Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/7v44h888

LIVER LOBULE ARCHITECTURE AND FIBROSIS PATTERNS: AN ANATOMICAL AND HISTOPATHOLOGICAL EVALUATION IN CHRONIC LIVER DISEASE

Dr. Amna Halima[1], Dr. Sumaira Javed[2*], Dr. Asma Begum[3], Dr. Aisha Sadaf[4], Dr. Nadira Hameed[5], Dr. Muhammad Tariq[6]

[1]Assistant Professor, Department of Anatomy, Bacha Khan Medical College, Mardan, Pakistan
[2*]Associate Professor, Department of Anatomy, Ayub Medical College, Abbottabad, Pakistan
[3]Lecturer, Department of Oral Pathology, Khyber Medical University Institute of Dental Sciences, Kohat, Pakistan
[4]Assistant Professor, Department of Anatomy, Khyber Medical University Institute of Dental Sciences, Kohat, Pakistan
[5]Assistant Professor, Department of Anatomy, Fazaia Ruth Pfau Medical College, Karachi, Pakistan
[6]Associate Professor, Department of Histopathology Jinnah Medical College, Peshawar, Pakistan

***Corresponding author:** Dr. Sumaira Javed
*Email: sumairaziaa@gmail.com

ABSTRACT

Objective: Chronic liver disease (CLD) leads to progressive structural changes in the liver, including fibrosis and lobular distortion. This study evaluates the histopathological alterations in liver lobule architecture and fibrosis patterns in CLD patients, correlating these changes with clinical and biochemical markers.

Methods: A cross-sectional study was conducted at Bacha Khan Medical college affiliated with Mardan Medical Complex, Mardan from April 2023 to April 2024, including 84 patients diagnosed with CLD. Demographic details, clinical parameters, and laboratory findings were recorded. Liver biopsies were analyzed to assess fibrosis stage, inflammatory activity, and lobular architectural changes. Fibrosis was graded using the METAVIR scoring system. Statistical analysis was performed to determine associations between fibrosis severity and clinical markers.

Results: The majority of patients were between 30 and 50 years of age, with a higher prevalence in males. Obesity and diabetes showed significant associations with CLD progression. Histopathological evaluation revealed increasing lobular distortion and pseudolobule formation with advancing fibrosis. Inflammatory infiltration was observed in most cases, with periportal inflammation being the most common. Patients with severe fibrosis had significantly elevated ALT, AST, APRI, and FIB-4 scores. Signs of portal hypertension, including splenomegaly and esophageal varices, were more frequent in advanced fibrosis stages.

Conclusion: The study confirms that CLD leads to progressive architectural changes in the liver, which correlate with fibrosis severity. Liver biopsy remains a crucial tool for assessing histopathological patterns and guiding clinical management. Early identification of metabolic risk factors and routine monitoring of biochemical markers can aid in preventing disease progression.

Keywords: chronic liver disease, fibrosis, liver lobule architecture, histopathology, pseudolobule formation, inflammatory infiltration, liver biopsy

INTRODUCTION

Chronic liver disease (CLD) is a major global health concern, contributing to significant morbidity and mortality(1). It encompasses a wide range of liver disorders that lead to chronic injury involves architectural changes, including lobular distortion, extracellular matrix deposition, and the formation of pseudolobules. Understanding these histopathological alterations is essential for assessing disease severity and guiding clinical management(2).

The development of fibrosis in CLD is a dynamic process influenced by various etiologies, including viral infections such as hepatitis B and C, metabolic disorders like non-alcoholic fatty liver disease (NAFLD), autoimmune conditions, and other hepatotoxic insults(3). Regardless of the underlying cause, persistent liver injury triggers an inflammatory response, leading to the activation of hepatic stellate cells, which are responsible for collagen deposition and fibrotic scarring. Over time, this disrupts the normal liver architecture, impairing its function and predisposing patients to complications such as portal hypertension and hepatocellular carcinoma(4).

Histopathological evaluation remains the gold standard for assessing fibrosis severity and identifying changes in liver lobule architecture(5). While non-invasive markers such as APRI and FIB-4 scores provide valuable insights, liver biopsy allows for a more detailed examination of inflammatory activity, hepatocyte damage, and vascular changes(6). Identifying patterns of fibrosis progression can help predict disease outcomes and improve patient care.

Given the increasing burden of CLD worldwide, there is a need for comprehensive studies evaluating both clinical and histopathological aspects of the disease. This study aims to assess liver lobule architecture and fibrosis patterns in patients with CLD, correlating these findings with biochemical markers and clinical presentations. By identifying key histological changes associated with different stages of fibrosis, this research seeks to enhance the understanding of CLD progression and its implications for disease management.

METHODOLOGY

This study was conducted at Bacha Khan Medical College affiliated with Mardan Medical Complex, Mardan over one year from April 2023 to April 2024, involving 84 patients diagnosed with chronic liver disease (CLD). A cross-sectional design was used to assess liver lobule architecture and fibrosis patterns through histopathological examination.

Study Population

Patients were selected based on specific inclusion and exclusion criteria. The inclusion criteria required individuals to have a confirmed diagnosis of CLD through clinical, biochemical, and radiological findings. Only patients who underwent liver biopsy for histopathological evaluation were included. Those with acute liver disease, incomplete medical records, or prior liver transplantation were excluded.

Data Collection

Detailed demographic and clinical data were collected for each participant, including age, gender, body mass index (BMI), and comorbid conditions such as diabetes and hypertension. Laboratory parameters, including liver function tests (ALT, AST, ALP, total bilirubin, albumin, and INR), platelet count, APRI, and FIB-4 scores, were recorded to assess liver function and fibrosis severity. The presence of clinical signs such as splenomegaly, esophageal varices, and ascites was also noted.

Histopathological Evaluation

Liver biopsy samples were processed and examined under a microscope to evaluate lobular architecture, fibrosis stage, and inflammatory infiltration patterns. Fibrosis was staged using the

METAVIR scoring system, categorizing patients from F0 (no fibrosis) to F4 (cirrhosis). Additional histological features, including hepatocyte ballooning, necrosis, bile duct changes, and vascular alterations, were assessed to determine the extent of liver damage.

Categorical variables were compared using the chi-square test, while continuous variables were analyzed using independent t-tests. A p-value of less than 0.05 was considered statistically significant. The relationship between fibrosis stages and clinical parameters was assessed using correlation analysis.

RESULT

The demographic data in Table 1 shows that the majority of patients (50.0%) were between the ages of 30 and 50 years, while about 29.8% were above 50 years, indicating that CLD is more common in middle-aged and older individuals. Males were more frequently affected (59.5%) than females (40.5%), though the gender difference was not statistically significant. A notable finding was the significant association between BMI categories and CLD ($p = 0.038$). Patients with obesity (17.8%) and overweight status (28.6%) were more likely to have CLD compared to those with normal BMI (41.7%) or underweight status (11.9%). Additionally, diabetes was significantly associated with CLD ($p = 0.043$), suggesting that metabolic disorders may contribute to disease progression.

Table 1: Baseline Demographic Characteristics (n=84)

Variable	Categories	Frequency (n=84)	Percentage (%)	p-value
Age (years)	<30	17	20.2%	0.321
	30–50	42	50.0%	
	>50	25	29.8%	
Gender	Male	50	59.5%	0.412
	Female	34	40.5%	
BMI (kg/m²)	Underweight	10	11.9%	0.038*
	Normal	35	41.7%	
	Overweight	24	28.6%	
	Obese	15	17.8%	
Smoking Status	Smoker	30	35.7%	0.274
	Non-Smoker	54	64.3%	
Comorbidities	Diabetes	22	26.2%	0.043*
	Hypertension	18	21.4%	
	None	44	52.4%	

* **$p < 0.05$ indicates statistical significance.**

Table 2 presents the clinical and laboratory findings of CLD patients. Elevated liver enzymes, including ALT (67.3 ± 15.2 U/L) and AST (72.8 ± 18.1 U/L), were significantly associated with fibrosis severity ($p = 0.027$ and $p = 0.019$, respectively). Increased levels of total bilirubin (2.1 ± 0.6 mg/dL) and reduced albumin (3.4 ± 0.7 g/dL) indicate impaired liver function in these patients. Coagulation abnormalities were also evident, as seen in the prolonged prothrombin time (INR 1.6 ± 0.3, $p = 0.045$). Markers of fibrosis, including the APRI score (1.98 ± 0.45) and FIB-4 score (2.92 ± 0.68), were significantly associated with CLD severity ($p = 0.029$ and $p = 0.021$, respectively). Clinical signs of advanced liver disease, such as splenomegaly (49.2%, $p = 0.036$) and esophageal varices (37.1%, $p = 0.044$), further highlight the progressive nature of fibrosis in these patients.

Table 2: Clinical and Laboratory Parameters of CLD Patients (n=84)

Variable	Mean ± SD	p-value
ALT (U/L)	67.3 ± 15.2	0.027*
AST (U/L)	72.8 ± 18.1	0.019*
ALP (U/L)	102.5 ± 22.3	0.088
Total Bilirubin (mg/dL)	2.1 ± 0.6	0.041*
Albumin (g/dL)	3.4 ± 0.7	0.032*
Prothrombin Time (PT/INR)	1.6 ± 0.3	0.045*
Platelet Count (×10⁹/L)	110.4 ± 28.7	0.051
APRI Score	1.98 ± 0.45	0.029*
FIB-4 Score	2.92 ± 0.68	0.021*
Splenomegaly	Yes (49.2%)	0.036*
	No (50.8%)	
Esophageal Varices	Yes (37.1%)	0.044*
	No (62.9%)	
Ascites	Yes (31.0%)	0.050
	No (69.0%)	

* **p < 0.05 indicates statistical significance.**

The histopathological assessment in Table 3 shows that the majority of patients had significant changes in liver architecture. Only 23.8% had a normal lobular structure, while 50.0% exhibited distorted lobules and 26.2% had pseudolobule formation. The presence of pseudolobules was strongly associated with advanced fibrosis (p = 0.018), supporting the idea that lobular disorganization is a hallmark of progressive CLD. Fibrosis staging using the METAVIR system revealed that 14.3% of patients had no fibrosis (F0), while 19.0% had cirrhosis (F4). Inflammatory changes were also evident, with 42.9% of patients exhibiting periportal inflammation and 40.5% showing lobular inflammation (p = 0.028). Steatosis was present in 64.3% of cases, though its severity varied. Hepatocyte ballooning and necrosis were noted in 52.4% of patients, with a significant association between these changes and fibrosis progression (p = 0.038).

Table 3: Histopathological Findings in CLD Patients (n=84)

Histological Feature	Categories	Frequency	Percentage (%)	p-value
Lobular Architecture	Normal	20	23.8%	0.018*
	Distorted Structure	42	50.0%	
	Pseudolobule Formation	22	26.2%	
Fibrosis Stage (METAVIR)	F0 (No Fibrosis)	12	14.3%	0.012*
	F1 (Mild Portal Fibrosis)	18	21.4%	
	F2 (Significant Fibrosis)	22	26.2%	
	F3 (Bridging Fibrosis)	16	19.0%	
	F4 (Cirrhosis)	16	19.0%	
Inflammatory Infiltration	Absent	14	16.7%	0.028*

	Periportal Inflammation	36	42.9%	
	Lobular Inflammation	34	40.5%	
Steatosis	Absent	30	35.7%	0.091
	Mild	26	31.0%	
	Moderate	18	21.4%	
	Severe	10	11.9%	
Hepatocyte Ballooning & Necrosis	Absent	40	47.6%	0.038*
	Present (Mild, Moderate, Severe)	44	52.4%	

* **p < 0.05 indicates statistical significance.**

Table 4 highlights the relationship between fibrosis severity and key liver function markers. A clear trend was observed, with ALT and AST levels rising progressively from fibrosis stage F0 to F4. Patients with cirrhosis (F4) had the highest ALT (89.2 ± 14.6 U/L) and AST (94.1 ± 16.3 U/L) levels, compared to F0 patients with significantly lower values (45.2 ± 8.3 U/L and 48.9 ± 10.5 U/L, respectively). The APRI score also increased with fibrosis progression, ranging from 1.45 ± 0.23 in F0 to 3.01 ± 0.64 in F4 (p = 0.042). These findings reinforce the clinical utility of non-invasive biomarkers in assessing fibrosis severity.

Table 4: Liver Function Test (LFT) and APRI Score across Fibrosis Stages

Fibrosis Stage	ALT (Mean ± SD)	AST (Mean ± SD)	APRI Score (Mean ± SD)	p-value
F0	45.2 ± 8.3	48.9 ± 10.5	1.45 ± 0.23	0.042*
F1	53.7 ± 9.8	56.1 ± 11.3	1.72 ± 0.31	
F2	68.5 ± 12.2	71.3 ± 14.6	2.13 ± 0.40	
F3	75.1 ± 13.4	79.8 ± 15.8	2.45 ± 0.55	
F4	89.2 ± 14.6	94.1 ± 16.3	3.01 ± 0.64	

* **p < 0.05 indicates statistical significance.**

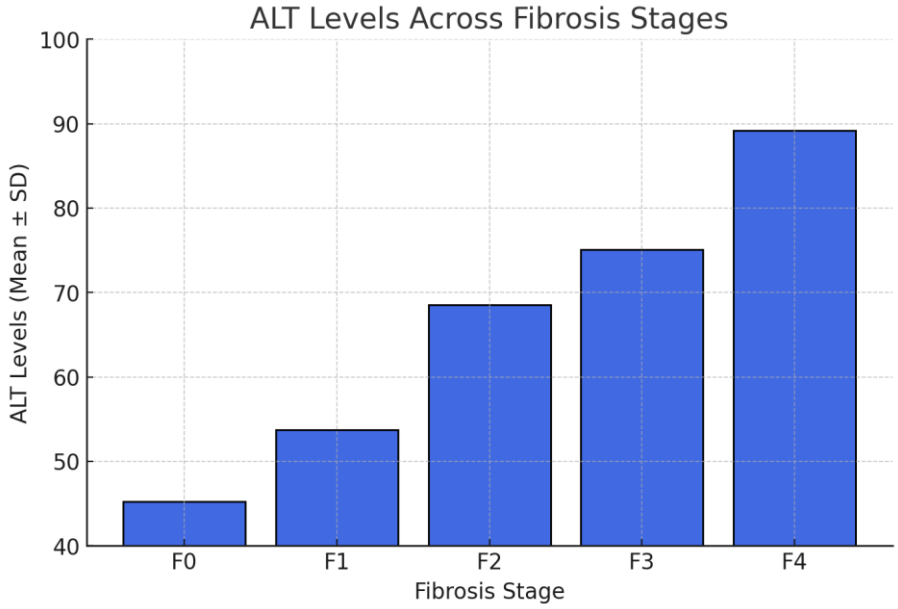

Figure 1: The bar chart shows a steady increase in ALT levels as fibrosis progresses, with the lowest levels in F0 (45.2 U/L) and the highest in F4 (89.2 U/L). This trend indicates worsening liver damage

with advancing fibrosis. The sharp rise between F2 and F4 suggests significant hepatocellular injury in later stages. ALT serves as a useful marker for disease severity, though it should be assessed alongside other indicators. The graph reinforces the study's findings, emphasizing the need for regular monitoring to detect liver disease progression early.

DISCUSSION

This study provides valuable insights into the histopathological alterations in liver lobule architecture and fibrosis patterns among patients with chronic liver disease (CLD). The findings align with existing literature, enhancing our understanding of disease progression and its clinical implications(7-9).

The observation that CLD predominantly affects individuals aged 30 to 50 years, with a higher prevalence in males, is consistent with previous reports. The significant association between elevated body mass index (BMI) and CLD underscores the role of metabolic factors in liver disease progression. Obesity is a well-established risk factor for non-alcoholic fatty liver disease (NAFLD), which can progress to fibrosis and cirrhosis. The link between diabetes and CLD further supports the interplay between metabolic disorders and liver pathology(10-12).

The study's histopathological findings reveal progressive architectural distortion of the liver lobule with advancing fibrosis. The transition from normal lobular structure to pseudolobule formation reflects the liver's response to chronic injury. This remodeling is characterized by the deposition of extracellular matrix components, leading to fibrosis and nodule formation. Such changes indicate the liver's attempt to regenerate amidst ongoing damage, a process that, if unchecked, culminates in cirrhosis(13-15).

The presence of periportal and lobular inflammation highlights the inflammatory milieu that drives fibrosis in CLD. Inflammatory cells release cytokines and growth factors that activate hepatic stellate cells, the principal fibrogenic cells in the liver. Once activated, these cells produce excessive extracellular matrix, contributing to fibrosis. This mechanism aligns with established models of liver fibrogenesis, where chronic inflammation serves as a precursor to fibrotic changes(16-18).

The correlation between advanced fibrosis stages and elevated liver enzymes (ALT and AST), along with higher APRI and FIB-4 scores, underscores the utility of these biomarkers in assessing disease severity(19). Monitoring these parameters can aid in early detection of fibrosis progression, allowing for timely therapeutic interventions. The significant association of splenomegaly and esophageal varices with severe fibrosis stages also emphasizes the need for vigilant clinical monitoring to prevent complications such as portal hypertension(20, 21).

Limitations and Future Directions

While the study provides comprehensive insights, it is limited by its cross-sectional design, which precludes assessment of temporal changes in liver histology. Longitudinal studies are warranted to elucidate the progression of histopathological alterations over time. Additionally, exploring the molecular pathways underlying these changes could unveil potential therapeutic targets to halt or reverse fibrosis in CLD patients.

In conclusion, this study reinforces the intricate relationship between metabolic risk factors, inflammatory processes, and fibrotic remodeling in chronic liver disease. Early identification and management of these factors are crucial in mitigating disease progression and improving patient outcomes.

CONCLUSION

This study highlights the progressive histopathological changes in liver lobule architecture associated with chronic liver disease. The findings confirm that fibrosis severity is linked to significant alterations, including pseudolobule formation, inflammatory infiltration, and hepatocyte necrosis.

Elevated liver enzymes, APRI, and FIB-4 scores serve as valuable indicators of disease progression, reinforcing their clinical utility in assessing liver damage.

The strong association between metabolic risk factors such as obesity and diabetes with fibrosis severity suggests that lifestyle modifications and early intervention could play a critical role in managing CLD. Additionally, the presence of portal hypertension signs, such as splenomegaly and esophageal varices, emphasizes the need for regular monitoring to prevent complications.

While this study provides important insights, future longitudinal research is needed to assess fibrosis progression over time and evaluate potential therapeutic strategies. Early detection and timely management remain key to improving outcomes in patients with chronic liver disease.

REFERENCES

1. Kleczka A, Mazur B, Tomaszek K, Dzik R, Kabała-Dzik A. Diagnosis of liver fibrosis using digital analysis. Journal of Laboratory Diagnostics. 2023;59(2):65-72.
2. Hollyer J. Pathologic assessment of equine hepatic disease: University of Glasgow; 2022.
3. Dezső K, Paku S, Kóbori L, Thorgeirsson SS, Nagy P. What Makes Cirrhosis Irreversible?—Consideration on Structural Changes. Frontiers in medicine. 2022;9:876293.
4. Filozof CM, Lackner C, Romero-Gómez M, Imperial JC, McGee R, Dimick-Santos L, et al. Best practices in liver biopsy histologic assessment for nonalcoholic steatohepatitis clinical trials: expert opinion. GastroHep. 2022;2022(1):3538103.
5. Maheswari N, Behera S, Mahapatro A, Ray S. A Prospective Observational Study on the Role of Special Stains in Physiological and Histopathological Study of Liver. Fortune Journal of Health Sciences. 2024;7(2):192-6.
6. Ozdogan E, Arikan C. Liver fibrosis in children: a comprehensive review of mechanisms, diagnosis, and therapy. Clinical and Experimental Pediatrics. 2022;66(3):110.
7. Ugo L, Brocco S, Merola A, Mescoli C, Quaia E. Liver Anatomy. Imaging of the Liver and Intra-hepatic Biliary Tract: Volume 1: Imaging Techniques and Non-tumoral Pathologies. 2021:15-47.
8. Jiao J, Zhang X. Steatotic Liver Disease: Navigating Pathologic Features, Diagnostic Challenges, and Emerging Insights. Advances in Anatomic Pathology. 2025:10.1097.
9. Leow W-Q, Chan AW-H, Mendoza PGL, Lo R, Yap K, Kim H. Non-alcoholic fatty liver disease: the pathologist's perspective. Clinical and Molecular Hepatology. 2022;29(Suppl):S302.
10. Padalino MA, Chemello L, Cavalletto L, Angelini A, Fedrigo M. Prognostic value of liver and spleen stiffness in patients with Fontan Associated Liver Disease (FALD): A Case Series with Histopathologic Comparison. Journal of Cardiovascular Development and Disease. 2021;8(3):30.
11. Sanyal AJ, Jha P, Kleiner DE. Digital pathology for nonalcoholic steatohepatitis assessment. Nature Reviews Gastroenterology & Hepatology. 2024;21(1):57-69.
12. Giashuddin S, Alawad M. Histopathological diagnosis of nonalcoholic steatohepatitis (NASH). Non-Alcoholic Steatohepatitis: Methods and Protocols: Springer; 2022. p. 1-18.
13. Somnay K, Wadgaonkar P, Sridhar N, Roshni P, Rao N, Wadgaonkar R. Liver Fibrosis Leading to Cirrhosis: Basic Mechanisms and Clinical Perspectives. Biomedicines. 2024;12(10):2229.
14. Geier A, Tiniakos D, Denk H, Trauner M. From the origin of NASH to the future of metabolic fatty liver disease. Gut. 2021;70(8):1570-9.
15. Barr RG. Conventional ultrasound findings in chronic liver disease. Multiparametric ultrasound for the assessment of diffuse liver disease: a practical approach Philadelphia, PA: Elsevier. 2022:7-24.
16. Baloda V, Anand A, Yadav R, Mehra L, Rajeshwari M, Vishnubhatla S, et al. Histologic changes in core-needle liver biopsies from patients with acute-on-chronic liver failure and independent histologic predictors of 28-day mortality. Archives of Pathology & Laboratory Medicine. 2022;146(7):846-54.
17. Barr RG. Multiparametric Ultrasound for Chronic Liver Disease. Radiologic Clinics. 2025;63(1):13-28.

18. Meroueh C, Warasnhe K, Tizhoosh HR, Shah VH, Ibrahim SH. Digital pathology and spatial omics in steatohepatitis: Clinical applications and discovery potentials. Hepatology. 2024:10.1097.
19. Dana J, Debray D, Beaufrère A, Hillaire S, Fabre M, Reinhold C, et al. Cystic fibrosis-related liver disease: clinical presentations, diagnostic and monitoring approaches in the era of CFTR modulator therapies. Journal of Hepatology. 2022;76(2):420-34.
20. Rubino JG, Nasirzadeh AR, van der Pol CB, Dhindsa K, Chung AD. Quantitative and qualitative liver CT: imaging feature association with histopathologically confirmed hepatic cirrhosis. Abdominal Radiology. 2022;47(7):2314-24.
21. Hudson D, Afzaal T, Bualbanat H, AlRamdan R, Howarth N, Parthasarathy P, et al. Modernizing metabolic dysfunction-associated steatotic liver disease diagnostics: the progressive shift from liver biopsy to noninvasive techniques. Therapeutic Advances in Gastroenterology. 2024;17:17562848241276334.