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ORIGINAL ARTICLE

Effectiveness of liver biopsy in diagnosing liver diseases using a five-point diagnostic scale among pediatric population.

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ABSTRACT… Objective: To determine the effectiveness of liver biopsy using a five-point scale for establishing the diagnosis of underlying liver diseases in children with unexplained derangement of liver function tests. **Study Design:** Cross-sectional study. **Setting:** Department of Pediatric Medicine, National Institute of Child Health Karachi, Pakistan. **Period:** 1st February 2024 to 30th July 2024. **Methods:** A total of 221 patients were enrolled setting the inclusion criteria as children of either gender of age up to 14 years with deranged liver function tests and unexplained diagnosis warranting liver biopsy, or those in whom ultrasound abdomen and CT scan findings indicated liver diseases requiring biopsy for diagnosis. A 5-point scale was used for confirming the diagnostic yield of the liver biopsy. **Results:** In a total of 221 children, 120 (54.3%) were male. The median age was 3.00 (1.30-6.00) years. The most common diagnosis at the time of admission were chronic liver disease, glycogen storage disease, and Neimann-Pick disease, 102 (46.2%), 53 (24.0%), and 21 (9.5%) patients, respectively. For CLD, the sensitivity and specificity were 55.4%, and 90.8%, respectively. Chronic liver disease with portal hypertension showed a sensitivity of 82.4% and specificity of 100%, while neonatal cholestasis exhibited 100% sensitivity and specificity. Glycogen storage disease also demonstrated high sensitivity and specificity at 94.3% and 98.2%, respectively. **Conclusion:** The five-point scale used in our study provides a comprehensive framework for interpreting biopsy results and guiding clinical management.

Key words: Cholestasis, Chronic Liver Disease, Glycogen Storage Disease, Neimann-Pick Disease, Portal Hypertension.

INTRODUCTION

Liver disease among pediatric population represent a rising problem with significant effects on public health.[1] Liver disease comprises of wide spectrum of conditions, including infectious, metabolic and hematologic disorders, congenital vascular and heart diseases, drug-related toxicity, hypoxia and gestational alloimmune liver disease associated with neonatal hemochromatosis.[2] In children liver disease presented either as: (i) an acute hepatitis with or without jaundice; (ii) incidental finding of abnormal liver function tests; or (iii) from a complication of portal hypertension with either hematemesis and/or incidental splenomegaly.[3]

The prevalence of liver diseases among the pediatric population is still unknown because liver disease in children is presented asymptotically and diagnosed late. In the United States of America, more than 15,000 children are hospitalized for liver diseases per year.[2,4] In Europe, liver disease affects one out of 10 children.[5] Liver diseases in children require long-term, life-long management, resulting in a huge burden on healthcare systems.[6]

Liver diseases in children are often asymptotic, and diagnosis requires appropriate diagnostic tests such as liver biopsy. Liver biopsy is an important investigative tool in the detection of liver diseases during infancy and childhood as compared to adults.[7] Liver biopsy is a safe and effective diagnostic procedure for exact diagnosis and has become routine procedure in many parts of the world.[8] Liver biopsy is a safe procedure but is associated with some complications, such as subcapsular hematoma, post-biopsy fever,

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ooze from the skin, and intraperitoneal bleed.[9] A study by Srikanth et al worked on the safe and effective role of liver biopsy in diagnosing liver diseases in children with the help of a 5-point diagnostic scale. The most common etiology was congenital hepatic fibrosis (16.2%), followed by glycogen storage disorder (11.5%), progressive familial intrahepatic cholestasis (16.7%), and biliary atresia (6.4%). The 5-point diagnostic scale reported the 82.6% confirmed and 17.4% supported cases in children with an age of<3 months, 68.2% confirmed, 14.8% confirmed changed, 9.1% supported, 1.1% supported changed, and 6.8% no benefit cases in children with an age of 4-12 months, 39.7% confirmed, 9.5% confirmed changed, 41.4% supported, 3.4% supported changed, and 6.0% no benefit cases in children with an age of>12 months.[10]

Internationally, very little work has been done on safe and effective use of ultrasound-guided liver biopsy in infants and children, whereas no such studies have been performed in Pakistan. Therefore, we planned the current study with the objective to determine the effectiveness of liver biopsy using a five-point scale for establishing the diagnosis of underlying liver diseases in children with unexplained derangement of liver function tests. By determining the role of liver biopsy in diagnosing liver diseases, early and appropriate diagnosis of liver disease in children can be made, and appropriate treatment and stopping or slowing the progression of liver damage can be achieved.

METHODS

This prospective cross-sectional study was inaugurated at the pediatric department of the National Institute of Child Health Karachi, Pakistan from 1st February 2024 to July 2024. The current study obtained approval from "Institutional Ethical Review Board" (letter number: IERB-27/2023, dated: 15-08-2023). A sample size of 221 was calculated using the OpenEPI software for sample size calculation by considering the expected proportion of confirmed cases of liver disease on liver biopsy as 82.6%[10], and keeping the confidence level at 95% and margin of error at 5%.

The inclusion criteria were children of either gender of age up to 14 years with deranged LFTs and unexplained diagnosis warranting liver biopsy, or those in whom ultrasound abdomen and CT scan findings indicated liver diseases requiring biopsy for diagnosis. The exclusion criteria were children with a platelet count<60,000/μL or an INR of more than 1.5. Children with acute liver diseases and gross ascites or those who were already diagnosed with chronic liver disease were also excluded. A child presented with one or more of the following symptoms, including jaundice, abdominal pain, abdominal swelling, loss of appetite, poor weight gain, nausea, vomiting, vomiting of blood, itching, tiredness, yellow urine, or grey or pale stool, was suspected to have liver disease. Informed and written consent was obtained from parents/caregivers of the patients once they were briefed about the study objective, safety, and data secrecy.

Demographic data on age, gender, weight (measured either by using a standard weighing tub or machine), and height (measuring tape or a standard stadiometer) was collected either from parents/caregivers or from medical files. Information about the presenting complaints, including jaundice, abdominal pain, abdominal swelling, loss of appetite, poor weight gain, nausea, vomiting, vomiting of blood, itching, tiredness, yellow urine, or grey or pale stool, was noted. A blood sample of each child was collected in a sterile container in an aseptic environment and sent to the institutional laboratory for measurement of hemoglobin, platelets, and INR. A clinical diagnosis prior to the liver biopsy was established. An ultrasound-guided liver biopsy was performed for each child using midazolam and ketamine as sedatives in an aseptic condition, and the sample was sent for histopathology. A 5-point scale was used for confirming the diagnostic yield of the liver biopsy. The distribution of five points is as follows: i) Confirmed: Histology confirmed the diagnosis, no further test required; ii) Confirmed, Changed: Histology confirmed the new diagnosis (different from clinically suspected), no further test required; iii) Supported: Histology supported the diagnosis, but further testing required; iv)

Supported, Changed: Histology supported a new diagnosis (different from clinically suspected), but further investigation required or just provide the severity of liver disease in form of fibrosis; v) No Benefit: No tissue obtained or tissue insufficient for reporting. Standard treatment protocol was followed for each child with liver disease. The data was collected on a specifically predesigned proforma by the researchers themselves.

The statistical analysis was performed using "IBM-SPSS Statistics" version 26.0. The quantitative variables like age, weight, height, duration of symptoms, hemoglobin, platelets, and INR were explained through mean and standard deviation. Whereas frequency and percentages were calculated for the representation of qualitative variables like gender, age groups, signs and symptoms, clinical diagnosis at the time of admission, clinical diagnosis prior to liver biopsy, and diagnostic yield on a 5-point scale. Sensitivity and specificity of liver biopsy with regards to various conditions diagnosed were calculated.

RESULTS

In a total of 221 children, 120 (54.3%) were male. The median age was 3.00 (1.30-6.00) years, ranging between 1 month to 12 years. There were 119 (53.8%) children who were aged between 1-5 years. Common presenting symptoms included abdominal swelling 132 (59.7%), 92 jaundice (41.6%), and hematemesis 34 (15.4%). Table-I is showing baseline demographical characteristics and presenting complaints.

Characteristics		Frequency (%)
Gender	Male	120 (54.3%)
	Female	101 (45.7%)
Age (years)	<1	42 (19.0%0
	1-5	119 (53.8%)
	6-14	60 (27.1%)
Frequency of presenting symptoms and clinical complaints	Jaundice	92 (41.6%)
	Abdominal pain	23 (10.4%)
	Abdominal swelling	132 (59.7%)
	Poor weight gain	19 (8.6%)
	Vomiting	25 (11.3%)
	Hematemesis	34 (15.4%)
	Itching	3 (1.4%)
	Tiredness	17 (7.7%)
	Grey stool	3 (1.4%)

Table-I. Demographical characteristics and presenting complaints (n=221)

Key laboratory findings included mean hemoglobin level of 9.69±1.67 g/dl, platelet count of 257.41±135.32 × 10 ^ 9/L, and markedly elevated levels of alanine aminotransferase (154.51±204.41 U/L) and alkaline phosphatase (511.67±621.19 U/L). Total bilirubin and direct bilirubin were elevated with means of 5.18±4.92 mg/dl and 3.18±3.11 mg/dl, respectively.

The most common diagnosis at the time of admission were chronic liver disease, glycogen storage disease, and Neimann-Pick disease, 102 (46.2%), 53 (24.0%), and 21 (9.5%) patients, respectively (Figure-1).

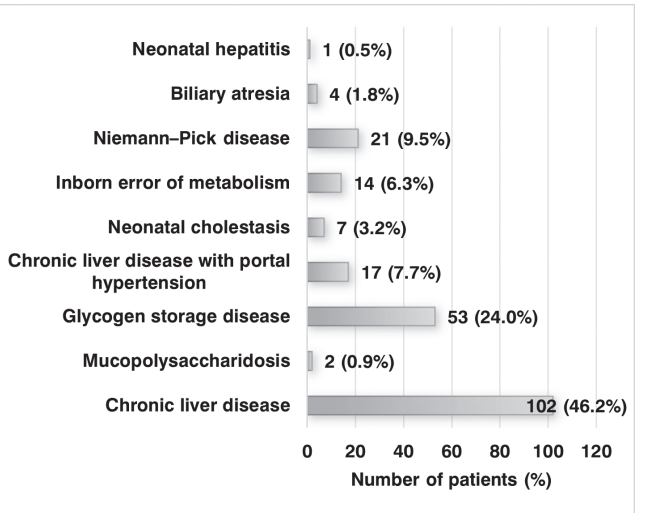

Figure-1. Frequency distribution of diagnosis at the time of admission

There were 141 (63.8%) patients whose initial diagnosis was definitively confirmed, and 56 (25.3%) had supported findings. There were 6 (2.7%) patients whose diagnosis was subsequently altered. There were 8 (3.6%) patients whose initial support for the diagnosis was altered or changed. There were 10 (4.5%) who showed that there was no perceived benefit from the assessment. Figure-2 is showing the outcomes of a patient assessment, categorizing them into five distinct groups.

Figure-3 is showing distribution of various liver diseases with respect to final diagnosis based on 5-scales following liver biopsy.

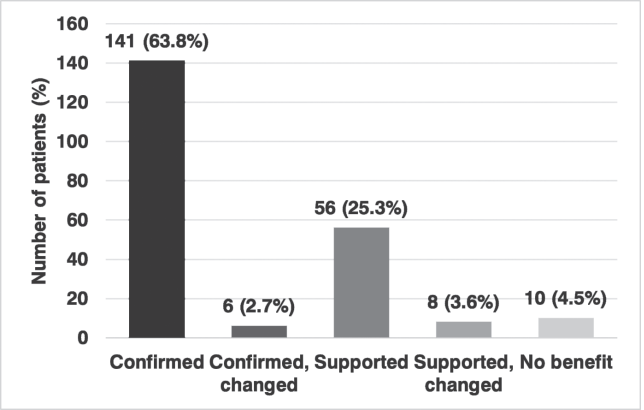

Figure-2. Liver Biopsy findings using a five-point diagnostic scale

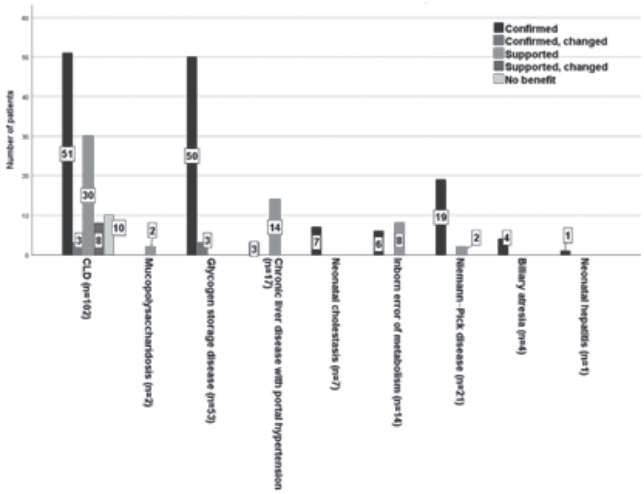

Figure-3. Distribution of various liver diseases with respect to final diagnosis based on 5-scales following liver biopsy

DISCUSSION

In this study, 63.8% of the cases were confirmed by histology, requiring no further diagnostic workup, and 25.3% had supported findings. However, 2.7% had their diagnosis confirmed with a change, and 3.6% were initially supported but altered based on biopsy findings. For 4.5% cases, no diagnostic benefit was achieved. These findings underscore the importance of liver biopsy in establishing early diagnoses to facilitate timely interventions and improve outcomes by halting or slowing liver disease progression. Srikanth et al.[10], reported that liver biopsy confirmed the specific etiologies in 82.6% of children with cholestasis, a proportion higher than our confirmed diagnostic rate of 63.8%. The higher yield in Srikanth et al study could be attributed to the study's focus on cholestatic infants, who tend to have a clearer clinical presentation and pathologies like biliary atresia and progressive familial intrahepatic cholestasis that are better elucidated by histology. In our study, the broader inclusion criteria of liver diseases with varying etiologies, such as CLD, Niemann-Pick disease, and glycogen storage disease, may have contributed to the slightly lower diagnostic yield. Hernandez-Chavez et al.[11], emphasized the role of liver biopsy in autoimmune hepatitis and chronic liver diseases, noting a confirmed diagnostic rate of over 65%. Our study noted the sensitivity of liver biopsy for CLD as 55.4%, with a specificity of 90.8%, indicating that while liver biopsy effectively rules out CLD in most cases, the biopsy alone might not capture all diagnostic nuances of CLD. The lower sensitivity could also result from sampling errors or disease heterogeneity, as noted by Pokorska-Spiewak et al.[12], who highlighted variability in liver biopsy findings. In this study, glycogen storage disease and Niemann-Pick disease were among the most frequently diagnosed conditions. The sensitivity and specificity of liver biopsy for glycogen storage disease were 94.3% and 98.2%, respectively, similar to the findings of Ahmad et al.[13], who identified glycogen storage disorders in 11.5% of their pediatric patients. This consistency suggests that histological evaluation is a reliable method for diagnosing metabolic liver diseases, especially those involving glycogen metabolism. Niemann-Pick disease was confirmed in 90.5% of cases in this study, underscoring the importance of histology for identifying lipid storage disorders. These diseases are often challenging to diagnose without liver biopsy, as non-invasive imaging and biomarkers may not be sufficient to provide a definitive diagnosis.[14]

The variations in diagnostic yield across studies may reflect differences in patient populations, study settings, and biopsy protocols. Studies focusing on specific disease subsets, such as Srikanth et al.[10] who focused on cholestasis or Chaudhry et al.[15], on neonatal jaundice, tend to report higher diagnostic yields. In contrast, our study included a broader spectrum of liver diseases, including children with CLD and portal hypertension, metabolic disorders, and

unexplained hepatomegaly, resulting in a more diverse diagnostic landscape. Differences in biopsy techniques, sample size, and the experience of pathologists interpreting the histology may have influenced the outcomes. As Ovchinsky et al.[16], noted, technical difficulties and smaller sample sizes in pediatric biopsies can pose challenges to obtaining diagnostic tissue, potentially contributing to the 4.5% non-diagnostic results in our study.

The use of sedation protocols and ultrasound-guided biopsy in this study aligns with Almeida et al.[17], who demonstrated that ultrasound guidance reduces complications and improves biopsy yield. However, Behairy et al.[18], argued for non-invasive alternatives, such as APRI, FIB-4, and elastography, for assessing fibrosis. While these alternatives are promising, they are yet to fully replace liver biopsy, particularly in pediatric populations, where diseases such as glycogen storage disorders and Niemann-Pick disease require histological confirmation.

The findings of this study have significant clinical implications. Firstly, the five-point scale used in our study offers a nuanced understanding of liver biopsy outcomes. It not only distinguishes between confirmed and supported diagnoses but also highlights cases where the diagnosis was changed or where biopsy provided insufficient information. This stratification allows clinicians to tailor subsequent management strategies based on the diagnostic yield. Children with confirmed diagnoses can immediately receive targeted treatment, while those with supported diagnoses may require further investigations, such as metabolic testing or repeat imaging, to refine the diagnosis. Liver biopsy played a crucial role in identifying metabolic and storage disorders, such as glycogen storage disease and Niemann-Pick disease, where timely diagnosis is essential for initiating enzyme replacement therapies or dietary interventions. Early intervention in these conditions can significantly improve the quality of life and prevent irreversible liver damage, emphasizing the value of liver biopsy as a diagnostic tool in pediatric patients.[19] The high specificity of liver biopsy for conditions like CLD with portal hypertension, and neonatal cholestasis in this study, with specificity rates of 100%, reinforces the biopsy's role in ruling out these conditions when histological evidence is absent. This finding is clinically relevant, as it allows clinicians to avoid unnecessary treatments and focus on alternative diagnoses, thereby reducing the burden of invasive procedures and minimizing patient discomfort.

Being a single center study, our findings need further verification in large multi-centric trials. Our study also highlights the limitations of liver biopsy. The sampling errors and inter-observer variability remain concerns, necessitating close collaboration between clinicians and experienced pathologists. Efforts to develop non-invasive diagnostic modalities, such as elastography and serum biomarkers, are ongoing, but liver biopsy remains the gold standard for diagnosing complex pediatric liver diseases.

CONCLUSION

The five-point scale used in our study provides a comprehensive framework for interpreting biopsy results and guiding clinical management. While liver biopsy is associated with challenges, including non-diagnostic samples and potential complications, it remains an indispensable tool in the evaluation of pediatric liver diseases. Further research is needed to refine biopsy techniques, reduce non-diagnostic rates, and explore the role of non-invasive alternatives, ultimately enhancing the diagnostic and therapeutic approach to pediatric liver diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1	Quratulain Ahmed Alvi	Data collection, Drafting, Responsible for data, Approval for publication.	
2	Arit Parkash	Study concept, Methodology, Proof reading, Approval for publication.	