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Oration

Will liver biopsy become obsolete in the near future?

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Abstract

Introduction: Liver biopsy forms the core of hepatopathology by providing tissue suitable for light microscopic, histochemical, immunochemical, ultrastructural and molecular biological studies. The possibility of the liver biopsy being obsolete will be discussed in this oration with evidence for and against this proposition being presented including our own experience and research.

The case for liver biopsy becoming obsolete: The case for the liver biopsy becoming obsolete includes, complications of liver biopsy, the inadequacy of liver tissue for assessment, the variability in the histopathological diagnoses and the availability of non-invasive markers for the assessment of liver disease. In considering the latter, a part of study 1, "The value of Brunt scoring in predicting the short-term outcome of non-alcoholic steatohepatitis", will be used to illustrate that there is moderate concordance between transaminase levels and the histological grade assessed by BRUNT scoring used in monitoring the underlying disease activity in non-alcoholic steatohepatitis (NASH). Study 2, "The histomorphological patterns of liver disease in a cohort of Sri Lankan children", assessed the diagnostic approach to paediatric liver disease based on histomorphological patterns adopted in the local context in the absence of electron microscopic facilities, sophisticated enzyme assays, biochemical investigations and genetic testing that aid in the diagnosis of paediatric liver disease especially the metabolic hepatopathies. Study 3, "Evaluating the usefulness of liver biopsy in the paediatric population", investigated the implications of the above approach on diagnosis and management of children with liver disease. In this study, 92% (56/61) of biopsy reports were shown to have a significant impact on the diagnosis and management of paediatric liver diseases. In assessing the adequacy of liver tissue obtained for histological examination, study 4 revealed that only 29 biopsies (33.7%) fulfilled both criteria of being more than 1 cm in length and having more than 6 complete portal tracts which was the recommendation given by Royal College of Pathologists of the United Kingdom. It was also revealed that the correlation between the length of the biopsy and the number of complete portal tracts present, was weak.

The case against liver biopsy becoming obsolete: The contribution of the liver biopsy in routine clinical practice as well as in research, such as in raising the awareness and describing emerging entities are described to support the case against the obsolescence of liver biopsy. Study 5 evaluates the usefulness of liver biopsies in adults and the findings reveal that 84.7% (98% CI-79.8%- 89.6%) of the biopsy reports made a significant contribution to the management of patients with liver disease. In study 6, the clinical, biochemical and histological profile of 100 NASH patients and the short term follow up and outcome of patients following lifestyle modification are described. This is the first reported series of NASH patients in a Sri Lanka. Despite cirrhosis in children due to non-alcoholic fatty liver disease (NAFLD) being considered extremely rare in the Asia Pacific region in 2008, study 7

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describes five children with advanced fibrosis and cirrhosis due to NAFLD in a preliminary report. A case report titled "Worsening cholestasis and possible cefuroxime-induced liver injury following successful therapeutic endoscopic retrograde cholangiopancreaticography for distal common bile duct stone" is presented to illustrate the value of liver biopsy in establishing the diagnosis in situations where multiple causes could account for the clinical picture. Finally, in Study 8, two audits of liver biopsies conducted in our institution during the periods 2012 - 2015 and 2019 - 2022 are presented as evidence that the number of liver biopsies performed and reported have not decreased.

In conclusion, despite the many draw backs of liver biopsy and the availability of several non-invasive markers of liver disease, there still appears to be a definite role for liver biopsy in clinical practice as well as in providing insights into and enhancing the awareness of liver diseases. It, therefore, appears unlikely that liver biopsy will become obsolete in the near future.

Introduction

Liver biopsy (LB) forms the core of hepatopathology by providing tissue suitable for light microscopic, histochemical, immunochemical, ultrastructural and more recently, molecular biological studies.

The first percutaneous liver aspiration was performed by Paul Ehrlich in 1883, more than 125 years ago (1). Dame Sheila Sherlock pioneered the use of the needle biopsy of the liver in 1945 (2). However, the credit for popularizing its use and thereby revolutionizing the practice of hepatology is bestowed on Menghini, who popularized the use of LB in 1958 (3).

LB is performed using percutaneous, transvenous (transjugular, transfemoral) and surgical-laparoscopic routes. Palpation /percussion, radiologic marking and real-time imaging guidance are the three methods for performing percutaneous biopsies (4,5). The needles used in the procedure are the aspiration needles (Menghini, Jamshidi, Klatskin) and the cutting type of needles which include manual (Vim-Silverman) or full/semi-automatic tru-cut needles (4,6). The technique and needle selection may vary depending on the personal experience of the physician, type of approach or biopsy indications. The percutaneous LB technique is the most widely practised in most centres. Each of these techniques has its advantages and disadvantages. A transjugular needle biopsy is preferred whenever a percutaneous route is contraindicated as in the presence of significant ascites or coagulopathy. An important advantage of this approach is the ability to obtain intrahepatic portal pressures that aid in the diagnosis and management of patients with cirrhosis (7). However, trans-jugular biopsies often render smaller fragmented tissue samples which makes pathological assessment challenging.

Percutaneous and transjugular biopsies are used to obtain samples from patients suffering from disorders that result in diffuse changes in the liver (7,8). Image-guided needle biopsies on the other hand are necessary for focal diseases/lesions (9,10). Laparoscopic/surgical LB enables the gross features of the liver to be assessed before taking the biopsy. During laparoscopy/surgery, either a needle core biopsy or a wedge biopsy can be obtained. Due to its cost and potential complications, surgical/laparoscopic biopsies are carried out mainly when surgery is performed for another indication or the lesion is difficult to approach by the standard methods. Laparoscopic LB has added costs and the potential for more complications (11). Though surgical biopsies provide a much larger sample and have the advantage of harvesting tissue directly from a macroscopically visible lesion or abnormal area, they are often suboptimal for the assessment of fibrosis and/or inflammation due to the presence of the Glisson capsule, wider portal tracts (PTs) in the subcapsular area and frequent but insignificant surgically induced hepatitis (12).

The role of LB in the fast changing field of hepatology will thus be debated in order to seek a possible answer to the question "Will liver biopsy become obsolete in the near future?", based on the many years of practice

and research I have been engaged in as a pathologist with an interest in liver disease.

The case for LB becoming obsolete

The main issues highlighted by those arguing against LB are its complications, the inadequacy of biopsy tissue, the variability of histopathological evaluation and the recent availability of a variety of noninvasive investigations (13). The latter is gaining much importance because of the ease of performance and its relative accuracy.

Complications of LB

The complications of LB may include minor events, such as pain and transient hypotension, or more major complications including haemorrhage (intraperitoneal, intrahepatic and haemothorax), puncture of a viscus (e.g. gallbladder, colon, pleura), inadvertent biopsy of the kidney or the pancreas and intrahepatic arteriovenous fistula formation. Significant bleeding and bile peritonitis are serious complications that lead to mortality, and the overall mortality rate from LB is 0.1 - 1.0% (14,15).

Although pain is regarded as a minor complication, this may become very distressing to many resulting in the reluctance of patients to undergo repeated LBs required for follow-up in some instances. Pain is experienced by 84% of individuals during LB and 20% of patients experience severe persisting pain beyond one day of the procedure (16).

Similarly, LB-induced bleeding is often considered an extremely rare complication, but major bleeding is reported in up to 4.5% of procedures and is the most common cause of death associated with LB (17).

Variability of histopathological interpretation

Variability of histopathological interpretation may also be a significant drawback, both in relation to the discordance in the diagnosis between academic/specialist histopathologists and community/general histopathologists and in the inter and intra-observer variation seen when grading and staging of chronic hepatitis.

Diagnostic errors made by non-specialist pathologists were reported in more than 25% of patients undergoing LB at academic centres (18,19). These interpreter errors accounted for 15-33% of the variability in the staging fibrosis (20,21,22) and 10% in the grading of necroinflammation (20,23).

Grading and staging of chronic hepatitis for which LB is frequently utilized is essentially subjective. This is despite the emergence of many grading and staging systems over the last 60 years, created to standardize the evaluation of LBs and minimize observer variability. These include the grading and staging systems by Scheurer (24), Batts and Ludwig (25), Modified HAI by Ishak et al. (25) which is a modification of that proposed by Knodell and the same group in 1981 (27), and the METAVIR system (28). However, the categorization of the degree and extent of inflammation and fibrosis is complicated by the complexity of these histology scoring systems. Although these scoring systems describe the same histological parameters, they allocate distinctly different numerical scores to each of these parameters. Hence, these scores are not wholly convertible or superimposable.

Availability of noninvasive investigation of liver disease

Noninvasive tests are relatively easy to perform and more easily reproducible than liver histology. The clinical course of chronic liver disease is dependent on the progression rate and extent of fibrosis, and the monitoring of this with repeated liver histology becomes obviously impractical. Additionally, simple numeric values as representative of the degree of the underlying disease process are more appealing than complex descriptive and semi-quantitative scoring methods that are inherent in histological assessments as alluded to above.

The commonly used noninvasive markers of liver disease utilize a combination of simple biochemical, haematological and demographic parameters. These include laboratory-based tests such as α2-macroglobulin, total bilirubin, gamma-glutamyl transpeptidase, apolipoprotein A1, haptoglobin, aspartate transaminase (ALT), alanine transaminase (AST), platelets, and the age, sex and weight of the patient. A composite of the above tests

calculated according to a patented formula or simple ratios between these different parameters offers mathematical scores that help distinguish between different levels of histologic disease (29). Some of these are given in Table 1.

Table 1: Non-invasive markers of liver histological assessment including tests for fibrosis, necroinflammation and steatosis (13)

Test	Component	Liver disease
Fibro Test - Acti Test	age, sex, A2M, GGT, haptoglobin, total bilirubin, apolipoprotein A1 ALT	HCV HBV NAFLD ALD
Fibrospect II	HA, TIMP-1, A2M	HCV
ELFGA	age, PIIINP, HA, TIMP-1	Mixed
Fibrometer	age, sex, HA A2M, GGT	Mixed
HepaScore	age, sex, HA, A2M, GGT	HCV
APRI	AST, platelet count	HCV HBV
Fibroindex	AST, platelet count, gamma globulins	HCV
AST/ALT ratio	AST, ALT	HCV HBV
Forns index	age, platelet count, GGT, cholesterol	HCV
Pohl index	AST, ALT, platelet count	HCV
AP index	age, platelet count	HCV
CDS	AST, ALT, platelet count, INR	HCV
Steato/ NASH Test	BMI, AST, serum glucose, triglycerides, cholesterol, age, sex, A2M, GGT, haptoglobin, total bilirubin, apolipoprotein A1, ALT	NAFLD
Fibroscan	hepatic transient elastography	HCV HBV PBC PSC ALD
SHASTA index	HA, AST, albumin	HCV
BAAT score	BMI, age, ALT, triglycerides	NAFLD
NAFLD score	age, BMI, platelet count, albumin, AST/ALT ratio, IFG/diabetes	NAFLD

A2M - α2-macroglobulin, ALD - alcoholic liver disease, ALT - alanine transaminase, BMI - body mass index, GGT - gamma-glutamyl transpeptidase, HA - Hyaluronic acid, HCV - hepatitis C virus, HBV - hepatitis B virus, IFG - impaired fasting glucose, INR - international normalized ratio, NAFLD - nonalcoholic fatty liver disease, PBC - primary biliary cholangitis, PSC - primary sclerosing cholangitis, PIIINP - Amino-terminal propeptideof Type III collagne, TIMP 1 - Tissue inhibior of metalloproteinases

Transient elastography provides simple numerical values that help to distinguish between different stages of fibrosis (30). Simple noninvasive indexes, such as AST/ALT ratio, platelet count, age-platelet index and APRI (aspartate transaminase to platelet ratio) have been evaluated and found to have moderate diagnostic accuracy for the prediction of significant fibrosis or cirrhosis (31,32,33).

Similarly, our experience in using AST and ALT values in assessing the degree of inflammation in non-alcoholic liver steatohepatitis (NASH) is presented below.

Study 1: The value of Brunt scoring in predicting the short-term outcome of non-alcoholic steatohepatitis (NASH) (34)

A part of this study is utilized to illustrate that there was moderate concordance between AST and ALT and the histological grade as assessed by BRUNT scoring in the monitoring underlying disease activity in NASH.

Objective: One of the objectives of this study was to determine whether the Brunt grading correlated with the AST and ALT levels which at that time were the most commonly used parameter to monitor patients with NASH following lifestyle modifications.

Method: Seventy-nine patients diagnosed as having NASH in 2003 were studied prospectively. Brunt grading was used to assign the LBs of these patients into three necroinflammatory grades. The mean serum transaminase values obtained at the time of LB were compared to these Brunt grades using ANOVA.

Results: The mean AST and ALT values (IU/L) in these three necroinflammatory grades were Grade 1- 62.4 and 102.1, Grade 2 - 87.6 and 139.4, and Grade 3 - 90.9 and 104.5, respectively. There was a significant difference between Grades 1 and 2 and 1 and 3, but not between Grades 2 and 3.

Conclusion: The ALT and AST levels provided some indication of the necroinflammatory activity in NASH at the two ends of the spectrum but were not of much value in

assessing moderate degrees of necroinflammation (i.e. Grades 2 and 3).

With the use of multivariate analysis models the next generation of noninvasive markers have been developed. These have been shown to be simple, practical and reasonably accurate in predicting liver fibrosis with a 85%-95% agreement with liver histology. Among these, FibroTest has been validated in several groups of patients. In addition, FibroTest has been shown be useful in predicting the severity of necroinflammation with the addition of aminotransferase levels (ActiTest) (34,35,36,37).

Accuracy in the diagnosis of paediatric liver disease

The diagnosis of childhood liver diseases on LB is challenging. Apart from conditions such as infections, autoimmunity and bile duct pathologies, a significant proportion of metabolic liver diseases enter the differential diagnosis. Some inherited metabolic disorders may have little or no impact on liver histology (e.g. urea cycle disorders). In such situations, the pathologist cannot offer a diagnosis, except a possible and exclusionary one. Many other metabolic disorders of the liver produce typical histological patterns in the liver that aid the pathologist in the diagnostic workup. Still, other disorders show a limited number of histological patterns that can evolve from one pattern to another as the disease progresses. The diagnosis and interpretation of LBs therefore requires a clear appreciation of this mosaicism, improved by the understanding of the pathogenesis, pace and course of the disease in question.

Hence, considering the course of disease as well as other clinical and biochemical features, a morphological pattern recognition approach is adopted in many centres. This is especially important in the local context where access to electron microscopy, sophisticated enzyme assays and genetic testing is not readily available.

Study 2: The histomorphological patterns of liver disease in a cohort of Sri Lankan children (36)

Objective: To describe the various histomorphological patterns encountered in the paediatric population.

Method: This was a retrospective study of 112 LBs reported at the Lady Ridgway Hospital that were categorized based on histomorphological patterns such as hepatitis, ductopenic/biliary, steatotic, cholestatic, neoplastic, storage and vascular patterns. Cases with overlapping patterns were excluded.

Results: The patterns identified were hepatitic pattern - 32.14% (36/112), ductopenic/biliary pattern - 31.25% (35/112), steatotic pattern - 15.18% (17/112), cholestatic pattern - 6.25% (7/112), neoplastic - 5.36% (6/112), storage pattern - 4.46% (5/112), fibrotic pattern - 3.57% (4/112) and vascular abnormalities pattern - 1.79% (2/112).

Conclusion: The commonest patterns encountered were the hepatitic pattern mostly presenting with a clinical picture of neonatal jaundice, the ductopenic/biliary pattern caused mainly by biliary atresia and the steatotic patterns resulting from underlying non-alcoholic fatty liver disease (NAFLD).

Next we evaluated the value of this pattern based approach in the diagnosis of paediatric liver disease in the following study.

Study 3: Evaluating the usefulness of LB in the paediatric population (37)

Method: The clinical and histological diagnoses of LBs received at Lady Ridgeway Hospital were reviewed over a period of one year, from the 1st March 2020. The diagnosis/conclusions of these LBs were grouped into five categories depending on the degree of certainty and impact on the management of the child. Categories 1 and 2 were deemed as having no impact, while categories 3, 4, and 5 were considered useful in the management of the child.

Results: Sixty-one LBs were studied. No unsatisfactory/inadequate samples were received (Category 1). Only 8.2% (5/61) of cases generated a descriptive report (Category

2). 29% (18/61) of LBs confirmed the clinical diagnosis without providing additional information (Category 3) and 42% (26/61) of biopsies provided further useful information (Category 4). Histology changed the clinical diagnosis in 20% (12/61) of cases (Category 5).

Conclusion: 92% (56/61) of biopsies had a significant impact on the diagnosis and management of pediatric liver diseases.

Inadequacy of liver biopsy

An adult biopsy sample corresponds to a fraction of just 1/50,000th of the entire liver and hence a biopsy specimen could be deemed insufficient and non-representative. This is especially true in diseases such as viral hepatitis, where the liver changes may be unevenly distributed. This also assumes a greater significance in that chronic viral hepatitis is one of the most common indications for LB, where biopsy is performed to grade and stage histological disease.

Therefore, the questions that arise is whether the sample size affects the histological assessment and what size would be deemed adequate for conclusive reporting. Various studies have evaluated the LB specimen size that would provide a representative sample for accurate disease estimation (39,40,41). It was thought that a specimen at least 1.5 cm long is needed for an acceptable accuracy in the diagnosis of chronic hepatitis, but a larger biopsy sample should be obtained when cirrhosis is suspected (40).

Attempts were made to quantify the size of the LB sample with respect to the number of complete PTs when it was ascertained that the diagnostic accuracy was dependent on this factor. Nevertheless, a consensus has not been reached with different investigators advocating varying numbers of PTs ranging from 6 - 11 (39, 40,41).

The following study attempted to address this issue by assessing the adequacy of LB specimens in the local context against the recommendations of the Royal College of Pathologists of the UK (RCPath-UK), as well as to determine whether the length of the LB and the number of complete PTs (CPTs) correlate.

Study 4: Assessing the adequacy of LB specimens (42)

Method: A total of 86 LBs were reviewed. All were performed under ultrasound guidance using 14 G Tru-cut needles. The length of the biopsy after fixation and the number of CPTs were documented, and these two parameters were compared with the RCPath-UK guidelines that recommended a biopsy of at least 1 cm long, containing a minimum of 6 PTs. The correlation between the length of the biopsy and the number of CPTs was assessed using the Pearson correlation coefficient.

Results: The mean length of the LB was 12.7 mm (median 13) and the mean number of CPT was 5.2 (median 5). Of 86 LBs, 53 (61.6%) were more than 10 mm in length. However, only 29 (33.7%) had more than six PTs. More than 6 CPTs were present in seven biopsies of less than 10 mm in length. The correlation between the length of the biopsy and the number of CPTs was weak (Pearson correlation coefficient = 0.35).

Conclusion: Only 29 biopsies (33.7%) fulfilled both criteria of being more than 1 cm long and having more than 6 CPTs. Many biopsies did not fulfil the criteria laid down by the RCPath-UK, which is modest compared to those suggested by the American Association for the Study of Liver Diseases, of a LB of 20-30 mm in length with at least 11 PTs.

However, we found that this does not always preclude a relatively reasonable histological diagnosis, as demonstrated by a simultaneous study which evaluated the usefulness of LB among adults which is further described below.

The case against liver biopsy becoming obsolete

As a proponent of the liver biopsy, I will now share, our own experience in terms of how LB has contributed to routine clinical practice of hepatology as well as research.

Study 5: Evaluating the usefulness of LB in a local setting (43)

Objective: To determine the impact of LB in the diagnosis and treatment of patients with liver disease.

Method: A total of 215 LBs reported at our institution were categorized as Category I - nondiagnostic, Category II - does not exclude or confirm the clinical diagnosis nor provide prognostic or therapeutic information (i.e. descriptive reports), Category III - confirms the clinical diagnosis but does not provide further information (e.g. aetiology), Category IV - confirms the clinical diagnosis and provides further information and Category V - changes the diagnosis completely and hence the management of patients.

Results: Of the 215 biopsies, 10.2% (22) were Category I, 5.1% (11) were Category II, 4.2% (9) were Category III, 57.2% (123) were Category IV and 23.3% (50) were Category V.

Conclusion: Only 15.3% biopsies (i.e. Category I and II) had no impact on patient management whilst 84.7% (98% CI- 79.8% - 89.6%) of the LBs had a significant impact on the management of patients with liver disease.

Contributing to awareness and the understanding of liver disease/NASH in Sri Lanka

In the late 1990s at a time when NAFLD/NASH was an almost unknown entity in Sri Lanka, we described 100 cases of NASH.

Study 6: The clinical, biochemical and histological profile of NASH patients (44)

Method: During a four year period, from May 1999 - May 2000, LBs were performed on 296 patients who had elevated serum transaminase levels for more than six months. One hundred were diagnosed as having NASH on histology. Their clinical and biochemical details and the presence of a family history of co-morbid factors were recorded and the body mass index (BMI) was calculated. The patients were followed up for a median period of 2.5 years (1 -4 years) at three monthly intervals after advice on lifestyle modifications.

Results: The risk factors for NASH, the biochemical indices and the histological grading (BRUNT grading) in this cohort of patients are given in Table 2.

TABLE 2 The clinical, biochemical and histological profile of patients with NASH

Risk Factors (n=100)	**Abnormal biochemical index (n=100)**		**Histological Grading (BRUNT) (n= 80)**
Diabetes mellitus 55%	Serum transaminase elevation	100%	Grade 1 (mild) 31/80 (38.8%)
Obesity 52%	AST/ALT ratio <1	90%	Grade 2 (moderate) 29/80 (36.3%)
Hyperlipidaemia 54%	Serum bilirubin elevation	15%	Grade 3 (severe) 20/80 (25%)
Family history 66% Athero-sclerosis 40%	GGT elevation	50%	
Liver disease 14%	Alkaline phosphatase	5%	
Hyperlipidaemia 13%	Abnormal lipid pattern	59%	
High-fat intake 66%	Fasting blood glucose/ Postprandial blood glucose*	18%	

*Patients with biochemical abnormalities only. Most patients with diabetes mellitus on treatment had normal indices.

The ages at presentation of these patients were low compared to the contemporary studies at that time (45-48). Seventy-nine patients were male and 21 were female. Thirty-five males (44.3%:35/79) and seven females (33.3%:7/21) were not overweight, and a lower proportion of obese females was evident in our series. It was also observed that 44.3% (35/79) of men were neither obese nor overweight, i.e. lean males. This has been reported in other studies as well (48,49). Most patients in this series (65/100,65%) were asymptomatic and elevated liver enzymes were an incidental finding. The serum transaminase levels showed only a 2 - 5-fold increase. This was in keeping with several studies that had reported similar results (50,51). Most patients (60.4%:55/91), who were followed up for a period of 2.5 years (Range 1-4 years) benefited from lifestyle

modifications in the short term with improvement of transaminase levels.

Study 7: Advanced fibrosis and cirrhosis due to NAFLD in Sri Lankan children: a preliminary report (52)

Cirrhosis in children due to NAFLD was considered extremely rare in the Asia Pacific region. In 2008, we described five children with LBs: two showing Stage III fibrosis and three showing Stage IV fibrosis. The demographic and biochemical characteristics of these patients are given in Table 3.

TABLE 3 Demographic and biochemical characteristics of the five paediatric patients with NAFLD

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at presentation (years)	11	10	12	11	11.5
Sex	Male	Male	Male	Male	Female
BMI (kg/m^2)	26	31	28	26	21.1
BMI centile	>95th	>95th	>95th	>95th	85th - 95th
Length of follow-up (years)	4	13	5	0.5	0.5
ALT (u/L)	171	183	218	100	86
AST (u/L)	90	68	73	40	42
Albumin (g/dL)	3.6	4.1	4.4	4.0	4.6
INR	1	1.2	1	1.17	1
Hepatitis screening	(-)	(-)	(-)	(-)	(-)
Autoantibody screening	(-)	(-)	(-)	(-)	(-)
Ceruloplasmin (µmol/L)	1.8	2	2.6	2.2	2.3
Urinary copper (µmol/L)	0.3	0.5	0.28	0.43	0.38
Fasting blood glucose (mmol/L)	3.61	3.45	3.8	4.83	4.77
Fasting insulin (µmol/L)	12.7	13.1	12.9	10.01	11.3
HOMA-IR	2.04	2.01	2.17	2.17	2.4
C peptide level (mg/dL)	2.0	2.6	2.8	2.0	2.7
Fasting triglycerides (mg/dL)	132	146	130	121	106
Fasting cholesterol (mg/dL)	194	187	103	200	166

Negative: (-)

Patient characteristics included M:F ratio of 4:1 and an age range of 10-12 years. Four of the five children were obese with a BMI of >95th centile. All five had acanthosis nigricans and high ALT levels (> twice normal) and ultrasonographic evidence of fat infiltration in the liver. None had diabetes mellitus. The calculated HOMA-IR (Homeostasis Model Assessment for Insulin Resistence) was > 2 in all five cases.

There are also several cases in which we are completely confused as to the aetiology and have implication in the management of patients which have been resolved with the aid of histology. A case to illustrate this point will be briefly discussed.

Case report - Worsening cholestasis and possible cefuroxime-induced liver injury following successful therapeutic endoscopic retrograde cholangiopancreaticography for distal common bile duct stone (53)

A 51-year-old previously healthy Sri Lankan man presented with obstructive jaundice caused by a distal common bile duct (CBD) stone. Endoscopic retrograde cholangiopancreatography/ERCP with stone extraction, CBD clearance, and stenting failed to improve cholestasis and there was a paradoxical worsening of his jaundice.

Worsening cholestasis following ERCP may be due to a retained CBD stone, ascending cholangitis, a blocked or migrated stent or drug-induced cholestasis. The absence of features of sepsis, including inflammatory markers and the absence of ductal dilation seen on an ultrasound scanning with a stent in situ in the CBD made a drug-induced aetiology more likely despite cefuroxime, which was used following stenting, being a rare cause.

Only five cases of cefuroxime-induced liver injury had been reported previously. However, the features presented on liver histology (i.e. Zone 3 intrahepatic cholestasis without features of inflammation, ascending cholangitis or extrahepatic bile duct obstruction) favoured intrahepatic cholestasis of drug-induced aetiology, confirming the clinical suspicion. The patient made a complete recovery in four months with supportive treatment and withdrawal of the offending drug.

The final evidence which I will share with you includes the comparison of two audits carried

out in our department during the periods 2012 – 2015 and 2019 – 2022.

Study 8: An audit of LBs carried out in a teaching hospital in Sri Lanka (53)
The findings of the two audits are presented for comparison in Table 4.

Table 4 Comparison of audits of LBs carried out during 2012 - 2015 (54) and 2019 – 2022

	2012-2015 Audit	**2019-2022 Audit**
Total number of LBs	216	327
Male	114 (52.8%)	165 (50.5%)
Females	102 (47.2%)	162 (49.5 %)
Age range	3 months - 79 years	2 months - 78 years
Commonest age group	51- 60 years	51 - 60 years
Broad indications Diagnostic Management Other	 182 23 10	
Diagnosis		
Normal	5	9
Minimal/nonspecific changes	12	12
Acute hepatitis	4	7
Chronic hepatitis	31	41
Granulomatous hepatitis	1	3
NAFLD	36	52
Cirrhosis	36	57
Focal lesion/neoplasms	36	77
Biliary disease	3	3
Childhood metabolic liver disease	5	5
Drug-induced hepatitis	3	3
Alcoholic liver disease	1	-
Depositions	4	-
Cholestasis	13	30
Nondiagnostic	1	10
Descriptive	3	3
Other	3	4
Post-transplant rejection	-	22

The comparison of these audits demonstrates that the number of LBs received in the department shows an increase in the latter period. This is despite the hospital and clinic attendance of patients being hampered by the Covid-19 pandemic and the economic crisis in the country.

Much of the other findings such as age of presentation and the histological diagnosis are comparable except that there were 22 post-transplant biopsies in the latter period following the setting up of the liver transplant services at the Faculty of Medicine, University of Kelaniya.

The establishment of Colombo North Center for Liver Disease (CNCLD) and the Revive project that was launched in 2020, to transform the Faculty of Medicine, University of Kelaniya into a center of excellence in liver disease management and research, may also have contributed to the rise in the number of biopsies.

Although hepatic transplantation is considered modern and more so in Sri Lanka, it is of interest to note that ancient Greek medico-philosophers believed that the liver was the center of the soul: A sentiment most likely driven by their understanding of the liver's vital role in maintaining homeostasis and its tremendous regenerative capacity. There are numerous recorded incidents in ancient Greek literature of operations on hepatic abscesses, malignancies and the use of slaves and convicts as research subjects that confirm their understanding of the regenerative capacity of the liver. But perhaps the most fascinating are the two tales in Greek mythology regarding hepatic regeneration namely the myths of Tityus and Prometheus. Tityus and Prometheus were both subjected to punishment for their crimes by enabling a vulture and an eagle, respectively, to devour the liver daily with the understanding that the liver would regenerate only to be devoured again and again thus prolonging their agony. Another testimony of the importance of liver tissue comes in the form of funeral rites of Egyptians in which the liver was one of the four organs preserved in canopic jars prior to mummification in the hope of a better life.

The liver tissue provided by LBs has given us many insights into the pathogenesis of diseases and provided the medical and scientific community with the knowledge and awareness of many liver diseases over time.

It would indeed be a pity to see LBs becoming obsolete, and I feel strongly that this will not happen in the near future based on some of the reasons alluded to.

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