VALUE OF TRANS-ABDOMINAL ULTRASOUND-GUIDED PERCUTANEOUS LIVER BIOPSY IN PATIENTS WITH FOCAL OR DIFFUSE LIVER LESIONS IN KURDISTAN CENTRE FOR GASTROENTEROLOGY AND HEPATOLOGY IN SULAIMANI CITY

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ABSTRACT

Background

Percutaneous Liver Biopsy (PLB) is commonly used for assessing the histopathological status of the liver and thus deciding on diagnosis, prognosis, and management plan of patients.

Objectives

To assess the value of Percutaneous Liver Biopsy in decision making in patients referred to Kurdistan Centre for Gastroenterology and Hepatology (KCGH), and searching the common causes of liver enzyme abnormalities especially in patients with the unknown clue of diagnosis.

Patients and Methods

This study was performed in Kurdistan Center for Gastroenterology and Hepatology, between April 2018 and January 2019; Sixty-three patients have been included in this study, which was referred for PLB with different intentions; after appropriate pre-procedural preparation PLB was performed with the aid of a radiologist, and post-procedural follow up of patients was done for 6 hours in the ward.

Results

The reason of referral for PLB was diagnostic, prognostic, and management in 79.8%, 14.3%, and 6.3% respectively. Common diagnoses in a diffuse parenchymal liver lesion with or without elevated liver enzymes were AIH in 15.8%, DILI in 14.3%, and NASH 14.2%. Percutaneous liver biopsy changed the preliminary diagnosis in 52.3%, and management plan in 34.9% of cases. As PLB is an invasive procedure, 31.7% of patients developed complications, which is in decreasing order including right upper quadrant pain 15.9%, right shoulder pain 5.9%, combined right upper quadrant pain, and right shoulder pain in 3.2%, and vasovagal reaction in 3.2 %.

Conclusion

Percutaneous liver biopsy is a valuable investigation in deciding on diagnosis, the prognosis of liver lesions, and it will help the management plan. The three most common diseases which should be excluded in every patient with diffuse parenchymal liver lesions or elevated liver enzymes are AIH, DILI, and NASH.

Keywords: *Percutaneous Liver Biopsy; KCGH; Autoimmune Hepatitis; Kurdistan, Iraq.*

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INTRODUCTION

Percutaneous liver biopsy (PLB) is a procedure that evaluates the histopathological features of any lesion in the liver whether diffuse or focal. There are many indications for doing PLB, including diagnostic like in abnormal liver biochemistry as in the diagnosis of autoimmune hepatitis and non-alcoholic steatohepatitis, focal or diffuse lesions detected by imaging modalities [1]; prognostic like staging (degree of fibrosis) and grading (necroinflammatory status) of known parenchymal liver disease as in case of viral hepatitis, hemochromatosis, and alcoholic liver disease [2, 3], and lastly as a treatment plan procedure which based on histological features as in case of viral hepatitis [4] (for example cirrhosis in hepatitis C virus HCV infection), hepatic mass lesion like hepatocellular carcinoma (HCC), and evaluating response to therapy as in case of autoimmune hepatitis (AIH) [3].

Liver biopsy is a gold standard for detecting fibrosis and cirrhosis [5, 6], but there are non-invasive measures like serum biomarkers (e.g. NAFLD fibrosis score and Fibrosis-4 test) and imaging-based tests (e.g. Transient elastography and Magnetic Resonance Elastography) used for assessing the status of liver fibrosis and the final decision of treatment [6], as there are limitations in doing PLB, like interpersonal variability, sampling error, cost of the procedure and patient's unwillingness to do such invasive procedure [7], Although non-invasive measures have limitations in intermediate stage classification, they have the same accuracy for low grade and high-grade hepatic fibrosis [5]. Non-invasive measures are making the use of PLB declining, but still in patients with difficulty in reaching diagnosis after a thorough history and physical examination and proper investigations are important resorts [8, 9].

Percutaneous Liver Biopsy is an invasive procedure; it has its complications which include: major complications like bleeding and symptomatic hematoma, intraperitoneal bleeding, intra-abdominal organ perforation, hemothorax and subcutaneous emphysema due to lung injury, gallbladder perforation, hemobilia, and even death; minor complications like abdominal pain, right shoulder pain due to diaphragmatic irritation, vasovagal reaction, infection at the site of intervention ([8, 10-13].

PATIENTS AND METHODS

A prospective case series study performed. Between April 2018 and January 2019, 63 patients were referred to KCGH and enrolled in this study to undergo PLB for unexplained abnormal liver biochemical tests or a focal liver lesion of unknown etiology.

Ethics committee approval of Sulaimani Health Directorate and Kurdistan Board for Medical Subspecialties were taken. Informed consent has been taken for each patient.

The questionnaire filled after history and physical examination, with checking of bleeding diatheses and platelet count. Cooperation was done with radiologists for guiding during a procedure. A procedure started by detecting the area of maximum dullness by percussion in the right upper quadrant, usually in the second or third intercostal space above the costal margin in the mid-axillary line, then sterilizing the area with povidone-iodine, later on, lidocaine 1% injected in both superficial and deep tissues, then a semi-automatic true-cut biopsy needle inserted (GEOTEK needle of 18 Fr X 20 cm or 16 Fr X 20 cm). After reaching adequate depth or targeted lesion the needle was shot. We put the biopsy sample in formaldehyde (formalin). Each biopsy sample was red by one pathologist, who has an interest in GI pathology. Knodell Index used for assessing the grade of necroinflammatory activity, Modified Ishak Method, and Metavir score is used for assessing the stage of fibrosis.

After the procedure, each patient stayed in our ward for 6 hours, with frequent monitoring of vital signs, and discharged from the hospital if the patient was hemodynamically stable and not having pain. Patients who have absolute contraindications to PLB excluded from the study, like uncooperative patient, history or diagnosis of bleeding tendency, INR more than 1.5, Platelet count <50,000/c.mm, use of a non-steroidal anti-inflammatory drug within the previous 7–10 days, blood for transfusion unavailable, and Infection of the hepatic bed [1,9].

The "IBM SPSS Statistics version 25" was used for the analysis of the data and both descriptive and inferential statistics were used. Furthermore, P-values of (≤ 0.05, and <0.001) were considered as statistically significant, and highly significant associations, respectively. Also, Pearson Chi-Square was used to find out the significance of the association between independent and dependent variable pairs, and Pearson's R Correlation was used to calculate the direction of the correlation between the two variables.

RESULTS

The patient's characteristics are shown in Table (1), with their presentation, all of the asymptomatic patients referred for PLB depending on their elevated liver enzymes, TAUS features of chronic liver disease or focal lesions as shown in both Table (2) and table (4), majority of patients are above the age of 40, and a most common complaint was jaundice, intending to do PLB clarified pre-procedurally as shown in Table (3), in which nearly 80% of them undergoing PLB for diagnostic purpose. The risk and type of complications after PLB determined as shown in Figure (1), in which the most common complication is Right upper quadrant pain.

According to Table (4), we could calculate the value of TAUS on detecting and evaluating liver lesions for example its sensitivity = 70%, specificity = 0%, positive predictive value (PPV) = 93.3%, negative predictive value (NPV) = 0% and its likelihood ratio (LR) = 70%, with a P-value of 0.003.

The effect of PLB on decision making is clarified in detail as shown in Table (5).

Table 1. Socio-demographic features of the patients.

Variables		Frequency	Percentage
Age groups (year)	16-39	26	41.2
	40-59	20	31.7
	60-75	17	26.9
Gender	Male	27	42.9
	Female	36	57.1
Residency	Rural	5	7.9
	Urban	37	58.7
	Suburban	21	33.3
Ethnicity	Kurd	44	69.8
	Arab	18	28.6
	Turkmen	1	1.6

Table 2. Clinical features of the study patients.

Clinical features	Frequency	Percentage
Jaundice	25	39.7
Abdominal pain	17	27
Asymptomatic	14	22.2
Jaundice and pruritis	3	4.8
Fatigue	3	4.8
Severe pruritis	1	1.6

Table 3. Reason for performing PLB.

Reasons	Frequency	Percent
Diagnostic	50	79.4
Prognostic	9	14.3
Management plan	4	6.3
Total	63	100

Table 4. Association between TAUS for liver status and liver biopsy results.

	TAUS for liver status					
Liver Biopsy Result	**Normal liver status (%)**	**Increase echo texture + periportal thickening (%)**	**Cirrhotic liver or preportal collaterals ± Ascites (%)**	**Focal Liver Lesion (s) (%)**	**Total (%)**	**P-value**
GVHD	2 (3.2)	2 (3.2)	0 (0)	0 (0)	4 (6.3)	
AIH	5 (7.9)	2(3.2)	3 (4.8)	0 (0)	10 (15.8)	
DILI	4 (6.3)	4 (6.3)	1 (1.6)	0 (0)	9 (14.3)	
NASH	1 (1.6)	8 (12.7)	0 (0)	0 (0)	9 (14.3)	
PBC	1 (1.6)	0 (0)	0 (0)	0 (0)	1 (1.6)	
Cirrhosis	1 (1.6)	1 (1.6)	3 (4.8)	0 (0)	5 (7.9)	
ACGH	0 (0)	1 (1.6)	0 (0)	0 (0)	1 (1.6)	
Overlap syndrome	0 (0)	0 (0)	2 (3.2)	0 (0)	2 (3.2)	
Active CVH - C	0 (0)	1 (1.6)	0 (0)	0 (0)	1 (1.6)	
HCC	0 (0)	0 (0)	0 (0)	2 (3.2)	2 (3.2)	0.003
AC involving liver	0 (0)	0 (0)	0 (0)	3 (4.8)	3 (4.8)	
Hemochromatosis	1 (1.6)	1 (1.6)	0 (0)	0 (0)	2 (3.2)	
Large duct obstruction	0 (0)	1 (1.6)	0 (0)	0 (0)	1 (1.6)	
CVH- B	2 (3.2)	1 (1.6)	2 (3.2)	0 (0)	5 (7.9)	
HVOO	0 (0)	1 (1.6)	0 (0)	0 (0)	1 (1.6)	
SGCH	1 (1.6)	0 (0)	0 (0)	0 (0)	1 (1.6)	
Normal liver tissue	0 (0)	1 (1.6)	1 (1.6)	0 (0)	2 (3.2)	
CCH	0 (0)	2 (3.2)	0 (0)	0 (0)	2 (3.2)	
AIH or DILI	0 (0)	2 (3.2)	0 (0)	0 (0)	2 (3.2)	
Total	18 (28.6)	28 (44.4)	12 (19)	5 (7.9)	63 (100)	

GVHD= Graft Versus Host Disease, AIH= Autoimmune Hepatitis, DILI= Drug-Induced Liver Injury, NASH= Non-Alcoholic Steato Hepatitis, PBC= Primary Biliary Cholangitis, ACGH= Active Chronic Granulomatous Hepatitis, CVH= Chronic Viral Hepatitis, HCC= Hepatocellular carcinoma, AC= adenocarcinoma, HVOO= Hepatic venous outflow obstruction, SGCH= Syncytial Giant Cell Hepatitis, CCH= chronic Cholestatic Hepatitis.

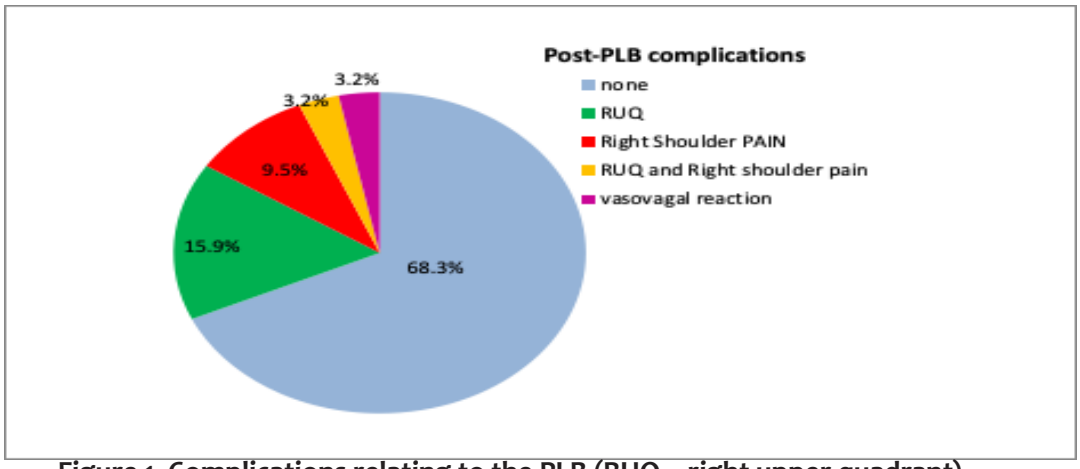

Figure 1. Complications relating to the PLB (RUQ = right upper quadrant).

Table 5. Effect of PLB on decision making.

Pre-PLB diagnosis (no.)	Post- PLB diagnosis (no.)	Post-PLB management plan (no.)
Chronic HCV infection (2)	Changed to NASH (1)	Changed (1)
Chronic HBV infection (9)	Confirmed (5) Change to NASH (3) Normal liver tissue (1)	Changed (2)
GVHD (5)	Confirmed (4) Change to hemochromatosis (1)	Changed (1)
DILI (7)	Changed to NASH (1) Changed to overlap syndrome (1) Exclude DILI (1) Confirmed (4)	Changed (3)
Unknown diagnosis (10)	DILI (3) AIH (2) DILI or AIH (2) Large duct obstruction (2) Chronic granulomatous hepatitis (1)	Changed (4)
AIH (10)	Confirmed (6) Change to DILI (1) Change to overlap syndrome (1) Change to PBC (1) Change to NASH (1)	Changed (4)
Hemochromatosis (1)	Change to hemosiderosis (1)	Changed (1)
NASH (2)	Confirmed (2)	
PBC (1)	Changed to NASH (1)	Changed (1)
Cirrhosis (11)	Excluded (4) Change to AIH (2) Change to DILI (1) Confirmed (4)	Changed (4)
Lymphoma (1)	Excluded (1)	Changed (1)
HCC (1)	Confirmed (1)	
Fibrolamellar type HCC (1)	Confirmed (1)	
Suspected secondaries (2)	Confirmed (2)	

HBV= Hepatitis B Virus, HCV= Hepatitis C Virus, GVHD= Graft Versus Host Disease, AIH= Autoimmune Hepatitis, DILI= Drug-Induced Liver Injury, NASH= Non-Alcoholic Steato Hepatitis, PBC= Primary Biliary Cholangitis, HCC= Hepatocellular carcinoma, HVOO= Hepatic venous outflow obstruction.

DISCUSSION

In the past liver biopsy (LB) was used as a diagnostic tool [14], with advancement its indication expanded to include both prognostic and management plan purpose as described by Sorbi et al [15], in our study still the main aim is for the diagnostic purpose (79.4%), with the least one is for management plan (6.3%), and (14.3%) for prognostic purpose, this will indicate the need for progression and more specialization in the field of hepatology in KCGH, in addition to a learning curve in the field of non-invasive measures for assessing liver status like elastography.

Regarding complications of PLB, in our study majority of patients did not develop any complications (68.3%) and 31.7% of patients developed complications, which is in decreasing order including right upper quadrant pain 15.9%, right shoulder pain 5.9%, combined right upper quadrant pain and right shoulder pain in 3.2%, and vasovagal reaction in 3.2 %. Compared to a study done by Kose et al [11], in which rate of RUQ pain and shoulder pain was 22.6%, the overall incidence of pain was 25% in our study, which is nearly similar despite a small sample size and limited period. There is no major complication in our study; this is related to small sample size in one hand, and meticulous pre-procedure care with the aid of radiologists in difficult procedures on the other hand.

In our study there were 4 out of 63 (6.3%) patients with histology of GVHD, all of them referred from the oncologic department, and underwent bone marrow transplantation (BMT). It is reported by Karen et al [16] that there are many differential diagnoses in liver dysfunction after BMT, including DILI, viral hepatitis, lymphoma, sepsis-related cholestasis, and many others, this makes PLB have a great role in the better management plan of these critically ill patients.

In our study, there are 5 patients with single or multiple focal hepatic lesions, 2 of them (3.2%) with hepatocellular carcinoma diagnosis of which one is Fibrolamellar variant, and another 3 patients (4.8 %) are of metastatic type adenocarcinoma, one patient has pancreatic head mass and another one has a history of breast carcinoma diagnosis with mastectomy 1 year before PLB, only one of 3 patients have adenocarcinoma of unknown origin, which was sent for immunohistochemistry. This indicates that PLB is important for making accurate diagnosis and next management plan especially if the whole workup including imaging will not give an accurate diagnosis, and there are other possibilities apart from HCC in solitary liver lesion even if there is the elevation of AFP as reported by Stolzel et al [17], like lymphoma infiltration to the liver, intrahepatic cholangiocarcinoma, and neuroendocrine tumor.

The difficulty of differentiating AIH from DILI was mentioned by Hye Young Ju et al [18], in a degree that it is very difficult to diagnose DILI without certainly excluding AIH, although there are histological features in favor of AIH, but both entities are immunologically mediated and there are features which are similar in both, e.g. Interphase hepatitis [18,19], in addition to the possibility of Drug-Induced AIH (DIAIH) as mentioned by Yilmaz et al [20] . In our study, 21 patients (33.3%) have PLB diagnosis of DILI and AIH, 10 patients (15.8%) with AIH, 9 patients (14.3%) with DILI, and 2 patients (3.2%) with features of both AIH and DILI.

Drugs causing DILI in our study were one high dose estradiol, one combined oral contraceptive pill, one methotrexate, one carbimazole, and one carbamazepine, these are confirmed after stopping the offending agent which followed by improvement in liver enzymes and TSB. Four patients without having a clear history of drug or herbal use, this may be partly explained by over usage of antibiotics and other medications as over the counter drugs (OTC) in our region, eg. Amoxicillin-clavulanic acid, metronidazole, and steroid medications.

In our study there is one patient with chronic lymphocytic leukemia (CLL), he developed jaundice after using herbal medicine and his PLB result was syncytial giant cell hepatitis (SGCH), this was mentioned by Chhagan Bihari et al [21] as a well-known factor that both CLL and herbal use may be a risk factor for SGCH.

It is reported by Boberg KM et al [22], that overlap syndrome should be considered when there is cholestasis in context of AIH diagnosis, and diagnosis of AIH should be in doubt every time if there is atypical presentation, suspicious histopathological features, and no response or suboptimal response to therapy. In our study there are 2 cases of a cholestatic pattern of elevated liver enzymes, with positive Anti-Nuclear Antibody (ANA); one is AIH-PSC (primary sclerosing cholangitis) and another one AIH-PBC (primary biliary cholangitis), another 2 cases with PLB diagnosis of non-specific chronic cholestatic hepatitis, this indicates that PLB is not almost always give us final definitive diagnosis [23] , and that is why Beuers et al constructed diagnostic criteria for overlap syndrome [24], so we can estimate that the significance of PLB will be diminished in case of inappropriate clinical judgment.

In our study, there are 9 patients (14.2%) with non-alcoholic steatohepatitis (NASH), as mentioned in table (5), there are only 2 cases suspected to have NASH before PLB, this indicates the importance of PLB for excluding or confirming the diagnosis to have a clear path for discussing future prognosis and further management plan, as discussed by Chalasani et al [25].

In our study there are 11 patients (17.4%) of viral hepatitis, of which 9 are chronic HBV infection and 2 are chronic HCV infection, 6 out of 11 patients underwent PLB for assessing the status of the liver, the other 5 patients were suspecting for other diagnoses, that means not every elevated transaminase level are due to viral hepatitis, there are other conditions like NASH which may be mistakenly not considered, as shown in Table (5). Although the prevalence of HBV infection (as determined by HBsAg) in Sulaimani city is decreasing from 2.3 % mentioned by Mohammed O. et al [26] to 0.67% mentioned recently by Muthana [27], still they are common for a tertiary center like KCGH to face those patients, and it is a standard of care for doing PLB whenever hepatic status is questionable or chronic viral hepatitis do not seem to be a culprit for deranged liver status, as reported by Rached AA et al [28].

It is well known that TAUS has low sensitivity in detecting cirrhosis, as reported by Erin et al [29], especially in the absence of portal hypertension, with a false-positive result of 20%, comparing to our study in which according to TAUS and other clinical features there were 11 patients with suspected cirrhosis, of which only 4 patients (36.3%) confirmed to have cirrhosis, although PLB is also prone to sampling error due to patchy evaluation of liver tissue [30].

In our study, PLB changed the presumptive diagnosis n 52.3%, and management plan in 34.9%, contrary to a study done by Sorbie et al [15], in which diagnosis and management plan changed 14% and 33.3 % respectively. Another study done on 411 patients by Claudia Spycher [31], showing confirmation of the presumptive diagnosis in 84.4%, and change in management plan in 12%, this difference in changing diagnosis and management plan partly related to interpersonal variability in histopathology reading in addition to the advance in pathologist experience, despite the advent of more serological and non-invasive markers for diagnosing and assessing liver status, our study result will be a good rationale for constructing consensus decision by more than one pathologist in addition to taking a step toward more specialization in the field of gastrointestinal pathology.

In conclusion, PLB is a valuable investigation regarding diagnosis, prognosis, and management plan especially in diffuse liver lesions, but to be more standardized a consensus decision by more than one pathologist is recommended, and immunohistochemistry should be available for a more accurate diagnosis. Autoimmune hepatitis, DILI, and NASH should be considered in any differential diagnosis of diffuse parenchymal liver disease.

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