

ORIGINAL RESEARCH

Shifts in liver biopsy indications and histopathological diagnoses: A report from a tertiary care center in Türkiye

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Highlights & Insights

- **Scientific Gap:** Although non-invasive methods for assessing liver fibrosis have become increasingly available, long-term data on how liver biopsy indications and histopathological diagnoses have changed over time remain limited.
- **Key Finding:** The total number of percutaneous liver biopsies remained relatively stable between 2000–2011 and 2012–2022. However, biopsy indications shifted over time, with fewer biopsies performed for treatment monitoring and hepatomegaly evaluation. Histopathological diagnoses also changed, showing a decline in chronic hepatitis C and significant increases in MASH, autoimmune hepatitis, and primary biliary cholangitis.
- **Clinical Impact:** These findings suggest that liver biopsy continues to play an important role in selected patients, particularly when non-invasive tests are insufficient for diagnostic clarification, fibrosis assessment, or treatment planning.

ABSTRACT

Background and Aim: Despite advances in non-invasive methods, liver biopsy remains essential for diagnosis, prognosis, and treatment planning, and this study aimed to evaluate trends in its indications and pathological findings.

Materials and Methods: A total of 1533 adult liver biopsies at a tertiary referral hospital (2000–2022) were retrospectively reviewed for indications and diagnoses.

Results: The annual number of liver biopsies performed remained stable over the last two decades (730 vs. 803; $p=0.06$). The mean patient age was 43 ± 15 years, with 52% being female. The leading indications were abnormal liver function tests (53.4%), fibrosis/cirrhosis (40.9%), treatment follow-up (2.7%), hepatomegaly (1.6%), and fever of unknown origin (0.9%). Between 2000–2011 and 2012–2022, the indications for liver biopsy changed significantly: biopsies for fibrosis/cirrhosis increased, whereas those for evaluation of treatment response and disease monitoring and for hepatomegaly decreased ($p=0.01$, $p<0.001$, and $p=0.02$, respectively). In the post-COVID-19 period, abnormal liver function tests became the predominant indication (42.2% vs. 69.2%), whereas fibrosis/cirrhosis decreased (54.2% vs. 28%). The most frequent pathological diagnosis was chronic hepatitis B virus (HBV) infection (38.6%), followed by chronic hepatitis C virus (HCV) (11.5%), metabolic dysfunction-associated steatohepatitis (MASH) (8.5%), autoimmune hepatitis (AIH) (7.7%), and primary biliary cholangitis (PBC) (4.2%). Across decades, MASH (6.4% vs. 10.3%; $p=0.008$), AIH (4% vs. 11.1%), and PBC (1.1% vs. 7%) increased significantly ($p<0.001$), while chronic HCV declined (17.3% vs. 6.1%; $p<0.001$). Chronic HBV remained stable (38.2% vs. 38.9%).

Conclusion: Over the past 22 years, the annual number of liver biopsies remained stable, with abnormal liver function tests as the leading indication, a decline in fibrosis/cirrhosis evaluation, chronic hepatitis B as the most common diagnosis, and a gradual rise in autoimmune liver diseases and MASH.

Keywords: Chronic liver diseases, etiology trends, liver biopsy indication.

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Introduction

Chronic liver diseases (CLD) are a major cause of morbidity and are associated with 2 million deaths from liver disease each year.^[1] CLD is the 11th leading cause of death worldwide.^[2] Chronic liver disease contributes to both mortality and reduced quality of life, imposing a substantial economic burden. Accurate identification of underlying etiologies is therefore essential, as the global burden of liver disease and its causes have changed over the years across the world.^[3] Global hepatitis elimination programs have reduced the burden of viral liver disease, whereas rising obesity and type 2 diabetes have driven the increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH).^[4] Furthermore, alcohol-related liver disease (ALD) remains a major problem in many parts of the world.^[5]

The first liver biopsy was performed by Paul Ehrlich in 1883, followed by a successful percutaneous liver biopsy (PLB) in 1925 in Germany. After a century, the liver biopsy still plays an important role in predicting prognosis and treatment planning.^[6] Liver biopsy can be done in a variety of ways, including percutaneous, transjugular, laparoscopic, and intraoperative approaches.^[7–9] Despite advances in serologic and radiologic techniques,^[10] histopathologic evaluation of liver biopsy remains the most reliable way to diagnose liver diseases and lesions,^[11] and so remains the gold standard diagnostic method.^[7,12]

Over time, advances in technology and shifts in clinical practice have altered the indications and use of liver biopsy. Updated guidelines, together with improved imaging and biochemical tests, have introduced non-invasive alternatives that allow assessment of liver fibrosis through serum biomarkers or measurement of liver stiffness by ultrasound or magnetic resonance (MR), reducing the need for biopsy in selected patients. Although liver biopsy is still considered the reference standard for the definitive diagnosis and prognosis assessment of many liver diseases, non-invasive tests have reduced the need for follow-up biopsies.^[13] In addition, the cost of biopsy processing and pathological evaluation remains an important consideration within healthcare systems. Given the evolving feasibility, cost, and indications of liver biopsy over time, this study aimed to examine temporal trends in biopsy indications and pathological diagnoses in an urban tertiary care center in Ankara, Türkiye.

Materials and Methods

Study Design

This retrospective, single-center, cross-sectional study included adult patients who underwent PLB for benign liver diseases at a tertiary referral hospital between January 2000 and March 2022. Biopsy indications were classified into six predefined categories and compared, together with pathological diagnoses, between two consecutive decades. The study protocol was approved by the Hacettepe University Ethics Committee (dated April 19, 2022, and numbered GO 22/406), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

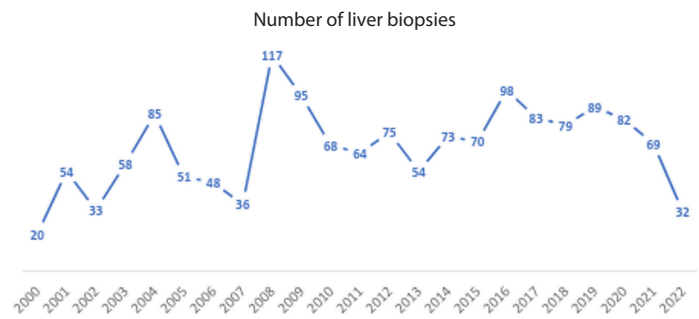


Figure 1. Distribution of liver biopsy numbers by years.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences Statistics for Windows, version 31.0 (IBM Corp., Armonk, NY, USA) and R. Data distribution was assessed with the Shapiro-Wilk test. Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate. Categorical variables were compared using the Chi-square test. The Poisson rate test and independent samples t-test were applied where appropriate. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 5003 liver biopsies were retrospectively reviewed, of which 1533 PLB were included. Excluded cases comprised biopsies performed for malignancy ($n=2503$), non-needle biopsy techniques ($n=507$), and specimens referred from other centers for re-evaluation ($n=460$).

The mean and median annual numbers of PLB were 66 and 69, respectively. Comparison of the two decades showed 730 biopsies in 2000–2011 and 803 in 2012–2022, with no significant difference by Poisson rate test ($p=0.06$). The highest number of PLBs was recorded in 2008 ($n=117$), followed by a marked decline during the COVID-19 pandemic, reaching 32 biopsies in 2022 (Fig. 1).

The mean age at biopsy was 43 ± 15 years, and 52% of patients were female (Table 1). Smoking and alcohol use were reported in 9% and 2% of patients, respectively. The most frequent comorbidities were diabetes mellitus (12.7%), hyperlipidemia (10.6%), and hypertension (10.3%), followed by malignancy (6.5%), rheumatologic disease (6.2%), chronic kidney disease (3.6%), thyroid disease (3.4%), and coronary artery disease (2.5%).

The Indications of PLB

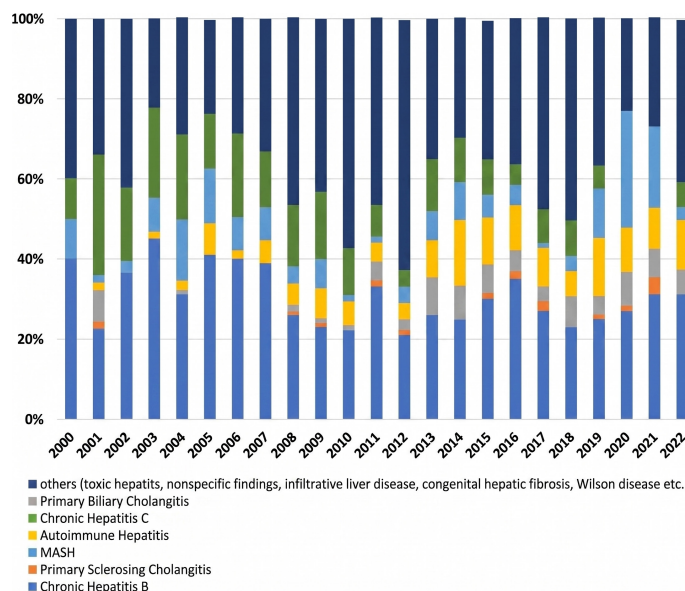
The most common indication for PLB was abnormal liver function tests (53.4%), followed by assessment of liver fibrosis or cirrhosis (40.9%). Less frequent indications included treatment response and disease monitoring (2.7%), evaluation of hepatomegaly (1.6%), and fever of unknown origin (0.9%) (Table 2). Postmortem and donor evaluations accounted for a small proportion of procedures.

Table 1. Characteristics of patients who underwent liver biopsy (n=1533)

Sociodemographic characteristics of patients		n (%)
Age; years, mean±standard deviation		43±15
Gender, n (%)		
Female		789 (52)
Male		744 (48)
Smoking, n (%)		
Non-smoker		1397 (91)
Smoker		136 (9)
Duration: Pack-years, median (interquartile range)		15 (10–20)
Alcohol		
Does not use		1495 (98)
Uses		37 (2)
Other comorbidities		
Diabetes mellitus		195 (12.7)
Hyperlipidemia		163 (10.6)
Hypertension		158 (10.3)
History of malignancy		99 (6.5)
Solitary		67 (4.4)
Hematologic**		32 (2.1)
Rheumatologic diseases		95 (6.2)
Rheumatoid arthritis		22 (1.4)
Sjögren's syndrome		15 (1.0)
Systemic lupus erythematosus		10 (0.7)
Other***		48 (3.1)
Chronic kidney disease		55 (3.6)
Thyroid disease		52 (3.4)
Hashimoto's disease		24 (1.6)
Multinodular goiter		23 (1.5)
Graves' disease		3 (0.2)
Toxic multinodular goiter		2 (0.1)
Coronary artery disease		39 (2.5)

*Breast (n=24), lung (n=21), prostate (n=8), stomach (n=4), colon (n=8), and brain tumors (n=2). **Leukemia and its subgroups (n=10), lymphoma and its subgroups (n=10), multiple myeloma (n=8), and myelodysplastic syndrome (n=4). ***Gout (n=16), osteoarthritis (n=8), familial Mediterranean fever (n=6), seronegative spondyloarthropathies (n=5), systemic sclerosis (n=3), inflammatory myopathies (n=3), mixed connective tissue diseases (n=3), Still's Disease (n=3), and small vessel and large vessel vasculitis (n=1).

Comparison of the two decades (2000–2011 vs. 2012–2022) revealed a clear change in biopsy indications, with a significant increase in biopsies performed for fibrosis and cirrhosis assessment in the latter

**Figure 2.** Trends in pathology diagnoses after percutaneous liver biopsy between 2000 and 2022.

period ($p=0.01$). In contrast, biopsies for treatment monitoring and investigation of hepatomegaly declined significantly ($p<0.001$ and $p=0.02$, respectively).

The impact of the COVID-19 pandemic was assessed by comparing the pre-pandemic (2017–2019) and pandemic (2020–2022) periods. The number of PLBs decreased by 27%, from 251 before to 182 during the pandemic. Patient characteristics were comparable between periods with respect to mean age (44 ± 16 vs. 45 ± 15 years), sex (56.1% vs. 51.6% female), smoking (13.5% vs. 11%), and alcohol use (2% vs. 3.3%). In contrast, biopsy indications shifted during the pandemic. Assessment of fibrosis and cirrhosis declined from 54.2% to 28%, whereas evaluation of abnormal liver enzymes became the most frequent indication (69%). Diabetes mellitus and hyperlipidemia were more common during the pandemic period (12.4% vs. 23.1%, $p=0.004$, and 6.8% vs. 20.3%, $p<0.001$, respectively) (Table 3).

The Final Pathology Diagnosis with PLB

The most frequent pathological diagnosis was chronic hepatitis B virus infection (38.6%), followed by chronic hepatitis C virus (HCV) (11.5%), MASH (8.5%), autoimmune hepatitis (AIH) (7.7%), and primary biliary cholangitis (PBC) (4.2%). The distribution of pathological diagnoses changed significantly over time (Fig. 2).

Across the two decades, chronic hepatitis B remained the most frequent diagnosis (38.2% vs. 38.9%), whereas Wilson's disease and primary sclerosing cholangitis were consistently rare ($\leq 1\%$). In contrast, the proportions of MASH (6.4% vs. 10.3%), AIH (4.0% vs. 11.1%), and PBC (1.1% vs. 7.0%) increased markedly, whereas chronic hepatitis C showed a substantial decline (17.3% vs. 6.1%). Other benign liver diseases accounted for 23.8–31.8% of diagnoses (Table 4).

Table 2. The change in indications for liver biopsy between decades

Indication	All years, n (%)	2000–2011, n (%)	2012–2022, n (%)	p
Abnormal liver function tests	818 (53.4)	396 (54.2)	422 (52.6)	0.51 ^a
Evaluation of fibrosis and cirrhosis	627 (40.9)	274 (37.5)	353 (44.0)	0.01^a
Evaluation of treatment response and disease monitoring	42 (2.7)	32 (4.4)	10 (1.2)	<0.001^a
Assessment of hepatomegaly etiology	24 (1.6)	17 (2.3)	7 (0.9)	0.02^a
Evaluation for fever of unknown origin	14 (0.9)	6 (0.8)	8 (1)	0.72 ^a
Other*	8 (0.5)	5 (0.7)	3 (0.4)	0.49 ^b
Total	1533 (100.0)	730 (100.0)	803 (100.0)	0.06 ^c

*Postmortem evaluation (n=3) and Donor liver evaluation (n=5). a: Chi-Square test; b: Fisher's Exact test; c: Poisson Rate test.

Table 3. The characteristics of patients who underwent liver biopsy before and during the pandemic

Patient characteristics	Before the pandemic (n=251) n (%)	During the pandemic (n=182) n (%)	p
Age; year, mean±standard deviation	44±16	45±15	0.506 ^a
Gender			
Female	141 (56.1)	94 (51.6)	0.403 ^b
Male	110 (43.9)	88 (48.4)	0.403 ^b
Smoking	34 (13.5)	20 (11)	0.517 ^b
Alcohol use	5 (2.0)	6 (3.3)	0.588 ^b
Concomitant diseases			
Diabetes mellitus	31 (12.4)	42 (23.1)	0.004^b
Hypertension	29 (11.6)	29 (15.9)	0.2 ^b
Hyperlipidemia	17 (6.8)	37 (20.3)	<0.001^b
Rheumatologic diseases	22 (8.8)	22 (12.1)	0.26 ^b
Chronic kidney disease	9 (3.6)	3 (1.6)	0.37 ^c
Coronary artery disease	8 (3.2)	5 (2.7)	1 ^c
Indications for biopsy			
Abnormal liver function tests	106 (42.2)	126 (69.2)	<0.001^b
Evaluation of fibrosis and cirrhosis	136 (54.2)	51 (28.0)	<0.001^b
Evaluation of treatment response and disease monitoring	1 (0.4)	2 (1.1)	0.58 ^c
Evaluation for fever of unknown origin	4 (1.6)	1 (0.5)	0.4 ^c
Other*	4 (1.6)	2 (1.1)	1 ^c
Total patients	251 (100.0)	182 (100.0)	<0.001^d

Postmortem (n=1), Rejection (n=1), donor evaluation (n=1), etiology of hepatomegaly (n=1). a: Independent Samples t-Test; b: Chi-Square Test; C: Fisher's Exact Test; d: Poisson Rate Test.

Discussion

This retrospective study analyzed 1533 PLBs performed between 2000 and 2022, demonstrating stable biopsy volumes over time, except for a 27% decline during the COVID-19 pandemic. During the study period, biopsy indications shifted from fibrosis and cirrhosis assessment toward evaluation of abnormal liver function tests, reflecting the impact of the pandemic and advances in imaging and non-invasive tests.

Makar et al.^[14] compared 427 parenchymal liver biopsies (2017–2018) with 166 biopsies from a decade earlier (2007–2008) and grouped indications as elevated liver enzymes, chronic viral hepatitis, or other causes. Over time, biopsies for elevated liver enzymes increased markedly (45.8–68.6%), whereas those for chronic viral hepatitis declined (33.1–6.6%). In this study, the most common indication for PLB was abnormal liver function tests (53.4%), whereas viral hepatitis – particularly hepatitis B – remained a major indication

Table 4. The trends across decades for pathology diagnoses after percutaneous liver biopsy

Histopathological diagnosis	All-years, n (%)	2000–2011, n (%)	2012–2022, n (%)	p
Chronic hepatitis B	591 (38.6)	279 (38.2)	312 (38.9)	0.834 ^a
Chronic hepatitis C	176 (11.5)	127 (17.3)	49 (6.1)	<0.001 ^a
Metabolic dysfunction associated steatohepatitis	130 (8.5)	47 (6.4)	83 (10.3)	0.008 ^a
Autoimmune hepatitis	118 (7.7)	29 (4)	89 (11.1)	<0.001 ^a
Primary biliary cholangitis	64 (4.2)	8 (1.1)	56 (7)	<0.001 ^a
Primary sclerosing cholangitis	13 (0.8)	5 (0.7)	8 (1.0)	0.585 ^b
Wilson's disease	14 (0.9)	6 (0.8)	8 (1.0)	0.793 ^b
Autoimmune hepatitis- primary biliary cholangitis variant	11 (0.7)	2 (0.3)	9 (1.1)	0.068 ^b
Others*	416 (27.1)	227 (31.2)	189 (23.5)	0.001 ^a
Total	1533 (100.0)	730 (100.0)	803 (100.0)	0.06 ^c

*Toxic hepatitis, non-specific findings, infiltrative liver diseases, hemochromatosis, etc. a: Chi-Square Test; b: Fisher's Exact Test; c: Poisson Rate Test.

and pathological diagnosis. The shift in biopsy indications observed over time likely reflects advances in non-invasive diagnostic methods, which have reduced the need for biopsy in treatment monitoring and evaluation of hepatomegaly. Increased recognition of hepatic steatosis and the clinical relevance of fibrosis staging may also explain the growing proportion of biopsies performed for fibrosis and cirrhosis assessment. Notably, the main indication for PLB changed from fibrosis and cirrhosis evaluation in the pre-pandemic period (54.2%) to abnormal liver function tests during the COVID-19 pandemic (69.2%), probably reflecting changes in healthcare priorities. In parallel, wider use of imaging techniques and non-invasive tests has enabled the identification and staging of fibrosis in asymptomatic patients with compensated disease, as supported by the introduction of MR elastography and FibroScan in our center since 2017 and 2022, respectively. A recent study from a tertiary care center showed that MASLD was the most common indication for FibroScan, accounting for about 51% of referrals.^[15] In contrast, viral hepatitis – particularly hepatitis B – remained a major indication in our biopsy-based cohort. This difference likely reflects the increasing use of non-invasive tests in patients with metabolic liver disease, whereas liver biopsy continues to be reserved for cases requiring histological staging or diagnostic clarification.

Idilman et al.^[16] published a study in 2021 that analyzed etiologic trends in 898 cirrhosis patients followed up for at least 6 months. Chronic hepatitis B was the most common cause (34%), followed by chronic hepatitis C (18%) and MASLD (8%). These findings were confirmed by Abayli et al.^[17] who retrospectively analyzed 554 liver biopsies of Turkish patients. The most common indication for liver biopsy was fibrosis staging in chronic hepatitis B, followed by elevation of abnormal liver function tests. The most common pathology diagnoses were 65% chronic hepatitis B, 16% MASLD, 3% chronic hepatitis C, and 3% AIH. Although the biopsy indications and pathology diagnoses were similar to these studies, our study is the first one showing the changing trends in benign liver diseases over decades, including the COVID-19 pandemic. Indeed, Abayli et al.^[17]

did exclude patients with non-specific histopathological findings, whereas Idilman et al.^[16] analyzed only cirrhotic patients. In our study, the most common pathology diagnosis was chronic hepatitis B (38.6%), followed by chronic hepatitis C (11.5%), MASH (8.5%), AIH (7.7%), and PBC (4.2%). Non-specific findings at pathologic evaluation were detected in 19.0% patients. When the analysis was done according to two equal time periods (2000–2011 and 2012–2022), chronic hepatitis B remained to be the most common pathology diagnosis (38.2% vs. 38.9%, $p=0.834$). There were statistically significant increases in the rates of pathology diagnoses of MASH (6.4–10.3%, $p=0.008$), AIH (4–11.1%, $p<0.001$), PBC (1.1–7%, $p<0.001$), and for AIH-PBC variant (0.3–1.1%, $p=0.068$) whereas the diagnosis of chronic hepatitis C decreased (17.3–6.1%, $p<0.001$).

In a multicenter Mexican cohort including 4584 cirrhosis patients diagnosed between 2000 and 2019, the leading etiology shifted from chronic hepatitis C to MASLD, whereas ALD consistently ranked second.^[18] A key difference between that study and ours lies in patient selection: while the former included only cirrhotic patients, our analysis encompassed all individuals undergoing PLB, irrespective of cirrhosis status. Similarly, in Brazil, Cunha-Silva et al.^[19] evaluated 532 biopsies in 524 patients (55.3% male) with a median age of 49 years, reflecting differences in study populations across regions. The main diagnoses were HCV infection (47.0%), autoimmune and cholestatic liver diseases (12.6%), and MASLD (12.1%). Unlike reports from Latin American countries, where hepatitis C continues to play a major role in chronic liver disease, our findings reflect a different epidemiological pattern in Türkiye. In line with previous studies, MASLD increased over time; however, since liver biopsy was performed only in selected cases, biopsy-based data likely underestimate its true burden. This suggests that MASLD accounts for a larger share of chronic liver disease in Türkiye, highlighting the need for studies combining biopsy results with non-invasive tests and imaging to better define its prevalence. In contrast to hepatitis C, hepatitis B maintained a high proportion among PLB diagnoses, underscoring its ongoing public health relevance in Türkiye. Hepatitis B vaccine implementation was

done in 1989; the expanded vaccination program included newborn hepatitis B vaccine in 1998.^[20] The antiviral treatments for both hepatitis B and C were reimbursed by the social security institution since 2000 and 2011, respectively.^[21] Despite these measures, the persistently high rates of hepatitis B require further explanation. In clinical practice, although chronic hepatitis B is usually diagnosed through serological and biochemical tests, liver biopsy has traditionally been used to evaluate the fibrosis stage and disease severity. In addition, reimbursement policies for antiviral therapy in Türkiye have previously required histological confirmation in some cases, which may have contributed to the relatively high number of biopsies among patients with chronic hepatitis B. Therefore, the prominence of abnormal liver enzyme elevation as an indication for liver biopsy in our cohort should be interpreted cautiously, as it may partly reflect underlying hepatitis B-related disease assessment rather than a purely diagnostic indication.

This study has several strengths and limitations. Its main limitation is the single-center design, which may limit generalizability, and the retrospective nature of data collection, particularly for periods preceding electronic medical records. In contrast, the major strength lies in the large cohort, with 1533 PLBs analyzed from over two decades, allowing assessment of temporal changes in both biopsy indications and histopathological diagnoses in patients with benign liver disease.

Conclusion

This study demonstrates that PLB remains a key diagnostic tool despite evolving indications over time. Biopsy volumes were largely stable across decades, apart from a decline during the COVID-19 pandemic, whereas indications shifted from fibrosis and cirrhosis assessment toward evaluation of abnormal liver function tests. Chronic hepatitis B remained the most frequent diagnosis, alongside a gradual increase in autoimmune liver diseases and MASH over the past two decades in Türkiye. Despite the growing use of non-invasive tests, PLB continues to provide essential diagnostic and prognostic information in selected patients with liver disease.

Ethics Committee Approval: The study protocol was approved by the Hacettepe University Ethics Committee (dated April 19, 2022, and numbered GO 22/406), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

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