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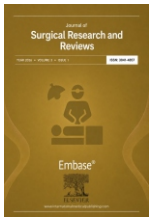

Research Article

Section: Pathology

Histopathological Spectrum of Gallbladder Lesions & Factors Associated with Metaplastic Changes: A Cross-Sectional Study

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HIGHLIGHTS

- Chronic cholecystitis predominated
- Metaplasia increased with age
- Multiple gallstones predicted
- Wall thickness associated
- Routine histology essential

Key Words:
Gallbladder
Cholecystitis
Metaplasia
Histopathology
Gallbladder carcinoma

ABSTRACT

Introduction: Gallbladder diseases are among the most common disorders requiring surgical intervention, with chronic cholecystitis and cholelithiasis accounting for most cholecystectomy specimens. Chronic inflammation induced by gallstones may result in metaplastic epithelial changes that represent important precursor lesions in gallbladder carcinogenesis. **Aim & Objective:** The present study evaluated the clinicopathological spectrum of gallbladder lesions and identified factors associated with metaplastic changes. **Materials & Methods:** This hospital-based observational cross-sectional study included 100 consecutive cholecystectomy specimens received in the Department of Pathology over 9 months (September 2024–May 2025). Clinical, demographic, dietary, and radiological data were collected from patient records. Histopathological examination was performed on hematoxylin and eosin-stained sections. Associations between clinicopathological variables and metaplastic changes were analyzed using the Independent Student's *t*-test, Chi-square test, or Fisher's exact test, followed by multivariable binary logistic regression. **Results:** Chronic cholecystitis with cholelithiasis was the most common histopathological diagnosis (57%), while metaplastic changes were identified in 14% of specimens. Patients with metaplasia were significantly older than those without metaplasia (p=0.048). Fat-rich diet (p=0.006), frequent fast-food intake (p=0.015), multiple gallstones (p=0.018), increased gallbladder wall thickness (p<0.001), abnormal body habitus (p=0.043), and weight loss (p=0.019) were significantly associated with metaplastic changes. Multivariable logistic regression identified increasing age (AOR 1.06), fat-rich diet (AOR 3.42), multiple gallstones (AOR 4.58), increased gallbladder wall thickness (AOR 1.87), and weight loss (AOR 2.94) as independent predictors of metaplastic changes. **Conclusion:** Chronic cholecystitis with cholelithiasis constituted the predominant gallbladder pathology. Metaplastic changes were significantly associated with chronic inflammatory and dietary risk factors, particularly multiple gallstones and increased gallbladder wall thickness. Routine histopathological examination of all cholecystectomy specimens is essential for the early detection of premalignant lesions and may facilitate timely identification of patients at increased risk for gallbladder carcinoma.

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INTRODUCTION

Gallbladder diseases constitute a major proportion of hepato-biliary surgical pathology, with cholelithiasis and chronic cholecystitis being the most frequent indications for cholecystectomy worldwide [1,2]. The histopathological spectrum of gallbladder lesions is broad and includes acute and chronic cholecystitis, cholesterolosis, adenomyomatous hyperplasia, xanthogranulomatous cholecystitis, metaplasia, dysplasia, and carcinoma [3,4]. Although most cholecystectomy specimens reveal benign inflammatory pathology, clinically unsuspected premalignant and malignant lesions may occasionally be detected only on microscopic examination, supporting the importance of routine histopathological evaluation [5,6]. Gallstones are considered an important initiating factor in gallbladder mucosal injury. Long-standing mechanical irritation, bile stasis, altered bile composition, and chronic inflammation can induce repeated epithelial damage and regeneration, leading to hyperplasia & metaplastic transformation [7,8]. Metaplastic changes, particularly pyloric and intestinal metaplasia, are regarded as potential precursor lesions in gallbladder carcinogenesis [9,10]. The proposed metaplasia dysplasia carcinoma sequence suggests that persistent chronic inflammation may result in epithelial metaplasia, followed by dysplasia and eventual invasive carcinoma in susceptible individuals [11,12]. Identification of these early mucosal alterations is therefore important, especially in regions where gallbladder carcinoma is relatively common. Gallbladder carcinoma is the most common malignancy of the biliary tract and is associated with poor prognosis because of its nonspecific symptoms, late presentation, and early invasion of adjacent

Its incidence shows marked geographic and ethnic variation, with higher rates reported from parts of northern and eastern India, South America, and certain Asian populations [15,16]. Several risk factors have been implicated, including increasing age, female sex, gallstones, chronic cholecystitis, obesity, dietary habits, environmental exposure, and genetic susceptibility [17,18]. Among these, chronic calculous cholecystitis remains one of the most consiste-ntly observed associations with gallbladder carcinoma and its precursor lesions [19]. Despite the frequency of cholecystectomy specimens in routine surgical pathology, the relationship between clinicodemographic variables, dietary factors, gallstone characteristics, gallbladder wall thickness, & metaplastic changes has not been uniformly documented across different populations. Studying these associations may help identify patients with a higher likelihood of premalignant mucosal alterations. The present study was therefore undertaken to evaluate the clinicopathological spectrum of gallbladder lesions in cholecystectomy specimens and to determine the demo-graphic, clinical, dietary, radiological, & histopathological factors associated with metaplastic changes.

Figure 1. Proposed mechanistic pathway of gallbladder carcinogenesis showing the progression from gallstone-induced chronic inflammation through metaplasia and dysplasia to invasive gallbladder carcinoma, together with the major clinicopathological factors influencing disease progression.

MATERIAL & METHODS

This hospital-based observational cross-sectional study was conducted in the Department of Pathology of a tertiary care

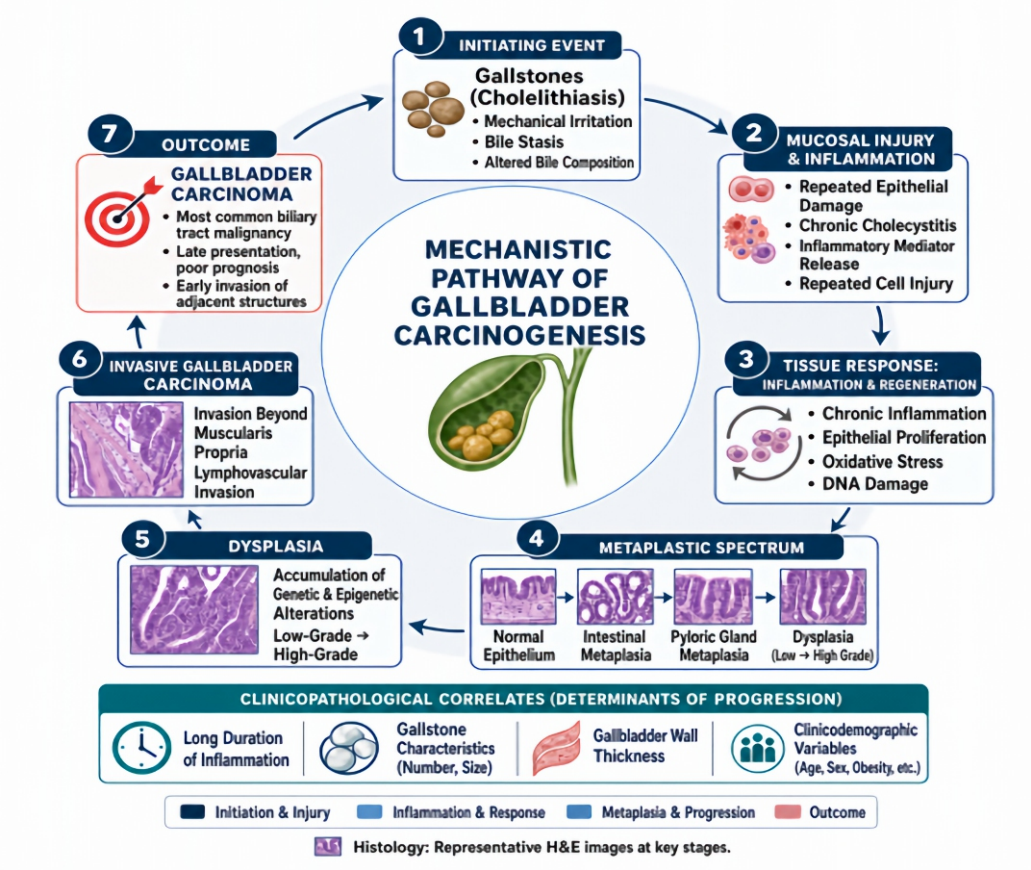

Figure 1: Mechanistic pathway of gallbladder carcinogenesis.

teaching hospital over 9 months **from September 2024 to May 2025**. A total of **100 consecutive cholecystectomy specimens** received during the study period were included. Demographic details, clinical presentation, dietary habits, lifestyle factors, associated comorbidities, ultrasonographic findings, & operative details were obtained from patient records & histopathology requisition forms. Specimens with inadequate tissue preservation or incomplete clinical information were excluded from the study. All gallbladder specimens underwent detailed gross examination, followed by routine tissue processing, paraffin embedding, & sectioning at 4–5 µm thickness. Hematoxylin & eosin (H&E) stained sections were examined microscopically for histopathological diagnosis. Attention was paid to chronic inflammatory changes, Rokitansky Aschoff sinuses, cholesterolosis, adenomyomatous hyperplasia, & metaplastic alterations, including intestinal & pyloric metaplasia. Histopathological findings were correlated with the available clinical and radiological parameters.

Data were entered into Microsoft Excel and analyzed using **IBM SPSS Statistics version 26.0**. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were summarized as frequencies and percentages. Comparisons between patients with and without metaplastic changes were performed using the Independent Student's *t*-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. Variables showing statistical significance on univariate analysis were entered into a multivariable binary logistic regression model to identify independent predictors of metaplastic changes. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were calculated, and a two-tailed p value of <0.05 was considered statistically significant.

RESULTS

A total of 100 gallbladder specimens were included in the present study. Demographic characteristics, dietary and clinical risk factors, gallstone characteristics, histopathological diagnoses, and factors associated with metaplastic changes were evaluated. Patients were categorized according to the presence (n = 14) or absence (n = 86) of metaplastic changes, and comparative analyses were performed using appropriate statistical tests. Multivariable logistic regression was subsequently carried out to identify independent predictors of metaplastic changes. Demographic characteristics **(Table 1 and Figure 2).** The mean age of the study population was 48.7 ± 12.3 years. Patients with metaplastic changes were significantly older than those without metaplasia (53.8 ± 10.2 vs. 47.9 ± 12.4 years; $p = 0.048$). Females constituted most of the study population (76%), while males accounted for 24%, with no significant association between sex and metaplastic changes ($p = 0.262$). Similarly, residence was not associated with metaplasia ($p = 0.706$). However, body habitus demonstrated a significant association, with thin/obese individuals showing a higher proportion of metaplastic changes than those with normal physique ($p = 0.043$). **Figure 1** illustrates the age and sex distribution of the study participants. Dietary factors associated with metaplastic changes **(Table 2).** Patients consuming a fat-rich diet showed a signific-antly higher frequency of metaplastic changes than those consuming a balanced diet ($\chi^2 = 7.41$, $p = 0.006$). Likewise, frequent fast-food intake was significantly associated with metaplasia ($\chi^2 = 5.92$, $p = 0.015$). In contrast, dietary pattern (vegetarian versus mixed/non-vegetarian) and regular fasting did not demonstrate statistically significant associations with metaplastic changes ($p > 0.05$). Gallstone characteristics and ultrasonographic findings **(Table 3 and Figure 3).** Multiple .gallstones were observed more frequently among patients with metaplastic changes than among those without metaplasia, demonstrating a significant association ($\chi^2 = 5.63$, $p = 0.018$). In addition, gallbladder wall thickness was significantly greater in the metaplasia group (5.8 ± 1.2 mm) compared with the non-metaplasia group (4.4 ± 1.1 mm; $p < 0.001$). **Figure 3** demonstrates the distribution of gallstone characteristics in the study population, with multiple gallstones being the predominant pattern. Clinical profile and histopathological spectrum **(Tables 4 & 5; Figure 4).** Weight loss was significantly associated with metaplastic changes ($\chi^2 = 5.47$, $p = 0.019$), whereas chronic illness, medication history, and associated liver or pancreatic disease showed no statistically significant relationship ($p > 0.05$). Histopathological examination revealed chronic cholecystitis with cholelithiasis as the most common diagnosis, accounting for 57% of cases, followed by chronic cholecystitis with Rokitansky–Aschoff sinuses (11%). Adenomyomatous hyperplasia and cholesterolosis each constituted 7% of cases, while chronic cholecystitis alone accounted for 4%. Acute cholecystitis, chronic cholecystitis with metaplasia, and acute-on-chronic cholecystitis each represented 3% of cases. Other diagnoses collectively accounted for 5%. **Figure 3** depicts the histopathological spectrum of gallbladder lesions. Predictors of metaplastic changes **(Table 6 & Figure 5).** Multivariable logistic regression identified increasing age (adjusted OR 1.06, 95% CI: 1.01–1.12; $p = 0.031$), fat-rich diet (adjusted OR 3.42, 95% CI: 1.12–10.46; $p = 0.030$), multiple gallstones (adjusted OR 4.58, 95% CI: 1.23–17.01; $p = 0.023$), increased gallbladder wall thickness (adjusted OR 1.87, 95% CI: 1.21–2.89; $p = 0.005$), and weight loss (adjusted OR 2.94, 95% CI: 1.01–8.52; $p = 0.047$) as independent predictors of metaplastic changes. Female sex was not independently associated with metaplasia ($p = 0.389$). The regression model demonstrated acceptable calibration (Hosmer–Lemeshow $p = 0.71$), explained 34% of the variance (Nagelkerke $R^2 = 0.34$), and achieved an overall prediction accuracy of 85%. Figure 4 presents the adjusted odds ratios and corresponding 95% confidence intervals for the independent predictors of metaplastic changes. Overall, metaplastic changes were identified in 14% of gallbladder specimens and were significantly associated with increasing age, abnormal body habitus, fat-rich dietary habits, frequent fast-food consumption, multiple gallstones, increased gallbladder wall thickness, and weight loss. Multivariable analysis confirmed age, fat-rich diet, multiple gallstones, gallbladder wall thickness, and weight loss as independent predictors of metaplastic changes, highlighting their potential role in the progression of chronic gallbladder pathology.

Table 1. Demographic characteristics according to metaplastic changes

Variable	Metaplasia Present (n=14)	Metaplasia Absent (n=86)	Total (n=100)	Statistical test	P value
Age (years), Mean ± SD	53.8 ± 10.2	47.9 ± 12.4	48.7 ± 12.3	Independent t-test	0.048*
Male	2	22	24	χ^2=1.26	0.262
Female	12	64	76		
Urban	9	50	59	χ^2=0.14	0.706
Rural	5	36	41		
Normal physique	7	56	63	χ^2=4.08	0.043*
Thin/Obese	7	30	37		

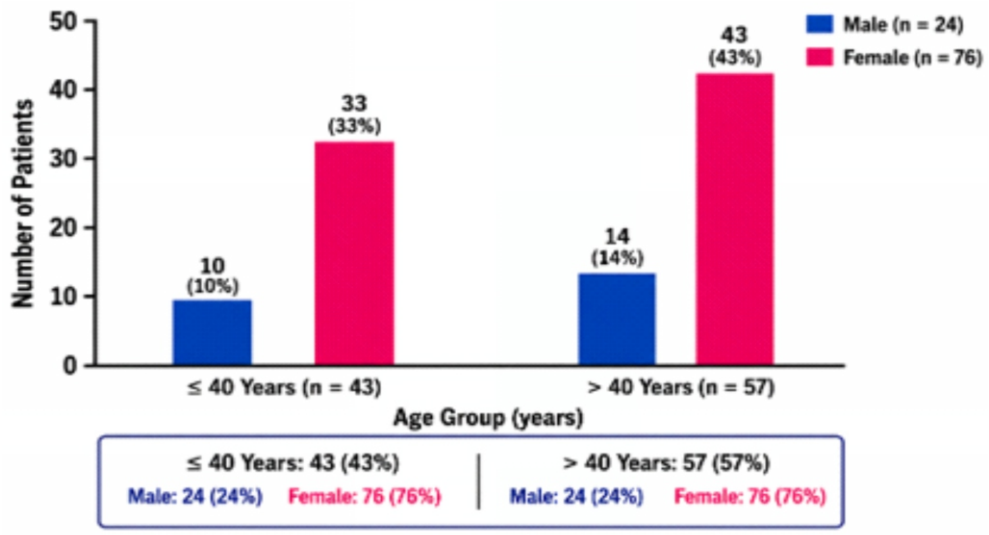

Figure 2. Age and sex distribution of the study participants (n = 100). Clustered bar chart showing the distribution of male and female patients according to age groups (≤40 years and >40 years).

Table 2. Association between dietary factors and metaplastic changes

Variable	Metaplasia Present	Metaplasia Absent	χ^2/Fisher	P value
Fat-rich diet	7	12	7.41	0.006*
Balanced diet	7	74		
Vegetarian	6	50	0.58	0.446
Mixed/Non -vegetarian	8	36		
Frequent fast-food intake	6	12	5.92	0.015*
Occasional/Never	8	74		
Regular fasting	3	6	1.89	0.169

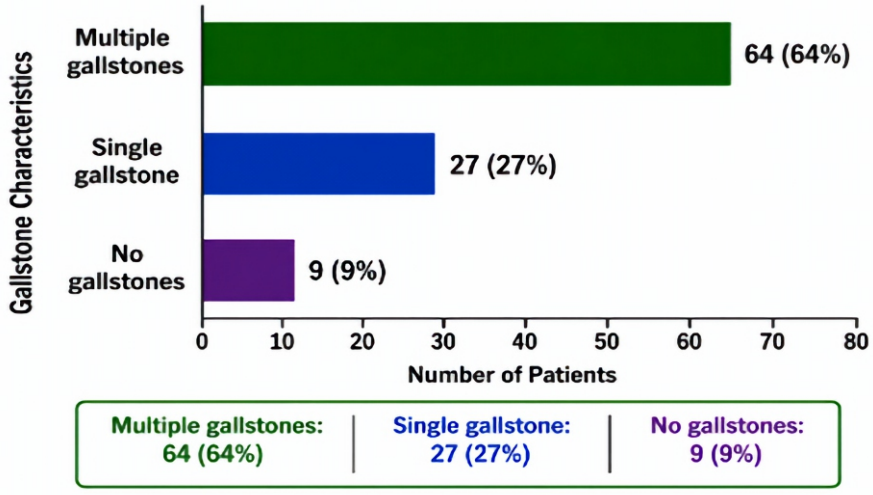

Figure 3. Distribution of gallstone characteristics among the study participants (n = 100). Horizontal bar chart depicting the frequency and percentage of patients with multiple gallstones, single gallstones, and no gallstones.

Table 3. Gallstone characteristics and metaplasia

Variable	Metaplasia Present	Metaplasia Absent	χ^2	P value
Multiple stones	12	52	5.63	0.018*
Single stone	2	25		
No stones	0	9		
Wall thickness (mm), Mean ± SD	5.8 ±1.2	4.4 ±1.1	t=4.21	<0.001*

Table 4. Clinical factors associated with metaplasia

Variable	Metaplasia Present	Metaplasia Absent	χ^2/Fisher	P value
Weight loss	9	26	5.47	0.019*
No weight loss	5	60		
Chronic illness	6	21	1.89	0.169
Medication history	3	8	0.52	0.471
Liver/Pancreatic disease	2	5	Fisher Exact	0.312

Table 5. Histopathological diagnosis

Diagnosis	Frequency	Percentage (%)
Chronic cholecystitis with cholelithiasis	57	57.0
Chronic cholecystitis with Rokitansky –Aschoff sinus	11	11.0
Adenomyomatous hyperplasia	7	7.0
Cholesterolosis	7	7.0
Chronic cholecystitis	4	4.0
Acute cholecystitis	3	3.0
Chronic cholecystitis with metaplasia	3	3.0
Acute-on-chronic cholecystitis	3	3.0
Others	5	5.0

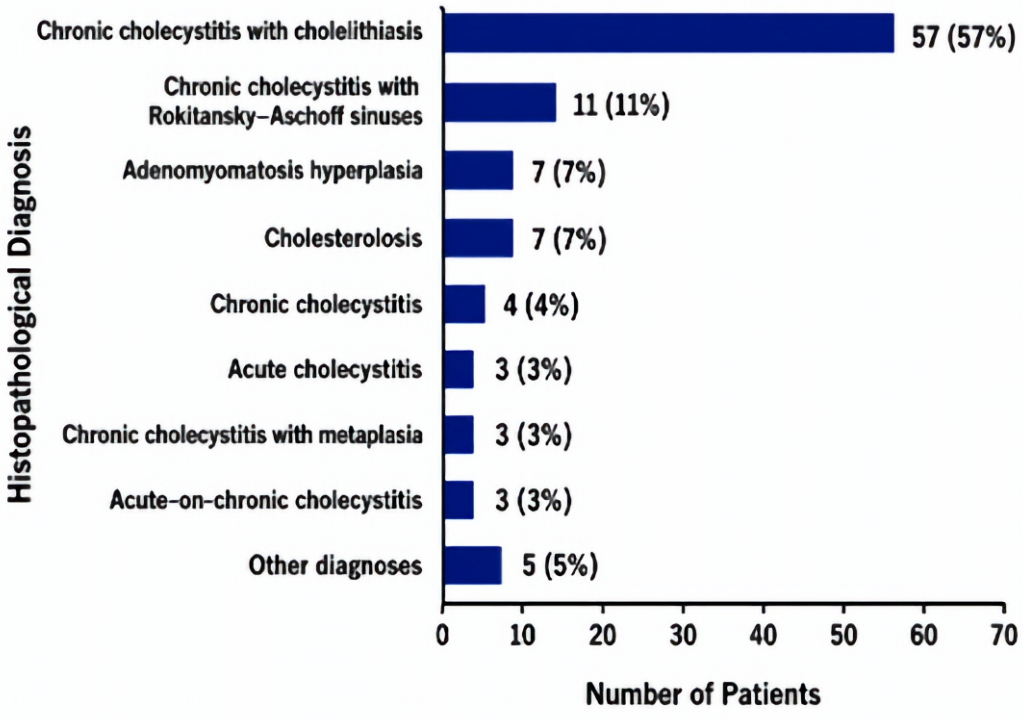

Figure 4. Histopathological spectrum of gallbladder lesions (n = 100). Horizontal bar chart illustrating the frequency and percentage distribution of histopathological diagnoses in gallbladder specimens, arranged in descending order of frequency.

Table 6. Binary logistic regression for predictors of metaplastic changes

Variable	Adjusted OR	95% CI	P value
Age (per year)	1.06	1.01–1.12	0.031*
Female sex	1.84	0.46–7.36	0.389
Fat-rich diet	3.42	1.12–10.46	0.030*
Multiple gallstones	4.58	1.23–17.01	0.023*
Wall thickness	1.87	1.21–2.89	0.005*
Weight loss	2.94	1.01–8.52	0.047*
Nagelkerke R^2 = **0.34**			
Hosmer–Lemeshow test = **0.71**			
Overall prediction accuracy = **85%**			

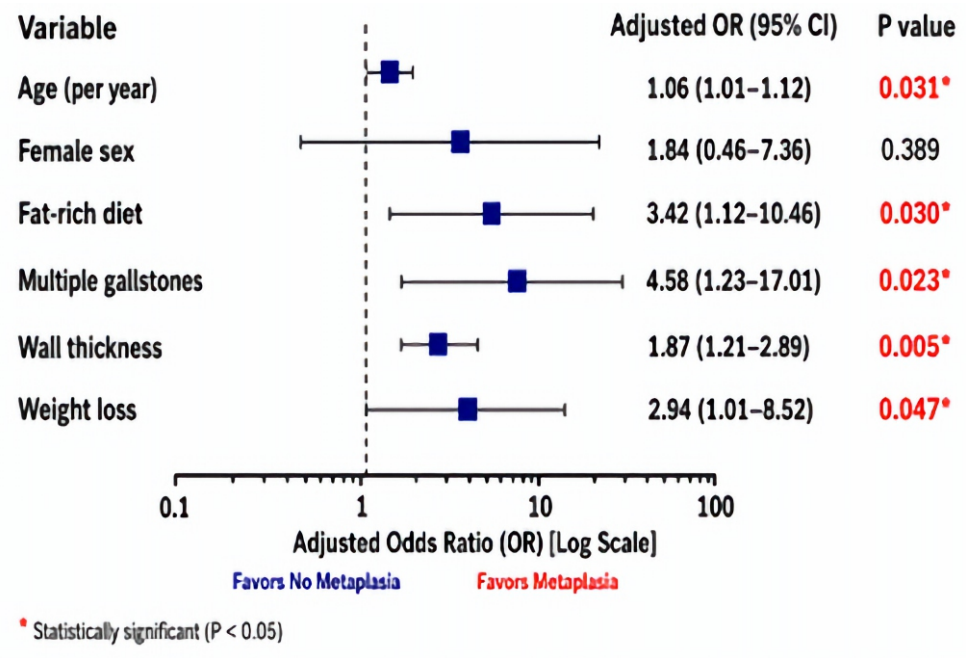

Figure 5. Forest plot of multivariable logistic regression analysis showing independent predictors of metaplastic changes. Forest plot displaying adjusted odds ratios (AORs) with 95% confidence intervals for age, female sex, fat-rich diet, multiple gallstones, gallbladder wall thickness, and weight loss. The vertical reference line represents an odds ratio of 1.0, with values to the right indicating increased odds of metaplastic changes.

DISCUSSION

The present study evaluated the clinicopathological spectrum of gallbladder lesions and factors associated with metaplastic changes in 100 cholecystectomy specimens. Chronic cholecystitis with cholelithiasis was the predominant histopathological diagnosis, while metaplastic changes were identified in 14% of cases. Increasing age, fat-rich diet, multiple gallstones, increased gallbladder wall thickness, and weight loss emerged as significant predictors of metaplasia, highlighting the importance of chronic inflammatory insults in the development of premalignant gallbladder lesions.

Chronic cholecystitis remains the most frequent indication for cholecystectomy worldwide and represents the commonest histopathological diagnosis in most published series [1–4]. In the present study, chronic cholecystitis with cholelithiasis accounted for 57% of specimens, followed by chronic cholecystitis associated with Rokitansky–Aschoff sinuses and adenomyomatous hyperplasia. Similar observations were reported by **Parikh et al.** and **Sharma et al.**, who demonstrated that chronic inflammatory lesions constitute most gallbladder specimens, whereas premalignant lesions are encountered less frequently but warrant careful microscopic examination [3,4]. Likewise, **Jha et al.** and **Kalita et al.** emphasized that routine histopathological examination facilitates the detection of incidental premalignant and malignant lesions that may be clinically unsuspected, thereby supporting the practice of submitting all cholecystectomy specimens for histopathological evaluation [5,6].

Metaplastic changes are widely considered early precursor lesions in the metaplasia–dysplasia–carcinoma sequence of gallbladder carcinogenesis [7–12]. In the present study, patients with metaplastic changes were significantly older than those without metaplasia, suggesting that prolonged exposure to chronic inflammation increases the likelihood of epithelial transformation. Similar observations have been described by **Seretis et al.**, who reported a strong association between chronic cholecystitis and intestinal or pyloric metaplasia, reinforcing the concept that persistent mucosal injury promotes sequential epithelial alterations [9]. **Duarte et al.** further demonstrated that

metaplastic lesions are frequently identified adjacent to dysplastic and malignant epithelium, providing additional evidence for the precursor role of metaplasia [10].

Gallstones remain the most important etiological factor responsible for chronic gallbladder inflammation and subsequent epithelial injury [7,8]. In the present study, multiple gallstones and increased gallbladder wall thickness were significantly associated with metaplastic changes and remained independent predictors on multivariable analysis. These findings are consistent with those reported by **Hundal et al.**, **Randi et al.**, and **Jain et al.**, who identified gallstone burden and chronic inflammatory changes as major risk factors for gallbladder carcinoma [13,15,17]. Chronic irritation caused by gallstones may induce repeated epithelial regeneration, thereby increasing the probability of metaplastic and dysplastic transformation. Dietary factors also demonstrated a significant influence on metaplastic changes in the present study. Patients consuming fat-rich diets and frequent fast food exhibited significantly higher frequencies of metaplasia than those consuming balanced diets. Similar findings were reported by **Ali et al.**, who observed that unhealthy dietary practices, particularly high-fat food consumption, were significantly associated with gallbladder carcinoma in a case-control study [18]. Although vegetarian status and regular fasting were not independently associated with metaplasia in the present study, dietary modification remains an important preventive strategy in populations with a high burden of gallstone disease. Furthermore, weight loss emerged as an independent predictor of metaplastic changes, possibly reflecting longstanding biliary pathology and chronic inflammation rather than a direct causal relationship.

The present study has certain limitations. Being a single-center observational study with a relatively modest sample size, the findings may not be generalizable to all populations. Immunohistochemical and molecular analyses were not performed to further characterize premalignant epithelial alterations. Nevertheless, the study comprehensively evaluated demographic, dietary, clinical, radiological, & histopathological variables and identified several independent predictors of metaplastic changes. These findings reinforce the importance of routine histopathological examination of all cholecystectomy specimens and careful evaluation of metaplastic lesions, particularly in older patients with multiple gallstones and chronic inflammatory changes, to facilitate early identification of individuals at increased risk for gallbladder carcinogenesis.

CONCLUSION

The present study highlights the diverse histopathological spectrum of gallbladder lesions, with chronic cholecystitis associated with cholelithiasis being the predominant diagnosis. Metaplastic changes were identified in a notable proportion of cholecystectomy specimens and were significantly associated with increasing age, fat-rich dietary habits, multiple gallstones, increased gallbladder wall thickness, and weight loss. Multivariable analysis confirmed these factors as independent predictors of metaplastic changes, emphasizing the role of chronic inflammation and gallstone-related mucosal injury in the early stages of gallbladder carcinogenesis. These findings support the concept of a metaplasia–dysplasia–carcinoma sequence & reinforce the importance of meticulous histopathological examination of all cholecystectomy specimens, even in patients with apparently benign disease. Early recognition of premalignant mucosal alterations may facilitate timely surveillance and appropriate clinical management, particularly in individuals with established risk factors, thereby contributing to improved strategies for the prevention and early detection of gallbladder carcinoma.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the broader applicability of the results. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-.care, diagnosis, and treatment outcomes. By highlighting real-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient world relevance, the study contributes to evidence based medicalpractice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

GBC: Gallbladder Carcinoma
H&E: Hematoxylin and Eosin
USG: Ultrasonography

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by

the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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None

ETHICAL APPROVAL & CONSENT TO PARTICIPATE

All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research diretions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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