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Original Article

Alcoholic vs. Nonalcoholic Steatohepatitis: Vascular Branching Heterogeneity on Magnetic Resonance Imaging as a Diagnostic Marker

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Abstract

Background and Aims: Distinguishing alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH) with biopsy alone is often difficult without a reliable clinical context. A novel finding on liver imaging, perivascular branching heterogeneity, has shown promise in distinguishing between these chronic liver diseases. Our study investigated the role of this finding on imaging to differentiate between ASH and NASH. The aim of this study was to determine the utility and reproducibility of this novel radiographic marker to help distinguish ASH from NASH. ***Methods:*** This was a retrospective cohort study conducted between 2016 and 2020 in patients with both liver biopsy-confirmed steatohepatitis/chronic hepatitis and abdominal magnetic resonance imaging within 13 months of each other. Two radiologists, blinded to patient clinical history and diagnosis, categorized the appearance of the liver as: 1- homogeneity, 2- mild heterogeneity, 3- moderate heterogeneity, 4- possible perivascular branching, 5- definite perivascular branching. ***Results:*** Of the 90 patients in the study, 60 were identified as NASH and 30 as ASH. The area under the curve (AUC) for both reader 1 and 2 when using the 5-point scale was 0.69 (CI: 0.56–0.82, p=0.006) and 0.72 (CI: 0.60–0.85, p=0.001), respectively. The positive predictive value (PPV) for identification of ASH when scoring 5 was 64.7% and 66.7% for reader 1 and 2, respectively. Interclass correlation coefficient was 0.74 in patients with ASH, indicating moderate reliability among both readers. ***Conclusions:*** Identification of this perivascular branching pattern on imaging is a promising novel diagnostic marker that can be used with other methods to help distinguish between ASH and NASH.

Keywords: Alcoholic liver diseases; Steatohepatitis; Magnetic resonance imaging; Nonalcoholic fatty liver disease.

Abbreviations: ALD, alcoholic liver disease; ASH, alcoholic steatohepatitis; BMI, body mass index; ICC, interclass correlation coefficient; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

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Introduction

Alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) are two major causes of chronic liver disease in the USA.[1–5] Current prevalence estimates for NAFLD are 10–30%, and 4.7% for fatty liver secondary to ALD, with ALD prevalence projected to rise with recent increases in alcohol consumption.[5–8] This poses a serious threat to public health, as both diseases may increase morbidity and mortality as they progress, with development of complications including cirrhosis and hepatocellular carcinoma.[2] In both ALD and NAFLD, the sequence of events that end in cirrhosis begins with hepatic steatosis, the deposition of triglycerides and other lipids within hepatocytes. This deposition may cause inflammation and hepatocellular injury, resulting in steatohepatitis.[9,10] Identifying steatohepatitis helps to better understand which patients are at risk of progressing to cirrhosis and developing decompensated liver disease. The current gold standard to identify steatohepatitis is through histologic evaluation on liver biopsy.[11] However, this procedure carries the risk of serious complications, including pain at the biopsy site, bleeding, and the possibility of sampling error.[12–14] In the absence of alcohol intake, hallmark histologic features of nonalcoholic steatohepatitis (NASH) include macrovesicular steatosis, ballooning degeneration, lobular inflammation, and Mallory-Denk bodies.[15] While these features may also be present in alcoholic steatohepatitis (ASH), characteristics unique to ASH are sclerosing hyaline necrosis, alcoholic foamy degeneration, inflammatory and occlusive lesions in hepatic outflow veins, and cholestasis.[16] Unfortunately, distinguishing between NASH and ASH on pathology often proves difficult, and largely depends on pathologist skills and experience. Clinical history-taking is a simple and effective way to help distinguish ASH from NASH. However, this often

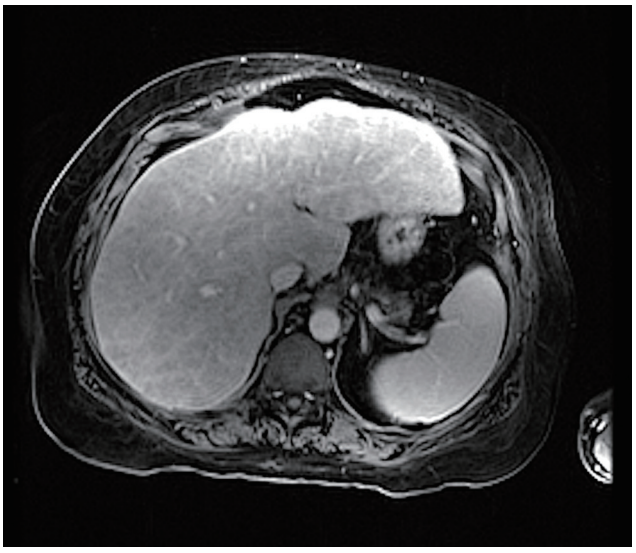

Fig. 1. Contrast-enhanced arterial phase MRI of the liver demonstrating moderate heterogeneity (score of 3). MRI, magnetic resonance imaging.

requires a reliable historian.[17] Thus, efforts have been made for other noninvasive assessments of steatohepatitis. This includes imaging and serological markers.

Magnetic resonance imaging (MRI) has recently developed expanded quantitative capabilities for evaluating hepatic steatosis and fibrosis, such as magnetic resonance elastography and MRI-proton density fat fraction.[18–20] However, our knowledge of how imaging findings vary in NASH and ASH has been limited. A small observational study noted perivascular steatosis on computed tomography and MRI images, predominantly in patients with alcoholic cirrhosis or with regular alcohol consumption.[21] At our medical center, we have seen a novel pattern of vascular branching heterogeneity on MRI examinations of patients with ALD, and conducted a small pilot study suggesting a relationship between this perivascular branching pattern and ASH.[22] Given the need for more tools to distinguish between ASH and NASH, especially in the setting of a poor patient history, the aim of this study was to better describe the pattern of imaging findings and to test a scoring system that can determine the presence of perivascular branching as a predictor for ASH. The primary outcome of this study was to determine the utility and reproducibility of this novel radiographic marker in distinguishing ASH from NASH. Secondary outcomes included determining any association between imaging findings and liver histopathology, as well as the relationship between the degree of steatosis as determined by MRI, and ASH, and NASH cases.

Methods

Patient population

This was a retrospective cohort study of MRI exams performed at a single tertiary medical center from January 2016 to December 2020. Patients were obtained by searching for medical records that had both a liver biopsy and abdominal MRI with contrast performed within 13 months of each other. Liver biopsies needed to show steatohepatitis or chronic hepatitis. Patients were excluded if there were positive markers for viral hepatitis A, B, or C, or autoimmune, genetic (i.e. alpha-1-antitrypsin), or metabolic diseases (i.e. hemochromatosis, Wilson's disease). Among eligible patients, final selection was determined to achieve a 2:1 ratio of NASH to ASH. The study protocol was approved by the Thomas Jefferson University Institutional Review Board with a waiver of patient informed consent.

Data collection

Baseline demographic data included age, patient sex, body mass index (BMI), and race/ethnicity along with pathology findings and MRI reports from review of the patient electronic medical record. A clear clinical history of alcohol use through clinician documentation was used to distinguish patients between ASH and NASH. The deidentified MRI examinations were scored independently by readers, placing them into one

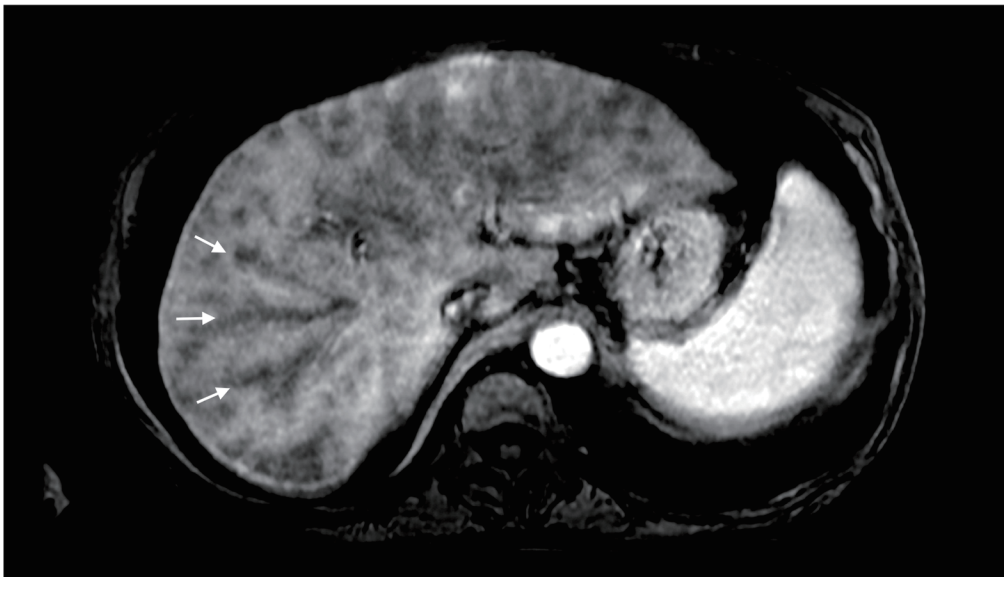

Fig. 2. Contrast-enhanced arterial phase MRI of the liver demonstrating perivascular branching pattern (score of 5) identified by white arrow. MRI, magnetic resonance imaging.

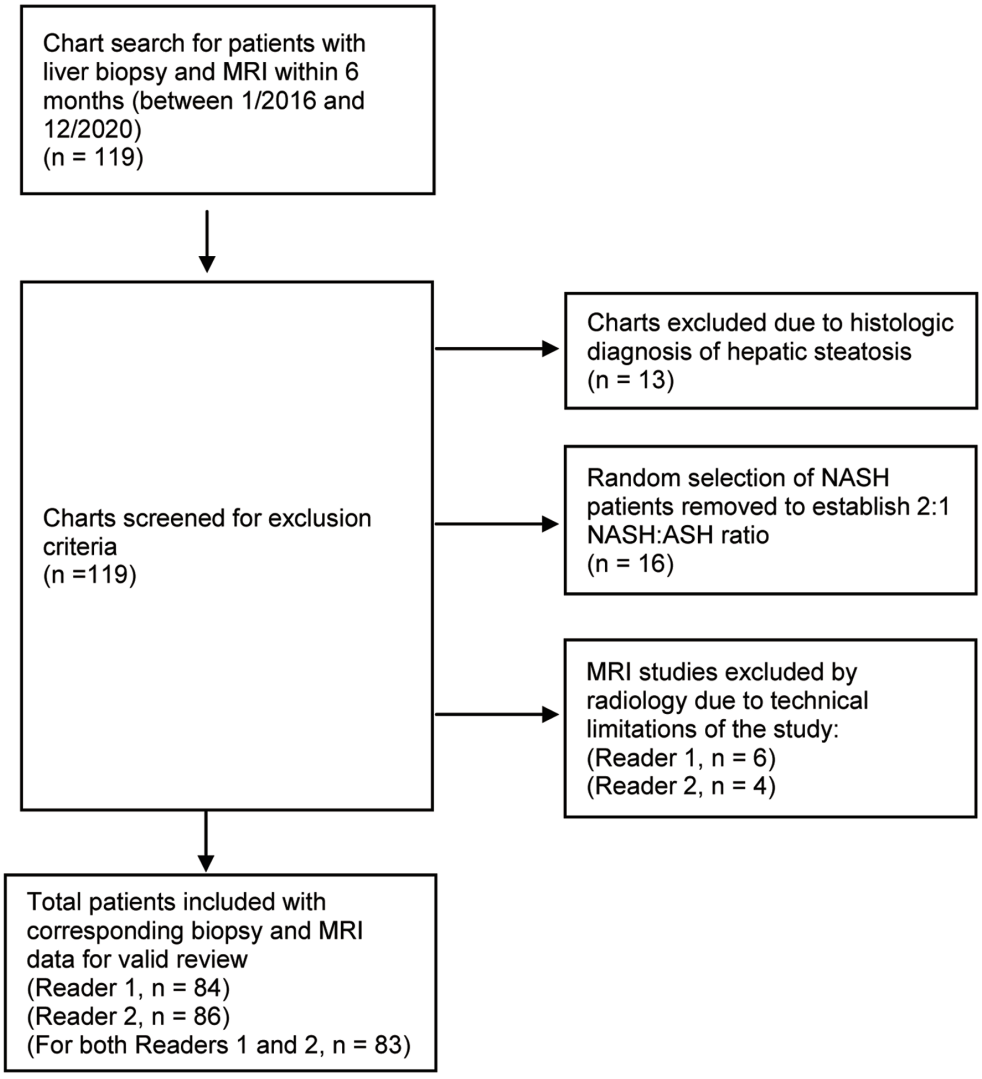

Fig. 3. Flowchart of chart review and patient selection for final study analysis. MRI, magnetic resonance imaging.

of five categories based on the presence of hepatic heterogeneity and whether it appeared randomly or was organized in a vascular branching pattern: 1- homogeneity, 2- mild heterogeneity, 3- moderate heterogeneity (Fig. 1), 4- possible perivascular branching, 5- definite perivascular branching (Fig. 2). Readers 1 and 2 were both subspecialty-trained abdominal radiologists. For exams that showed a branching pattern of heterogeneity, each radiologist was given the option of listing one or more pulse sequences that clearly showed the pattern. Images with scores of 4 or 5 were compared to their liver biopsy samples to observe the degree of steatohepatitis noted on the specimens. MRI exams were also scored for hepatic steatosis as 1- absent, 2- mild, 3- moderate, and 4- severe based on decreased signal on opposed phase versus in-phase T1-weighted images.

Statistical analysis

Simple statistics were used for calculation of patient demographics. Interclass correlation coefficients (ICC) were used to assess reliability, reflecting both the agreement and correlation, between scoring performed by the two readers based on a mean rating (k=2), absolute agreement, 2-way random-effects model. Receiver operative characteristic (ROC) analysis was conducted for each reader-scale combination. The optimal cutoff value (i.e. the point where the reader score was most sensitive and specific) for each scale were obtained by a ROC curve based on maximum value of the sum of resulting sensitivity and specificity. Positive predictive values (PPV) and negative predictive values (NPV) were calculated with definitive perivascular branching heterogeneity (score of 5) indicative of ASH. Chi-square analysis was performed to determine if there was any association between radiological ASH scoring and necroinflammatory pathology noted on liver biopsy. Potential correlation or lack thereof between steatosis on imaging between ASH and NASH groups was evaluated with Mann-Whitney U tests. The statistical analysis was performed with SPSS v. 26 (IBM Corp., Armonk, NY, USA).

Results

Overall, 119 patients had both MRI and liver biopsy within 13 months of each other (Fig. 3). Pathology revealing simple he-

Table 1. Baseline characteristics of NASH and ASH patients

Characteristics	NASH, *n*=60	ASH, *n*=30	*p*-value
Age (mean years)	60.5 (SD 9.38)	54.1 (SD 11.48)	0.012
BMI	33.9 (SD 5.37)	26.1 (SD 5.76)	<0.002
Race (%)			
Caucasian	93.3% (56/60)	66.7% (15/30)	
African American	5% (3/60)	16.7% (5/30)	
Hispanic	1.7% (1/60)	16.7% (5/30)	
Sex (%)			
Male	50% (30/60)	50% (15/30)	
Female	50% (30/60)	50% (15/30)	

ASH, alcoholic steatohepatitis; BMI, body mass index; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

patic steatosis was present in 13 of the patients, which were then excluded. Thirty patients with a history and pathology consistent with ASH were identified, and 76 were both clinically and pathologically confirmed to have NASH. To achieve a randomly arranged ratio of 2:1 NASH to ASH patients, 16 NASH patients were randomly excluded, resulting in a total of 60 patients diagnosed with NASH and 30 with ASH. An additional seven studies were excluded by radiologists as they were found to be of poor quality with difficulty in interpretation (six cases for reader 1 and four cases for reader 2) leaving 83 valid MRI reports shared by both radiologists for statistical analysis.

Baseline demographics of the patient population are summarized in Table 1. The mean ages of NASH and ASH patients were 60.5 and 54.1, respectively (p=0.012). NASH patients had a mean BMI of 33.9 kg/m^2, but that of ASH patients was 26.1 kg/m^2 (p<0.001). After image exclusion by radiologists due to technical limitations in the quality of the study preventing classification, MRI scoring of 57 patients with NASH and 26 patients with ASH between both radiologists were analyzed. Among exams scored as branching heterogeneity, the pulse sequences best showing this pattern was noted by reader 1 in arterial phase (n=26), diffusion-weighted imaging n=12), T2-weighted (n=6), portal venous phase (n=4), and opposed phase (n=2). Reader 2 noted the branching pattern most clearly on the arterial phase (n=78), diffusion-weighted imaging (n=12), portal venous and delayed phases (n=1 for each).

ICC analysis revealed moderate overall reliability between the two radiologists at 0.69 (CI: 0.46–0.82). For true NASH patients the ICC value was 0.57 (CI: 0.26–0.75), and for true ASH patients the ICC was 0.74 (CI: 0.38–0.89, Table 2). The steatosis ICC value for the overall dataset was 0.82 (CI: 0.71–0.88).

Among the 84 MRI-valid cases reviewed by reader 1, 68% (57/84) had a true diagnosis of NASH. Of the 57 true NASH cases, 70% were categorized as homogenous or nonspecific heterogeneous (score of 1, 2, or 3), and 30% were characterized with possible or definite perivascular branching heterogeneity (score of 4 or 5). Of the remaining 32% (27/84) of true ASH cases for reader 1, 37% were classified as homogeneous or nonspecific heterogeneity (score of 1, 2, or 3) and 63% had possible or definite perivascular branching heterogeneity (score of 4 or 5). For reader 2, 86 valid cases were reviewed, 67% (58/86) of which had true NASH. Of the 58 true NASH patients, 93% were categorized as homogeneous or nonspecific heterogeneity (score of 1, 2, or 3) and 7% as possible or definite perivascular branching (score of 4 or 5). Among the remaining 33% (28/86) patients with true ASH, 68% were classified as homogeneous or nonspecific heterogeneity (score of 1, 2, or 3), and 32% as perivascular branching heterogeneity (score of 4 or 5).

Cases scored as 5 (definite perivascular branching), were further analyzed as a true marker for identifying ASH. Of the 84 cases reviewed by reader 1, 17 cases (20%) were categorized as 5, yielding a PPV of 65% and NPV of 76% for identification. Of the 86 cases reviewed by reader 2, only three were scored as 5, yielding a PPV of 67% and a NPV of 69%. The area under the curve (AUC) for reader 1, using the 5-point scoring system, was 0.69 (CI: 0.56–0.82, p=0.006, Table 3). The optimal cutoff, defined as where the reader scoring was most sensitive and specific, for reader 1 occurred with a score of 5, with a sensitivity of 42.3% and a specificity of 89.5%. ROC analysis for reader 2 had an AUC of 0.72 (CI: 0.60–0.85, p=0.001). Reader 2 was most sensitive and specific at a score of 2, with a sensitivity of 76.9% and a specificity of 59.6%. Additionally, the severity of necroinflammatory activity on pathology was reviewed for patients with some presence of perivascular branching identified on imaging identified by both readers, noted by a score of 4 or 5. A total of 17 patients with true ASH were given a score of 4 or 5 by either of both readers. Of these, 29.4% (5/17) had steatohepatitis with severe activity, 17.6% (3/17) steatohepatitis with moderate activity, and 52.9% (9/17) steatohepatitis with mild activity. A score of 4 or 5 was also given to 19 patients identified with NASH. Review of pathology revealed 26.3% (5/19) had steatohepatitis with moderate activity, 68.4% (13/19) had steatohepatitis with mild activity, and 5.2% (1/19) had steatohepatitis with minimal activity. A chi-square test was performed to see if there was any association between the ASH necroinflammatory activity determined by pathology on liver biopsy and scores assigned by the readers. The results revealed that there was no significant association between the scores determined

Table 2. Interclass correlation analysis of MRI between both readers

Condition	Valid cases	ICC value
Overall	83/90	0.69 (0.46–0.82)
NASH	57/60	0.57 (0.26–0.75)
ASH	26/30	0.74 (0.38–0.89)
Steatosis	83/90	0.82 (0.71–0.88)

ASH, alcoholic steatohepatitis; ICC, interclass correlation coefficient; NASH, nonalcoholic steatohepatitis.

Table 3. Receiver operating characteristic curve analysis and optimal cutoff scores of both readers

Reader	AUC	*p*-value	Optimal cutoff point for classification		
			Cutoff point score	Sensitivity	Specificity
1	0.69 (0.56–0.82)	0.006	5	42.3%	89.5%
2	0.72 (0.60–0.85)	0.001	2	76.9%	59.6%

AUC, area under the curve.

by radiology readers and the pathology findings ($p \geq 0.158$). Mann-Whitney *U* tests revealed that the MRI scores for steatosis assigned by each reader were not significantly different between ASH and NASH patients ($p \geq 0.134$).

Discussion

The findings of this retrospective study show that perivascular branching heterogeneity, as seen on MRI, helped to differentiate ASH and NASH. That is clinically helpful if liver biopsy alone does not definitively distinguish ASH from NASH, and the reporting of alcohol use is unreliable. We are aware of only one other study that described perivascular heterogeneity. It was a small observational study in conducted 2005 without pathologic correlation noting perivascular steatosis in both computed tomography and MRI.[21] Our research strengthens existing literature not only by reporting this pattern of steatosis in the liver, but also detailing a scoring system for radiologists to adopt at similar institutions, reading MRIs of the abdomen with contrast. Our study also had a larger sample size.

Identification of possible or definite perivascular branching (scores of 4 or 5) differed between readers 1 and 2 (63% and 32.1%, respectively). When using a score of 5 as a definitive identifier of ASH, the novel grading system was able to distinguish ASH from NASH based on ROC analysis. Both readers were more likely to correctly identify ASH on imaging when identifying perivascular branching heterogeneity. However, the score at which each reader was most sensitive and specific differed. Reader 1 achieved it when scoring 5 and reader 2 achieved it when scoring 2. Reader 1 identified more cases with a score of 5 (definite perivascular branching) as opposed to reader 2, at 17 and 3, respectively. That may have resulted in part because of a difference in the experience of the readers in identifying this novel marker. However, when calculating the PPV and NPV using a score of 5 for the identification of ASH, the reader-results were similar (PPVs of 64.7% and 66.7% for readers 1 and 2, respectively, and NPVs of 76.1% and 68.7% for readers 1 and 2, respectively). The findings support previous observations and show that this unique imaging marker may help distinguish ASH from NASH.

While the identification of perivascular fat deposition seems to be associated with ALD, its pathogenesis is unclear.[23,24] It is also not understood if it occurs in other disease entities. Hamer *et al*.[21] reported that fat accumulated in different zones of the liver depending on the variation in perfusion.[21] Differential portal blood flow may affect the distribution of steatosis, given that portal perfusion supplies the lipid, and decreased portal flow leads to hepatocellular atrophy and dysfunction.[25] However, we do not have a clear explanation for the potential difference in portal flow with this pattern. An attempt to correlate our findings on MRI with the necroinflammatory activity on hepatic histopathology yielded no significant association. It is not clear whether microscopic pathologic changes are at all causative or even correlative to gross findings we appreciate on imaging. It is also difficult to even attempt correlation when there exists variation in nomenclature used (i.e. steatohepatitis/chronic hepatitis) both within and between pathologist review. Furthermore, a biopsy in a heterogeneous liver may have large sampling variation. The answer may therefore lie in a more detailed understanding in the pathophysiology between ASH and NASH, for which the mechanisms of injury remain unclear. Additionally, a more detailed examination of gross liver specimens may help with understanding this perivascular heterogeneity, which may be incorporated in future studies.

Our findings also found no significant difference between ASH and NASH when scoring the degree of steatosis. However, that is likely in part because both disease states result in the deposition of fat within hepatocytes. Another limitation of our study is its retrospective nature. While biopsies and imaging were 13 months apart, we cannot exclude the possibility of significant changes in patient alcohol consumption or overall health (i.e. diabetes control) during the interval. Our study only included two radiologists. Future studies should include more radiologists to identify perivascular branching to ensure the identification and replication of this finding and expand to include more patients as well. Future studies may also consider a prospective design in which radiologists can be blinded to reading MRIs from healthy controls that did not undergo liver biopsy versus NASH, ASH, and other liver diseases, although, we are not aware of any in addition to NASH and ASH that may have that finding). Further, we did not conduct a systematic training session for identifying the branching pattern; the lack of such education likely contributed to some of the variability between the two readers. This may be done in future studies with a few training cases before independent reading. To our knowledge, this is the largest study using both pathology and diagnostic imaging to distinguish ASH from NASH. Our proposed method of detecting perivascular branching on MRI to distinguish ASH from NASH is not necessarily superior to other noninvasive methods. For example, some studies reported that serum markers such as lipidomic markers, carbohydrate-deficient transferrin, or gamma-glutamyl transferase levels were of help.[26–28] However, they are not as widely available in the clinical setting, nor as understood, compared with performing and reading an MRI study. Indeed, our methods may even be incorporated into a scoring system that combines multiple modalities (e.g. serum markers, imaging findings, pathology, and others). For example, the ALD/NAFLD index, a model created by Dunn *et al*.[29] in 2006 called includes several variables including mean corpuscular volume, AST/ALT, BMI, and sex score to estimate the probability of a patient having ALD. Use of our scoring as a diagnostic imaging marker may further support other existing models and guide future studies investigating noninvasive tools to diagnose NASH and ASH. Especially in a time when alcohol use is expected to continue to increase, these findings are important and relevant.

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None to declare.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (DG, DM, DH), acquisition of data (DG, NN, JR, DM, HN), analysis and interpretation of data (DG, NN, JKD), manuscript writing (DG), critical revision (DM, DH), statistical analysis (JKD). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The study protocol was approved by the Thomas Jefferson University Institutional Review Board with a waiver of patient informed consent.

Data sharing statement

All deidentified data are available upon request.

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