The Evolving Role of Liver Biopsy in Assessing Liver Diseases

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Historically, liver biopsy has been considered the gold standard for the diagnosis of liver diseases. However, in recent years, it is increasingly perceived to have lost part of its central role in clinical practice. This shift can be attributed to several factors. On one hand, significant epidemiological changes in liver diseases over the past years, driven by advances in antiviral therapies and the rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), have influenced the role and frequency of biopsy in routine evaluation [1]. On the other hand, the development of non-invasive diagnostic tools (NITs) has offered safer and more accessible alternatives. This shift happened particularly due to the invasive nature of liver biopsy, the relatively high costs and its potential complications such as pain and hemorrhage [2]. Although these factors have limited the use of liver biopsy to more complex clinical scenarios, its role remains unquestionable in certain situations, such as hepatic neoplasms where imaging is inconclusive or in the presence of co-existing liver diseases [3].

Nowadays, the epidemiology of liver diseases has undergone significant changes. The widespread use of direct-acting antivirals (DAAs) for the treatment of hepatitis C has markedly reduced the prevalence of this disease [4]. Similarly, nucleos(t)ide analogues in patients with chronic hepatitis B have led to effective long-term viral suppression, with sustained antiviral efficacy, favorable safety profiles, and the convenience of oral administration. Combined with universal vaccination programs, these advances have substantially impacted the epidemiology of hepatitis B, particularly in Western countries [5]. At the same time, the prevalence of MASLD continues to rise and is currently estimated to affect around 30% of the global population. MASLD is a multifactorial disease closely linked to metabolic syndrome, the components of which play a key role in its development and progression [6]. These epidemiological shifts not only influence the spectrum of liver diseases encountered in clinical practice, but also redefine clinical assessment needs, demanding tools that address new population-level challenges, and allow for the early identification of progressive disease.

The increasing need for early diagnosis and prognostic assessment has driven the development of non-invasive alternatives to liver biopsy. These methods have significantly reshaped clinical practice, as reflected in numerous clinical guidelines. For fibrosis assessment, several widely used serum-based scores, such as ELF, APRI, NAFLD Fibrosis Score and FIB-4, offer high negative predictive value for ruling out advanced fibrosis, particularly in primary care settings. However, their positive predictive value remains limited [7]. In parallel, imaging techniques are commonly used, although their accuracy depends on the underlying liver disease and can be affected by factors such as obesity. Out of these, vibration-controlled transient elastography (VCTE) is widely used and allows simultaneous estimation of fibrosis and steatosis [6,7]. MRI-based techniques like PDFF provide even greater precision in fat quantification, but their clinical utility is often restricted due to their cost and limited accessibility [8]. As far as hepatic neoplasms are concerned, advanced imaging techniques can be used to successfully diagnose hepatocellular carcinoma

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(HCC), especially in cases where HCC exceeds 1 cm and arises in a background of known cirrhosis and/or HBV, where LI-RADS criteria are applicable [3].

International guidelines recommend the use of NITs as the first-line approach for staging disease severity in all patients with chronic hepatitis B or C prior to antiviral therapy [5,9]. In MASLD, they are widely employed for screening at-risk individuals, guiding treatment initiation and monitoring therapeutic response [7]. Despite their growing role in clinical practice and the substantial reduction in the need for liver biopsy, NITs have notable limitations. These include their reduced capacity to identify subclinical hepatic inflammation, detect mild to moderate fibrosis and reliably distinguish between adjacent fibrosis stages, factors that limit their ability to fully replace biopsy's diagnostic granularity in complex or borderline cases [10].

In this context, liver biopsy continues to play a critical role in specific clinical scenarios. It remains essential when the clinical presentation is atypical, serological tests are inconclusive, or co-existing liver conditions complicate the diagnostic process. In clinical practice, this commonly occurs in patients with suspected primary biliary cholangitis (PBC) without disease-specific autoantibodies, in cases of possible overlap syndromes, or for autoimmune hepatitis (AIH) diagnosis. It is also frequent in cases of suspected drug-induced liver injury (DILI) where symptoms overlap with other liver diseases, such as AIH [3,11]. In patients with MASLD, liver biopsy remains the gold standard for diagnosis since other disease processes should be safely excluded and is also considered in patients with advanced fibrosis [6]. In chronic viral hepatitis, it is only used in cases with inconclusive non-invasive results, suspected mixed etiologies or uncertainty regarding fibrosis stage [12].

Its contribution is also crucial in patients with liver neoplasms. When imaging is inconclusive, histological diagnosis is used in order to differentiate hepatocellular adenoma from focal nodular hyperplasia and well-differentiated HCC. Additionally, for patients with HCC, biopsy provides confirmation of diagnosis when the lesion is smaller or atypical, as well as prognostic information through the identification of morphologic subtypes, helping physicians to evaluate the prognosis. [3]. Moreover, liver biopsy provides valuable material for research and it can be used in order to facilitate the identification of novel therapeutic targets and drive the development of more effective, personalized treatment strategies.

In the transplant setting, liver biopsy retains an undeniable role, whether it is used to assess steatosis and overall suitability in donor livers when imaging is inconclusive, or to clarify abnormal liver tests, confirm rejection or detect recurrent disease in graft recipients [11]. The importance of biopsy in such scenarios underlines its continued importance alongside the expanding use of non-invasive diagnostic approaches.

In a setting where liver biopsy is used to provide personalized care for patients, digital pathology (DP) and artificial intelligence (AI) emerge as valuable tools [3]. With AI capabilities evolving rapidly, they hold the potential to play a transformative role across all pathology subspecialties, including liver pathology. DP/AI tools have been used in several studies to evaluate the histological features of liver biopsies from patients with MASLD, showing good correlation with the assessments of experienced pathologists [13]. Additionally, other studies have demonstrated the potential of DP/AI in the differential diagnosis of hepatocellular nodular lesions, risk stratification and more accurate prediction to support personalized therapeutic strategies. In the short term, DP/AI tools are being developed to assist pathologists in the grading and staging of liver biopsies. Nevertheless, important limitations remain, including the need for proper training of AI models to ensure reliable and reproducible results, the high cost of AI software and the requirement for further validation and regulatory approval before widespread clinical implementation [3,13].

While the landscape of liver diseases is undeniably evolving, NITs are gradually gaining traction and are often preferred by patients over liver biopsy. However, they still have important limitations with respect to sensitivity and specificity. As such, even though the indications for liver biopsy may become more selective and better defined, its role remains irreplaceable in the assessment of complex or overlapping conditions, an area where advances in AI may assist in achieving more accurate diagnosis and staging. NITs are thus meant to complement, rather than replace, histological evaluation. In this context, we must define more precisely when and how to use liver biopsy so that we provide more personalized care for each patient, ensuring it complements, rather than competes with, emerging technologies.

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