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Advanced Liver Fibrosis and the Metabolic Syndrome in a Primary Care Setting

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Abstract

Aims: The Fibrosis-4 Index (FIB-4) and NAFLD fibrosis score (NFS) are non-invasive and accessible methods for assessing advanced liver fibrosis risk in primary care. We evaluated the distribution of FIB-4 and NFS scores in primary care patients with clinical signals for non-alcoholic fatty liver disease (NAFLD).

Materials and Methods: This retrospective cohort study of electronic record data between 2007–2018 included adults with at least one abnormal aminotransferase and no known (non-NAFLD) liver disease. We calculated patient-level FIB-4 and NFS scores, the proportion of patients with mean values exceeding advanced fibrosis thresholds (indeterminate risk: FIB-4>1.3, NFS>-1.455; high-risk: FIB-4>2.67, NFS>0.676), and the proportion of patients with a NAFLD ICD-9/10 code. Logistic regression models evaluated the associations of metabolic syndrome components with elevated FIB-4 and NFS scores.

Results: The cohort included 6,506 patients with a median of 6 (IQR: 3–13) FIB-4 and NFS scores per patient. Of these patients, 81% had at least 2 components of metabolic syndrome, 29% had mean FIB-4 and NFS scores for indeterminate fibrosis risk, and 11% had either mean FIB-4 or NFS scores exceeding the high advanced fibrosis risk thresholds. Regression models identified associations of low HDL, hyperglycemia, Black race, and male gender with high-risk FIB-4 and NFS values. Only 5% of patients had existing diagnoses for NAFLD identified.

Conclusions: Many primary care patients have FIB-4 and NFS scores concerning for advanced fibrosis, but rarely a diagnosis of NAFLD. Elevated FIB-4 and NFS scores may provide signals for further clinical evaluation of liver disease in primary care settings.

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Author Contributions

All named authors contributed to the study design, interpretation of data, writing and editing of the manuscript, and the decision to submit. Ms. Zhang, Mr. Marsden, and Dr. Schreiner performed the data collection. Ms. Zhang, Ms. Livingston, Dr. Durkalski-Mauldin, Dr. Mauldin, and Dr. Schreiner performed the analyses.

IRB Approval

This study was approved by the Interval Review Board at the Medical University of South Carolina prior to data collection.

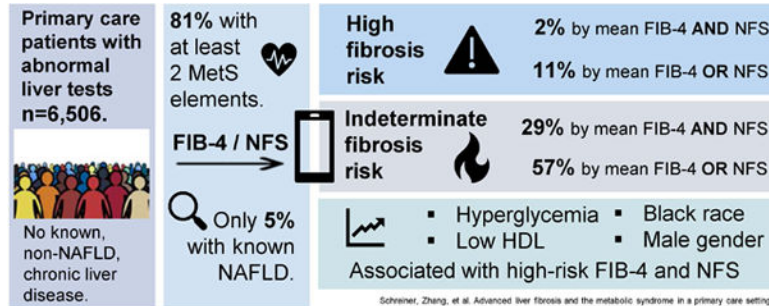
Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflict of Interests

All authors report no conflicts of interest with this work.

Graphical Abstract



Keywords

non-alcoholic fatty liver disease; non-invasive testing; fibrosis; cirrhosis; hepatology; FIB-4; NFS

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects an estimated 25% of the global population, and is a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation.^{1–5} NAFLD is associated with obesity, diabetes mellitus, hypertension, and dyslipidemia.^{1,5–7} More than just a manifestation metabolic syndrome (MetS), recent evidence suggests NAFLD increases the incident risk of MetS, diabetes, and cardiovascular disease.^{8–10} Despite the close relationship to these primary care conditions, NAFLD is underdiagnosed in primary care.^{11–16} Broad screening recommendations for at-risk patients are conflicting, but multiple guidelines address the importance of NAFLD detection in patients with abnormal liver tests (with NAFLD the most common cause of aminotransferase abnormality) and those with diabetes.^{1,5,17–22}

Fibrosis is the result of advanced NAFLD liver injury and accurate identification is critical, because fibrosis itself predicts adverse outcomes.^{16,23,24} The prevalence of NAFLD-associated fibrosis has surged, with a more than 2-fold increase over the past 2 decades, and is associated with increased mortality, liver cancer, and liver transplantation.^{25,26} While liver biopsy is the best method for detecting fibrosis, its cost and invasiveness limit its utility for such a large population.²⁷ Measurement of liver stiffness (i.e. with transient elastography) has proven useful in this regard, but the familiarity and accessibility of the technology currently limit its use in the primary care setting.²⁸

Non-invasive blood testing addresses the need for accessible NAFLD fibrosis risk stratification.^{29–31} The Fibrosis 4 index (FIB-4) and the NAFLD fibrosis score (NFS), non-invasive tests that combine age and commonly available biochemical lab results, stand out for their ability to exclude advanced fibrosis (Metavir stage 3 [F3] and stage 4 [F4]) in NAFLD patients.^{32–35} In a meta-analysis of non-invasive fibrosis assessment tools, FIB-4 and NFS exceeded all other non-imaging tests with summary areas under the ROC curve (AUROC) of 0.84 (for each) for detecting advanced fibrosis.³⁰ In one study comparing FIB-4 to other non-invasive fibrosis markers, FIB-4 most effectively “ruled out” advanced fibrosis with values < 1.3 (negative predictive value 90%), and correctly identified F3-F4

fibrosis with values > 2.67 (positive predictive value 80%) in biopsy-proven NAFLD patients. Using these values as cutoffs, the absence (<1.3) or presence (>2.67) of advanced fibrosis was identified with 89% accuracy.³⁴ In a meta-analysis of 13 studies and 3,064 patients, the NFS had an AUROC of 0.85 for detecting F3 or greater fibrosis. Specifically, an NFS value of -1.455 had a sensitivity of 90% and a negative likelihood ratio (LR) of 0.17 for advanced fibrosis, and an NFS of 0.676 had a specificity of 97% and a positive LR of 20.3 for advanced fibrosis.^{36–38}

Applying FIB-4 and NFS to primary care patients with NAFLD can reliably exclude advanced fibrosis (FIB-4 < 1.3 , NFS < -1.455), and reduce unnecessary further testing and hepatology referrals.^{39–43} Conversely, non-invasive risk scores above these limits can identify patients in need of confirmatory testing (e.g. elastography) and consultation with a hepatology specialist. Unfortunately, many primary care patients with NAFLD remain undiagnosed.^{11,16} FIB-4 and NFS values concerning for advanced fibrosis in patients with elevated aminotransferases and no known liver disease may represent undiagnosed NAFLD, and elevated non-invasive fibrosis risk scores could provide a signal to improve the primary care diagnosis of NAFLD and other chronic liver diseases.

We hypothesized that in a sample of primary care patients with elevated aminotransferases and a high burden of MetS, many would have elevated FIB-4 (> 1.3) and NFS (> -1.455) values, likely reflecting unrecognized advanced NAFLD diagnoses. Therefore, we calculated FIB-4 and NFS scores in primary care patients with abnormal serum aminotransferases and no other known liver disease diagnoses. We analyzed the relationship between objective measures of MetS and elevated mean FIB-4 and NFS scores in this sample.

Materials and Methods

This retrospective study of electronic health record (EHR) data from a large patient-centered medical home (PCMH) between 2007 and 2018 analyzed a sample of patients with elevated aminotransferases for: (1) the distribution of patient-level FIB-4 and NFS scores and the proportion of patients with values greater than the indeterminate and high-risk thresholds for advanced fibrosis; and (2) demographic and clinical factors associated with non-invasive tests scores above these thresholds.³⁴ The Institutional Review Board at the Medical University of South Carolina (MUSC) approved this study.

Study Population

All patients seen in the Internal Medicine PCMH at MUSC between January 1, 2007 and December 31, 2018 were evaluated. The practice conducts 32,000 patient visits yearly and delivers care to a diverse (39% non-white) adult (mean age 59 years) population with chronic and complex medical problems. The PCMH is a primary care clinic that utilizes an EHR fully integrated with the tertiary care academic medical center, allowing for primary care access to patient data from the emergency room and inpatient settings. Key patient-level variables included demographics, vital signs, laboratory test results, and International Classification of Diseases (ICD)-9 and -10 codes.

We constructed a sample of patients with at least one aminotransferase abnormality defined as: aspartate aminotransferase (AST) > 34 U/L, or alanine aminotransferase (ALT) > 45 U/L, or both. The ALT threshold, though too high to adequately detect all patients with NAFLD or advanced fibrosis, was chosen because it is the value designated as “abnormal” in the EHR at MUSC.⁴⁴ We calculated FIB-4 and NFS scores for each liver test panel using the equations:^{45,46}

$$FIB-4 = \frac{Age (years) \times AST(U/L)}{Plt (10^9/L) \times \sqrt{ALT(U/L)}}$$

$$NFS = -1.675 + 0.037 \times Age (years) + 0.094 \times BMI \left(\frac{kg}{m^2} \right) + 1.13 \times diabetes (Yes = 1; No = 0) + 0.99 \times \frac{AST(U/L)}{ALT(U/L)} - 0.013 \times Plt (10^9/L) - 0.66 \times albumin(g/dL)$$

Both calculations used platelet count assessments from the same day as the liver tests when available, and the most recent prior platelet value otherwise. Each unique patient possessed a FIB-4 and NFS score for each liver test panel completed (normal or abnormal), provided there was a simultaneous or previous platelet assessment. For the NFS calculations, the most recently recorded BMI was used, and diabetes was assigned to those patients with hemoglobin A1c values equal to or exceeding 6.5% (measures of fasting glucose impairment were not included). Due to concerns of confounding and loss of specificity for FIB-4 and NFS in patients of advanced age, only those assessments gathered in patients prior to the age of 66 years were included (Figure 1).⁴⁷⁻⁴⁹

We excluded patients with diagnoses of chronic liver disease, hepatocellular carcinoma, history of liver transplantation, and cirrhosis by ICD-9/10 codes (Table S1).^{50,51} Patients with elevated aminotransferases and an ICD code for alcohol abuse were also excluded. Formal diagnoses of NAFLD included patients with at least one ICD-9 code of 571.8 or an ICD-10 code of K75.81 or K76.0.¹¹

Outcomes

The primary outcomes of interest were the FIB-4 and NFS scores. We calculated functions (mean, median, maximum, and minimum) of patient-level scores and evaluated the proportion exceeding the thresholds for indeterminate (FIB-4 > 1.3, NFS > -1.455) and high-risk (FIB-4 > 2.67, NFS > 0.676) of advanced fibrosis. Patient-level mean FIB-4 and NFS scores surpassing the advanced fibrosis risk cutoffs served as the binary dependent variables in the logistic regression models.

Primary Independent Variables

The independent variables of greatest interest were those associated with obesity and MetS. Variables associated with MetS deviated from the classical metabolic syndrome criteria on account of administrative data availability, with us choosing to use body mass index (BMI) in place of waist circumference and glycosylated hemoglobin (A1c) in place of fasting glucose. The population was characterized by BMI as a binary variable (BMI > 30 kg/m²),

and BMI was evaluated as a continuous variable in the logistic regression model. BMI values were the mean patient-level values during the study period. MetS elements were categorical variables defined by recordings of the following on at least one occasion during the study period: hyperglycemia (hemoglobin A1C $\geq 6.5\%$), low high-density lipoprotein (HDL < 40 mg/dL in men, HDL < 50 mg/dL in women), and hypertriglyceridemia (TG > 150 mg/dL). Elevated blood pressure required at least two readings greater than 130/85 mm Hg.^{1,5}

Other Independent Variables

Gender was coded as Male / Female.—Race was categorically coded as Black / non-Black, owing to a small number of non-Black, non-White patients in the sample (n=281). The presence of alcohol, tobacco, and drug use were identified by an Elixhauser ICD-9/10 coding algorithm.⁵²

Data Sources—All data came from Medical University Hospital Authority Enterprise and EPIC© (EPIC Systems Corporation, WI) Clarity databases. Clinical, laboratory, and demographic data were obtained in the ambulatory, emergency room, and inpatient settings at MUSC during the study period.

Analysis—The proportion of patients in the sample with an elevated mean FIB-4, mean NFS, or both were calculated. We also performed univariate analyses of patient-level mean FIB-4 and NFS scores by the components of the MetS, the proportion of patients with mean scores exceeding the fibrosis risk thresholds, and the proportion of patients receiving diagnostic codes for NAFLD. Multivariable logistic regression models for four dependent variables (mean FIB-4 > 1.3 , mean FIB-4 > 2.67 , mean FIB-4 > 1.3 and mean NFS > -1.455 , and mean FIB-4 > 2.67 and mean NFS > 0.676) were developed. A model with NFS scores as the sole dependent variable was not utilized given the endogeneity of the primary variables of interest (including BMI and the presence of diabetes) and NFS calculation. The MetS variables were forced into the model based on clinical relevance.¹ Interactions between obesity and elevated blood pressure and hyperglycemia were assessed at a significance level of 0.20. Sensitivity analyses, including development of regression models for the outcome of median summary scores were performed.

Statistical analyses were performed using SAS version 9.4 (Cary, NC).

Post-Hoc Analysis: After identifying patients with a mean FIB-4 and a mean NFS exceeding the threshold for high-risk of advanced fibrosis, we performed a chart review for a convenience sample of 25 randomly selected patients for evidence of prior abdominal imaging and the presence of steatosis or cirrhosis in the radiology report. We also sought alternative diagnoses (i.e. malignancy resulting in thrombocytopenia) that may have resulted in elevated FIB-4 and NFS scores.

Results

The 6,506 unique patients included had 73,067 liver test panel results, with a median of 6 (IQR: 3–13) values per patient during the study period (Figure 1, Table 1). Of these liver

test panels, 27,019 had at least one abnormal aminotransferase value and the median number of abnormal liver panels per patient was 2 (IQR: 1–4). Platelet counts for non-invasive risk calculations were from the same day for 84% of scores and within the preceding 3 months for 90%. Of the sample, 97.6% had at least one component of metabolic syndrome, 81.1% had at least 2 elements, and 9.6% had all five components. Only 313 (4.8%) patients carried a NAFLD ICD-9/10 code.

Based on the patient-level mean FIB-4 scores, 37.3% patients had values exceeding 1.3, and 5.4% patients surpassed 2.67 (Table 2). Using the maximum scores, 38.1% of patients had no FIB-4 scores > 1.3. When applying the NFS, 48.5% of patients had mean values above -1.455, and 8.0% had mean values greater than 0.676. With the maximum NFS scores, 31.2% of patients had no values greater than -1.455. When combining the fibrosis risk assessment tools, 56.9% of patients had either a mean FIB-4 or mean NFS above the indeterminate risk threshold, and 28.9% had both a mean FIB-4 and mean NFS exceeding indeterminate risk. Using maximum values, 24.0% never had an elevated FIB-4 or NFS score.

In the patient sample, 731 (11.2%) patients had either a mean FIB-4 or NFS above the threshold for high-risk of advanced fibrosis, and 142 (2.2%) patients had both a mean FIB-4 and a mean NFS score in the high-risk range. In-depth analysis of 25 randomly selected patients from this latter group revealed that 56% (14/25) had imaging reports documenting liver steatosis and/or the appearance of cirrhosis with or without portal hypertension. Two patients had a non-liver malignancy, and one was diagnosed with thrombotic thrombocytopenic purpura.

In the univariate analysis (Table 3), there were no statistically significant differences in average mean FIB-4 scores by the presence of elevated blood pressure, low HDL, or hypertriglyceridemia. Patients with a mean BMI > 30 kg/m² had a lower average mean FIB-4 score (1.25 [SD 1.05]) compared to those with a BMI ≤ 30 kg/m² (1.59 [SD 2.61], $p < 0.01$), and patients with an A1c > 6.5% had higher mean FIB-4 scores (1.50 to 1.34, $p=0.03$). Mean of mean NFS scores were significantly higher for patients with elevated blood pressure, hyperglycemia, low HDL, hypertriglyceridemia, and obesity. Patients with triglycerides ≤ 150 mg/dL and BMI ≤ 30 kg/m² had a higher proportion of high-risk mean FIB-4 scores, whereas patients with triglycerides > 150 mg/dL and BMI > 30 kg/m² had a higher proportion of high-risk mean NFS scores. Patients with hypertension, hyperglycemia, and low HDL also had a higher proportion of high-risk mean NFS scores. Patients with hyperglycemia had the highest proportion of NAFLD ICD-9/10 assignment (8.2%), followed by 7.6% of patients with hypertriglyceridemia, and 6.0% of patients with a BMI exceeding 30 kg/m².

In the logistic regression models (Table 4), male gender (OR 1.52, 95% CI 1.22–1.89), Black race (OR 1.75, 95% CI 1.40–2.19), and low HDL (OR 1.42, 95% CI 1.11–1.82) were associated with a mean FIB-4 score greater than 2.67. Patients with higher BMI values (OR 0.96, 95% CI 0.94–0.98) and triglycerides > 150 mg/dL had lower odds of having mean FIB-4 scores exceeding 2.67. No significant interactions appeared between obesity and hyperglycemia or elevated blood pressure. Male gender (OR 1.52, 95% CI 1.08–2.14),

Black race (OR 1.88, 95% CI 1.31–2.70), hyperglycemia (OR 2.30, 95% CI 1.60–3.32), and low HDL (OR 2.26, 95% CI 1.40–3.65) were associated with having mean FIB-4 and mean NFS scores exceeding the high-risk thresholds for advanced fibrosis.

Interpretation

Our data reveal a high prevalence of elevated (indeterminate and high-risk for advanced fibrosis) FIB-4 and NFS scores in a large primary care sample with a heavy burden of metabolic syndrome elements. These data are striking, with 57% of patients having either a mean FIB-4 or mean NFS above the indeterminate risk threshold and 29% having both mean FIB-4 and mean NFS values at this level. Additionally, 11% had either a mean FIB-4 or mean NFS in the high-risk range, and 142 patients had mean FIB-4 and NFS scores exceeding the high-risk threshold for advanced fibrosis, suggesting that this group may have cirrhosis and not know it. Only 5% of patients carried an ICD-9/10 code for NAFLD.

Optimistically, FIB-4 and NFS may effectively rule out advanced fibrosis in 24% of our sample (76% with either a maximum FIB-4 > 1.3 or NFS > -1.455). However, a large proportion likely requires further evaluation with additional blood testing (i.e. ELF™), imaging (transient elastography), or referral. FIB-4 and NFS in sequence may help to better select patients for more advanced evaluation, as only 29% of this sample had both mean FIB-4 and mean NFS scores above the indeterminate threshold.^{53,54} The proportion of elevated non-invasive fibrosis assessment scores is higher than other primary care samples, but similar to that found in a study of patients with biopsy-proven NAFLD.^{33,40} Our sample patients were older and had high burdens of diabetes, hypertension, and dyslipidemia, factors associated with advanced fibrosis which may explain the higher FIB-4 and NFS scores. Additionally, our study liberalized the liver test abnormality requirements to include AST (vs. only ALT elevation) due to mounting evidence that ALT abnormalities alone may not detect NAFLD with advanced fibrosis.^{33,55,56} While a high burden of comorbidities and a broader abnormal liver test definition may impact the proportion of patients with elevated FIB-4 and NFS scores, limiting this work to patients with high ALT (>45 IU/L) inclusion criteria and excluding those FIB-4 and NFS scores after age 65 neglects a large component of the primary care population at risk for advanced fibrosis.

Though FIB-4 and NFS scores may not carry the same clinical significance as a histological analysis of the liver, we attempted to overcome this concern by using a combination of the two non-invasive assessments to evaluate fibrosis risk. We believe this should provide reassurance in our findings. Additionally, the relationships observed between male gender, elevated blood pressure, and hyperglycemia with elevated risk scores in the regression models are consistent with previous work.^{1,5–7,54,57–59} However, the relationship with FIB-4 and BMI was surprising. We analyzed BMI continuously and as a 2-level (< 30, or > 30) categorical variable, each time finding similar associations.

The findings from this study underscore the pervasiveness of NAFLD (and perhaps all liver disease) under-diagnosis in primary care. Despite an overall population prevalence of 30% and high proportions of objective measures of obesity and diabetes, only 5% of our sample carried an ICD-9/10 code for NAFLD in the presence of known clinical signals and risk factors. Possible reasons for this diagnostic gap are complex. ICD-9/10 codes are

suboptimal tools in identifying cases of chronic liver disease in administrative datasets, and this under-diagnosis may reflect these coding limitations.⁶⁰ Also, PCPs may not feel this diagnosis alters their treatment plan in patients with components of the metabolic syndrome, as they already address cardiovascular risk factors and counsel on behavioral modifications. But knowledge of advanced fibrosis may spur more intensive weight loss efforts, which can lead to reductions in fibrosis and improved outcomes.^{61–63} Application of FIB-4 or NFS scoring in primary care, especially in patients with type 2 diabetes, could prompt further testing or diagnostic assignment in those without a known liver disease diagnosis.²²

We were surprised by the number of patients with both mean FIB-4 and NFS scores above the high-risk fibrosis thresholds and no diagnosis of cirrhosis. More than half of the sub-sample (14/25) had radiographic evidence of steatosis or cirrhosis, consistent with the conclusion that when both of these tests are elevated, there is likely underlying liver disease. Only 3 of the 25 had another definitive diagnosis that might lead to raised FIB-4 and NFS values, driven largely by thrombocytopenia. These findings suggest possible utility in applying non-invasive tests to carefully selected subsets (i.e. patients with aminotransferase elevations) of PCMH patient registries to identify undiagnosed patients with advanced fibrosis.

We recognize the limitations of this study. First, we cannot be sure of the burden of NAFLD in this population. But, the selection of patients with abnormal aminotransferases, the exclusion of other known liver diseases, the burden of metabolic syndrome, the relationships observed in the univariate analyses, and the findings on the post hoc chart review would support the presence of undiagnosed NAFLD in this sample. Secondly, the outcome of interest (elevated FIB-4 and NFS scores) is a proxy for liver disease, and structural analysis was not possible in all patients. Nonetheless, this patient sample is a realistic representation of what primary care clinicians encounter in the U.S. Also, we used summary statistics. Maximum FIB-4 and NFS values may reflect acute situations unrelated to fibrosis, so mean statistics were used for the logistic regression models. Means were chosen because this summary measure captures data from every FIB-4 and NFS value (unlike the median), adding robustness to the analyses. Similar associations appeared when using median scores as the outcome in the logistic regression models. We intentionally used a high threshold for ALT inclusion to simulate the real-life signal delivered to PCPs, but this signal would miss patients with NAFLD and possible fibrosis. The predictor variables for MetS include BMI and A1c instead of waist circumference and fasting glucose, respectively, a departure from the most recent definitions of metabolic syndrome. We do not have reliable waist circumference data in our EHR, and we were unable to ascertain the fasting state of patients.⁶⁴ However, we opted to use objective measures to define MetS components to optimize authenticity (compared to ICD-9/10 coding). ICD coding was used for exclusion criteria, which may have inadequately identified all patients in the sample with other chronic liver disease. Also, this study does not include imaging data (e.g. ultrasound) which currently resides in the EHR in an unstructured format and would contribute to diagnostic assignment. Unfortunately, medication data was not yet available for analysis. Additionally, this study relied upon measures not included in the classical definition of MetS (BMI and A1c) and omitted waist circumference and fasting glucose. This exchange was done due to

data availability and could influence the MetS relationships observed. Finally, this is a single site study with patients located in a PCMH, which could limit generalizability.

Our data suggest that NAFLD is under-diagnosed in primary care and that a sizable subgroup of patients may have advanced fibrosis. As the burden of NAFLD and the complications from it grow, PCPs need strategies to improve the diagnosis of NAFLD, especially in patients with metabolic syndrome, and assess for the presence of advanced fibrosis. FIB-4 and NFS may prove to be useful tools in this setting, applied not only after a formal NAFLD diagnosis, but also used to identify those patients with elevated values in need of a more intensive liver evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUROC	area under the receiver operating characteristic
BMI	body mass index
EHR	electronic health record
FIB-4	Fibrosis-4 Index
HDL	high-density lipoprotein
ICD	International Classification of Diseases
IQR	inter-quartile range
LR	likelihood ratio
MetS	metabolic syndrome
NAFLD	nonalcoholic fatty liver disease
NFS	NAFLD fibrosis score
PCMH	patient-centered medical home
Plt	platelet

ROC receiver operating characteristic

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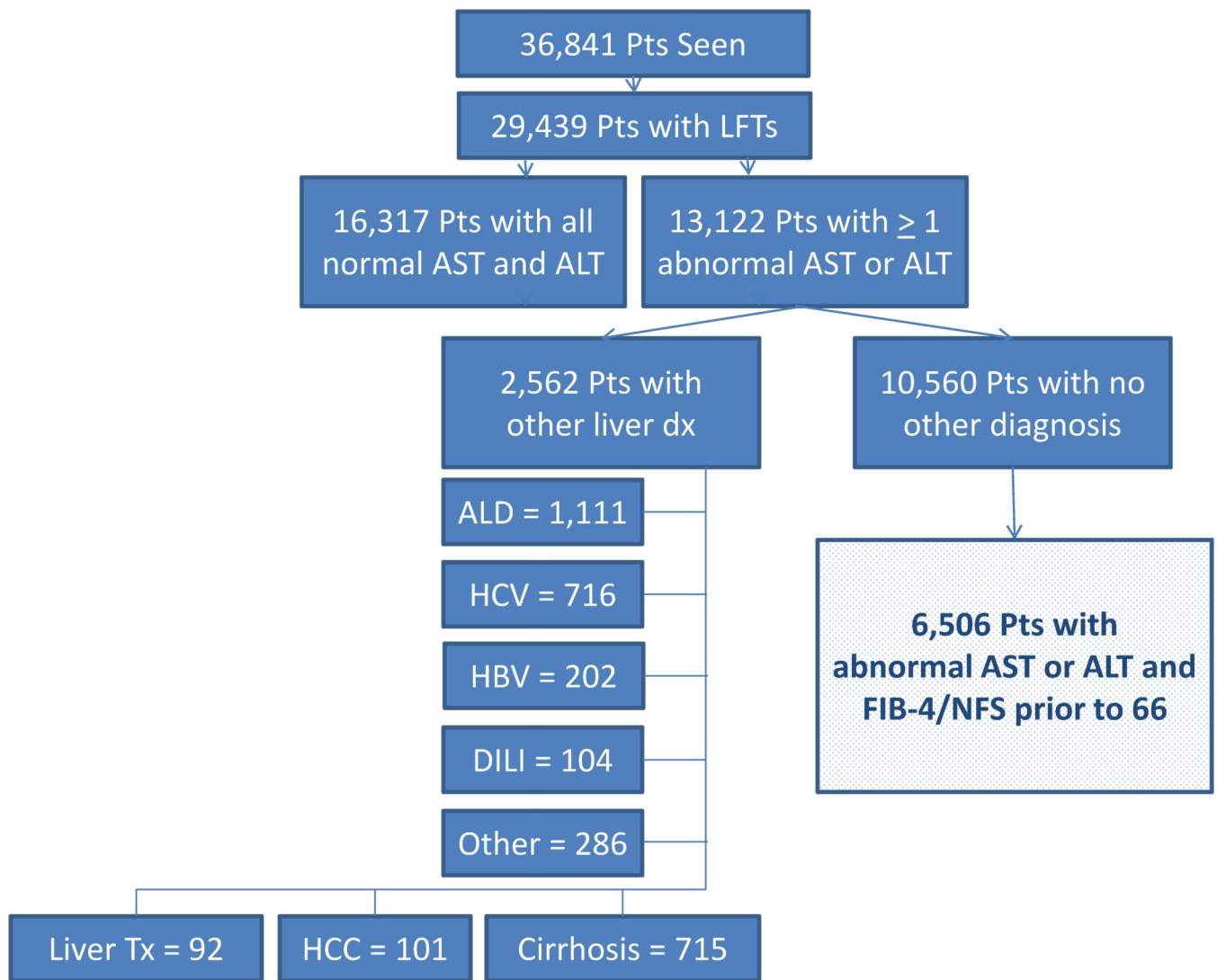


Figure 1.
Consort diagram of included patients

Table 1:

Characteristics of patient sample (N=6,506)

	N (%)
Demographics	
Age (years) *	
Mean	53.8 (13.9)
Gender	
Female	3,791 (58.3%)
Male	2,715 (41.7%)
Race	
Black	2,657 (40.8%)
Non-Black	3,849 (59.2%)
Liver Tests	
LFT Panel Results **	
Mean per patient (SD)	11.2 (16.0)
Median per patient (IQR)	6 (3–13)
LFT Panels with Abnormal	
Mean per patient (SD)	4.5 (8.2)
Median per patient (IQR)	2 (1–4)
NAFLD Diagnoses †	313 (4.8%)
MetS Components	
BP > 130/85	5,820 (89.5%)
A1c > 6.5%	1,693 (26.0%)
Low HDL	4,504 (69.2%)
Triglyceride > 150	2,729 (42.0%)
BMI > 30	3,025 (46.5%)
# of MetS Components	
0	159 (2.4%)
1	1,072 (16.5%)
2	1,654 (25.4%)
3	1,719 (26.4%)
4	1,276 (19.6%)
5	626 (9.6%)
Comorbidities ‡	
Smoking history	2,813 (43.2%)
Drug Use	530 (8.2%)

* Age is calculated by the patient's last data point in the study period

** total number of liver function test panel results, not the individual components (transaminases)

*** Pattern assigned on the first liver test abnormality.

† NAFLD and NASH diagnosis codes (571.8, K75.81, or K76.0).

[‡]Comorbidities according to ICD-9/10 Elixhauser coding algorithm (38). LFT=liver function test; NAFLD=nonalcoholic fatty liver disease; MetS=metabolic syndrome; BP=blood pressure; HDL=high-density lipoprotein; BMI=body mass index (kg/m²)

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Table 2:

The proportion of patients with non-invasive prognostic tests exceeding threshold for fibrosis by patient-level summary statistic (N=6,506).

Clinical Thresholds		
FIB-4	% > 1.3 (n)	% > 2.67 (n)
Mean	37.3% (2,424)	5.4% (354)
Median	32.7% (2,125)	3.5% (229)
Maximum	61.9% (4,029)	20.3% (1,320)
Minimum	14.9% (970)	1.3% (87)
NFS	% > -1.455 (n)	% > 0.676 (n)
Mean	48.5% (3,157)	8.0% (519)
Median	48.4% (3,149)	7.9% (516)
Maximum	68.8% (4,475)	23.2% (1,510)
Minimum	27.3% (1,774)	2.9% (190)
FIB-4 OR NFS	% > 1.3 OR -1.455 (n)	% > 2.67 OR 0.676 (n)
Mean	56.9% (3,703)	11.2% (731)
Median	55.3% (3,598)	9.8% (638)
Maximum	76.0% (4,947)	30.6% (1,990)
Minimum	31.5% (2,052)	3.7% (240)
FIB-4 AND NFS	% > 1.3 AND -1.455 (n)	% > 2.67 AND 0.676 (n)
Mean	28.9% (1,878)	2.2% (142)
Median	25.8% (1,676)	1.6% (107)
Maximum	54.7% (3,557)	12.9% (840)
Minimum	10.6% (692)	0.6% (37)

Table 3:

Patient-level mean FIB-4 and NFS scores by component of metabolic syndrome, the proportion of patients by metabolic syndrome component with mean FIB-4 and NFS values exceeding the thresholds for advanced fibrosis, and the proportion of patients receiving a NAFLD ICD-9/10 code.

	FIB-4			NFS			NAFLD Dx	
	Mean (SD)	%>1.3 (n)	%>2.67 (n)	Mean (SD)	%>-1.455 (n)	%>0.676 (n)	%(n)	
Metabolic syndrome component								
BP > 130/85	Yes (n=5,820)	1.38 (1.98)	38.0% (2,209)	5.5% (322)	-1.36 (1.49)	51.3% (2,986)	8.6% (499)	5.2% (301)
	No (n=686)	1.35 (2.80)	31.3% (215)	4.7% (32)	-2.33 (1.48)	24.9% (171)	2.9% (20)	1.8% (12)
	p-value	0.78 *	<0.01 **	0.34 **	<0.01 *	<0.01 **	<0.01 **	<0.01 **
A1c > 6.5%	Yes (n=1,693)	1.50 (3.09)	41.1% (696)	5.6% (95)	-0.35 (1.39)	80.5% (1,362)	21.4% (362)	8.2% (139)
	No (n=4,813)	1.34 (1.58)	35.9% (1,728)	5.4% (259)	-1.85 (1.37)	37.3% (1,795)	3.3% (157)	3.6% (174)
	p-value	0.03 *	<0.01 **	0.72 **	<0.01 *	<0.01 **	<0.01 **	<0.01 **
Low HDL	Yes (n=4,504)	1.36 (1.50)	35.6% (1,603)	5.8% (260)	-1.37 (1.60)	51.6% (2,323)	9.6% (433)	5.4% (243)
	No (n=2,002)	1.42 (3.00)	41.0% (821)	4.7% (94)	-1.66 (1.31)	41.7% (834)	4.3% (86)	3.5% (70)
	p-value	0.39 *	<0.01 **	0.08 **	<0.01 *	<0.01 **	<0.01 **	<0.01 **
Trig > 150	Yes (n=2,729)	1.39 (1.42)	38.1% (1,040)	4.6% (125)	-1.19 (1.45)	56.0% (1,528)	9.8% (266)	7.6% (206)
	No (n=3,777)	1.37 (2.45)	36.6% (1,384)	6.1% (229)	-1.66 (1.54)	43.1% (1,629)	6.7% (253)	2.8% (107)
	p-value	0.74 *	0.23 **	<0.01 **	<0.01 *	<0.01 **	<0.01 **	<0.01 **
BMI > 30	Yes (n=3,025)	1.24 (1.06)	31.9% (966)	3.9% (117)	-0.85 (1.46)	66.1% (1,998)	14.0% (423)	6.0% (182)
	No (n=3,481)	1.50 (2.66)	41.9% (1,458)	6.8% (237)	-1.99 (1.38)	33.3% (1,159)	2.8% (96)	3.8% (131)
	p-value	<0.01 *	<0.01 **	<0.01 **	<0.01 *	<0.01 **	<0.01 **	<0.01 **

Dx=diagnosis. BP=blood pressure (mm Hg). A1c=hemoglobin a1c. HDL=high-density lipoprotein (mg/dL).Trig= Triglycerides (mg/dL). BMI=body mass index (kg/m²).

* Comparison using 2 sample t-test.

** Comparison using Chi square test.

Table 4:

Logistic regression models in patients with abnormal liver tests for the outcomes of 1) mean FIB-4 > 1.30; 2) mean FIB-4 > 2.67; 3) mean FIB-4 >1.3 and mean NFS > -1.455; and 4) mean FIB-4 > 2.67 and mean NFS > 0.676.

Sample	Patient Sample (N=6,506)					
	Mean FIB-4 > 1.30			Mean FIB-4 > 2.67		
Dependent variable	OR	95% CI	p-value	OR	95% CI	p-value
Male	1.52	1.37 – 1.69	<0.0001	1.52	1.22 – 1.89	0.0002
Black	1.28	1.15 – 1.42	<.00001	1.75	1.40 – 2.19	<0.0001
BP > 130/85	1.43	1.20 – 1.71	<0.0001	1.39	0.94 – 2.04	0.0969
A1C > 6.5%	1.36	1.20 – 1.54	<0.0001	1.10	0.84 – 1.43	0.4914
Low HDL	0.83	0.74 – 0.93	0.0013	1.42	1.11 – 1.82	0.0060
Triglycerides > 150	1.07	0.95 – 1.19	0.2675	0.76	0.59 – 0.96	0.0229
BMI	0.97	0.96 – 0.97	<0.0001	0.96	0.94 – 0.98	<0.0001
Dependent variable	Mean FIB-4 > 1.30 AND Mean NFS > -1.455			Mean FIB-4 > 2.67 AND Mean NFS > 0.676		
	OR	95% CI	p-value	OR	95% CI	p-value
Male	1.68	1.50 – 1.88	<0.0001	1.52	1.08 – 2.14	0.0173
Black	1.41	1.26 – 1.58	<0.0001	1.88	1.31 – 2.70	0.0006
BP > 130/85	1.53	1.24 – 1.88	<0.0001	1.33	0.63 – 2.78	0.4537
A1C > 6.5%	1.76	1.55 – 2.01	<0.0001	2.30	1.60 – 3.32	<0.0001
Low HDL	1.04	0.92 – 1.18	0.5274	2.26	1.40 – 3.65	0.0008
Triglycerides > 150	1.10	0.98 – 1.24	0.1054	0.75	0.52 – 1.07	0.1133
BMI	1.00	0.99 – 1.01	0.7929	1.02	1.00 – 1.04	0.0704

BP=blood pressure (mm Hg). A1c=hemoglobin a1c. HDL=high-density lipoprotein (mg/dL). Trig= Triglycerides (mg/dL). BMI=body mass index (kg/m²).