

Evidence for the evolving role of liver biopsy in clinical practice: significant changes between two time periods

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Abstract

Background Recent changes in liver disease epidemiology and the wider use of noninvasive methods for fibrosis assessment have had an impact on the indications for liver biopsy in clinical practice. This study evaluated temporal changes in liver biopsy use by hepatologists in a single tertiary center during two 5-year periods.

Methods This retrospective, single-center study reviewed liver biopsies performed in our department during 2010-2014 (Group A) and 2020-2024 (Group B). Patients with malignant tumors were excluded. Data collected included demographics, liver enzymes, prior biopsy or transplant, referral indication, histological diagnosis, and fibrosis stage.

Results: A total of 703 biopsies were analyzed (452 in Group A, 251 in Group B). Prior biopsy was more frequent in Group A (26.1% vs. 5.5%, $P<0.001$). The annual number of biopsies declined significantly (90 vs. 50, $P=0.03$), particularly for staging-only procedures (195 vs. 25, $P<0.001$). Viral hepatitis diagnoses decreased markedly ($P<0.001$), while biopsies because of metabolic dysfunction-associated steatotic liver disease (MASLD) increased ($P<0.001$). Advanced fibrosis (F3-F4) was more common in Group B ($P=0.026$).

Conclusions Liver biopsy use decreased over time, with a shift from viral hepatitis toward MASLD indications, while biopsies for staging alone markedly declined. The inclusion of the COVID-19 pandemic years in the second study period should be considered when interpreting this reduction. Nonetheless, liver biopsy remains a valuable diagnostic tool in patients with liver dysfunction of uncertain etiology or complex disease etiologies.

Keywords Liver biopsy, metabolic dysfunction-associated steatotic liver disease, viral hepatitis, fibrosis staging, retrospective study

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Introduction

Since the first transcutaneous liver biopsy was performed in 1883 [1], continuous methodological advances have established liver biopsy as the gold standard for the diagnosis and investigation of liver diseases. However, in recent years, liver biopsy is increasingly perceived to have lost part of its central role in clinical practice. This shift may be attributed to the development of noninvasive diagnostic tools [2], the relatively high cost of the biopsy procedure, as well as risks related to its invasive nature, such as pain and hemorrhage [3,4]. At the same time, 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) [5], have influenced the role and frequency of biopsy in routine evaluation. In most clinical centers liver biopsy is now performed less frequently,

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mostly in complex clinical scenarios, in liver dysfunction of uncertain etiology and in tumors of uncertain type [6].

Such changes in liver biopsy use have been documented by several retrospective studies [5,7,8], and are associated with shifts in biopsy indications and the frequency of histological diagnoses. While occasional studies report an increasing number of biopsies over time [9], the majority suggest an overall decline [5,7,8], alongside a consistent reduction in biopsies performed for viral hepatitis and a corresponding increase in referrals for MASLD. Nevertheless, available evidence remains limited, and is largely derived from older study periods and predominantly non-European populations, where epidemiological patterns and referral practices may differ.

In this context, and given the limited data from Southern European settings, particularly Greece, the present study aimed to describe changes in the use of liver biopsy by hepatologists in our department by comparing 2 distinct time periods, examining biopsy indications, diagnostic trends and fibrosis stage. In this way, we sought to partially address this gap in the existing literature.

Materials and methods

This was an observational, retrospective, single-center study. We reviewed liver biopsy indications and outcomes in patients from the 4th Department of Internal Medicine, School of Medicine, Aristotle University of Thessaloniki, whose biopsy specimens were examined at the Department of Pathology during 2 distinct 5-year periods: 2010-2014 (Group A) and 2020-2024 (Group B). Patients' data were retrieved from our local database. All data were fully anonymized, and no patient identification was possible. The study was reviewed and approved by the local Institutional Review Board. Patient consent was waived in view of the retrospective design of the study and the use of fully anonymized data.

Inclusion criteria: patients ≥ 16 years old with liver biopsy specimens archived at the Department of Pathology, School of Medicine, Aristotle University, during at least 1 of these time periods. Patients with liver biopsy diagnosis of malignant neoplasm were excluded from the study. Data recorded included age, sex, liver enzyme levels, prior liver transplant or biopsy, referral indication, histological diagnosis and stage of fibrosis. In patients who underwent multiple liver biopsies during the study period, only the first biopsy was included in the analysis. Patients could be classified under more than 1 histological diagnosis category (Fig. 1). Protocol biopsies in liver transplant recipients had been abandoned at our center before the study period; therefore, biopsies in these patients were clinically indicated, mainly for unexplained liver injury or elevated transaminases.

Referral indication was classified as "staging", if the sole reason for referral was staging chronic liver disease, or as "etiological assessment" if liver biopsy was performed to

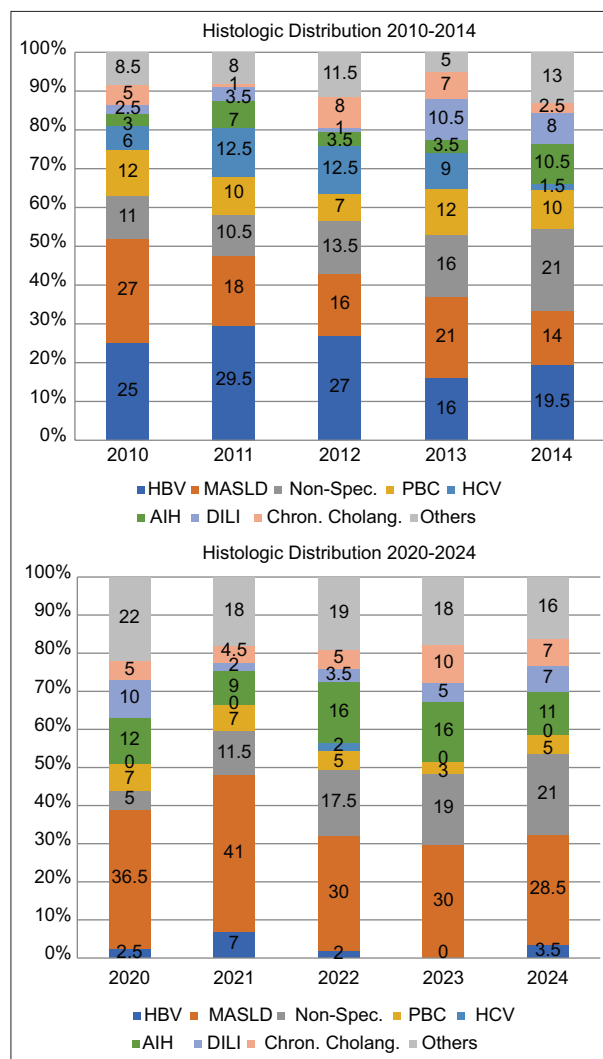


Figure 1 Categories and incidences (%) of diagnoses following histological examination

AIH, autoimmune hepatitis; Chron. Cholang., chronic cholangiopathy (other than PBC); DILI, drug-induced liver injury; HBV, chronic hepatitis B; HCV, chronic hepatitis C; MASLD, metabolic dysfunction-associated steatotic liver disease; Non-spec., non-specific histological changes; PBC, primary biliary cholangitis

investigate or confirm the underlying liver disease when the clinical workup was inconclusive or a specific diagnosis was suspected and required confirmation. Fibrosis staging was performed according to the METAVIR scoring system for chronic hepatitis and the NASH CRN system for MASLD, with stages ranging from F0 (no fibrosis) to F4 (cirrhosis) [10,11]. For analysis, fibrosis stage was dichotomized into 2 groups: F0-F2 (no fibrosis, or mild to moderate fibrosis) and F3-F4 (advanced fibrosis), reflecting clinically relevant thresholds commonly used in the literature. Data on complications associated with liver biopsy were not systematically available in our database, and therefore could not be reliably assessed, given the retrospective nature of the study.

Statistical analysis

Statistical analysis was performed using RStudio (version 2025.05.1+513). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test, presented as means $\pm$ standard deviation or medians with interquartile ranges, as appropriate. Normally distributed continuous variables were compared between groups using independent *t*-tests. Categorical variables were expressed as counts and percentages, and compared using the chi-square test or Fisher's exact test, as appropriate. To evaluate changes over time, we compared the mean annual number of liver biopsies between the 2 study periods (2010-2014 vs. 2020-2024) using an independent *t*-test. Additional comparisons included the proportion of patients with a prior liver biopsy, history of liver transplantation, and the frequency of biopsies performed solely for staging purposes. Univariate logistic regression models were used to explore associations between the study period and: (a) histological diagnoses of MASLD, viral hepatitis, including both hepatitis B (HBV) and C (HCV) viruses, and autoimmune hepatitis (AIH); and (b) fibrosis severity, dichotomized as absent, mild or moderate (F0-F2) vs. advanced (F3-F4). Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CI). A 2-tailed *P*-value <0.05 was considered statistically significant.

Results

Use of liver biopsy and main patients' characteristics

A total of 703 liver biopsies were analyzed: 452 during the 2010-2014 period (Group A) and 251 during 2020-2024 (Group B). A significant decrease in the mean annual number of biopsies was observed between the 2 time periods (90 in Group A vs. 50 in Group B, $P=0.03$). The annual number of liver biopsies was 129, 110, 85, 55 and 73 in Group A and 39, 43, 55, 61 and 53 in Group B, respectively. Baseline demographic and clinical characteristics of the study population are summarized in Table 1. In Group A, the most common histological diagnoses were HBV (25.6%) and MASLD (20.4%), followed by non-specific histological changes and primary biliary cholangitis. In contrast, in Group B (2020-2024), MASLD became the predominant diagnosis (33.1%), while autoimmune hepatitis and non-specific histological changes were also more frequent. The full diagnostic distribution is illustrated in Table 1.

Factors associated with the use of liver biopsy

Univariate logistic regression analysis showed significantly lower odds of a histological diagnosis of viral hepatitis in Group B compared with Group A (OR 0.05, 95%CI 0.02-0.11; $P<0.001$), whereas the odds of a histological diagnosis

Table 1 Characteristics of patients who underwent liver biopsy in each group: Group A (2010-2014) and group B (2020-2024)

Characteristics	Group A (n=452)	Group B (n=251)	P-value
Male sex	50%	49.4%	-
Age (years, IQR)	51 (41-60)	54 (43-63)	-
Previous biopsy	26.1%	5.5%	<0.001
Liver transplantation	6.4%	5.9%	0.94
Staging as referral indication	44%	11.5%	<0.001
MASLD	20.4%	33.1%	<0.001
HBV	25.7%	2%	-
HCV	8.8%	0.4%	-
AIH	5.5%	12.7%	0.001
PBC	10.8%	5.6%	-
DILI	4.9%	6%	-
Chron. Cholang	4.2%	6.8%	-
Non-Spec.	13.7%	19.4%	-
Others	9%	17.9%	-

Data are presented as percentages unless otherwise indicated. Age is presented as median (IQR). Histological diagnoses are not mutually exclusive, as more than 1 diagnosis could be recorded for the same liver biopsy. "Others" includes less frequent histological diagnoses not presented as separate categories in the table, including alcoholic liver disease, overlap syndromes, vascular or circulatory liver injury, granulomatous liver disease and other miscellaneous liver disorders. "Non-specific" refers to histological findings showing non-specific inflammatory and/or other changes that were insufficient to establish a specific histological diagnosis. "Previous biopsy" refers to a documented history of liver biopsy performed before the biopsy included in the present analysis

AIH, autoimmune hepatitis; Chron. Cholang., chronic cholangiopathy; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; IQ, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; Non-Spec., non-specific histological changes; PBC, primary biliary cholangitis

of MASLD were significantly higher (OR 1.93, 95%CI 1.36-2.74; $P<0.001$). Similarly, the odds of an AIH diagnosis were significantly higher in the second study period (OR 2.50, 95%CI 1.44-4.32; $P=0.001$). Advanced fibrosis (F3-F4) was also more frequently observed in Group B than in Group A (OR 1.47, 95%CI 1.05-2.05; $P=0.026$). Female sex was associated with lower odds of a histological diagnosis of viral hepatitis (OR 0.44, 95%CI 0.31-0.63; $P<0.001$).

Discussion

The aim of this study was to evaluate changes in liver biopsy use in our department between 2 distinct time periods. We observed a significant reduction in the number of liver biopsies performed in 2020-2024 compared with 2010-2014, which was particularly pronounced for

biopsies performed solely for fibrosis staging. The decline in the total number of biopsies was paralleled by a notable decrease in histological diagnoses of viral hepatitis. These findings probably reflect the widespread availability and effectiveness of antiviral therapies, including direct-acting antivirals for hepatitis C and nucleos(t)ide analogs for hepatitis B [12]. These advances, combined with universal vaccination programs for HBV, have substantially impacted the epidemiology of viral hepatitis, particularly in Western countries [13,14]. Additionally, the increasing adoption of noninvasive tools for fibrosis assessment, such as transient elastography and serum biomarkers [15], has further reduced the reliance on liver biopsy for staging of viral hepatitis, in line with published evidence and guidelines regarding the assessment and management of both HCV and HBV [13,16-18]. Transient elastography, however, has been routinely available at our center since 2008, preceding both study periods. Therefore, its introduction cannot explain the observed decline, although changes in its use over time may have contributed. Our findings are consistent with most previous retrospective studies from France [7], Asia [8] and Latin America [5], which have reported similar reductions in the use of liver biopsy, although another study [9] has described stable or even increasing use of liver biopsy. With respect to HBV and HCV, these findings are also consistent with the reported decline in viral hepatitis diagnoses among biopsied patients. Our study adds to the existing literature by providing data from a Southern European setting and a more recent time period.

Our results also demonstrate that female sex is associated with a lower likelihood of viral hepatitis diagnosis. This aligns with epidemiological data showing a higher prevalence of chronic HBV and HCV infection among men, which has been attributed primarily to sex-specific immune responses and hormonal regulation, with possible additional contributions from gender-related factors [19].

A significant increase in biopsies with a histologically confirmed diagnosis of MASLD was observed in the more recent time period. This trend probably reflects the growing clinical burden of MASLD in hepatology practice, in the context of the global rise in obesity, type 2 diabetes and metabolic comorbidities [20]. This finding supports the results of previous studies [5,8] that found similar trends, with an increase of biopsies establishing a diagnosis of MASLD.

The observed increase in liver biopsies for suspected AIH may reflect the continued central role of liver histology in establishing the diagnosis of AIH. Current guidelines consider liver biopsy necessary for establishing a firm diagnosis of AIH, although serological and biochemical assessment remain essential for the diagnostic workup [21,22].

Regarding fibrosis severity, patients in the more recent period (2020-2024) appeared more likely to present with

advanced fibrosis (F3-F4) compared to the earlier period (2010-2014). This finding may reflect an increasing tendency to reserve liver biopsy for patients with more advanced or diagnostically complex disease, although other factors, including potential delays in diagnosis, may also have contributed.

Overall, this study highlights the evolving role of liver biopsy in clinical practice, suggesting a reduced overall utilization in recent years and a shift away from biopsies performed for the purpose of fibrosis staging. Instead, liver biopsy appears to be increasingly reserved for more complex clinical scenarios, as well as patients with uncertain disease etiology. At the same time, our findings reflect ongoing epidemiological changes in chronic liver diseases, providing contemporary data from a southern European setting.

This study has several strengths. It includes a relatively large number of liver biopsies across 2 distinct time periods, allowing for the assessment of temporal trends in clinical practice within the same tertiary care center. The manual review of histological and clinical data provided detailed insights into referral indications and fibrosis staging. However, some limitations should be acknowledged. First, the retrospective design limits control over unmeasured confounders, and some analyses were constrained by missing data. Second, biopsy indications may have been influenced by changing institutional practices or subjective clinical judgment. Third, the single-center setting may affect generalizability. Finally, the time period of Group B includes the years 2020-2022, corresponding to the COVID-19 pandemic, during which a reduction in elective invasive procedures, including liver biopsies, was reported [23]. In line with this, EASL-ESCMID recommendations advised deferring liver biopsy for disease grading and staging, and prioritizing biopsy for more urgent indications during the pandemic [24].

In conclusion, our study highlights a significant reduction in the number of liver biopsies performed in the time period 2020-2024, as compared to the period 2010-2014. This reduction may reflect, at least in part, the development and increasing adoption of noninvasive methods for the assessment of liver fibrosis, as well as the widespread use of antiviral therapies for HBV and HCV. In parallel, the decline in biopsies showing viral hepatitis was accompanied by an increasing proportion of biopsies establishing a diagnosis of MASLD, a finding consistent with changes in the underlying indications for liver biopsy over time and, potentially, the increasing importance of metabolic risk factors in MASLD. Nevertheless, despite the overall reduction in liver biopsy use, this invasive procedure remains a valuable diagnostic tool and continues to play an essential role in the evaluation of liver dysfunction of uncertain etiology, and of complex or overlapping liver conditions where noninvasive approaches are insufficient.

Summary Box

What is already known:

- In recent years, liver biopsy has progressively lost its central role in the evaluation of liver diseases, mainly because of the availability of noninvasive tools and antiviral therapies
- Previous retrospective studies have reported changes in biopsy indications, with decreasing rates of biopsies for underlying viral hepatitis infections and increasing rates for the diagnosis or assessment of metabolic dysfunction-associated steatotic liver disease (MASLD)

What the new findings are:

- We observed a significant reduction in total biopsy numbers and in biopsies performed in patients with underlying viral hepatitis, alongside an increase in biopsies establishing a diagnosis of MASLD
- Advanced fibrosis was more frequently observed among patients undergoing liver biopsy in the more recent study period

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