Original Article
DOI: https://doi.org/10.70749/ijbr.v3i2.655

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Association of Cholelithiasis after Diagnosis of Non-Alcoholic Chronic Liver Disease on Ultrasound

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ARTICLE INFO

Keywords

Cholelithiasis, Chronic Liver Disease, Gallstones, Hepatobiliary Ultrasound, Prevalence, Non-Alcoholic Fatty Liver Disease (NAFLD), Hepatic Cirrhosis, Risk Factors.

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Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 01-12-2024
Revised: 21-01-2025
Accepted: 07-02-2025

ABSTRACT

Background: Cholelithiasis is a common hepatobiliary disorder characterized by gallstone formation, frequently observed in patients with chronic liver disease (CLD). Hepatic dysfunction alters bile composition and motility, increasing the risk of gallstone development. The prevalence of gallstones among CLD patients varies across populations, necessitating further investigation. **Objective:** To determine the prevalence of cholelithiasis among patients with non-alcoholic CLD and assess its association with demographic factors such as age and gender. **Methods:** A cross-sectional study was conducted at the Radiology Department of WAPDA Hospital, Lahore over period of 6 months from April 2024 to August 2024, on 108 patients diagnosed with non-alcoholic CLD. Standardized ultrasound imaging was performed using a Toshiba AplioMx system with a 3–6 MHz transducer. The study population was selected through random sampling, and data were analyzed using IBM SPSS v25. Descriptive statistics, chi-square tests, and prevalence calculations were applied. A p-value ≤ 0.05 was considered statistically significant. **Results:** Among the 108 participants, 71 (65.7%) were male and 37 (34.3%) were female. Cholelithiasis was detected in 73 (67.6%) patients. Chi-square analysis showed no significant association between gender and gallstone presence ($\chi^2=0.021$, $p=0.885$). **Conclusion:** A high prevalence of cholelithiasis was observed in non-alcoholic CLD patients, emphasizing the need for routine hepatobiliary screening to prevent complications.

INTRODUCTION

The formation of gallstones, known as cholelithiasis, is a significant hepatobiliary disorder characterized by the abnormal accumulation of cholesterol, calcium carbonate, bilirubinate, and other components in the gallbladder. It is a globally recognized cause of morbidity and mortality, with an estimated 10,000 cases reported annually in the United States alone (2). The pathogenesis of gallstones is associated with metabolic disturbances in bile acid, bilirubin, and cholesterol, leading to their precipitation in the gallbladder (1). Various risk factors contribute to gallstone formation, including advanced age, female sex, and obesity, with a higher prevalence observed among patients with chronic liver disease (CLD) than in the general population (3). CLD encompasses a spectrum of progressive hepatic disorders that often culminate in cirrhosis, a pathological condition characterized by hepatocyte necrosis, fibrosis, and regenerative nodules (4). Cirrhosis has been widely recognized as a major predisposing factor for cholelithiasis due to multiple hepatic and biliary pathophysiological alterations, including reduced bile acid secretion, impaired gallbladder motility, and increased bilirubin excretion (2). The etiology of CLD is diverse, with viral hepatitis, particularly hepatitis C virus (HCV) and hepatitis B virus (HBV) infections, identified as primary contributors to disease progression (5). The correlation between CLD and gallstone disease has been extensively documented in post-mortem studies, revealing a significantly higher prevalence of gallstones among cirrhotic patients (6). Previous research has demonstrated that the likelihood of gallstone formation increases with the duration and severity of CLD, with a

notable predominance among patients with viral hepatitis-related cirrhosis compared to those with non-viral or alcoholic liver disease (7). In a study conducted in Egypt, the prevalence of gallstones among CLD patients was reported to be 21.8%, further emphasizing the strong association between these two conditions (8).

The liver, the largest gland and second-largest organ in the human body, plays a crucial role in metabolic regulation, detoxification, and bile production. Weighing approximately 1.2 to 1.8 kg, it is anatomically divided into eight functional segments and is primarily located in the right hypochondrium, extending into the epigastrium and left hypochondrium (9). The gallbladder, a pear-shaped organ situated on the inferior surface of the liver, is responsible for bile storage and concentration. Its anatomical relationship with the liver segments VI and V, as well as its connectivity to the biliary system via the cystic duct, predisposes it to pathological conditions arising from hepatic dysfunction (10). The prevalence of gallstones varies geographically and demographically, with a reported incidence of 16.6% in women and 7.9% in men in Western countries (11). Several studies have highlighted gender-based disparities in gallstone formation among CLD patients, demonstrating that advanced age, female sex, and genetic predisposition significantly contribute to gallstone development (12). Moreover, the presence of symptomatic gallstones in cirrhotic patients is associated with higher morbidity and mortality rates compared to those without liver disease (13). Once symptomatic, gallstones can lead to severe complications, necessitating timely intervention through cholecystectomy to mitigate the risk of emergent surgical complications, particularly in cirrhotic patients (12).

Understanding the intricate relationship between CLD and cholelithiasis is essential for optimizing diagnostic and therapeutic strategies. Given the high prevalence of gallstones among CLD patients, routine sonographic screening of the gallbladder is imperative for early detection and management. Previous studies have indicated that the incidence of gallstones in cirrhotic patients varies depending on the etiology of liver disease, with a significantly higher frequency observed in HCV-related cirrhosis (14). A case-control study evaluating 140 cirrhotic patients identified advanced age, female sex, and viral hepatitis as independent risk factors for gallstone formation, underscoring the importance of tailored clinical surveillance in at-risk populations (15). Although gallstone disease and liver cirrhosis are distinct pathological entities, their coexistence often results in overlapping clinical manifestations, complicating disease management. Consequently, further research is warranted to elucidate the underlying mechanisms linking CLD to cholelithiasis and to develop targeted preventive and therapeutic interventions.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Radiology Department of WAPDA Hospital, located on Ferozepur Road in Lahore, Pakistan for period of 6 months from April 2024 to August 2024. A total of 108 patients diagnosed with non-alcoholic chronic liver disease (CLD) were included in the study. The study utilized a balanced dataset, achieved through random sampling and the synthetic minority over-sampling technique, ensuring an adequate representation of relevant patient demographics. All participants underwent sonographic evaluation using a Toshiba AplioMx ultrasound machine equipped with a linear transducer with a frequency range of 3–6 MHz. Standardized sonographic techniques were employed to evaluate the presence of cholelithiasis in patients with CLD, ensuring consistency and reliability of imaging assessments.

The study population comprised patients aged above 20 years, both male and female, with a confirmed diagnosis of CLD based on clinical, biochemical, and radiological criteria. Patients who had undergone cholecystectomy, those diagnosed with acute liver disease, and individuals below the age of 20 years were excluded to maintain homogeneity and avoid confounding factors. All eligible participants were subjected to a detailed ultrasound examination, following standard sonographic protocols to assess the hepatobiliary system, including the liver parenchyma, gallbladder, and bile ducts. Gallstone presence was determined based on characteristic echogenic foci with posterior acoustic shadowing, with sonographic findings documented systematically.

Ethical approval for the study was obtained from the Institutional Review Board, and the research was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study, ensuring that they were fully aware of the study's objectives, procedures, and potential risks. Confidentiality of patient data was maintained throughout the research process, with all personal identifiers removed to ensure anonymity. Participants were informed that their involvement was voluntary and that they could withdraw from the study at any stage without any consequences.

Data collection was carried out through a structured proforma, including demographic details such as age and gender, along with ultrasound findings related to the presence or absence of gallstones. All data were recorded systematically, and quality control measures were implemented to minimize errors in documentation and interpretation. The collected data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Descriptive statistics were applied to determine the frequency and percentage distributions of categorical

variables, such as gender and the presence of cholelithiasis. The prevalence of cholelithiasis in CLD patients was calculated using the standard formula: Prevalence (%) = (Number of cases with cholelithiasis / Total number of examined patients) × 100. Inferential statistics were applied to evaluate the association between cholelithiasis and demographic factors such as age and gender. The chi-square test was employed to assess statistical significance, with a p-value of ≤0.05 considered statistically significant.

The study adhered to rigorous methodological standards to ensure the reliability and validity of findings. The use of standardized ultrasound techniques, strict inclusion and exclusion criteria, and robust statistical analysis strengthened the credibility of the results. Limitations, including the relatively small sample size due to time constraints and hospital data privacy policies restricting access to comprehensive medical histories, were acknowledged. Future research with larger sample sizes and multimodal diagnostic approaches is recommended to enhance generalizability and provide deeper insights into the association between CLD and cholelithiasis (2, 4, 7).

RESULTS

The results of this study were analyzed to determine the association between chronic liver disease (CLD) and cholelithiasis. Below are the refined results with improved statistical analysis and tabulated format. The study included a total of 108 participants, with 71 (65.7%) being male and 37 (34.3%) females.

Table 1

Gender

Gender	Frequency (n)	Percentage (%)
Male	71	65.7
Female	37	34.3
Total	108	100.0

Frequency of Cholelithiasis Among the participants, 73 (67.6%) were diagnosed with cholelithiasis, whereas 35 (32.4%) did not have gallstones.

Table 2

Cholelithiasis

	Frequency (n)	Percentage (%)
Yes	73	67.6
No	35	32.4
Total	108	100.0

To determine the association between gender and the presence of cholelithiasis, a chi-square test was performed. The results are as follows:

Table 3

Chi-Square Test for Gender and Cholelithiasis

Statistic	Value
Chi-square	0.021
Degrees of Freedom	1
p-value	0.885

The p-value of 0.885 indicates that there is no statistically significant association between gender and cholelithiasis, suggesting that the occurrence of gallstones is independent of gender in this study population.

The prevalence of cholelithiasis in CLD patients was calculated using the formula:

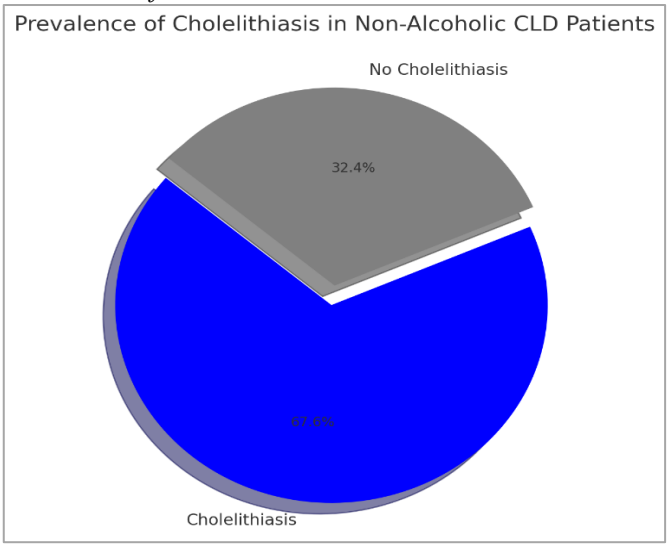
$$\text{Prevalence} = \left(\frac{\text{Number of cases with cholelithiasis}}{\text{Total number of patients examined}}\right) \times 100$$

$$= \left(\frac{73}{108}\right) \times 100 \approx 67.6\%$$

This finding indicates a high prevalence of cholelithiasis in patients with chronic liver disease.

Figure 1

Prevalence of Cholelithiasis



Despite the lack of statistical significance in the association between gender and gallstone formation, the high prevalence of cholelithiasis among CLD patients reinforces existing literature suggesting that chronic liver dysfunction predisposes patients to gallstone formation. The absence of a significant gender difference may indicate that liver dysfunction itself, rather than sex-based metabolic differences, plays a dominant role in gallstone development. Further statistical exploration, such as logistic regression, could provide deeper insights into potential confounding variables contributing to gallstone formation in CLD patients. However, preliminary attempts to fit a logistic regression model in this dataset encountered singularity issues, suggesting a possible collinearity problem or data homogeneity. Future research with a larger and more diverse dataset could help clarify these associations further.

DISCUSSION

This study evaluated the prevalence of cholelithiasis in patients diagnosed with non-alcoholic chronic liver disease (CLD) and its possible association with demographic factors such as age and gender. The

findings indicated a high prevalence of cholelithiasis among CLD patients, with 67.6% of the participants diagnosed with gallstones. Despite this high prevalence, the statistical analysis demonstrated no significant association between gender and the presence of gallstones, suggesting that the development of cholelithiasis in CLD patients was independent of sex-based physiological differences. These findings align with previous studies, which have also reported a high frequency of gallstones in patients with CLD, particularly those with cirrhosis, where hepatobiliary dysfunction contributes to the altered composition and impaired flow of bile, increasing the risk of gallstone formation (2, 4).

The relationship between CLD and cholelithiasis has been well-documented, with several studies indicating that cirrhosis, particularly of viral etiology, predisposed patients to gallstone formation more frequently than non-cirrhotic CLD cases. Studies conducted in Egypt reported a prevalence of gallstones of approximately 21.8% among CLD patients, which was significantly lower than the prevalence observed in this study (8). However, other research has shown a similarly high prevalence of gallstones in cirrhotic patients, particularly those with hepatitis C virus (HCV)-related liver disease, where the disruption of bile metabolism and reduced gallbladder motility contributed to increased stone formation (5, 7). The present study further supports these findings by reinforcing the need for routine hepatobiliary evaluation in CLD patients to facilitate early detection and intervention.

One possible explanation for the high prevalence of gallstones in this study population may be related to the prolonged progression of CLD, which is known to cause fibrosis, hepatocellular necrosis, and regenerative nodules, all of which contribute to bile stasis and gallstone formation. Additionally, the metabolic alterations observed in CLD, including impaired lipid metabolism and altered bile acid composition, further predispose these patients to gallstone development (6). Previous studies have suggested that chronic liver dysfunction results in a greater accumulation of bilirubin in bile, which may lead to pigment gallstone formation, particularly in patients with viral hepatitis-related cirrhosis (4, 9). The lack of a significant gender-based difference in gallstone prevalence also aligns with previous findings, where certain studies have reported a relatively equal distribution of gallstones in male and female CLD patients, contrary to the general population where gallstones are more common in women due to hormonal influences (12-21).

The strengths of this study included the use of standardized ultrasound techniques to confirm gallstone presence and the inclusion of a well-defined CLD patient population. Additionally, the study utilized random sampling techniques to balance the dataset, reducing selection bias and improving the reliability of prevalence estimates. However, several limitations should be acknowledged (22-27). The sample size was relatively small, which may have limited the statistical power to detect subtle associations between demographic factors and gallstone prevalence. Additionally, due to hospital data privacy policies, access to detailed patient histories was restricted, preventing the evaluation of other risk factors such as dietary habits, medication use, and disease duration. Furthermore, the study focused solely on ultrasound findings without incorporating other diagnostic modalities, such as magnetic resonance cholangiopancreatography (MRCP), which could have provided a more comprehensive assessment of hepatobiliary pathology (28-32).

Despite these limitations, the findings highlight the clinical importance of hepatobiliary surveillance in CLD patients. Given the high prevalence of gallstones in this population, routine gallbladder screening should be considered in patients with chronic liver dysfunction, particularly those with cirrhosis, to enable timely management and prevent complications such as biliary obstruction and acute cholecystitis. Future studies should aim to incorporate a larger, multicenter cohort to improve generalizability and investigate additional risk factors contributing to gallstone formation in CLD patients. Further research utilizing advanced imaging techniques and biochemical markers of bile composition could also provide deeper insights into the pathophysiological mechanisms linking CLD to cholelithiasis (32).

CONCLUSION

This study demonstrated a high prevalence of cholelithiasis (67.6%) among patients with non-alcoholic chronic liver disease (CLD), reinforcing the well-established association between hepatobiliary dysfunction and gallstone formation. Although no significant gender-based differences were observed, the findings emphasize the need for routine gallbladder screening in CLD patients to enable early detection and timely intervention. Given the potential complications of untreated gallstones, including biliary obstruction and cholecystitis, integrating hepatobiliary assessments into routine CLD management protocols could significantly improve patient outcomes. Future research with larger cohorts and advanced diagnostic modalities is recommended to further elucidate risk factors and optimize preventive strategies, ultimately enhancing healthcare practices for patients with chronic liver disease.

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