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A Comparison of Brunt Criteria, the Non Alcoholic Fatty Liver Disease Activity Score (NAS) & a Proposed NAS-including fibrosis as Valid Diagnostic Scores for NASH

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Abstract

Objective—Non-alcoholic steatohepatitis (NASH) can result in cirrhosis and end stage liver disease. It is of utmost importance to differentiate NASH from simple steatosis. The aim of this study is to determine the prevalence of NASH in Latino veterans with metabolic syndrome and compare histologic grading using Brunt Criteria, the NAFLD activity score (NAS), and a proposed NAS score including fibrosis.

Methods—Veterans with metabolic syndrome, hepatic steatosis and elevation of ALT/AST who underwent a liver biopsy from 2004-2010 were included in this study. Biopsies were evaluated by a single blinded Hepatopathologist. Steatosis, lobular inflammation, ballooning and fibrosis were graded per specimen. Each biopsy was evaluated using Brunt criteria, NAS and NAS plus fibrosis.

Results—Sixty patients were included in this study, 88.3% men with a mean age of 50.4 (± 12.8). 50.0% met criteria for NASH according to the Brunt system. When classifying biopsies using NAS, only 30.0% (18/60) had a score ≥5, while when adding fibrosis, the number of patients with a score ≥5 increased to 33 (55.0%). When evaluating the predictive ability of the two scoring systems, we found that NAS including fibrosis had a higher sensitivity than NAS (86.7% vs. 40.0%) and a lower specificity (76.7% vs. 80.0%).

Conclusion—In our population with metabolic syndrome and altered liver function tests, about 50-55% had steatohepatitis. There were significant differences between the scoring systems. When using NAS-plus-fibrosis more patients were recognized and the sensitivity increased. Further validation studies are required to evaluate this proposed NAS scoring System.

MeSH Terms

Non-alcoholic Fatty Liver Disease; Nonalcoholic steatohepatitis; Abdominal Obesity Metabolic syndrome; histology

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Introduction

Nonalcoholic fatty liver disease (NAFLD) represents one of the most common emerging diseases in the western countries. It may account for approximately 80% of cases with elevated liver enzymes in USA (1,2). Attention has shifted from innocent fatty liver (steatosis) to nonalcoholic steatohepatitis (NASH), a progressive fatty liver disease that may evolve into fibrosis and cirrhosis. The pathogenesis of nonalcoholic and viral negative liver steatosis appears to be multifactorial and many mechanisms have been described as its cause. There is evidence that NAFLD is associated to metabolic diseases such as hyperlipidemia, diabetes mellitus and hypertension (3). It is closely related to obesity, which is unquestionably becoming one of the worse epidemics in the United States and Northern America (3,4). NASH and obesity have received significant attention in the last two decades due to their strong association to coronary artery and cardiovascular diseases (CVD).

The National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP-III) treated these common metabolic diseases as individual components and subsequently, after achieving consensus, the necessary criteria for the diagnosis of Metabolic Syndrome (Met S) was established and validated in adults. Hence, ATP-III defines Met S as the conglomerate of components including insulin resistance, obesity, hypertensive disease and hyperlipidemia (5). During the last few decades in the United States, there has been a significant increase in the incidence and prevalence of the Met S. For example, it is estimated that approximately 22% of individuals in the general population are affected by the Met S (6). Epidemiological evidence has shown that the prevalence of diabetes in Hispanics is among the highest; expected to reach epidemic proportions. The correct identification of Met S components is of utmost importance in order to prevent the high morbidity and mortality associated to chronic liver disease (CLD) and cardiovascular disease (CVD).

Hilden & Ground (7,8) identified in random histopathologic studies that the relative proportion of NASH to NAFLD is approximately 1:10. NASH can range from fibrosis to cirrhosis depending on the presence of risk factors which could accelerate (e.g. cardiometabolic risk factors [CMRF's] & metabolic syndrome) or protective factors that might attenuate (e.g. adiponectin) progression of the disease (9). Nevertheless, even without severe fibrosis patients with NASH continue to be at increased risk for developing cirrhosis, terminal liver failure and hepatocellular carcinoma (10,11) Hence, the early and accurate identification of such individuals at risk for developing NASH could prove to be beneficial to these patients.

Sonographic and computerized tomographic imaging of the liver have been useful in determining the presence of fatty liver (bright liver) but failed to identify the extent of fibrosis (12). Serologic markers like AST and ALT have also failed to predict the degree of liver inflammation, necro inflammatory activity and progression of disease (6,10,11,12). Liver biopsy has been the only method that accurately quantifies these factors and therefore it is considered the gold standard diagnostic tool and the only method for establishing prognosis (9,12). There is consensus favoring the use of liver biopsy due to the importance of detecting the presence of fibrosis(9). Fibrosis in the presence of NASH is the best and

most accurate predictor of determining progression to cirrhosis. Non-Invasive assessment of fibrosis severity are under investigation. Biomarkers such a cytokeratin-18 have been validated although imperfect.(12,13) Transient elastography which has been successful in identifying advanced fibrosis in hepatitis B and C, seems promising nevertheless need further investigation specially in the setting of obesity(13). Mathematic calculations such as the NAFLD Fibrosis Score which is based on easily and readile available variables such as age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio, have been used to predict the presence of fibrosis as well. (14) The Enhanced Liver Fibrosis Score, claims predicting over 75% of adult patients who would not need a liver biopsy. (15)

While liver biopsy remains as the goldstandard to establish the diagnosis of NASH and to predict risk of disease progression, the relevance of using a standardized histopoathologic examination scoring system to assure reproductibility of pathologists reports and a common language is of utmost importance. On 1999, Dr. Elizabeth Brunt proposed for the first time a histological grading and staging system for non-alcoholic steatohepatitis. (16) On 2005, a separate system scoring the features of NAFLD called the NAFLD Activity Score was developed by a group of experts as a tool to measure changes during therapeutic trials. (17) The valididy of this research scoring has not been extensively evaluated although there is widespread use. The drawback fo this scoring system is that it proposed using only the unweighted sum of steatosis, lobular inflammation and ballooning since the intent of the scoring was to allow for detailed analysis of histologic changes associated to therapeutic interventions. The Nonalcoholic Clinical Reserach Network although measured fibrosis in their original study, recommended not including it in the NAS score since it is less reversible and a result of disease activity. (17) In clinical practice, the relevance of the overall histologic changes deserve the inclussion of fibrosis which is the best predictor of disease progression, liver failure and hepatocellular carcinoma. Using NAS without the inclusion of fibrosis would underestimate the presence of significant liver disease.

Our study primary aim was to compare the sensitivity and specificity of Brunt Criteria with the NAFLD Activity Score (NAS), and with a proposed score defined as NAS-Plus-Fibrosis.

A secondary aim was to determine the prevalence and severity of non-alcoholic steatohepatitis (NASH) and examine the differences in the frequency distribution of socio-demographics (age), anthropometric measurements (WC & BMI), biomarkers of liver fibrosis (AST, ALT, AST:ALT), separate cardio-metabolic risk factors (CMRFs), CMRF clustering & histological parameters according to NASH among Puerto Rican veterans with NAFLD and the metabolic syndrome.

Significance of this research

We tried to determine the degree of liver disease among Puerto Rican veterans with the metabolic syndrome who have steatosis by imaging studies and evidence of altered LFT's. We noticed that this is a common problem that remains underrecognized in most instances. After reviewing the literature there is no data regarding the extent and significance of liver disease in the Hispanic or Puerto Rico veteran's population with the metabolic syndrome. The present analysis could possibly confirm the association between metabolic syndrome

and NAFLD, and therefore help us to better identify Puerto Rican veterans at a higher risk for developing the serious complications of chronic liver disease (CLD). Early preventive measures may be instituted to prevent further progression into CLD and in some patients to reverse the liver damage.

This analysis allowed us to examine the validity and reliability of the NAFLD Activity Score (NAS) system and NAS-including fibrosis, with the “definite/correct” diagnosis of NASH in a population of Puerto Rican veterans with the metabolic syndrome and varying severity of NAFLD.

Methods

Study Design

We reviewed existing data in the electronic medical record of Hispanic Veterans diagnosed with the metabolic syndrome (defined by the ATP III criteria), fatty liver (evidenced by either an abdominal sonogram or abdominal CT scan) and unexplained elevation of ALT/AST who underwent liver biopsies between January 1, 2004 through December 31, 2010. Enrolled subjects were identified from radiology database and gastroenterology, hepatology, primary care and endocrinology clinics. This data was encoded upon collection. The local Institutional Review Board approved this study.

Study measures and variables included demographic data to include: age (21-88), sex and waist circumference. Information about diagnosis or treatment for hypertension, diabetes, hypercholesterolemia or hypertriglyceridemia was collected. Laboratory results included: AST, ALT, triglycerides, LDL, HDL, total cholesterol, fasting blood sugar, and glucose tolerance test. Results of abdominal sonogram(s) or abdominal CT were reviewed as well as the pathologic interpretation of liver biopsies by Brunt, NAS and NAS with fibrosis scores

All liver biopsies were revised by an independent Hepatopathogist using scoring Brunt, NAS and NAS including fibrosis scores.

Brunt criteria (13) include the following parameters: Amount of fat: graded 1 to 3 according to the percentage of fatty droplets (1, 0%-33%; 2, 34-66%; 3, 67-100%). Fibrosis: graded 0 (absent) to 4 (1, perisinusoidal/pericellular fibrosis; 2, periportal fibrosis; 3, bridging fibrosis; 4, cirrhosis). Necroinflamation: graded 0 (absent) to 3 (1, occasional ballooned hepatocytes and no or very mild inflammation; 2, ballooning of hepatocytes and mild to moderate portal inflammation; 3, intra-acinar inflammation and portal inflammation). NASH is defined by the presence of fibrosis (grade 1 or more) or necroinflammation (grade 2 or more).

Non-alcoholic Fatty Liver Disease Scoring System, (**NAS**) was designed to measure specifically only features of active injury. There it is a result of the unweighted sum of scores of steatosis (0-3), lobular inflammation (0-3), and hepatocellular ballooning (0-2); thus ranging beteween 0-8. According to this score system a calculated value of NAS > 5, correlates with a diagnosis of NASH, and biopsies with scores of less than 3 are diagnosed as “not NASH”(14). Scores between 3 and 4 were classified as possible or borderline.

The proposed NAS Score plus fibrosis, uses the same scoring system of NAS but adds the fibrosis staging (0-4) to the equation; therefore the score would range from 0 to 12.

With the modified NAS plus fiboris score system a calculated value of NAS > 5, was defined as NASH, and biopsies with scores of less than 3 are diagnosed as “not NASH”.

Participants

The data was collected from subjects that met three or more of the following ATP III diagnosis criteria for the metabolic syndrome: Abdominal obesity (by waist circumference) for men ≥ 102 cm and women ≥ 88 cm. Fasting triglycerides ≥ 150mg/dl or receiving treatment for hypertriglyceridemia. Fasting HDL cholesterol or receiving treatment for hypercholesterolemia in men < 40 and women < 50. Blood pressure (taken by average of two readings every 2 mins each) or previous treatment for high blood pressure ≥ 130/85 mm Hg. Fasting blood glucose > 110 mg/dl or being treated for DM2 with oral hypoglycemics or insulin.

Interpretation of liver biopsy by NAS, NAS plus fibrosis and the Brunt scoring systems.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study population. To test for non-normality distributions we applied the Shapiro-Wilk test. Data are expressed as mean (SD), median (25th and 75th percentiles) or frequency (%). Differences in sociodemographic, clinical, and cardiometabolic characteristics of the study population according to NASH diagnosis by Brunt criteria were examined. We used the two-group mean comparison t-test on normally distributed variables, Wilcoxon rank-sum (Mann-Whitney) test for non-parametric continuous data, and Chi-square or Fisher's exact test on categorical data, when appropriate. Subsequently, the same independent variables were compared according to the NAS and NAS including fibrosis. Furthermore, Fisher's exact test was used to assess the association between histological features (steatosis grade, lobular inflammation, ballooning, and fibrosis) and diagnosis of NASH based on Brunt criteria.

To evaluate the ability of the two histological scoring systems (NAS and NAS including fibrosis) to accurately identify NASH, receiver-operating characteristic (ROC) curve analysis was performed. Specificity, sensitivity and area under the curve (AUC) for both scores are reported. Finally, we compared the AUC's for the two scoring systems while adjusting for variables significantly associated with a positive diagnosis of NASH (score ≥5) in any of the two scores. Bootstrapped corrected estimates of the ROC-AUC's with their respective biased corrected confidence interval (95% CI) were computed. Statistical significance for all statistical analyses was set a priori ($p < 0.05$) and Stata Software version 12.0 was used (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

Results

A total of 60 patients were included in this study. Mean age of participants was 50.4 (± 12.8) and 88.3% were male. Demographic and clinical characteristics of study cohort according to

non-alcoholic steatohepatitis (NASH) by Brunt criteria and by NAFLD severity score (NAS) and NAS including fibrosis is described on Table 1.

Thirty patients (50.0%) met criteria for NASH according to the Brunt system. When classifying biopsies using NAS 18 patients (30.0%) had a score ≥5, and when considering fibrosis as part of NAS, the number of patients with a score ≥5 increased to 33 (55.0%).

After comparing the sociodemographic, clinical, and cardiometabolic variables based on NASH according to Brunt criteria and NAS scores, statistically significant differences were found between groups. Age and prothrombin time were significantly higher among patients with a NASH diagnosis according to Brunt criteria ($p<0.05$). Participants with a NAS ≥5 took medications for hypertension at a significantly higher frequency (83.3%) than those with a score ≤4 (45.2%) and had lower total bilirubin levels ($p<0.05$). On the other hand, patients with a score ≥5 in the NAS including fibrosis, had significantly higher levels of alanine and aspartate enzymes, when compared to patients with a score ≤4 ($p<0.05$) (Table 1).

In table 2 are presented the results of the relationship between definite NASH and the different histological features that were evaluated in the NAS. A higher proportion of patients with NASH had: higher grades of steatosis, more foci of lobular inflammation, more ballooned cells, and advanced stages of fibrosis. See Figure 1 for identified histopathologic changes. However, only lobular inflammation and fibrosis were significantly associated with NASH ($p<0.05$).

When evaluating the predictive ability of the two scoring systems for detecting NASH, we found that NAS including fibrosis had a higher sensitivity than NAS (86.7% vs. 40.0%) and a lower specificity (76.7% vs. 80.0%). Regarding the unadjusted AUC's we obtained, NAS including fibrosis detected more accurately the presence of NASH (0.87 vs 0.71, $p<0.001$). Finally, after comparing the scoring systems while controlling for alanine amino-T, aspartate amino-T, total bilirubin, and hypertension medications, the NAS including fibrosis was more accurate than NAS at diagnosing NASH (score ≥5), and this result was statistically significant (AUC's: 0.81 vs. 0.65, $p=0.002$) (Table 3).

Discussion

Nonalcoholic fatty liver disease and its progression to nonalcoholic steatohepatitis is not a benign liver disease. It has an estimated risk of progression to cirrhosis in 20% of cases with a liver-related mortality of up to 12% over years. Earlier identification of risk factors leading to this serious illness is of outmost importance. Patients with the metabolic syndrome, of increased incidence in the United States, are at higher risk for developing this disease. Liver biopsy remains the gold standard for establishing an accurate histological diagnosis. (18) Various histological scoring systems have been developed to achieve this goal. In this analysis, we compared the sensitivity and specificity of Brunt Criteria with the NAFLD Activity Score (NAS), and with a proposed score defined as NAS-Plus-Fibrosis as determinants of “definite/correct” diagnosis of NASH in a population of Puerto Rican veterans with the metabolic syndrome and varying severity of NAFLD.

In our study, including, fibrosis as part of the NAS scoring system, increased the accuracy of NASH diagnosis when compared with the original Brunt Scoring system and the NAS. Recent publication by some of the members of the Nonalcoholic Steatohepatitis Clinical Research group addresses the common use in clinical practice of NAS ≥5 as a surrogate for the histologic diagnosis of steatohepatitis, and concludes that a definite diagnosis or absence of steatohepatitis does not always correlate with the threshold values of the NAS score.(19) The proposed inclusion of fibrosis in the NAS score may result in better identification of patients with significant disease activity and severity of liver damage. Our findings support further investigation and validation with a larger sample.

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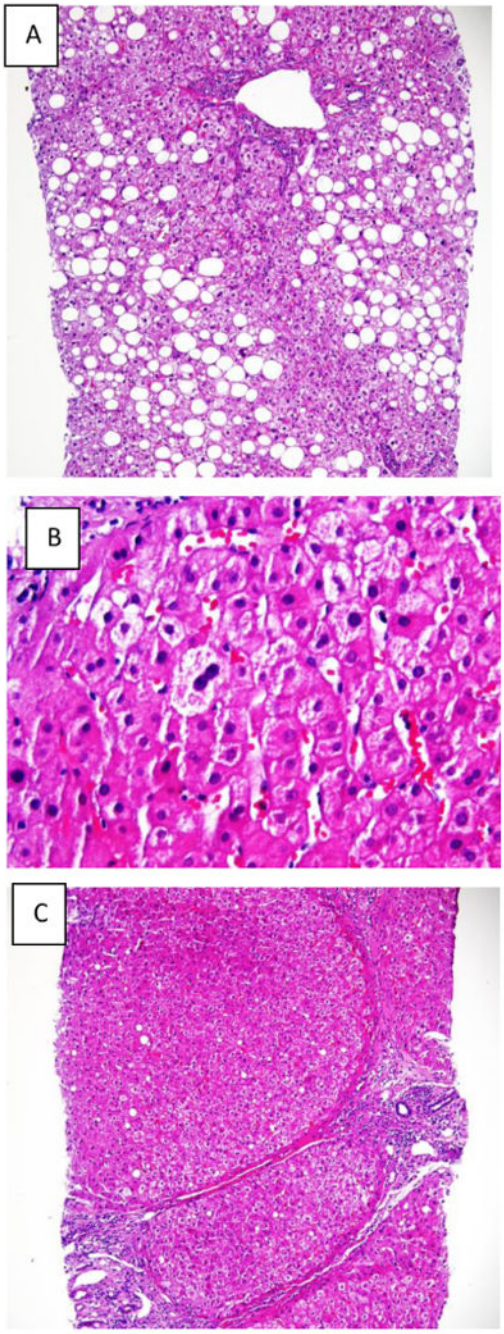

Figure 1. Histopathologic changes in NASH: (A)Steatosis (B) Balloning and (C) Fibrosis

Steatosis: Liver needle biopsy, hematoxylin and eosin (H&E) stain - 150x showing macrovesicular and microvesicular steatosis.

Ballooning: Liver needle biopsy, hematoxylin and eosin (H&E) stain - 450x showing ballooning degeneration.

Fibrosis: Liver needle biopsy, hematoxylin and eosin (H&E) stain - 150x showing nodules of hepatic parenchyma surrounded by fibrous bands.

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Table 1

Demographic and clinical characteristics of Puerto Rican veterans according to non-alcoholic steatohepatitis (NASH) by Brunt criteria and by NAFLD severity score (NAS) and NAS including fibrosis

	All patients	NASH		NAS		NAS (including fibrosis)	
		+Dx	-Dx	≥5	≤4	≥5	≤4
Total N (%)	60 (100.0)	30 (50.0)	30 (50.0)	18 (30.0)	42 (70.0)	33 (55.0)	27 (45.0)
Age (years)	50.4 (12.8)	54.1 (11.4)*	46.6 (13.3)*	51.6 (14.6)	49.8 (12.2)	50.9 (13.3)	49.7 (12.4)
Males	53 (88.3)	26 (86.7)	27 (90.0)	15 (83.3)	38 (90.5)	28 (84.9)	25 (92.6)
Diabetes Mellitus	25 (41.7)	16 (53.3)	9 (30.0)	10 (55.6)	15 (35.7)	17 (51.5)	8 (29.6)
Diabetes Mellitus Medications	18 (30.0)	12 (40.0)	6 (20.0)	7 (38.9)	11 (26.2)	12 (36.4)	6 (22.2)
Hypertension	44 (73.3)	21 (70.0)	23 (76.7)	15 (83.3)	29 (69.1)	25 (75.8)	19 (70.4)
Hypertension Medications	34 (56.7)	17 (56.7)	17 (56.7)	15 (83.3)*	19 (45.2)*	22 (66.7)	12 (44.4)
Dyslipidemia	47 (78.3)	22 (73.3)	25 (83.3)	14 77.8)	33 (78.6)	25 (75.8)	22 (81.5)
Lipid Medications	29 (48.3)	15 (50.0)	14 (46.7)	9 (50.0)	20 (47.6)	17 (51.5)	12 (44.4)
Waist Circumference cm‡	103.0 (91.3, 109.0)	104.0 (95.0, 114.0)	97.0 (47.0, 108.0)	99.0 (94.0, 110.0)	103.0 (90.5, 108.0)	103.0 (94.0, 111.5)	103.0 (72.0, 108.0)
BMI kg/m^2	31.9 (4.4)	32.2 (4.6)	31.6 (4.4)	32.1 (4.4)	31.8 (4.5)	32.0 (4.5)	31.8 (4.4)
Alanine Amino-T	67.5 (54.5, 95.5)	69.5 (55.0, 112.0)	66.5 (54.0, 85.0)	78.5 (62.0, 120.0)*	65.0 (53.0, 85.0)*	72.0 (61.0, 117.0)*	64.0 (53.0, 80.0)*
Aspartate Amino-T	42.0 (35.5, 57.5)	48.0 (37.0, 63.0)	39.5 (34.0, 51.0)	49.0 (37.0, 63.0)	40.0 (34.0, 53.0)	49.0 (37.0, 63.0)*	38.0 (34.0, 48.0)*
Alp	84.0 (69.0, 106.0)	86.0 (70.0, 111.0)	83.0 (69.0, 99.0)	80.5 (66.0, 106.0)	85.0 (70.0, 101.0)	81.0 (69.0, 106.0)	84.0 (70.0, 100.0)
Total Bilirubin	0.6 (0.5, 0.9)	0.6 (0.5, 1.1)	0.6 (0.5, 0.9)	0.6 (0.5, 0.7)*	0.7 (0.6, 1.1)*	0.6 (0.5, 0.9)	0.7 (0.5, 0.9)
Platelets	217.8 (58.6)	205.5 (71.1)	230.1 (40.0)	215.4 (61.6)	218.9 (58.0)	209.9 (70.4)	227.6 (38.8)
Prothrombin Time	13.5 (0.8)	13.7 (0.9)*	13.3 (0.6)*	13.4 (0.7)	13.5 (0.8)	13.6 (0.8)	13.3 (0.6)
Ferritin	234.7 (152.8, 364.5)	264.5 (131.1, 358.7)	222.2 (171.7, 366.0)	329.3 (180.4, 365.1)	223.0 (136.1, 324.7)	290.7 (136.3, 365.1)	223.0 (168.9, 318.9)
Iron	92.0 (73.0, 117.0)	96.6 (64.0, 118.5)	91.0 (83.0, 112.0)	86.5 (71.0, 103.5)	93.0 (75.0, 117.0)	93.0 (70.7, 116.0)	90.9 (82.1, 117.0)
Transferrin Saturation	31.0 (24.0, 38.8)	35.0 (23.0, 39.0)	30.0 (25.0, 34.7)	29.0 (23.0, 35.1)	31.5 (25.0, 42.0)	32.0 (23.0, 39.0)	30.5 (25.6, 38.3)

Data are expressed as mean (SD), median (25th and 75th percentiles) or frequency (%).

*P <0.05. P values derived from student t test or Mann-Whitney test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables.

‡16 participants had missing information on waist circumference.

Table 2

Histologic Spectrum of Non-Alcoholic Steatohepatitis in 60 Puerto Rican veterans according to NASH by Brunt

	Total (N = 60)	NASH Assessed by Brunt		P-value
		+Dx (n=30)	-Dx (n=30)	
Steatosis Grade				
< 5%	6 (10.0)	1 (3.3)	5 (16.7)	0.149
5-33%	14 (23.3)	5 (16.7)	9 (30.0)	
34-66%	19 (31.7)	12 (40.0)	7 (23.3)	
67-100%	21 (35.0)	12 (40.0)	9 (30.0)	
Lobular Inflammation				
No Foci	17 (28.3)	3 (10.0)	14 (46.7)	0.005
< 2 Foci	35 (58.3)	21 (70.0)	14 (46.7)	
2 - 4 Foci	8 (13.3)	6 (20.0)	2 (6.7)	
Ballooning				
None	20 (33.3)	6 (20.0)	14 (46.7)	0.061
Few Ballooned Cells	36 (60.0)	21 (70.0)	15 (50.0)	
Many Ballooned Cells	4 (6.7)	3 (10.0)	1 (3.3)	
Fibrosis				
Absent	32 (53.3)	2 (6.7)	30 (100.0)	<0.001
Perisinusoidal/Pericellular Fibrosis	12 (20.0)	12 (40.0)	0 (0)	
Periportal Fibrosis	6 (10.0)	6 (20.0)	0 (0)	
Bridging Fibrosis	8 (13.3)	8 (26.7)	0 (0)	
Cirrhosis	2 (3.3)	2 (6.7)	0 (0)	

Data are shown as frequency percent distribution. P values derived from Fisher's exact test.

Table 3

Sensitivity, specificity and area under the ROC curve (AUC) for NAS and NAS including fibrosis

	NAS		NAS (including fibrosis)	
Brunt Criteria	≥5	≤4	≥5	≤4
+Dx	12	18	26	4
−Dx	6	24	7	23
Sensitivity (95% CI)	40.0 (22.7-59.4)		86.7 (69.3-96.2)	
Specificity (95% CI)	80.0 (61.4-92.3)		76.7 (57.7-90.1)	
AUC (95% CI)	0.71 (0.58-0.84)*		0.87 (0.78-0.96)*	
Adjusted AUC (95% CI)	0.65 (0.44-0.85)^		0.81 (0.61-0.97)^	

*P <0.05. P value derived from testing the statistical significance of equality of AUC estimates.

^P <0.05. P value derived from testing the statistical significance of equality of adjusted AUC estimates based on bootstrap assumption. Adjusted for alanine amino-T, aspartate amino-T, total bilirubin and hypertension medications.