# Indications of Liver Biopsy in the Era of Noninvasive Assessment of Liver Fibrosis

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***Background:*** **Liver biopsy (LB) has been used as diagnostic modality in liver diseases (LD). Over last two decades, there has been remarkable improvement in understanding of natural history, molecular diagnostics of viral hepatitis, genetic of LD, and also limitations of LB. There is current trend in avoiding LB in the management of various LDs.** ***Aim:*** **To determine utility of LB in clinical practice.** ***Material and Methods:*** **In a prospective study, 2413 patients of LD were followed up, 219 (9%) were acute, and remaining 2194 (90.9%) were chronic LD. Patients were evaluated by biochemical parameters, virological studies, and imaging endoscopy as and when required. LB was performed in 176 (7.2%) patients when no conclusion could be drawn from the noninvasive workup. Patients with platelet count <50,000/cm$^2$, ascites, and overt bleeding were excluded. Patients with international normalization ratio (INR) more than 1.5 were not excluded. No prophylactic use of fresh frozen plasma and platelet transfusion was done. There was no major complication related to the procedure. Indications for LB were as follows: cryptogenic LD 38 cases, hepatitis B infection 35, suspected autoimmune hepatitis 30, mass lesion in the liver and lymphoma 29, evaluation of portal hypertension 15, elevated liver enzymes 11, hepatitis C infection 9, and drug-induced LD 4, and miscellaneous 5 cases which were primary biliary cholangitis, primary sclerosing cholangitis, cholestatic LD, sarcoidosis, and amyloidosis.** ***Results:*** **LB changed the diagnosis in 55 (31.2%). These were cryptogenic LD in 24 cases, portal hypertension 15, elevated liver enzymes 11, and 5 others. In remaining, LB confirmed clinical diagnosis and helped in making management decisions.** ***Conclusion:*** **LB was required in 7.2% of patients with chronic LD. In 31.2% cases, LB changed the diagnosis. LB was a safe procedure even in presence of low platelet count and abnormal INR. (J Clin Exp Hepatol 2015;5:314–319)**

Liver Fibrosis

First percutaneous liver biopsy (LB) was done in 1883.[1] Since then, it has been used as a primary tool for diagnosis and staging of liver disease (LD). LB provides qualitative information regarding structural integrity of liver such as type and degree of liver injury, host response to injury, diagnosis, and classification of tumors which cannot be obtained by other means like serology or imaging. Percutaneous LB can be performed safely with various types of needles with or without imaging guidance. It can be performed by transjugular route or peritoneoscopically. The risk associated with the procedure is low and acceptable. Traditionally, LB has been utilized for diagnosis, structural damage to the liver, prognosis, and evaluation of treatment response.[2,3] With increased understanding of new bio-chemical tests, molecular tests, and serum markers of fibrosis, the need for LB has gone down drastically.[4,5] Currently, diagnostic use of LB is limited to the diseases like autoimmune LD (AIH), granulomatous LD, when multiple etiologies are suspected, abnormal liver tests of unknown etiology, cryptogenic LD, severe portal hypertension with no liver dysfunction, and focal liver abnormalities on imaging.[6] In structural alterations, necroinflammatory activity can be ascertained by biochemical parameters like liver enzymes, serum HBV DNA, HCV RNA levels, and serum IgG levels in AIH. Fibrosis can be ascertained by various commercially available tests (fibrotest, fibrosure, fibrometer, fibrospect II, ELF and hepascopre), aspartate transaminases to platelet ratio index and various imaging techniques, which are ultrasound based (transient elastography, Acoustic radiation force impulse elastography (ARFI), magnetic resonance elastography).[7–11] Simple, inexpensive, and reliable noninvasive means to assess disease severity in chronic viral hepatitis are being explored. Among the routine laboratory parameters such as decreased platelet count, increased AST/ALT ratios, prolonged prothrombin time (PT) are the earliest indicators of cirrhosis. Serum markers of fibrosis like products of collagen synthesis, procollagen III, amino terminal peptide, extra-cellular matrix enzymes like metalloproteinase 1, hyluronic acid, and laminin have limited accuracy in predicting fibrosis.[12,13] Combination of biochemical markers, alpha 2 macroglobulin, apolipoprotein A1, hepatoglobulin, GGTP and total bilirubin (fibrotest), and ALT (actitest) have been

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*Abbreviations:* AIH: autoimmune hepatitis; APRI: aspartate transaminases to platelet ratio index; CMV: cytomegalovirus; EBV: Epstein bar virus; HCC: hepatocellular carcinoma; HEV: hepatitis E virus; INCPH: idiopathic noncirrhotic portal hypertension; LB: liver biopsy; LD: liver disease; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NRH: nodular regenerative hyperplasia
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shown to be accurate noninvasive markers in chronic viral hepatitis [14,15] If these findings are confirmed by large trials in various parts of the world, need for LB will go down. In spite of these advances, LB remains in perfect gold standard for assessing pre cirrhotic stage.

There are certain limitations for LB. It can be associated with abdominal pain in almost 30% patients while with severe complication, bleeding in 0.3% and death in 0.03% patients. [6,16,17] Around 10–20% sampling errors are known in biopsy and there is 15–30% chance of underestimating cirrhosis in percutaneous biopsies. Intra- and inter-observer agreement is seen in 60–90% of cases.[18,19] LB estimates the static mass of fibrosis and may not assess dynamic process of constant degradation, formation, and remodeling. Because of above-mentioned problems, there is reluctance in accepting LB by patients and many of the physicians. In spite of these limitations, the LB remains imperfect gold standard for assessing precirrhotic stage. To our knowledge, there is no single study in real life scenario which has assessed the need of LB. There has been lot of discussion about avoiding LB but still there is certain population of patients who need LB to ascertaining etiology, grade of activity, progression, presence of other diseases, and risk factors for malignancy. Majority of studies on liver are based on individual disease group but the collective utility has not been studied. Hence, this study is planned to determine utility of LB in clinical practice.

## MATERIAL AND METHODS

In a prospective, observational study, 2413 patients with suspected LD were seen at our center from January 2010 till 30 April 2012. Of these, 219 (9%) were acute while remaining 2194 were chronic LD. All patients were evaluated by biochemical parameters, virological studies, imaging, and endoscopy as and when required. Etiology of chronic hepatitis was nonalcoholic fatty LD 783 (35.6%), alcoholic LD 343 (15.6%), hepatitis B infection 341 (15.5%), hepatitis C infection 138 (6.2%), cryptogenic chronic LD 123 (5.6%), space occupying lesions of liver 108 (4.9%), autoimmune hepatitis 40 (1.8%), vascular disorders of liver 23(1.04%), noncirrhotic portal hypertension 37 (1.6%), liver abscesses 58 (2.6%), drug-induced LD 29 (1.3%), infective hepatitis other than viral hepatitis 38 (1.7%), biliary diseases 55 (2.5%), hematological disorders involving liver 7 (0.3%), Wilson's disease 6 (0.2%), and miscellaneous 65 (2.9%) (Table 1). Of these, 11 patients fulfilled criteria of acute on chronic liver failure. There were 3 cases each of alcoholic cirrhosis, autoimmune hepatitis, and Wilson's disease. One case was of NASH and remaining were cases of drug-induced LD on background of NASH.

Liver cirrhosis was present in 508 (23.15%) cases of chronic LD. Etiology of cirrhosis was alcohol 179 (35.2%), HBV 64 (12.5%), HCV 74(14.5%), autoimmune 18 (3.5%), nonalcoholic fatty LD 34 (6.6%), PBC 1(0.5%), hematological disorders 6 (1.1%), Wilson's disease 3 (0.5%), cryptogenic 117 (23%), and miscellaneous 12 (2.3%).

**Table 1 Etiology of Liver Disease (*n* = 2413).**

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|---|---|
| Acute liver disease | 219 (9%) |
| Chronic liver disease | 2194 (90.9%) |
| • Nonalcoholic Fatty liver disease | 783 (35.6%) |
| • Alcoholic liver disease | 343 (15.6%) |
| • Hepatitis B infection | 341 (15.5%) |
| • Hepatitis C infection | 138 (6.2%) |
| • Cryptogenic chronic liver disease | 123 (5.6%) |
| • Space occupying lesions of liver | 108 (4.9%) |
| • Autoimmune hepatitis | 40 (1.8%) |
| • Vascular disorders of liver | 23 (1.04%) |
| • Non-cirrhotic portal hypertension | 37 (1.6%) |
| • Liver abscesses | 58 (2.6%) |
| • Drug induced liver disease | 29 (1.3%) |
| • Infective hepatitis other than viral hepatitis | 38 (1.7%) |
| • Biliary diseases | 55 (2.5%) |
| • Hematological disorders involving liver | 7 (0.3%) |
| • Wilson's disease | 6 (0.2%) |
| • Miscellaneous | 65 (2.9%) |

Etiology of acute LD was as follows: hepatitis A 19 (9%) cases, HEV 81 (37%), HBV 17 (8%), drugs 15 (6.9%), and others where etiology was not specific 87 (39%). Out of these 2413 patients, LB was performed in 176 patients (7.2%) when no conclusion could be drawn from noninvasive workup. It was performed with biopsy gun under ultrasound guidance. Patients with platelet count <50,000, with ascites, and overt bleeding were excluded. Patients with international normalization ratio (INR) more than 1.5 were not excluded. No prophylactic use of fresh frozen plasma and platelet transfusion was done. Thirty-eight (21.5%) patients had platelet count ranging from 50,000 to l00,000. Twenty-eight (15.9%) patients had INR more than 1.5 (range 1.6–4). There was no major complication related to the procedure.

## RESULTS

From total 2413 cases, 1766 (73.1%) were males and 647 (26.8%) females with male:female ratio 2.5:1. Mean age was 45 ± 15.34 years. LB was performed in 176 (7.2%) cases. Indications for LB were: cryptogenic LD 38 cases, hepatitis B infection 35, suspected autoimmune hepatitis 30 cases, mass lesion in the liver and lymphoma 29, evaluation of portal hypertension 15, elevated liver enzymes 11, hepatitis C infection 9, and drug-induced LD 4 and miscellaneous 5 cases which were primary biliary cholangitis, primary sclerosing cholangitis, cholestatic LD, sarcoidosis, and amyloidosis (Table 2). LB changed the diagnosis in 55 (31.2%) cases. These included cryptogenic LD 24 cases, portal

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