
<tr>
<td>F0/F2/F3/F4</td>
<td>65/8/0/0 (89/11/0/0%)</td>
<td>39/4/0/0 (90/10/0/0%)</td>
<td>26/4/0/0 (87/13/0/0%)</td>
</tr>
<tr>
<td>CAP [dB/m]</td>
<td>240(100-367)</td>
<td>211(100-251)</td>
<td>295(257-367)*****</td>
</tr>
<tr>
<td>S0/S1/S2/S3</td>
<td>24/19/16/14 (33/26/22/19%)</td>
<td>24/19/0/0 (56/44/0/0%)</td>
<td>0/0/16/14 (0/0/53/47%)</td>
</tr>
<tr>
<td>Ultrasound no / steatosis a</td>
<td>15/27 (36/64%)</td>
<td>13/11 (54/46%)</td>
<td>2/16 (11/89%)**</td>
</tr>
<tr>
<td>Creatinine [mg/dl]</td>
<td>1.0(0.6-1.6)</td>
<td>0.9(0.7-1.6)</td>
<td>1.0(0.6-1.6)</td>
</tr>
<tr>
<td>Bilirubin [mg/dl]</td>
<td>0.4(0.2-16.0)</td>
<td>0.4(0.2-16.0)</td>
<td>0.4(0.2-1.4)</td>
</tr>
<tr>
<td>AST [U/l]</td>
<td>23(13-145)</td>
<td>22(13-52)</td>
<td>27(13-145)</td>
</tr>
<tr>
<td>ALT [U/l]</td>
<td>33(8-149)</td>
<td>28(8-90)</td>
<td>38(23-149)*</td>
</tr>
<tr>
<td>gGT [U/l]</td>
<td>44(21-9273)</td>
<td>37(21-9273)</td>
<td>59(23-568)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>192(28-5501)</td>
<td>150(28-5501)</td>
<td>257(96-1199)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>202(72-291)</td>
<td>193(72-288)</td>
<td>211(124-291)*</td>
</tr>
<tr>
<td>HDL</td>
<td>43(18-92)</td>
<td>46(22-77)</td>
<td>40(18-92)</td>
</tr>
<tr>
<td>LDL</td>
<td>118(42-210)</td>
<td>118(42-210)</td>
<td>122(57-195)</td>
</tr>
<tr>
<td>WBC [g/l]</td>
<td>5.8(2.5-13.6)</td>
<td>5.5(2.5-11.5)</td>
<td>6.2(2.9-13.6)</td>
</tr>
<tr>
<td>Hemoglobin [g/dl]</td>
<td>15.0(8.7-17.7)</td>
<td>14.9(8.7-17.7)</td>
<td>15.0(13.7-16.5)</td>
</tr>
<tr>
<td>Platelets [x10⁹/L]</td>
<td>223(78-455)</td>
<td>225(78-455)</td>
<td>221(110-317)</td>
</tr>
<tr>
<td>CD4 cell count / µl</td>
<td>563(46-1478)</td>
<td>509(46-1478)</td>
<td>676(184-967)</td>
</tr>
<tr>
<td>HIV viral load [copies / ml]</td>
<td>0(0-104071)</td>
<td>0(0-104071)</td>
<td>0(0-43006)</td>
</tr>
</tbody>
</table>

S0:<215 S1:216-252 S2:253-296 S3:>292

**/*** p< 0.05/0.01/0.001

* data of 42 patients available

Table 1. General characteristics of study population.

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Table 2. Diagnostic performance of FGF-21 for severe liver steatosis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>c-index</th>
<th>Sensitivity [%]</th>
<th>Specificity [%]</th>
<th>Positive Predictive Value [%]</th>
<th>Negative Predictive Value [%]</th>
<th>Diagnostic Accuracy [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF-21</td>
<td>0.649</td>
<td>66.7</td>
<td>62.8</td>
<td>55.6</td>
<td>73.0</td>
<td>64.4</td>
</tr>
</tbody>
</table>

Table 3. Uni- and multivariate binary logistic regression analysis with severe liver steatosis (S2-3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>univariate binary logistic regression</th>
<th>multivariate binary logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
<td>HR</td>
</tr>
<tr>
<td>age</td>
<td>0.632</td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>FGF-21</td>
<td>0.005</td>
<td>1.301</td>
</tr>
<tr>
<td>BMI</td>
<td>0.156</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.005</td>
<td>6.500</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.028</td>
<td>1.039</td>
</tr>
<tr>
<td>ALT</td>
<td>0.642</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.035</td>
<td>1.012</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.035</td>
<td>1.012</td>
</tr>
</tbody>
</table>

*Italic* - Inclusion in multivariate analysis; *Bold* - significant in multivariate analysis
246 pt with HIV infection

118 pt w/o serum sample

128 HIV positive pt with serum available

14 pt BMI ≥ 30

114 non-obese HIV positive pt

25 pt with co-infection
- 13 HCV / 11 HBV
- 1 HCV+HBV

89 non-obese HIV monoinfected pt

14 pt w/o valid CAP measurement

75 non-obese HIV monoinfected pt with CAP available

2 pt with decompensated cirrhosis

73 non-obese, non-cirrhotic HIV monoinfected pt with CAP available
AUROC analysis for FGF-21 with severe steatosis as endpoint

51.4 pg/ml

AUC 0.649  p 0.031  95% CI 0.517-0.782