A Comparison of Brunt’s Criteria, the Non-Alcoholic Fatty Liver Disease Activity Score (NAS), and a Proposed NAS Scoring that Includes Fibrosis in Non-Alcoholic Fatty Liver Disease Staging

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Objective: The aim of this study was to determine the prevalence of NASH in veterans with metabolic syndrome and compare histologic grading using the Brunt criteria, the NAFLD activity score (NAS), and a proposed NAS scoring system that has been modified to include fibrosis staging.

Methods: Veterans with metabolic syndrome, hepatic steatosis, and elevated ALT and AST levels and who underwent liver biopsies from 2004 through 2010 were included in this study. Biopsies were evaluated by a single hepatopathologist. Each biopsy was analyzed using the Brunt criteria, the NAS system, and the NAS system plus fibrosis staging.

Results: Sixty patients having a mean age of 50.4 (±12.8 years) were included in the study; 88.3% were men. Fifty percent met criteria according to the Brunt system. When biopsies were classified using the NAS system, only 30.0% (18/60) were found to have a score of 5 or more, while, when adding fibrosis staging, the number of patients with a score of 5 or more increased to 33 (55.0%). Upon evaluating the predictive ability of the NAS scoring system, we found that when including fibrosis staging we obtained a higher sensitivity (86.7% vs. 40.0%) and a lower specificity (76.7% vs. 80.0%).

Conclusion: In our population of patients with metabolic syndrome about 50 to 55% had steatohepatitis. There were significant differences between the scoring systems. When our NAS plus fibrosis system was used, more patients were recognized and the sensitivity increased. Further validation studies are required to evaluate this proposed modified NAS scoring system. [PR Health Sci J 2015;34:189-194]

Key words: Non-Alcoholic Fatty Liver Disease, Non-Alcoholic Steatohepatitis, Abdominal Obesity, Metabolic Syndrome, Histology

Non-alcoholic 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 the United States (US) (1,2). Attention has shifted from innocent fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH), a progressive fatty liver disease that may evolve into fibrosis and cirrhosis. The pathogenesis of non-alcoholic and viral-negative liver steatosis appears to be multifactorial, with many mechanisms having been proposed. There is evidence that NAFLD is associated with such metabolic diseases as hyperlipidemia, diabetes mellitus, and hypertension (3). It is closely related to obesity, which is unquestionably becoming one of the worse epidemics in the US and other parts of North America (3,4). NASH and obesity have received significant attention in the last 2 decades because of their strong association with both coronary artery disease (CAD) and cardiovascular disease (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 (MetS) were established and validated in adults. Hence, ATP-III defines MetS as a conglomerate of components including insulin resistance, obesity, hypertensive disease, and hyperlipidemia (5). During the last few decades in the US, there has been a significant increase in the incidence and prevalence of MetS. For example, it is estimated that approximately 22% of individuals in the general population are...

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affected by MetS (6). Epidemiological evidence has shown that
the prevalence of diabetes in Hispanics is among the highest
and is expected to reach epidemic proportions. The correct
identification of MetS components is of utmost importance in
order to prevent the high morbidity and mortality associated
with chronic liver disease (CLD) and CVD.

Hilden and Ground (7,8) determined, 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 [CMRFs]
and metabolic syndrome) or protective factors that might
attenuate (e.g. adiponectin) the progression of the disease (9).
Nevertheless, even without severe fibrosis, patients with NASH
continue to be at increased risk of developing cirrhosis, terminal
liver failure, or hepatocellular carcinoma (10,11). Therefore,
being able to promptly and accurately identify whether an
individual is at risk of developing NASH would almost certainly
be of benefit to him or her.

Sonographic and computerized tomographic imaging of the
liver have been useful in determining the presence of fatty liver
(“bright liver”) but have failed to identify the extent of fibrosis
(12). Serologic markers such as AST and ALT have also failed
to predict the degree of liver inflammation, necroinflammatory
activity, and the progression of disease (6,10,11,12). Liver
biopsy has been the only method that accurately quantifies these
factors, and therefore it is considered to be the gold standard
diagnostic tool and the only method for establishing a reliable
prognosis (9,12). There is a consensus that favors the use of the
liver biopsy because of 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 methods for the assessment of fibrosis severity
are under investigation. Biomarkers such as a cytokeratin-18 have
been validated for such use, although that particular biomarker
is imperfect (12,13). Transient elastography, which has been
successful in identifying advanced fibrosis in hepatitis B and C,
seems promising but nevertheless needs further investigation,
especially in the setting of obesity (13). Mathemetic models
such as the NAFLD fibrosis score calculator, which is based on
easily and readily available variables (age, BMI, hyperglycemia,
platelet count, albumin, and AST:ALT ratio), have also been
used to predict the presence of fibrosis (14).

Another way to dispense with the need for a liver biopsy is
to use the Enhanced Liver Fibrosis test; this is a non-invasive
diagnostic technique that has been used to predict the absence
or presence of fibrosis in adult patients with NAFLD, thus,
according to the claims, making it possible for up to 75% of
patients to avoid having to have a liver biopsy (15).

While liver biopsy remains as the gold standard to establish
a diagnosis of NASH and to predict risk of disease progression,
implementing a standardized histopathologic examination
scoring system to assure reproducibility of pathologists’ reports
and using a common language are of utmost importance. In

190, Dr. Elizabeth Brunt proposed a histological grading and
staging system for non-alcoholic steatohepatitis (16). In 2005,
a separate system scoring the features of NAFLD, called the
NAFLD activity score (NAS), was developed by a group of
experts as a tool to measure changes during therapeutic trials
(17). The validity of this scoring tool has not been extensively
evaluated, although it is in widespread use. The drawback of this
scoring system is that it proposes that only the unweighted sum
of steatosis, lobular inflammation, and ballooning be used, since
the intent of the scoring is to allow for the detailed analysis of
histologic changes associated with therapeutic interventions.
The Nonalcoholic Steatohepatitis Clinical Research Network
measured fibrosis in their original study but recommended not
including it in the NAS since it, fibrosis, is less reversible and is
a result of disease activity(17). Fibrosis is the best predictor of
disease progression; therefore of extreme relevance in clinical
practice. Using the NAS system without including fibrosis
scoring leads to underestimations in terms of the presence of
significant liver disease.

Our primary aim was to compare the sensitivity and specificity
of the Brunt criteria with that of the NAS system as well as with
that of a proposed scoring system that combines the NAS with
fibrosis staging and which we call “NAS plus fibrosis.”

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

Significance of this research
The present analysis could help us to better identify Puerto
Rican veterans who are at a high risk of developing the serious
complications associated with chronic liver disease (CLD). By
instituting the appropriate measures at an early stage, it may
be possible to halt the progression to CLD or even, in some
patients, reverse current liver damage.

This analysis allowed us to examine the validity and reliability
of the NAS system as well as that of the NAS plus fibrosis system
of our own devising and, subsequently, to compare the outcomes
of each scoring system with the actual NASH diagnoses in
our population of Puerto Rican veterans with both metabolic
syndrome and NAFLD of varying degrees of severity.

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

Study measures and variables consisted of demographic data including age (21–88 years), sex, and waist circumference. Information about diagnosis of or treatment for hypertension, diabetes, hypercholesterolemia, or hypertriglyceridemia was collected, as well. Laboratory tests examined the following: AST, ALT, triglycerides, LDL, HDL, total cholesterol, fasting blood sugar, and glucose tolerance. The results of abdominal sonogram(s) or abdominal CT(s) were reviewed; in addition, pathologic interpretations of liver biopsies were made (by an independent hepatologist) using Brunt’s criteria, the NAS system, and the NAS plus fibrosis score system.

Brunt’s criteria (13) include the following parameters: the 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]); and necroinflammation (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).

The NAS system was designed to specifically measure only features of active injury. Its result consists of the unweighted sum of scores of steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2), meaning that a result can range from 0 to 8. According to this scoring system, a calculated value of NAS that is less than 5 correlates with a diagnosis of NASH, and biopsies with scores of less than 3 are diagnosed as not being NASH (14). Scores between 3 and 4 are classified as possible or borderline NASH.

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

With the modified NAS plus fibrosis score system, a calculated value of NAS that was less than 5 was defined as NASH, and biopsies with scores of less than 3 were diagnosed as not being NASH.

Participants

The data were collected from subjects (60, in total) who met 3 or more of the ATP III diagnosis criteria for metabolic syndrome, which criteria look at abdominal obesity (by waist circumference, which, for men ≥ 102 cm and for women ≥ 88 cm); fasting triglycerides (≥ 150 mg/dl) and whether or not an individual is receiving treatment for hypertriglyceridemia; fasting HDL cholesterol or whether or not an individual is receiving treatment for hypercholesterolemia (in men<40, and in women<50); blood pressure (determined using the average of 2 readings taken at 2 minutes apart) or having previously received treatment for high blood pressure (defined as ≥ 130/85 mm Hg); and fasting blood glucose (>110 mg/dl) or whether or not an individual is being treated for DM2 with oral hypoglycemics or insulin.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study population. To test for non-normal distributions, we used 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’s criteria) were examined. We used the 2-group mean comparison t-test on normally distributed variables, the Wilcoxon rank-sum (Mann–Whitney) test for non-parametric continuous data, and chi-square or Fisher’s exact test on categorical data, whichever was appropriate. Subsequently, the same independent variables were compared according to the NAS and the NAS plus fibrosis score systems. Finally, Fisher’s exact test was used to assess the association between histological features (steatosis grade, lobular inflammation, ballooning, and fibrosis) and a diagnosis of NASH (based on Brunt’s criteria).

To evaluate the ability of the 2 histological scoring systems (NAS and NAS plus 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 AUCs for the 2 scoring systems while adjusting for variables significantly associated with a positive diagnosis of NASH (score ≥5) in any of the 2 scores. Bootstrap-corrected estimates of the ROC AUCs with their respective bias-corrected confidence intervals (95% CI) were computed. Statistical significance for all statistical analyses was set a priori (p<0.05) and Stata software was used (Stata Statistical Software: Release 12; 2011 StataCorp LP, College Station, TX).

Results

A total of 60 patients were included in this study. The mean age of the participants was 50.4 (±12.8), and 88.3% were male. The demographic and clinical characteristics of the study cohort (these last according to NASH by Brunt’s criteria, the NAS, and the NAS plus fibrosis score) are described in Table 1.

Thirty patients (50.0%) met the criteria for NASH, according to the Brunt system. Upon classifying biopsies using the NAS, 18 patients (30.0%) had a score of 5 or more; when we included fibrosis as part of the NAS, the number of patients with a score of 5 or more increased to 33 (55.0%).

After comparing the sociodemographic, clinical, and cardiometabolic variables based on NASH (as determined by the Brunt criteria and the 2 NAS scores), statistically significant differences were found between groups. Age and prothrombin time were significantly higher among patients with a NASH
Table 1. Demographic and clinical characteristics of Puerto Rican veterans with NASH, by Brunt’s criteria, by NAS, and by NAS plus fibrosis

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>NASH +Dx</th>
<th>NASH -Dx</th>
<th>NAS ≥ 5</th>
<th>NAS ≤ 4</th>
<th>NAS plus fibrosis ≥ 5</th>
<th>NAS plus fibrosis ≤ 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N (%)</td>
<td>60 (100.0)</td>
<td>30 (50.0)</td>
<td>30 (50.0)</td>
<td>18 (30.0)</td>
<td>42 (70.0)</td>
<td>33 (55.0)</td>
<td>27 (45.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.4 (12.8)</td>
<td>54.1 (11.4)*</td>
<td>46.6 (13.3)*</td>
<td>51.6 (14.6)</td>
<td>49.8 (12.2)</td>
<td>50.9 (13.3)</td>
<td>49.7 (12.4)</td>
</tr>
<tr>
<td>Males</td>
<td>53 (86.3)</td>
<td>26 (86.7)</td>
<td>27 (90.0)</td>
<td>15 (83.3)</td>
<td>38 (90.5)</td>
<td>28 (84.9)</td>
<td>25 (92.6)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>25 (41.7)</td>
<td>16 (53.3)</td>
<td>9 (30.0)</td>
<td>10 (55.6)</td>
<td>15 (35.7)</td>
<td>17 (51.5)</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Diabetes Mellitus Meds.</td>
<td>18 (30.0)</td>
<td>12 (40.0)</td>
<td>6 (20.0)</td>
<td>7 (38.9)</td>
<td>11 (26.2)</td>
<td>12 (36.4)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44 (73.3)</td>
<td>21 (70.0)</td>
<td>23 (76.7)</td>
<td>15 (83.3)</td>
<td>19 (69.1)</td>
<td>22 (75.8)</td>
<td>12 (70.4)</td>
</tr>
<tr>
<td>Hypertension Meds.</td>
<td>34 (56.7)</td>
<td>17 (56.7)</td>
<td>17 (56.7)</td>
<td>15 (83.3)</td>
<td>19 (45.2)*</td>
<td>22 (66.7)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>47 (78.3)</td>
<td>22 (73.3)</td>
<td>25 (83.3)</td>
<td>14 (77.8)</td>
<td>33 (78.6)</td>
<td>25 (75.8)</td>
<td>22 (81.5)</td>
</tr>
<tr>
<td>Lipid Meds.</td>
<td>29 (48.3)</td>
<td>15 (50.0)</td>
<td>14 (46.7)</td>
<td>9 (50.0)</td>
<td>20 (47.6)</td>
<td>17 (51.5)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Waist Circumference cm‡</td>
<td>103.0 (91.3, 109.0)</td>
<td>104.0 (95.0, 114.0)</td>
<td>97.0 (47.0, 108.0)</td>
<td>99.0 (94.0, 110.0)</td>
<td>103.0 (90.5, 108.0)</td>
<td>103.0 (94.0, 111.5)</td>
<td>108.0 (72.0, 108.0)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>31.9 (4.4)</td>
<td>32.2 (4.4)</td>
<td>31.6 (4.4)</td>
<td>32.1 (4.4)</td>
<td>31.8 (4.4)</td>
<td>32.0 (4.4)</td>
<td>31.8 (4.4)</td>
</tr>
<tr>
<td>Alanine Amino-T</td>
<td>67.5 (54.5, 95.5)</td>
<td>48.0 (35.5, 63.0)</td>
<td>39.5 (34.0, 51.0)</td>
<td>49.0 (37.0, 63.0)</td>
<td>40.0 (34.0, 53.0)</td>
<td>49.0 (37.0, 63.0)*</td>
<td>80.0 (34.0, 48.0)*</td>
</tr>
<tr>
<td>Aspartate Amino-T</td>
<td>42.0 (35.5, 57.5)</td>
<td>48.0 (37.0, 63.0)</td>
<td>39.5 (34.0, 51.0)</td>
<td>49.0 (37.0, 63.0)</td>
<td>40.0 (34.0, 53.0)</td>
<td>49.0 (37.0, 63.0)*</td>
<td>80.0 (34.0, 48.0)*</td>
</tr>
<tr>
<td>Alp</td>
<td>86.0 (69.0, 106.0)</td>
<td>86.0 (70.0, 111.0)</td>
<td>83.0 (69.0, 99.0)</td>
<td>80.5 (66.0, 106.0)</td>
<td>85.0 (70.0, 101.0)</td>
<td>81.0 (69.0, 106.0)</td>
<td>84.0 (70.0, 100.0)</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.6 (0.5, 0.9)</td>
<td>0.6 (0.5, 1.1)</td>
<td>0.6 (0.5, 1.1)</td>
<td>0.6 (0.5, 1.1)</td>
<td>0.6 (0.5, 1.1)</td>
<td>0.6 (0.5, 1.1)</td>
<td>0.7 (0.5, 1.1)</td>
</tr>
<tr>
<td>Platelets</td>
<td>217.8 (25.8, 36.8)</td>
<td>205.5 (27.1, 30.0)</td>
<td>230.1 (40.0)</td>
<td>215.4 (61.6)</td>
<td>218.9 (58.0)</td>
<td>209.9 (58.0)</td>
<td>227.6 (58.0)</td>
</tr>
<tr>
<td>Prothrombin Time</td>
<td>13.5 (0.8)</td>
<td>13.7 (0.9)*</td>
<td>13.3 (0.6)*</td>
<td>13.4 (0.7)</td>
<td>13.5 (0.8)</td>
<td>13.6 (0.8)</td>
<td>13.3 (0.8)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>234.7 (152.8, 364.5)</td>
<td>264.5 (131.1, 358.7)</td>
<td>222.2 (171.7, 366.0)</td>
<td>329.3 (180.4, 365.1)</td>
<td>223.0 (136.1, 324.7)</td>
<td>290.7 (136.3, 365.1)</td>
<td>223.0 (168.9, 318.9)</td>
</tr>
<tr>
<td>Iron</td>
<td>92.0 (73.0, 117.0)</td>
<td>96.6 (64.0, 118.5)</td>
<td>91.0 (83.0, 112.0)</td>
<td>93.0 (71.0, 103.5)</td>
<td>90.0 (75.0, 117.0)</td>
<td>93.0 (70.7, 116.0)</td>
<td>90.0 (82.1, 117.0)</td>
</tr>
<tr>
<td>Transferrin Saturation</td>
<td>31.0 (24.0, 38.8)</td>
<td>35.0 (23.0, 39.0)</td>
<td>30.0 (25.0, 34.7)</td>
<td>29.0 (23.0, 35.1)</td>
<td>31.5 (25.0, 42.0)</td>
<td>32.0 (23.0, 39.0)</td>
<td>30.5 (25.6, 38.3)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD), median (25th and 75th percentiles), or frequency (%). *P<0.05. P-values derived from student’s t-test or the Mann–Whitney test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. ‡16 participants were missing information on waist circumference.

The percentage of participants with a NAS of 5 or more and who were taking medication for hypertension was higher than that of those participants with a NAS of 4 or lower who were also taking such medication (83.3% vs. 45.2%); in addition, the former had lower total bilirubin levels (p<0.05). On the other hand, patients with a score of 5 or more in the NAS plus fibrosis system had significantly higher levels of alanine and aspartate enzymes than did patients with a score of 4 or lower (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 with the NAS system. A high proportion of patients with NASH had high 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 found to be significantly associated with NASH (p<0.05).

Upon evaluating the ability of the 2 scoring systems to detect NASH, we found that the NAS plus fibrosis scoring system had a higher sensitivity (86.7% vs. 40.0%) and a lower specificity (76.7% vs. 80.0%) than the NAS system alone did. Regarding the unadjusted AUCs we obtained, our NAS plus fibrosis scoring system more accurately detected 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 plus fibrosis system was more accurate than was the NAS alone at diagnosing NASH (score ≥5), and this result was statistically significant (AUCs: 0.81 vs. 0.65; p = 0.002) (Table 3).
Discussion

Non-alcoholic fatty liver disease (along with its eventual progression to NASH) is not a benign liver disease. It is associated to an increased overall mortality when compared to matched control populations; mostly due to cardiovascular disease. Furthermore, patients with NASH have a 20% lifetime risk of developing cirrhosis and an increased liver-related mortality. Earlier identification of the risk factors leading to this serious illness is of outmost importance. Patients with metabolic syndrome, the incidence of which has increased in the US, are at high risk of developing this disease. Liver biopsy remains the gold standard for establishing an accurate histological diagnosis (18). Various histological scoring systems have also been developed to achieve the goal of accurate diagnosis. In this analysis, we compared the sensitivity and specificity of the system that makes use of Brunt’s criteria with those of the NAS system as well as with those obtained using our proposed NAS plus fibrosis scoring system, doing so by comparing the outcomes arrived at by each system with the actual NASH diagnoses in our population of Puerto Rican veterans with both metabolic syndrome and varying levels of severity of NAFLD.

Table 2. Histologic spectrum of NASH in 60 Puerto Rican veterans with NASH, according to Brunt’s criteria

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

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 plus fibrosis

<table>
<thead>
<tr>
<th>Brunt’s Criteria</th>
<th>NAS</th>
<th>NAS plus fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>+Dx</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>-Dx</td>
<td>6</td>
<td>24</td>
</tr>
</tbody>
</table>

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

Figure 1. Histopathologic changes in NASH: (A) steatosis, (B) ballooning, and (C) fibrosis.
In our study, including fibrosis as part of the NAS scoring system increased the accuracy of the NASH diagnosis compared to that of both the original Brunt scoring system and that of the NAS without fibrosis staging. A recent publication by some of the members of the Nonalcoholic Steatohepatitis Clinical Research group addresses the common use in clinical practice of a NAS score greater than or equal to 5 as a substitute for the histologic diagnosis of steatohepatitis, concluding 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 staging in the NAS score may result in the better identification of patients with significant disease activity and the severity of liver damage sustained by those patients. Our findings indicate that there is a need for further investigation and validation with a larger sample.

Resumen

Objetivo: El propósito de este estudio era determinar la prevalencia de NASH en veteranos con el síndrome metabólico y comparar los sistemas de puntuación histológica de Brunt, NAS ("NAS activity score," en inglés) y un propuesto NAS incluyendo fibrosis. Métodos: Los veteranos con el síndrome metabólico, estesatosís hepática y elevación de las enzimas hepáticas ALT/AST que se sometieron a una biopsia de hígado entre el 2004 y 2010 fueron incluidos en este protocolo. Las biopsias fueron evaluadas por un hepatopatólogo. Todas las biopsias se catalogaron utilizando los criterios de Brunt, NAS, y NAS incluyendo fibrosis. Resultados: Sesenta pacientes con edad promedio de 50.4 (±12.8) fueron incluidos en el estudio; de los cuales 88.3% eran hombres. Cincuenta por ciento cumplieron criterios para NASH según Brunt. Cuando se clasificaron usando NAS, 30% (18/30) obtuvieron puntuación de ≥5; mientras al añadir fibrosis, aquellos con puntuación ≥5 aumentó a 33 (55.0%). Cuando se evaluó la capacidad predictiva de NAS se encontró que al incluir fibrosis se obtuvo una mayor sensividad (86.7% vs. 40.0%) y una menor especificidad (76.7% vs. 80.0%). Conclusión: Aproximadamente el 50-55% de nuestra población con síndrome metabólico se diagnosticó con estesatohepatitis. Se encontraron diferencias significativas entre los sistemas de puntuación histológica. Al usar NAS más fibrosis se reconocieron más pacientes y la sensitividad aumentó. Se requieren estudios futuros de validación para evaluar el NAS modificado propuesto.

Acknowledgments

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References