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**Research Letter**

**ONLINE FIRST**

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# Mortality Among Users of Anabolic Steroids

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Androgenic anabolic steroids (AAS) are highly effective in promoting muscle growth.<sup>1,2</sup> In 2014, it was estimated that about 3 million to 4 million individuals in the US had used AAS in their lifetime.<sup>1</sup> Unfortunately, these drugs are associated with a range of serious adverse effects including severe cardiovascular and psychiatric morbidity and death.<sup>2,3</sup> However, data are limited to case reports and smaller cohorts.<sup>2</sup> We investigated mortality and cause of death among a large cohort of AAS users, with a comprehensive follow-up period, and compared the cohort with a control group.



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# Radiological diagnosis of hepatocellular carcinoma does not preclude biopsy before treatment

## Authors

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**Background & Aims:** The diagnosis of hepatocellular carcinoma (HCC) in patients with cirrhosis relies on non-invasive criteria based on international guidelines. The advent of systemic therapies warrants reconsideration of the role of biopsy specimens in the diagnosis of HCC. Accordingly, we investigated the diagnostic performance of the LI-RADS 2018 and the AASLD 2011 criteria.

**Methods:** Consecutive patients with cirrhosis who underwent a biopsy for suspected HCC between 2015 and 2020 were included. The available imaging studies (computed tomography and/or magnetic resonance imaging) were blindly reviewed by two independent radiologists. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed for LI-RADS, AASLD, and biopsies.

**Results:** In total, 167 patients underwent both available biopsy and imaging. Of the 137 relevant biopsies, 114 patients had HCC (83.2%), 12 (9%) had non-HCC malignant lesions, and 11 (8%) had benign nodules. The PPV and NPV of the biopsies were 100% and 62%, respectively; 30 biopsies were non-contributive. The PPV and NPV of the LI-RADS categories were 89% and 32.8% for LR-5 and 85.5% and 54.5% for LR-4 + 5 + TIV, respectively. The PPV and NPV of the 2011 AASLD criteria were 93.2% and 35.6%, respectively. The interobserver kappa ( $k = 0.380$ ) for the LR-5 categories was reasonable. Of 100 LR-5 nodules, 11 were misclassified, in particular one case was a colorectal metastasis, and two cases were cholangiocarcinomas, of which nine were identified through biopsy, whereas six were correctly classified according to LI-RADS (LR-M or LR-TIV). Fifty percent of macrotrabecular HCC and 48.4% of poorly differentiated HCC (Edmonson 3 and 4) were not classified as LR-5.

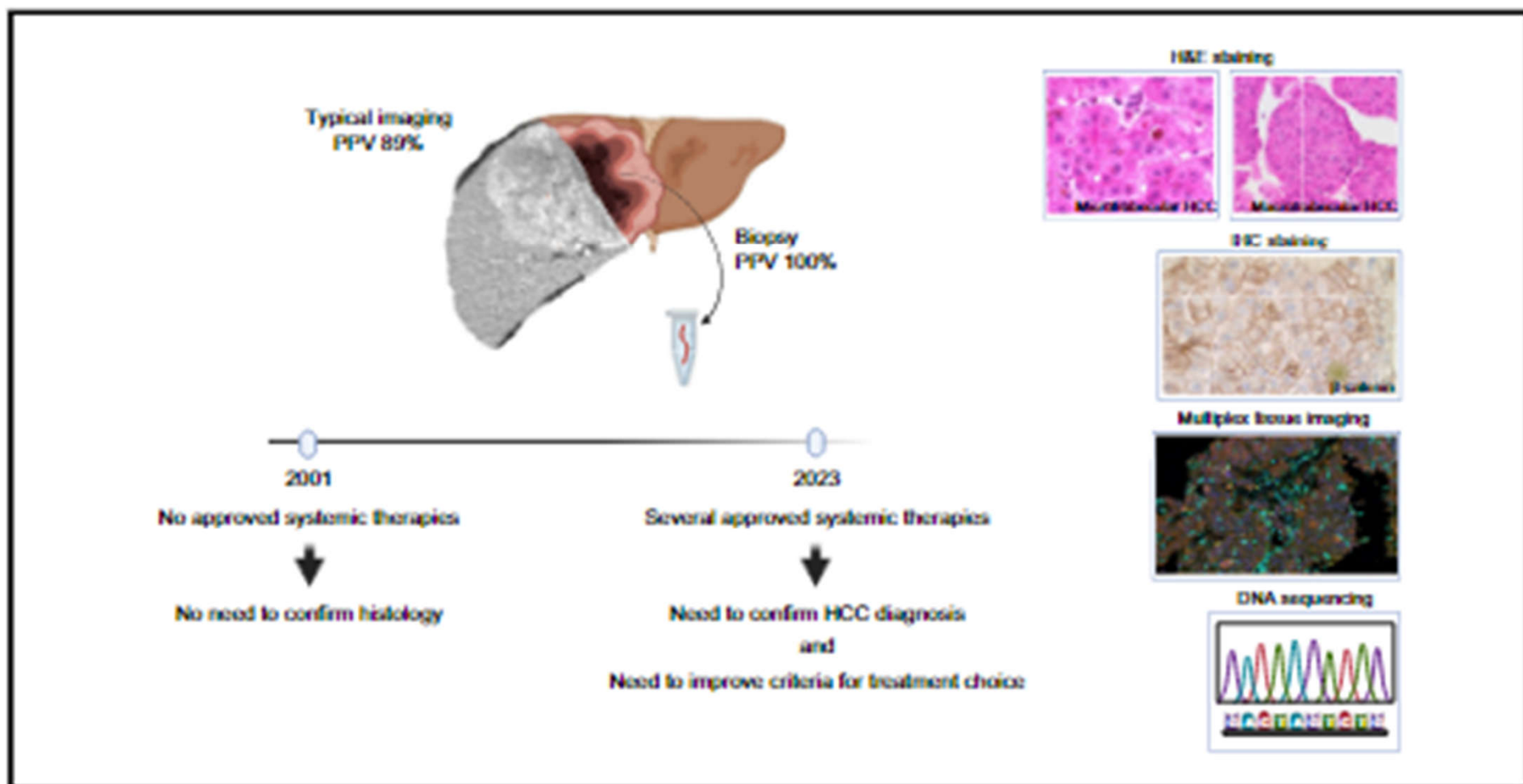
**Conclusions:** LI-RADS 2018 did not outperform the AASLD 2011 score as a non-invasive diagnosis of HCC. Tumor biopsy allowed restoration of an accurate diagnosis in 11% of LR-5 cases. A combined radiological and histological diagnosis should be considered mandatory for good treatment assessment.

**Impact and Implications:** Although biopsy is not required for hepatocellular carcinoma diagnosis when the LI-RADS criteria are met according to current guidelines, our study underscores the limits of radiology and the need for biopsy when hepatocellular carcinoma is suspected. Histological findings could change therapeutics of liver tumors even if only for a small proportion of patients. Histological proof of the type of cancer is a standard in oncology.

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## Graphical abstract





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# EDITORIAL

## Statins for Chronic Liver Disease and the Need for Randomized Controlled Trials



A large body of data shows that statins offer potential benefits in patients with chronic liver disease.<sup>1</sup> However, most of the supportive clinical evidence stems from observational studies or from randomized trials that rely on surrogate outcomes, such as portal pressure.<sup>2,3</sup> So far, the BLEPS trial<sup>4</sup> stands out as the only fully published randomized trial evaluating clinical outcomes. This trial included patients with cirrhosis and a previous variceal hemorrhage and compared simvastatin with placebo (in addition to standard of care). The study did not show any improvement on the primary outcome (rebleeding or death), but it did demonstrate a marked benefit in mortality (hazard ratio [HR] 0.39 or a 61% relative reduction in the mortality rate). Studies with positive

followed by alcohol and viral and autoimmune-related liver disease, reflecting biopsy practices rather than disease prevalences. Employing robust methodologies within the framework of causal inference, the study demonstrated that statin use was associated with a decreased risk of progressing to severe liver disease. The beneficial effects were observed mainly in patients with MASLD (HR 0.68) and alcohol-related liver disease (HR 0.30), both of which are characterized by challenging-to-resolve primary causal factors, highlighting the importance of disease-modifying agents when etiological treatment is not successful.

The limitations of the study are inherent to observational studies and are extensively addressed by the authors. However, we believe there is an additional limitation that may affect the interpretability of the findings. Specifically, 1151 patients (29.8% of the total non-statin group) were censored due to receiving a new prescription for statins during the study period. This progressive decrease in the denominator of the non-



trial and the magnitude of that effect needs to be met with skepticism. Indeed, preliminary results (only available in abstract form) from the LIVERHOPE trial,<sup>7</sup> which included patients with more advanced liver disease than the BLEPS study, did not demonstrate a benefit with statins. Consequently, the current evidence is insufficient to recommend statins for any liver-specific indication, and their use has to be very cautious in decompensated cirrhosis due to the risk of rhabdomyolysis,<sup>8</sup> a risk confirmed in the LIVERHOPE trial.<sup>7</sup>

In this issue of *Clinical Gastroenterology and Hepatology*, Sharma et al contribute valuable evidence supporting the potential of statins as disease-modifying agents in liver disease.<sup>9</sup> The authors studied patients with a previous liver biopsy showing non-cirrhotic chronic liver disease from a nationwide cohort of patients from Sweden. The study aimed to investigate the potential causal role of statins in reducing the risk of disease progression. The endpoint defining progression was a composite, including the development of cirrhosis, hepatocellular carcinoma, liver-related mortality, or liver transplantation. To establish a comparison group, time zero was synchronized by selecting patients with non-statin prescriptions around the same time as the statin prescriptions. The duration from the initial biopsy to time zero was comparable between the groups (12 years). The most common etiology was metabolic dysfunction-associated steatotic liver disease (MASLD),

statin group) translates into a substantial protective effect (40% relative reduction) when expressed as an HR (which can be interpreted as an incidence rate ratio).<sup>10</sup> Furthermore, the sensitivity analysis considering statin treatment as a time-dependent variable, which resulted in a change in the point estimate of the HR from 0.60 to 0.87, further supports this notion.

Although this study undeniably provides valuable data, we believe that the addition of further studies to the wealth of observational data already available is unlikely to significantly advance the field. We fully concur with the authors on the necessity of conducting randomized controlled trials. However, conducting such trials in patients with non-cirrhotic liver disease poses challenges due to the low likelihood of liver-related events, as demonstrated in this study. Therefore, innovative trial designs are clearly warranted, such as incorporating noninvasive tests and refining the definition of outcomes using an ordinal scale.<sup>11</sup> Large-scale studies with cholesterol-lowering drugs in MASLD have been assumed to be unfeasible since many of those patients (particularly those with advanced fibrosis) have an indication for a statin.<sup>12</sup> However, a recent randomized trial has questioned this notion by including ~14,000 patients with high cardiovascular risk who were identified as “statin-intolerant.”<sup>13</sup>

Patients with alcohol-related liver disease have high rates of disease progression.<sup>14</sup> Therefore, effective

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*EDITORIAL*

## Changes in the etiology of liver cirrhosis and the corresponding management strategies

Jin-Jin Dai, Yue-Ying Liu, Zhen-Hua Zhang



## Abstract

We read with interest the article by Xing Wang, which was published in the recent issue of the *World Journal of Hepatology* 2023; 15: 1294-1306. This article focuses particularly on the prevalence and trends in the etiology of liver cirrhosis (LC), prognosis for patients suffering from cirrhosis-related complications and hepatocellular carcinoma (HCC), and management strategies. The etiology of cirrhosis varies according to geographical, economic, and population factors. Viral hepatitis is the dominant cause in China. Vaccination and effective treatment have reduced the number of people with viral hepatitis, but the overall number is still large. Patients with viral hepatitis who progress over time to LC and HCC remain an important population to manage. The increased incidence of metabolic syndrome and alcohol consumption is likely to lead to a potential exponential increase in metabolic dysfunction-associated steatotic liver disease (MASLD)-associated LC and alcoholic liver disease in the future. Investigating the evolution of the etiology of LC is important for guiding the direction of future research and policy development. These changing trends indicate a need for greater emphasis on tackling obesity and diabetes, and implementing more effective measures to regulate alcohol consumption in order to reduce the occurrence of MASLD. In an effort to help cope with these changing trends, the authors further proposed countermeasures for healthcare authorities doctors, and patients.

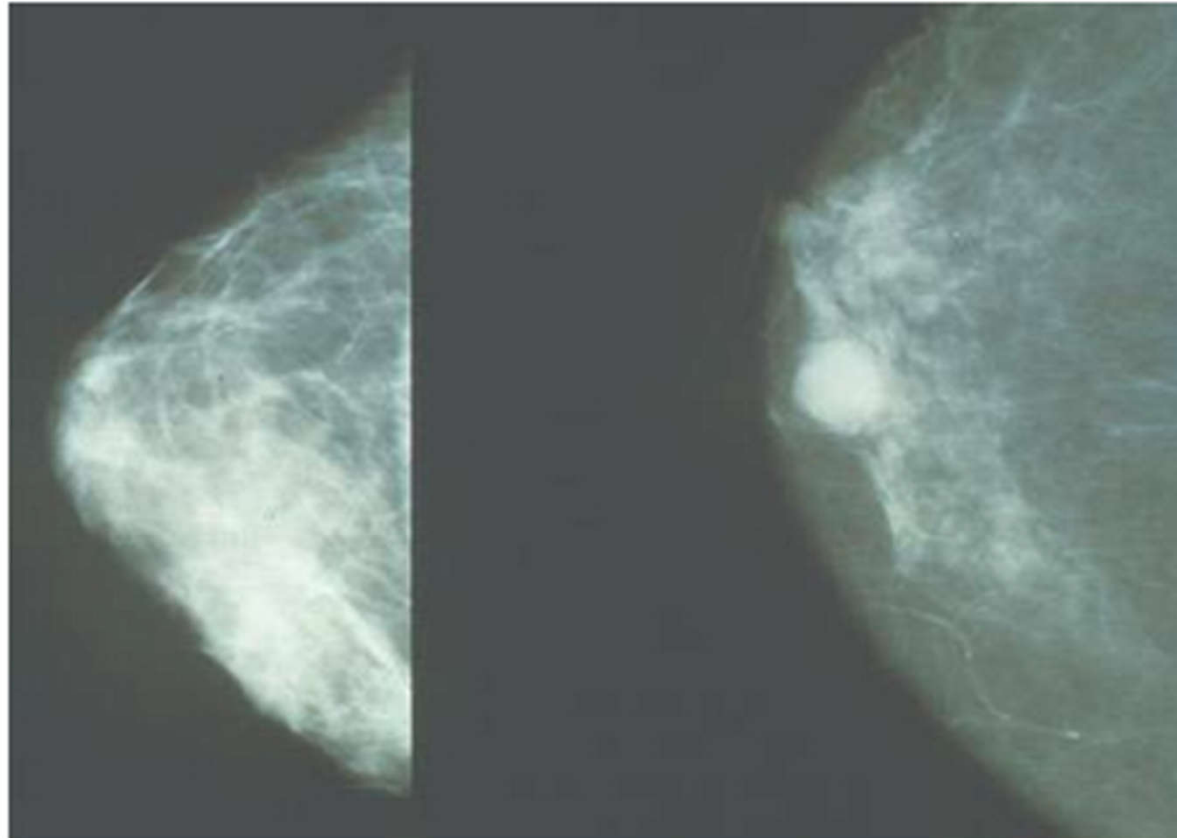
**Core Tip:** China is aiming to eradicate viral hepatitis as a public health threat by 2030. It is expected that the prevalence of viral hepatitis will decrease in the coming years. The increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) may emerge as a leading cause of liver cirrhosis. Additionally, excessive alcohol consumption is a significant risk factor. These shifting trends necessitate innovative management strategies. There is a need for sustained implementation of measures to eliminate viral hepatitis, as well as greater efforts to control obesity, diabetes and alcohol consumption to reduce the incidence of MASLD and Alcoholic liver disease.

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**Citation:** Dai JJ, Liu YY, Zhang ZH. Changes in the etiology of liver cirrhosis and the corresponding management strategies. *World J*

# Cryoablation found highly effective for breast cancer patients with large tumors

by The Reis Group





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Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Do...

A minimally invasive technique that uses ice to freeze and destroy small, cancerous tumors has now been proven effective for breast cancer patients with large tumors, providing a new treatment path for those who are not candidates for surgery, according to new research to be presented at the [Society of Interventional Radiology Annual Scientific Meeting](#) held March 23–28 in Salt Lake City.

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"For patients who have larger tumors but can't undergo surgery, this approach could be more effective than the current standard of care for patients who are not surgical candidates," said Yolanda Bryce, M.D., an interventional radiologist at Memorial Sloan Kettering Cancer Center. "When treated with only radiation and hormonal therapy, tumors will eventually return. On the fact that we can achieve 100% response

placement for each centimeter of disease). In a follow-up after 16 months, the recurrence rate was just 10%.

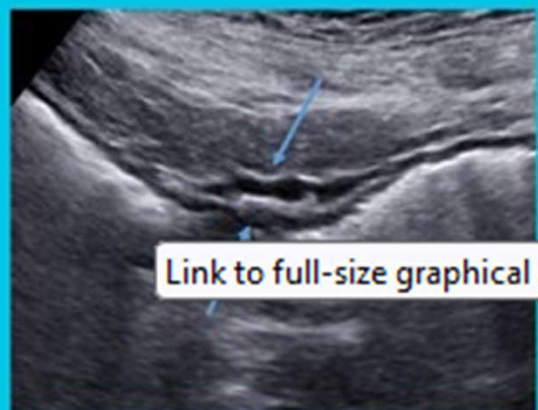
"Surgery is still the best option for tumor removal, but there are thousands of women who, for various reasons, cannot have surgery," said Bryce. "We are optimistic that this can give more women hope on their treatment journeys."

The procedures were performed with local anesthesia or minimal sedation, depending on the eligibility and preference of the patient. The freeze-thaw cycle started with 5–10 minutes of freezing, followed by 5–8 minutes of passive thaw, and then 5–10 minutes freezing at 100% intensity. Patients were able to go home on the same day, following the treatment.

The researchers will continue to follow the patient cohort to collect data on long-term effectiveness and to better understand the impact that adjuvant (e.g., hormone therapy and radiation) therapies combined with cryoablation can have on this patient population.

## Defining, Diagnosing and Monitoring Small Bowel Strictures in Crohn's Disease on Intestinal Ultrasound: A Systematic Review

### Bowel Wall Thickness



**Bowel wall thickness > 3mm**

### Luminal Apposition



**Luminal narrowing < 1cm**

### Pre-Stenotic Dilation



**Pre-stenotic dilation > 2.5cm**



## Summary

**Background:** Strictureing Crohn's disease (CD) occurs most commonly in the terminal ileum and poses a clinical problem. Cross-sectional imaging modalities such as intestinal ultrasound (IUS), computed tomography enterography (CTE), and magnetic resonance enterography (MRE) allow for assessment of the entire bowel wall and associated peri-enteric findings. Radiologic definitions of strictures have been developed for CTE and MRE; their reliability and responsiveness are being evaluated in index development programs. A comprehensive assessment strategy for strictures using IUS is needed.

**Aims:** To provide a detailed summary of definitions, diagnosis and monitoring of strictures on IUS as well as technical aspects of image acquisition.

**Methods:** We searched four databases up to 6 January 2024. Two-stage screening was done in duplicate. We assessed risk of bias using QUADAS-2.

**Results:** There were 56 studies eligible for inclusion. Definitions for strictures on IUS are heterogeneous, but the overall accuracy for diagnosis of strictures is high. The capability of IUS for characterising inflammation versus fibrosis in strictures is not accurate enough to be used in clinical practice or trials. We summarise definitions for improvement of strictures on IUS, and discuss parameters for image acquisition and standardisation.

**Conclusions:** This systematic review is the first step for a structured program to develop a stricture IUS index for CD.

sonographers.<sup>75</sup> These findings require confirmation, and further standardisation will likely improve inter-observer reliability.

The development of a validated IUS index for small bowel CD strictures is essential for accurate diagnosis and assessment. Unlike MRE, CTE and endoscopy, IUS is easily performed, which enables frequent assessments. The next step towards a rigorously developed, validated IUS stricture index is the completion of an international consensus process in which the results of the current study will determine how to optimally standardise CD stricture definitions, inclusion criteria, endpoints and response criteria for use in clinical practice and drug development.

In summary, the current systematic review summarises definitions and data on diagnostic accuracy, therapeutic response, image capture and technical aspects pertaining to IUS evaluation of small bowel CD strictures. This work provides the basis for future index development, which remains a critical barrier to the development of anti-stricture therapies in CD.

**THE END**